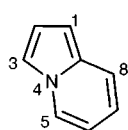
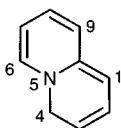


## 25 Heterocycles containing a ring-junction nitrogen

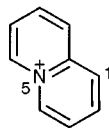
In addition to the biologically important purines and pteridines and the major benzo-fused heterocycles such as indole, many other aromatic, fused heterocyclic ring systems are known, and of these, the most important are those containing a ring-junction nitrogen – that is, where a *nitrogen is common to two rings*.<sup>1</sup> The vast majority of these systems do not occur naturally, but they have been the subject of many studies from the theoretical viewpoint, for the preparation of potentially biologically active analogues, and for other industrial uses. For reasons of space, only combinations of five- and six-membered rings are considered here, though other combinations are possible and are known.



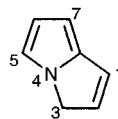
indolizine



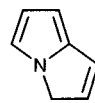
4*H*-quinolizine



quinolizinium



3*H*-pyrrolizine

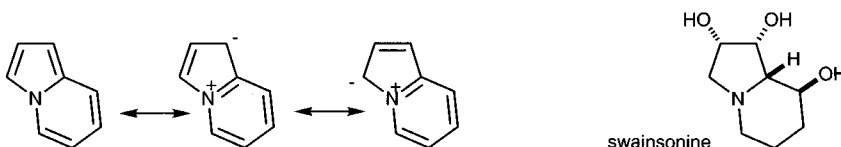


pyrrolizine anion

Of the parent systems which have the ring-junction nitrogen as the *only* heteroatom, only indolizine (often ‘pyrrocoline’ in the older literature) has a neutral, fully conjugated 10-electron  $\pi$ -system, comprising four pairs of electrons from the four double bonds and a pair from nitrogen, much as in indole. 4*H*-Quinolizine is not aromatic – there is a saturated atom interrupting the conjugation – but the cation, quinolizinium, formed formally by loss of hydride from quinolizine, *does* have an aromatic 10-electron system: it is completely isoelectronic with naphthalene, the positive charge resulting from the higher nuclear charge of nitrogen *versus* carbon. Similarly, pyrrolizine, which is already aromatic in being a pyrrole (with an  $\alpha$ -vinyl substituent), on conversion into its conjugate anion, attains a 10-electron  $\pi$ -system.

### 25.1 Indolizines<sup>2</sup>

The aromatic character of indolizine is expressed by three main mesomeric contributors, two of which incorporate a pyridinium moiety; other structures (not shown) incorporating neither a complete pyrrole nor a pyridinium are less important.



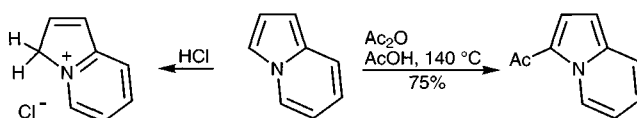
swainsonine

Aromatic indolizines are very rare in nature, but the fully reduced (indolizidine) nucleus is widespread, particularly in alkaloids, of which swainsonine is a typical example. Synthetic indolizines have found use in photographic dyes.

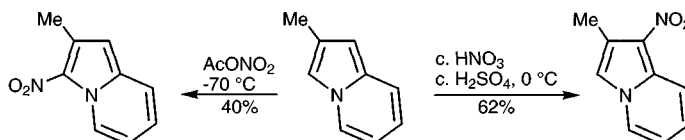
### 25.1.1 Reactions of indolizines

Indolizine is an electron-rich system and its reactions are mainly electrophilic substitutions, which occur about as readily as for indole, and go preferentially at C-3, but may also take place at C-1. Consistent with their similarity to pyrroles, rather than pyridines, indolizines are not attacked by nucleophiles, nor are there examples of nucleophilic displacement of halide.

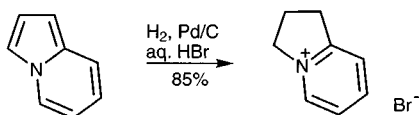
Indolizine,  $pK_a$  3.9,<sup>3</sup> is much more basic than indole ( $pK_a$  -3.5) and the implied relative stability of the cation makes it less reactive and thus indolizines resistant to acid-catalysed polymerisation (*cf.* Section 17.1.9). Indolizine protonates at C-3, but 3-methylindolizine protonates mainly (79%) at C-1; the delicacy of the balance is further illustrated by 1,2,3-trimethyl- and 3,5-dimethylindolizines, each of which protonate exclusively at C-3. Electrophilic substitutions such as acylation,<sup>4</sup> Vilsmeier formylation,<sup>5</sup> and diazo-coupling<sup>6</sup> all take place at C-3.



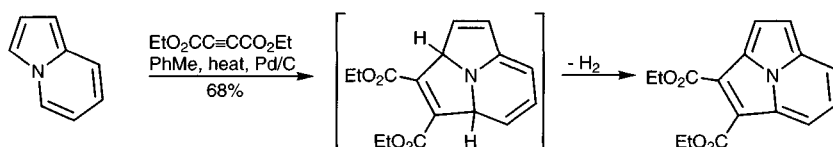
Nitration of 2-methylindolizine under mild conditions results in substitution at C-3,<sup>7</sup> but under strongly acidic conditions it takes place at C-1,<sup>8</sup> presumably *via* attack on the indolizinium cation.



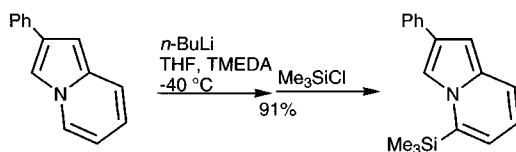
Indolizine and its simple alkyl derivatives are sensitive to light and to aerial oxidation, which lead to destruction of the ring system. Catalytic reduction in acidic solution – reduction of the indolizinium cation – gives a pyridinium salt;<sup>9</sup> complete saturation, affording indolizidines, results from reductions over platinum.<sup>10</sup>



Despite its 10-electron aromatic  $\pi$ -system, indolizine apparently participates as an 8-electron system in its reaction with diethyl acetylenedicarboxylate, though the process may be stepwise and not concerted. By carrying out the reaction in the presence of a noble metal as catalyst, the initial adduct is converted into an aromatic cyclazine (Section 25.5).<sup>11</sup>



5-Methylindolizine undergoes lithiation at the side-chain methyl;<sup>12</sup> 2-phenylindolizine lithiates at C-5.<sup>13</sup>



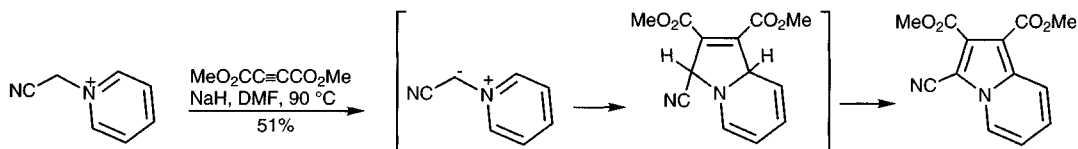
Of its functional derivatives, worth noting is the easy cleavage of carboxyl and acyl groups on heating with aqueous acid, and the instability of amino-derivatives, which cannot be diazotised, but which can be converted into stable acetamides.

### 25.1.2 Synthesis of indolizines<sup>14</sup>

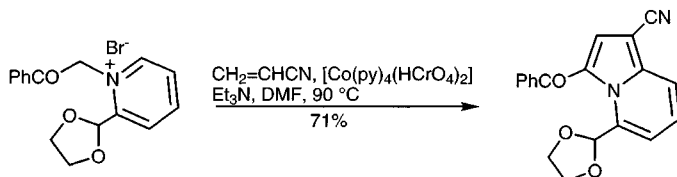
The most general approach to indolizines is the Chichibabin synthesis<sup>15</sup> which involves quaternisation of a 2-alkylpyridine with an  $\alpha$ -haloketone, followed by base-catalysed cyclisation *via* deprotonation of the pyridinium  $\alpha$ -methyl<sup>16</sup> which is of course easier if that alkyl groups is further acidified.<sup>17</sup>



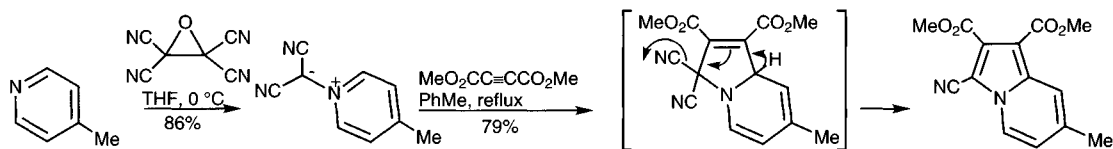
Another useful method involves the intermediacy of a pyridinium ylide as a 1,3-dipole in a cycloaddition.<sup>18</sup>



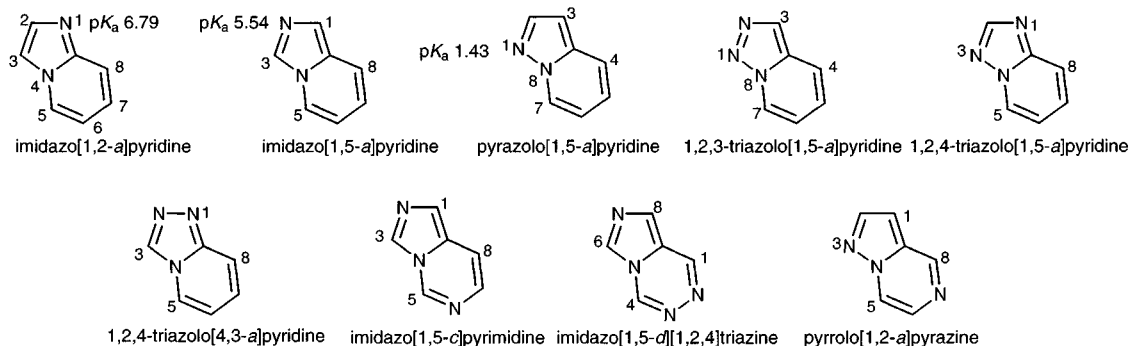
An important feature of this type of reaction (which can also be used in an analogous fashion to prepare aza-indolizines) is that although a dihydroindolizine is the logical product from a mechanistic viewpoint, the fully aromatic compound is usually obtained. The mechanism of aromatisation is not clear: it could be by air oxidation during work up, or *via* hydride transfer to some other component in the reaction mixture. When dihydro-compounds are isolated they can be easily aromatised using the usual reagents such as palladium/charcoal or quinones. An extension of this analysis is the production of aromatic indolizines from reaction of an ylide with an alkene (which would be expected to give the tetrahydro-product) *in the presence* of a suitable oxidant such as the cobalt chromate<sup>19</sup> shown below.<sup>20</sup>



In reaction with alkynes, aromatisation can occur by loss of  $\text{HX}$  when a leaving group is present in one of the reactants.<sup>21</sup>

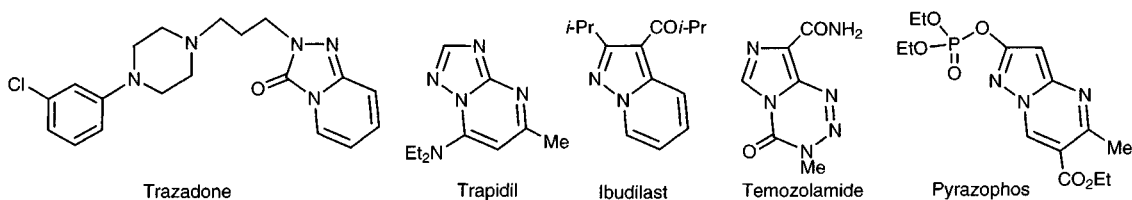


## 25.2 Aza-indolizines



Note: as can be seen from the examples above, numbering sequences vary with the number and disposition of the nitrogen atoms.

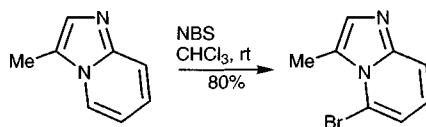
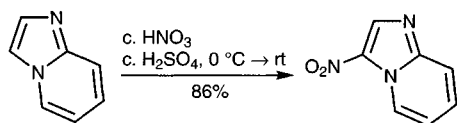
Seven monoaza- and many more polyaza-indolizines (some are shown above) are possible, indeed compounds with up to six nitrogen atoms have been frequently reported. Despite the great rarity of such systems in nature, there is much interest in aza-indolizines stemming from their structural similarity to both indoles and purines. The imidazopyrazine ring occurs in *Cypridina* luciferin (ch. 11). The antidepressant Trazadone is an example of the large number of aza-indolizines which have been prepared for assessment of their pharmacological activity. Trapadil is a coronary vasodilator, Ibudilast is used in the treatment of asthma and Temozolomide is an anti-cancer agent. Compounds of use in other areas include the plant antifungal agent Pyrazophos.



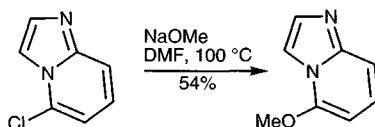
Apart from pyrrolo[1,2-*b*]pyridazine, all the monoaza-indolizines protonate on the second (non-ring-junction) nitrogen, rather than on carbon.<sup>3,22</sup> Alkylation similarly goes on nitrogen however other electrophilic reagents attack with regioselectivity similar to indolizine itself – they effect substitution of the five-membered ring at positions 1 and 3 (where these are carbon).

### 25.2.1 Imidazo[1,2-*a*]pyridine

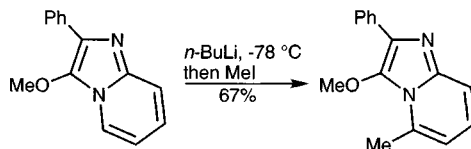
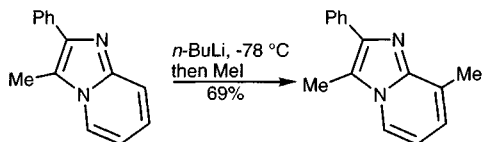
Electrophilic substitutions such as halogenation, nitration *etc.* go at C-3, or at C-5 if position 3 is blocked.<sup>23</sup> Acylation does not require a catalyst.<sup>24</sup>



Of all the positional chloro-isomers, nucleophilic displacement reactions are known only for the 5-isomer; 7-chloroindolizine, where one might have anticipated similar activation, is not reactive in this sense.<sup>25</sup>

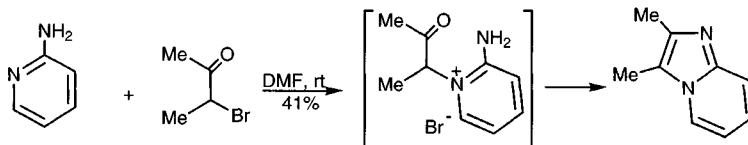


Base-catalysed deuterium exchange goes at C-3 and C-5;<sup>26</sup> preparative lithiation occurs at C-3, or if C-3 is blocked, at C-5 or C-8 depending on other substituents<sup>27</sup> but the 2,6-dichloro compound reacts selectively at C-5, even in the presence of hydrogen at C-3.<sup>28</sup>



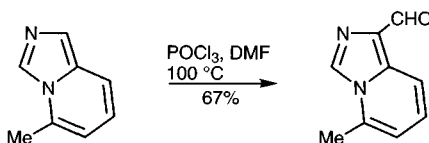
Amino-imidazo[1,2-*a*]pyridines are even more unstable than aminoindolizines; they exist as amino tautomers, but 2- and 5-oxygenated derivatives are in the keto form. These last react as usual with phosphoryl chloride yielding chloro-compounds.<sup>20</sup>

The ring synthesis of imidazo[1,2-*a*]pyridines is based on the Chichibabin route to indolizines (Section 25.1.2), but using 2-aminopyridines instead of 2-alkylpyridines. The initial reaction with the halo-ketone is regioselective for the ring nitrogen, so isomerically pure products are obtained.<sup>29</sup> 2-Oxoimidazo[1,2-*a*]pyridines are the products when an  $\alpha$ -bromo-ester is used instead of a ketone.<sup>30</sup>



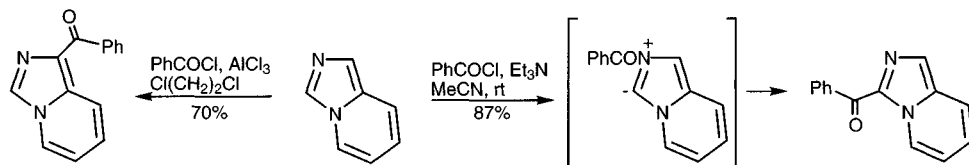
## 25.2.2 Imidazo[1,5-*a*]pyridines

Electrophilic substitution in this system again occurs in the five-membered ring, at C-1, or at C-3 if the former position is occupied.<sup>31,32</sup> Reaction with bromine gives a 1,3-dibromo-product.<sup>33</sup>



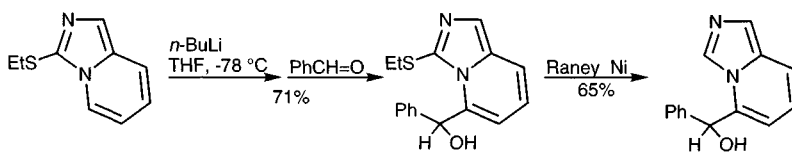
Benzoylation provides an instructive example: under normal conditions C-substitution occurs at C-1, however in the presence of triethylamine, 3-benzoylimi-

dazo[1,5-*a*]pyridine is the product.<sup>34</sup> This can be explained by assuming the intermediacy of an ylide formed by deprotonation of an initial  $N^+$ -benzoyl salt (*cf.* Section 21.1.2.5).

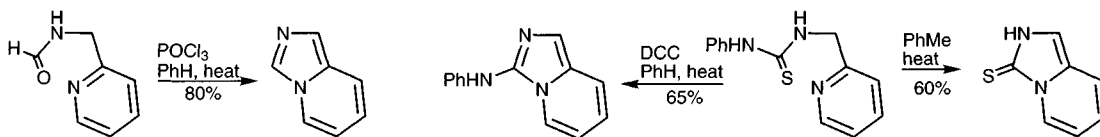


Five-membered ring cleavage occurs relatively easily: hot aqueous acid converts these heterocycles into 2-aminomethylpyridines.

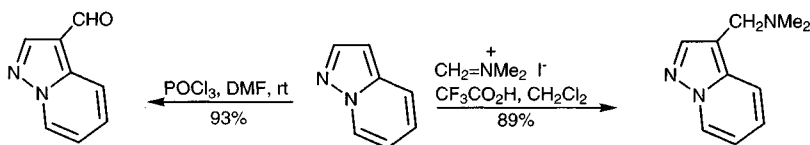
Lithiation, by direct analogy with imidazole, results in loss of the 3-proton,<sup>5</sup> but 5-lithiation occurs on comparable treatment of 3-ethylthio-derivative, the substituent both blocking attack at C-3 and assisting lithiation at the *peri* position; the ethylthio group can of course be subsequently easily removed.<sup>35</sup>



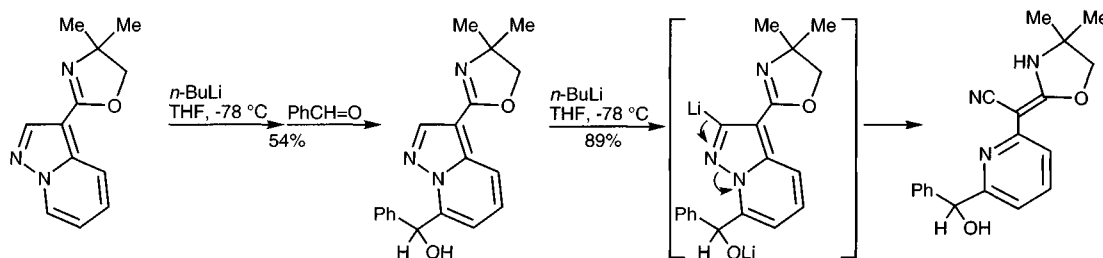
Imidazo[1,5-*a*]pyridines are synthesised by the dehydrative cyclisation of *N*-acyl-2-aminomethylpyridines.<sup>32</sup> 3-Amino-,<sup>36</sup> oxy-<sup>37</sup> and thio-<sup>38</sup> derivatives are available *via* related cyclisations.



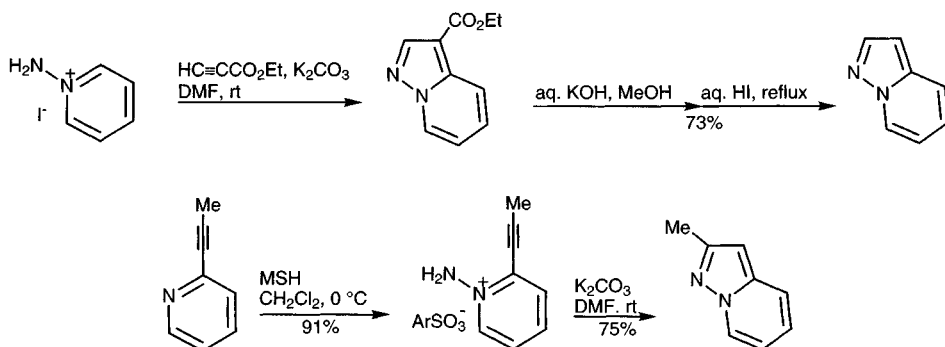
### 25.2.3 Pyrazolo[1,5-*a*]pyridines



In this system, electrophilic substitution occurs at C-3<sup>39</sup> and lithiation takes place at C-7, though a 3-oxazoline can direct a second metallation to C-2, leading to ring cleavage,<sup>40</sup> as shown below.



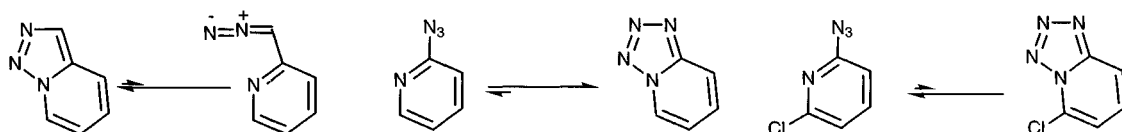
Pyrazolo[1,5-*a*]pyridines can be prepared by cycloaddition of *N*-aminopyridinium ylides with alkynes<sup>41</sup> or *N*-amination of 2-alkynylpyridines.<sup>42</sup> Interestingly, the cycloaddition of *N*-amino-3-benzyloxypyridine goes preferentially to the more hindered C-2.<sup>43</sup>



Pyridinium *N*-imide, the ylide produced by removal of a proton from 1-aminopyridinium iodide, serves as a 1,3-dipole and reacts with propiolate (shown above) or fumarate to give bicyclic compounds.<sup>44</sup>

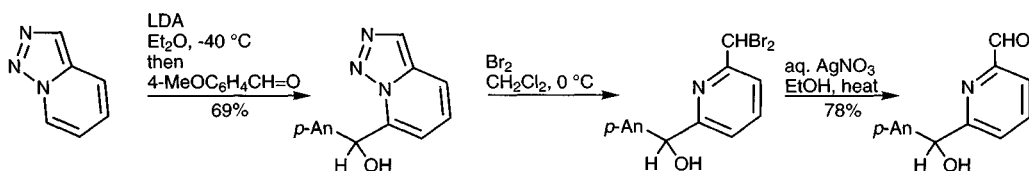
## 25.2.4 Triazolo-<sup>45</sup> and tetrazolopyridines

1,2,3-Triazolo[1,5-*a*]pyridine can be, in theory, in equilibrium with its ring-opened diazo tautomer;<sup>46</sup> although it actually exists in the closed form, its reactions tend to reflect this potential equilibrium: reaction with electrophiles can take two courses. Acylation and nitration occur normally, at C-1, but reagents such as bromine lead to a very easy ring cleavage.<sup>47</sup> Aqueous acid similarly brings about ring cleavage and the formation in this case of 2-hydroxymethylpyridine.

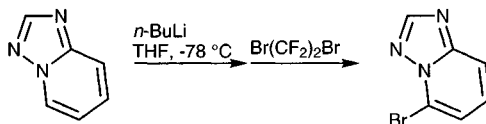


2-Azido-azines are in equilibrium with fused tetrazoles, the position of the equilibrium being very sensitive to substituent influence, for example in the unsubstituted case the equilibrium lies predominantly towards the closed form whereas the analogous 6-chloro-compound is predominantly open.<sup>48</sup>

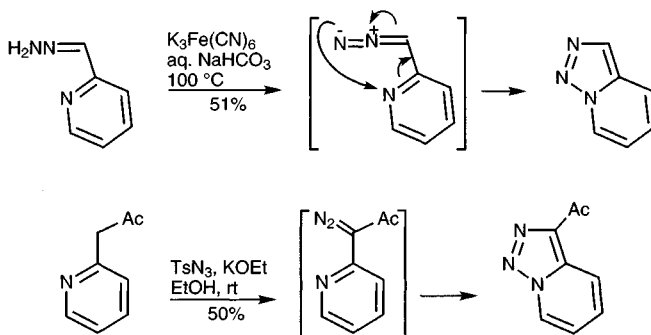
Direct lithiation of 1,2,3-triazolo[1,5-*a*]pyridines occurs with ease, at C-7, subsequent reaction with electrophiles being unexceptional, for example conversion into the 7-bromo-derivative then allows nucleophiles to be introduced *via* displacement of halide, thus providing, overall, a route to 2,6-disubstituted pyridines.<sup>49</sup> However, lithiation in tetrahydrofuran as solvent leads to formation of a 7,7-linked dimer.<sup>50</sup> The 7-lithio compound is also formed by cleavage of the 7-*N,N*-diethylcarboxamide with *n*-butyllithium.<sup>51</sup>



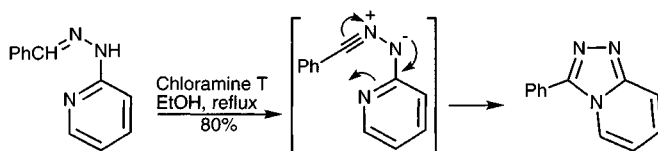
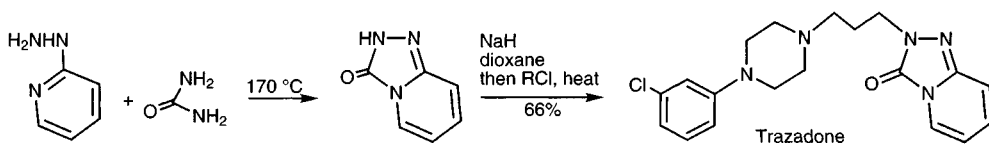
1,2,4-Triazolo[1,5-*a*]pyridine seems to be resistant to electrophilic attack but can be lithiated at C-5; in contrast, 1,2,4-triazolo[4,3-*a*]pyridine readily undergoes electrophilic substitution at C-3.<sup>52</sup>



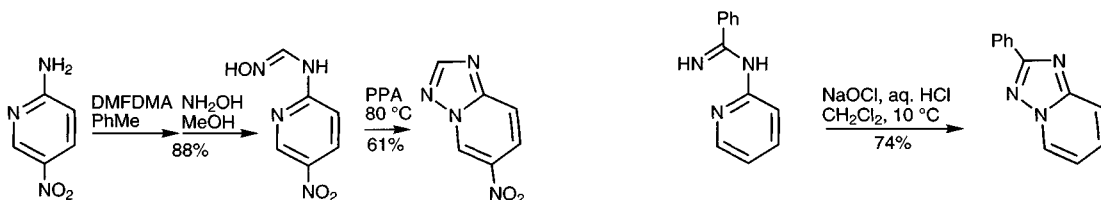
1,2,3-Triazolo[1,5-*a*]pyridines can be synthesised by oxidation of pyridine 2-carboxaldehyde hydrazones, presumably by way of the diazo-species,<sup>53</sup> or by diazo-transfer reactions.<sup>54</sup>



The 1,2,4-triazolo[4,3-*a*]pyridine nucleus can be accessed by cyclocondensation of 2-hydrazinopyridines; the synthesis of Trazadone shown below is an example.<sup>55</sup> Oxidative closure of pyridin-2-ylhydrazones produces 1,2,4-triazolo[4,3-*a*]pyridines.<sup>56</sup>

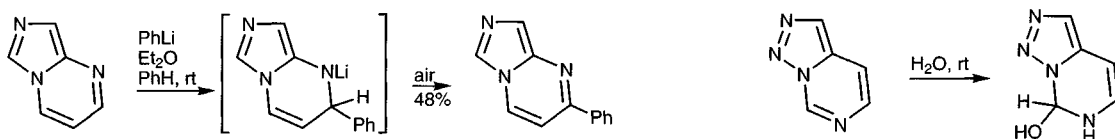


1,2,4-Triazolo[1,5-*a*]pyridines can be prepared *via* oxidative cyclisation of amidines<sup>57</sup> or acid-catalysed cyclisation of amidoximes<sup>58</sup> – each of these is illustrated below.

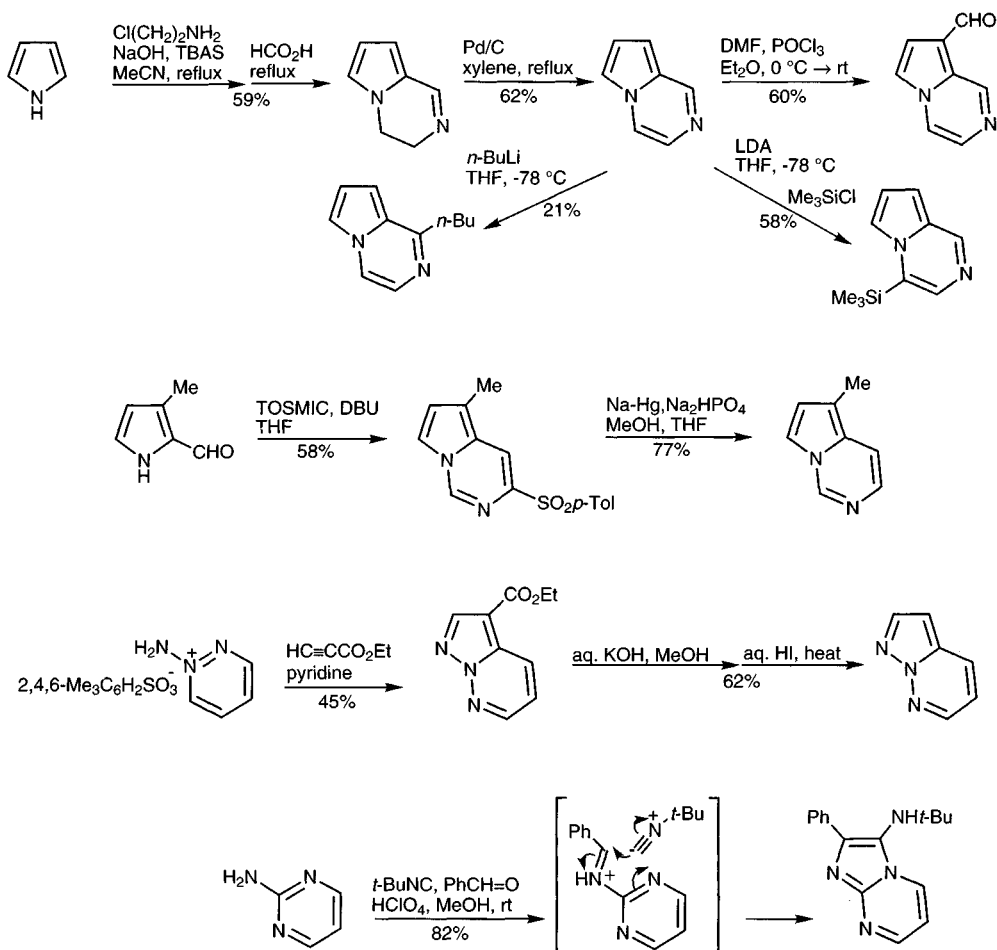


## 25.2.5 Compounds with an additional nitrogen in the six-membered ring

In addition to the propensity for electrophilic substitution at C-1/C-3 (see above), the main feature of this class of heterocycle is that they undergo relatively easy nucleophilic attack in the six-membered ring,<sup>59</sup> which is now considerably electron-deficient (through the incorporation of imine units) – the analogy with the ease of nucleophilic addition to diazines is obvious – some are so susceptible to nucleophilic addition that they form ‘hydrates’ even on exposure to moist air.<sup>46</sup> However, preparative lithiations can be carried out using less nucleophilic bases.

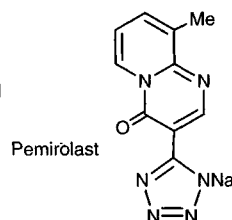
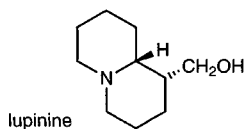
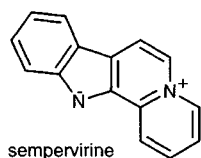


Ring synthesis of such molecules can proceed from diazines<sup>60,61</sup> using methods analogous to those described for the synthesis of azolopyridines from pyridines, or by various methods from the five-membered ring component<sup>62,63</sup> – some representative routes are shown below.

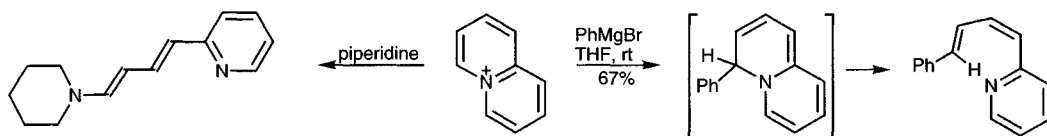


## 25.3 Quinoliziniums<sup>64</sup> and related systems

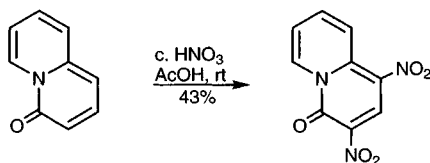
The quinolizinium ion occurs naturally only rarely, for example as a fused ylide in the alkaloid sempervirine, however there are hundreds of indole alkaloids which have the same tetracyclic system, but with the quinolizine at an octahydro-level, in addition, many simpler quinolizidine alkaloids, such as lupinine, are known. Amongst synthetic compounds the anti-asthma drug Pemirolast is an aza-analogue.



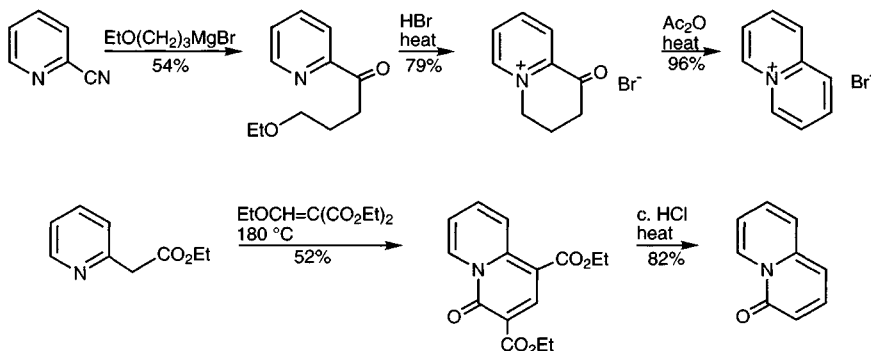
Practically all the reactions of quinolizinium ion are similar to those of pyridinium salts, thus it is resistant to electrophilic attack but readily undergoes nucleophilic addition, the initial adducts undergoing spontaneous electrocyclic ring opening to afford, finally, 2-substituted pyridines,<sup>65</sup> however the susceptibility of the cation to nucleophiles is not extreme – like simpler pyridinium salts it is stable to boiling water.



Quinazolones *can* be made to undergo electrophilic substitution, at C-1/C-3,<sup>66</sup> there being a clear analogy with the reactivity of pyridones.

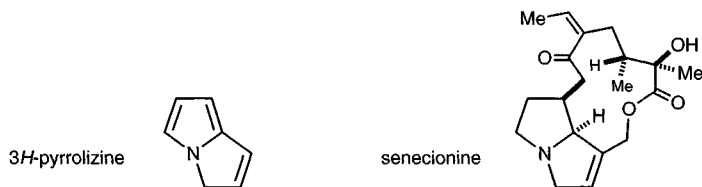


Quinolizine derivatives are usually prepared by cyclisations onto the nitrogen in a precursor pyridine.<sup>67</sup>

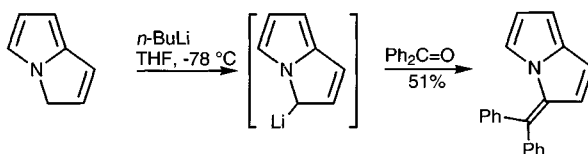


## 25.4 Pyrrolizines and related systems

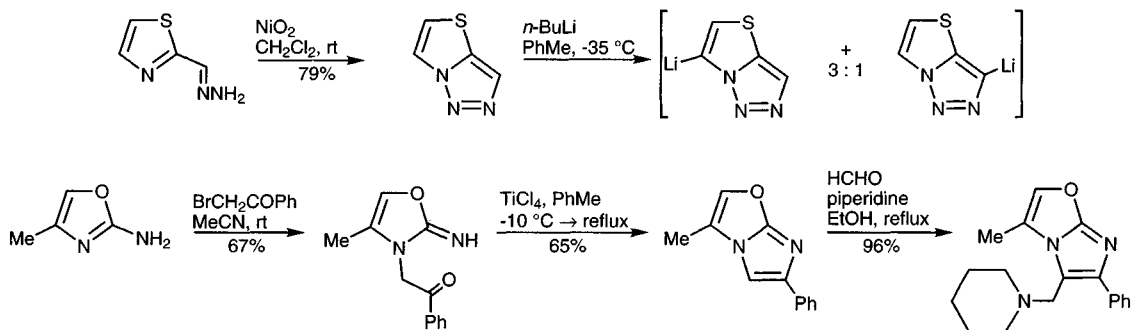
The saturated or partially saturated pyrrolizidine alkaloids are the main naturally occurring pyrrolizines; senecionine is an example.



The relatively high  $pK_a$  of 29 for deprotonation of 3*H*-pyrrolizine (*cf.* indene  $pK_a$  18.5) indicates that formation of the 10-electron pyrrolizine anion adds only minor stabilisation relative to the simple pyrrole originally present. Its reactions are those of a highly reactive carbanion, for example benzophenone condenses to generate a fulvene-like product.<sup>68</sup>

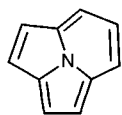


Isoelectronic replacement of a carbanionic carbon by a heteroatom gives much more stable compounds, and such 5,5-bicyclic aromatic systems have received considerable attention. In these compounds, sulfur and oxygen can also be incorporated into fully conjugated systems, unlike the 5,6-compounds where only nitrogen can be used. Because of the variety of such systems, it is difficult to generalise about reactivity but electrophilic substitution, which can take place in either ring, has been most widely reported with occasional examples of nucleophilic displacements and lithiations. Some representative reactions and self-explanatory syntheses are shown below.<sup>69,70</sup>

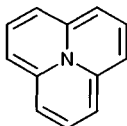


## 25.5 Cyclazines

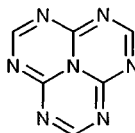
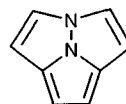
The cyclazines (a trivial name) are tricyclic fused molecules containing a central bridgehead nitrogen and a peripheral  $\pi$ -system. The definition of aromaticity in these compounds is not as straightforward as for the simple bicyclic molecules discussed above, and a more detailed analysis of the molecular orbitals may be required.



(3.2.2)cyclazine



(3.3.3)cyclazine

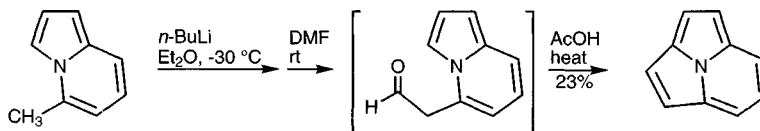
hexa-aza-analogue  
of (3.3.3)cyclazine

(2.2.2)azacyclazine

(3.2.2)Cyclazine is a stable aromatic system with a ring current, has a 10-electron annular  $\pi$ -system (excluding nitrogen), and is stable to light and air but, unlike its close analogue indolizine, is non-basic indicating the much weaker interaction between the nitrogen lone pair and the peripheral  $\pi$ -system. It does however react as an electron-rich aromatic, undergoing electrophilic substitution readily.

In contrast, (3.3.3)cyclazine has no aromatic resonance stabilisation and is unstable and highly reactive, displaying some diradical character. However, its hexa-aza-analogue is extremely stable, this stabilisation being attributed to perturbation of the molecular orbitals by the electronegative atoms leading to a much larger separation of the HOMO and LUMO.<sup>71</sup> The double ring-junction nitrogen system, (2.2.2)azacyclazine is isoelectronic with (3.2.2)cyclazine and is similarly a stable system.

Cyclazines can be prepared by cyclisation of bicyclic precursors, for example (3.2.2)cyclazine is prepared *via* a cycloaddition reaction on indolizine (Section 25.1.1), or by cyclocondensation.<sup>72</sup>



## Exercises for Chapter 25

### Straightforward revision exercises (consult chapter 25)

- At what position(s) does indolizine undergo electrophilic substitution? Why that position(s)?
- At what position does indolizine undergo strong base deprotonation?
- How could 2-methylpyridine be converted into 3-methylindolizine?
- What would be the product of reacting 2-aminopyridine with methyl bromoacetate?
- Draw resonance contributors to the quinolizinium cation to rationalise the position at which nucleophiles add to it.
- Is pyrrolizine aromatic? If so, how many electrons are there in the aromatic  $\pi$ -system?

### More advanced exercises

- Suggest a structure for the final, monocyclic product of the following sequence: quinolizinium bromide with  $\text{LiAlH}_4$  and then  $\text{H}_2/\text{Pd}$  giving  $\text{C}_9\text{H}_{13}\text{N}$ .
- Write down the structures of the intermediates in the following synthesis of the quinolizinium cation: 2-methylpyridine was reacted with LDA, then  $\text{EtO}(\text{CH}_2)_2\text{CH}=\text{O}$  to give  $\text{C}_{11}\text{H}_{17}\text{NO}_2$  which was heated with HI ( $\rightarrow \text{C}_9\text{H}_{12}\text{NO}^+ \text{I}^-$ ); this

salt was then heated with  $\text{Ac}_2\text{O}$  ( $\rightarrow \text{C}_9\text{H}_{10}\text{N}^+ \text{I}^-$ ) and this, finally heated with Pd-C to afford quinolizinium iodide.

3. Which indolizines would be formed from the following combinations: (i) 2-picoline with (a)  $\text{BrCH}_2\text{CO.Me/NaHCO}_3$ , (b)  $\text{MeCHBrCHO/NaHCO}_3$ ? (ii) What would be the products if the 2-picoline was replaced by 2-aminopyridine?
4. Deduce the structures of intermediates and final product in the following sequence: 5-methoxy-2-methylpyridine reacted with  $\text{KNH}_2/i\text{-AmONO}$   $\rightarrow \text{C}_7\text{H}_8\text{N}_2\text{O}_2$  then this with  $\text{Zn/AcOH}$   $\rightarrow \text{C}_7\text{H}_{10}\text{N}_2\text{O}$ , and finally this with  $\text{HCO}_2\text{Me/PPE}$  (polyphosphate ester)  $\rightarrow \text{C}_8\text{H}_8\text{N}_2\text{O}$ .
5. Imidazo[1,5-*a*]pyridine, on reaction with aqueous  $\text{HNO}_2$  gave 3-(pyridin-2-yl)-1,2,4-oxadiazole. Suggest a mechanism. What product would be obtained by reaction of indolizine with nitrous acid?
6. Give the structures of the bicyclic compounds formed by the following reactions: (i) 2-hydrazinothiazole with nitrous acid  $\rightarrow \text{C}_3\text{H}_2\text{N}_4\text{S}$ ; (ii) 2-aminothiazole with  $\text{BrCH}_2\text{COPh}$   $\rightarrow \text{C}_{11}\text{H}_8\text{N}_2\text{S}$ .

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