PYRROLIZIN-3-ONES

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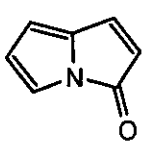
Abstract - The preparation, and physical and chemical properties of the pyrrolizin-3-one system (1) and its 1,2-dihydro derivatives (2) are reviewed.

Dedicated to Professor A. R. Katritzky, in recognition of his contributions to heterocyclic chemistry and as founder of the 'Katritzky Memorial Walk' at the Grasmere Heterocyclic meetings.

1. INTRODUCTION

Whereas hexahydro- and tetrahydropyrrolizin-3-ones are well documented, particularly with regard to their importance as pyrrolizidine alkaloids,[1-3] relatively little attention has been paid to the fully unsaturated system (1). In this review, we aim to cover the synthetic methods which have been used to prepare such compounds, together with a survey of their physical properties and what little has been reported of their chemistry. Because their chemistries are often closely linked, the 1,2-dihydro system (2) is also considered here, and in the final section we briefly survey the small selection of natural products which are found at this oxidation level.



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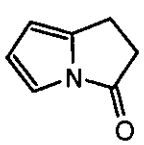

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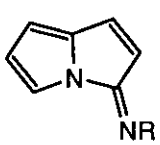

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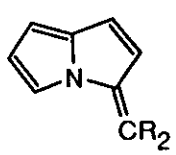

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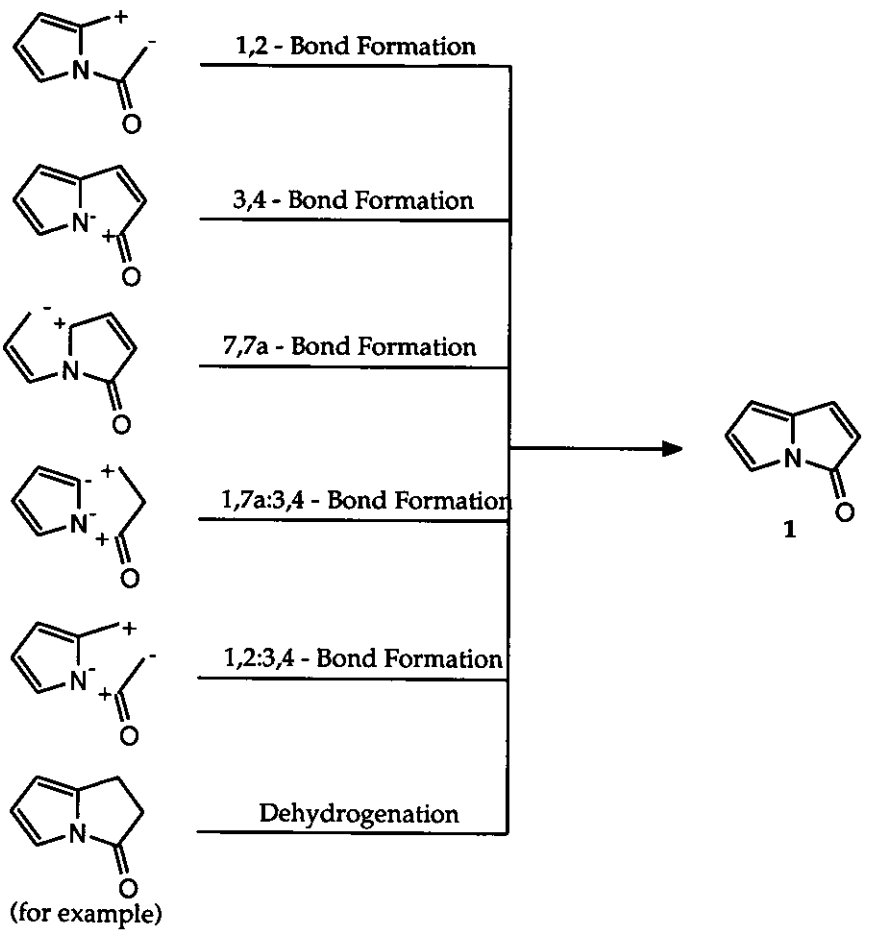
Pyrrolizin-3-ones have not themselves been the subject of any previous review, though aspects have been covered in more general treatments of pyrrolizine chemistry.[4-6] The article by Flitsch and Jones[5] is particularly comprehensive, and includes the related imines (3) and ylidene derivatives (4).

2. SYNTHESIS



Scheme 1

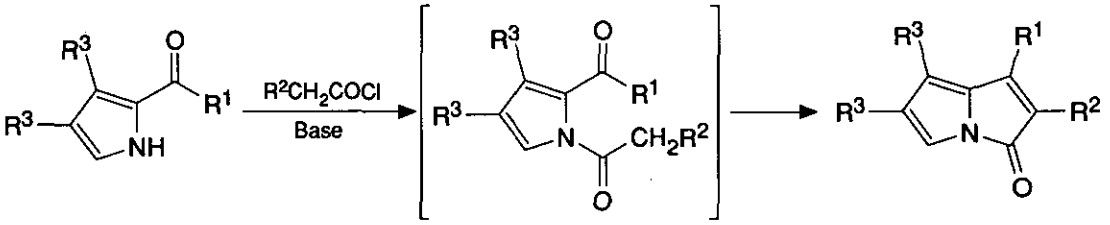
Not surprisingly, routes to pyrrolizin-3-ones have generally commenced from a simple pyrrole, often with a carbonyl substituent in the 2-position to facilitate formation of the 1,2-olefinic bond. Flitsch and Jones[5] have classified synthetic routes to pyrrolizines according to the number and positions of new bonds formed in the ring closure step. A modification of this classification,

outlined in Scheme 1, will be used here. All known examples of each class shown are discussed in turn.

2.1. PREPARATION OF PYRROLIZIN-3-ONES BY FORMATION OF ONE BOND

2.1.1 1,2-Bond Formation

Only a few examples exist in which formation of the olefinic bond is the final step in ring formation. In each case, *N*-acylation of a 2-acylpyrrole was followed by an intramolecular Knoevenagel type condensation, thus producing pyrrolizin-3-ones (**5**),[7] (**6**),[8] and (**7**)[9] (Scheme 2).



	R^1	R^2	R^3	
5	Ph	Ph	H	
6	H	Ph	H	32%
7	H	H	Ph	72%

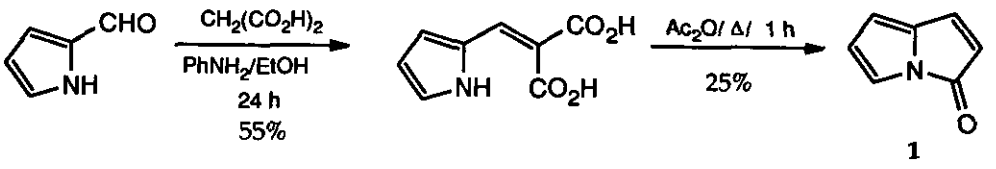
Scheme 2

2.1.2 3,4-Bond Formation

The pyrrolizin-3-one lactam function has most commonly been generated by intramolecular acylation of the pyrrole *N*-atom. The means by which this has been achieved can be separated into three types:

2.1.2.1 Activated Amide Formation

Although this method generally results in low yields of products, there is considerable scope for variation of the condensing agent. The parent compound (**1**) was first obtained by the means outlined in Scheme 3.[8] Formation of a mixed anhydride is followed by ring closure and decarboxylation. The substituted pyrrolizin-3-ones (**8-11**) had previously been prepared in low yield by this method.[8,10-12]



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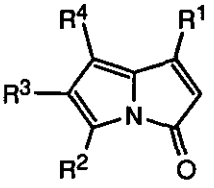
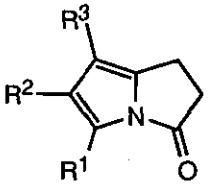
Scheme 3



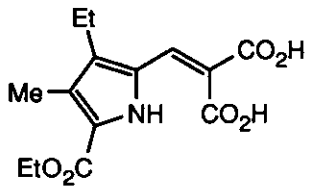
	R1	R2	R3	R4	Yield for Ring Closure
8	H	H	Me	CO_2Et	20-37%
9	Me	H	H	H	23%
10	H	H	C_6H_4OMe	C_6H_4OMe	9%
11	H	H	H	CH_2OBn	-----

Several 1,2-dihydropyrrolizin-3-ones **(12-15)** have been obtained in a similar fashion from pyrrolyl propanoic acids.[11,13] An example **(14)** obtained by this means, has subsequently undergone dehydrogenation to the fully unsaturated pyrrolizin-3-one, in low yield, upon treatment with DDQ.[11] Treatment of the propanoic acids with hot polyphosphoric acid has given the isomeric pyrrolizin-1-ones,[11] although a small amount of a 1,2-dihydropyrrolizin-3-one may be observed.[14]



	R1	R2	R3
12	H	Me	CO_2Et
13	Ph	Ph	H
14	C_6H_4OMe	C_6H_4OMe	H
15	C_6H_4Cl	C_6H_4Cl	H

Micheel and Kimper reported in 1936[15] that the diacid **(16)** gave a pyrrolizine-3,3-diol on treatment with hot acetic anhydride, but it is more likely that open chain products were obtained.[4,5]



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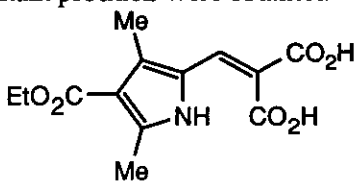
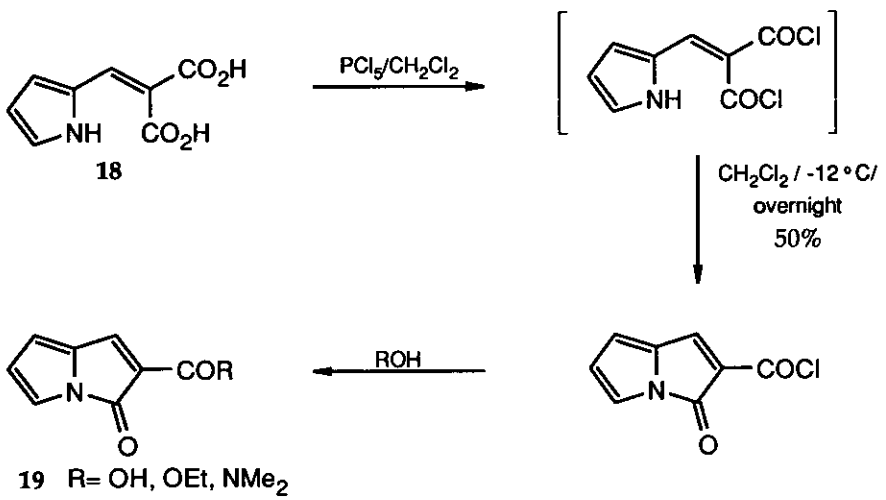


17

Similarly, cyclisation of **17** in hot methanol[16] has subsequently been found to be irreproducible.[10]

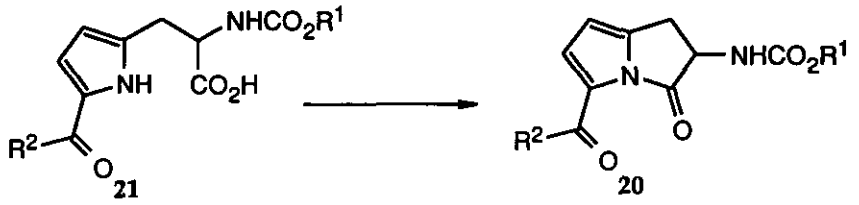
A useful modification of the rather severe conditions outlined above is shown in Scheme 4 below. Conversion of pyrrol-2-ylidenemalonic acid **(18)** to its dichloride allowed ring closure to occur under mild conditions without decarboxylation. Thus, a variety of 2-functionalised pyrrolizin-3-ones **(19)** has been obtained in reasonable yield.[17]



Scheme 4

Gilchrist and Lemos have recently described the synthesis of several 2-acylamino-5-acyl-1,2-dihydropyrrolizin-3-ones **(20)** from pyrrole *via* cyclisation of a propanoic acid **(21)** upon treatment with a dehydrating agent (Scheme 5).[18] The cyclisation to the lactam through treatment of the acid with dicyclohexylcarbodiimide was low yielding (20-22%), but the use of 2-chloro-4,6-dimethoxy-1,3,5-triazine subsequently allowed the ring closure to proceed in excellent yield (80-94%). However, an acyl substituent in the 5-position is required, both to protect this position and to

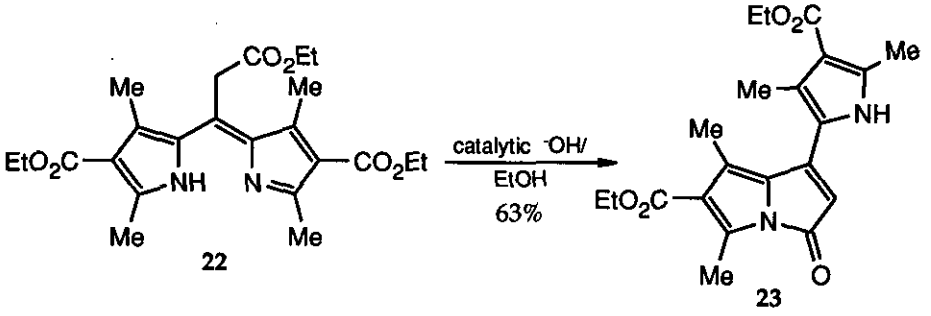
activate the ring closure.



Scheme 5

2.1.2.2 Base Catalysed Ring Closure

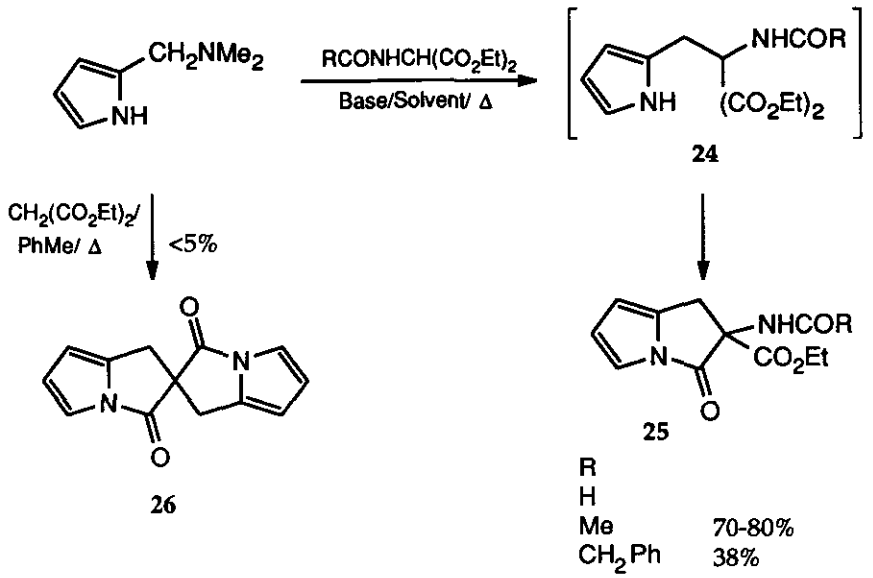
3,4-Bond formation may also occur through base catalysed elimination from pyrrolepropenoic and propanoic acid derivatives. For example, treatment of the dipyrrylmethene **(22)** with a small amount of alkali resulted in the formation of a 1-(pyrrol-2-yl)-pyrrolizin-3-one **(23)** (Scheme 6).[19]



Scheme 6

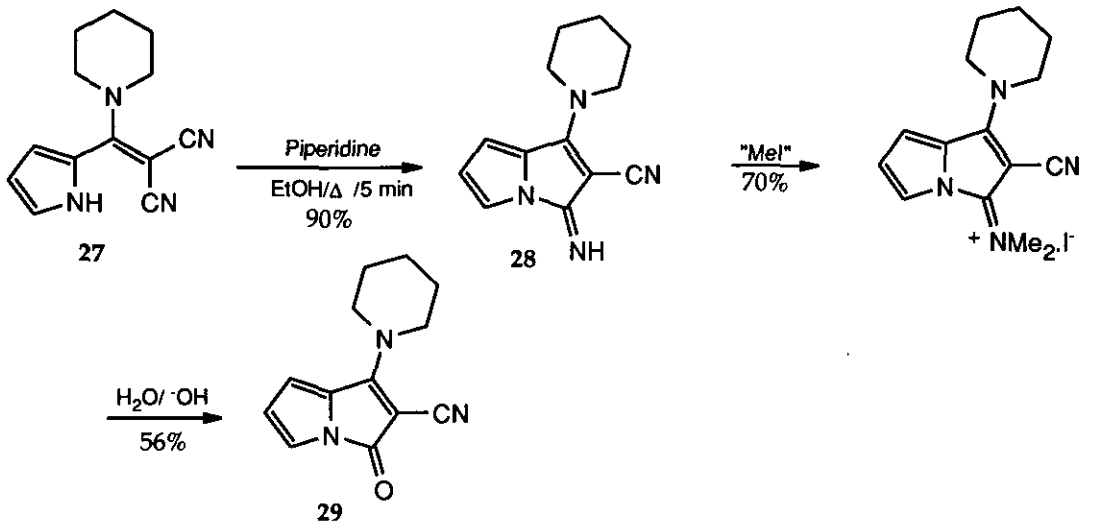
2-Phenylpyrrolizin-3-one **(6)** has been observed[8] as a minor product (12%) from the Wittig reaction of 2-formylpyrrole and triphenylphosphine(α-ethoxycarbonylbenzylidene), presumably *via* base catalysed ring closure of the expected 2-phenyl-3-(pyrrol-2-yl)propenoate ester.

A number of 2,2-disubstituted 1,2-dihydropyrrolizin-3-ones have been obtained in a related manner from pyrrole Mannich bases,[20-22] as outlined in Scheme 7. Reaction of 2-dialkylaminomethylpyrroles and acylaminomalonic esters gave the expected alkylation products **(24)**. Under the reaction conditions these then cyclised to 1,2-dihydropyrrolizin-3-ones such as **(25)**. In an analogous reaction, alkylation of diethyl malonate with pyrrole Mannich base gave a compound tentatively identified as bis-2,2'-(1,2-dihydropyrrolizin-3-one) **(26)**.[20]



Scheme 7

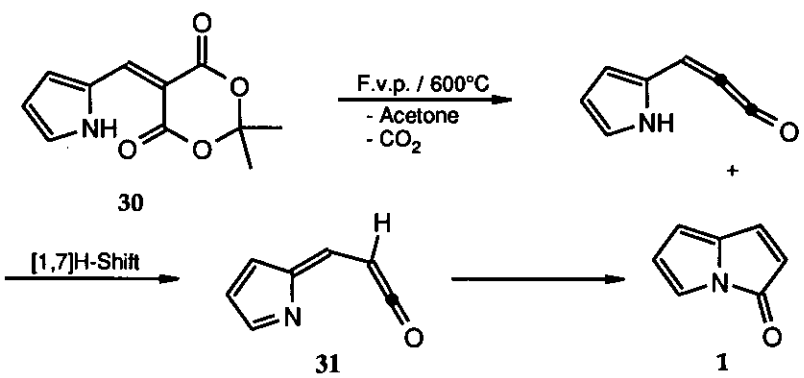
The dinitrile **(27)**, formally a masked pyrrol-2-ylidenemalonic acid, similarly cyclised in hot ethanol upon treatment with a catalytic amount of piperidine, to form an iminopyrrolizine **(28)**. Alkylation with methyl iodide followed by hydrolysis of the resulting ammonium salt produced the 1,2-disubstituted pyrrolizin-3-one **(29)** (Scheme 8).[23]



Scheme 8

2.1.2.3 *Flash Vacuum Pyrolysis*

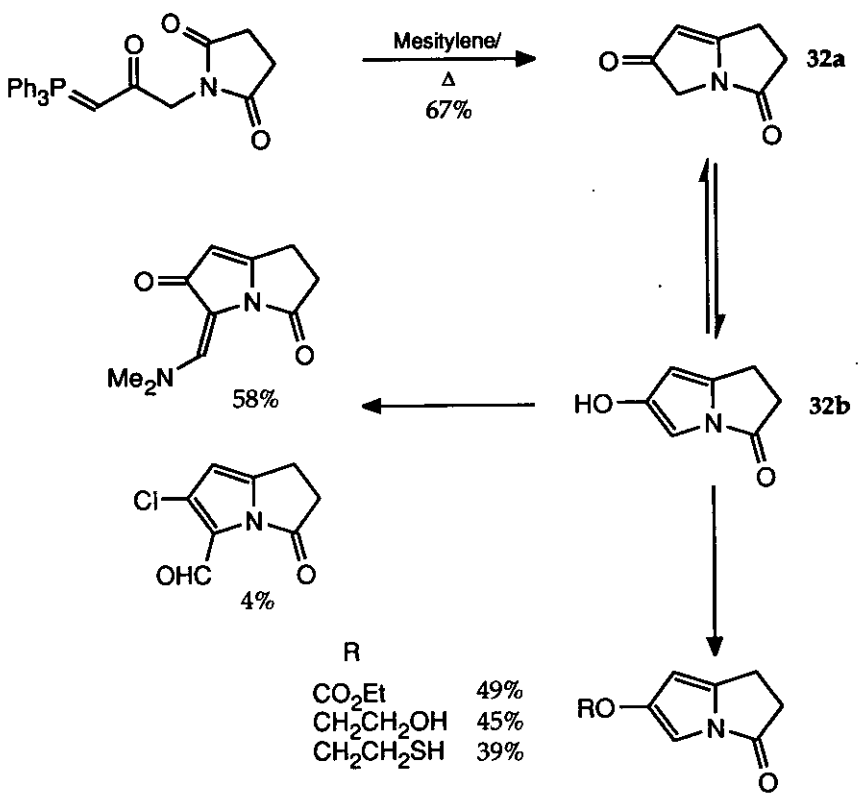
The efficient synthesis of pyrrolizin-3-one **(1)** by flash vacuum pyrolysis of the precursor **(30)**, obtained from the Knoevenagel condensation of 2-formylpyrrole and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid), has been reported.[24] Evidence exists[25] for the lactam function being generated through the involvement of a ketene intermediate in the intramolecular *N*-acylation, as shown in Scheme 9. Several 1-,5-,6-, and 7-monosubstituted pyrrolizin-3-ones have since been prepared in good yield by this method.[26,27] The major disadvantages are the relative involatility of highly substituted precursors, and the [1,7]*H*-shift which prevents the introduction of substituents in the 2-position of pyrrolizin-3-one. Both of these problems can be overcome by direct thermal generation of the ketene intermediates **(31)** *via* pyrrolylacrylate precursors.[28]



Scheme 9

2.1.3 7,7a Bond Formation

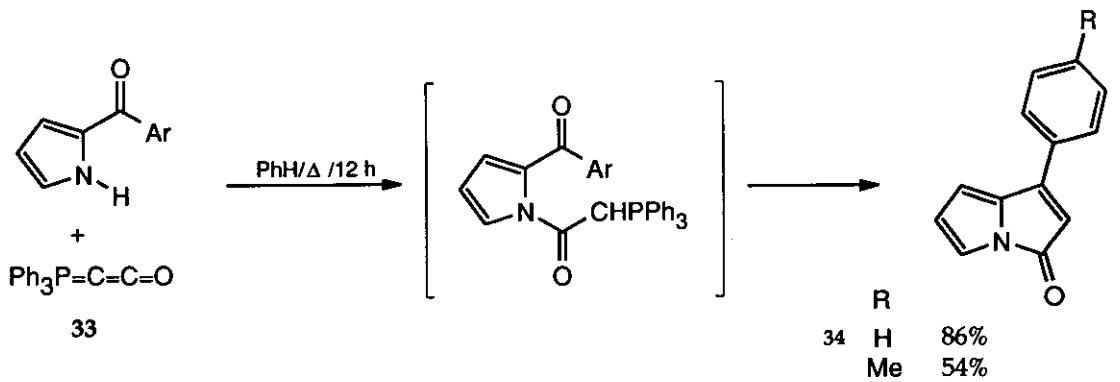
Flitsch has recently described[29] the synthesis, by an intramolecular Wittig reaction, of 1*H*-pyrrolizin-3,6(2*H* ,5*H*)-dione **(32a)** from which a number of 6-substituted 1,2-dihydropyrrolizin-3-ones has been obtained by alkylation or formylation reactions. (Scheme 10).



Scheme 10

2.2. PREPARATION OF PYRROLIZIN-3-ONES BY FORMATION OF TWO BONDS

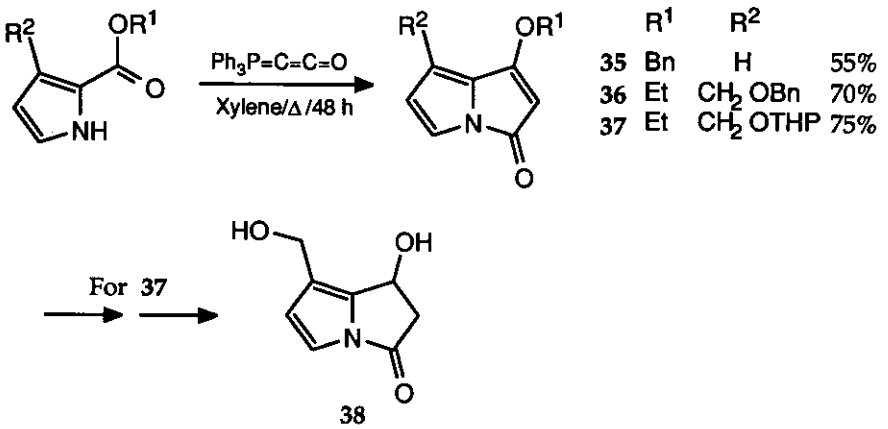
2.2.1 1,2:3,4 Bond Formation



Scheme 11

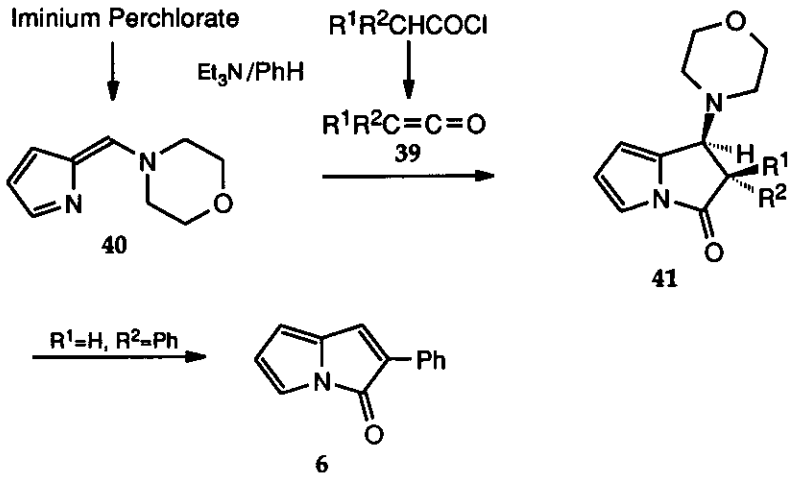
Bestmann and co-workers[30] have employed triphenylphosphoranylideneketene **(33)**, which combines with 2-acylpyrroles by *N*-acylation and intramolecular Wittig reactions to give 1-substituted pyrrolizin-3-ones in high yield (Scheme 11).[31] 1-Phenylpyrrolizin-3-one **(34)** has been prepared with similar efficiency using the equivalent arsenic cumulated ylide.[32]

Bohlmann *et al.* have subsequently shown that **33** can also react with alkyl 2-pyrrolecarboxylates to produce the 1-alkoxypyrrolizin-3-ones **(35-37)**,[33] and have utilised this in the synthesis of 5,7a-didehydroheliotridin-3-one **(38)** (Scheme 12) (Section 4.2.2).[34] However, as with the Meldrum's acid method described previously, it is not possible to prepare 2-substituted pyrrolizin-3-ones by this phosphacumulene ylide methodology.



Scheme 12

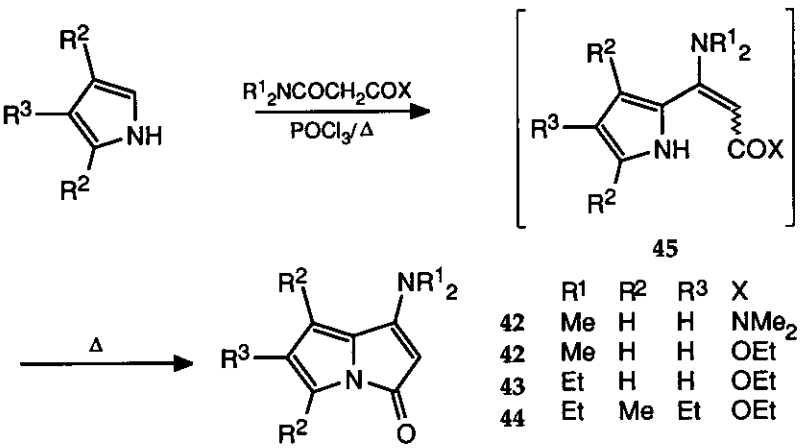
1,2-Dihydropyrrolizin-3-ones have been produced, in moderate yield, from more conventional ketenes (Scheme 13).[35] In this case, the reaction involved the [6+2] cycloaddition of a ketene **(39)** with a 6-morpholino-1-azafulvene **(40)**. Where R^1=H, R^2=Ph, the 'anti' cycloadduct **(41)** was formed stereospecifically. This spontaneously underwent *cis*-elimination to produce fully oxidised 2-phenylpyrrolizin-3-one **(6)** in low yield.



Scheme 13

2.2.2 1,7a:3,4 Bond Formation

The 1-aminopyrrolizin-3-ones **(42-44)** have been isolated in low yield from the Vilsmeier-Haack acylation reaction of pyrroles with certain amides.[36,37] Where the pyrrole ring is heavily substituted, the likely propenoate intermediate **(45)** has been isolated, and shown to proceed to the pyrrolizin-3-one **(44)** *via* thermal elimination of ethanol (Scheme 14).[37]

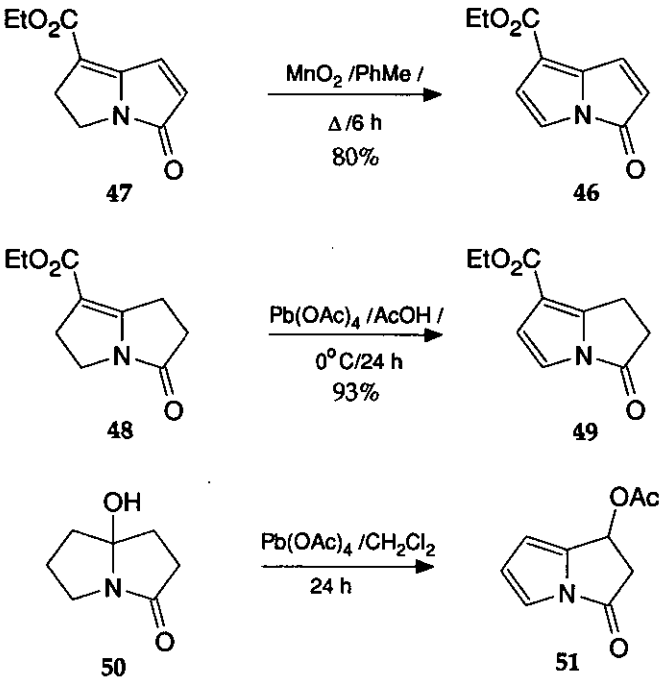


	R1	R2	R3	X	
42	Me	H	H	NMe_2	6%
42	Me	H	H	OEt	29%
43	Et	H	H	OEt	31%
44	Et	Me	Et	OEt	24%

Scheme 14

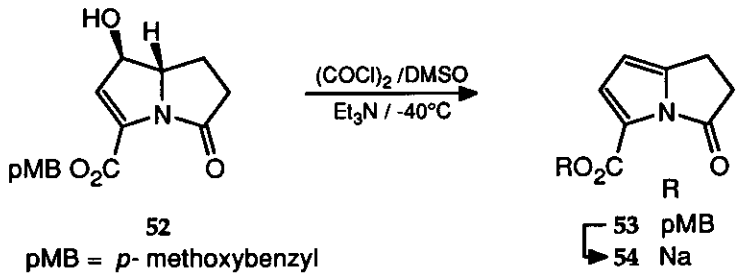
2.3 MISCELLANEOUS METHODS

Pyrrolizin-3-ones have been obtained by Flitsch and co-workers *via* dehydrogenation of partially hydrogenated derivatives, in excellent yield, as shown in Scheme 15. Ethyl 3-oxo-3*H*-pyrrolizine-7-carboxylate **(46)** was prepared by treatment of the dihydro system **(47)** with manganese dioxide.[38] Selective dehydrogenation of **48** with lead tetraacetate gave the corresponding 1,2-dihydro-3-oxo-3*H*-pyrrolizinecarboxylate **(49)**.[39] Dehydrogenation of the pyrrolizidine **(50)** using the same reagent gave 1-acetoxy-1,2-dihydropyrrolizin-3-one **(51)**, but only as a minor product.[29]



Scheme 15

The attempted oxidation of the alcohol **(52)** to a ketone led instead to the formation of the dehydration product **(53)** in 35% yield. Subsequent removal of the protecting group gave the sodium salt **(54)** of a γ-lactam type system (Scheme 16).[40]



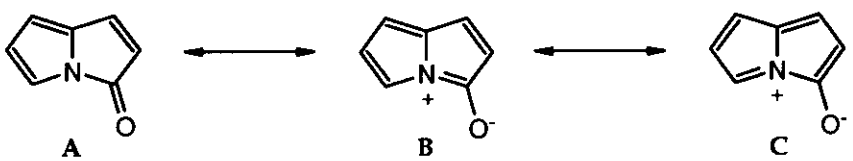
52
pMB = *p*- methoxybenzyl

Scheme 16

Preparation of 1,2-dihydropyrrolizin-3-ones by hydrogenation of pyrrolizin-3-ones is discussed in Section 4.1.1.

3. PHYSICAL PROPERTIES

The contribution made to the overall structure of pyrrolizinones by the antiaromatic 8π-electron canonical forms **B** and **C**, which would be obtained upon amide type delocalisation of the *N*-lone pair (Scheme 17) is of particular interest.



Scheme 17

3.1 ULTRAVIOLET AND VISIBLE SPECTRA

The intensely coloured pyrrolizin-3-ones have characteristic absorption bands at 290-310 nm and 410-450 nm (Table 1). The stronger band at 290-310 nm is consistent with the bathochromic shift associated with the introduction of an electron withdrawing substituent to pyrrole.[42] The extinction co-efficient (log ε ~ 4) is similar to those reported for pyrroles conjugated with a *cis*-alkene.[43] Variation in substituent has little effect on this absorption band.

The much weaker absorption band in the visible region is more susceptible to variation according to the substituents present; but no pattern is apparent. Any substituent, other than a simple methyl

Table 1 Uv/Visible Absorption Maxima of Pyrrolizin-3-one and Derivatives (1)

Substituent	Solvent	$\lambda_{max.}$ /nm (log ε)						References
H	EtOH			292 (5.0)		416 (3.7)		8
1-Me	EtOH			285 (3.87)		412 (2.83)		8
2-Ph	EtOH		256 (4.11)	293 (3.74)			440 (3.38)	8
1,2-Ph_2	-------	204 (4.58)	252 (4.31)				490 (3.50)	41
6,7-Ph_2	$CHCl_3$		255 (4.29)		354 (4.06)		446 (3.06	9
5,6-$(MeOPh)_2$	EtOH		263 (4.32)	291 (4.24)			490 (3.25)	11
2-CO_2H	EtOH	230 (3.98)		302 (3.61)	352 (3.52)		442 (3.06)	17
2-COCl	CH_2Cl_2	232 (3.79)	264 (3.6)	300 (3.59)	376 (3.56)		465 (3.08)	17
2-CO_2Et	EtOH	230 (4.13)		296 (3.71)			448 (3.16)	17
2-$CONEt_2$	EtOH	228 (3.83)		294 (3.94)			434 (3.26)	17
7-CO_2Et	EtOH	227 (4.04)		303 (3.94)			425 (3.1)	38
5,7-Me_2-6-CO_2Et	Cyclohexane		255 (4.2)	300 (3.8)			439 (3.22)	10
1-Me_2N	EtOH	212 (4.13)	274 (4.18)	308 (4.10)			431 (3.32)	36
1-(*N*-piperidinyl)-2-CN	MeOH	237 (4.37)	277 (4.15)	302 (4.27)			421 (3.38)	23

group, increases the wavelength of the longer wavelength absorption relative to the parent. It would appear that vicinal phenyl disubstitution may cause a particularly large bathochromic shift of this band to 490 nm. The occurrence of this longer wavelength band is due to a low energy π - π^* electronic transition[44] and is not particularly associated with the the pyrrolone ring as has been previously suggested.[10] Other maxima (Table 1) are associated with the substituent.

Table 2 Uv/ Visible Absorption Maxima of 1,2-Dihydropyrrolizin-3-ones **(2)**

Substituents	Solvent	$\lambda_{max.}$/nm (log ε)			Reference
5,6-Me_2	CH_2Cl_2	228 (4.0)	270 (3.6)		14
1,2-Ph_2	---------	214 (4.2)	238 (4.4)	315 (3.7)	41
5,6-$(MeOPh)_2$	EtOH		250 (4.5)	302 (4.1)	11
7-CO_2Et	EtOH	223 (4.3)		290	39
5,7-Me_2-6-CO_2Et	C_6H_{12}	225 (4.4)	260 (4.2)		10

Insufficient data on the 1,2-dihydropyrrolizin-3-ones **(2)** have been published for any pattern to emerge; there is, however, no absorption in the visible region (Table 2).

3.2 INFRARED SPECTRA

The main feature of interest in the ir spectra of pyrrolizin-3-ones has been the position of the carbonyl stretching frequency. This band is generally found at 1730-1745 cm^{-1} (parent 1740 cm^{-1}).[8] These values are remarkably high for amides, even for acyl pyrroles,[45] and are consistent with a lack of normal amide type delocalisation. The presence of an amino group at the 1-position reduces the carbonyl absorption frequency by 15-30 cm^{-1}, presumably due to an increased degree of conjugation. As would be expected of enones and their saturated analogues, 1,2-dihydropyrrolizin-3-ones appear to have a slightly greater carbonyl stretching frequency than the fully unsaturated system, normally in the range 1740-1765 cm^{-1} (parent 1750 cm^{-1})[8] with 2-acylamino derivatives at even higher frequency (1769-1787 cm^{-1}).[18]

3.3 NMR SPECTRA

A thorough investigation of the nmr spectra of pyrrolizin-3-one has been reported.[46] However no specific studies have been made of the effect of substituents, nor of the nmr spectra of 1,2-dihydropyrrolizin-3-ones.

The ^1H nmr spectra of pyrrolizin-3-ones contain two characteristic sets of signals. The pyrrole resonances are found at δ_H 6.80-7.05 (H-5) and δ_H 5.90-6.30 (H-6/7), and are typical of *N*-acylpyrroles;[47] the enone resonances occur at δ_H 7.00-7.15 (H-1) and δ_H 5.55-5.80 (H-2). These values can however vary markedly according to the nature and position of substituents (Table 3).

Table 3 Selected ^1H Nmr Data for Pyrrolizin-3-ones (1)

Substituent	Solvent	δ_H /ppm					Reference
		H-1	H-2	H-5	H-6	H-7	
———	$CDCl_3$	7.04	5.63	6.85	5.95	5.95	46
1-Me	$CDCl_3$	—	5.39	6.86	(5.97	5.99)	27
2-Me	$CDCl_3$	6.68	—	6.83	5.93	5.82	27
5-Me	$CDCl_3$	7.02	5.59	—	5.63	5.89	27
7-Me	$CDCl_3$	7.05	5.56	6.81	5.56	—	27
1-Ph	$CDCl_3$	—	5.80	6.85	6.25	6.25	31
2-Ph	$CDCl_3$	7.05	—	6.83	5.92	5.92	35
5-Ph	$CDCl_3$	7.10	5.69	—	6.19	6.07	27
6-Ph	$CDCl_3$	7.13	5.73	7.18-7.46	—	6.35	27
7-Ph	$CDCl_3$	7.32	5.72	6.97	6.27	—	27
2-CN	$CDCl_3$	7.67	—	7.05	6.20	6.42	27
2-COMe	$CDCl_3$	7.82	—	7.01	6.15	6.38	27
2-CO_2H	DMSO	8.1	—	7.29	6.23	6.52	17
2-COCl	Acetone	8.07	—	7.18	6.24	6.51	17
2-$CONEt_2$	Acetone	7.39	—	7.03	6.12	6.24	17
2-CO_2Et	$CDCl_3$	7.84	—	7.04	6.14	6.35	17
5-CO_2Et	$CDCl_3$	7.12	5.80	—	6.78	6.01	27
7-CO_2Et	$CDCl_3$	7.50	5.80	6.90	6.40	—	38
1-Me_2N	$CDCl_3$	—	4.22	6.98	6.06	6.06	37
1-Et_2N	$CDCl_3$	—	4.35	7.03	6.10	6.10	37
1-BnO	$CDCl_3$	—	5.12	6.95	6.15	6.05	33
1-EtO-7-$BnOCH_2$	$CDCl_3$	—	4.73	6.96	6.14	—	34
6-Br	$CDCl_3$	7.09	5.72	6.93	—	6.00	26

A weakly electron releasing methyl substituent causes a low frequency shift of $\Delta\delta_H$ 0.2-0.4 ppm of protons in adjacent positions. Conversely the anisotropic effect associated with a phenyl group

causes a high frequency shift of adjoining protons of similar magnitude. Introduction of an electron withdrawing substituent in the 2-position results in deshielding of all protons. The effect is especially strong at those positions with which the substituent is conjugated [(H-1), $\Delta\delta_H$ 0.4-1.0 ppm, and (H-7), $\Delta\delta_H$ 0.3-0.6 ppm]. As has been observed in many fused ring systems,[48] the presence of a phenyl or a carboxylate substituent at the 1- or 7-positions of a pyrrolizin-3-one causes a significant increase in the chemical shift of the *peri* proton, $\Delta\delta_H$ 0.2-0.5 ppm.

Conjugating electron donating groups at the 1-position result in a substantial shielding of H-2; for example, $\Delta\delta_H$ 1.3-1.4 ppm for 1-aminopyrrolizin-3-ones, and $\Delta\delta_H$ 0.5-0.9 ppm for 1-alkoxypyrrolizin-3-ones. A slight deshielding ($\Delta\delta_H$ < 0.25 ppm) of the pyrrole protons also occurs.

Variation in substituents has little effect on ^{1}H-^{1}H coupling constants. Typical values are shown in Figure 1. It has previously been noted[46] that couplings from H-5 to H-7 are broadly consistent with those found in simple pyrroles, while $^3J_{1,2}$ 6 Hz is typical of cyclopentenones. Some cross ring couplings are also present; of particular note is $^6J_{2,6}$ 0.9 Hz, which appears to be characteristic of conjugated fused 5-membered rings with a bridgehead nitrogen atom.[49]

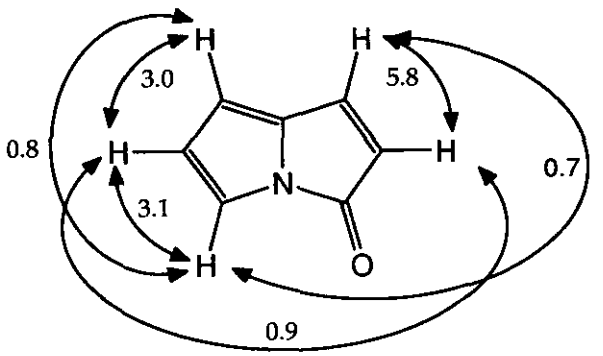
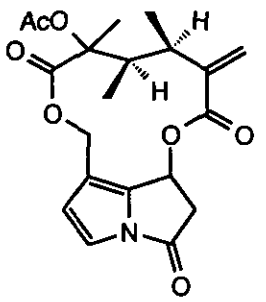


Figure 1 ^{1}H Nmr coupling constants (Hz) for pyrrolizin-3-one[46]

1,2-Dihydropyrrolizin-3-ones **(2)** have similar pyrrole type resonances to their fully unsaturated parent (Table 4). The signals corresponding to the protons in the 1- and 2-positions are found at δ_H 2.80-3.10. A resonance at δ_H 5.70-5.95 is typical of H-1 in 1-oxygenated 1,2-dihydropyrrolizin-3-one containing natural products[50-56] such as **55** .

Table 4 ^{1}H Nmr Data for Selected 1,2-Dihydropyrrolizin-3-ones (2)

R^1	R^2	R^5	R^6	R^7	Solvent	δ_H /ppm					Coupling Constants /Hz	References
						H-1	H-2	H-5	H-6	H-7		
H_2	H_2	H	H	H	CS_2	2.95	2.95	6.90	6.37	5.88	———	8
H_2	H_2	Me	Me	H	CCl_4	2.80	2.80	—	—	5.53	———	14
H_2	H_2	MeOPh	MeOPh	H	$CDCl_3$	3.00	3.00	—	—	6.25	———	11
H_2	H_2	H	H	CO_2Et	$CDCl_3$	3.06	3.26	7.02	6.81	—	$^3J_{5,6}$ 3	39
H_2	H_2	CHO	Cl	H	$CDCl_3$	3.05	3.10	—	—	6.13	———	29
Br.H	H_2	H	Br	H	$CDCl_3$	5.40	3.67, 3.31	7.17	—	6.34	$^2J_{2a,b}$ 19.4; $^3J_{1,2a}$ 7.3; $^3J_{1,2b}$ 2.1	26
EtO.H	H_2	H	H	$BnOCH_2$	$CDCl_3$	4.97	3.28, 2.94	7.05	6.51	—	$^2J_{2a,b}$ 18; $^3J_{1,2a}$ 7; $^3J_{1,2b}$ 2; $^3J_{5,6}$ 3	34
OH.H	H_2	H	H	CH_2OH	$CDCl_3$	5.36	3.37, 2.98	7.02	6.34	—	———	34
H_2	NHBoc. H	$COCF_3$	H	H	$CDCl_3$	3.57, 3.18	4.64-4.61	7.55	6.24		$^2J_{2a,b}$ 17.6; $^3J_{1,2a}$ 8.7; $^3J_{1,2b}$ 5.5.	18
H_2	H_2	H	OCO_2Et	H	$CDCl_3$	2.93	3.04	7.08	—	5.91	$^4J_{5,7}$ 1.2	29
H_2	H_2	H	OCH_2-$-CH_2OH$	H	$CDCl_3$	2.90	2.99	6.58	—	5.80	$^4J_{5,7}$ 1.3	29
N-Mor. H	Me_2	H	H	H	$CDCl_3$	3.67	—	6.99	6.43	6.15	———	35
N-Mor. H	Ph_2	H	H	H	$CDCl_3$	4.71	—	—	6.42	6.18	———	35
OR.H	H_2	H	H	CH_2OR	$CDCl_3$	5.93	3.69, 3.14	7.10	6.57	—	^2J 19; $^3J_{1,2a}$ 7.5; $^3J_{1,2b}$ 3.3	50



55

Similar patterns of resonances are observed for 2-acylamino-1,2-dihydropyrrolizin-3-ones. In both 1- and 2-substituted systems the proton *anti* to the substituent is particularly deshielded. The vicinal couplings associated with the H-1 and H-2 resonances (Table 4) suggest that the partially reduced ring is essentially planar, and the H-2 geminal coupling is consistent with the presence of an adjacent π-bond.[48]

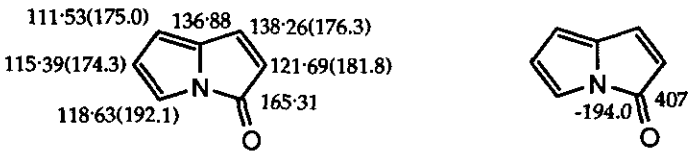


Figure 2. ^{13}C, $^{1}J_{CH}$ (Hz) (in parentheses), ^{15}N and ^{17}O Nmr Chemical Shifts of Pyrrolizin-3-one (relative to TMS, nitromethane and H_2O respectively)[46]

The ^{13}C nmr spectrum of **(1)** (Figure 2)[46] follows a similar pattern to the ^{1}H nmr spectrum, with the chemical shift and $^{1}J_{C\text{-}H}$ values of the pyrrole ring again being analogous to those of simpler systems.[57] The chemical shift of the carbonyl carbon atom in **1** suggests that the group is amidic in nature. Similarly the chemical shifts of both the enone methine carbon and proton resonances are much closer than would be expected for simple cyclic enones. In contrast, the ^{15}N and ^{17}O spectra of pyrrolizin-3-one[46] indicate rather more ketone character. A number of long range ^{1}H-^{13}C couplings are seen in the ^{13}C nmr spectra of **(1)** (Figure 3).[46] It is noticeable that in this case there is a complete absence of cross ring couplings.

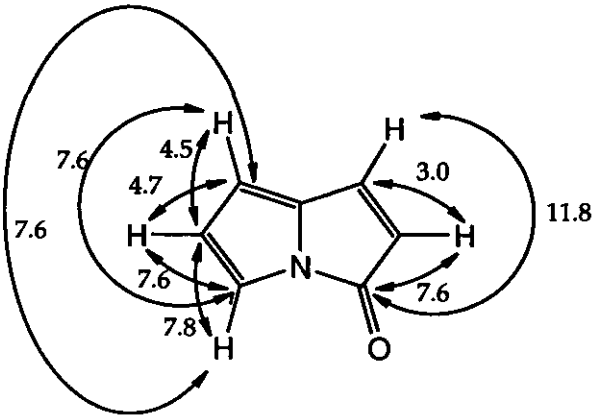


Figure 3 Long Range $^{n}J_{CH}$ (Hz) of Pyrrolizin-3-one [46]

The only ^{13}C nmr data published for a 1,2-dihydropyrrolizin-3-one is that for the natural product (**55**) (Figure 4). There are no significant changes in the resonances of the pyrrole ring carbons, nor of the carbonyl, compared with pyrrolizin-3-one and the chemical shifts of C-1 and C-2 are much as would be expected. However, the original assignment of the C-5 and C-6 resonances (Figure 4) should be reversed on account of the large $^{1}J_{CH}$ values. for the α-positions of pyrroles.

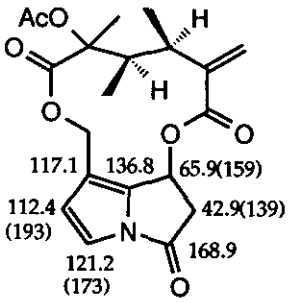
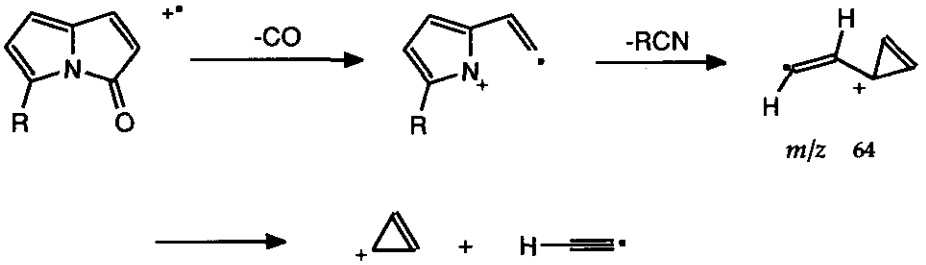


Figure 4. ^{13}C Nmr Chemical Shifts and $^{1}J_{CH}$ (Hz) (in parentheses) of **55** [50]

3.4 MASS SPECTRA

Although mass spectrometry has been used in the characterisation of pyrrolizin-3-ones, few fragmentation patterns have been reported and no specific study has been carried out. Under electron impact conditions, pyrrolizin-3-ones show strong M+ peaks, these often being the base peak.

Substantial peaks are observed due to initial loss of CO, followed by HCN (Scheme 18, R=H).[8,26] This may result in the formation of the cyclopropenium radical cation, *m/z* = 64. A peak is also observed at *m/z* = 63/64 for pyrrolizin-3-ones containing substituents in the 6- and 7-positions; hence, loss of substituent must occur prior to the generation of the cyclopropenium species. When the 5-position is blocked by R=Me,[27] or by R=Ph,[27] M-HCN (*m/z* = 78 and *m/z* = 139/140 respectively) is present along with M-RCN, (*m/z* = 63). Further study is required to explain the loss of HCN when the 5-position is blocked. An alternative rearrangement must therefore be involved in the fragmentation mechanism.



Scheme 18

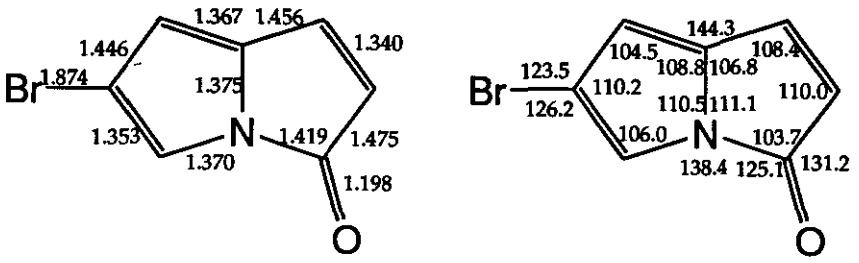
2-Acylpyrrolizin-3-ones undergo loss of X and COX (X= Cl,OH, NEt_2, OEt, and Me) prior to fragmentation of the pyrrolizin-3-one moiety,[17,27] while ethyl 3-oxo-3*H*-pyrrolizine-7-carboxylate **(46)** loses either CO_2Et or CO/HCN as the first fragmentation step.[38] 2-Cyanopyrrolizin-3-one is rather more stable with the usual losses of CO and HCN being the initial fragmentations.[27]

In each of the examples of 1,2-dihydropyrrolizin-3-ones for which fragmentation patterns have been reported,[26,38,39] partial or complete loss of side chains has occurred before the usual fragmentations have been observed.

3.5 STRUCTURE

Only one X-ray structure has been published for a fully oxidised pyrrolizin-3-one,[26] the bond lengths and angles of which are shown in Figure 5. 6-Bromopyrrolizin-3-one exhibits planar geometry at all positions including the bridgehead nitrogen. Alternation of the bond lengths in the pyrrole ring indicates a reduction in delocalisation compared with pyrrole. Similarly, the bond lengths in the pyrrolone ring imply limited conjugation of the olefinic [C(1)-C(2)] bond with the

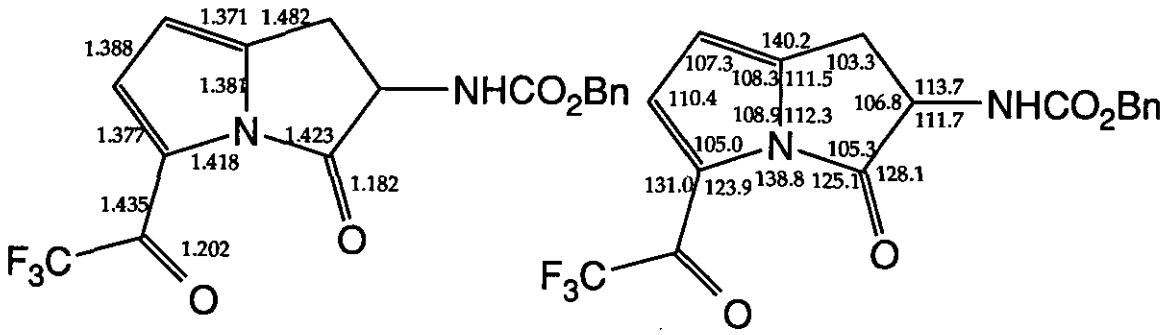
pyrrole ring. Of particular note are the C-N bond (1.419 Å) and the C=O bond (1.198 Å) which are significantly longer and shorter respectively than would be expected for an amide.



(a) (b)

Figure 5. (a)Bond lengths and (b) bond angles of 6-bromopyrrolizin-3-one.[26]

The structure of a 5-acyl-2-acylamino-1,2-dihydropyrrolizin-3-one,[18] has been reported recently, and selected details are shown in Figure 6. As in the fully unsaturated 6-bromopyrrolizin-3-one, the amide C-N bond (1.423 Å) and C=O bond (1.182 Å) are consistent with a lack of amide character. The system is again planar at all positions, with the exception of a small displacement (6°) of the carbonyl oxygen atom from planarity. It is likely that the increased length of the N(4)-C(5) bond is due to the presence of the 5-acyl substituent. Few details of the bond lengths of the dihydropyrrolone ring were given, but the small differences (2-3 standard deviations) in bond angles in this ring, in comparison with the fully unsaturated system may be significant.



(a) (b)

Figure 6.

(a)Bond lengths and (b) bond angles of a 1,2-dihydropyrrolizin-3-one .[18]

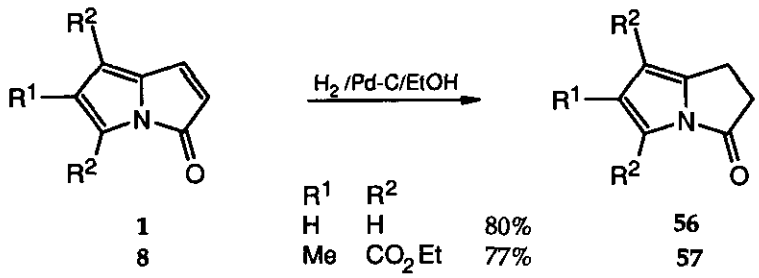
4. CHEMICAL PROPERTIES

4.1 REACTIONS OF PYRROLIZIN-3-ONES

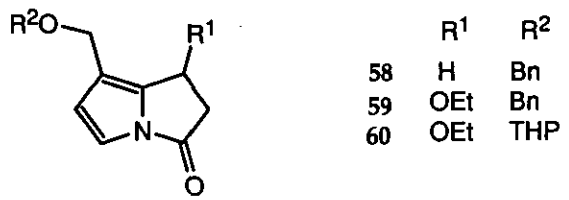
The pyrrolizin-3-one nucleus is potentially a highly reactive system containing as it does, enone, lactam, and pyrrole functionality. However, as yet little study has been made of the reactivity of the ring system due to its limited accessibility.

4.1.1 *Reduction of the Pyrrolizin-3-one Nucleus*

Pyrrolizin-3-one **(1)**[8] and the substituted pyrrolizin-3-one **(8)**[10] have both been reduced to the corresponding 1,2-dihydropyrrolizin-3-ones **(56)** and **(57)** under mild Pd-C catalysed hydrogenation conditions (Scheme 19). Similarly, the 7-alkoxymethyl-1,2-dihydropyrrolizin-3-ones **(58-60)** have been obtained from the parent pyrrolizin-3-ones by hydrogenation with Pd on barium sulphate as catalyst.[12,34]

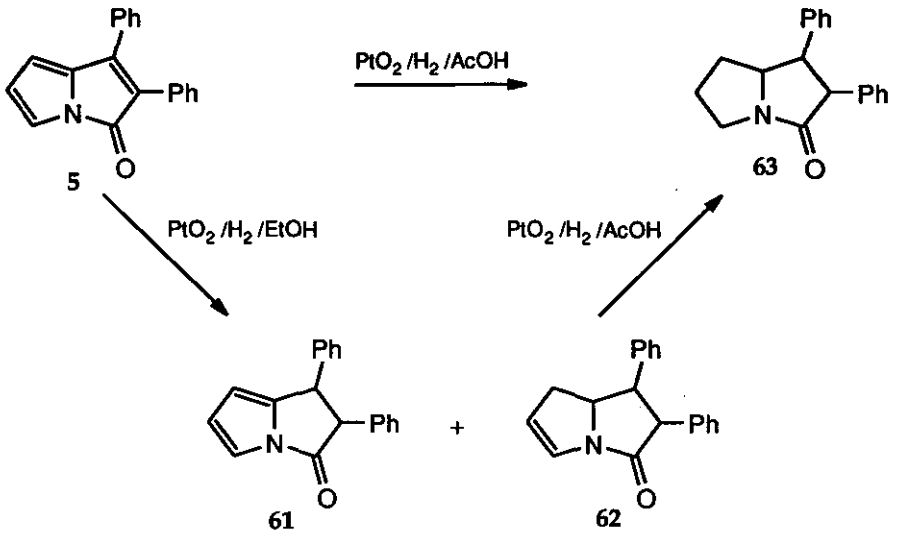


Scheme 19



THP:- Tetrahydro-2-pyranyl

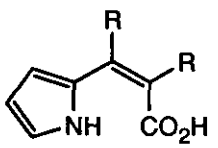
An Italian group has reported[41] that hydrogenation of the diphenylpyrrolizin-3-one **(5)** in ethanol in the presence of Adam's catalyst gave a mixture of 1,2-dihydro- and 1,2,6,7-tetrahydropyrrolizin-3-ones **(61)** and **(62)**. In acetic acid, hydrogenation of **5** and of the mixture of partially reduced systems resulted in the production of the fully hydrogenated pyrrolizidine **(63)** (Scheme 20).



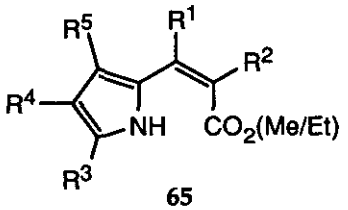
Scheme 20

4.1.2 Reactions with Nucleophiles

Pyrrolizin-3-ones generally react readily with hydroxide[7,58] or alkoxide[8,10,38] ions to give the ring-opened (*Z*)-3-(pyrrol-2-yl)propenoic acids (**64**), or the appropriate ester (**65**), respectively. Agosta has reported[10] a comparative study on the kinetics of ring opening by ethoxide of the pyrrolizin-3-one (**8**) and its 1,2-dihydro derivative (**57**). The results indicated no significant difference in the 'pseudo first order' rate constants for the two systems, although the unsaturated system was slightly more rapidly cleaved.

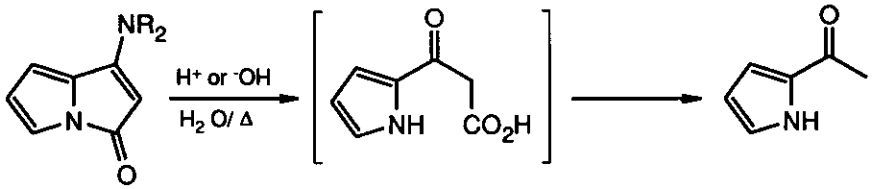


64 R = H; Ph



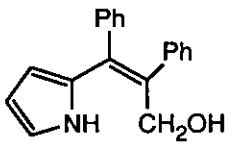
65

In contrast with the above, 1-diethylaminopyrrolizin-3-one (**43**) was stable to ethanolic sodium ethoxide.[37] However, upon treatment with aqueous acid or alkali, **42** and **43** have been hydrolysed to 2-acetylpyrrole,[36,37] probably *via* a β-keto acid (Scheme 21).



Scheme 21

Treatment of 1,2-diphenylpyrrolizin-3-one **(5)** with sodium borohydride in ethanol, resulted in the production of the allylic alcohol **(66)**.[41]

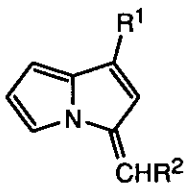


66

Soft nucleophiles such as thiophenol undergo conjugate addition to the 1,2-double bond to give 1-substituted1,2-dihydropyrrolizinones.[28]

4.1.3 Substitution Reactions

Pyrrolizin-3-ones have been reported by Flitsch[8,59] to undergo Wittig reactions to give the azafulvenes **(67)**; no experimental details were recorded.

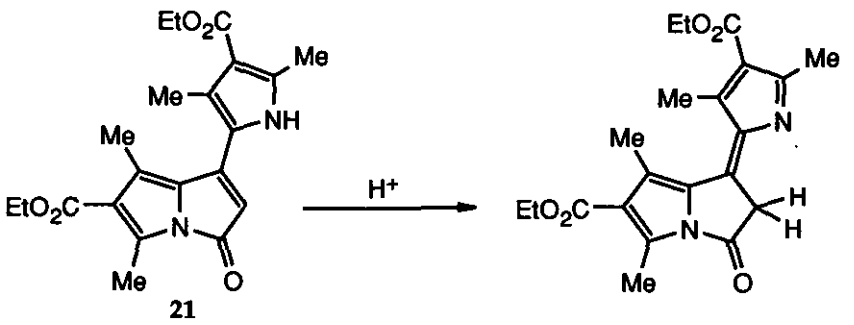


R^1	R^2
H	CN
H	CO_2Et
Me	CO_2Et

67

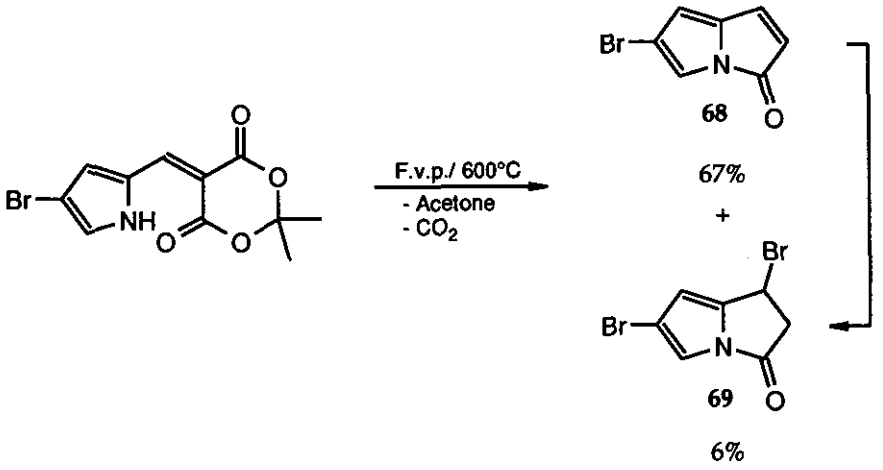
4.1.4 Reactions with Electrophiles

Under acid conditions, changes have been observed in the uv/visible spectrum of the 1-(pyrrol-2-yl)-pyrrolizin-3-one **(21)**.[60] The maximum at *ca.* 410-420 nm typical of pyrrolizin-3-ones, was replaced by an absorption at 595 nm. This observation may be attributed to a rearrangement such as that shown in Scheme 22. Rearrangements of this type are well known for dipyrrylmethenes.[42]



Scheme 22

It has been noted that under the flash vacuum pyrolysis conditions of its synthesis (Section 2.1.2.3), 6-bromopyrrolizin-3-one **(68)** is formed in the presence of small amounts of HBr. Subsequent electrophilic addition of HBr to **68** gave a low yield of the 1,6-dibromo compound **(69)** (Scheme 23).[26] The corresponding 1-chloro-1,2-dihydropyrrolizinone has been made in high yield by reaction of **1** with dry hydrogen chloride in dichloromethane.[28]



Scheme 23

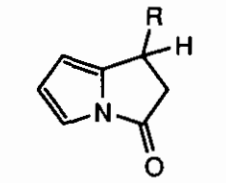
4.2 REACTIONS OF 1,2-DIHYDROPYRROLIZIN-3-ONES

4.2.1 Reactions with Nucleophiles

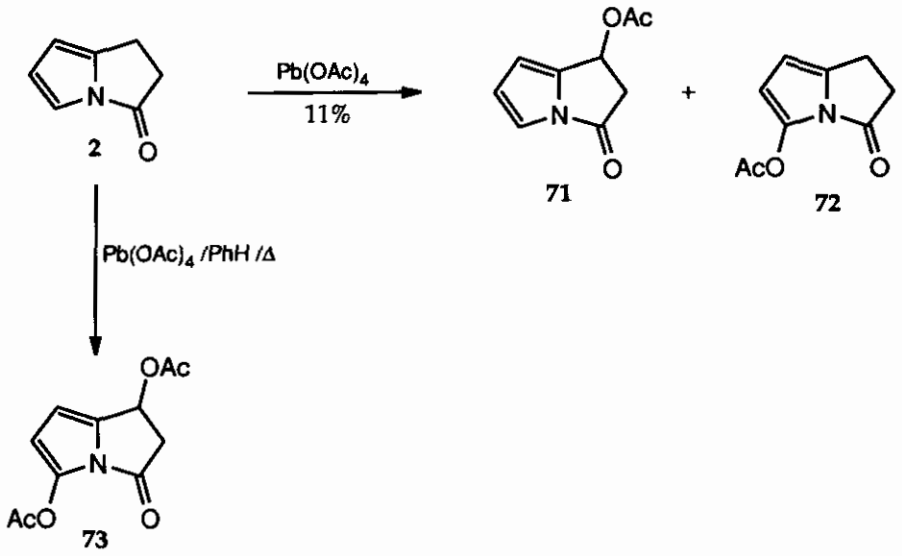
As mentioned in Section 4.1.2, the 1,2-dihydropyrrolizin-3-one **(57)** has been ring opened with sodium ethoxide.[10]

4.2.2 Substitution Reactions

Bohlmann has described[12] the introduction of *O-functionality* to the 1-position of 1,2-dihydropyrrolizin-3-ones by two means. Reaction of 1,2-dihydropyrrolizin-3-one **(2)** with perbenzoic acid *tert*-butyl ester gave the 1-benzoate **(70)** in moderate yield whereas the 1-acetoxy-1,2-dihydropyrrolizin-3-ones **(71-73)** were obtained in low yield upon treatment of **(2)** with lead tetraacetate (Scheme 24). The first of these methods was subsequently used in the preparation of **74** *en route* to 5,7a-didehydroheliotridin-3-one **(38)**.[12]



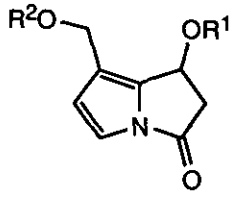
2 R = H
70 R = OCOPh



Scheme 24

4.2.3 Reactions of Substituents

O-Deprotection of 1-oxy-1,2-dihydropyrrolizin-3-ones has been achieved by acid hydrolysis,[12,34] to give 1,2-dihydro-1-hydroxypyrrolizin-3-ones, such as **38** , from an ether (**60**) or an ester (**74**). The ring system is stable under these conditions.



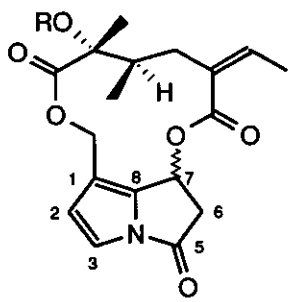
60 R^1 = Et; R^2 = THP
74 R^1 = COPh; R^2 = Bn
(* THP = Tetrahydro-2-pyranyl)

⟶ **38** $R^1 = R^2 = H$

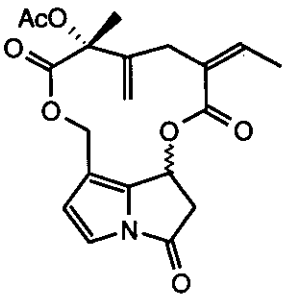
5. NATURAL PRODUCTS

A series of dilactonic pyrrolizidine alkaloids containing a 1,7-disubstituted 1,2-dihydropyrrolizin-3-one moiety has been isolated from the *senecio* plant species of Chile, Australia, and South Africa by Bohlmann and co-workers.[50-56] The first example, pterophoron (**55**), was isolated in 1977;[50] other typical examples include isosenaetnin (**75**) and dehydroisosenaetnin (**76**).[51] Whereas the absolute stereochemistry of each of the C-7 epimers of **76** was determined,[52] in many of the examples, including **75** , it has not been possible to identify the absolute stereochemistry at C-7.

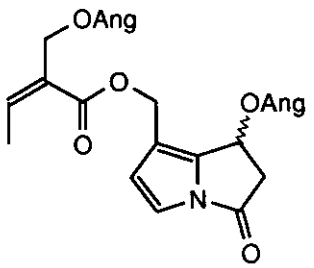
Other than **77** ,[53] all members of this series of pyrrolizine alkaloids contain a macrocycle such as in **75** and **76** . No variation is observed in the pyrrolizin-3-one moiety in any example; all structural variations occur in the macrocyclic portion of the molecules. The most recently identified member of the series, 7-*epi*-desacetylsenaetnin (**78**), is one of only two examples containing a free hydroxyl group rather than an acetate;[54] the other example is its C-7 epimer.[55]



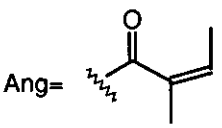
75 R= Ac
78 R= H



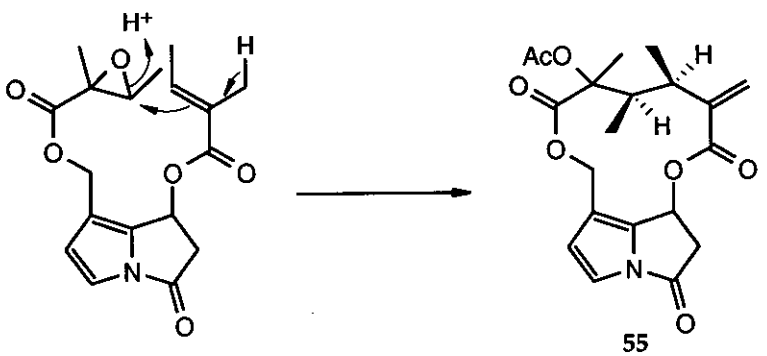
76



77



No study of the biosynthesis of these alkaloids has been detailed. However, it has been proposed[50] that the final step involves the acid catalysed ring closure shown in Scheme 25.

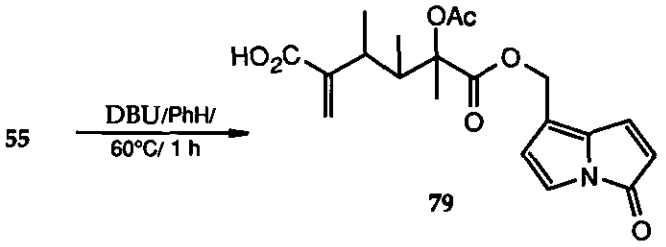


55

Scheme 25

A reaction of particular interest in the present context which was used in establishing the structures of **55** [50] and **77** ,[53] involved treatment of the pyrrolizine with diazabicycloundecene to generate

pyrrolizin-3-ones such as **79** (Scheme 26).



Scheme 26

There has been no total synthesis of any of the alkaloids in this series, though three syntheses of the pyrrolizin-3-one portion **(38)** have been reported.[12,28,34] Routes to the angelate moiety found in **(77)** are known,[61] as are syntheses of macrocyclic fragments similar to those found in this series.[1,2,62]

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