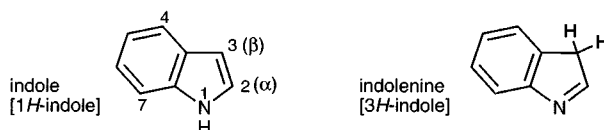


# 17 Indoles: reactions and synthesis

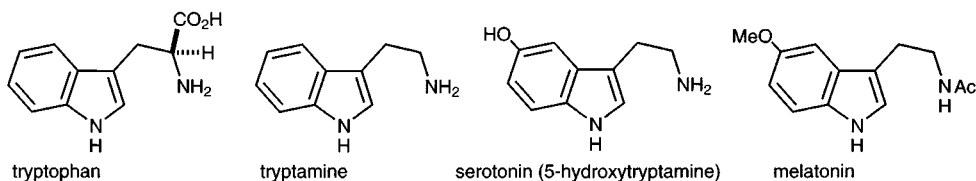


Indole<sup>1</sup> and the simple alkylindoles are colourless crystalline solids with a range of odours from naphthalene-like in the case of indole itself to faecal in the case of skatole (3-methylindole). Many simple indoles are available commercially and all of these are produced by synthesis: indole, for example, is made by the high-temperature vapour-phase cyclising dehydrogenation of 2-ethylaniline. Most indoles are quite stable in air with the exception of those which carry a simple alkyl group at C-2: 2-methylindole autoxidises easily even in a dark brown bottle.

The word indole is derived from the word India: a blue dye imported from India was known as indigo in the sixteenth century. Chemical degradation of the dye gave rise to oxygenated indoles (section 17.14) which were named indoxyl and oxindole; indole itself was first prepared in 1866 by zinc dust distillation of oxindole.

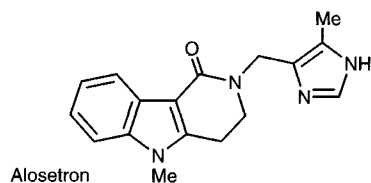
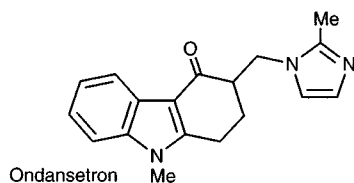
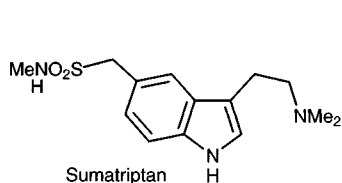
For all practical purposes, indole exists entirely in the 1*H*-form, 3*H*-indole (indolenine) being present to the extent of only *ca.* 1 ppm. 3*H*-indole has been generated in solution and found to tautomerise to 1*H*-indole within about 100 seconds at room temperature.<sup>2</sup>

Indoles are probably the most widely distributed heterocyclic compounds in nature. Tryptophan is an essential amino acid and as such is a constituent of most proteins; it also serves as a biosynthetic precursor for a wide variety of tryptamine-, indole-, and 2,3-dihydroindole-containing secondary metabolites.

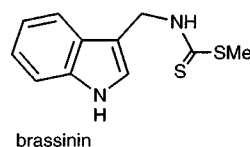
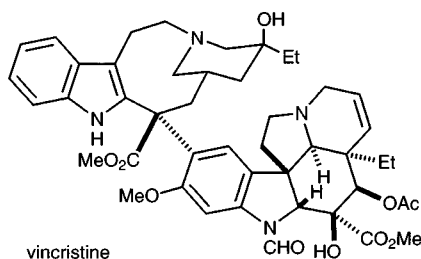
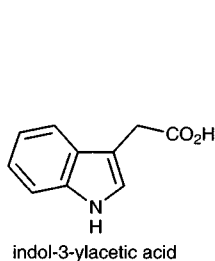


In animals, serotonin (5-hydroxytryptamine) is a very important neurotransmitter in the central nervous system and also in the cardiovascular and gastrointestinal systems. The structurally similar hormone melatonin is thought to control the diurnal rhythm of physiological functions.

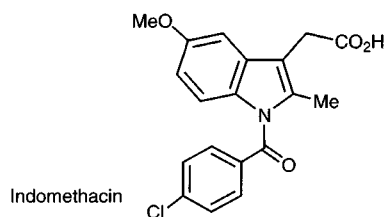
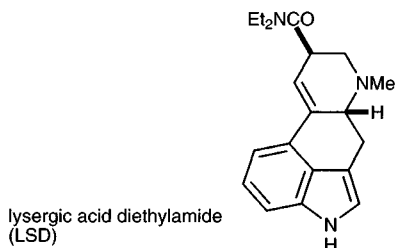
Study and classification of serotonin receptors has resulted in the design and synthesis of highly selective medicines such as Sumatriptan, for the treatment of migraine, Ondansetron for the suppression of the nausea and vomiting caused by cancer chemotherapy and radiotherapy, and Alosetron for treatment of irritable bowel syndrome.



Tryptophan-derived substances in the plant kingdom include indol-3-ylacetic acid, a plant growth-regulating hormone, and a huge number and structural variety of secondary metabolites – the indole alkaloids.<sup>3</sup> In the past, the potent physiological properties of many of these led to their use in medicine, but in most instances these have now been supplanted by synthetic substances, although vincristine, a ‘dimeric’ indole alkaloid is still extremely important in the treatment of leukemia. Brassinin, isolated from turnips, is a phytoalexin – one of a group of compounds produced by plants as a defense mechanism against attack by microorganisms.



The physiological activity of lysergic acid diethylamide (LSD) is notorious. The synthetic indol-3-ylacetic acid derivative Indomethacin is used for the treatment of rheumatoid arthritis.

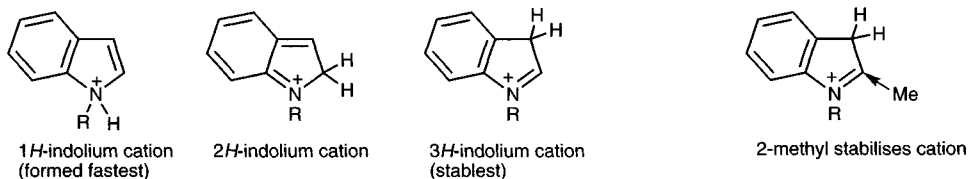


## 17.1 Reactions with electrophilic reagents

### 17.1.1 Protonation

Indoles, like pyrroles, are very weak bases: typical  $pK_a$  values are indole,  $-3.5$ ; 3-methylindole,  $-4.6$ ; 2-methylindole,  $-0.3$ .<sup>4</sup> This means, for example, that in 6M sulfuric acid two molecules of indole are protonated for every one unprotonated, whereas 2-methylindole is almost completely protonated under the same conditions. By NMR and UV examination, only the 3-protonated cation (3*H*-indolium cation) is detectable;<sup>5</sup> it is the thermodynamically stablest cation, retaining full benzene aromaticity (in contrast to the 2-protonated cation) with delocalisation of charge over the nitrogen and  $\alpha$ -carbon. The spectroscopically undetectable *N*-protonated cation must be formed, and formed very rapidly, for acid-catalysed deuterium exchange at nitrogen is 400 times faster than at C-3,<sup>6</sup> indeed the *N*-hydrogen

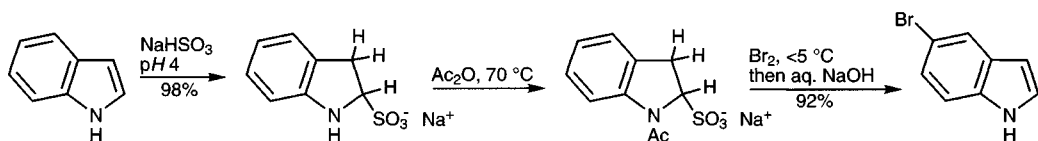
exchanges rapidly even at pH 7, when no exchange at C-3 occurs: clean conversion of indole into 3-deuterioindole can be achieved by successive deuterio-acid then water treatments.<sup>7</sup> Base-catalysed exchange, *via* the indolyl anion (section 17.4) likewise takes place at C-3.<sup>8</sup>



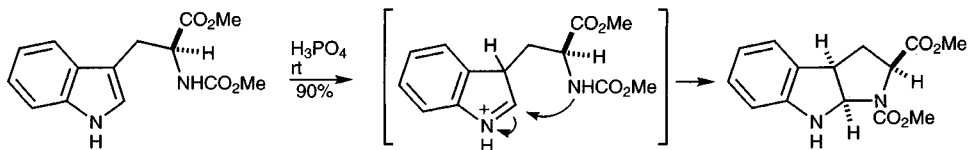
That 2-methylindole is a stronger base than indole can be understood on the basis of stabilisation of the cation by electron release from the methyl group; 3-methylindole is a somewhat weaker base than indole.

### Reactions of $\beta$ -protonated indoles (see also sections 17.1.6 and 17.1.9)

3-*H*-Indolium cations are of course electrophilic species, in direct contrast with neutral indoles, and under favourable conditions will react as such. For example, the 3H-indolium cation itself will add bisulfite at pH 4, under conditions which lead to the crystallisation of the product, the sodium salt of indoline-2-sulfonic acid (indoline is the widely used, trivial name for 2,3-dihydroindole). The salt reverts to indole on dissolution in water, however it can be *N*-acetylated and the resulting acetamide used for halogenation or nitration at C-5, final hydrolysis with loss of bisulfite affording the 5-substituted indole.<sup>9</sup>

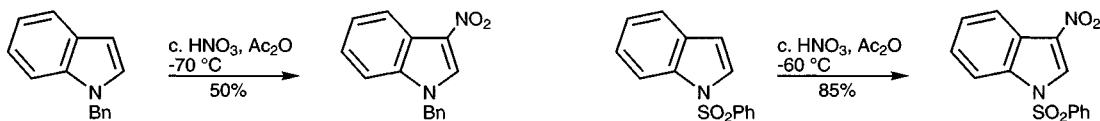


When *N*<sub>5</sub>-acyl tryptophans are exposed to strong acid, the 3-protonated indolium cation is trapped by intramolecular cyclisation of the side-chain nitrogen.<sup>10</sup>

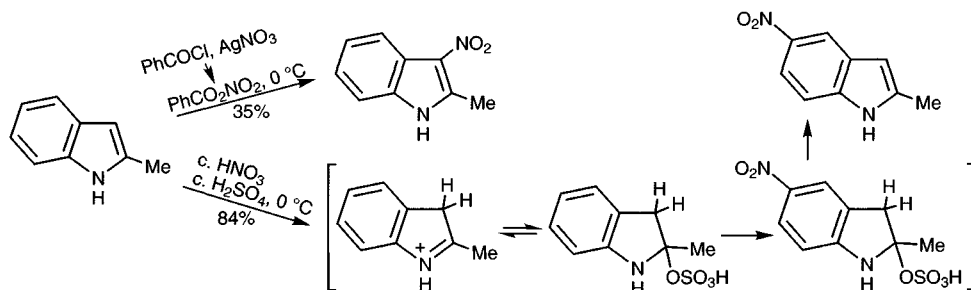


### 17.1.2 Nitration; reactions with other nitrogen electrophiles

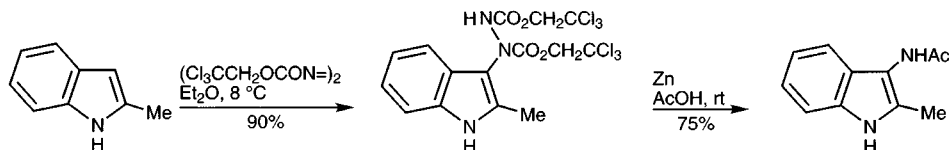
Indole itself can be nitrated using benzoyl nitrate as a non-acidic nitrating agent; the usual mixed acid nitrating mixture leads to intractable products, probably because of acid-catalysed polymerisation. This can be avoided by carrying out the nitration using concentrated nitric acid and acetic anhydride at low temperature – under these conditions, *N*-alkylindoles, and indoles carrying electron-withdrawing *N*-substituents, but *not* indole itself, can be satisfactorily nitrated.<sup>11</sup>



2-Methylindole gives a 3-nitro-derivative with benzoyl nitrate,<sup>12</sup> but can also be nitrated successfully with concentrated nitric/sulfuric acids, but with attack at C-5. The absence of attack on the heterocyclic ring is explained by the complete protonation of 2-methylindole under these conditions; the regioselectivity of attack, *para* to the nitrogen, may mean that the actual moiety attacked is a bisulfate adduct of the initial 3-*H*-indolium cation, as shown in the scheme. 5-Nitration of 3-*H*-indolium cations has been independently demonstrated using an authentic 3,3-disubstituted 3-*H*-indolium cation.<sup>13</sup> With an acetyl group at C-3, nitration with nitronium tetrafluoroborate in the presence of tin(IV) chloride takes place at either C-5 or C-6 depending on the temperature of reaction.<sup>14</sup>

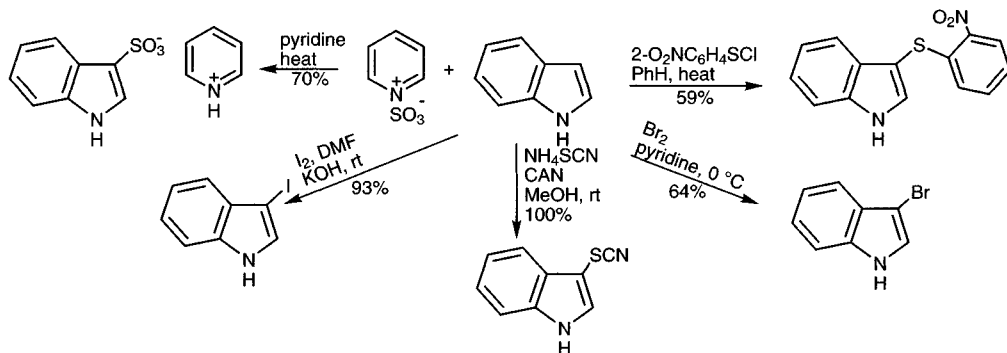


Indoles readily undergo electrophilic amination with bis(2,2,2-trichloroethyl)azodicarboxylate, the resulting acylated hydrazine being cleaved by zinc dust to give a 3-acylaminoindole.<sup>15</sup>



### 17.1.3 Sulfonation; reactions with other sulfur electrophiles

Sulfonation of indole,<sup>16</sup> at C-3, is achieved using the pyridine-sulfur trioxide complex in pyridine as solvent. Gramine is sulfonated in oleum to give 5- and 6-sulfonic acids, attack being on a diprotonated (C-3, side-chain-N) salt.<sup>17</sup> Sulfenylation of indole also occurs readily, at C-3.<sup>18</sup> The reversibility of this process has been demonstrated by desulfenylation in the presence of acid and a trap for the sulfenyl cation,<sup>19</sup> and by the acid-catalysed isomerisation of 3-sulfides to 2-sulfides.<sup>20</sup> Thiocyanation of indole can be achieved in virtually quantitative yield with a combination of ammonium thiocyanate and cerium(IV) ammonium nitrate.<sup>21</sup>

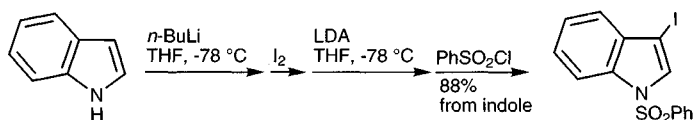


### 17.1.4 Halogenation

3-Halo-, and even more so, 2-haloindoles are unstable and must be utilised as soon as they are prepared. A variety of methods are available for the  $\beta$ -halogenation of indoles: bromine or iodine (the latter with potassium hydroxide) in dimethylformamide<sup>22a</sup> give very high yields; pyridinium tribromide<sup>22b</sup> works efficiently; iodination<sup>22c</sup> and chlorination<sup>22d</sup> tend to be carried out in alkaline solution and, at least in the latter case is believed to involve initial *N*-chlorination then rearrangement. Reaction of 3-substituted indoles with halogens is more complex; initial 3-halogenation occurs generating a 3-halo-3*H*-indole,<sup>23</sup> but the actual products obtained then depend upon the reaction conditions, solvent etc. Thus, nucleophiles can add at C-2 in the intermediate 3-halo-3*H*-indoles when, after loss of hydrogen halide, a 2-substituted indole is obtained as final product, for example in aqueous solvents, water addition produces oxindoles (section 17.14); comparable methanol addition gives 2-methoxyindoles.

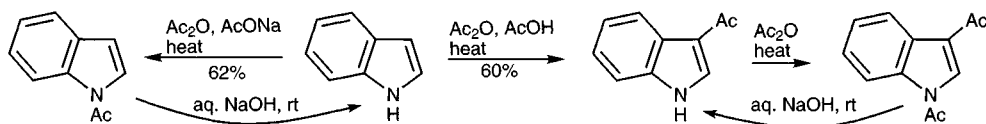
Direct 2-bromination of 3-substituted indoles can be carried out using *N*-bromosuccinimide in the absence of radical initiators.<sup>24</sup> 2-Bromo- and 2-iodoindoles can be prepared very efficiently *via*  $\alpha$ -lithiation (section 17.6.1),<sup>25</sup> 2-haloindoles are also available from the reaction of oxindoles with phosphoryl halides.<sup>26</sup> Bromination of methyl indole-3-carboxylate gives a mixture of 5- and 6-bromo derivatives.<sup>27</sup>

The formation of 3-iodoindole shown below, and its advisable immediate stabilisation by formation of a 1-phenylsulfonyl derivative, probably involves initial *N*-iodination of the indolyl anion and then rearrangement.<sup>28</sup>



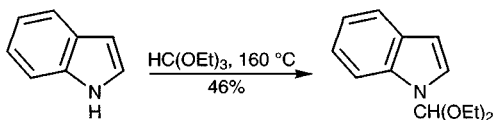
### 17.1.5 Acylation

Indole only reacts with acetic anhydride at an appreciable rate above 140 °C, giving 1,3-diacetylindole predominantly, together with smaller amounts of *N*- and 3-acetylindoles; 3-acetylindole is prepared by alkaline hydrolysis of product mixtures.<sup>29</sup> That  $\beta$ -attack occurs first is shown by the resistance of 1-acetylindole to *C*-acylation, but the easy conversion of the 3-acetylindole into 1,3-diacetylindole. In contrast, acetylation in the presence of sodium acetate, or 4-dimethylaminopyridine,<sup>30</sup> affords exclusively *N*-acetylindole, probably *via* the indolyl anion (section 17.4). Trifluoroacetic anhydride, being much more reactive, acylates at room temperature, in dimethylformamide at C-3, but in dichloromethane at nitrogen.<sup>31</sup>

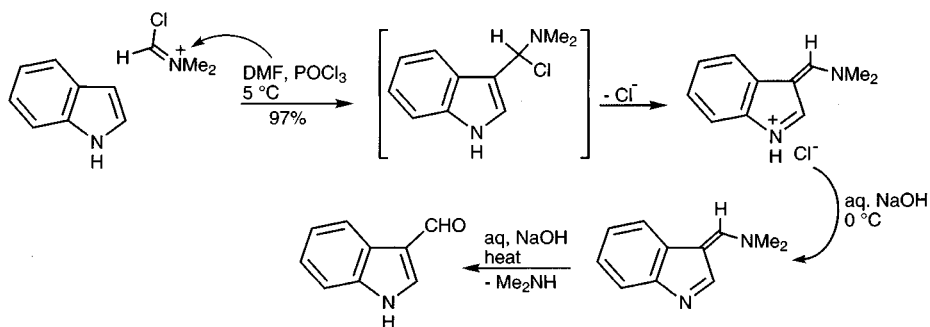


*N*-Acyindoles are much more readily hydrolysed than ordinary amides, aqueous sodium hydroxide at room temperature being sufficient: this lability is due in part to a much weaker mesomeric interaction of the nitrogen and carbonyl groups, making the latter more electrophilic, and in part to the relative stability of the indolyl anion, which makes it a better leaving group than amide anion.

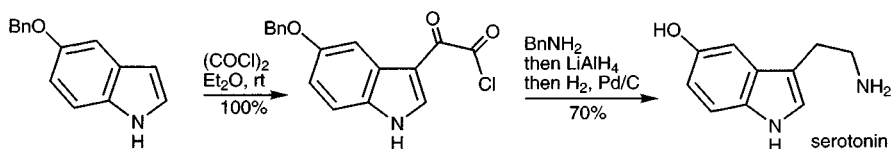
Simply heating indole with triethyl orthoformate at 160 °C leads to the alkylation of the indole nitrogen introducing a diethoxymethyl (DEM) group which can be used as a reversible *N*-blocking substituent with considerable potential – it allows 2-lithiation (*cf.* section 17.4.2) and can be easily removed with dilute acid at room temperature.<sup>32</sup>



The Vilsmeier reaction is the most efficient route to 3-formylindoles<sup>33</sup> and to other 3-acylindoles using tertiary amides of other acids in place of dimethylformamide.<sup>34</sup> Even indoles carrying an electron-withdrawing group at the 2-position, for example ethyl indole-2-carboxylate, undergo smooth Vilsmeier  $\beta$ -formylation.<sup>35</sup>



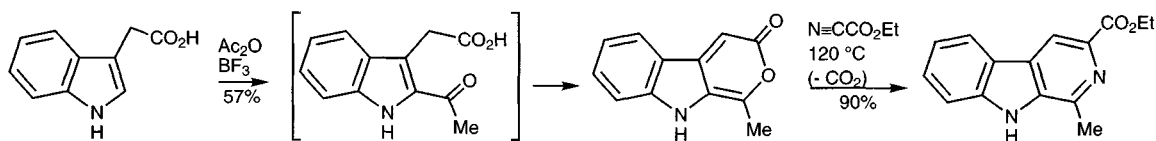
A particularly useful and high-yielding reaction is that between indole and oxalyl chloride, which gives a ketone-acid chloride convertible into a range of compounds, for example tryptamines; a synthesis of serotonin utilised this reaction.<sup>36</sup>



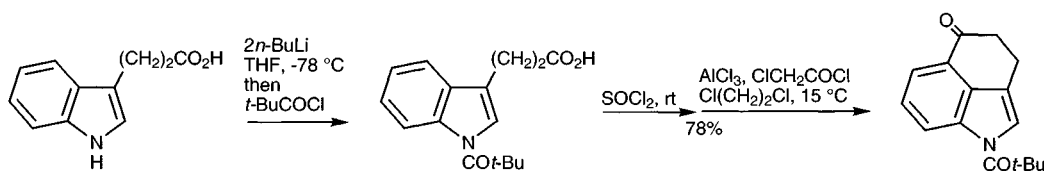
Indoles, with a side-chain acid located at C-3, undergo cyclising acylation forming cyclic 2-acylindoles.<sup>37</sup> Intramolecular Vilsmeier processes using tryptamine amides lead to the imine, rather than a ketone, as the final product; the cyclic nature of the imine favours its retention rather than hydrolysis to amine plus ketone.<sup>38</sup>



Acylation of 3-substituted indoles is more difficult: 2-acetylation can be effected with the aid of boron trifluoride catalysis.<sup>36</sup> When the 3-substituent is an acetic acid moiety, a subsequent enol-lactonisation produces an indole fused to a 2-pyrone; these can be hydrolysed to the keto-acid, or the diene character of the 2-pyrone (section 8.2.2.4) utilised, as illustrated.<sup>39</sup>

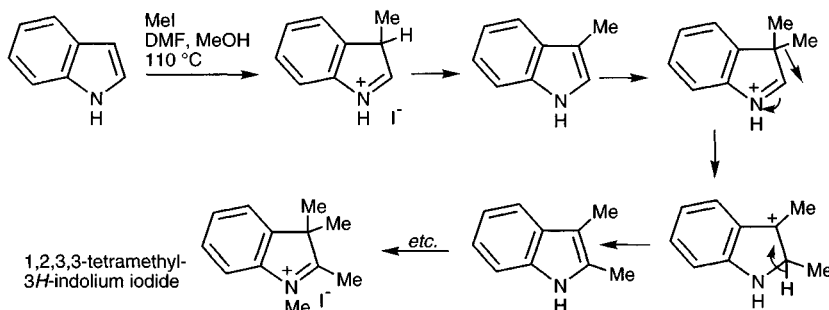


Deactivation of the five-membered ring by electron-withdrawing substituents allows acylation in the six-membered ring. 1-Pivaloylindole gives high yields of 6-substituted ketones on reaction with  $\alpha$ -halo acid chlorides and aluminium chloride; simple acid chlorides react only at C-3.<sup>40</sup> Another device which can be used to direct acylation to the benzene ring is to carry out the substitution on an iminium salt intermediate from a Vilsmeier reaction, when attack is at C-5 and C-6 with the former predominating.<sup>41</sup> The sequence below shows how a pivaloyl group can be introduced onto the indole nitrogen of 3-(indol-3-yl)propanoic acid using two mol equivalents of base and then the subsequent Friedel-Crafts cyclisation away from the deactivated heterocyclic ring, to C-4.<sup>42</sup>



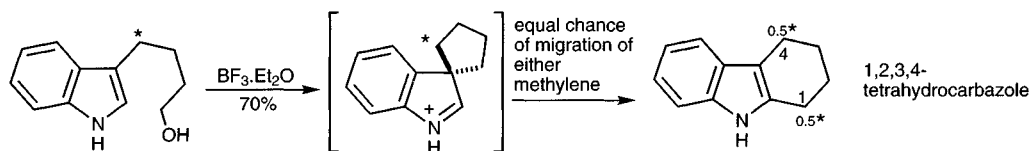
### 17.1.6 Alkylation

Indoles do not react with alkyl halides at room temperature. Indole itself begins to react with iodomethane in dimethylformamide at about 80 °C when the main product is skatole. As the temperature is raised, further methylation occurs until eventually 1,2,3,3-tetramethyl-3H-indolium iodide is formed.

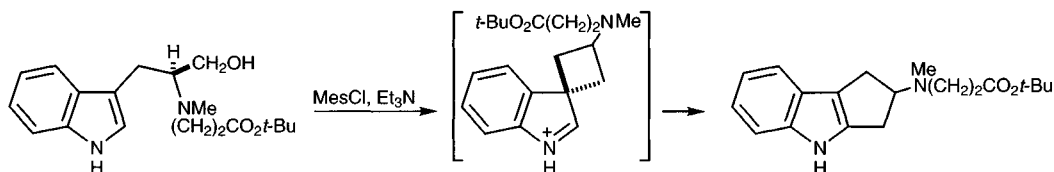


The rearrangement of 3,3-dialkyl-3H-indolium ions by alkyl migration to give 2,3-dialkylindoles, as shown in the sequence above, is related mechanistically to the Wagner-Meerwein rearrangement, and is known as the Plancher rearrangement.<sup>43</sup> It is likely that most instances of 2-alkylation of 3-substituted-indoles by cationic reagents proceed by this route, and this was neatly verified in the formation of 1,2,3,4-tetrahydrocarbazole by boron trifluoride catalysed cyclisation of 4-(indol-3-yl)butan-1-ol. The experiment was conducted with material labelled at the benzylic carbon. The consequence of the rearrangement of the symmetrical spirocyclic intermediate, which results from attack at C-3, was the equal distribution of the label between the C-1 and C-4 carbons of the product.<sup>44</sup> It is important to note that other

experiments demonstrated that direct attack at C-2 can and does occur,<sup>45</sup> especially when this position is further activated by a 6-methoxyl group.<sup>46</sup>



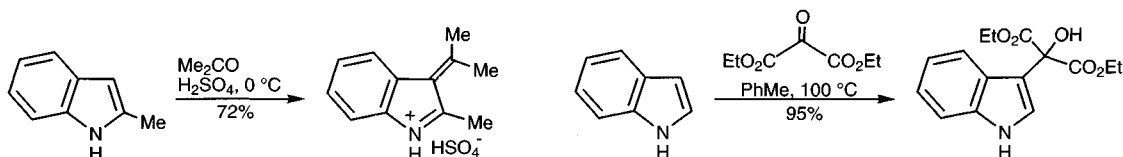
In another elegant experiment, the intervention of a 3,3-disubstituted 3*H*-indolium intermediate in an indole overall  $\alpha$ -substitution was proved by cyclisation of the mesylate of an optically active alcohol to give an optically *inactive* product, *via* an achiral, spirocyclic intermediate from initial attack at the  $\beta$ -position.<sup>47</sup>



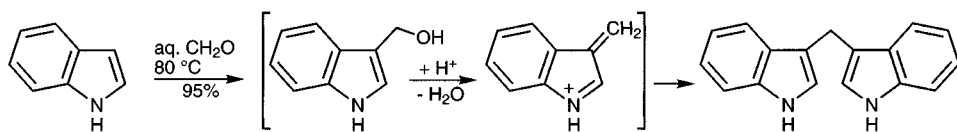
Indoles react with epoxides and aziridines in the presence of Lewis acids (see section 17.5 for reaction of indolyl anions with such reactants) with opening of the three-membered ring and consequent 3-(2-hydroxyalkylation) and 3-(2-aminoalkylation) of the heterocycle. Both ytterbium triflate and phenylboronic acid are good catalysts for reaction with epoxides under high pressure;<sup>48</sup> silica gel is also an effective catalyst, but slow at normal pressure and temperature.<sup>49</sup> Lewis acid-mediated reaction with aziridines can be catalysed by zinc triflate or boron trifluoride.<sup>50</sup> More reactive alkylating electrophiles react at lower temperatures, at room temperature with dimethylallyl bromide for example.<sup>51</sup>

### 17.1.7 Reactions with aldehydes and ketones

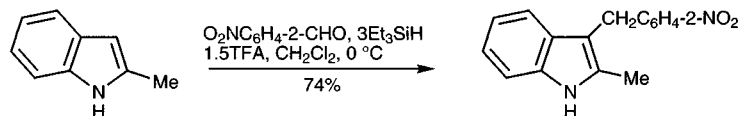
Indoles react with aldehydes and ketones under acid catalysis – with simple carbonyl compounds, the initial products, indol-3-ylcarbinols are never isolated, for in the acidic conditions they dehydrate to 3-alkylidene-3*H*-indolium cations; those from aromatic aldehydes have been isolated in some cases;<sup>52</sup> reaction of 2-methylindole with acetone under anhydrous conditions gives the simplest isolable salt of this class.<sup>53</sup> Only where dehydration is not possible have hydroxyalkylindoles been isolated, for example from reaction with diethyl mesoxalate.<sup>54</sup> Reaction with 4-dimethylaminobenzaldehyde (the Ehrlich reaction, see section 13.1.7) gives a mesomeric and highly-coloured cation.



3-Alkylidene-3*H*-indolium cations are themselves electrophiles and can react with more of the indole, as illustrated for reaction with formaldehyde.<sup>55</sup> Cyclic ketones react with 1,2-dimethylindole producing 3-cycloalkenylindoles.<sup>56</sup>

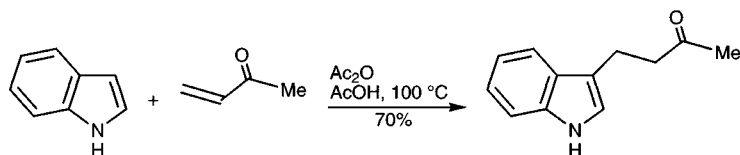


3-Alkylation of 2-alkyl- and 2-arylindoles can be achieved by trifluoroacetic acid-catalysed condensation with either aromatic aldehydes or aliphatic ketones in the presence of the triethylsilane to reduce the immediate 3-(hydroxyalkyl) products.<sup>57</sup>

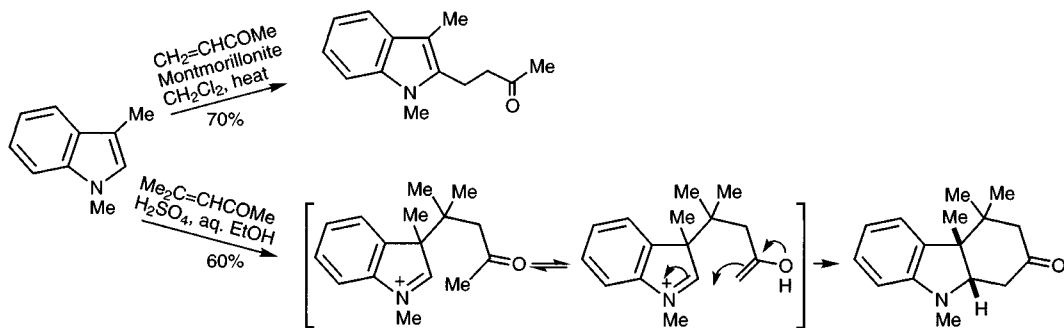


### 17.1.8 Reactions with $\alpha,\beta$ -unsaturated ketones, -nitriles and -nitro-compounds

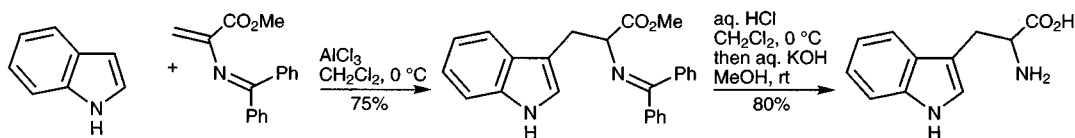
Such reactions are usually effected using acid, for catalysis, and can be looked on as an extension of the reactions discussed in 17.1.7 above. In the simplest example indole reacts with methyl vinyl ketone in a conjugate fashion.<sup>58</sup>



The use of Montmorillonite clay, a very efficient 'acidic' catalyst, allows  $\alpha$ -alkylation of  $\beta$ -substituted indoles;<sup>59</sup> ytterbium triflate can also be used to catalyse such alkylations.<sup>60</sup> This efficient catalysis contrasts with the different, but very instructive, reaction pathway followed when mesityl oxide and 1,3-dimethylindole are combined in the presence of sulfuric acid – electrophilic attack at the already substituted  $\beta$ -position is followed by intramolecular nucleophilic addition of the enol of the side-chain ketone to C-2.<sup>61</sup>



An extension of this methodology allows the synthesis of tryptophans by aluminium chloride catalysed alkylation with an iminoacrylate, as illustrated<sup>62</sup> (for the same transformation but biocatalysed see section 2.9).

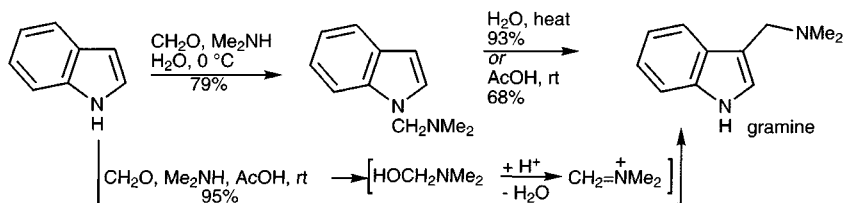


Nitroethene is sufficiently electrophilic to substitute indole without the need for acid catalysis;<sup>63</sup> the employment of 2-dimethylamino-1-nitroethene in trifluoroacetic acid leads to 2-(indol-3-yl)nitroethene – the reactive species is the protonated enamine and the process is similar to a Mannich condensation (section 17.1.9).<sup>64</sup> The use of 3-trimethylsilylindoles, with *ipso* substitution of the silane,<sup>65</sup> is an alternative means for effecting alkylation avoiding the need for acid catalysis.

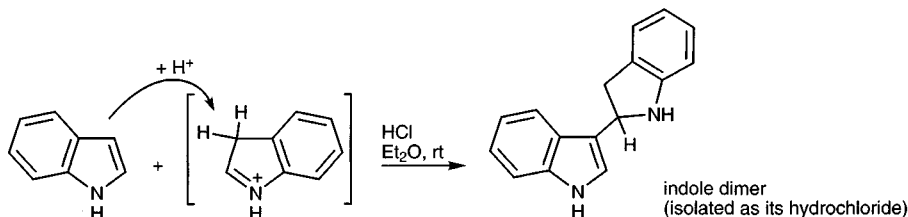


### 17.1.9 Reactions with iminium ions: Mannich reactions<sup>66</sup>

Under neutral conditions and at low temperature indole reacts with a mixture of formaldehyde and dimethylamine by substitution at the indole nitrogen;<sup>67</sup> it seems likely that this reaction involves a low equilibrium concentration of the indolyl anion. In neutral solution at higher temperature or in acetic acid, conversion into the thermodynamically more stable, 3-substituted product, gramine, takes place. Gramine is formed directly, smoothly and in high yield, by reaction in acetic acid.<sup>68</sup> The Mannich reaction is very useful in synthesis because not only can the electrophilic iminium ion be varied widely, but the product gramines are themselves intermediates for further manipulation (section 17.12).

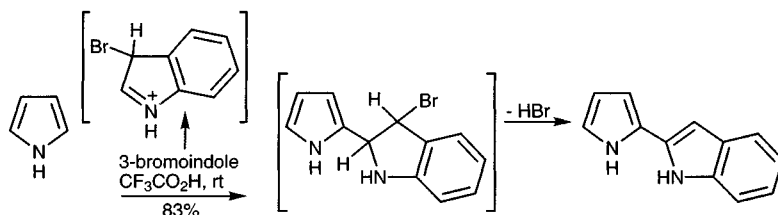


The iminium ion electrophile can be synthesised separately, as a crystalline solid known as ‘Eschenmoser’s salt’ ( $\text{Me}_2\text{N}^+=\text{CH}_2 \text{I}^-$ )<sup>69</sup> and with this reactive electrophile the reaction is normally carried out in a non-polar solvent. Examples which illustrate the variation in iminium ion structure which can be tolerated, include the reaction of indole with pyrimidine,<sup>70</sup> with benzylidene derivatives of arylamines catalysed by lanthanide triflates,<sup>71</sup> and the mineral acid-catalysed dimerisation of indole.<sup>72</sup> In the first example protonated pyrimidine is the electrophile, in the last indole is attacked by *protonated* indole! as shown below.

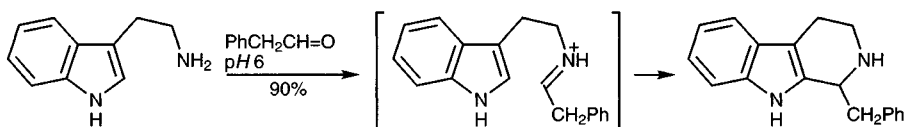


Skatole is converted into an  $\alpha,\alpha'$ -linked dimer in acid; 2-methylindole, in contrast, is not susceptible to acid-catalysed dimerisation, reflecting the lower electrophilic character of the 3-protonated 2-substituted 3*H*-indolium cation, much as ketones are less reactive than aldehydes.

When protonated 3-bromoindole is employed as electrophile, a final elimination of hydrogen bromide gives rise to rearomatised 2-substituted indoles; pyrrole (illustrated) or indoles will take part in this type of process.<sup>73</sup>

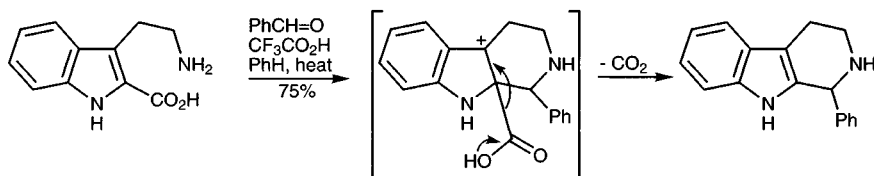


Conducted in an intramolecular sense, both Mannich and Vilsmeier reactions have been much used for the construction of tetrahydro- $\beta$ -carbolines<sup>74</sup> (dihydro- $\beta$ -carbolines), such as are found in many indole alkaloids ( $\beta$ -carboline is the widely-used, trivial name for the pyrido[3,4-*b*]indole).

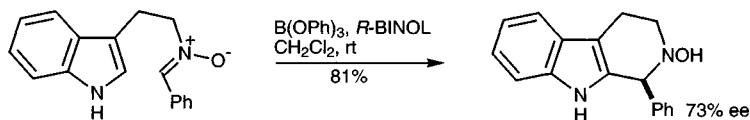


There is still controversy as to whether such cyclisations proceed by direct electrophilic attack at the  $\alpha$ -position, or whether by way of  $\beta$ -attack then rearrangement. It may be significant that Mannich processes, as opposed to the alkylations discussed in section 17.1.6, are reversible, which would allow a slower, direct  $\alpha$ -substitution to provide the principal route to the  $\alpha$ -substituted structure.

It has been shown that tryptamines carrying a 2-carboxylic acid group, which can be conveniently prepared (section 17.17.6.3) but are not easily decarboxylated, undergo cyclising Mannich condensation with aldehydes and ketones, with loss of the carbon dioxide in a final step.<sup>75</sup>



The cyclisation of nitrones derived from tryptamines is a similar process and can be carried out enantioselectively using a chiral Lewis acid.<sup>76</sup>



### 17.1.10 Diazo-coupling and nitrosation

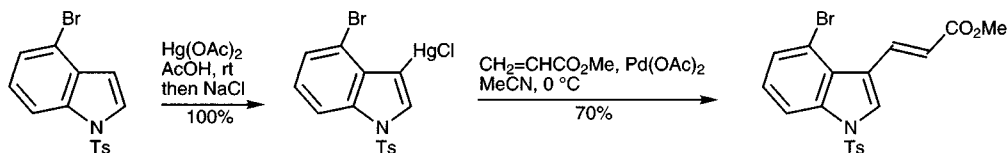
The high reactivity of indole is shown up well by the ease with which it undergoes substitution with weakly electrophilic reagents such as benzenediazonium chloride and nitrosating agents. Indoles react rapidly with nitrous acid; indole itself reacts in a complex manner, but 2-methylindole gives a 3-nitroso-product cleanly. This can also be obtained by a base-catalysed process using amyl nitrite as a source of the nitroso

group; these basic conditions also allow clean 3-nitrosation of indole itself. 3-Nitrosoindoles exist predominantly in the oximino tautomeric form.<sup>77</sup> Skatole and other 3-substituted indoles give relatively stable *N*-nitroso products with nitrous acid,<sup>78</sup> consistent with kinetic studies on 2-methylindole which show that *N*-substitution precedes *C*-substitution. *N*-Nitrosoindoles may be produced from indoles, following ingestion – such compounds may be mutagenic.

## 17.1.11 Electrophilic metallation

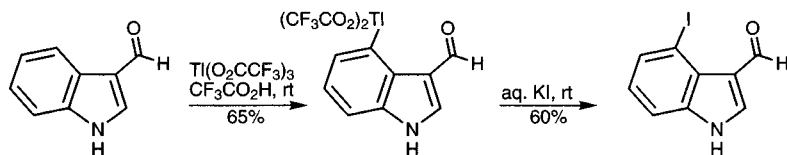
### 17.1.11.1 Mercuration

Indole reacts readily with mercuric acetate at room temperature to give a 1,3-disubstituted product.<sup>79</sup> Even *N*-acylindoles are substituted under mild conditions; the 3-mercured compounds thus produced are useful in palladium-catalysed couplings.<sup>80</sup>



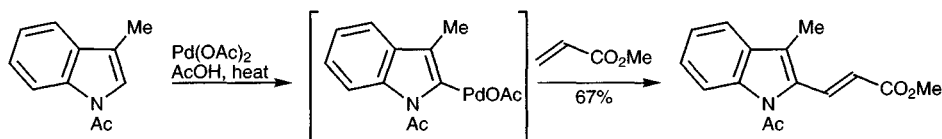
### 17.1.11.2 Thallation

Thallium trifluoroacetate reacts rapidly with simple indoles, but well defined products cannot be isolated. 3-Acylindoles, however, undergo a very selective substitution at C-4, due to chelation and protection of the heterocyclic ring by the electron-withdrawing 3-substituent.<sup>81</sup> The products are good intermediates for the preparation of 4-substituted indoles, for example 4-iodo- and thence 4-alkoxy-,<sup>82b</sup> 4-alkenyl<sup>82</sup> and 4-methoxycarbonyl,<sup>83</sup> *via* palladium-mediated couplings. The regiochemistry is neatly complemented by thallation of *N*-acetylindoline, which goes to C-7, allowing introduction of substituents at this carbon<sup>84</sup> (cf. sections 17.17.1.8 and 17.3).



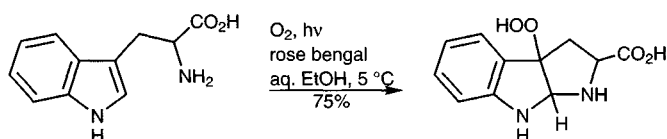
### 17.1.11.3 Palladation

Even indoles bearing acyl or phenylsulfonyl substituents on nitrogen, are easily palladated at moderate temperatures, substitution occurring at C-3, or at the 2-position if C-3 is occupied. The metallated products are seldom isolated but allowed to react with acrylates, other alkenes (Heck reaction), or carbon monoxide<sup>85</sup> *in situ*.<sup>86</sup> Although electrophilic palladation normally requires one equivalent of palladium(II), the incorporation of reoxidants selective for  $\text{Pd}(0)$ , such as *t*-butyl perbenzoate or copper(II) compounds, allows catalytic conversions to be carried out.<sup>87</sup>

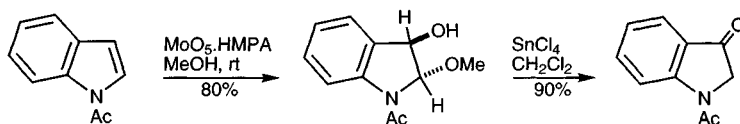


## 17.2 Reactions with oxidising agents

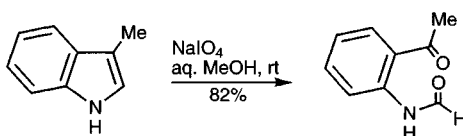
Autoxidation occurs readily with alkyl indoles, thus for example, 2,3-diethylindole gives an isolable 3-hydroperoxy-3*H*-indole. Generally such processes give more complex product mixtures resulting from further breakdown of the hydroperoxide; singlet oxygen also produces hydroperoxides, but by a different mechanism. If the indole carries a side-chain capable of trapping the indolenine by intramolecular nucleophilic addition, then tricyclic hydroperoxides can be isolated, as shown.<sup>88</sup>



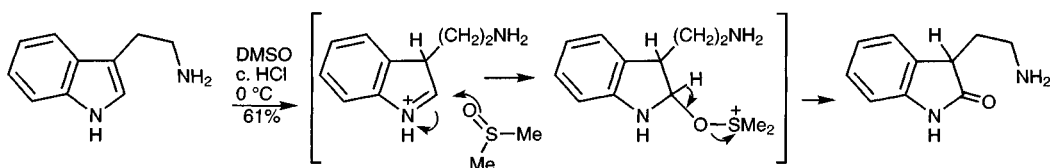
The reagent  $\text{MoO}_5\cdot\text{HMPA}$ , known as 'MoOPH', in methanol, brings about addition of the elements of methyl hydrogen peroxide to an *N*-acylindole, and these adducts in turn, can be utilised: one application is to induce loss of methanol, and thus the overall transformation of an indole into an indoxyl.<sup>89</sup>



Oxidative cleavage of the indole 2,3-double bond has been achieved with ozone,<sup>90</sup> sodium periodate,<sup>90</sup> potassium superoxide,<sup>91</sup> with oxygen in the presence of cuprous chloride,<sup>92</sup> and with oxygen photochemically in ethanolic solution,<sup>93</sup> irradiation in an organic acid as solvent leads to oxidation at 2- and 3-alkyl groups.<sup>94</sup>

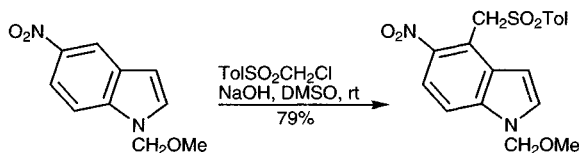


The efficient conversion of 3-substituted indoles into their corresponding oxindoles can be brought about by reaction with dimethylsulfoxide in acid; the scheme below shows a reasonable mechanism for the process.<sup>95</sup>

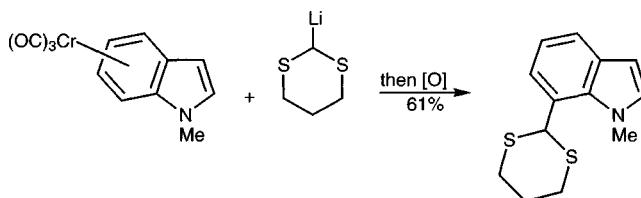


## 17.3 Reactions with nucleophilic reagents (see also section 17.14.4)

As with pyrroles and furans, indoles undergo very few nucleophilic substitution processes. Those that are known involve special situations: benzene-ring-nitroindoles, in which the *N*-hydrogen has been removed as well, undergo vicarious nucleophilic substitutions (section 2.3.3).<sup>96</sup>



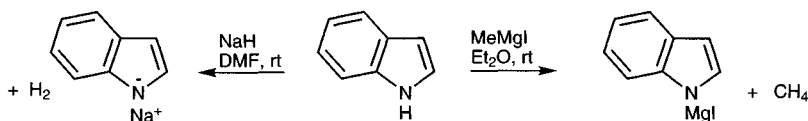
In chromium carbonyl complexes of indole, the metal is associated with the benzene ring, hence nucleophilic additions take place in that ring, usually at C-4; the example shows the relatively unusual attack at C-7; this regioselectivity can be induced to revert to the usual C-4 if an indole with a bulky *N*-protecting group is utilised.<sup>97</sup>



## 17.4 Reactions with bases

### 17.4.1 Deprotonation of *N*-hydrogen

As in pyrroles, the *N*-hydrogen in indoles is much more acidic (p*K*<sub>a</sub> 16.2) than that of an aromatic amine, say aniline (p*K*<sub>a</sub> 30.7). Any very strong base will effect complete conversion of an *N*-unsubstituted indole into the corresponding indolyl anion, amongst the most convenient being sodium hydride, *n*-butyllithium, or an alkyl Grignard reagent.

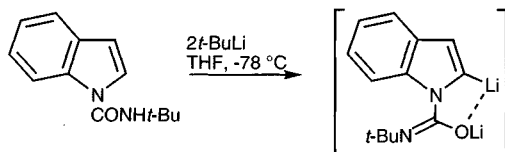


Electron-withdrawing substituents, particularly at the  $\beta$ -position, increase the acidity markedly, for example 3-formylindole is about 5 p*K*<sub>a</sub> units more acidic than indole and the  $\alpha$ -isomer is some 3 units more acidic.<sup>98</sup>

### 17.4.2 Deprotonation of C-hydrogen

Deprotonation of C-hydrogen in indoles requires the absence of the much more acidic *N*-hydrogen i.e. the presence of an *N*-substituent like methyl,<sup>99</sup> or if required, a removable group: phenylsulfonyl,<sup>100</sup> lithium carboxylate,<sup>101</sup> and *t*-butoxycarbonyl<sup>102</sup> have been used widely, dialkylaminomethyl,<sup>103</sup> trimethylsilylethoxymethyl,<sup>104</sup> and methoxymethoxy<sup>105</sup> have also been recommended; clearly in the last case the *N*-substituent cannot be introduced into an indole – it requires a preformed 1-hydroxyindole – but it is possible to reduce it off to leave an *N*-hydrogen-indole. *t*-

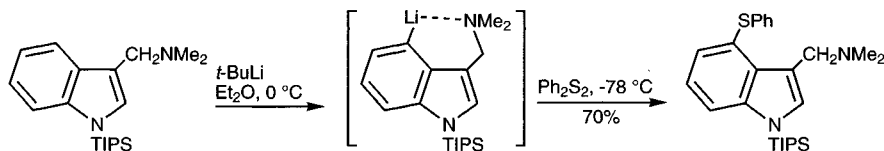
Butylaminocarbonyl,<sup>106</sup> methoxymethoxy, are said to be the optimal protecting/activating groups. Each of these removable substituents assists lithiation by intramolecular chelation and in some cases by electron withdrawal, reinforcing the intrinsic tendency for metallation to proceed at the  $\alpha$ -position.



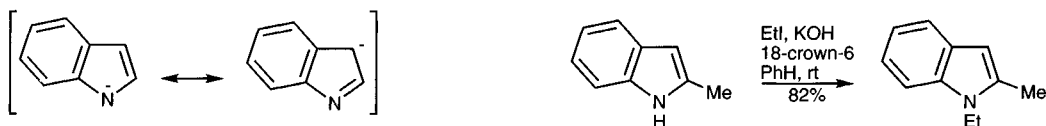
Magnesiation at C-2 can be carried out at room temperature; as well as serving in the usual way as nucleophiles, magnesioindoles can also be used directly for palladium-catalysed couplings.<sup>107</sup>



The dimethylamino group of gramine directs lithiation to C-4 when the indolic nitrogen is protected by the bulky tri-*i*-propylsilyl group but metallation occurs normally at C-2 when this nitrogen bears a simple methyl.<sup>108</sup>



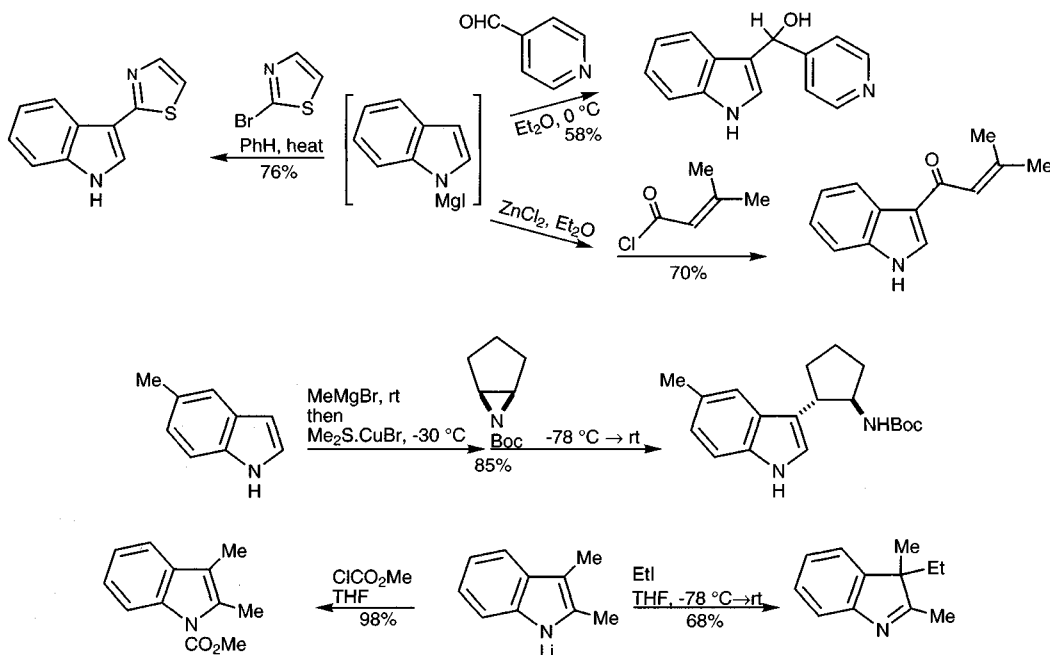
## 17.5 Reactions of *N*-metallated indoles



The indolyl anion has two main mesomeric structures showing the negative charge to reside mainly on nitrogen and the  $\beta$ -carbon. In its reactions, then, this anion behaves as an ambident nucleophile; the ratio of *N*- to  $\beta$ -substitution with electrophiles depends on the associated metal, the polarity of the solvent, and the nature of the electrophile. Generally, the more ionic sodio- and potassio-derivatives tend to react at nitrogen, whereas magnesio-derivatives have a greater tendency to react at C-3.<sup>109</sup> However, reaction of indolyl Grignards in HMPA leads to more attack at nitrogen, whereas non-polar solvents favour attack at carbon.<sup>110</sup> Complimentarily, more reactive electrophiles show a greater tendency to react at nitrogen than less electrophilic species.

*N*-Alkylation of indoles can utilise indol-1-ylsodiums,<sup>111</sup> generated quantitatively as above, or it can involve a small concentration of an indolyl anion, produced by phase-transfer methods;<sup>112</sup> indole *N*-acylation<sup>113</sup> and -arylsulfonylation<sup>114</sup> can also be achieved efficiently using phase-transfer methodology (see also section 17.1.4).

Indolyl *N*-Grignards,<sup>115</sup> or even better their zinc equivalents,<sup>116</sup> undergo reaction predominantly at C-3 with a variety of carbon electrophiles such as aldehydes, ketones and acid halides, and for example 2-bromothiazole.<sup>117</sup> Including aluminium chloride in the reaction mixture produces high yields of 3-acylindoles.<sup>118</sup> The copper-catalysed reactions of indolyl *N*-Grignards with *N*-*t*-butoxycarbonylaziridines also proceed well at C-3.<sup>119</sup> 1-Lithioindoles are equally useful; again, the position of attack depends on both solvent and the nature of the electrophile.<sup>120</sup>

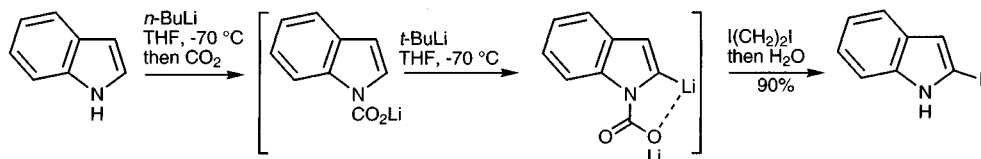


It is important to note that when an *N*-metallated 3-substituted indole alkylates at carbon, necessarily a 3,3-disubstituted-3*H*-indole (an indolenine) is formed, which cannot rearomatise to form an indole (see section 17.1.6 for rearrangements of 3,3-disubstituted indolenines).

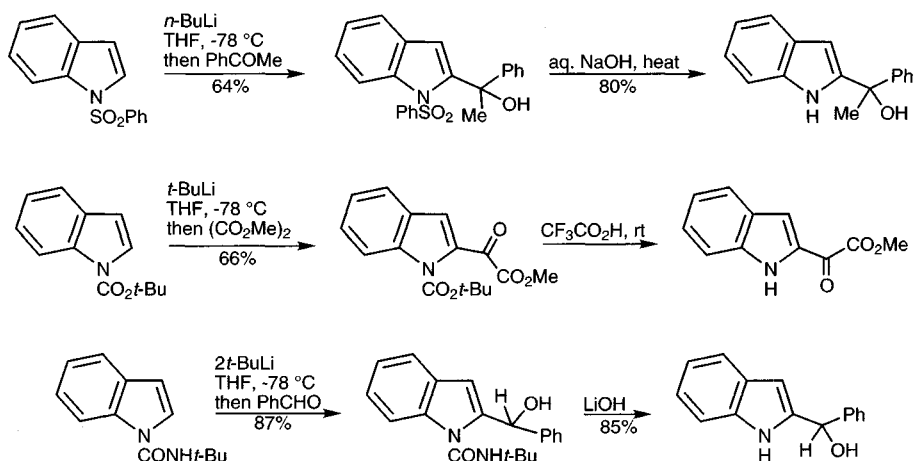
## 17.6 Reactions of C-metallated indoles

### 17.6.1 Lithium derivatives

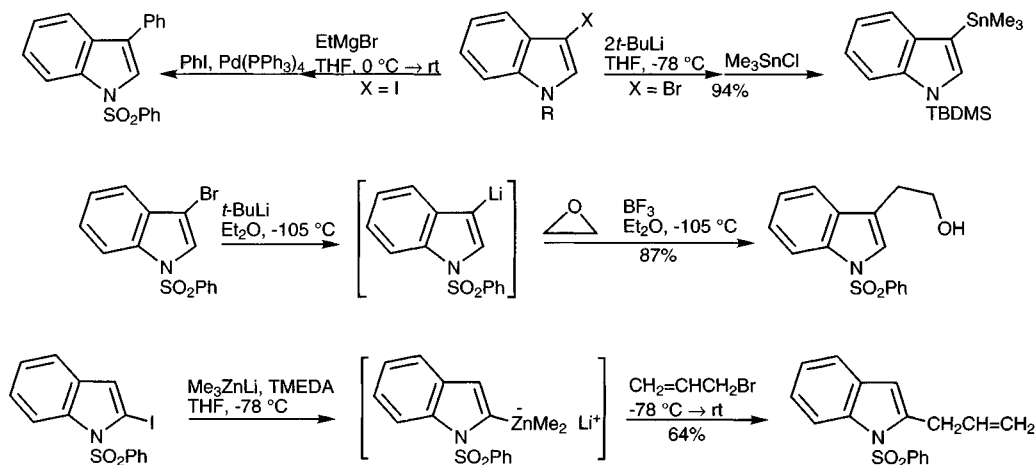
One of the most convenient *N*-protecting groups to be used in indole  $\alpha$ -lithiations is carbon dioxide<sup>102</sup> because the *N*-protecting group is installed *in situ* and, further, falls off during normal work-up. This technique has been used to prepared 2-haloindoles<sup>25</sup> and to introduce a variety of substituents by reaction with appropriate electrophiles – aldehydes, ketones, chloroformates etc.



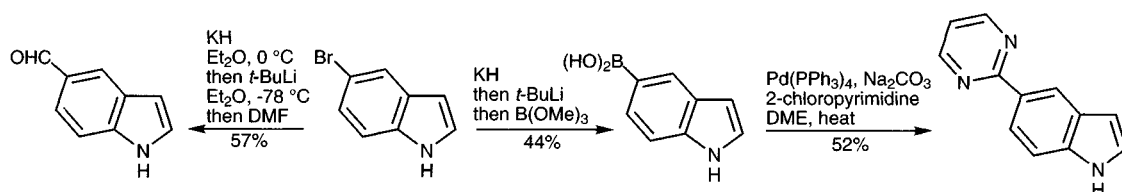
Given below is a selection of  $\alpha$ -substitutions achieved with various  $N$ -blocking/activating groups.<sup>100–107, 121</sup>



3-Lithioindoles can be prepared by halogen exchange;<sup>122</sup> the *N*-*t*-butyldimethylsilyl derivative is regiospecific, even at 0 °C,<sup>123</sup> whereas 3-lithio-1-phenylsulfonylindole isomerises to the 2-isomer at temperatures above -100 °C though at that temperature, hetero-ring opening and production of an alkyne, with the nitrogen anion acting as a leaving group, (cf. section 18.3) is not a problem.<sup>124,125</sup> The corresponding *N*-phenylsulfonyl 3-magnesium<sup>126</sup> and 3-zinc<sup>127</sup> species are stable even at room temperature: they can be prepared from the 3-iodoindole by reaction with ethylmagnesium bromide and lithium trimethylzincate respectively. 3-Lithiation with replacement of a 3-hydrogen has also been accomplished with *ortho* assistance from a 2-(2-pyridyl)<sup>126</sup> or a 2-carboxyl group,<sup>128</sup> which block C-2. Direct 3-lithiation even without a substituent at C-2 can be achieved with an *N*-di(*t*-butyl)fluorosilyl substituent in place.<sup>129</sup> Other examples of the directed metallation process in indole chemistry include: 2-lithiation of 1-substituted indole-3-carboxylic acids and amides,<sup>130</sup> and of 3-hydroxymethyl-1-phenylsulfonylindole;<sup>131</sup> 4-lithiation of 5-(dimethylcarbamoyloxy)-1-(*t*-butyldimethylsilyl)indole and the 6-lithiation of 4-substituted-5-(dimethylcarbamoyloxy)-1-(*t*-butyldimethylsilyl)indoles.<sup>132</sup>

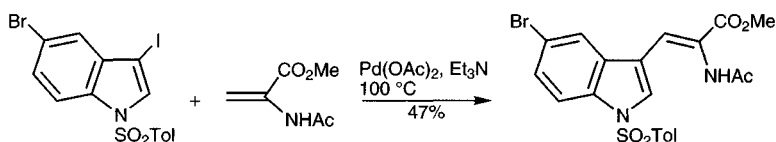


Amazingly, metal-halogen exchange can be achieved with each of the benzene ring-bromoindoles *without* *N*-protection; the indole is first converted into its *N*-potassio-salt.<sup>133</sup>



## 17.6.2 Palladium-catalysed reactions

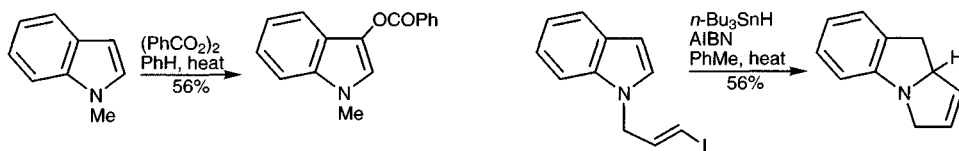
2-/3-Bromo- and -iodoindoles, and the similarly reactive 2- and 3-triflates,<sup>134</sup> undergo palladium-catalysed couplings as normal aryl halides. Since 2- and 3-haloindoles are unstable it is expedient to employ their *N*-acyl derivatives.<sup>135</sup> Halogen and triflate on the benzene ring of indoles take part unexceptionally in coupling reactions.



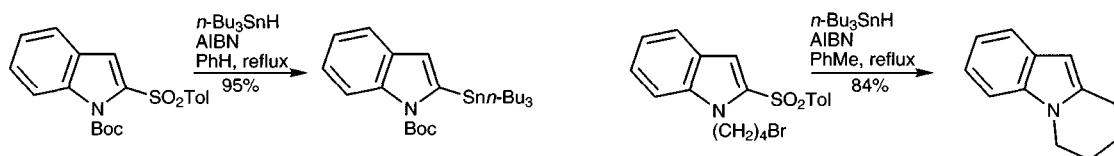
When an organometallic derivative of indole is required for a coupling reaction, boronic acids are to be preferred<sup>136</sup> although 2-zinc and 2-stannyl derivatives can be used.<sup>137</sup> The palladium-catalysed coupling of 6-bromo or 6-iodoindoles with allyl and heteroaryltin compounds does not require masking of the indole *N*-hydrogen.<sup>138</sup>

## 17.7 Reactions with radicals

Radicals such as benzyl and hydroxyl are unselective in their interaction with indoles resulting in mixtures of products, so such reactions are of little synthetic use. On the other hand, benzoyloxylation of indoles having no *N*-hydrogen gives benzoates of indoxyl,<sup>139</sup> i.e. it effectively oxidises the indole heterocyclic ring, via  $\beta$ -attack by the strongly electrophilic benzoyloxy radical. In contrast, the weakly electrophilic radical derived from malonate reacts selectively at C-2, via an atom transfer mechanism.<sup>140</sup>



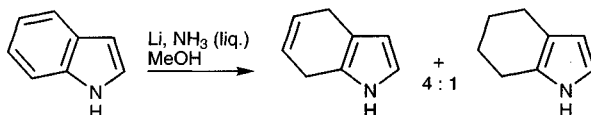
Some efficient oxidative<sup>141</sup> and reductive<sup>142</sup> intramolecular carbon radical additions can be carried out. *Ips*o replacement of toluenesulfonyl by tributylstannyl radical occurs readily at C-2<sup>143</sup> (but not C-3) as does intramolecular replacement by carbon radicals.<sup>144</sup>



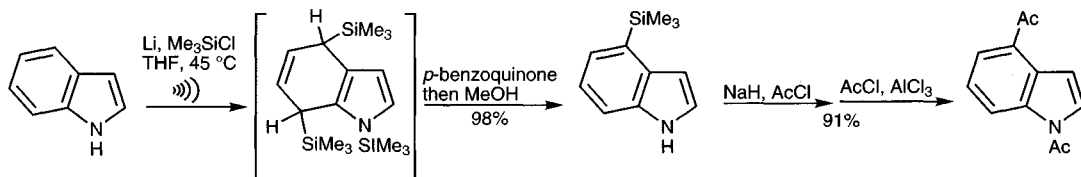
2-Indolyl radicals can be generated under standard conditions by reacting 2-bromoindole with tributyltin hydride.<sup>145</sup>

## 17.8 Reactions with reducing agents

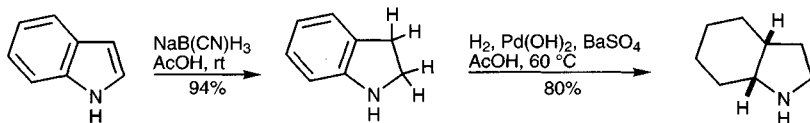
The indole ring system is not reduced by nucleophilic reducing agents such as lithium aluminium hydride and sodium borohydride; lithium/liquid ammonia does however reduce the benzene ring; 4,7-dihydroindole is the main product.<sup>146</sup>



Reduction with lithium in the presence of trimethylsilyl chloride, followed by rearomatisation, produces 4-trimethylsilylindole, an intermediate useful for the synthesis of 4-substituted indoles *via* electrophilic *ipso* replacement of silicon.<sup>147</sup>

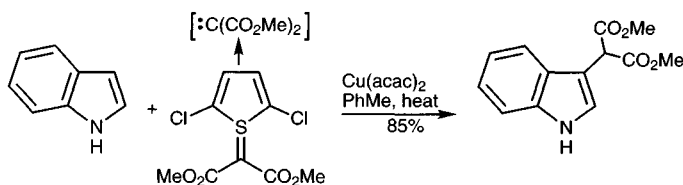


Reduction of the heterocyclic ring is readily achieved under acidic conditions; formerly, metal-acid combinations<sup>148</sup> were used, but now much milder conditions employ relatively acid-stable metal hydrides such as sodium cyanoborohydride. Triethylsilane in trifluoroacetic acid is another convenient combination; 2,3-disubstituted indoles give *cis* indolines by this method.<sup>149</sup> Such reductions proceed by hydride attack on the  $\beta$ -protonated indole – the 3*H*-indolium cation.<sup>150</sup> Catalytic reduction of indole, again in acid solution, produces indoline initially, further slower reduction completing the saturation.<sup>151</sup> Rhodium-catalysed high pressure hydrogenation of indoles with a *t*-butoxycarbonyl group on nitrogen proceeds smoothly to give 2,3-*cis* indolines.<sup>152</sup>



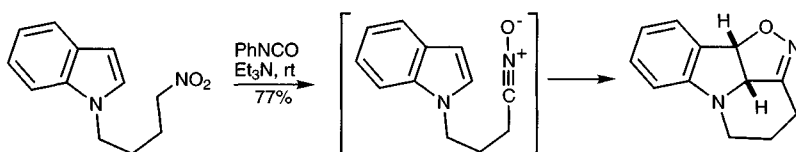
## 17.9 Reactions with carbenes

No cyclopropane-containing products have been isolated from the interaction of indoles with carbenes (cf. section 13.10). Methoxycarbonyl-substituted carbenes give only a substitution product.<sup>153</sup>

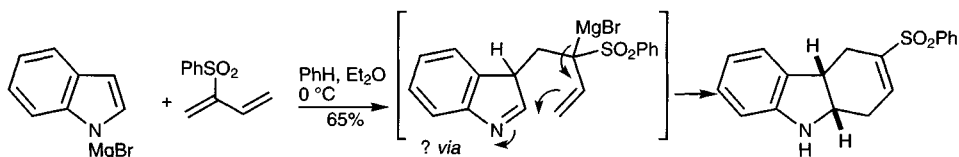


## 17.10 Electrocyclic and photochemical reactions

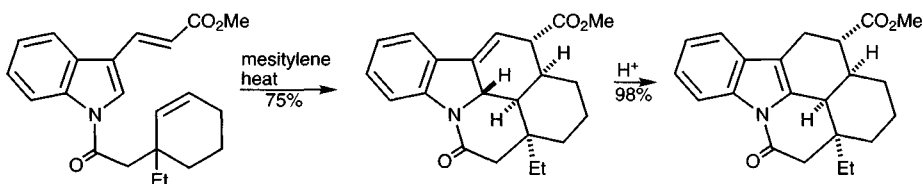
The heterocyclic double bond in simple indoles will take part in cycloaddition reactions with dipolar  $4\pi$  components,<sup>154</sup> and with electron-deficient dienes (i.e. inverse electron demand), in most reported cases, held close using a tether;<sup>155</sup> a comparable effect is seen in the intermolecular cycloaddition of 2,3-cycloalkyl indoles to *ortho*-quinone generating a 1,4-dioxane.<sup>156</sup> The introduction of electron-withdrawing substituents enhances the tendency for cycloaddition to electron-rich dienes: 3-acetyl-1-phenylsulfonylindole, for example, undergoes aluminium chloride-catalysed cycloaddition with isoprene,<sup>157</sup> and 3-nitro-1-phenylsulfonylindole reacts with 1-acylaminobuta-1,3-dienes without the need for a catalyst.<sup>158</sup>



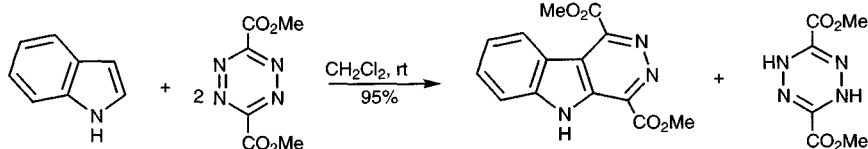
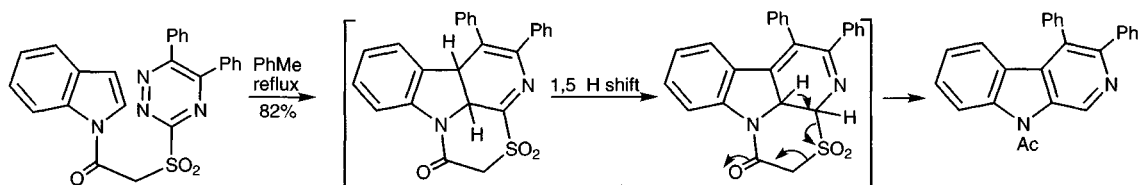
Some other, apparent cycloadditions probably proceed by non-concerted pathways, for example addition of 1,3-cyclohexadiene in the presence of light and 2,4,6-triphenylpyrylium, probably involves radical intermediates,<sup>159</sup> and reactions of 2-phenylsulfonyl-dienes with indolyl Grignard reagents probably proceed in stepwise fashion as shown.<sup>160</sup>



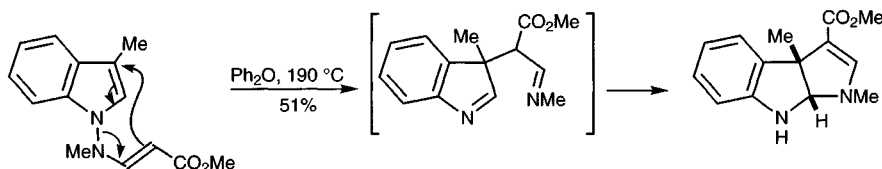
Both 2- and 3-vinylindoles take part quite readily as  $4\pi$  components in Diels-Alder cycloadditions;<sup>161</sup> often, but not always,<sup>162</sup> these employ *N*-acyl- or *N*-arylsulfonylindoles, in which the interaction between nitrogen lone pair and  $\pi$ -system has been reduced.<sup>163</sup> The example below shows how this process can be utilised in the rapid construction of a complex pentacyclic indole.<sup>164</sup>



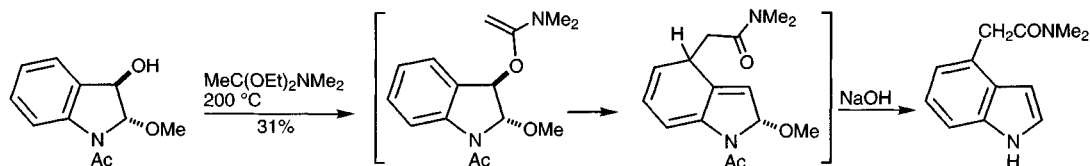
Tethered 1,2,4-triazenes are particularly useful 'dienes' as their interaction with the indole 2,3-double bond generates carbolines. The tether can be incorporated into the product molecule,<sup>165</sup> or be designed to be broken *in situ*, as in the example below.<sup>166</sup> 1,2,4,5-Tetrazines react with the indole 2,3-bond in an intermolecular sense; the initial adduct loses nitrogen and then is oxidised to the aromatic level by a second mol equivalent of the tetrazine.<sup>167</sup>



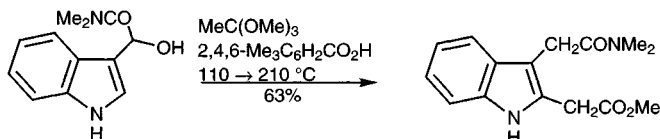
A 1-vinylaminoindole undergoes a 3,3-sigmatropic rearrangement giving the tricyclic rings system of the eseroline alkaloids.<sup>168</sup>



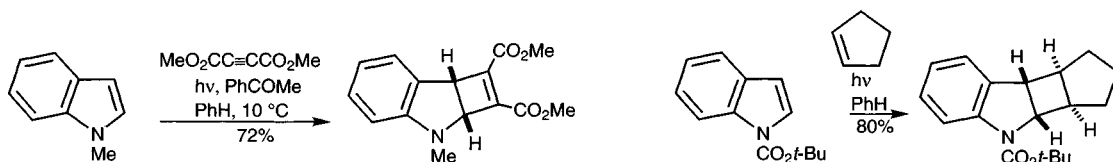
An alternative route to 4-substituted indoles relies on an orthoamide Claisen rearrangement.<sup>169</sup>



Claisen ortho ester rearrangement of indol-3-ylalkanol introduces the migrating group to the indole 2-position.<sup>170</sup>

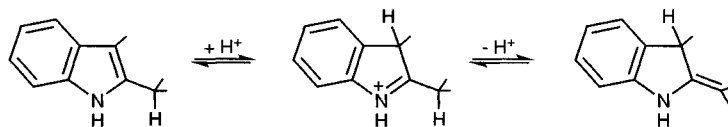


Under the influence of light, *N*-methylindoles add dimethyl acetylenedicarboxylate, generating cyclobuteno-fused products,<sup>171</sup> and even simple alkenes add in an apparent 2 + 2 fashion to *N*-acylindoles, but the mechanism probably involves radical intermediates.<sup>172</sup> Other photochemical additions to form *N*-benzoylindolines fused to four-membered rings include: addition to the carbonyl group in benzophenone, and the double bond in methyl acrylate.<sup>173</sup>

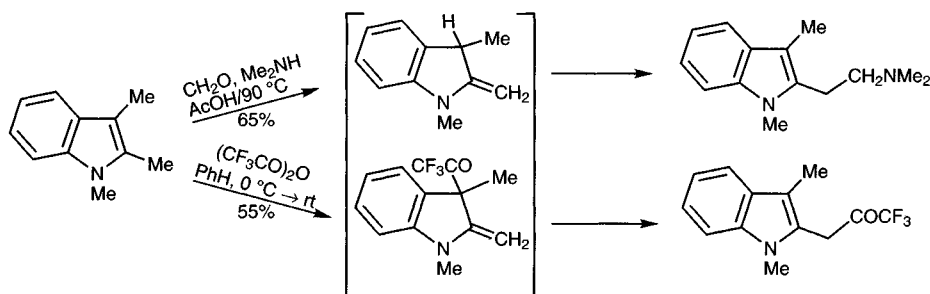


## 17.11 Alkylindoles

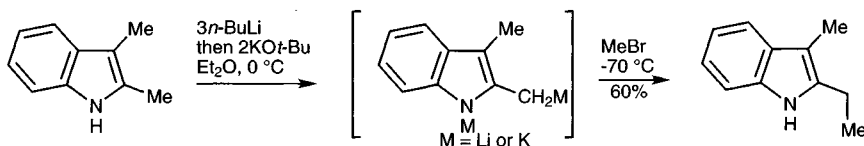
Only alkyl groups at indole  $\alpha$ -positions show any special reactions. Many related observations confirm that in a series of equilibria,  $\beta$ -protonation can lead to 2-alkylidene-indolines, and hence reactivity towards electrophiles at an  $\alpha$ -, but not a  $\beta$ -alkyl group, for example in DCl at 100 °C 2,3-dimethylindole exchanges H for D only at the 2-methyl.



This same phenomenon is seen in Mannich condensation<sup>174</sup> and trifluoroacetylation<sup>175</sup> of 1,2,3-trimethylindole at the  $\alpha$ -methyl.

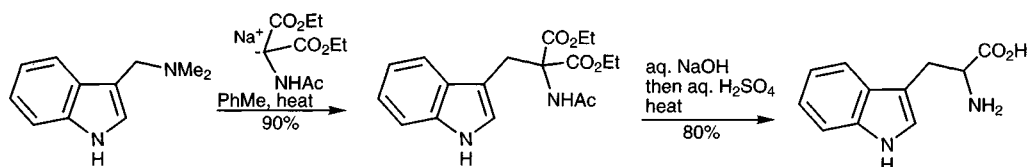


Side-chain lithiation is again specific for an  $\alpha$ -substituent, first achieved *via* an *N*-lithium carboxylate<sup>176</sup> and subsequently even without *N*-protection.<sup>177</sup>



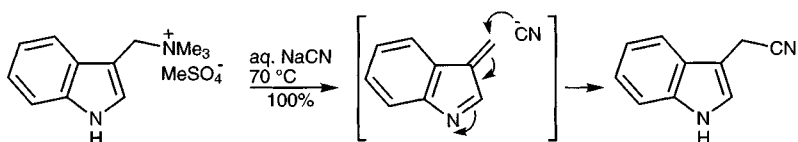
## 17.12 Reactions of indolyl-C-X compounds

Gramine and, especially, its quaternary salts are very useful synthetic intermediates in that they are easily prepared and the dimethylamino group is easily displaced by nucleophiles – reactions with cyanide<sup>178</sup> and acetamidomalonate<sup>179</sup> anions are typical.

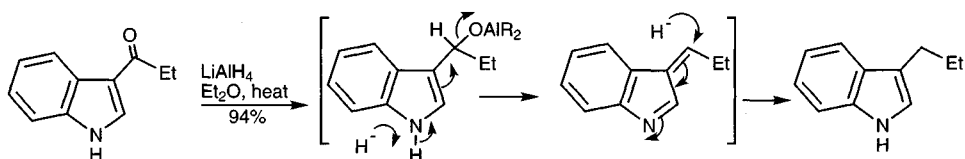


The easy displacement of the amine (ammonium) group proceeds by way of an elimination, involving loss of the indole hydrogen, and thus the intermediacy of a  $\beta$ -alkylidene-indolenine which then readily adds the nucleophile, regenerating the indole. This mechanism has been verified by observing (i) very much slower displacement with a corresponding 1-methylgramine, and (ii) racemisation on

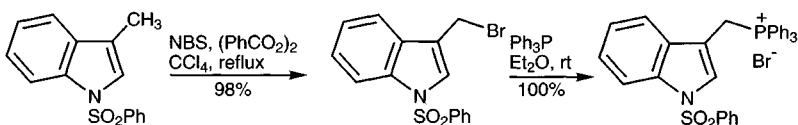
displacement using a substituted gramine in which the nitrogen-bearing carbon was a chiral centre.<sup>180</sup>



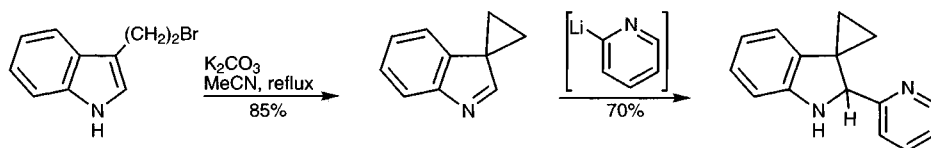
A related sequence is involved in the lithium aluminium hydride reduction of indol-3-ylcarbinols (which can be obtained from the corresponding ketones using milder reducing agents) with formation of the alkylindole. This constitutes a useful synthesis of 3-alkylindoles.<sup>181</sup> The one-pot conversion of 3-formylindole into 3-cyanomethylindole with a mixture of sodium cyanide and sodium borohydride probably involves a comparable elimination and then reduction of the cyanohydrin.<sup>182</sup>



Although haloalkylindoles are generally unstable and not synthetically useful, *N*-acylated derivatives are much more stable, can be prepared by side-chain radical substitution, and can be utilised in nucleophilic substitution processes.<sup>183</sup>

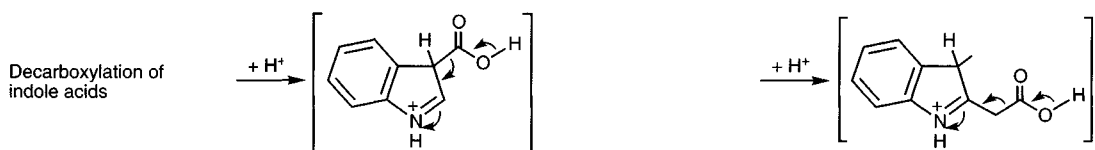


This section is an appropriate place to include the remarkable,<sup>184</sup> and reproducible<sup>185</sup> mild transformation of 2-(indol-3-yl)bromoethane into a cyclopropyl-indolenine, with consequent loss of the hetero ring aromaticity; in the later work it was shown that organolithiums will add straightforwardly to the imine unit of the cyclopropyl-indolenine without disruption of the small ring.

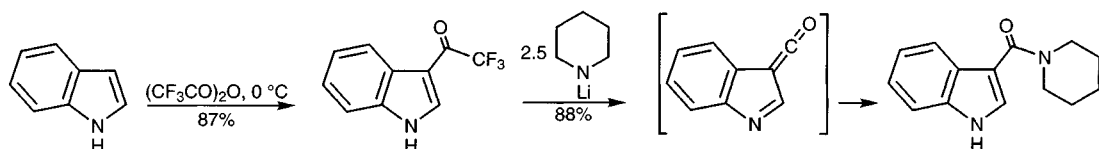


### 17.13 Indole carboxylic acids

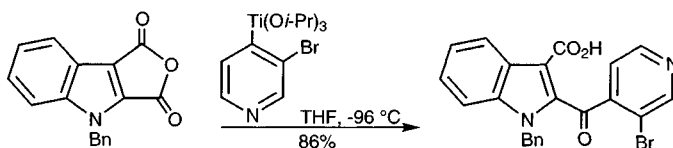
Both indole-3-carboxylic<sup>186</sup> and indol-2-ylacetic acids are easily decarboxylated in boiling water. In each case carbon dioxide is lost from a small concentration of  $\beta$ -protonated 3*H*-indolium cation, the loss, in each case, being analogous to the decarboxylation of a  $\beta$ -keto-acid. Indole-1-carboxylic acid also decarboxylates very easily but is sufficiently stable to allow isolation and use in acylation reactions.<sup>187</sup> Indole-2-carboxylic acids can only be decarboxylated by heating in mineral acid or in the presence of copper salts.<sup>188</sup>



Trifluoroacetylindoles are useful stable equivalents of acid chlorides, giving amides or acids in haloform reactions with lithium amides or aqueous base respectively. The reactivity of the *N*-hydrogen compounds is greater than of those with *N*-alkyl, indicating the intermediacy of a ketene in the reactions of the former.<sup>189</sup>



In a nice exemplification of the mesomeric interaction between indole nitrogen and a 3-carbonyl which renders the 3-carbonyl somewhat amide-like (see also 17.12), 2,3-dicarboxylic acid anhydrides react selectively with some nucleophiles at the 2-carbonyl; inductive withdrawal by the ring nitrogen may also play a part in achieving this selectivity.<sup>190</sup>

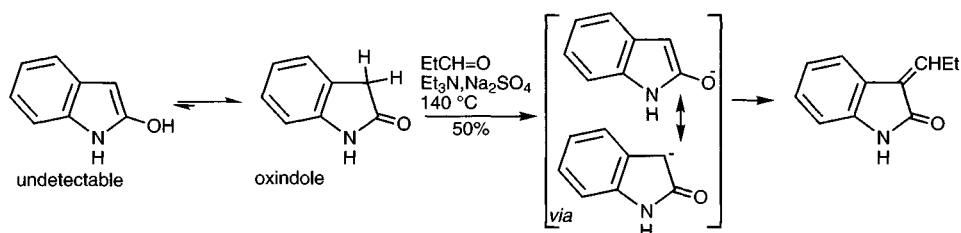


## 17.14 Oxyindoles

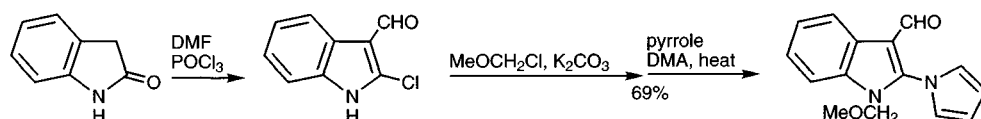
Indoles with a hydroxy group on the benzene ring behave like normal phenols; indoles with an oxygen at either of the heterocyclic ring positions are quite different.

### 17.14.1 Oxindole

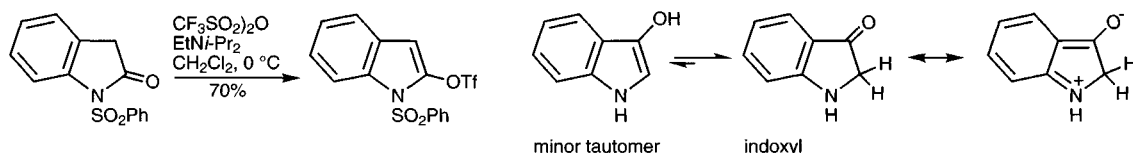
2-Hydroxyindole does not exist as such: the stable form is the carbonyl tautomer; the hydroxy tautomer cannot be detected. There is nothing remarkable about the reactions of oxindole, for the most part it is a typical 5-membered lactam, except that deprotonation at the  $\beta$ -carbon ( $pK_a \sim 18$ ) occurs more readily than with simple amides, because the resulting anion is stabilised by an aromatic indole canonical contributor. This anion will react with electrophiles like alkyl halides and aldehydes<sup>191,192</sup> at the  $\beta$ -carbon, the last with dehydration and the production of aldol condensation products. It is interesting that the 3-position is three times more reactive than the 1-position.<sup>193</sup> Oxindoles can be effectively oxidised to isatins (section 17.14.3) *via* easy 3,3-dibromination, then hydrolysis.<sup>194</sup> Bromination of oxindole with *N*-bromosuccinimide gives 5-bromo-oxindole.<sup>193</sup>



The interaction of oxindole with the Vilsmeier reagent produces 2-chloro-3-formylindole efficiently;<sup>195</sup> this difunctional indole has considerable potential for elaboration, for example nucleophilic displacement of the halogen, activated by the *ortho* aldehyde, can produce indoles carrying a nitrogen substituent at C-2.<sup>196</sup>

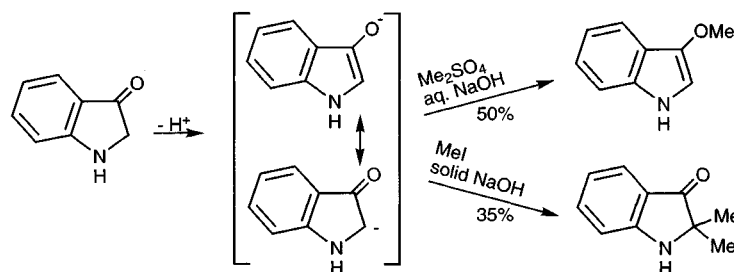


Of potential in coupling processes to the indole 2-position is the 1-phenylsulfonylated 2-triflate readily obtained from 1-phenylsulfonyloxindole.<sup>197</sup>

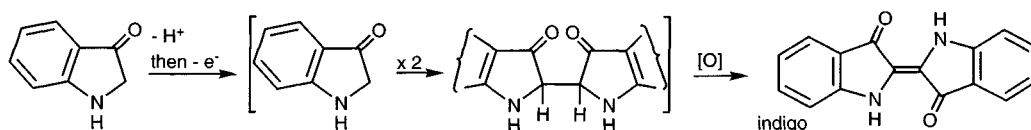


### 17.14.2 Indoxyl<sup>198</sup>

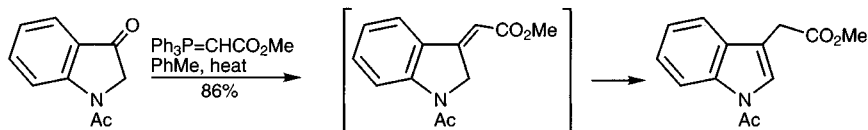
3-Hydroxyindole certainly contributes in the tautomeric equilibrium with the carbonyl form, though it is the minor component. Indoxyl,  $pK_a$  10.46,<sup>199</sup> is more acidic than oxindole, the anion produced is ambident; reactions with electrophiles at both oxygen and carbon are known.<sup>200</sup>



The indoxyl anion is particularly easily autoxidised producing the ancient blue dye, indigo. The mechanism probably involves dimerisation of a radical formed by loss of an electron from the anion.

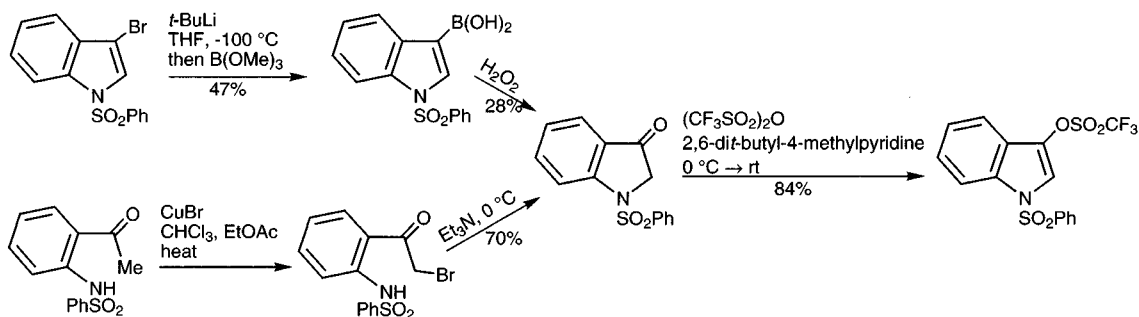


*O*-Acetylindoxyl<sup>201</sup> and *N*-acylindoxyls are more stable substances; the latter undergo normal ketone-carbonyl reactions, such as the Wittig reaction.<sup>202</sup>



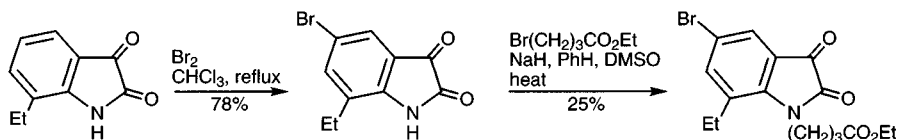
Mirroring oxindoles, aldol-type condensation at the 2-position in indoxyls can be accomplished either using the acetate of the enol form and base catalysis,<sup>203</sup> or with indoxyl itself, in either acid or basic conditions.<sup>204</sup> Borohydride reduction and dehydration allows these alkylidene condensation products to be converted into 2-substituted indoles.

Peroxide oxidation of *N*-phenylsulfonylindole-3-boronic acid gives *N*-phenylsulfonylindoxyl, which can be converted into the triflate of the 3-hydroxyindole tautomer,<sup>205</sup> and this in turn utilised in palladium-catalysed cross-coupling processes.<sup>206</sup> The same *N*-protected indoxyl can be prepared by ring synthesis, as shown below.

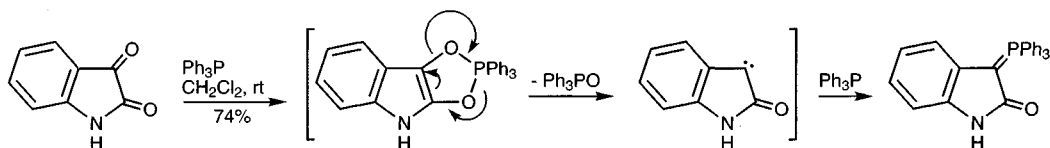


### 17.14.3 Isatin<sup>207</sup>

Isatin is a stable, bright orange solid which is commercially available in large quantities. Because it readily undergoes clean aromatic substitution reactions at C-5, *N*-alkylation *via* an anion, and ketonic reactions at the C-3-carbonyl group, for example enolate addition,<sup>208</sup> it is a very useful intermediate for the synthesis of indoles and other heterocycles.

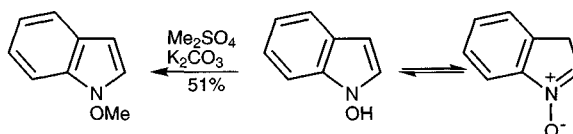


Conversion of isatins to oxindoles can be achieved by catalytic reduction in acid,<sup>209</sup> or by the Wolff-Kischner process.<sup>193,210</sup> 3-Substituted indoles result from Grignard addition at the ketone carbonyl, followed by lithium aluminium hydride reduction of the residual amide, then dehydration.<sup>211</sup> The reaction of isatin with triphenylphosphine provides an easy synthesis of the Wittig reagent 3-(triphenylphosphorylide)-indole.<sup>212</sup>

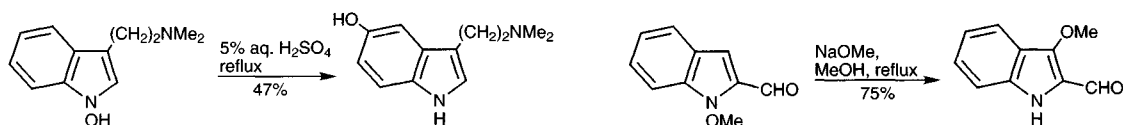


#### 17.14.4 1-Hydroxyindole<sup>213</sup>

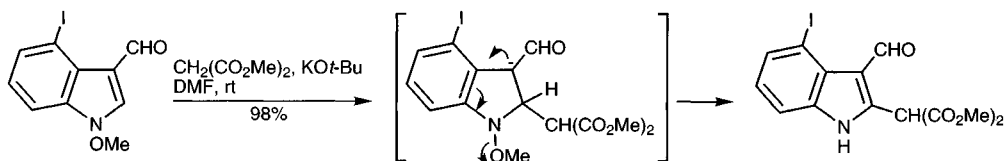
1-Hydroxyindole can be prepared in solution, but attempted purification leads to dimerisation *via* its nitron tautomer, however *O*-alkyl derivatives can be formed easily and are stable.<sup>214</sup>



1-Hydroxy- and 1-alkoxyindoles are being developed for various synthetic purposes; for example lithiation of 1-methoxyindole takes place at C-2 and thus substituents can be introduced. More importantly, various nucleophilic substitutions, with departure of the 1-substituent take place. One of the reactions below shows the introduction of a hydroxy group onto the indole 5-position by an acid-catalysed reaction of a 1-hydroxyindole.<sup>215</sup> 1-Methoxy groups allow nucleophilic attack on the heterocyclic ring, as illustrated by the second example.<sup>216</sup>



*Cine*-nucleophilic substitution of methoxy in 1-methoxy-3-formylindole produces the 2-substituted product.<sup>217</sup>



#### 17.15 Aminoindoles

2-Aminoindole exists mainly as the *3H*-tautomer, presumably because of the energy advantage conveyed by amidine-type resonance. 3-Aminoindole is very unstable, and easily autoxidised<sup>218</sup> however its acetamide is stable (section 17.1.2). 1-Aminoindoles can be prepared by direct amination of the indolyl anion.<sup>219</sup>

