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# 2,3,4,5-Tetrahydropyridine ($\Delta^1$-piperideine) and its derivatives. Synthesis and chemical properties

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**Abstract. The data on the synthesis and transformations of 2,3,4,5-tetrahydropyridine and its derivatives published after 1970 are surveyed and described systematically. The bibliography includes 251 references.**

## I. Introduction

The enhanced interest in the pyridine derivatives is due to some specific chemical and physical properties peculiar to this class of compound. The fact that pyridine bases exhibit a broad spectrum of biological activities is equally important. 2,3,4,5-Tetrahydropyridine ($\Delta^1$-piperideine) and its derivatives also attract attention. $\Delta^1$-Piperideine itself is a key compound participating in the biosynthesis of some alkaloids (for example, alkaloids of the coniine and lobeline groups). Substituted 2,3,4,5-tetrahydropyridines are convenient starting compounds for the synthesis of other families of alkaloids, the structures of which are often fairly complex.

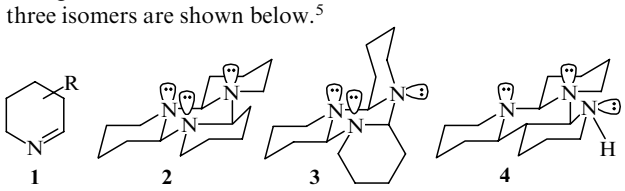
Published data on the chemistry of tetrahydropyridines were surveyed for the first time in a volume.[1] This volume contains only one mention of $\Delta^1$-piperideines, namely, it presents a scheme for the synthesis of 3,5-dimethyl-2-phenyl-$\Delta^1$-piperideine. More recent volumes [2,3] contain data on the methods of synthesis and properties of 1,2,3,4-tetrahydropyridines, 2,3,4,5-tetrahydropyridines and 1,2,5,6-tetrahydropyridines, mostly published before 1971. The chemistry of 2-alkoxy-3,4,5,6-tetrahydropyridines has been discussed in a review [4] devoted to the lactim ethers containing heterocyclic nuclei of various sizes.

In the present review, we consider systematically the data on the chemistry of $\Delta^1$-piperideines published from 1970 to the present time. Among the compounds synthesised, the products belonging to one or another family of alkaloids are mentioned, and their biological activities are discussed.

## II. Structure of $\Delta^1$-piperideines

The unsubstituted 2,3,4,5-tetrahydropyridine (**1**) stands out in the series of $\Delta^1$-piperideines. In fact, almost all 2,3,4,5-tetrahydropyridine derivatives are monomers under ordinary conditions, whereas unsubstituted 2,3,4,5-tetrahydropyridine (**1a**) exists at pH $\geqslant$ 7 as three isomeric trimers, α-isomer **2**, β-isomer **3** and isotripiperideine **4**.[5]

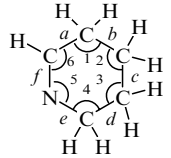
The structures, configurations and conformations of these three trimers were determined by $^{13}$C NMR spectroscopy.[5,6] It was established that at low temperatures, the compound occurs as the trimer **3**, while at room temperature, it is converted into the trimer **2**. The trimer **4** can also exist at room temperature. The trimer **2** has $C_3$ symmetry and exists as a racemic mixture of the *RRR* and *SSS* configurations, while the trimer **3** is characterised by $C_1$ symmetry and is a racemic mixture of the *RRS* and *SSR* configurations. The most favourable conformations for all the three isomers are shown below.[5]



**1** **2** **3** **4**

The monomer – trimer equilibrium has been studied by NMR, UV and IR spectroscopy.[7] It was found that at pH 7, the compound **1a** occurs as a trimer, while in solutions in anhydrous acids, aqueous acids and aqueous alcohols, the equilibrium shifts towards the monomer. In strongly acidic solutions 2,3,4,5-tetrahydropyridine exists only as the monomer **1a**.

All the bond lengths and the internal angles in the six-membered ring of 2,3,4,5-tetrahydropyridine (**1a**) have been determined by *ab initio* quantum-chemical calculations.[8,9]



| Bond | Length /Å | Angle | Magnitude /deg. |
|---|---|---|---|
| *a* | 1.5080 | 1 | 111.5 |
| *b* | 1.5242 | 2 | 108.6 |
| *c* | 1.5233 | 3 | 109.5 |
| *d* | 1.5241 | 4 | 115.5 |
| *e* | 1.4670 | 5 | 118.2 |
| *f* | 1.2830 | 6 | 128.0 |

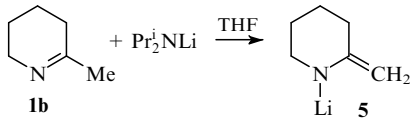
The cyclic imine **1** exists in a half-chair conformation, having the lowest energy. Of the three piperideines, $\Delta^1$-piperideine **1a** is

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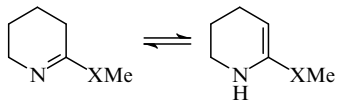
characterised by the minimum energy; if the relative energy of the compound **1a** is taken to be zero, the energy of 1,2,3,4-tetrahydropyridines is 6.39 kcal mol$^{-1}$ and that of 1,2,5,6-tetrahydropyridine is 11.9 kcal mol$^{-1}$. The calculated bond lengths and internal angles are in good agreement with the corresponding values determined for substituted $\Delta^1$-piperideines by X-ray diffraction analysis.[8,9]

Some derivatives of the imine **1a** containing substituents at the 2-position exist as two tautomers. Thus 2-methyl-3,4,5,6-tetrahydropyridine **1b** is readily converted into the lithium derivative of 2-methylenepiperidine (**5**) on treatment with lithium diisopropylamide (LDA).[10] In the presence of perchloric acid, the compound **1b** also reacts as 2-methylenepiperidine.[11]




**1b** **5**

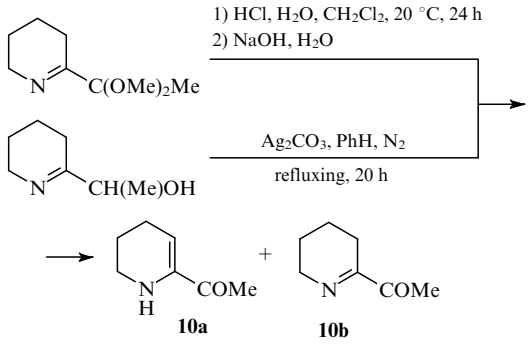
2-Methoxy-3,4,5,6-tetrahydropyridine **6**[12–14] and 2-methylthio-3,4,5,6-tetrahydropyridine **7**[14] can participate in reactions as the enamine forms **8** and **9**.




**6**, **7** **8**, **9**

X = O (**6**, **8**), S (**7**, **9**).

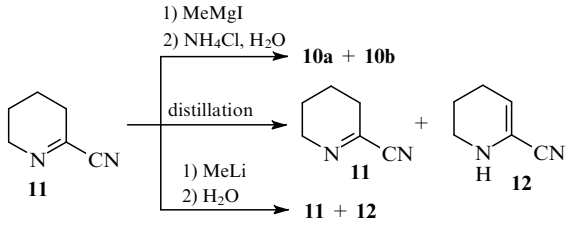
In the case of 2-acetyl-3,4,5,6-tetrahydropyridine **10**, the equilibrium is shifted towards the enamine form **10a**. Having been formed, the compound **10** first exists as the less stable tautomer **10b**, which is then partially converted into the more stable tautomer **10a** (the **10a** : **10b** ratio is 2 : 1).[15,16]




**10a** **10b**

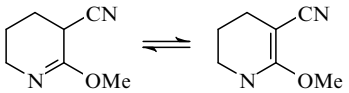
When 2-cyano-3,4,5,6-tetrahydropyridine **11** is made to react with MeMgI and then the reaction mixture is treated with an aqueous solution of ammonium chloride, a mixture of the tautomers **10a** and **10b** in 1 : 4 ratio is formed. During storage, the content of **10a** increases (**10a** : **10b** = 2 : 1).[17]

On distillation, the nitrile **11** is partially converted into 6-cyano-1,2,3,4-tetrahydropyridine **12** (ratio **11** : **12** = 1 : 1.3).[17] The compound **11** isomerises to **12** upon the reaction with MeLi and subsequent treatment with water.



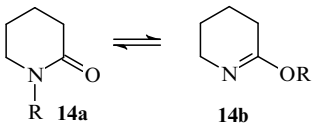

**11** **11** **12**

3-Cyano-2-methoxy-3,4,5,6-tetrahydropyridine **13** exists as two tautomers **13a** and **13b**, which is confirmed by the presence of two absorption bands in its IR spectrum, at 2180 cm$^{-1}$ (for the conjugated CN group) and 2260 cm$^{-1}$ (for the non-conjugated CN group).[13]




**13a** **13b**

It was found by ion cyclotron resonance that in the series of alkylated derivatives, tautomers **14b** are stronger bases than **14a**.[18]




**14a** **14b**

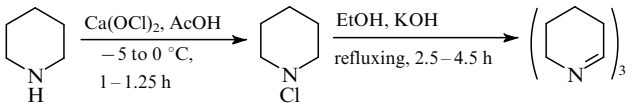
R = H, Me.

## III. Methods of synthesis of $\Delta^1$-piperideines

### 1. Synthesis from piperidine and its derivatives

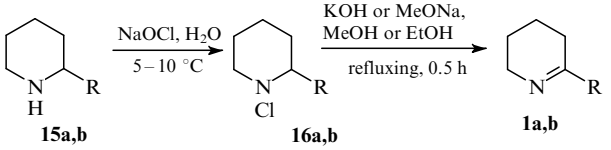
The unsubstituted imine **1a** is commonly prepared by a two-stage procedure which includes treatment of piperidine with chlorinating agents and reaction of the resulting 1-chloropiperidine with nucleophilic reagents.

Treatment of amine **15a** with calcium hypochlorite in acetic acid gave the chloro-derivative **16a**, which was converted into the trimerised compound **1a** (yields 39% – 64%) by treatment with an ethanolic solution of KOH.[19–21]




**15a** **16a**

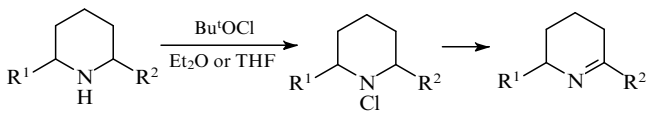
In other studies,[22,23] piperidine and 2-methylpiperidine were converted into the cyclic imines **1a**,**b** on treatment with sodium hypochlorite in water followed by refluxing of the resulting *N*-chlorinated derivatives **16a**,**b** in a 10% ethanolic solution of potassium hydroxide[22] or in a solution of sodium methoxide in methanol.[23]




**15a,b** **16a,b** **1a,b**

R = H (**a**), Me (**b**).

On treatment with Bu$^t$OCl in ether[17] or THF,[24] the derivatives **15c**,**d** are transformed into the *N*-chlorinated compounds **16c**,**d**, which react with MeONa in MeOH, triethylamine in Et$_2$O[17] or KOH in EtOH and THF[24] to give the $\Delta^1$-piperideines **1c**,**d**.



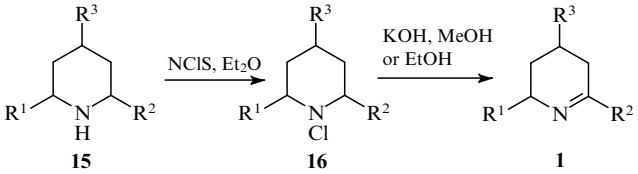

**15c,d** **16c,d** **1c,d**

R$^1$ = H, R$^2$ = CN (**c**); R$^1$ = R$^2$ = Ph (**d**).

In several studies,[25–27] *N*-chlorosuccinimide in Et$_2$O was used to convert the amine **15a** into 1-chloropiperidine **16a**, and dehydrochlorination of the chloro-derivative was carried out using potassium hydroxide.

Gas-phase chlorination of piperidine **15a** with *N*-chlorosuccinimide (47 °C, $10^{-1}$ – $10^{-2}$ mm Hg) and gas-phase dehydrochlorination of the resulting *N*-chloropiperidine **16a** (which is formed in 90% yield) over AdOK (Ad is 1-adamantyl) at 2 °C[22] or over Bu$^t$OK at –97 to –77 °C[22,28] have been reported.

*N*-Chlorosuccinimide (NClS) has been used to chlorinate the substituted piperidines **15**; the resulting chlorinated derivatives **16** were converted into the $\Delta^1$-piperideines **1** using KOH in an alcohol.[29–32]

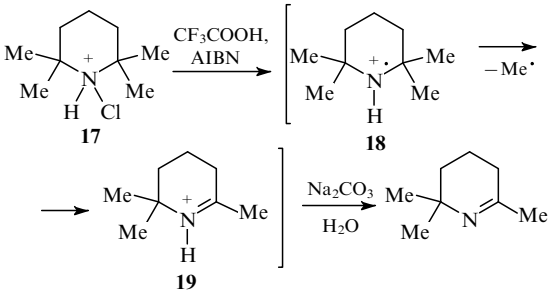



**15** **16** **1**

$R^1 = R^3 = H$, $R^2 = Me$; $R^1 = R^2 = Me$, $R^3 = H$;
$R^1 = R^3 = H$, $R^2 = Et$, Pr;

$R^1 = R^2 = H$, $R^3 = CH_2(Me)CH$–.

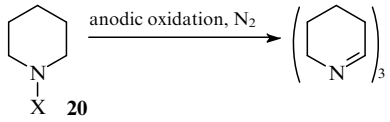
Heating of tetramethylpiperidinium chloride **17** in trifluoroacetic acid in the presence of azobisisobutyronitrile yields radical cation **18**, which is converted into cation **19** with elimination of $Me^{\bullet}$. Treatment of the reaction mixture with an aqueous solution of sodium carbonate affords 2,6,6-trimethyl-$\Delta^1$-piperideine (yield 67%).[33]




**17** **18** **19**

AIBN is azoisobutyronitrile.

The piperideine trimer is formed in a relatively low yield upon anodic oxidation of piperidine derivatives **20** under an inert atmosphere.[34]

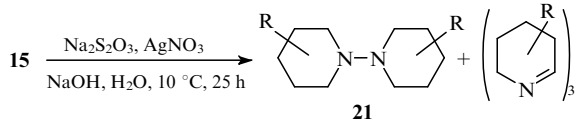



**20**

| X | Anolyte | Current density /A dm$^{-2}$ | The charge passed /F mol$^{-1}$ | Yield (%) |
|---|---|---|---|---|
| Li | $LiClO_4$ | 0.21 | 1 | 6 |
| MgBr | – | 0.84 | 1 | 15 |

The transformation of piperidine **15a** into the piperideine trimer (yield 58%) upon oxidation with chloroiron(III) mesoporphyrin IX dimethyl ester has been reported.[35]

The piperidines **15** react with sodium hyposulfite in the presence of catalytic amounts of silver nitrate giving a mixture of 1-(1-piperidyl)piperidines **21** and piperideine trimers.[36]

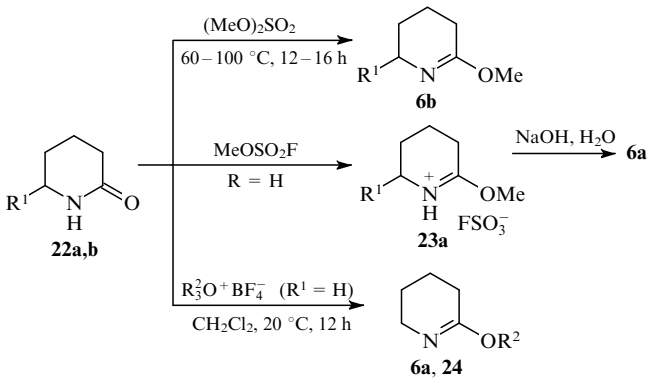



**21**

R = H, 2-Me, 3-Me, 4-Me, 4-Ph.

A popular method for the synthesis of $\Delta^1$-piperideines is treatment of piperidin-2-one **22a** or piperidine-2-thione or their substituted derivatives with various reagents.

Thus heating of the lactam **22a** with dimethyl sulfate in benzene or toluene gives 2-methoxy-3,4,5,6-tetrahydropyridine **6a** in 70%–90% yield.[37–42] 2-Methoxy-6-methyl-3,4,5,6-tetrahydropyridine **6b** was prepared by treatment of methylpiperidone **22b** with dimethyl sulfate.[40]




**22a,b** **6b** **23a** **6a** **6a, 24**

$R^1$ = H (**a**), Me (**b**); $R^2$ = Me, Et.

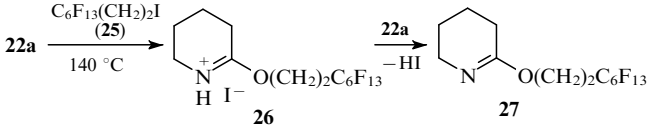
The imidate **6a** is produced in 78% yield in the reaction of the lactam **22a** with methyl fluorosulfonate followed by treatment of the resulting salt **23a** with aqueous sodium hydroxide.[43]

The imidate **6a** and 2-ethoxy-3,4,5,6-tetrahydropyridine **24** have been synthesised in 92% and 89% yields, respectively, by the reaction of lactam **22a** with trimethyloxonium or triethyloxonium tetrafluoroborate.[41]

A method for the synthesis of the methoxy-derivative **6a** consisting in the reaction of the lactam **22a** with diazomethane in ether in the presence of silica gel and sodium bicarbonate has been patented.[44]

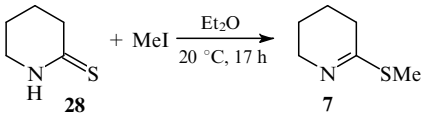
When piperidin-2-one **22a** reacts with $POCl_3$ at 20 °C, 2-chloro-3,4,5,6-tetrahydropyridine is formed.[45]

Heating of iodo-derivative **25** with the lactam **22a** in a sealed tube affords salt **26**, which reacts with a second molecule of the lactam **22a** yielding lactim ether **27** and the hydroiodide of the lactam **22a**.[46]



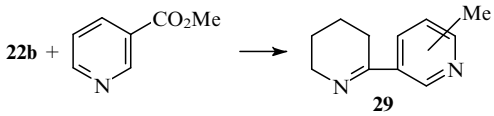

**26** **27**

The reaction of piperidine-2-thione **28** with methyl iodide in anhydrous ether at 20 °C gives rise to 2-methylthio-3,4,5,6-tetrahydropyridine **7**.[47]



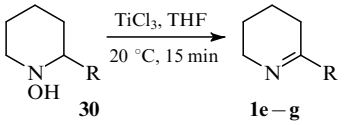

**28** **7**

The synthesis of piperideine **29** from the lactam **22b** and methyl nicotinate has been patented.[48]




**29**

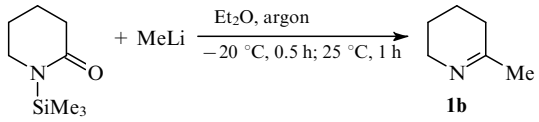
In the presence of $TiCl_3$, 1-hydroxypiperidines **30**, substituted at the 2-position, are rapidly converted into the $\Delta^1$-piperideines **1e–g**, which are formed in high yields.[49, 50]



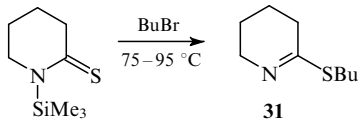

**30** **1e–g**

| Compound | R | Yield (%) | Ref. |
|---|---|---|---|
| **1e** | Pr | 83 | 49 |
| **1f** | $CH=CH_2$ | 73 | 49 |
| **1g** | Ph | 89 | 49 |
| | | 70 | 50 |

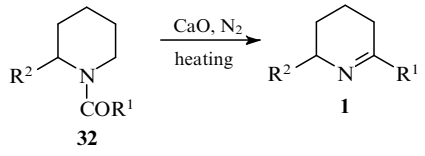
1-Trimethylsilylpiperidin-2-one is converted into 2-methyl-3,4,5,6-tetrahydropyridine **1b** on treatment with methyllithium under an inert atmosphere.[51]




2-Butylthio-3,4,5,6-tetrahydropyridine **31** has been synthesised in 59% yield by heating 1-trimethylsilylpiperidine-2-thione with butyl bromide.[52]

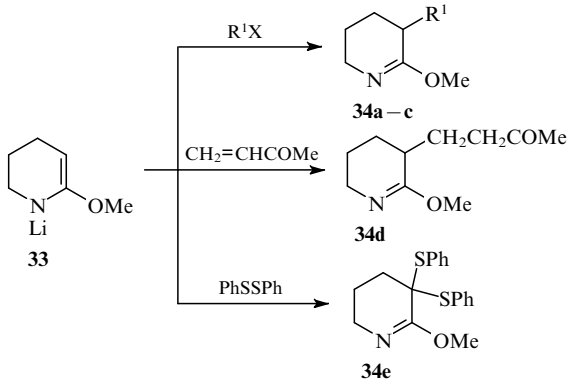


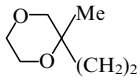

When piperidine derivatives **32**, containing an acyl group at the nitrogen atom, are heated with calcium oxide, carbon monoxide is removed and the $R^1$ radical migrates to the α-position of the heterocyclic ring to give the piperideines **1**.[53–55]



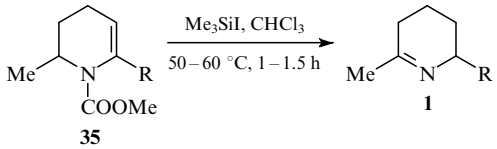

| $R^1$ | $R^2$ | Yield (%) | Ref. |
|---|---|---|---|
| Pr | H | 69 | 53 |
|  | H | 62 | 53 |
| $CH_2=CH(CH_2)_3$ | Me | 39 | 54 |

Methods for the preparation of $\Delta^1$-piperideines from N-substituted $\Delta^2$-piperideine derivatives have been reported. Thus the reaction of 1-lithio-2-methoxy-$\Delta^2$-piperideine **33** with alkyl halides resulted in the synthesis of imidate **34**, substituted at the 3-position of the heterocyclic centre; the reactions of **33** with methyl vinyl ketone and diphenyl sulfide yielded the corresponding ethers **34d** and **34e**.[56]



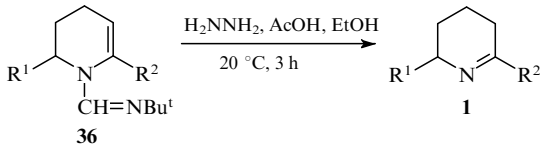

| Compound | $R^1$ | X | Temperature /°C (time /h) | Yield (%) |
|---|---|---|---|---|
| **34a** |  | I | 20(4) | 56 |
| **34b** | $CH_2=C(Me)CH_2CH_2$ | I | −78(3) to 22(0.3) | 60 |
| **34c** | $Me(Cl)C=CHCH_2$ | Cl | −78(2) to 20(12) | 37 |
| **34d** | | | −78(0.1) to 20(0.3) | 31 |
| **34e** | | | −78(0.05) to 20(0.3) | 66 |

The $\Delta^2$-piperideine derivatives **35** lose the methoxycarbonyl group when heated with iodotrimethylsilane and are thus converted into $\Delta^1$-piperideines **1** in almost quantitative yields.[57, 58]



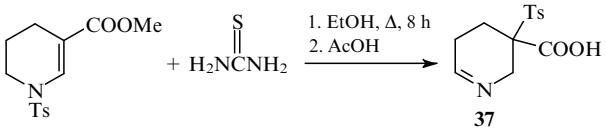

R = $C_{11}H_{23}$, $C_8H_{17}$.

Hydrazinolysis of the C–N bond in the Schiff's bases **36** affords the $\Delta^1$-piperideines **1** in almost quantitative yields.[59]



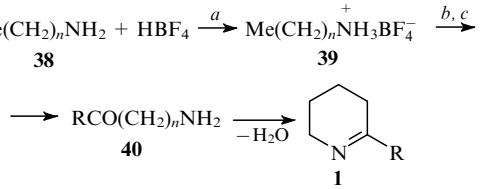

$R^1$, $R^2$ = H, $C_{11}H_{23}$; H, $CH_2Ph$; Me, $C_{11}H_{23}$.

Methyl 1-tosyl-1,4,5,6-tetrahydronicotinate has been found to undergo an unexpected transformation on heating with thiourea yielding acid **37**.[60]



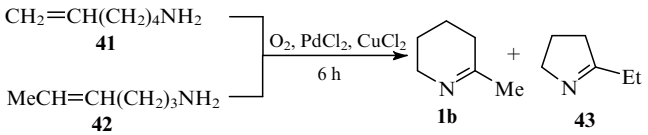

## 2. Synthesis from primary amines and their derivatives

Primary amines **38** react with $HBF_4$ to give the corresponding salts **39**, which are converted into the imines **1** upon reaction with methyl(trifluoromethyl)dioxirane at 0 °C followed by treatment with sodium carbonate. Presumably, this reaction yields initially amino ketones **40**.[61, 62] The reaction can be carried out either with or without isolation of the intermediate salts **39**.

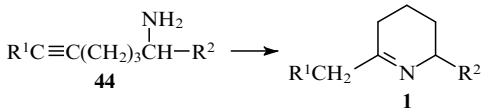



(*a*) $H_2O$, MeCN, pH 2–3; (*b*) methyl(trifluoromethyl)dioxirane, $CH_2Cl_2$; (*c*) $Na_2CO_3$; $n$ = 5–7, R = Me (90%), Et (95%), Pr (92%).

Oxidative cyclisation of aminoalkenes **41** and **42** in the presence of palladium(II) chloride and copper(II) chloride gives rise to a mixture of the imine **1b** and 2-ethyl-$\Delta^1$-pyrroline in 66 : 34 ratio and in a total yield of 75% and 71%, respectively.[63]



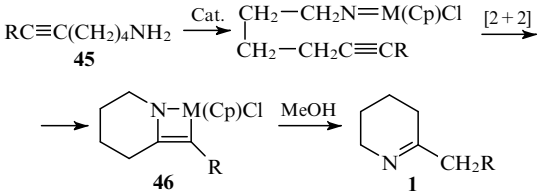

Alkynylamines **44** have been converted into the $\Delta^1$-piperideines **1** by refluxing in acetonitrile or THF in the presence of $NaAuCl_2 \cdot 2H_2O$ for 1–2 h (yield 64%–90%) [64] or by refluxing in propionitrile in the presence of $PdCl_2 \cdot (MeCN)_2$ for 10–20 h (yield 42%–92%).[65]




$R^1$ = H, Et, $C_5H_{11}$, $C_6H_{13}$, $C_7H_{15}$, $CH_2=CH(CH_2)_2$, Ph;
$R^2$ = H, Me, $C_{11}H_{23}$.

Cyclisation of the amines **44** ($R^1$ = Ph, $Me_3Si$; $R^2$ = H) in the presence of catalytic amounts of the samarium complex $(\eta^5\text{-}Me_5C_5)_2SmCH(SiMe_3)_2$ also results in the formation of the $\Delta^1$-piperideines **1** ($R^1$ = Ph, $Me_3Si$; $R^2$ = H).[66]

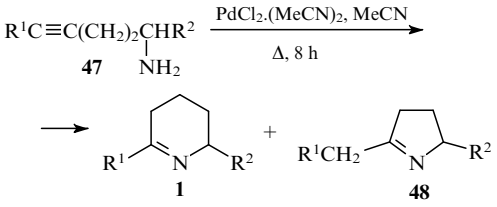
The synthesis of the $\Delta^1$-piperideines **1** from alkynylamines **45** in the presence of Group IV metal complexes occurs as intramolecular [2+2]-cycloaddition with the intermediate formation of metallocyclic compounds **46**.[67]



| R | Catalyst | Solvent | Temperature /°C | Yield (%) |
|---|---|---|---|---|
| Ph | $CpZrMe_2Cl$ | THF | 25 | 69 |
| Ph | $CpTiCl_3$, $PhNMe_2$ | PhMe | 80 | 88 |
| Bu | $CpZrMe_2Cl$ | THF | 25 | 74 |
| Bu | $CpTiCl_3$, $PhNMe_2$ | PhMe | 80 | 83 |

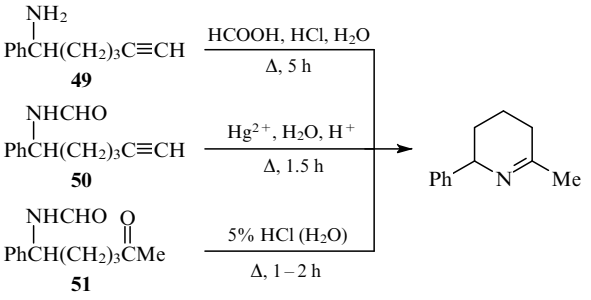
The transformation of the alkynylamine **45** (R = $C_7H_8$) into the corresponding $\Delta^1$-piperideine **1** (R = $C_7H_8$) was carried out in *N*,*N*-dimethylaniline in the presence of $CpTiCl_3$ at 80 °C.[67]

In the presence of $PdCl_2\cdot(MeCN)_2$ as a catalyst, alkynylamines **47** are converted into mixtures of the $\Delta^1$-piperideines **1** and $\Delta^1$-pyrrolines **48**, which are formed in a quantitative yield in 4 : 1 ratio.[65]

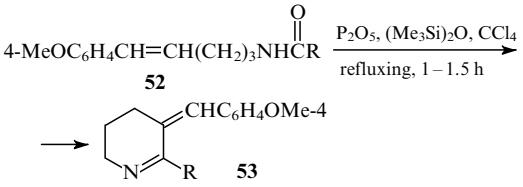


$R^1$ = $C_7H_{15}$, $R^2$ = H; $R^1$ = $C_6H_{13}$, $R^2$ = Me.

Three procedures have been proposed for the synthesis of 2-methyl-6-phenyl-3,4,5,6-tetrahydropyridine,[68] namely, heating of 6-amino-6-phenylhex-1-yne **49** with formic and hydrochloric acids, Kucherov hydration of its *N*-formyl derivative **50** and cyclisation of keto amide **51** in boiling hydrochloric acid.

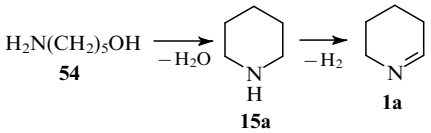


Heating of unsaturated amides **52** with $P_2O_5$ in $CCl_4$ in the presence of hexamethyldisiloxane is accompanied by their cyclisation to give $\Delta^1$-piperideines **53**.[69]

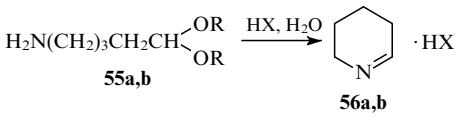


R = Me, $(CH_2)_2CH(CH_2Ph)COOEt$.

The transformation of the amino alcohol **54** into $\Delta^1$-piperideine **1a** in the presence of various catalysts and at a temperature of 200, 225, 250 or 300 °C (in some cases, under a hydrogen atmosphere) has been studied. The process was shown [70] to occur in two stages comprising cyclodehydration of the amino alcohol **54** and dehydration of the piperidine **15a** thus formed. The highest yields of the piperidine **15a** were attained in the presence of $Cu/Al_2O_3$ at 200 °C or Cu/MgO at 225 °C (99% and 62%, respectively). The yield of piperideine **1a** at 250 °C was not greater than 20% – 22%, while at 300 °C, it was only 5%.

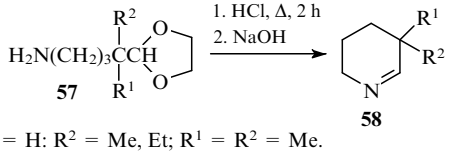


On treatment with 20% sulfuric acid, 5-aminopentanal acetal **55** is converted into sulfate **56a** in 92% yield.[71] A similar cyclisation of the acetal **55b** induced by hydrochloric acid gives hydrochloride **56b**.[71]



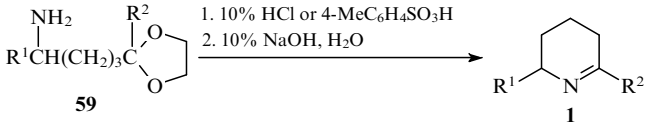
$R_2$ = $Me_2$ (**a**), $CH_2CH_2$ (**b**); X = $HSO_4$ (**a**), Cl (**b**).

3,3-Disubstituted $\Delta^1$-piperideines **58** have been synthesised by heating amino aldehyde acetals **57** with hydrochloric acid followed by treatment with NaOH.[72]



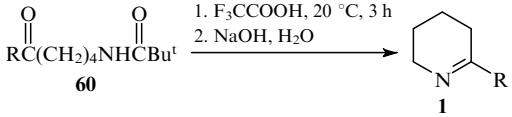
$R^1$ = H: $R^2$ = Me, Et; $R^1$ = $R^2$ = Me.

Treatment of amino ketone ketals **59** with dilute hydrochloric acid in ether [73] or THF [74] as well as treatment with toluene-*p*-sulfonic acid in acetone [75] gives the $\Delta^1$-piperideines **1** in 70% – 90% yields.



$R^1$, $R^2$ = $C_5H_{11}$, Me, Br, $C_{11}H_{23}$, $(MeO)_2CH(CH_2)_3$.

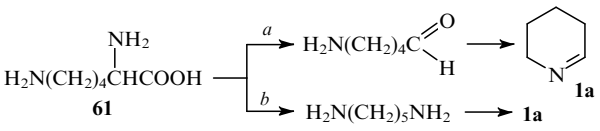
The 2-substituted 3,4,5,6-tetrahydropyridines **1** are formed upon cyclisation of oxo amides **60** in the presence of trifluoroacetic acid.[76]



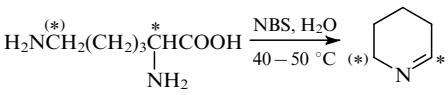
R = $C_6H_{13}$ (74%), Ph (71%), Pr (44%), $C_{11}H_{23}$ (48%), 3-pyridyl (56%).

2,6-Diaminocaproic acid (lysine **61**) serves as the starting compound in the biosynthesis of about 150 alkaloids, which are produced from this acid *via* oxidative rearrangements occurring in plants with the intermediate formation of the imine **1a**.

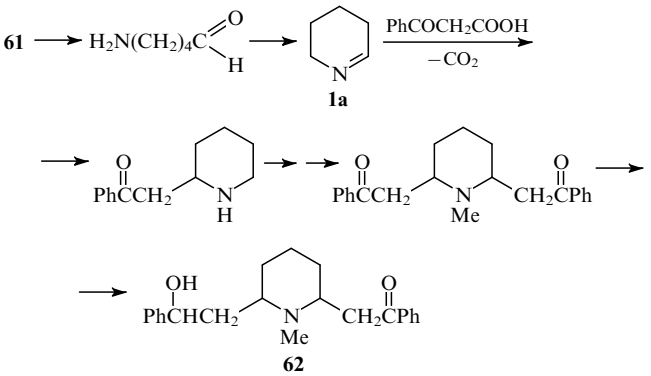
In nature, 2,3,4,5-tetrahydropyridine **1a** can arise from lysine **61** *via* two routes, namely, Strecker degradation to 5-aminopentanal followed by intramolecular dehydration (a) and decarboxylation of the acid **61** to give 1,5-diaminopentane (cadaverine) and its subsequent cyclisation (b).[77,78]



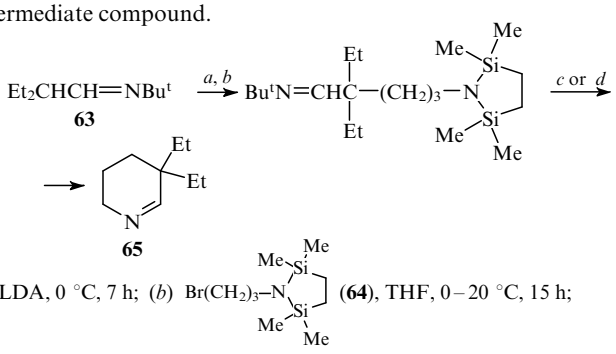
In order to identify the intermediate compounds which may form in these reactions, 2,3,4,5-tetrahydropyridines labeled by $^{14}C$ at the 2- or 6-position have been synthesised [79, 80] by the reaction of the corresponding labelled D,L-lysine hydrochlorides with *N*-bromosuccinimide.



In another study,[77] $^{14}C$-labelled (±)-[2-$^{14}C$]-lysine, [1,5-$^{14}C$]-cadaverine and [2-$^{14}C$]-$\Delta^1$-piperideine were introduced into the *Lobelia inflata* plant, together with non-labelled lobeline **62**. After some time, $^{14}C$-containing lobeline **62** was found in the plant. Based on the ratio of the introduced to recovered $^{14}C$, it was concluded that biosynthesis of the alkaloid **62** involves the intermediate formation of 5-aminopentanal. A probable scheme for the formation of lobeline **62** was proposed.



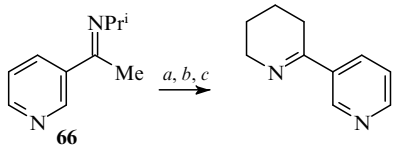
3,3-Diethyl-$\Delta^1$-piperideine **65** was prepared in 53% yield by the reaction of amine **63** with bis-silylated aminobromopropane **64** in the presence of LDA followed by desilylation of the intermediate compound.



(*a*) LDA, 0 °C, 7 h; (*b*) $Br(CH_2)_3-N$(SiMe$_2$)$_2$ (**64**), THF, 0–20 °C, 15 h;

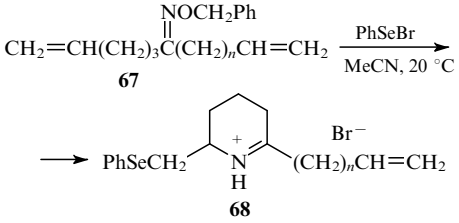
(*c*) $Bu_4N^+F^-$, 20 °C; (*d*) $K_2CO_3$, MeOH, Δ, 3 h.

2-(3-Pyridyl)-3,4,5,6-tetrahydropyridine was synthesised from imine **66** and bromide **64** in 88% yield.[81]



(*a*) LDA, THF, 0 °C, 2 h; (*b*) **64**, THF, 0–20 °C, 15 h;
(*c*) $K_2CO_3$, MeOH, Δ, 3 h.

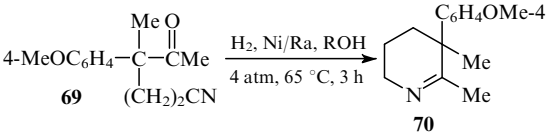
The hydrobromides of selenium-containing $\Delta^1$-piperideines **68** are formed in the reaction of *O*-benzoyloximes **67** with PhSeBr at room temperature.[82]



*n* = 3, 4.

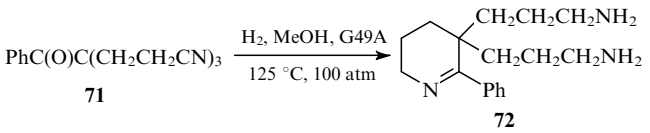
## 3. Synthesis from nitriles

Nitriles containing functional groups such as carbonyl or alkoxycarbonyl groups, halogen atoms or a multiple bond in their molecules are convenient starting compounds for the synthesis of $\Delta^1$-piperideines. The reduction of oxo nitriles **69** over Raney nickel in ethanol or methanol results in the formation of compound **70** as a mixture of equal amounts of enantiomers in 65% and 83% total yield, respectively.

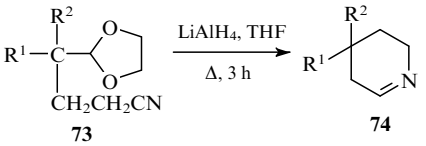


R = Me, Et.

During hydrogenation of trinitrile **71** in the presence of the G49A catalyst (manufactured by Gierdler company), all the three nitrile groups are reduced to $CH_2NH_2$; after that, cyclisation giving a tetrahydropyridine nucleus occurs. The reaction affords 3,3-bis(2-aminopropyl)-2-phenyl-$\Delta^1$-piperideine **72** (yield 22%).[72]

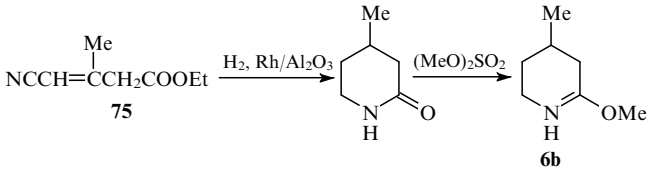


Compounds **74** have been synthesised by reductive cyclisation of acetals or ketals **73** on treatment with lithium aluminium hydride in boiling THF. The piperideine **74** [$R^1-R^2 = (CH_2)_5$] was patented as a repellent.[85, 86]



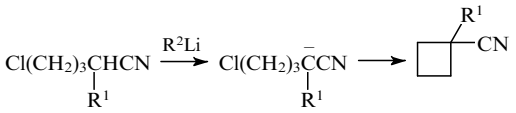
$R^1-R^2$ = $(CH_2)_2CH=CHCH_2$, $CH(Me)CH_2CH=CHCH_2$, $(CH_2)_5$, $(CH_2)_6$, $(CH_2)_{10}$, $(CH_2)_3CH(OH)CH_2$, $(CH_2)_2C(Me)=C(Me)CH_2$;
$R^1$, $R^2$ = H, Me, Et, Pr, Ph, CH(Me)Et, $C_9H_{19}$, cyclo-$C_5H_9$.

2-Methoxy-4-methyl-3,4,5,6-tetrahydropyridine **6b** has been prepared by reductive cyclisation of nitrile **75** on a rhodium catalyst followed by treatment of the resulting 4-methylpiperidin-2-one with dimethyl sulfate.[87]

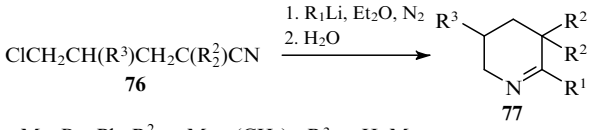


Cyclisation of 5-halo-substituted nitriles induced by organometallic compounds is used quite often to synthesise $\Delta^1$-piperideines.

French investigators [88] established that the transformation of 5-chloro-substituted nitriles into the corresponding $\Delta^1$-piperideines on treatment with lithium reagents occurs successfully only when no hydrogen atoms are present in the α-position relative to the nitrile group. Otherwise, the reaction results in the formation of cyclobutane derivatives.

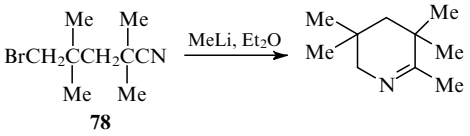


The reaction of nitriles **76** with organolithium compounds was carried out in ether under an inert atmosphere for 0.5 h at 0–5 °C and then for 4 h at 20 °C (in the case of phenyllithium, the reaction mixture should be refluxed for 4 h). After hydrolysis, compounds **77** were isolated in 48%–93% yields.[88]

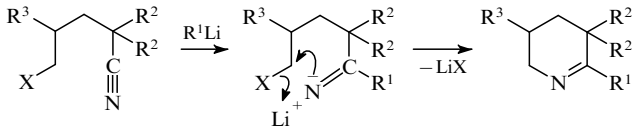


$R^1$ = Me, Bu, Ph; $R^2_2$ = $Me_2$, $(CH_2)_5$; $R^3$ = H, Me.

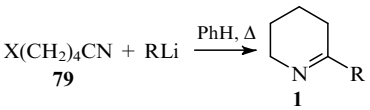
2,3,3,5,5-Pentamethyl-$\Delta^1$-piperideine was also synthesised from bromo-derivative **78** and methyllithium (yield 84%).[88]



The following scheme was proposed [88] for the formation of $\Delta^1$-piperideines from 5-halo-substituted nitriles:

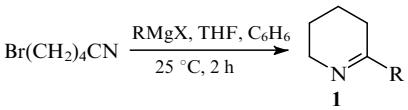


When studying cyclisation of 5-halo-substituted nitriles **79** induced by organolithium compounds on refluxing in benzene, Gallulo *et al.*[89] found that with bromo-substituted nitriles **79** the reaction time is shorter and the yields of the piperideines **1** are higher than those attained with chloro-derivatives. In another study,[90] the piperideine **1** (R = Ph) was prepared in 37% yield in a similar way by refluxing 5-chloropentanenitrile and PhLi in an $Et_2O$–cyclohexane mixture.



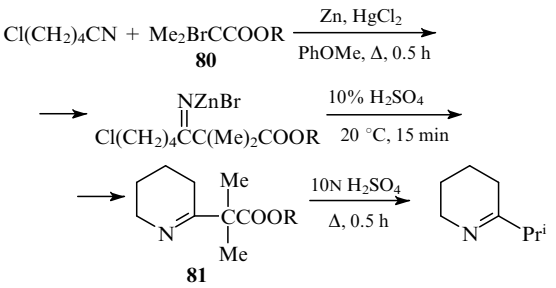
X = Cl, Br; R = Bu, Ph, Me.

The reaction of 5-bromopentanenitrile with Grignard reagents in a THF–$C_6H_6$ mixture affords the corresponding $\Delta^1$-piperideines **1** in good yields.[91]



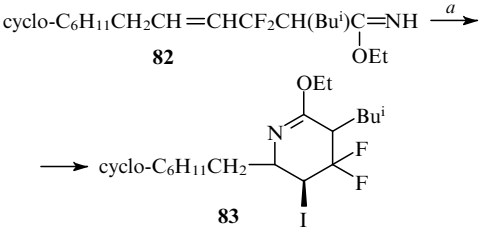
X = Cl, Br; R = Bu (75%), Ph (85%), $Bu^i$ (58%), $PhCH_2$ (64%), Me (34%), $Pr^n$ (84%).

The modified Favorsky reaction between 5-chloropentanenitrile and brominated esters **80** was used to prepare alkyl 2-(3,4,5,6-tetrahydropyridin-2-yl)-2-methylpropanoates **81**. On boiling in sulfuric acid, these products are hydrolysed with decarboxylation to give 2-isopropyl-3,4,5,6-tetrahydropyridine.[92]



R = Me, Et.

Imidate **82**, prepared from the corresponding nitrile, cyclises in the presence of iodine and 4,4′-thiobis(2-*tert*-butyl-6-methylphenol) (TBP) in the dark giving rise to $\Delta^1$-piperideine **83** (yield 83%).[93]

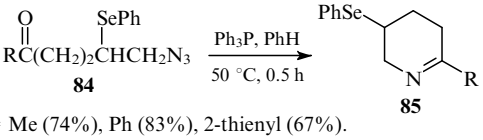


(*a*) $I_2$, TBP, $NaHCO_3$, $CH_2Cl_2$, $H_2O$, 25 °C, 24 h.

The rates of cyclisation in the $CH_2Cl_2$–$H_2O$ and $CHCl_3$–$H_2O$ biphase systems are higher than that in the $CCl_4$–$H_2O$ system; the lowest reaction rates were observed in THF and MeCN. The compound **83** is produced in 75%–80% yield upon ultrasonic treatment of the imidate **82** in a nonaqueous medium (Bransonic 221 bath).[93]

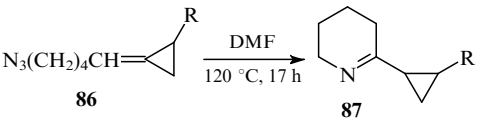
## 4. Synthesis from azides

When selenium-substituted azido ketones **84** are heated with triphenylphosphine in benzene, they cyclise to give the corresponding 2,5-disubstituted $\Delta^1$-piperideines **85**.[94]



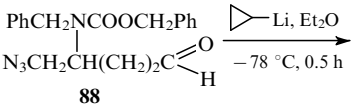
R = Me (74%), Ph (83%), 2-thienyl (67%).

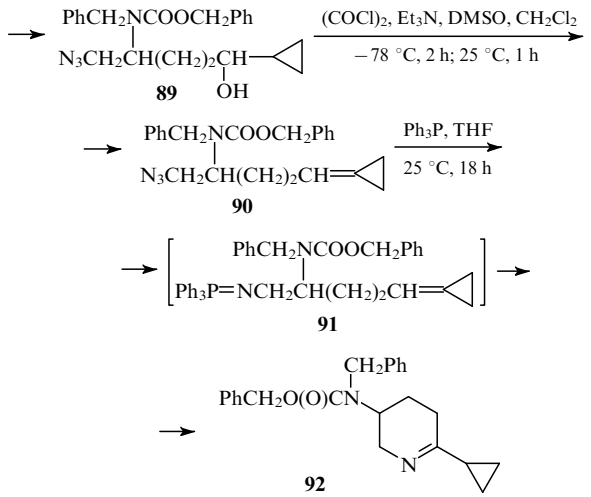
$\Delta^1$-Piperideines containing a cyclopropane ring at the 2-position are prepared by cyclisation of methylenecyclopropane azides. Heating of azides **86** in DMF affords cyclopropane-substituted piperideines **87** (yield ~60%).[95]



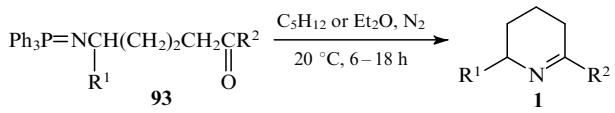
R = H, Me (a 3 : 1 mixture of isomers).

To synthesise compound **92**, the starting compound in the synthesis of the alkaloid (−)-8*a*-*epi*-desacetoxyslaframine, azide **88** was made to react with cyclopropyllithium, and the resulting alcohol **89** (yield 89%) was converted into methylenecyclopropane azide **90** (yield 85%) by treatment with oxalyl chloride in the presence of triethylamine. Cyclisation of the azide was induced by triphenylphosphine. The reaction proceeds *via* unstable ylide **91**.[95]



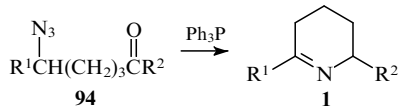



The intramolecular Wittig aza reaction has been used [96] in the synthesis of several $\Delta^1$-piperideines **1** from oxo ylides **93**.




| $R^1$ | $R^2$ | Yield (%) |
|---|---|---|
| H | Me | 71 |
| H | Pr | 76 |
| H | cyclo-$C_3H_6$ | 90 |
| Me | Me | 79 |
| H | Ph | 83 |

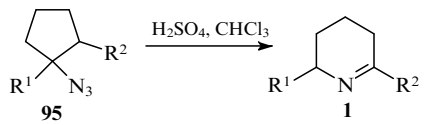
The $\Delta^1$-piperideines **1** were synthesised by the reaction of δ-azido ketones **94**, containing one more carbonyl group (either free or as acetal), with triphenylphosphine without isolation of the intermediate ylides.[15, 97]




| $R^1$ | $R^2$ | Temperature /°C | Time /h | Solvent | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| $C(OEt)_2Me$ | H | refluxing | 5 | $Et_2O$ | 72 | 15 |
| $CH(OMe)_2$ | H | 20 | 17 | pentane | 71 | 15 |
| MeCO | Me | 20 | – | $Et_2O$ | 27 | 97 |

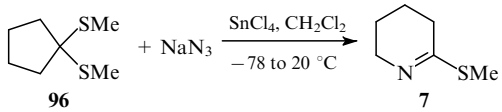
## 5. Synthesis by recyclisation reactions

1-Azido-1-alkylcyclopentanes **95** recyclise on treatment with sulfuric acid in chloroform to give the cyclic imines **1** in good yields.[98]



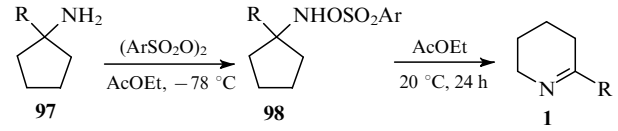

$R^1$, $R^2$ = H, Me, Pr, Bu.

1,1-Bis(methylthio)cyclopentane **96** reacts with sodium azide in the presence of tin chloride giving 2-methylthio-3,4,5,6-tetrahydropyridine **7** in 95% yield.[90]



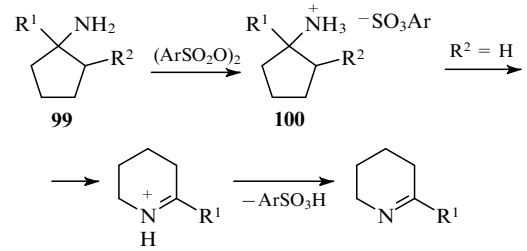

When L-proline is heated with monosaccharides or aldehydes of the furan series for 1.5 h at 150 °C, the corresponding $\Delta^1$-piperideines are produced.[100]

Recyclisation of aminocyclopentane derivatives **98**, formed in the reaction of amines **97** with arylsulfonyl peroxides, occurs at room temperature to give 2,6-disubstituted-$\Delta^1$-piperideines **1** (yields 43% – 79%).[101]

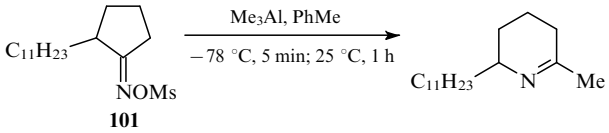



R = Me, Bu, $PhCH_2$; Ar = 3-$F_3CC_6H_4$, 4-$O_2NC_6H_4$.

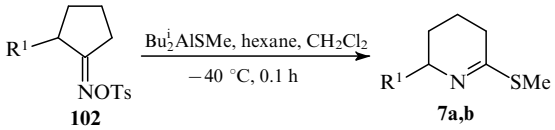
If the compound **97** contains a substituent at the 2-position, recyclisation does not occur. This fact was explained [101] by assuming that salts **100**, formed from amines **99** in the first stage of the process, are unable to recyclise if $R^2 \neq H$.




On treatment with trimethylaluminium, 2-undecylcyclopentanone oxime mesylate **101** is converted into 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine in 54% – 57% yield.[102, 103]

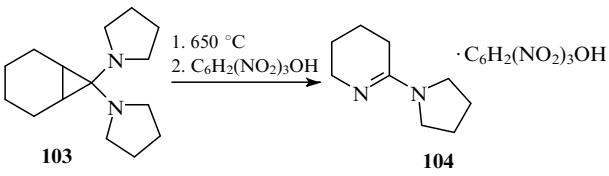



Transformation of oxime tosylates **102** into $\Delta^1$-piperideines **7a**,**b** was attained by heating these substrates in the presence of diisobutyl(methylthio)aluminium.[103]

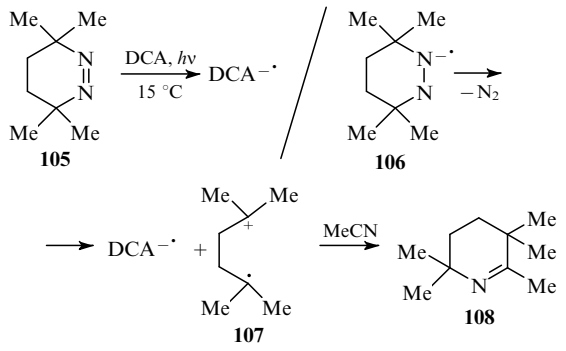



R = H (**a**, 5%), Me (**b**, 46%).

2-(Pyrrolidin-1-yl)-3,3,5,6-tetrahydropyridine picrate **104** was obtained in 88% yield by the pyrolysis of 7,7-bis(pyrrolidin-1-yl)bicyclo[4.1.0]heptane **103** followed by treatment of the reaction product with picric acid.[104]



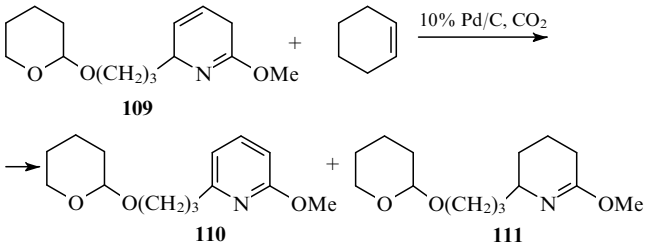

Exposure of 3,3,3,6-tetramethyl-1,2-diazacyclohex-1-ene **105** to radiation ($\lambda$ = 420 nm) in the presence of 9,10-dicyanoanthracene in acetonitrile gives 2,3,3,6,6-pentamethyl-$\Delta^1$-piperideine **108** in 75% yield. Evidently, this reaction occurs *via* the successive formation of radical anion **106** and radical cation **107**.[105]



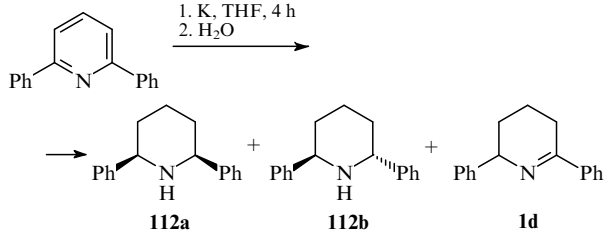
DCA is 9,10-dicyanoanthracene.

## 6. Other methods

To synthesise the substituted piperideine **111** from the 2,5-dihydropyridine derivative **109**, the modified Zelinsky method of irreversible catalysis has been used.[106] In the presence of Pd/C under an inert atmosphere, the compound **109** undergoes an exothermic reaction with cyclohexene giving a mixture of the pyridine derivative **110** (yield 68.4%) and the piperideine derivative **111** (yield 10.6%).

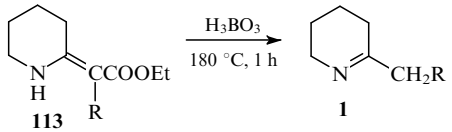


The reaction of 2,6-diphenylpyridine with metallic potassium gives rise to a mixture of *cis*-2,6-diphenylpiperidine **112a**, *trans*-2,6-diphenylpiperidine **112b** and 2,6-diphenyl-3,4,5,6-tetrahydropiperidine **1d**.[107]



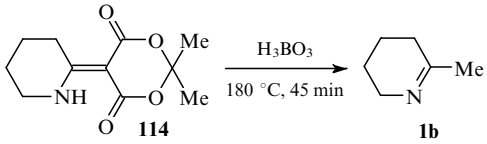
At 25 °C, the compounds **112** are the main reaction products (total yield 34%, **112a** : **112b** ratio ~1 : 2), while the imine **1d** is formed in 11% yield. At −75 °C, the yield of **1d** increases to 31%, while the compounds **112** are formed in 21% yield (the **112a** : **112b** ratio is ~1.5 : 1).[107]

When substituted piperideines **113** are heated with boric acid, hydrolysis of the ester group, decarboxylation and subsequent isomerisation with double bond migration occur to give the $\Delta^1$-piperideines **1** in good yields.[10, 108]

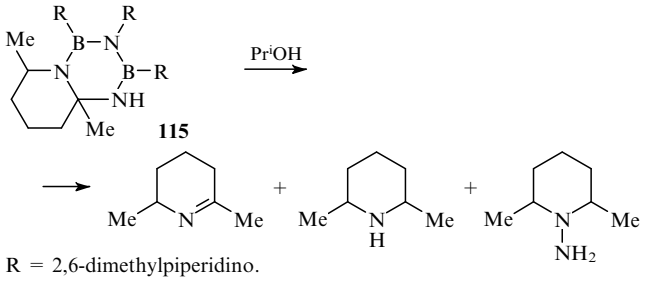


R = H (70%), Me (65%), $PhCH_2$ (70%), $CH_2=CH(CH_2)_8$ (70%), $Me(CH_2)_9$ (80%).

Under the same conditions, compound **114** is converted into 2-methyl-3,4,5,6-tetrahydropyridine **1b** in a yield of only 47%.[109]

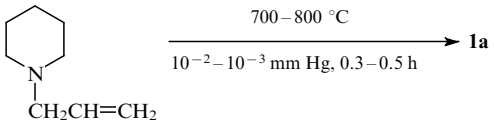


The reaction of compound **115** with isopropyl alcohol gives 2,6-dimethyl-3,4,5,6-tetrahydropyridine, in addition to the piperidine derivatives.[110]

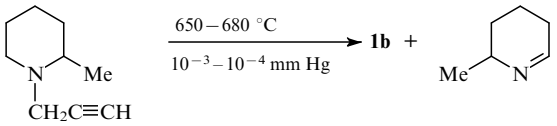


R = 2,6-dimethylpiperidino.

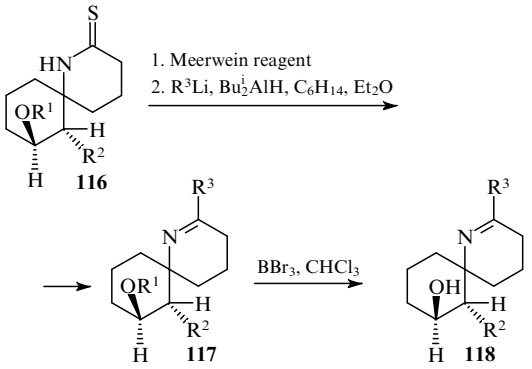
Under conditions of vacuum flash pyrolysis, *N*-allylpiperidine is converted into 2,3,4,5-tetrahydropyridine **1a**.[111]



Under similar conditions, 2-methyl-1-(propyn-3-yl)piperidine is converted into a mixture of the imine **1b** and 2-methyl-2,3,4,5-tetrahydropyridine (quantitative yield; ratio 5 : 1). The imine **1b** was isolated in a pure state in 54% yield using preparative TLC.[112]

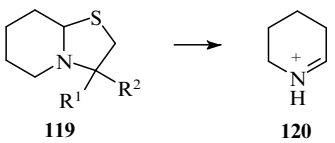


On treatment with the Meerwein reagent, spiro compounds **116** (R′ = tetrahydropyran-2-yl) are converted into thioimidates, which react with organolithium compounds in the presence of diisobutylaluminium hydride giving 1-azaspiro[5.5]undec-1-ene derivatives **117**. The protection of the hydroxyl group is removed by boron bromide; this gives compounds **118**.[113, 114]



$R^1$, $R^2$, $R^3$ = $C_5H_{11}$, $Pr^i$, $Bu^n$; $CH_2=CH(CH_2)_3$, tetrahydropyran-2-yl, $CH_2=CH(CH_2)_2$.

It was found that fragmentation of bicyclic compounds **119** under the action of the electron impact yields cation **120**.[115]

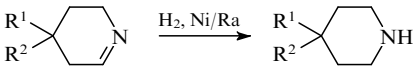


# IV. Reactions of $\Delta^1$-piperideines

## 1. Reduction

Addition of hydrogen to the double bonds of $\Delta^1$-piperideine can be attained by catalytic hydrogenation and also by other reduction techniques.

The addition of hydrogen to to the C=N bond in 4,4-disubstituted $\Delta^1$-piperideines in the presence of the Raney nickel (2–8 atm; 2 h) gives piperidine derivatives **121**.[85]

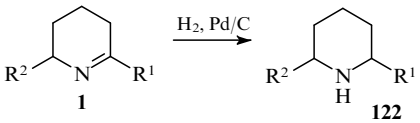



**121**

$R^1$—$R^2$ = $(CH_2)_5$ (90%), $CH_2CH=CH(CH_2)_2$, $CH(Me)CH_2CH=CHCH_2$, $(CH_2)_6$, $(CH_2)_{10}$, $CH_2O(CH_2)_3$, $CH_2C(Me)C=C(Me)(CH_2)_2$, $CH_2CH(OH)(CH_2)_3$;
$R^1$, $R^2$ = H, Me, Et, Pr, Ph, Bu, $C_9H_{19}$, cyclo-$C_5H_9$.

2,6,6-Trimethyl-3,4,5,6-tetrahydropyridine was converted into 2,6,6-trimethylpiperidine (yield 87%) by hydrogenation over the Raney nickel at 80 °C and 100 atm.[33]

2,6-Disubstituted $\Delta^1$-piperideines **1** are hydrogenated to the corresponding piperidine derivatives **122** in the presence of palladium supported on carbon.[98]



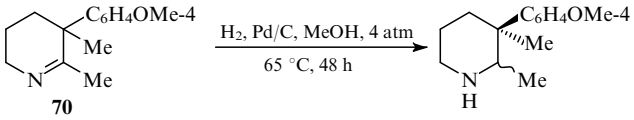

**1** **122**

$R^1$, $R^2$ = H, Me, Pr, Bu, Ph.

2,6-Dimethyl-3,4,5,6-tetrahydropyridine is hydrogenated over Pd/C in the presence of 10% hydrochloric acid over a period of 35 h to give 2,6-dimethylpiperidine in 74.5% yield.[55]

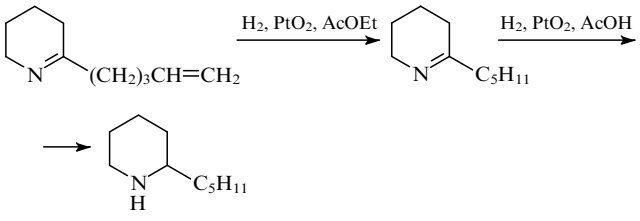
The heat of hydrogenation of the piperideine trimer to piperidine over Pd/C was found to be $-30.2\pm0.5$ kcal mol$^{-1}$; this value was used to estimate the enthalpy of hydrogenation of monomeric piperideine **1a**, $\Delta H^0 = -20.8$ kcal mol$^{-1}$.[116]

Hydrogenation of 2,3-dimethyl-3-(4-methoxyphenyl)-$\Delta^1$-piperideine **70** over Pd/C in methanol affords equal amounts of diastereoisomeric 2,3-dimethyl-3-(4-methoxyphenyl)piperidines.[84]

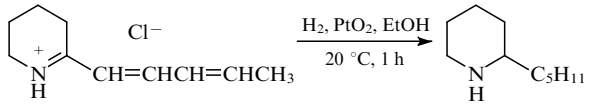



**70**

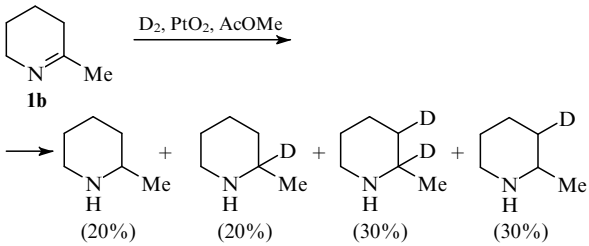
Stepwise hydrogenation of 2-(pent-4-en-1-yl)-3,4,5,6-tetrahydropyridine to 2-pentylpiperidine has been reported.[54] Hydrogenation was carried out in the presence of $PtO_2$. In the first stage, a hydrogen molecule adds to the double bond of the substituent to give 2-pentyl-3,4,5,6-tetrahydropyridine, which is subsequently converted into 2-pentylpiperidine by hydrogenation over $PtO_2$ in acetic acid.




During hydrogenation of 2-(penta-1,3-dien-1-yl)-3,4,5,6-tetrahydropyridine over $PtO_2$ in ethanol at room temperature and atmospheric pressure, hydrogen adds to the three double bonds, and 2-pentylpiperidine is formed.[117]




Catalytic deuteration of 2-methyl-3,4,5,6-tetrahydropyridine **1b** was carried out over $PtO_2$ in methyl acetate. This yielded a complex mixture of products with different deuterium contents.[117]



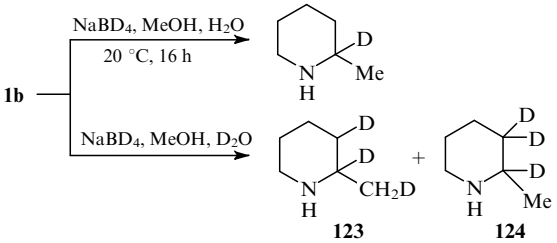

**1b**

The last two compounds result presumably from deuteration of 6-methyl-3,4,5,6-tetrahydropyridine, a tautomer of the imine **1b**.[118]

Most often, $\Delta^1$-piperideines are reduced by complex metal hydrides, lithium aluminium hydride or sodium borohydride.

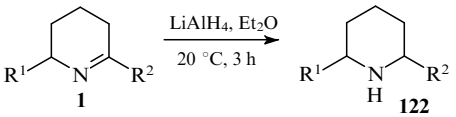
Treatment of the imine **1b** with $NaBD_4$ in aqueous methanol gives 2-deuterio-2-methylpiperidine in 80% yield.[118]

If the reaction of the imine **1b** with $NaBD_4$ is carried out in the presence of $D_2O$, a mixture of deuterated compounds, **123** and **124**, is produced.[117]




**123** **124**

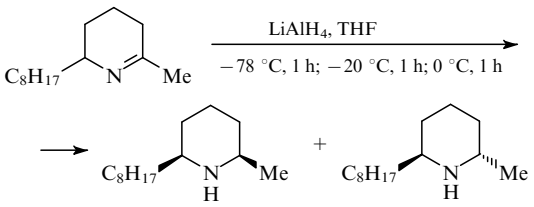
Reduction of the $\Delta^1$-piperideines **1** to the corresponding piperidine derivatives **122** has been attained by treatment with lithium aluminium hydride in ether at room temperature.[59]



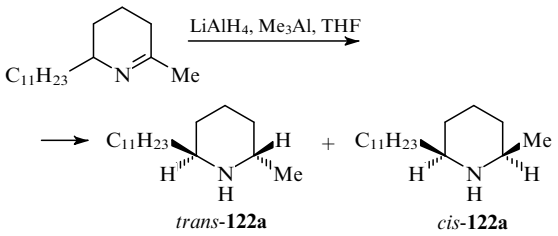

**1** **122**

$R^1$, $R^2$ = H, Me, $C_{11}H_{23}$, $PhCH_2$.

2-Methyl-6-octyl-3,4,5,6-tetrahydropyridine is reduced by lithium aluminium hydride in THF at −78 to 0 °C giving rise to a mixture of *cis*- and *trans*-isomers of the corresponding piperidine in 5 : 7 ratio; their overall yield is 70%.[57, 58]

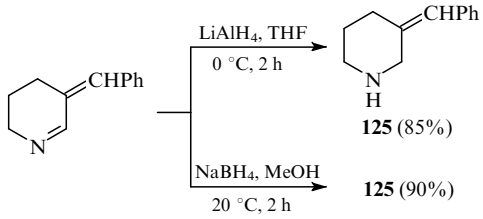



On treatment with lithium aluminium hydride and trimethylaluminium in hexane, 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine is reduced to give 2-methyl-6-undecylpiperidine [alkaloid (±)-solenopsine] as a mixture of diastereoisomers *trans*-**122a** and *cis*-**122a** in 95 : 5 ratio.[57, 58, 119]

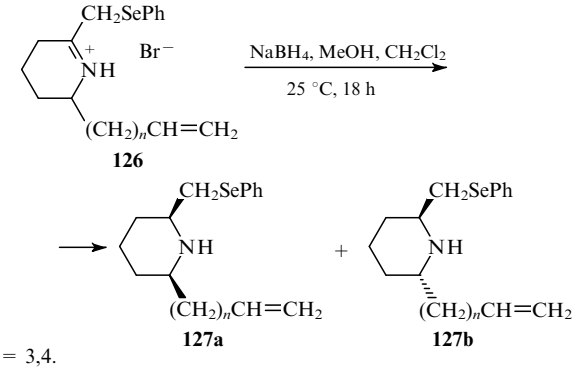



*trans*-**122a** *cis*-**122a**

When the benzylidene derivative of piperideine is treated with lithium aluminium hydride in ether or with sodium borohydride in methanol, only the C=N bond is reduced to give 3-benzylidenepiperidine **125**.[120]



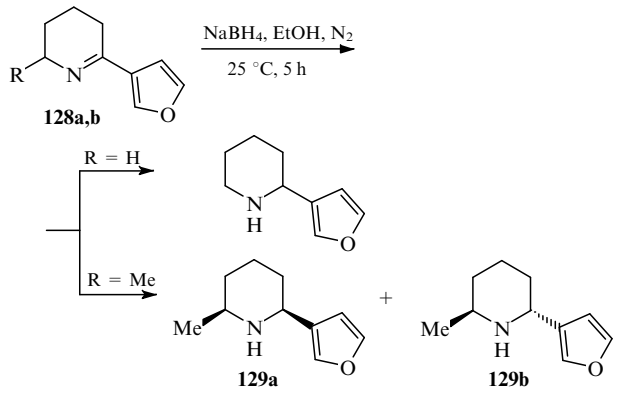

The reduction of compounds **126** by sodium borohydride occurs regioselectively, only the intracyclic bond being involved in the reaction. This affords a mixture of diastereoisomeric piperidines in which the *cis*-isomers **127a** predominates.[82]



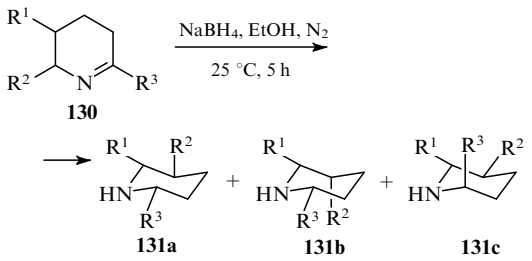

$n$ = 3,4.

The reduction of $\Delta^1$-piperideine **70** with sodium borohydride in methanol gives rise to a mixture of diastereoisomers of 2,3-dimethyl-3-(4-methoxyphenyl)piperidine (yield 70%).[83]

The reduction of $\Delta^1$-piperideines **128a,b**, containing a furyl substituent at the 2-position, has been studied.[121] The compound **128a** is converted into one reaction product, while the imine **128b** gives two isomeric products, **129a** and **129b**, in 91 : 9 ratio. Piperideine **130** is reduced by sodium borohydride yielding three isomeric piperidines [ratio **131a** : (**131b** + **131c**) = 85 : 15].

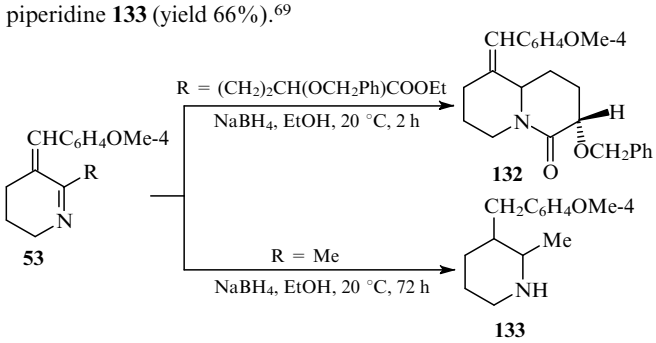



R = H (**128a**), Me (**128b**).

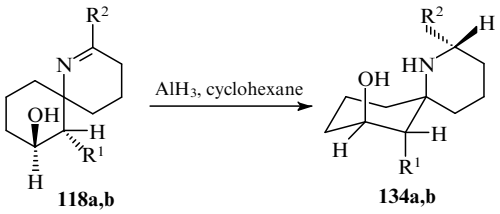



$R^1$ = $Me_2C{=}CHCH_2$, $R^2$ = Me, $R^3$ = 3-furyl.

The structure of the products of reduction of the compounds **53**, containing an intracyclic C=N bond and an exocyclic C=C bond at the 3-position, depends on the nature of the substituent. When R = $(CH_2)_2CH(OCH_2Ph)COOEt$, reduction of the C=N bond and subsequent cyclisation occur over a period of 2 h to give bicyclic derivative **132** (yield 70%). When R = Me, both double bonds are reduced over a period of 72 h affording substituted piperidine **133** (yield 66%).[69]

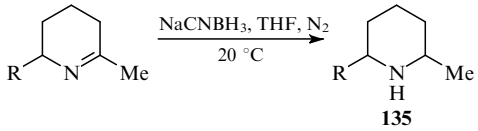



Alkaloids of the nicotoxin group have been prepared by selective hydrogenation of the C=N bond in the $\Delta^1$-piperideines **118** by aluminium hydride in cyclohexane.[113, 114]



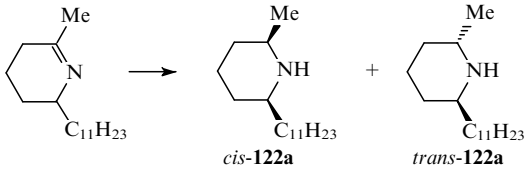

$R^1$ = Bu, $R^2$ = $C_5H_{11}$ (**a**);
$R^1$ = $(CH_2)_2CH{=}CH_2$, $R^2$ = $(CH_2)_3CH{=}CH_2$ (**b**).

6-Alkyl-2-methyl-3,4,5,6-tetrahydropyridines are reduced on treatment with sodium cyanoborohydride in THF in a citrate–phosphate buffer solution to give piperidines **135** in high yields.[74]




R = Pr (81%), $C_{11}H_{23}$ (95%), $(MeO)_2CH(CH_2)_3$ (82%).

Study of the reduction of 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine by various reducing reagents and solvents has demonstrated that, depending on the reaction conditions, the ratio of the resulting *cis*- and *trans*-2-methyl-6-undecylpiperidines varies from 99 : 1 to 5 : 95. The results are summarised in Table 1.[102]

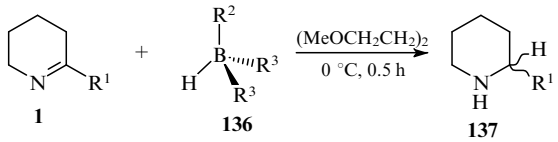



*cis*-**122a** *trans*-**122a**

**Table 1**. Reduction of 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine.[102]

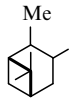
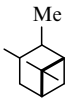
| Reducing agent | Solvent | Ratio *cis*-**122a** : *trans*-**122a** |
|---|---|---|
| $Bu^i_2AlH$ | $CH_2Cl_2$ | 99 : 1 |
| $LiAlH_4$ – NaOMe | THF | 99 : 1 |
| $NaCNBH_3$ – HCl | MeOH | 98 : 2 |
| $LiAlH_4$ – $Ti(OPr^i)_4$ | THF | 90 : 10 |
| BuLi – $Bu^i_2AlH$ | $Et_2O$ | 83 : 17 |
| $LiAlH_4$ – LiCl | THF | 80 : 20 |
| $LiAlH_4$ – $NiCl_2$ | THF | 75 : 25 |
| $LiAlH_4$ – $TiCl_3$ | THF | 67 : 33 |
| $LiAlH_4$ | $CH_2Cl_2$(THF) | 67 : 33 |
| $LiAlH_4$ | $Et_2O$ | 20 : 80 |
| $Mg(AlH_4)_2$ | $Et_2O$ | 33 : 67 |
| $LiAlH_4$ – $BF_3 \cdot Et_2O$ | $Et_2O$ | 33 : 67 |
| $LiAlH_4$ – $Bu^i_3Al$ | THF | 6 : 94 |
| $LiAlH_4$ – $Me_3Al$ | $MeO(CH_2)_2OMe$ | 6 : 94 |
| $LiAlH_4$ – $Me_3Al$ | THF | 5 : 95 |
| $LiAlH_4$ – $TiCl_4$ | THF | 25 : 75 |
| $LiAlH_4$ – $Me_3Al$ | $Et_2O$ | 13 : 87 |

When 2-alkyl-$\Delta^1$-piperideines react with lithium alkyl(or phenyl)bis(isopinocamphyl)borates **136**, compounds **137** of the (+)-(*S*)- or (−)-(*R*)-series are formed, depending on the stereochemistry of the substituent $R^3$ in the borate.[30] The results obtained are listed in Table 2.

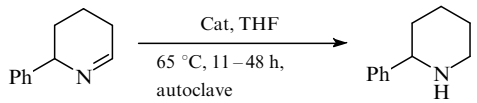



**1** **136** **137**

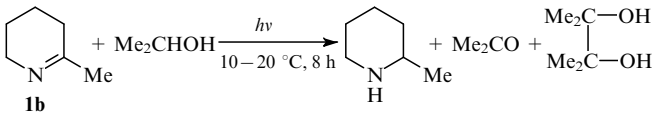
**Table 2**. Hydroboration of $\Delta^1$-piperideines.

| $R^1$ | $R^2$ | $R^3$ | Isomer [*ee* (%)] | Yield (%) |
|---|---|---|---|---|
| Me | Bu |  | *R* (25) | 37 |
| Me | Ph | | *R* (10) | 32 |
| Et | Bu | | *R* (5) | 48 |
| Pr | Bu | | *R* (4) | 75 |
| Pr | Me | | *R* (11) | 82 |
| Me | Bu |  | *S* (22) | 32 |
| Me | Ph | | *S* (10) | 30 |

Catalytic hydrogenation of 2-phenyl-3,4,5,6-tetrahydropyridine is highly enantioselective. The catalyst was prepared by treating (*R*,*R*)-ethylene-1,2-bis($\eta^5$-4,5,6,7-tetrahydroinden-1-yl)-titanium-(*R*)-1,1′-bisnaphthalene-2,2′-diolate with butyllithium and phenylsilane. The *R*-isomer of 2-phenylpiperidine was obtained in 70% – 81% yield with *ee* 95% – 98%.[90, 122, 123]




The irradiation of a mixture of 2-methyl-3,4,5,6-tetrahydropyridine **1b** and propan-2-ol with the light of a Hanovia-450W high-pressure mercury lamp through a quartz filter results in a redox process giving 2-methylpiperidine (yield 72%), acetone and the product of reductive dimerisation of acetone, 2,3-dimethylbutane-2,3-diol.[124]

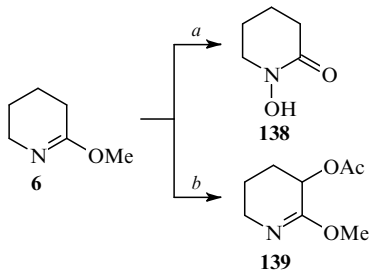



**1b**

## 2. Oxidation

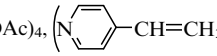
On treatment with 3-chloroperbenzoic acid at −60 °C, 2-methoxypiperideine **6** is oxidised to 1-hydroxypiperid-2-one **138** (yield 87%).[125]

3-Acetoxy-2-methoxy-3,4,5,6-tetrahydropyridine **139** was obtained (yield 79%) upon oxidation of the imine **6** with lead tetraacetate in the presence of the polymer of 4-vinylpyridine.[126]

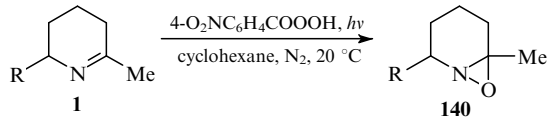



**6** **138** **139**

(*a*) 3-$ClC_6H_4COOH$, $CH_2Cl_2$, −60 °C;

(*b*) $Pb(OAc)_4$, , THF, 20 °C, 2 h; 50 °C, 1 h.

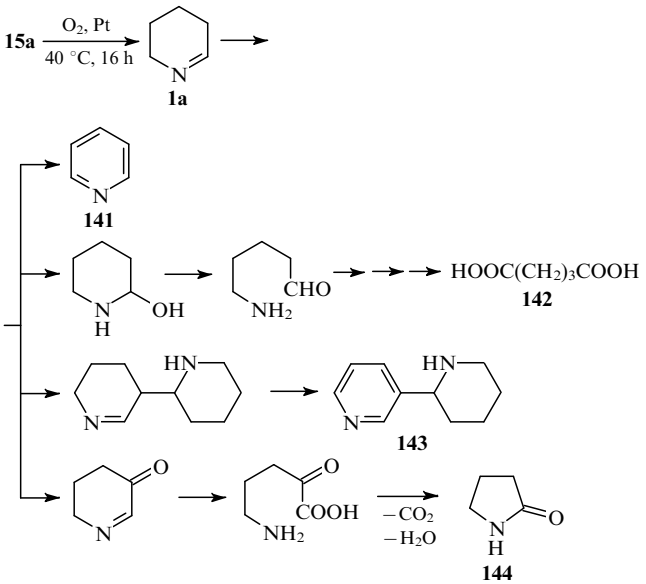
1-Aza-7-oxabicyclo[4.1.0]heptanes **140** are formed in almost quantitative yields when the $\Delta^1$-piperideines **1** are treated with 4-nitroperbenzoic acid on exposure to the light of a low-pressure mercury lamp ($\lambda$ = 2537 Å) under an inert atmosphere.[29]




**1** **140**

R = H, Me.

Passing oxygen through the piperidine **15a** for 16 h at 40 °C in the presence of a platinum catalyst (according to Adams) affords 2,3,4,5-tetrahydropyridine **1a**, which is further oxidised to give a broad range of products, as shown in the scheme

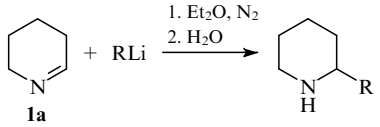



The following compounds were isolated from the oxidation products: piperideine (**1a**, 6%), pyridine (**141**, 8%), pentane-1,5-dioic acid (**142**, 10%), 3-(2-piperidyl)pyridine (**143**, 3%), pyrroli-

din-2-one (**144**, 7%), *N*-acetylpiperidine (8%) and *N*-formylpiperidine, resulting from acylation of piperidine with formic acid.[127]

## 3. Reactions with organometallic compounds

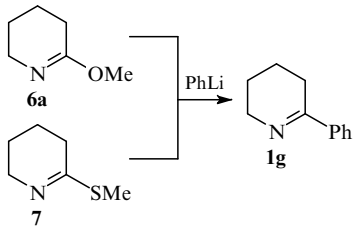
When unsubstituted piperideine **1a** is made to react with organolithium compounds, these reagents add to the C = N double bonds giving 2-substituted pyridine derivatives.[31]



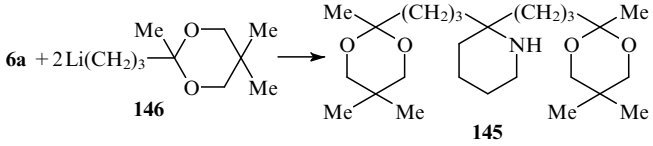

**1a**

| R | Temperature /°C | Time /min | Yield (%) |
|---|---|---|---|
| $Bu^n$ | 20 | 70 | 58 |
| $Bu^t$ | −80 | 60 | 63 |
| Ph | 20 | 30 | 55 |
| 3-pyridyl | −100, −40 | 60, 60 | 44 |

The $\Delta^1$-piperideine **1g** is formed in 50% yield in the reaction of the imidate **6a** with phenyllithium or thioimidate **7** with phenyllithium in the presence of diisobutylaluminium hydride.[121]



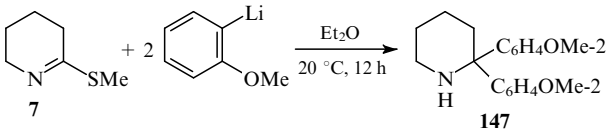

Piperidine derivative **145**, used as the initial compound in a total synthesis of the alkaloid (±)-porantherine, was prepared by the reaction of the imidate **6a** with two moles of organolithium derivarive **146**; the yield of **145** varied over a wide range depending on the reaction conditions.[128]



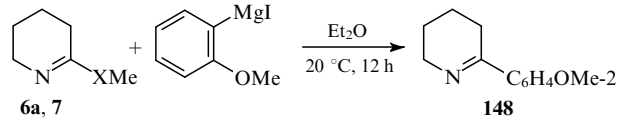

| Temperature /°C | Time /h | Solvent | Yield (%) |
|---|---|---|---|
| 0 | 24 | $Et_2O$ | 14.4 |
| 20 [a] | 1 | PhH, $Et_2O$ | 70.2 |
| 0 | 12 | pentane | 80.0 |
| 20 | 120 | pentane | 80.0 |

[a] The reaction was carried out under argon.

2-Methylthio-3,4,5,6-tetrahydropyridine **7** reacts with 2-methoxyphenyllithium at room temperature to give the bisarylation product, 2,2-bis(2-methoxyphenyl)piperidine **147**, its yield being only 2%.[129]



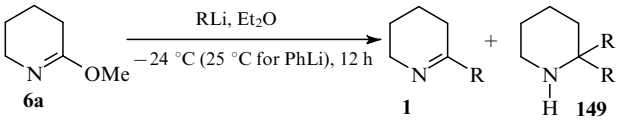

When the imidate **6a** and thioimidate **7** react with one equivalent of 2-methoxyphenylmagnesium iodide under the same conditions, the monoarylation product, 2-(2-methoxyphenyl)-3,4,5,6-tetrahydropyridine **148**, is formed.[129]




**6a**, **7** **148**

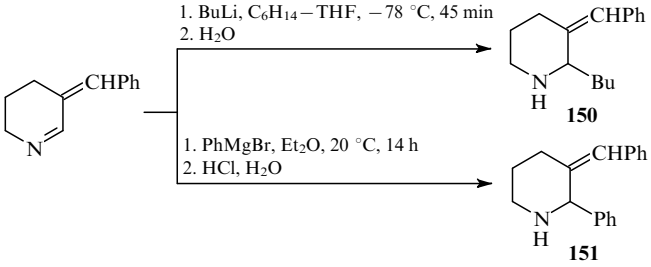
X = O (**6a**), S (**7**).

By varying the ratios of the reactants in the reaction of the imidate **6a** with organolithium compounds, one can synthesise selectively either only monosubstituted piperideines **1** or disubstituted piperidines **149**.[130]



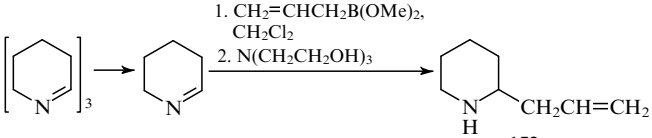

| R | Reactant ratio | Yield (%) | |
|---|---|---|---|
| | | **1** | **149** |
| Ph | 1 : 1 | 47 | – |
| Pr | 1 : 5 | – | 63 |
| Bu | 1 : 5 | – | 65 |
| $Bu^t$ | 1 : 5 | 68 | – |
| Ph | 1 : 5 | – | 60 |

3-Benzylidene-$\Delta^1$-piperideine **124** was made to react with butyllithium or with phenylmagnesium bromide; after quenching of the reaction mixtures, the corresponding 2-substituted compounds **150** (yield 95%) or **151** (yield 56%) were isolated.[120]



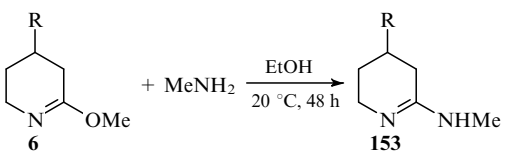

The reaction of 2-cyano-3,4,5,6-tetrahydropyridine with methylmagnesium iodide involves the C≡N bond and gives a mixture of 2-acetyl-3,4,5,6-tetrahydropyridine **10b** and 2-acetyl-1,2,3,4-tetrahydropyridine **10a** (ratio 4 : 1, total yield 44%).[17]

2-Allylpiperidine **152** has been prepared in 90% yield from the piperideine trimer and allyldimethoxyborane in the presence of triethanolamine.[131]




## 4. Reactions with amines and their derivatives

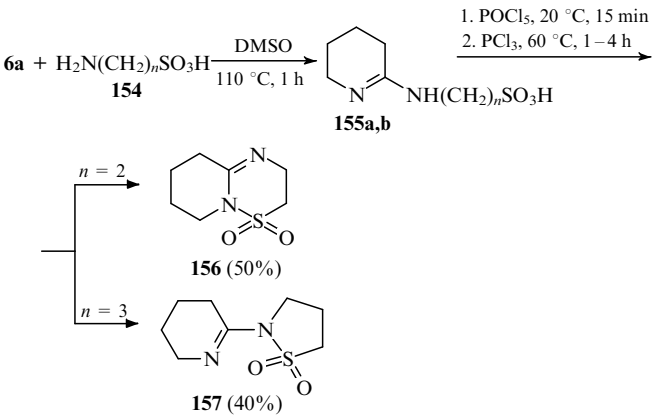
When the imidates **6** react with excess methylamine at room temperature, the methoxy group is substituted yielding aminoderivatives **153**.[87]



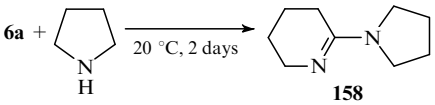

R = H, Me.

Treatment of 2-methoxy-3,4,5,6-tetrahydropyridine **6a** with diethylamine hydrochloride in methanol results in the formation of 2-dimethylamino-3,4,5,6-tetrahydropyridine.[132]

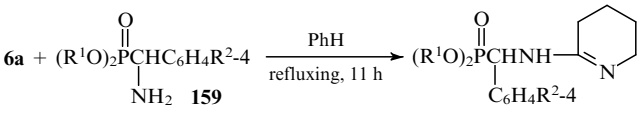
When the imidate **6a** is heated with aminoalkanesulfonic acids **154** in DMSO, compounds **155a,b**, resulting from substitution of the methoxy group, are formed (yields 79% and 90%, respectively). On treatment with $POCl_3$ and $PCl_5$, these products are converted into either bicyclic compound **156** or $\Delta^1$-piperideine **157**, depending on the number of methylene units in the initial amine.[133]




The imidate **6a** reacts with pyrrolidine for 2 days at 20 °C to give 2-(pyrrolidin-1-yl)-3,4,5,6-tetrahydropyridine **158** in 94% yield.[120]

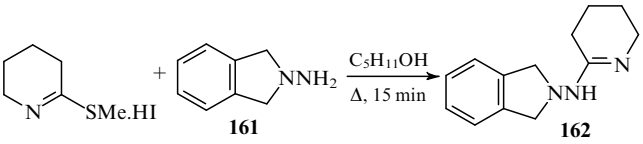



Refluxing of phosphorus-containing primary amines **159** with the imidate **6a** in benzene gives rise to $\Delta^1$-piperideine **160**.[134]

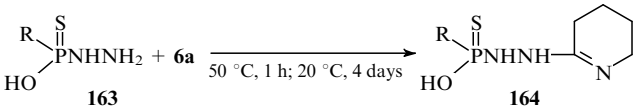



$R^1$ = Et: $R^2$ = H, OMe.

The reaction of 2-methylthiopiperideine hydroiodide with cyclic hydrazine derivative **161** in boiling pentyl alcohol yields compound **162**, which has been patented as a hypotensor.[135]

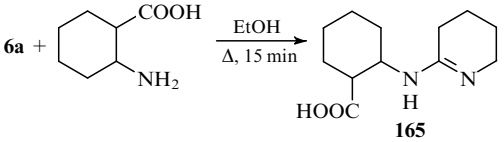



The reactions of the imidate **6a** with *O*-alkyl phosphorothioic acid hydrazides **163** occur as substitution of the methoxy group by the hydrazide residue and give *N*,*N*′-disubstituted hydrazine derivatives **164**.[136]

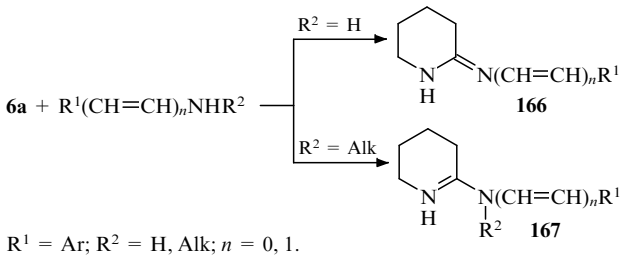



R = OMe (44%), OEt (24%).

The reaction of the imidate **6a** with *cis*-2-aminocyclohexanecarboxylic acid in boiling ethanol affords the product of substitution of the methoxy group **165** in 84% yield.[137]

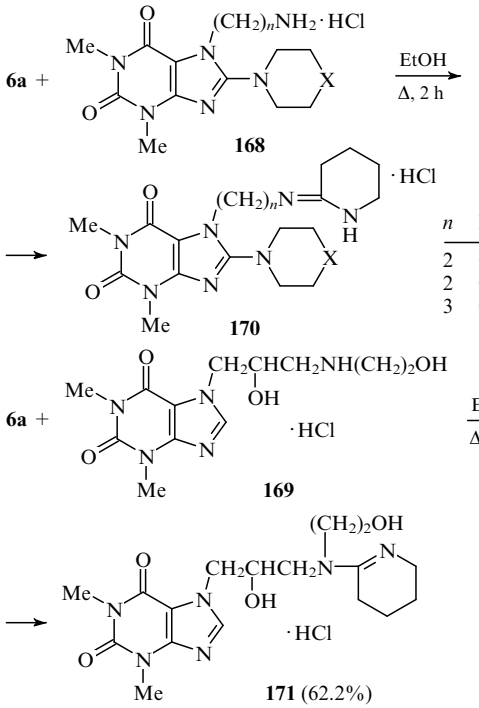



Compounds **166** and **167**, patented as animal growth stimulators, have been prepared by the reaction of the imidate **6a** with primary or secondary amines.[138]



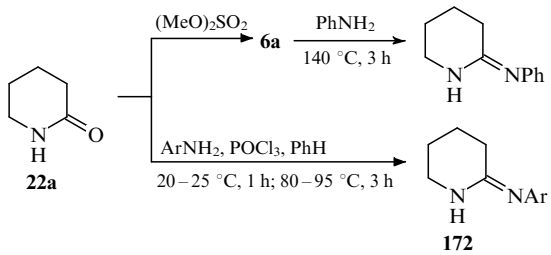

$R^1$ = Ar; $R^2$ = H, Alk; $n$ = 0, 1.

On refluxing in ethanol, the imidate **6a** reacts with hydrochlorides of primary (**168**) or secondary (**169**) amines being thus converted into compounds **170** or **171**.[139, 140]



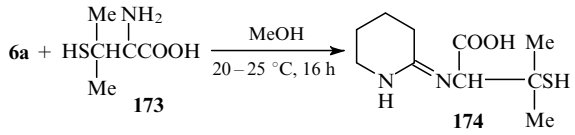

| n | X | Yield (%) |
|---|---|---|
| 2 | $CH_2$ | 50 |
| 2 | O | 64 |
| 3 | O | 65 |

2-Phenyliminopiperidine has been synthesised from the lactone **22a**; first, the lactone was converted into the imidate **6a** by treatment with dimethyl sulfoxide, and then the latter was made to condense with aniline. A large number of analogous aryliminopiperidines **172** were prepared directly from the lactone **22a** by its condensation with arylamines in the presence of $POCl_3$.[141]

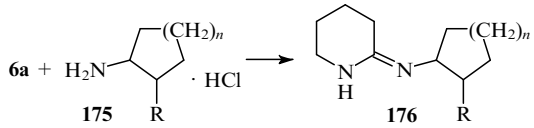



Ar = 2-$ClC_6H_4$ (44.7%), 4-$ClC_6H_4$ (50.9%), 4-$BrC_6H_4$ (75.9%), 4-$MeOC_6H_4$ (39.2%), 2,4-$Cl_2C_6H_3$ (62.6%), 3,4-$Cl_2C_6H_3$ (78.9%), 3-Cl-4-Me-$C_6H_3$ (28.8%), 3-$F_3CC_6H_4$ (63.2%).

Penicillamine **173** reacts with the imidate **6a** at room temperature to give Schiff's base **174** in 48% yield.[142]

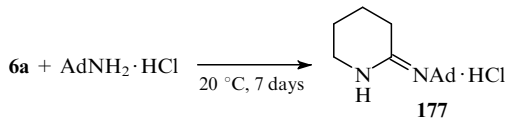


Piperidine derivatives **176** have been synthesised by the reaction of the imidate **6a** with hydrochlorides of alicyclic amines **175**.[143]



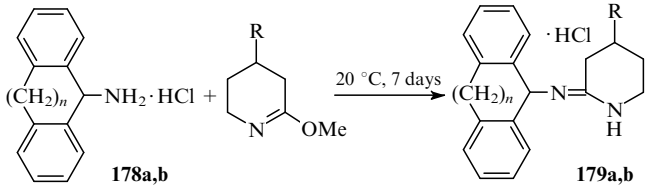
$n$ = 1–3; R = Ph, 4-$ClC_6H_4$, cyclohexyl, 2-thienyl.

Adamantyliminopiperidine hydrochlorides **177**, which exhibit antiviral and antidiabetic activities, are produced by the reaction of the imidate **6a** with adamantylamine hydrochlorides.[144, 145]



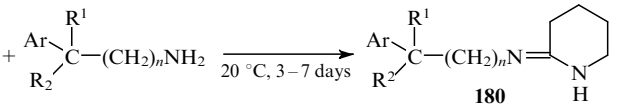
Ad is 1-adamantyl or 2-adamantyl.

The condensation of 9-aminofluorene (**178a**)[146, 147] or 5-aminodibenzocycloheptane (**178b**)[147, 148] hydrochlorides with the $\Delta^1$-piperideines **6** gives compounds **179a**,**b**, possessing hypoglycemic,[146, 147] antiphlogistic,[147, 148] anticoagulant and diuretic [146–148] properties.



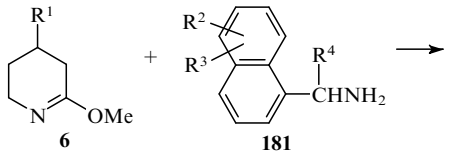
$n$ = 0 (**a**), 2 (**b**); R = H, Bu.

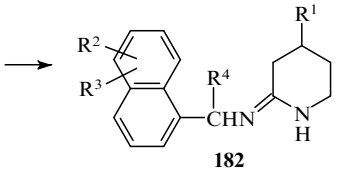
Amidines **180**, which have been recommended as anticoagulants and diuretics [147, 149–151] and also possess hypoglycemic activity [152, 153] or are used in the synthesis of hypoglycemic preparations,[147] are obtained by the reaction of the imidate **6a** with alkylaromatic amines.



$R^1$ = H, Pr; $R^2$ = Ph, 4-$ClC_6H_4$, 3-$F_3CC_6H_4$, cyclo-$C_3H_5$;
Ar = Ph, 4-$FC_6H_4$, 2-$ClC_6H_4$, 3-$ClC_6H_4$, 4-$ClC_6H_4$, 4-$Pr^iC_6H_4$, 3-$F_3CC_6H_4$, 4-$F_3CC_6H_4$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-$BuOC_6H_4$, 4-$PhOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$;
$n$ = 0, 1, 2.

A series of piperidine derivatives **182** have been synthesised from the piperideines **6** and primary (1-naphthyl)alkylamines **181** or their hydrochlorides.[154]

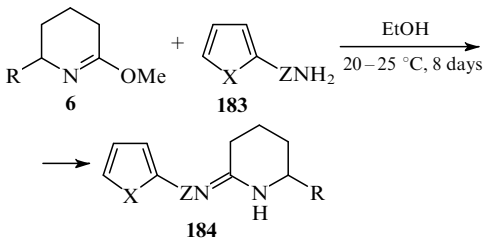




$R^1$ = H, $Bu^t$; $R^2$ = H: $R^3$ = H, 2-Me, 4-Cl, 4-F; $R^2$ = 5-Me, $R^3$ = 8-Me; $R^4$ = H, Me, $Pr^i$, $Bu^n$, Ph, 2-$MeC_6H_4$.

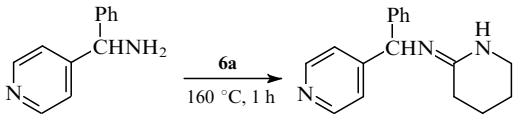
The compounds **182** exhibit hypoglycemic, diuretic and anticoagulant activities.[154]

Condensation of substituted imidates with hydrochlorides of primary amines **183**, containing a furyl or a thienyl substituent, results in the synthesis of amidine hydrochlorides **184**, which possess hypoglycemic activity.[38, 155]

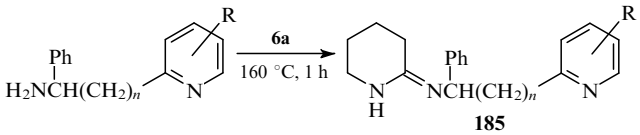


X = O, R = H, Z = $CHCH_2Ph$;
X = S, R = H, Z = cyclo-$C_3H_5$, C(Me)Et;
X = O, S, R = H, Me, Z = $CH_2$, CHPh, $(CH_2)_3$, $CH_2CH(Et)$, cyclo-$C_3H_5$, $CH_2CH(Me)$, $CH(Me)CH_2CH_2$.

On heating without a solvent, α-(4-pyridyl)benzylamine reacts with the imidate **6a** to give 2-[α-(4-pyridyl)benzylimino]piperidine in 48% yield.[156]

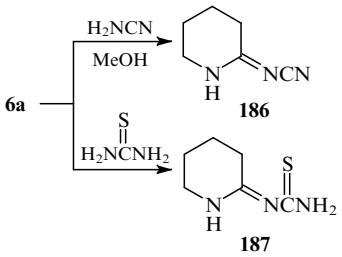


Compounds **185** have been synthesised by the condensation of **6a** with the corresponding primary amines under similar conditions.[156]



| $n$ | R | Yield (%) |
|---|---|---|
| 0 | H | 52 |
| 0 | 4-Me | 80 |
| 0 | H | 72 |
| 1 | H | 43 |

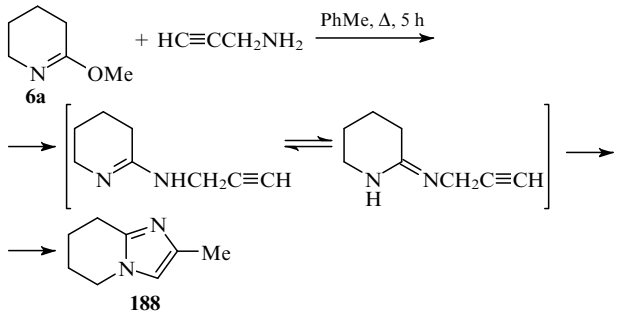
2-Cyanoiminopiperidine **186** has been prepared in 91% yield by the reaction of the imidate **6a** with cyanamide at room temperature.[157] Piperidine derivative **187** is formed in 72% yield upon condensation of **6a** with thiourea.[158]



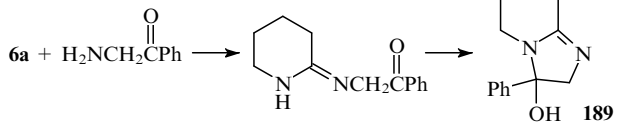
Compounds containing a primary amino group and a triple carbon–carbon bond or a carbonyl group at the 1- and 3-posi-

tions react with the imidate **6a** with cyclisation giving five-membered heterocycles.

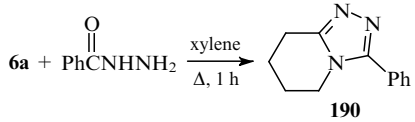
The product of condensation of the imidate **6a** with prop-2-ynylamine, which exists as two tautomers, cyclises *in situ* to give 8-methyl-1,7-diazabicyclo[4.3.0]nona-6,8-diene **188** (yield 52%).[159]



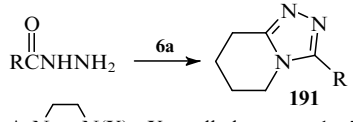
The product of condensation of **6a** and aminoacetophenone undergoes spontaneous cyclodehydration yielding bicyclic derivative of 2-imidazoline **189**.[160]



Refluxing of benzoic acid hydrazide with the imidate **6a** in xylene affords 9-phenyl-1,7,8-triazabicyclo[4.3.0]nona-6,8-diene **190**.[161]



Synthesis of 1,7,8-triazabicyclo[4.3.0]nona-6,8-diene derivatives **191** from acylhydrazides and the imidate **6a** has been patented.[162, 163]

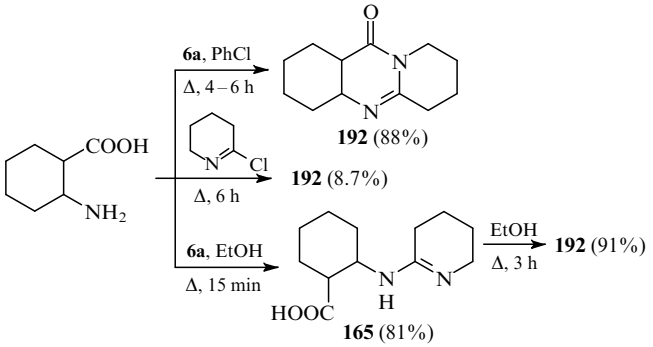


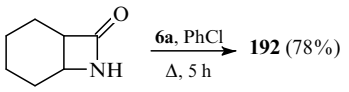
R = ArN N(X)$_n$; X = alkylene; $n$ = 1–5.

The compounds **191** are recommended as tranquilizers,[163] remedies against glaucoma [162, 163] and schizophrenia.[162]

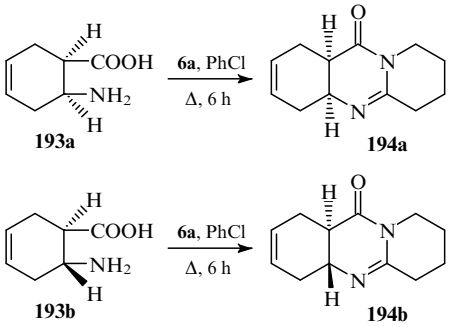
Cyclocondensation of $\Delta^1$-piperideines with compounds containing $NH_2$ (or NH) and carboxy (or alkoxycarbonyl, or nitrile) groups at neighbouring positions has been studied in detail. Polycyclic pyrimidine derivatives were synthesised in this way.

Thus heating of 2-aminocyclohexanecarboxylic acid with the imidate **6a** in chlorobenzene gives 1,2,3,4,4*a*,6,7,8,9,11*a*-decahydropyrido[2,1-*b*]quinazolin-11-one **192** in 88% yield.[137] A similar reaction with 2-chloropiperideine affords the compound **192** in a yield of only 8.7%.[164] Several more methods for the synthesis of the compound **192** from 2-aminocyclohexanecarboxylic acid or its lactam are described.[164]

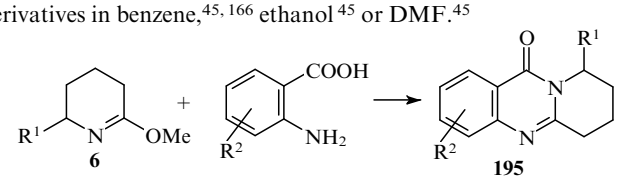




The cyclocondensation of the imidate **6a** with *cis*- and *trans*-2-aminocyclohex-4-enecarboxylic acids **193** occurs enantioselectively to give *cis*- and *trans*-1,4,4*a*,6,7,8,9,11*a*-octahydroquinazolin-11-ones **194a** and **194b**, respectively.[165]

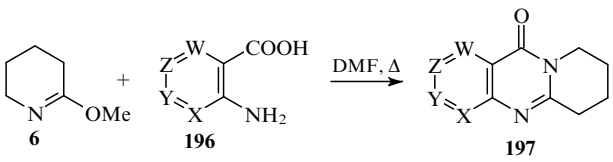


Tricyclic compounds **195** have been prepared in 64%–82% yields by heating the imidates **6** with anthranilic acid or its derivatives in benzene,[45, 166] ethanol [45] or DMF.[45]



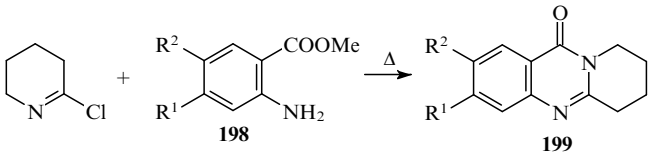
$R^1$ = H, Me; $R^2$ = H, 2-COOH, 2-COOEt.

Deoxyvasicinone analogues **197** have been prepared in relatively low yields by condensation of heterocyclic amino acids **196** with the imidate **6a** in boiling DMF.[167]



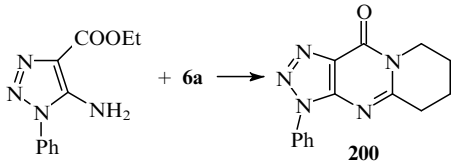
| X | Y | Z | W | Time /min | Yield (%) |
|---|---|---|---|---|---|
| N | CH | CH | CH | 10 | 12 |
| CH | N | CH | CH | 210 | 38 |
| CH | CH | CH | N | 150 | 20 |
| N | CH | CH | N | 120 | 12 |

The reaction of 2-chloro-3,4,5,6-tetrahydropyridine with methyl anthranilate derivatives **198** gives compounds **199**.[45, 168]

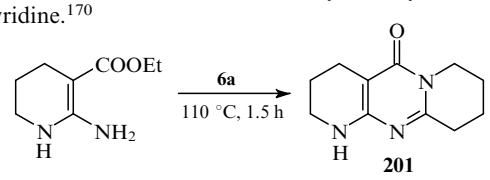


| $R^1$ | $R^2$ | Solvent | Time /h | Yield (%) | Ref. |
|---|---|---|---|---|---|
| H | COOMe | PhH | 5 | 53 | 45 |
| $NO_2$ | H | dioxane | 1 | 94 | 168 |

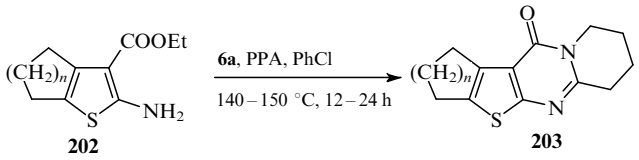
The imidate **6a** reacts with 5-amino-4-ethoxycarbonyl-1-phenyl-1,2,3-triazole to give compound **200** in 25% yield.[169]



1,2,3,4,7,8,9,10-Octahydro-5*H*-dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one **201** has been synthesised in 66% yield by heating the imidate **6a** with 6-amino-5-ethoxycarbonyl-1,2,3,4-tetrahydropyridine.[170]

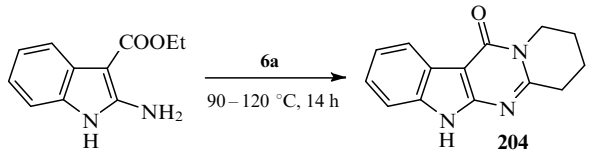



Tetracyclic compounds **203** are formed in 75% – 85% yield as a result of cyclocondensation of 2-methoxy-3,4,5,6-tetrahydropyridine **6a** with 2-amino-3-ethoxycarbonyl-4,5-polymethylenethiophenes **202** in the presence of polyphosphoric acid (PPA).[171]

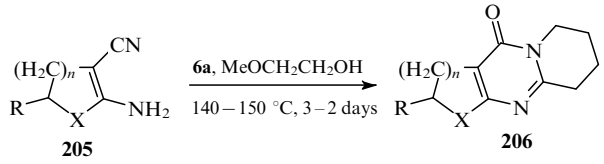



$n$ = 1, 2, 3.

Cyclocondensation of the imidate **6a** with 2-amino-3-ethoxycarbonylindole gives rise to 5,7,8,9,10,12-hexahydropyrido[1′,2′:1,2]pyrimido[4.5-*b*]indol-12-one **204** in 39% yield.[172]



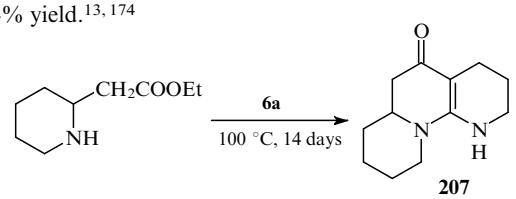

On heating in 2-methoxyethanol, compounds **205**, containing amino and nitrile groups in vicinal positions, enter into condensation with the imidate **6a** to give pyrimidin-4-one derivatives **206**.[173]



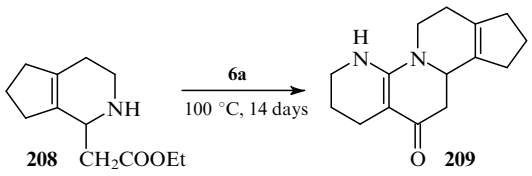

| R | *n* | X | Yield (%) |
|---|---|---|---|
| Me | 1 | O | 25 |
| H | 1 | S | 71 |
| H | 2 | O | 39 |

A well-studied synthesis of angular polynuclear heterocyclic compounds is cyclocondensation of $\Delta^1$-piperideines with cyclic compounds containing NH and $CH_2COOEt$ groups in vicinal positions.

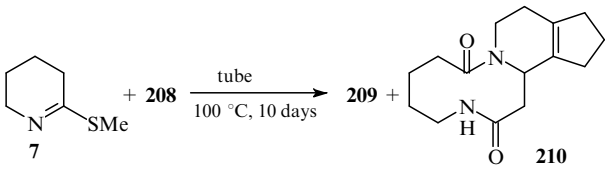
Thus prolonged heating of the imidate **6a** with 2-ethoxycarbonylpiperidine in a sealed tube affords 1,2,3,4,6,7,8,9,9*a*,10-decahydro-13*H*-isoquino[2,1-*a*]-[1,8]naphthiridin-13-one **207** in 54% yield.[13, 174]



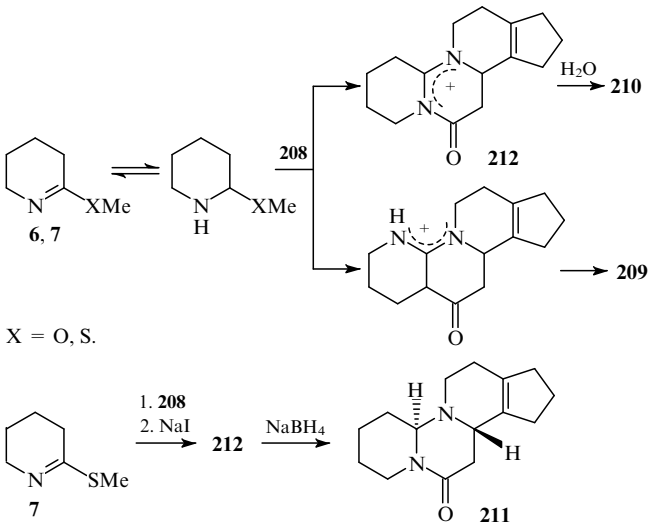

The yield of compound **209** formed in the condensation of the imidate **6a** with compound **208** under similar conditions is only 20%.[14, 174]



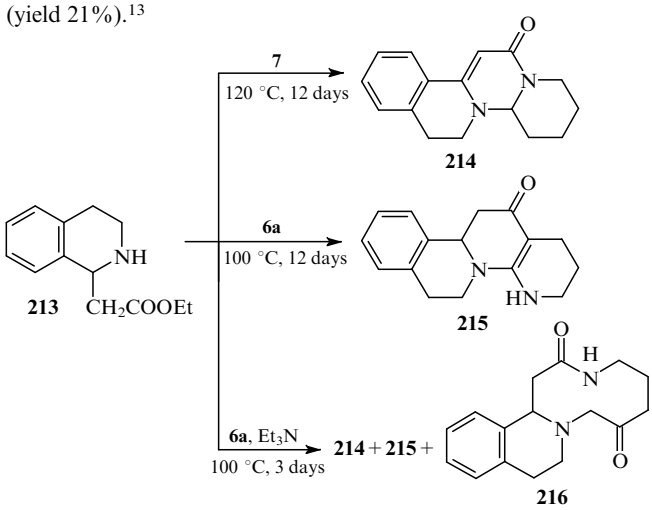

When the compound **208** is heated with methylthiopiperideine **7** in a tube at 100 °C, cyclic diamide **210** (yield 20.5%) is formed in addition to the condensation product **209** (yield 9%).[14]



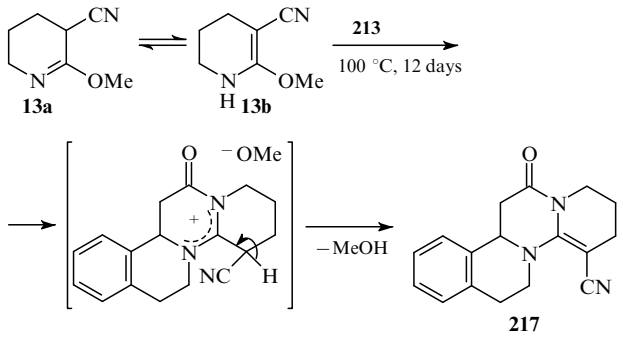

If the mixture formed upon the reaction of the compounds **7** and **208** is treated with 5% hydrochloric acid and then with sodium iodide and the reaction product is reduced with sodium borohydride in methanol (20 °C, 12 h), tetracyclic compound **211** is formed (yield 14%).[14] The following scheme was proposed for the formation of the compounds **209** – **211**:



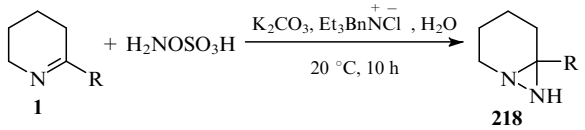

The reaction of 1-(ethoxycarbonylmethyl)-1,2,3,4-tetrahydroisoquinoline **213** with 2-methylthiopiperideine **7** on heating in a sealed tube affords compound **214** (yield 81.1%).[47] When the isoquinoline derivative **213** reacts with 2-methoxypiperideine **6a** under similar conditions, isomeric tetracyclic product **215** is produced.[13, 174] The reaction between **6a** and **213** carried out in the presence of triethylamine affords tricyclic product **216** (yield 19%), together with the compounds **214** (yield 14%) and **215** (yield 21%).[13]



2-Methoxy-3-cyano-3,4,5,6-tetrahydropyridine **13** exists as a mixture of two tautomers, **13a** and **13b**, and can be converted into different products depending on which tautomer is involved in the reaction. Since only compound **217** was isolated (yield 36%) upon the reaction of the $\Delta^1$-piperideine **13** with the isoquinoline derivative **213**, it is clear that in this case the imidate **13** reacts as the tautomer **13a**.

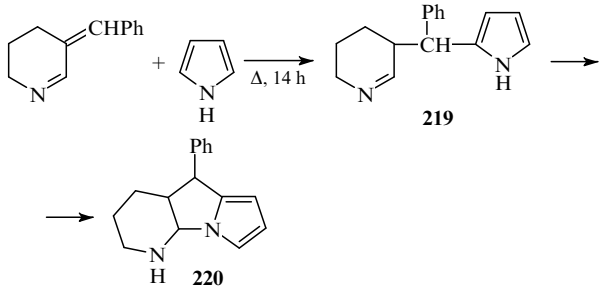



Treatment of the $\Delta^1$-piperideines **1** with *O*-hydroxylaminosulfonic acid in the presence of potassium carbonate and benzyltriethylammonium chloride results in the formation of 1,7-diazabicyclo[4.1.0]heptanes **218**.[23, 175]



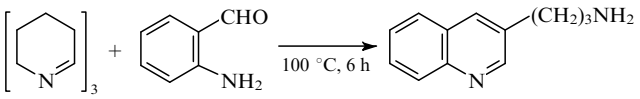

R = H (17%), Me (35%), CONHMe (52%).

The formation of tricyclic compound **220** (yield 32%) from 3-benzylidene-3,4,5,6-tetrahydropyridine and pyrrole can be represented as two consecutive reactions — addition to the C=C bond in the benzylidene derivative owing to the C–H group at the 2-position of pyrrole and cycloaddition, involving pyrrole nitrogen, to the C=N bond in the intermediate compound **219**.[120]

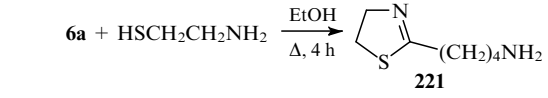



Some reactions of $\Delta^1$-piperideines with primary amines occur with opening of the heterocyclic ring.

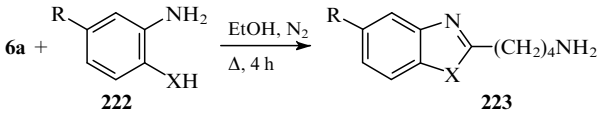
Thus heating of the piperideine trimer with 2-aminobenzaldehyde in a citrate buffer solution gives 3-(3-aminopropyl)quinoline in 70% yield.[80]




When the imidate **6a** is refluxed with thioethanolamine in ethanol, the heterocyclic ring is cleaved and 1,3-thiazoline derivative **221** is formed as the reaction product (yield 69%).[176]

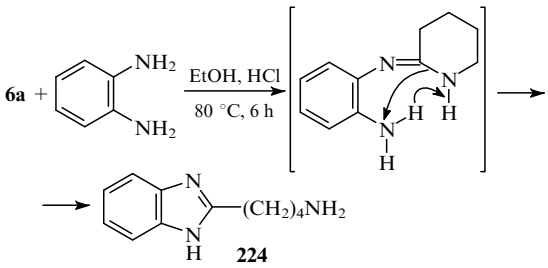



Compounds **223**, serving as the starting compounds in syntheses of medicines and pesticides, were prepared by condensation of the imidate **6a** with aniline derivatives **222** under an inert atmosphere. This reaction also proceeds with opening of the $\Delta^1$-piperideine ring.[176]

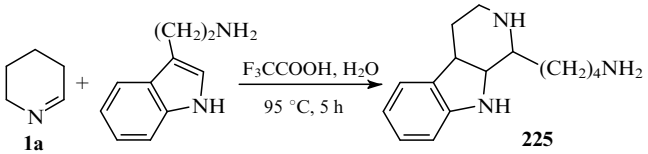



R = H, Me; X = O, S.

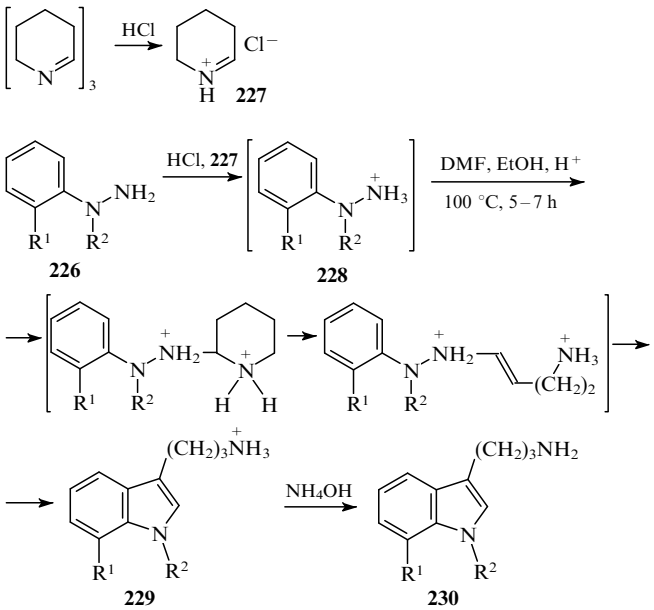
The reaction of the imidate **6a** with *o*-phenylenediamine in boiling ethanol in the presence of hydrogen chloride gives rise to compound **224** in 74% yield.[177]




The piperideine **1a** reacts with 3-(2-aminoethyl)indole in the presence of trifluoroacetic acid with opening of the imine heterocycle to give the alkaloid nazlinin **225** in 72% yield.[178]

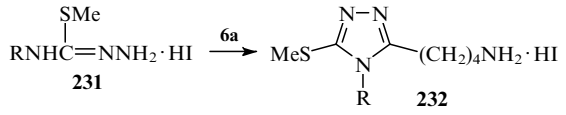



Arylhydrazines **226** and the piperideine trimer react in the presence of hydrogen chloride as salts **227** and **228** to give aminoalkylindole salts **229**. On treatment with aqueous ammonia, these products are converted into amines **230**.[179]




$R^1$ = H: $R^2$ = H (18%), Me (33%), Ph (23%), $CH_2Ph$ (52%);
$R^1$–$R^2$ = $CH(Me)CH_2CH_2$ (26%).

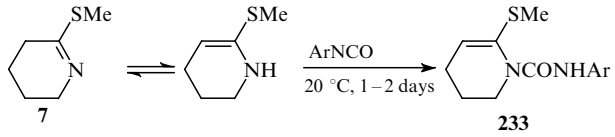
The reaction of 2-methoxypiperideine **6a** with *S*-methylisothiosemicarbazide hydroiodides **231** yields 1,3,5-triazole derivatives **232**.[180]



R = H, Ph.

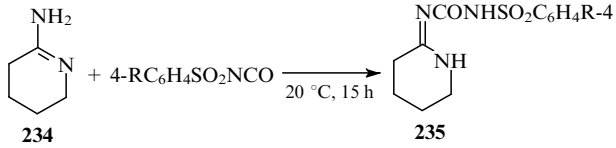
## 5. Reactions with isocyanates

2-Methylthio-3,4,5,6-tetrahydropyridine **7** reacts with aryl isocyanates ArNCO giving rise to compounds **233**.[181]



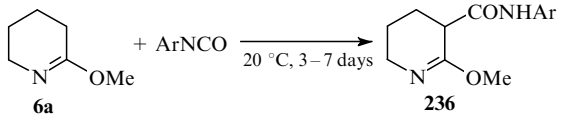
Ar = Ph (77%), 4-$ClC_6H_4$ (73%), 4-$EtOC_6H_4$ (82%).

Urea derivatives **235**, which exhibit high antiglycemic activity and decrease the level of glucose in blood, have been synthesised by the reaction of 2-amino-3,4,5,6-tetrahydropyridine with sulfonyl isocyanates **234**.[182]



R = H (42%), Me (49%), Cl (44%).

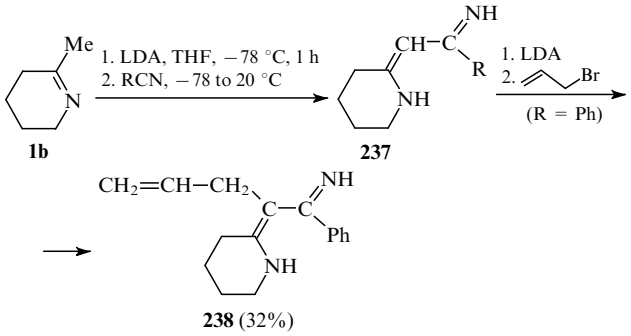
2-Methoxy-3,4,5,6-tetrahydropyridine **6a** reacts with aryl isocyanates to give piperideines **236**, containing an arylamide group.[12]



Ar = Ph (68%), 4-$ClC_6H_4$ (65%), 4-$EtOC_6H_4$ (70%).

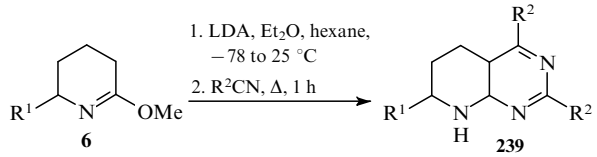
## 6. Reactions with nitriles

Treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA [183, 184] and subsequent reaction of the lithiated product with nitriles RCN results in the formation of heterodienes **237**. If allyl bromide is added to the reaction mixture together with benzonitrile, compound **238** is formed in 32% yield.



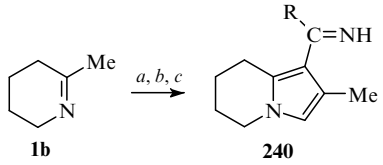
R = $C_5H_{11}$ (94%), Ph (66%), cyclo-$C_6H_{11}$ (56%).

By heating lithium derivatives of the imidates **6** with nitriles, bicyclic pyrimidine derivatives **239** have been synthesised in 17% – 26% yield.[185]



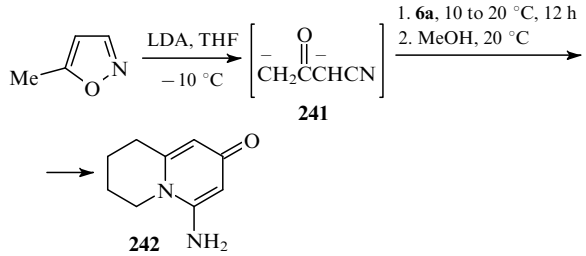
$R^1$ = H, Me; $R^2$ = Ph, 2-furyl, 2-thienyl, 2-pyridyl, 4-pyridyl.

Indolizine derivatives **240** have been obtained by the reaction of lithium derivatives of the imine **1b** with nitriles followed by treatment of the product with propargyl bromide.[186]



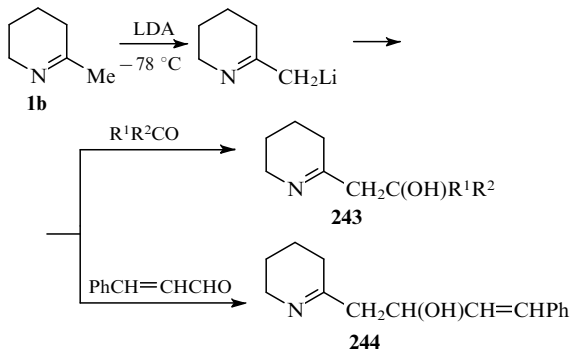
R = Ph (70%), cyclo-$C_3H_5$ (75%), 2-thienyl (71%);
(*a*) LDA, THF, −78 °C; (*b*) RCN, 3.5 h;
(*c*) $HC{\equiv}CCH_2Br$, −78 °C to −20 °C, 14 h.

The dianion **241**, generated on treatment of 5-methylisoxazole with LDA in THF, reacts with the imidate **6a** giving rise to 2-amino-1-azabicyclo[4.4.0]deca-2,5-dien-4-one **242** (yield 40%).[187]



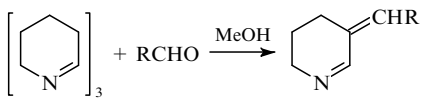
## 7. Reactions with aldehydes and ketones

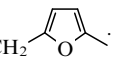
Alcohols **243** have been synthesised (yields 56% – 88%) by treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA and subsequent condensation of the resulting lithium derivative with carbonyl compounds.[188, 189] Treatment of the imine **1b** with LDA followed by the reaction with cinnamaldehyde gave secondary unsaturated alcohol **244**.[190]



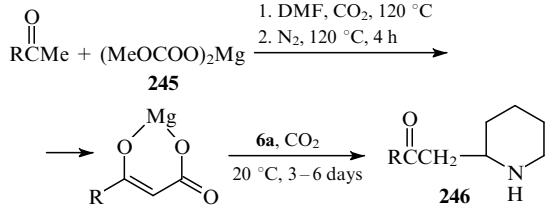
$R^1$ = H: $R^2$ = Me, Et, $Pr^i$, $Bu^t$, Ph; $R^1$ = $R^2$ = Me

The piperideine trimer readily reacts with aromatic aldehydes according to the crotonic condensation route to give arylmethylene derivatives.[120, 191, 192]



R = Ph, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$, 4-$NCC_6H_4$, 4-$O_2NC_6H_4$, $Pr^i$, , .

An interesting method for the synthesis of ketones **246**, containing a 2-piperidyl fragment, has been developed. The method consists in the reaction of methyl ketones RCOMe with magnesium methyl carbonate **246** and the imidate **6a**.[19,20,193] Methyl ketones and the salt **245** were kept in DMF in a flow of $CO_2$ at 120 °C, then $CO_2$ was displaced by nitrogen and the reaction mixture was held at 120 °C under nitrogen, the MeOH evolved being evaporated. After cooling the reaction mixture, the imine **6a** [193] or its α-trimer [19,20] was added, and the mixture was kept at 20 °C in an atmosphere of $CO_2$ for several days.

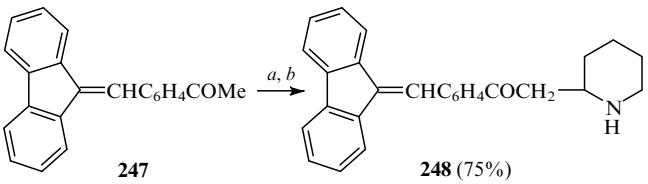


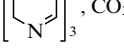
R = 2,5-$(MeO)_2C_6H_3$ (75%), 4-$PhSC_6H_4$ (50%), dibenzofuran-2-yl (32%), $Ph_2CH$ (37%), 4-$MeOC_6H_4CH=CH$ (43%), $PhCH=C(Me)CH=CH$ (48%), $PhCH=CHC_6H_4$ (57%), 4-pyridyl, (8%) 1-adamantyl (6%), Ph, 4-$MeOC_6H_4$, 4-$Bu^tC_6H_4$, 4-$Bu^nOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 4-$PhC_6H_4$, 3,4-$(MeO)_2C_6H_3CH=CH$, $PhCH=CMe$, $PhCH=CH$, 4-$MeSC_6H_4$, 4-(fluoren-9-ylidenemethyl)-phenylene (73%).

When the reaction between the imidate **6a** and 1-acetyladamantane is conducted for 28 h at 120 °C and then for 120 h at 20 °C, the yield of the ketone **246** (R = 1-adamantyl) increases to 37%.[19] The compounds **246** were obtained in low yields from ketones RCOMe with R = 4-$NCC_6H_4$ or 4-$Me_2NSO_2C_6H_4$. In the case of R = 4-$HOC_6H_4$, 4-$H_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-$HOOC_6H_4$ or 4-$HO_3SC_6H_4$, these products did not form at all.[19]

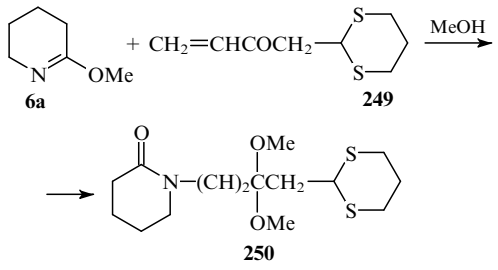
A similar procedure for the preparation of the ketones **246** at 20 °C over a period of 70 h has been described in a patent.[20] The synthesised compounds [R = 4-$MeOC_6H_4CH=CH$, $PhCH=CH$, 4-$Bu^tC_6H_4CH=CH$, 4-$Bu^nOC_6H_4CH=CH$, 3,4-$(MeO)_2C_6H_3CH=CHCH=CH$, 3,4,5-$(MeO)_3C_6H_2CH=CH$, 4-$PhC_6H_4CH=CH$, $PhCH=CHCH=CH$, 4-$MeSC_6H_4CH=CH$, $PhCH=C(Me)CH=CH$] were claimed to be anticoagulants.

Ketone **247** was introduced into the reaction with the salt **245** in an atmosphere of $CO_2$; then the piperideine trimer was added and condensation product **248** was obtained in 73% yield.[19]

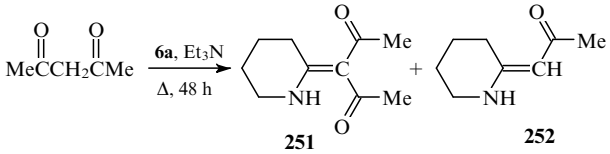


(*a*) **245**, $CO_2$, DMF, 120 °C, 4 h; (*b*) , $CO_2$, 24 h.

The reaction of the imidate **6a** with unsaturated ketone **249** at 20 °C for 24 h affords piperidin-2-one derivative **250** in 46% yield. At a low temperature (−15 °C for 62 h), the yield increases to 65%.[194]



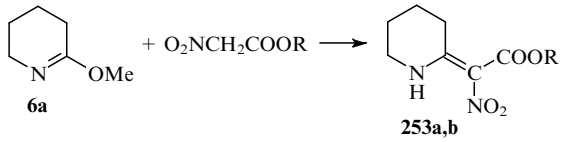
Condensation of acetylacetone with the imidate **6a** results in the formation of a mixture of compounds **251** and **252** (yields 26% and 25%, respectively).[195]



## 8. Reactions with acids and their derivatives

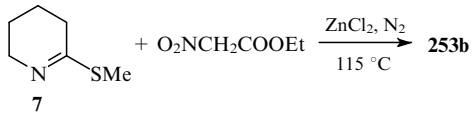
Carboxylic acids and their derivatives can be used as the methylene components in the condensation of $\Delta^1$-piperideine.

Thus the imidate **6a** condenses with methyl [196] or ethyl [197] nitroacetate giving rise to piperideine derivatives **253a**,**b**, which are used to synthesise insecticides.[196]

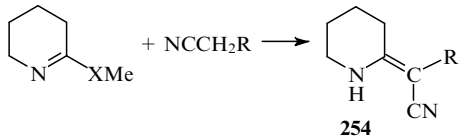


R = Me (**a**), Et (**b**).

The compound **253b** can also be synthesised by heating 2-methylthio-3,4,5,6-tetrahydropyridine **7** and ethyl nitroacetate in the presence of zinc chloride.[198]

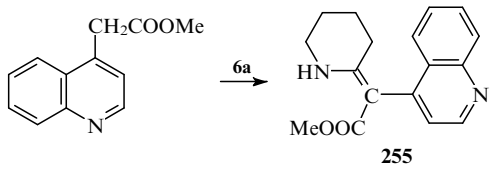


Condensation products **254** have been prepared in good yields from cyanoacetic acid derivatives and the imidate **6a** or the thioimidate **7**.[199–202]

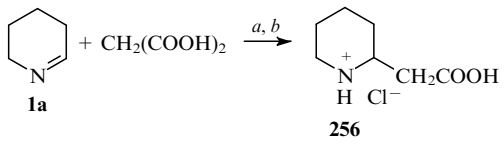


| X | R | Reaction conditions | Yield (%) | Ref. |
|---|---|---|---|---|
| O | $CONH_2$ | DMF, refluxing for 3 h | 77 | 199 |
| O | CONHPh | the same | 66 | 200 |
| O | $CONHCH_2Ph$ | " | 75 | 200 |
| O | CN | EtOH, 20 °C, 1 h | 79 | 201 |
| S | COOEt | diazabicyclononene, $N_2$, 120 °C, 12 h | 60 | 202 |

The reaction of the imidate **6a** with 4-methoxycarbonylmethylquinoline gives piperidine derivative **255**.[203]

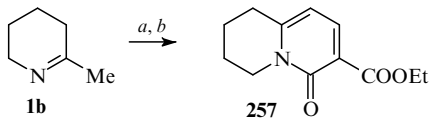



The hydrochloride of (2-piperidyl)acetic acid has been obtained in 69% yield by the reaction of 2,3,4,5-tetrahydropyridine **1a** with malonic acid in the presence of triethylamine at 50–60 °C.[204]




(*a*) $Et_3N$, $Me_2CO$, 50–60 °C, 2.5 h; (*b*) 20% HCl, $H_2O$.

Treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA and then with ethyl ethoxymethylenemalonate affords 9-ethoxycarbonyl-1-azabicyclo[4.4.0]deca-6,8-dien-10-one **257** in 90% yield.[205]




(*a*) LDA, hexane, THF, $N_2$, −30 °C, 15 min;
(*b*) $EtOCH=C(COOEt)_2$, −78 °C, 12 h.

The condensation of the imidates **6** with cyclic malonates **258** giving compounds **259** has been reported.[40, 195, 206, 207] The products **259** are recommended as pre- and post-emergent herbicides.[207] The reaction conditions and product yields are listed in Table 3.

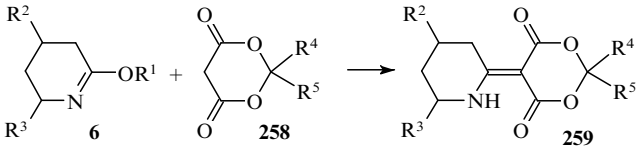


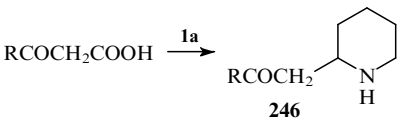

**Table 3**. Conditions of synthesis and yields of the compounds **259**.

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | *T*, °C | Time/ h | Yield (%) | Ref. |
|---|---|---|---|---|---|---|---|---|
| Me | H | H | Me | Me | see [a] | 12 | – | 40 |
| Me | H | Me | Me | Me | see [a] | 12 | 84 | 40 |
| Me | H | H | Me | Me | see [b] | 24 | 90 | 195 |
| Me | H | H | Me | Me | see [c] | 12 | 76 | 206 |
| Et | Me | H | Me | Me | 112–113 | 2 | 16 | 207 |
| Et | H | H | $Bu^t$ | H | 112–113 | 2 | – | 207 |
| Et | H | H | $Et_2CH$ | H | 112–113 | 2 | – | 207 |
| Et | H | H | $(CH_2)_5$ | | 112–113 | 2 | – | 207 |
| Et | H | Me | Me | Me | 112–113 | 2 | – | 207 |
| Et | H | H | $Pr^i$ | H | 112–113 | 2 | – | 207 |
| Et | H | H | Me | Me | 112–113 | 2 | – | 207 |

[a] Refluxing in $CHCl_3$ in the presence of $Ni(OAc)_2$; [b] refluxing in PhH in the presence of triethylamine and piperidine; [c] refluxing in the presence of triethylamine.

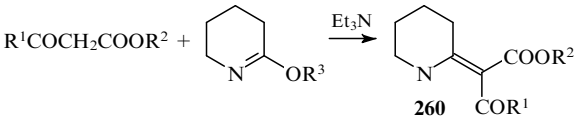
In the previous Section, we considered the reactions of the imine **1a** with ketones in the presence of magnesium methyl carbonate **245** to give the compounds **246**. These reactions involve the intermediate formation of magnesium enolates of β-oxo acids, which react with $\Delta^1$-piperideine **1a** to give, after decarboxylation, the compounds **246**. It is quite natural that in several other studies, it has been proposed to prepare the piperidine derivatives **246** by the condensation of the imine **1a** with β-oxo acids [77, 79, 208–210] or their sodium salts.[26, 27]

(±)-Isopelletierine (**246**, R = Me) was synthesised in a higher yield (42%–51%) by condensation of the imidate **1a** with sodium acetoacetate on refluxing in water for 4 h.[26, 27]




| R | Reaction conditions | Yield (%) | Ref. |
|---|---|---|---|
| Pr | 20 °C, 24 h, $H_2O$, pH 7 | – | 77 |
| Ph | the same | – | 77 |
| Me | " | 7 | 79 |
| 3,4-$(MeO)_2C_6H_3$ | 27 °C, 24 h, $H_2O$, pH 7 | 79 | 208, 209 |
| 3,4-$(MeO)_2C_6H_3$ | the same | 55 | 210 |
| 4-$MeOC_6H_4$ | " | 60 | 210 |

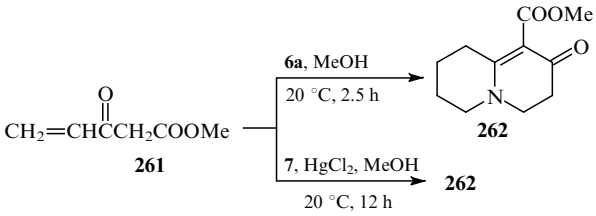
In the presence of $Et_3N$, esters of β-oxo acids condense with 2-methoxy-3,4,5,6-tetrahydropyridine, being thus converted into compounds **260**.[211, 212]



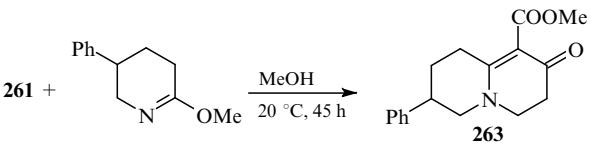

| $R^1$ | $R^2$ | $R^3$ | Temperature /°C | Time /h | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| Me | Me | Me | 100 [a] | 50 | 47 | 211 |
| Me | Et | Et | 100 [a] | 50 | – | 211 |
| 2,4-$Cl_2$-5-$FC_6H_2$ | Et | Me | 80 | 48 | 63 [b] | 212 |

[a] The reaction was carried out in a tube; [b] a mixture of the methyl and ethyl ester **260** in 1 : 2 ratio was obtained.

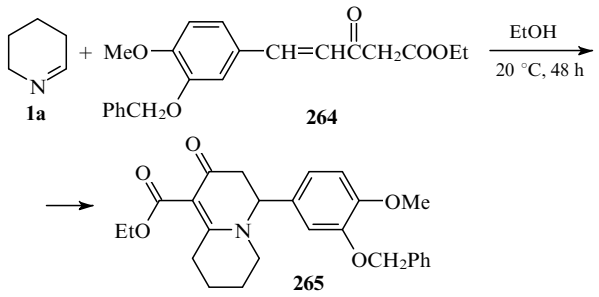
5-Methoxycarbonyl-1-azabicyclo[4.4.0]dec-5-en-4-one **262**, the initial compound in the synthesis of (±)-epilupinine, has been prepared from 3-oxopent-4-enoic acid **261** and the imidate **6a** (yield 54%) [194] or the thioimidate **7** (yield 62%).[213]



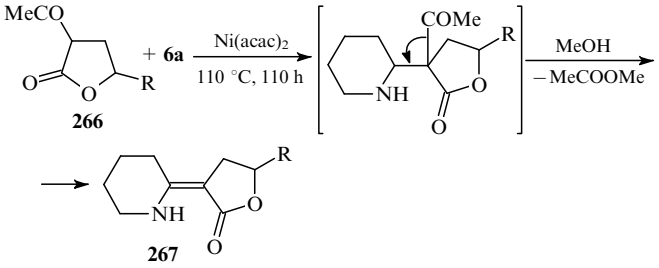

At room temperature, the dicarbonyl compound **261** reacts with 2-methoxy-5-phenyl-3,4,5,6-tetrahydropyridine to give 5-methoxycarbonyl-9-phenyl-1-azabicyclo[4.4.0]dec-5-en-4-one **263** (yield 65%).[214]




When developing approaches to the synthesis of alkaloids of the *Lythraceae* family, Rosazza *et al.*[215] synthesised compound **265** (yield 84%) by cyclocondensation of the imine **1a** with unsaturated oxo ester **264**.

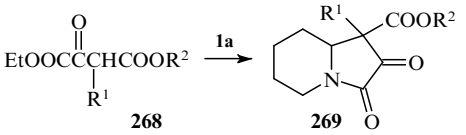


In the presence of nickel acetylacetonate, the imidate **6a** enters into the reaction with oxo lactones **266** to give compounds **267**.[216]



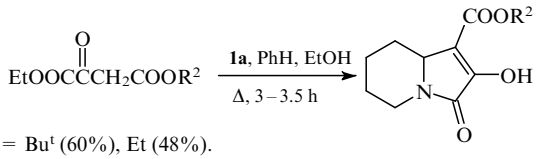
R = H (56%), Et (33%).

1-Azabicyclo[4.3.0]nonane-8,9-dione derivatives **269** have been synthesised from 2,3,4,5-tetrahydropyridine **1a** and esters of oxo dicarboxylic acids **268**.[217,218]



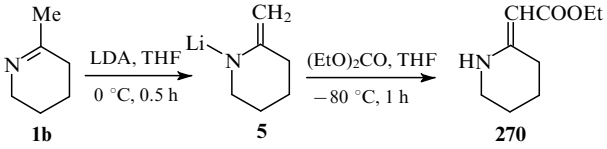
| $R^1$ | $R^2$ | Reaction conditions | Yield (%) | Ref. |
|---|---|---|---|---|
| Me | Et | $C_6H_6$, Δ, 18 h | 30 | 217 |
| OMe | $Bu^t$ | $Et_2O$, EtOH, 20 °C, 6 h | 30 | 218 |

The reaction of the imine **1a** with alkyl oxalylacetates (**268**, $R^1$ = H) affords tautomers of the compounds **269**, 7-alkoxycarbonyl-8-hydroxy-1-azabicyclo[4.3.0]non-7-en-9-ones.[25]

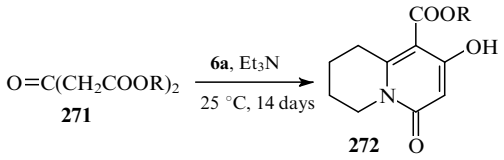


$R^2$ = $Bu^t$ (60%), Et (48%).

*N*-Lithio-2-methylenepiperidine **5**, formed on treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA, reacts *in situ* with diethyl carbonate to give 2-ethoxycarbonylmethylenepiperidine **270** in 59% yield.[10]



Cyclocondensation of the imidate **6a** with esters of oxo dicarboxylic acid **271** in the presence of $Et_3N$ affords quinolizine derivatives **272**.[219]

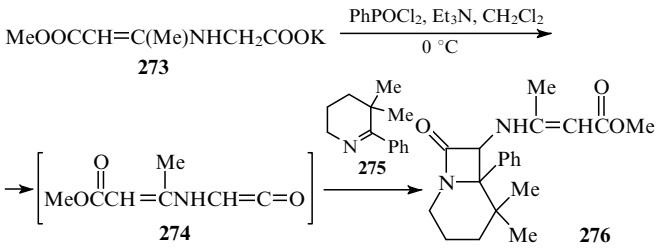


R = Me (57%), Et (92%).

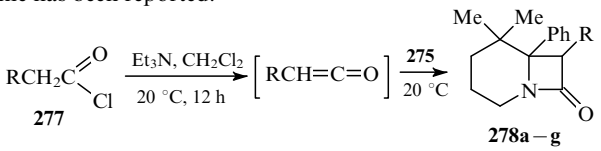
## 9. Reactions with ketenes

$\Delta^1$-Piperideines and ketenes react according to the [2+2] cycloaddition pattern yielding bicyclic compounds — 1-azabicyclo-[4.2.0]octane derivatives.

Thus treatment of potassium *N*-(2-methoxycarbonylpropen-2-yl)glycinate **273** with $PhPOCl_2$ and $Et_3N$ gives ketene **274**, which enters *in situ* into the cycloaddition reaction with 3,3-dimethyl-2-phenyl-3,4,5,6-tetrahydropyridine giving rise to 7-(2-methoxycarbonylpropen-2-yl)amino-5,5-dimethyl-6-phenyl-1-azabicyclo-[4.2.0]octan-8-one **276** in 74% yield.[220]



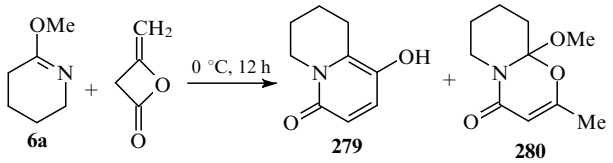
Synthesis of 1-azabicyclo[4.2.0]octane derivatives **278a–g** (yields 42%–87%) by the reaction of the imine **275** with the ketenes formed on treatment of acyl chlorides **277** with triethylamine has been reported.[221]



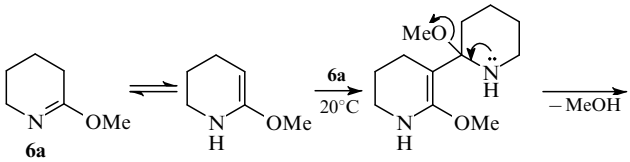
R = $N_3$ (**a**), MeO (**b**), PhO (**c**), $PhCH_2O$ (**d**), 4-$ClC_6H_4SO_3$ (**e**), phthaloimid-1-yl (**f**), Cl (**g**).

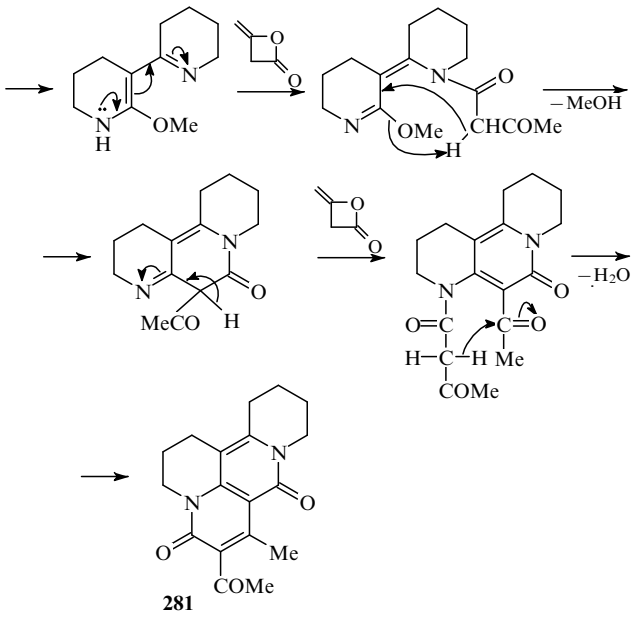
The azido-derivative **278a** is formed over a period of 2 h, while in the majority of cases, completion of the reaction requires 12 h. In the case of the synthesis of **278g** (yield 61%), more drastic conditions were used: the reaction mixture was refluxed for 1.5 h and then kept at room temperature for 16 h.[221]

The imidate **6a** reacts with diketene even at 0 °C according to two pathways — giving quinolizine derivative **279** (yield 10%) and pyrido[2.1-*b*]oxazine **280** (yield 43%).[222]



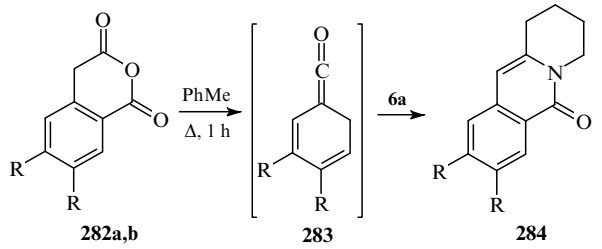
When the reaction is carried out in acetic acid at 20 °C, only the tetracyclic compound **281** is formed; this product results from condensation of two molecules of **6a** with two diketene molecules. The following scheme has been proposed for this reaction:[223]





**281**

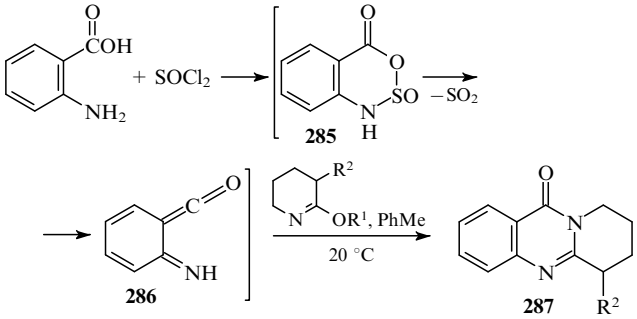
In some cases, ketenes synthesised by other methods have also been introduced in reactions with $\Delta^1$-piperideines. Thus on refluxing in toluene, homophthalic anhydride **282a** and 4,5-dimethoxyhomophthalic anhydride **282b** eliminate a $CO_2$ molecule being thus converted into the corresponding ketenes **283**, which react with 2-methoxy-3,4,5,6-tetrahydropyridine **6a** to give tricyclic compounds **284**.[224]



**282a,b** **283** **284**

R = H (52%), OMe (55%).

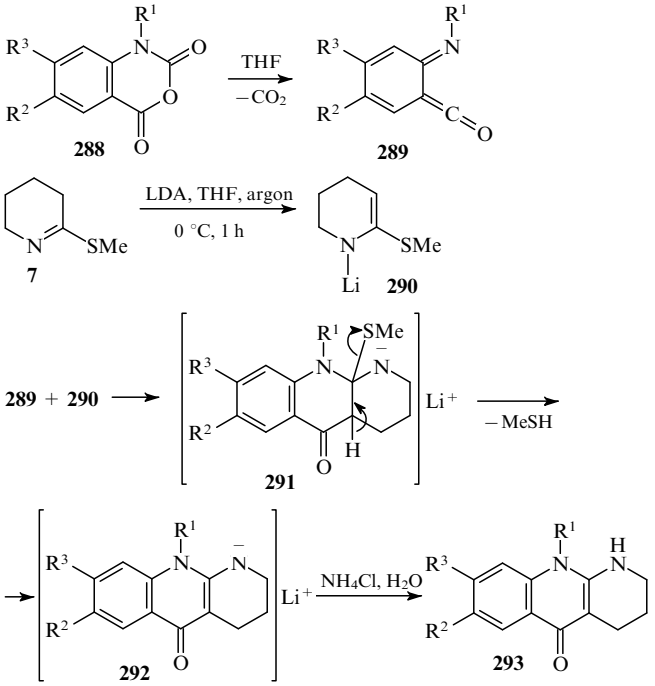
Compound **285**, formed from anthranilic acid under the action of thionyl chloride, eliminates an $SO_2$ molecule even at room temperature and is thus converted into ketene **286**, which enters into cyclocondensation with imidates to give quinazoline derivatives **287** (yields 71% – 82%).[225, 226]



**285** **286** **287**

$R^1$ = Me, Et; $R^2$ = H, OMe.

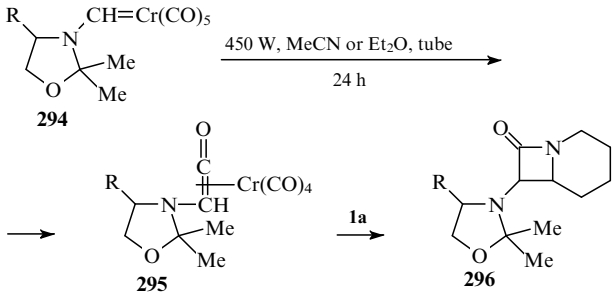
Benzo[*b*]-1,8-naphthiridine derivatives **293** have been prepared by the reaction of 2-methylthio-3,4,5,6-tetrahydropyridines **7** with N-substituted isatic anhydrides **288** in the presence of LDA. Evidently, the anhydrides **288** lose a $CO_2$ molecule under the reaction conditions giving rise to ketenes **289**, which react according to the [4 + 2] cycloaddition pattern with the lithium derivative **290**, resulting from the reaction of the thioimidate **7** with LDA. The salts **291** thus formed are converted into salts **292** upon elimination of an MeSH molecule. The latter give the final products **293** upon treatment with an aqueous solution of ammonium chloride.[227]



**288** **289** **7** **290** **291** **292** **293**

| $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|
| Me | H | H | 64 |
| $PhCH_2$ | H | H | 53 |
| Me | Me | H | 42 |
| Me | H | Cl | 62 |
| Ph | H | Cl | 14 |

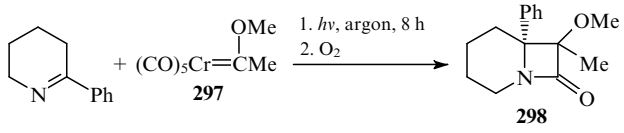
Ketene chromium tricarbonyl complexes **295**, which are produced upon photolysis of the carbene complexes **294**, react *in situ* with 2,3,4,5-tetrahydropyridine **1a** yielding 1-azabicyclo-[4.2.0]octan-8-one **296**.[228, 229]



**294** **295** **296**

| $R^1$ | *de* | Yield (%) | Ref. |
|---|---|---|---|
| Ph | 97 | 91 | 228, 229 |
| $Me_2CH$ | 97 | 55 | 228 |

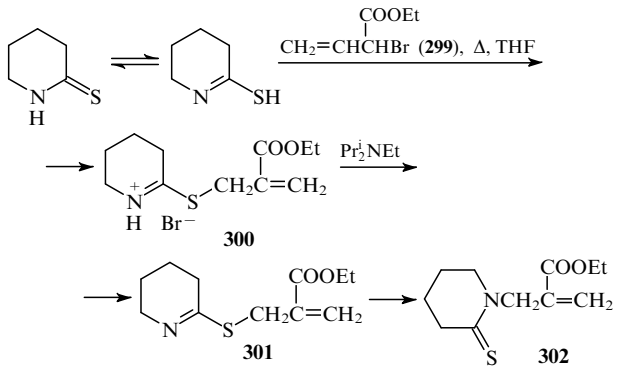
When a mixture of 2-phenyl-3,4,5,6-tetrahydropyridine and carbene complex **297** is exposed to sunlight under an argon atmosphere and then oxidised by atmospheric oxygen, 7-methoxy-7-methyl-6-phenyl-1-azabicyclo[4.2.0]octan-8-one **298** is formed in 63% yield.[230]



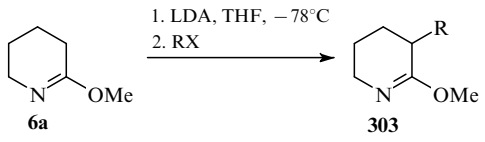
**297** **298**

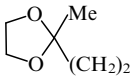
## 10. Reactions with alkyl halides

Piperidine-2-thione in the thiol tautomeric form reacts with ethyl 2-bromobut-3-enoate **299** to give salt **300**. Subsequent treatment of the compound **300** with ethyldiisopropylamine affords N-substituted piperidine-2-thione **302** (yield 70%); the formation of this product was explained by the S,N-allyl rearrangement of intermediate **301** under the reaction conditions.[231]

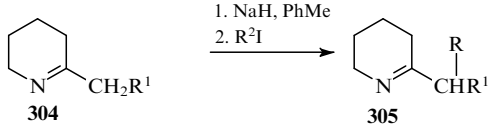



Treatment of the imidate **6a** with LDA and then with halogenated compounds results in the formation of product **303**, alkylated at the 3-position.[56, 194]




| R | X | Temperature /°C | Time /h | Yield (%) | Ref. |
|---|---|---|---|---|---|
|  | I | 20 | 4 | 56 | 56 |
| | I | −15 | 6 | 51.5 | 194 |
| $CH_2=C(Me)(CH_2)_2$ | I | −78 | 3 | 60 | 194 |
| | I | 20 | 0.33 | 60 | 194 |
| $MeC(Cl)=CHCH_2$ | Cl | −78 | 2 | 37 | 56 |

When $\Delta^1$-piperideines **304** ($R^1$ = COOEt) are treated successively with sodium hydride and halo-derivatives $R^2X$, alkylation of the side-chain methylene group occurs and compounds **305** are formed in 35% – 80% yields.[109]




$R^1$ = COOEt, H, Me; $R^2$ = Me, Et, Pr, $PhCH_2$, $Ph(CH_2)_3$, $Me(CH_2)_9$, $CH_2=CH(CH_2)_8$.

The compounds **305** ($R^1$ = H, Me; $R^2$ = Me) have been synthesised in >95% yields by the reaction of the $\Delta^1$-piperideines **304** ($R^1$ = H, Me) with methyl iodide in the presence of LDA in THF at −78 to 20 °C for 1 h.[232]

When imidates **306** are heated with halo-containing compounds, the nitrogen atom in the heterocyclic nucleus is alkylated giving substituted piperidones **307**.[39, 233] The reaction conditions and the product yields are listed in Table 4.

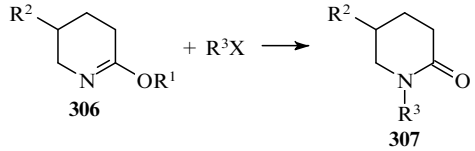


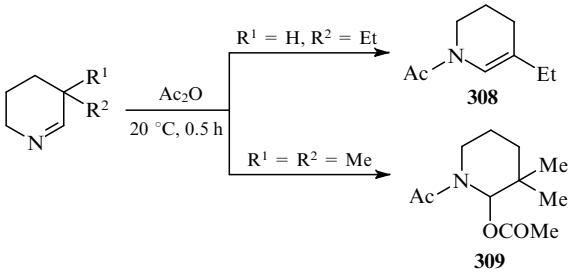

**Table 4**. Alkylation of the imidates **306**.

| $R^1$ | $R^2$ | $R^3$ | X | Temperature/°C | Time/h | Yield (%) | Ref. |
|---|---|---|---|---|---|---|---|
| Me | H | Me | I | 60 | 6 | 93 | 39 |
| Me | H | Et | I | 60 | 48 | 52 | 39 |
| Me | H | $PhCH_2$ | Br | 60 | 10 | 80 | 39 |
| Me | H | $Ph(CH_2)_2$ | Br | 100 | 28 | 7 | 39 |
| Me | H | $3,4\text{-}(MeO)_2C_6H_3(CH_2)_2$ | Br | 90 | 24 | 8 | 39 |
| Et | H | $Ph(CH_2)_2$ | Br | 100 | 48 | 27 | 39 |
| Me | H | $PhCOCH_2$ | Br | 60 | 3 | 91 | 39, 233 |
| Et | H | $PhCOCH_2$ | Br | 60 | 4 | 94 | 39 |
| Me | H | $3,4\text{-}(MeO)_2C_6H_3COCH_2$ | Br | 60 | 5 | 88 | 39, 233 |
| Et | H | $3,4\text{-}(MeO)_2C_6H_3COCH_2$ | Br | 60 | 5 | 92 | 39 |
| Me | Et | $PhCOCH_2$ | Br | 60 | 3 | – | 233 |
| Me | Et | $3,4\text{-}(MeO)_2C_6H_3COCH_2$ | Br | 60 | 5 | – | 233 |

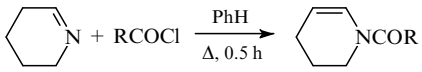
## 11. N-Acylation reactions

N-Acylation of 3-substituted $\Delta^1$-piperideines with acylating agents is accompanied by isomerisation of the double bond.

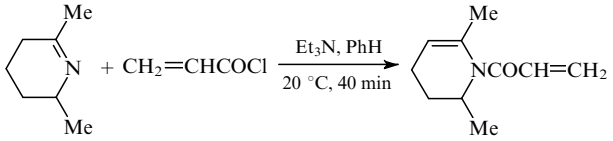
Thus treatment of 3-ethyl-$\Delta^1$-piperideine with acetic anhydride affords compound **308** (yield 57%). Under the same conditions, 3,3-dimethyl-$\Delta^1$-piperideine is converted into diacetyl derivative **309** in 78% yield.[72]



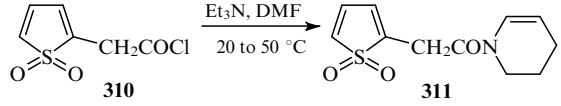

N-Acylation of the imine **1a** with polyunsaturated acid chlorides was carried out by refluxing in benzene.[234, 235] 2,6-Dimethyl-3,4,5,6-tetrahydropyridine was N-acylated with acryloyl chloride in the presence of triethylamine at room temperature.[236]



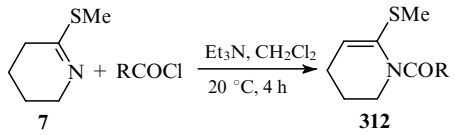

R = $Me(CH_2)_2C\equiv C(CH=CH)_2$ (60%), $Me(CH=CH)_4$ (35%).




Compound **311** was synthesised in 76% yield by the reaction of the imine **1a** with chloride **310** in the presence of $Et_3N$ in DMF.[237]



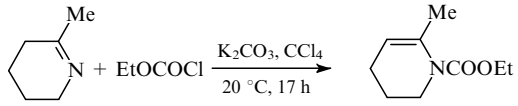

The thioimidate **7** reacts with acetyl or benzoyl chloride at room temperature to give N-acylated derivatives **312**.[238]




7 312

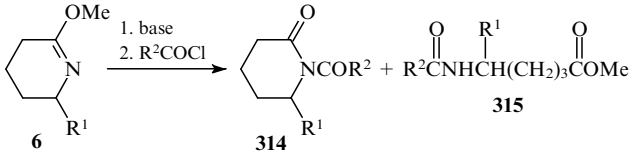
R = Me (73%), Ph (83%).

Ethyl chlorocarbonate reacts with the imine **1b** in the presence of potassium carbonate to give N-acylated product **313** (yield 79%).[239]




**1b** **313**

When the $\Delta^1$-piperideines **6** are heated with lithium hydride in THF and the resulting organolithium compounds are treated with acyl chlorides, N-acylation products **314** are formed in low yields, acyclic compounds **315** being the main products (yields 72%–77%). Treatment of the $\Delta^1$-piperideines **6** with lithium or sodium hydride or lithium hydroxide in benzene and subsequent reaction with acid chlorides give the N-acylated derivatives **314** as the main reaction products (see Table 5).[185]



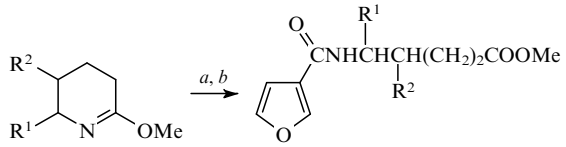

**6** **314**

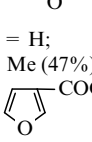
**Table 5**. *N*-Acylation of the piperideines **6**.

| $R^1$ | $R^2$ | Base | Solvent | Reaction conditions | | Yield of **314** (%) |
|---|---|---|---|---|---|---|
| | | | | 1st stage | 2nd stage | |
| Me | 3-furyl | LiH | THF | Δ, 3 h | 25 °C, 88 h | 4 |
| H | | LiH | THF | Δ, 3 h | 25 °C, 88 h | 6 |
| Me | | LiOH | $C_6H_6$ | Δ, 3 h | 25 °C, 19 h | 75 |
| H | | NaH | $C_6H_6$ | Δ, 3 h | 25 °C, 19 h | 70 |
| H | Ph | LiH | $C_6H_6$ | Δ, 3 h | 25 °C, 19 h | 67 |

Heating of the imidate **6a** with lithium hydride in benzene for 3 h followed by treatment of the reaction product with benzoyl chloride also gives compound of the type **315** ($R^1$ = H, $R^2$ = Ph) in 32% yield.[185]

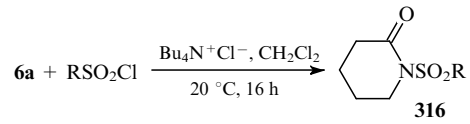
Later the investigation of the reaction of $\Delta^1$-piperideines with lithium hydride and the chloride of furan-3-carboxylic acid has been continued. The formation of only the product of piperideine ring opening in this reaction has been reported.[121]




$R^1$ = $R^2$ = H; $R^1$ = Me, $R^2$ = H;
$R^1$ = $Me_2C{=}CHCH_2$, $R^2$ = Me (47%);
(*a*) LiH, THF, $N_2$, Δ, 3 h; (*b*) 

, 25 °C.

The reaction of the imidate **6a** with sulfonyl chlorides in the presence of $Bu_4N^+Cl^-$ in $CH_2Cl_2$ at room temperature results in the formation of *N*-sulfonyl-substituted derivatives **316**.[41]



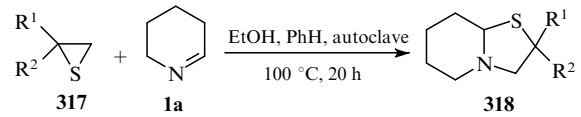

**316**

R = Me (73%), Ph (66%), 4-$C_6H_4$ (66%).

## 12. Reactions with labile cyclic systems

In this Section, we discuss the reactions of $\Delta^1$-piperideines with labile cyclic systems accompanied by ring opening or recyclisation.

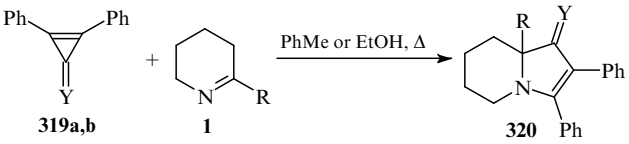
Thus 2,3,4,5-tetrahydropyridine **1a** enters into the reaction with thiiranes **317** on heating to 100 °C; these reactions yield 1-aza-7-thiabicyclo[4.3.0]nonane **318**.[240]




**317** **1a** **318**

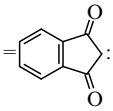
$R^1$ = $R^2$ = H (63%); $R^1$ = H, $R^2$ = Me (67%); $R^1$ = $R^2$ = Me (32%).

Bicyclic compounds **320** have been synthesised by heating the $\Delta^1$-piperideines **1** with diphenylcyclopropenone **319a**[241] or methylenecyclopropene derivative **319b**.[242]



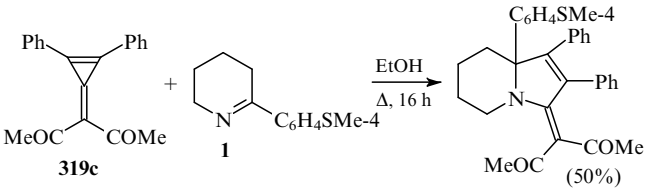

**319a,b** **1** **320**

Y = O: R = Me (79%), Et (76%), 2,5-$(MeO)_2C_6H_3$ (80%).

Y = 

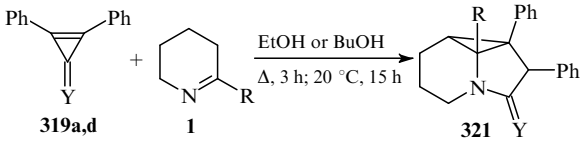
: R = $MeSC_6H_4$ (60%), 2,5-$(MeO)_2C_6H_3$ (77%).

The reaction of 2-(4-methylthio)phenyl-3,4,5,6-tetrahydropyridine with the methylenecyclopropene **319c** follows a different pathway.[242]




**319c** **1**

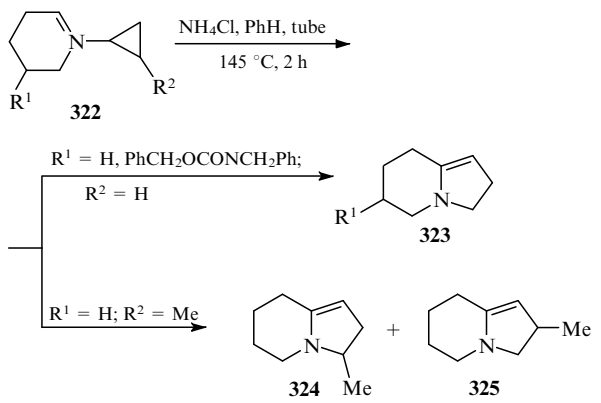
The reaction of the $\Delta^1$-piperideines **1** with diphenylcyclopropenone **319a** or with the cyclopropenethione **319d** giving tricyclic compounds **321** (yields 46%–82%) is evidently a two-stage process. The first stage gives bicyclic compounds of the type **320**; under the reaction conditions, these products undergo intramolecular cyclisation involving the $CH_2$ group at the 5-position of the piperidine ring and the C=C bond of the five-membered ring.[241]



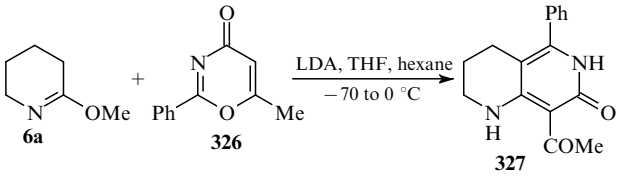

**319a,d** **1** **321**

Y = O: R = Ph, 4-$MeSC_6H_4$; Y = S: R = Me, Et, Ph, 4-$MeSC_6H_4$, 2,5-$(MeO)_2C_6H_3$.

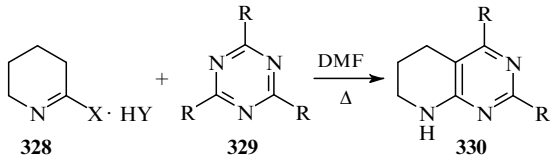
$\Delta^1$-Piperideines **322**, containing a cyclopropyl substituent at the 2-position, isomerise on heating in the presence of ammonium chloride to give 1-azabicyclo[4.3.0]non-6-ene derivatives; the imines **322** ($R^2$ = H) are converted into individual compounds **323**, whereas the imine **322** ($R^1$ = H, $R^2$ = Me) gives two isomeric reaction products **324** and **325**.[95]



10-Acetyl-7-phenyl-2,8-diazabicyclo[4.4.0]deca-6,10-dien-9-one **327** is formed in 56% yield in the reaction of the imidate **6a** with 6-methyl-2-phenyl-1,3-oxazin-4-one **326**.[243]

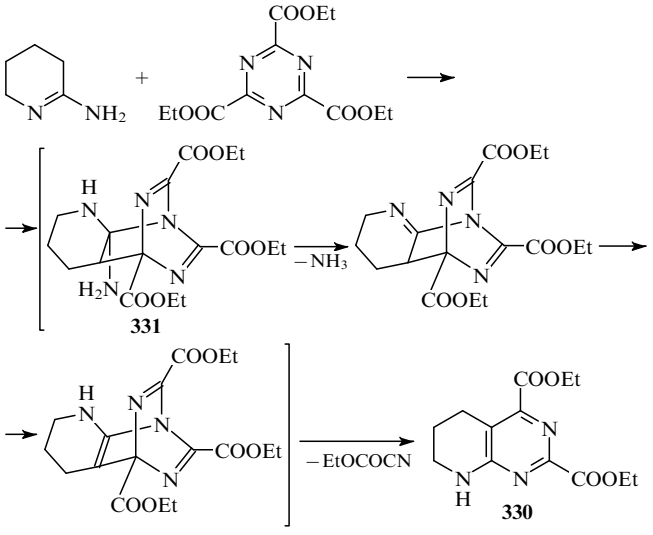


Heating of 2-amino-3,4,5,6-tetrahydropyridine hydrochloride **328** with 1,3,5-triazine or its 2,4,6-tris(triethoxycarbonyl) derivative **329** in DMF gives rise to bicyclic compounds **330** in 63%–75% yields. The reaction of 2-methylthio-3,4,5,6-tetrahydropyridine hydroiodide **328** (X = SMe, Y = I) with triazines follows a similar pathway; however, the corresponding derivatives **330** are formed in low yields.[244]



X = $NH_2$, Y = Cl; X = SMe, Y = I; R = H, COOEt.

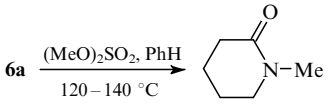
It was shown that the first stage in the reaction of 2-amino-3,4,5,6-tetrahydropyridine with 1,3,5-triazine is [2 + 4] cycloaddition giving tricyclic compound **331**; this product loses an $NH_3$ molecule and undergoes the retro Diels–Alder reaction to give the final product **330**.[244]



Neither interaction of the imidate **6a** with the triazines **329** (R = H, COOEt) nor the reaction of the hydrochloride **328** (X = $NH_2$, Y = Cl) with 2,4,6-tris(methylthio)triazine gives products of the type **330**.[244]

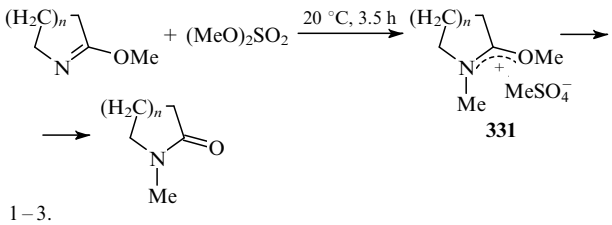
## 13. Isomerisation

When the imidate **6a** is heated with a catalytic amount of dimethyl sulfate, it is converted into *N*-methylpiperidin-2-one in a yield of > 90%.[37]



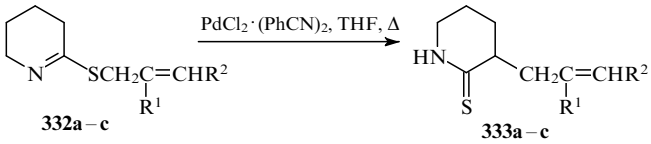
*N*-Methylpiperidone is also formed (yield 76%) in the absence of dimethyl sulfate when the imidate **6a** is heated in boiling benzene for 6 h.[245]

In a study of the isomerisation of imidates into *N*-methylated lactams, it has been found that the rate of formation of the intermediate adducts **331** decreases as the size of the ring increases.[246]



*n* = 1–3.

On heating in THF in the presence of $PdCl_2 \cdot (PdCN)_2$, allyl thioimidates **332** isomerise to allyl-substituted piperidinethiones **333**.[231]

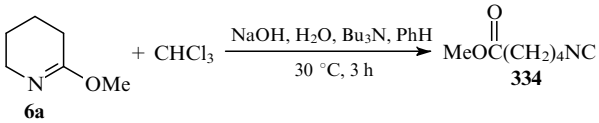


$R^1 = R^2 = H$ (**a**, 74%), $R^1 = H$, $R^2 = Ph$ (**b**, 58%), $R^1 = Me$, $R^2 = H$ (**c**, 25%).

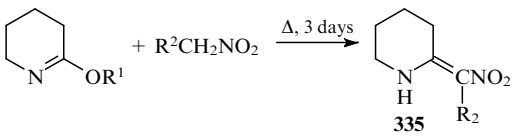
When the rearrangement of the compound **332a** is carried out without a catalyst for 40 h, the yield of the product **333a** is 60%.[231]

## 14. Other reactions

The reaction of the imidate **6a** with chloroform in the presence of 50% aqueous sodium hydroxide and tributylamine at 30 °C is accompanied by opening of the tetrahydropyridine ring and gives isonitrile **334** in 41% yield.[247]

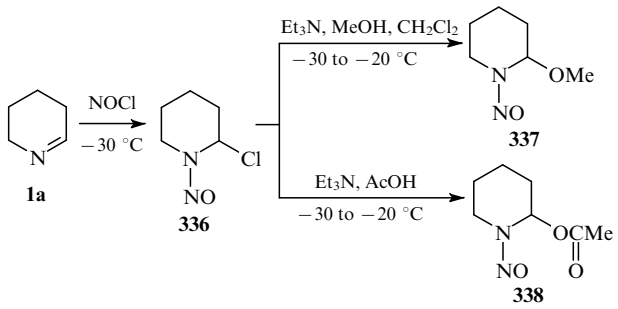


Compounds **335**, serving as the initial compounds in the synthesis of insecticides, have been prepared by condensation of 2-methoxy-3,4,5,6-tetrahydropyridine or 2-ethoxy-3,4,5,6-tetrahydropyridine with nitromethane or nitroethane.[42, 248]



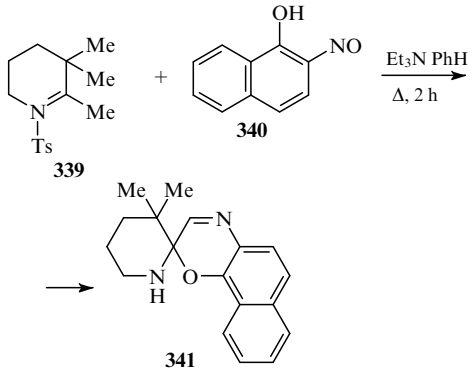
$R^1$ = Me, Et; $R^2$ = H, Me.

Nitrosyl chloride adds to the C=N bond of 2,3,4,5-tetrahydropyridine **1a** at −30 °C yielding unstable product **336**. Subsequent treatment of this product with methanol or acetic acid in the presence of triethylamine affords relatively stable methoxy-derivative **337** (yield 30%) or acetoxy-derivative **338** (yield 20%).[249]



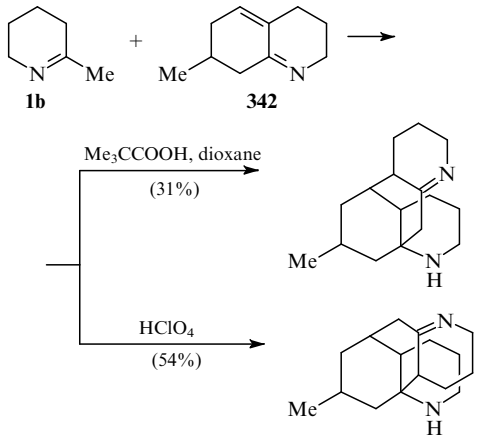

**1a** **336** **337** **338**

Spiro compound **341** has been synthesised by condensation of 2,3,3-trimethyl-3,4,5,6-tetrahydropyridine tosylate **339** with 1-hydroxy-2-nitrosonaphthalene **340** in the presence of $Et_3N$.[250]



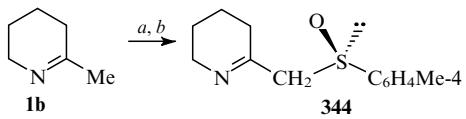

**339** **340** **341**

The cyclocondensations of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with 9-methyl-2-azabicyclo[4.4.0]deca-1,7-diene **342** in the presence of trimethylacetic and perchloric acid give different products.[11]




**1b** **342**

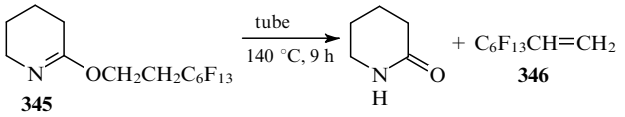
The reaction of the imine **1b** with (−)-(1*R*,2*S*,5*R*)-menthyl-(*S*)-*p*-tolylsulfinate **343** in THF in the presence of LDA gives (+)-2,3,4,5-tetrahydro-6-(*R*)-(*p*-tolyl)sulfinylmethylpyridine **344**.[251]




**1b** **344**

(*a*) LDA, THF, −25 to −20 °C, 15 min, argon;
(*b*) **343**, THF, −20 °C, 1.5 h; −10 °C, 0.5 h.

On heating, imidate **345** is cleaved to give piperidin-2-one and the corresponding alkene **346**.[46]




**345** **346**

## V. Conclusion

The data considered above demonstrate that piperideine and its derivatives arouse obvious and continuing interest. At the same time, some aspects of the chemistry of these highly reactive compounds receive undeservedly little attention. For example, addition to the endocyclic C=N bond has not been adequately studied. Virtually no data on the cycloaddition involving the piperideine C=N bond, except for the reactions with ketenes, have been reported, although these reactions would provide the possibility of preparing starting compounds for the synthesis of other interesting heterocyclic systems.

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