11.01 Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: No Extra Heteroatom

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11.01.1 Introduction

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Bicyclic 5-5 systems with one ring junction nitrogen atom and no extra (endocyclic) heteroatoms were first covered by W. Flitsch in CHEC-II(1996) <1996CHEC-II(8)1>.

The parent compound 1 is usually named 3H-pyrrolyzine instead of 3H-pyrrolo[1,2-a]pyrrole, the systematic name; numbering is shown.



Pyrrolizines, partially reduced pyrrolizines, benzopyrrolizines, and pyrrolizinones are covered in this chapter; however, the chemistry of naturally occurring pyrrolizidines and analogous compounds is beyond the scope of this chapter.

11.01.2 Theoretical Methods

A theoretical (*ab initio* and density functional theory (DFT) calculation) and experimental (X-ray and gas-electron diffraction (GED)) study has been devoted to pyrrolizin-3-one **2** and 1,2-dihydropyrrolizin-3-one **3** <2001J(P2)2195>. This work provides definitive structural parameters for **2** (solid and gas phases) and **3**. Good agreement was reached between experimental data (X-ray and GED) and those calculated by *ab initio* methods. Force fields calculated at the B3LYP/6-31G^{*} and B3LYP/6-311+G^{*} level (B3LYP/6-31G^{*} on H-atoms) confirmed the C_s symmetry of **2** and **3** (as free molecules) with pronounced distortion of the exocyclic bonds and angles at the bridgehead. As expected, partial hydrogenation on going from **2** to **3** has considerable effect on the bond lengths and angles in the semisaturated ring. A noteworthy effect which was predicted by calculation (in good agreement with X-ray data) concerns the amide group; among the three C–N bonds, the one involved in the amide moiety (N(4)–C(3)) changes the most, shortening by ca. 0.03 Å. The unusual N(4)–C(3) bond lengthening in **2** is consistent with its reluctance to create an antiaromatic 8π -electron system by delocalization (see Tables 1 and 2).



Table 1	Selected data comparing solid-state (XRD), experimental gas-phase (GED, $r_{ m h1}$) and
calculated	gas-phase (MP2, $r_{ m e}$) geometries for 2 ; bond lengths in Å and angles in degree	ЭS

Parameter	XRD	GED	MP2
C(7)–C(8)	1.364(2)	1.395(5)	1.3875
C(6)–C(7)	1.437(2)	1.439(4)	1.4362
C(5)–C(6)	1.365(2)	1.394(2)	1.3863
C(1)–C(8)	1.457(2)	1.461(3)	1.4584
C(1)–C(2)	1.344(2)	1.363(10)	1.3605
C(2)–C(3)	1.489(2)	1.498(3)	1.4941
C(4)-C(5)	1.384(2)	1.389(7)	1.3813
N(4)-C(8)	1.381(2)	1.380(7)	1.3763
N(4)-C(3)	1.408(2)	1.437(4)	1.4319
C(3)–O(3)	1.207(2)	1.215(4)	1.2098
O(3)-C(3)-N(4)	125.22(12)	124.4(9)	125.4
C(5)-N(4)-C(8)	110.03(10)	108.7(7)	110.6
C(3)-N(4)-C(5)	138.68(11)	137.5(6)	138.2
C(3)-N(4)-C(8)	111.13(10)	111.17(10)	111.16
C(7)-C(8)-N(4)	107.85(11)	107.7(4)	107.8
C(1)-C(8)-N(4)	106.85(10)	107.6(4)	107.3
C(1)–C(8)–C(7)	145.23(13)	141.8(6)	144.9

<2001J(P2)2195>.



 Table 2
 Selected data comparing solid-state (XRD) and calculated gasphase (MP2) for 3; bond lengths in Å and angles in degrees

Parameter	XRD	MP2
C(7)–C(8)	1.358(2)	1.3800
C(6)–C(7)	1.437(2)	1.4367
C(5)–C(6)	1.363(2)	1.3847
C(1)–C(8)	1.502(2)	1.503 3
C(1)–C(2)	1.545(2)	1.5479
C(2)–C(3)	1.515(2)	1.5268
C(4)–C(5)	1.387(2)	1.3801
N(4)-C(8)	1.390(2)	1.3846
N(4)-C(3)	1.392(2)	1.4068
C(3)–O(3)	1.216(2)	1.2095
O(3)-C(3)-N(4)	124.35(13)	125.4
C(5)-N(4)-C(8)	110.62(12)	111.0
C(3)-N(4)-C(5)	135.58(13)	135.4
C(3)-N(4)-C(8)	113.76(11)	113.7
C(7)-C(8)-N(4)	107.34(12)	107.4
C(1)-C(8)-N(4)	109.71(12)	110.3
C(1)-C(8)-C(7)	149.92(13)	142.3

Recent studies (calculation at the B3LYP/6-311+G(d,p) level) on the hapticity of unsolvated monomeric complexes of two pyrrolizine anions with Li, Na, and K were described <2005JCD1157>. These calculations suggest two hapticities for 4-azapentalenyl complexes: η^5 -binding mode 4, which prevails in the case of lithium complex, and folded structure 5, which prevails in the case of Na and K analogues. Similar calculations on the benzannulated anion complexes were also undertaken. According to these calculations, η^5 -binding structures 6, 8, and η^6 -binding structure 9 are more stable (ca. 1.2 kcal mol⁻¹) than η^6 -binding folded structure 7 in the case of lithium complex. For sodium complex, structures 7 and 9 were the only minima located (7 is 2.15 kcal mol⁻¹ below 9). The folded structure 7 was the only minimum located in the case of potassium complex.



A series of calculations was performed in order to rationalize the easy isomerization of pyrrolam A 10 during its synthesis and/or isolation from plants and insects extracts <2004JOC6105>. A partial potential energy surface for the interconversion 11/10 through 13 and 11/12 through 14 was constructed using DFT geometry optimization and energy evaluation (MP2/6-311+G*//B3LYP6-311+G*). The relative stabilities calculated by molecular mechanics and semi-empirical methods could not predict the easy rearrangement of 10 to 11; only the MP2 model comes close to the experimental data.



Giordan *et al.* <1996JCC156> have performed a theoretical study to compare the relative stability of *endo*- and *exo*-conformers of retronicine **15** and heliotridine **16** alkaloids. The *ab initio* calculations (HF/6-31G^{*}) suggested a greater stability of *exo*-conformers for both diastereomers (retronicine (2.6 kcal mol⁻¹), heliotridine (3.1 kcal mol⁻¹)) in excellent agreement with the available experimental structural data (X-ray and ¹H nuclear magnetic resonance (NMR)). Semi-empirical and molecular mechanics methods appeared inappropriate for these conformational analyses. However, using MM3(92) with reoptimized H-bonding parameters, Giordan <1998JCC1853> has found a set of probable *exo*-puckered conformers for retronicine and *exo/endo*-puckered conformers for heliotridine **16**.



Schmitz *et al.* <2001JPO90> developed two group increment schemes for converting HF/6-31G(d) and B3LYP/6-31G(d) calculated energies of aliphatic amines to estimations of heats of formation. Application to the pyrrolizidine yielded calculated values of -1.09 (HF) and -1.02 (B3LYP) instead of -0.93 kcal mol⁻¹ (experimental).

11.01.3 Experimental Structural Methods

11.01.3.1 X-Ray

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X-Ray investigation of pyrrolizinones 2 and 3 (see Tables 1 and 2) showed that both compounds are essentially planar with a butterfly angle (about the junction bond) of 3.06° for 2 and (surprisingly) only 1.14° for 3. Moreover, these X-ray data clearly show that the amide C–N bond is shorter in 3 than in 2 (see discussion in Section 11.01.2). The same C–N bond elongation was noticed in the case of 5*H*-pyrrolo[2,1-*a*]isoindol-5-one 17 <1999J(P1)2047>. Flamini *et al.* <2001J(P1)3069> reported the X-ray and molecular structure of 5-amino-3-(hex-5-enylimino)-1,2,6,7-tetracyano-3*H*-pyrrolizine 18 which consists of highly planar 5-amino-3-iminopyrrolizine moiety: C(3)–N(14) (1.27 Å) and C(5)–N(9) (1.32 Å).



The X-ray structure analysis carried out for the 6-(2-hydroxybenzoyl)-5-(pyrrolo-2-yl)-3H-pyrrolizine 19 unambiguously showed the allylic double bond to be located between C-1 and C-2 <2003AXo321>.



X-Ray data of tricarbonylchromium complex of 6-methylsulfanyl-5-phenyl-2,3-dihydro-1*H*-pyrrolizine 20 showed that the benzene ring is inclined at about 40° to that of the dihydropyrrolizine. Moreover, the tricarbonylchromium group is positioned *syn* to the nitrogen atom <1998J(P1)1175>.



11.01.3.2 NMR Spectra

Typical NMR data were compiled in CHEC-II(1996) <1996CHEC-II(8)2> for *3H*-pyrrolizine 1, its lithium salt, the pyrrolizin-3-one 2, and its regioisomer (pyrrolizin-2-one). More recently, Kissounko *et al.* <1998JOM(556)145> reported the ¹H chemical shifts of the parent pyrrolizine anion and anion 21a as well as those of their silylated or stannylated derivatives 22–26.



¹¹⁹Sn Chemical shifts were also reported for isomers **24a** (115.3 ppm) and **24b** (116.15 ppm). The reported ${}^{2}J_{Sn-H}$ for **24** and **26** range between 42 and 54 Hz except ${}^{2}J_{H(1)-Sn}$ for **24b** which is surprisingly high (95 Hz)!

By using ¹H and ¹³C NMR spectroscopy, Watson *et al.* <2004JOC6105> could assign the structure of each pyrrolam regioisomer 10–12.



Owing to signal overlap, only partial assignment 1 H (6.55–7.99 ppm) and 13 C resonances were possible for anions 6–9. Of course, most of the compounds described in this chapter were well characterized mainly due to the NMR techniques.

11.01.3.3 UV and IR Spectroscopy

Ultraviolet (UV) data are seldom reported for new pyrrolizine derivatives. Flamini *et al.* <2001 J(P1)3069> described the optical spectra of 5-amino-3-imino-1,2,6,7-tetracyano-*3H*-pyrrolizines **18**, which exhibit an intense broad absorption band centered at ca. 580 nm.

No characteristic IR data were reported for pyrrolizines or dihydropyrrolizines. An almost complete set of vibrational frequencies was deduced by combining an infrared (IR) and a Raman spectrum of pyrrolizinone 2 < 2001J(P2)2195>. The experimental values thus obtained were used to scale the theoretical complete set of vibrational frequencies of 2. Using the same scaling constant, the authors proposed a set of calculated vibrational frequencies for dihydropyrrolizinone 3.

11.01.3.4 Mass Spectrometry

This subject was not covered in CHEC-II(1996) <1996CHEC-II(8)1>. This technique is frequently employed for identification of metabolites in extracts from leaving organisms. The parent ions of pyrrolizine derivatives are usually observed by mass spectrometry even in electronic impact mode. The mass spectrum of the thallium salt of *3H*-pyrrolizine was described by Kissounko *et al.* <1998JOM(556)145> as follows: (electronic ionization (EI), 70 eV) *m/z*: 309 (23%, M⁺ for ²⁰⁵Tl); 307 (9.5%, M⁺ for ²⁰³Tl); 205 (100%, ²⁰⁵Tl⁺); 203 (43%, ²⁰³Tl⁺); 104 (76%, C₇H₆N⁺); 66 (35%, C₄H₄N⁺); 39 (38%, C₃H₃⁺). The parent ions M⁺ of pyrrolizinones are also detected <2005JOC6629> and, generally, a characteristic loss of carbon monoxide (–28) is observed <1981JOC2809>. Ji *et al.* <2000MI117> reported a rapid and accurate method for the pyrrolizinones' molecular weight determination by matrix-free laser desorption/ionization time-of-flight mass spectrometry (LDI-TOF-MS) technique.

11.01.4 Thermodynamic Aspects

11.01.4.1 Aromaticity

The p K_a value (~29) attributed by Okamura and Katz <1967T2941> to pyrrolizine seems too high, as was pointed out by Flitsch <1996CHEC-II(8)3>. Kissounko *et al.* <1998JOM(556)145> reported the preparation of pyrrolizine anion by using thallium ethoxide (for deprotonation of 3*H*-pyrrolizine) which is indicative of a rather moderate p K_a value for the pyrrolizine anion. The benzannulated analogue of the latter was reported by Bermingham *et al.* <2005JCD1157>, who described its preparation by reacting its conjugate acid with potassium at low temperature. No data were given concerning the p K_a value of this *a priori* aromatic anion.

11.01.4.2 Tautomerism

As summarized in CHEC-II(1996) <1996CHEC-II(8)3>, 3*H*-pyrrolizinones are more stable than the corresponding 1*H*-pyrrolizinones. Moreover, for substituted ones, there is equilibrium between 3*H*- and '5*H*'-tautomer depending on the position and the electronic nature of the substituent(s) of the pyrrolizine framework. Thus, treatment of pyrrolizine anion 4 with group 14 electrophiles (R_3SiCl and R_3SnCl) gives a mixture of 1-substituted-1*H*- and 3-substituted-3*H*-pyrrolizines; the latter slightly predominate in the case of tin derivatives and the former predominate in the case of silylated ones. In the case of 1-methylpyrrolizine anion, only the 1-methyl-3-substituted-3*H*-pyrrolizine isomers were detected when the reaction was performed in tetrahydrofuran (THF). In 1,2-dimethoxyethane (DME), both 3- and 5-silylated regioisomers (25a/25b = 3/1) were obtained exclusively as their 3*H*- and '5*H*-tautomer, respectively <1998JOM(556)145>.

1*H*-Pyrrolizine **29** could be obtained from the corresponding stable phosphorus ylide **28** (with Z = H), which was prepared by reacting dialkyl acetylenedicarboxylate with triphenylphosphine and 2-acyl-1*H*-pyrrole **27** <1999JCM382>. Only 3*H*-tautomer **30** was obtained when $Z = CF_3 < 2006ARK55>$, while 1*H*-tautomers **31** were exclusively isolated when starting from pyrrole **27** bearing $Z = CO_2R$ or CONHR <2001T5873>.



Previously, Llopart and Joule <2004ARK20> obtained a mixture of tautomers **32a** and **33a** when 2-benzoylpyrrole was reacted with vinyltriphenylphosphonium bromide and sodium hydride. Starting from 4-acetyl-2-benzoylpyrrole, the same reaction only resulted in the (somewhat unstable) tautomer **32b**. Surprisingly, no 1*H*-tautomers were observed in these cases. Similar tautomerization was observed in the case of 3*H*-pyrrolizines bearing 2(6)-diethylphosphonate substituent <1996PS275>.

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The enol form 10' of pyrrolam A 10 could not be detected despite its aromatic character <2004JOC6105>. Also, its pyrrolinone analogues 34 exist mainly as β -enaminones <1985TL833>; the tautomeric hydroxypyrrole 34' was only observed when R = CO₂Et (Scheme 1) <1988JOC5680>.



Scheme 1

11.01.4.3 Miscellaneous

Recently, Mascal and Cerón Bertran <2005JA1352> reported the preparation and characterization of 35 (azaanalogue anions of triquinacenes) which are stable enough in THF solution (in the absence of acid). Moreover, the hexachloro anion 35b could be isolated as tetraethylammonium salt by column chromatography on alumina. As expected, anion 35a was more nucleophilic than 35b. Indeed, only the former could be benzylated leading to 36a. However, 35b reacts easily with molecular bromine at low temperature yielding the corresponding α, α, α -tribromide 37b or dibrominated ether 37'b when this bromination was conducted in THF.



Vianello and Maksić <2005TL3711> reported a theoretical prediction (DFT calculations) of the acidity of the conjugate acid of azatriquinanes **35a** and its still unknown hexacyano analogue **35c**. These calculations predict a pK_a value of 10.7 (in dimethyl sulfoxide (DMSO)) for the couple involving anion **35a** and -26.5 for that involving anion **35c**. Earlier, Jiao *et al.* <2001JOC3902> described a DFT computation devoted to the enthalpies of formation and hydrogenation, ionization potential, proton affinities of the neutral aza-tricyclic compounds **38–41**, and the spin properties of their corresponding radical ammoniums.



11.01.5 Reactivity of Fully Conjugated Rings

11.01.5.1 Reduction

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As expected, when using Pd/C in alcohols at room temperature, exclusively hydrogenation of the C(1)–C(2) double bond in **32b** takes place; the pyrrole ring remains unsaturated despite an overnight reaction period <2004ARK20>. Blockhuys *et al.* <2001J(P2)2195> described once more the selective enone C=C bond reduction of pyrrolizin-3-one **2** under mild conditions (1 atm H₂, Pd/C), as described earlier <1971CB2170>. Beccalli *et al.* <2002EJO2080, 2001T8323> studied the hydrogenation of substrate **42** using Pd(OH)₂ under atmospheric pressure of hydrogen in methanol, and found that the pyrrole ring saturation requires the presence of HCl. Using 1 equiv of HCl, a mixture of **43a** and **43b** was obtained. When a large amount of HCl is used (e.g., 20 equiv), the pyrrole nucleus saturation becomes faster than the cleavage of the isoxazolidine ring and hydrogenolysis of the benzylic and pseudobenzylic amino group, leading selectively to a mixture of compounds **44a** and **44b**. In the absence of hydrochloric acid, only hydrogenolysis of N–O and N–Bn bonds took place with no saturation of the pyrrole ring. A similar study was performed with the benzo-annulated analogues **45**. The use of Pd(OH)₂ in methanol, or Pd/C in acetic acid, resulted in the *N*-debenzylation and isoxazolidine ring cleavage leading to compounds **46**. Semireduction of the indole moiety, leading to **47**, requires the presence of hydrochloric acid <2000JOC8924>.



As expected, under a hydrogen atmosphere in the presence of Pd/C in ethanol, the benzannulated pyrrolizine 48 leads to the dihydropyrrolizine derivative 49. However, semireduction of the pyrrole ring could be performed via the tricarbonyl chromium complex of 49 with various hydrides. Use of cyanoborohydride in trifluoroacetic acid (TFA) gave the best results for compound 50, both in terms of chemical yield (92%) and diastereoselectivity (90% of the *trans*-isomer) <2000TL1123>.



The pyrrole ring reduction in the benzannulated pyrrolizin-3-one **51** seems to take place easily in the presence of Pd/C in methanol under atmospheric pressure of hydrogen, at room temperature, and, noteworthy, under neutral conditions. The nitro group is also reduced under these mild conditions <2001JME4615>. Unlike **51**, under the same conditions, 1,2-diphenylpyrrolizin-3-one gave the 1,2-dihydro analogue with no pyrrole ring reduction. The pyrrole nucleus saturation of this pyrrolizinone required Adams catalyst <1996CHEC-II(8)4>. As expected, reduction of 1,2-dihydropyrrolizin-1-one takes place smoothly with sodium borohydride in methanol <2002T10407>. Deoxygenation of the benzannulated pyrrolizin-1-one **52** was performed under Wolff–Kishner conditions in 49% yield <2004JOC5476>.



The azatriquinane 36a which may be regarded as an annulated bis-pyrrolizine readily undergoes stereoselective hydrogenation in presence of rhodium on alumina, leading to the fully saturated tricyclic compound with a *trans* relative orientation between the benzyl group and the two hydrogen atoms located on the two other junctions' carbon atoms <2005JA1352>.

11.01.5.2 Electrophilic Attack

No significant examples of electrophilic attack on 3H-pyrrolizines were reported since CHEC-II(1996). Nevertheless, treatment of the tricyclic pyrrolizine 53 with aqueous bromine in THF afforded, as expected, the corresponding bromohydrin 54 <1997T4549>.



Electrophilic substitutions at the pyrrole nucleus were described only with 1,2-dihydropyrrolizines which react with the same regioselectivity as would do equivalently substituted monocyclic pyrroles.

McNab and Thornley reported a detailed study related to the reactivity of 3*H*-pyrrolizin-3-one **2** toward various electrophilic reagents <2000J(P1)3584>. In the presence of dry hydrochloric acid in dichloromethane, pyrrolizinone **2** gave in 93% yield the corresponding electrophilic addition compound **55a** which easily undergoes nucleophilic substitution when treated with water, thus leading to **55b**. The same sequence carried out with 7-hydroxymethyl-3*H*-pyrrolizin-3-one afforded in 63% yield, 1-hydroxy-7-hydroxymethylpyrrolizin-3-one **56**, which constitutes the base of a number of alkaloids isolated from various *Senecio* species <1991P2691>. Treatment of **2** with dry HCl in refluxing methanol gives only the methoxy compound **55c**; this reaction goes either through **55a** or directly by trapping of the transient pseudobenzylic cation intermediate. Also, pyrrolizinone **2** was allowed to react with *N*-bromosuccinimide (NBS), either in methanol or acetic acid leading to the corresponding oxobromination adducts **57** in up to 82% yield. These results were not reproducible; for instance, in some cases, **57b** was obtained along with the fully conjugated compound **58** and traces of the dibromo derivative **57c**. Under free radical conditions (NBS, PhCOO₂COPh) pyrrolizin-3-one **2** gives only traces of the expected derivative **57c**, and it probably undergoes spontaneous β -elimination leading to **58** which was isolated in 55% yield (**Scheme 2**).



Attempts to perform the formylation of 2 under Vilsmeier conditions (POCl₃, dimethylformamide (DMF)) in refluxing dichloroethane (15 min) followed by work-up with an aqueous solution of sodium acetate afforded a mixture of recovered 2 and six other products: 55b, 55d, 59a–c, and 60. As outlined by the authors <2000J(P1)3584>, formylation may not take place directly on 2; they suggested a plausible mechanism, assuming that all products of this reaction, including recovered 2, would arise from the hydrochlorination compound 55a which may partially undergo formylation leading to 61. After work-up, 55a leads to 2, 55b and 55d, whereas 61 leads to 59 and 60.



The same authors <2000J(P1)3584> studied the reactivity of 2 toward benzenediazonium (chloride or tetrafluoroborate) salts. No diazo coupling took place under neutral or slightly acidic conditions. However, under basic conditions (NaOH in H₂O/MeOH), a mixture of 62 and 63 was obtained. This result clearly indicates that the diazo coupling takes place through the anion of 62 which arises from the base-catalyzed methanolysis of amide 2 in which the pyrrole ring is obviously not nucleophilic enough.



11.01.5.3 Nucleophilic Attack

Pyrrolizine itself is not prone to nucleophilic attack. Treatment of 3*H*-pyrrolizine as well as 1-methyl-3*H*-pyrrolizine with *n*-butyllithium gives the corresponding conjugated bases **4** and **21a**, respectively <1998JOM(556)145>. As with the pyrrole nucleus, pyrrolizines show no electrophilic behavior. On the other hand, most of the additions described with pyrrolizin-3-one **2** were performed via electrophilic additions as seen above <2000JCS(P1)3584>, except in the case of the soft reducing agent, sodium borohydride, which reacts with **2** in ethanol via a conjugate 1,4-addition to afford the corresponding 1,2-dihydro-3*H*-pyrrolizin-3-one **3** <1999J(P1)2049>. As expected, treatment of 2,3-dihydro-1*H*-pyrrolizin-1-ones **64** with sodium borohydride leads to the corresponding pseudobenzylic alcohols <2002T10407>.



Katritzky *et al.* <1997JOC4148> achieved some transformations of 1-(benzotriazol-1-yl)-2,3-dihydro-1*H*-pyrrolizine **65** based on nucleophilic attacks either at 1- or 5-position. Indeed, reaction of **65** with Grignard reagents and thiophenolate gives smoothly the *ipso*-substitution of the benzotriazol-1-yl group leading to **66** and **66'**, respectively, while sodium cyanide in DMF leads to **67** via nucleohilic substitution of benzotriazol-1-yl group via a conjugated nucleophilic attack on the pyrrole nucleus and concerted or subsequent departure of benzotriazole anion, followed by rearomatization of the pyrrole nucleus. Treatment of **65** with the malonate anion resulted in an elimination of benzotriazole leading to the corresponding 3*H*-pyrrolizine **68** (Scheme **3**).



Scheme 3

11.01.5.4 Cycloaddition and Cyclization

Since the examples compiled in CHEC-II(1996) <1996CHEC-II(8)7>, no new examples of cycloaddition involving pyrrolizines have been described. However, Comer et al. reported two types of cycloaddition involving the pyrrolizin-3-one moiety. Flash vacuum pyrolysis (FVP) of 69 leads to 1-carbomethoxy-3H-pyrrolizin-3-one 70, which spontaneously dimerizes to give [2+2] cycloadduct 71b as a mixture of syn- and anti- (head-to-head) stereomers, whose structures were secured by X-ray analysis <1996CC1083>. Moreover, it was also found that 70 reacts with its precursor 69 leading to the cyclocondensation compound 72 via a formal [4+2] cycloaddition <1996AXC3064>. Unlike 70, the parent pyrrolizin-3-one 2 needs photochemical activation to promote its dimerization leading to synand *anti*-71a and their (head-to-tail) regioisomer 71'a, which was isolated as a single syn-stereomer <2000ARK252>. Assignment of structures and relative stereochemistry of dimers 71a and 71'a rely mainly on NMR data. The ratio of regioisomers 71a/71'a is highly dependent on reaction conditions: in methanol an almost equimolar mixture of the three isomers was obtained; meanwhile in the presence of slight excess of benzophenone (triplet sensitizer) the photodimerization becomes faster and more selective in favor of the (head-to-head) regioisomer 71a which was isolated in 80% yield along with 5% of the (head-to-tail) regioisomer 71'a. As stated by the authors, these photochemical reactions involving 2 were initially performed in order to achieve a photochemically promoted regiospecific conjugate 1,4-addition of alcohols by analogy with similar experiments performed with butenolides <1993J(P1)2141>. No nucleophilic 1,4-addition adducts were detected in the case of substrate 2 (Scheme 4).



Scheme 4

11.01.5.5 Ring Openings

As seen in Section 11.01.5.2, pyrrolizinone 2 easily undergoes ring opening in the presence of aqueous sodium hydroxide during the base-catalyzed diazo coupling, leading to the corresponding *cis*-acrylate 62. In order to get

7-hydroxymethyl-3*H*-pyrrolizin-3-one **73b** by selective methanolysis of the acetate moiety, compound **73a** was allowed to react with anhydrous potassium carbonate in methanol at room temperature, but even under such mild base-catalyzed conditions, **73b** undergoes quantitative methanolysis of the pyrrolizinone moiety to give exclusively the (*Z*)-methyl acrylate **74** <2000J(P1)3584>. Easy base-catalyzed methanolysis was also observed with pyrrolizinone derivatives **75** where the 2-benzyl-5-carbonyl-3*H*-pyrrolizin-3-one substructure acts as a characteristic red tag for various amino acids. The stereochemistry of the resulting acrylates **76** depends on the nature of the amino acid bearing this pyrrolizinone moiety; only (*Z*)-isomers were obtained in the case of leucine and phenylalanine whereas the glycine derivative affords a mixture of (*Z*)- and (*E*)-isomers (**Scheme 5**) <2002TL3673>.



Scheme 5



Scheme 6

Unlike with sodium borohydride (see Section 11.01.5.2), pyrrolizin-3-one 2 reacts with lithium aluminohydride mainly as an amide. No conjugate addition occurs, and only the reductive lactam cleavage takes place to give stereoselectively the (Z)-allylic alcohol 77. Similarly, benzo-annulated pyrrolizin-3-one 17 gives the corresponding benzylic alcohol 78. The same reactivity was observed with organometallics such as methyllithium which gives exclusively the tertiary (Z)-allylic alcohol 79 (Scheme 7).



Scheme 7

As with many $N(sp^3)$ -azaheterocycles, monocrotaline 80 undergoes regioselective ring opening leading to 81 when treated with 2,2,2-trichloroethylchloroformate (Troc-Cl) in presence of potassium iodide (Scheme 8) <1999JA2951>.



Scheme 8

11.01.5.6 Miscellaneous

Under singlet oxygen conditions (O₂, $h\nu$, methylene blue), the dihydropyrrolizine 82 gives the hydroxy-pyrrolidinone 83 in only 24% yield. The authors speculated that a possible ring opening promoted by a suitable silylating agent such as TMSOTf would lead to the azadiene 83' (Scheme 9) <2004ARK20>.



Scheme 9

Upon treatment with dimethyldioxirane (DMDO), benzannulated dihydropyrrolizine 84 afforded two dimers 86 and 86', each as a mixture of two diastereomers <1997JA1159>. The zwitterionic species 85 is postulated as intermediate in these dimerizations (Scheme 10).



Reaction of dihydropyrrolizine 87 with DMDO in aqueous acetone gives the oxidative rearrangement compound 88 in 59% yield <2003OL785>. A plausible mechanism was proposed as shown in Scheme 11.



Scheme 11

11.01.6 Reactivity of Substituents Attached to Ring Carbon Atoms

3-Aryldihydropyrrolizin-1-ones 89 were involved in aldolization reactions with a number of aromatic aldehydes, either in ethanolic solution of sodium hydroxide or using tetrabutylammonium hydrogenosulfate as catalyst in a heterogeneous system (CH₂Cl₂/H₂O). Whatever the conditions used, these aldolizations led selectively to the (Z)-stereomers 90 <2000BMC945>. Benzo-annulated analogues 91 were reacted with various 2-acylanilines 92 leading with low to moderate yields to 93 according to Friedländer reaction (Scheme 12) <2004BML2363>.



Scheme 12

Carbonyl groups positioned on the pyrrole nucleus of dihydropyrrolizines may undergo reduction to the corresponding pseudobenzylic methylene under various reductive conditions. Thus, treatment of 1-aryl-6-acetyl-1,2-dihydropyrrolizines 94 with *t*-BuNH₂·BH₃ complex and AlCl₃ resulted in the reduction of the acetyl group into ethyl as shown in 95 <2004ARK20>. Similar reduction was observed when 96 was treated with LiAlH₄ thus leading to alkaloid (*R*)-(+)-myrmicarin 217 97 (Scheme 13) <2000JOC2824>, which was discovered in the secretions of *Myrmicaria* ants <1996T13539>.



Catalytic reduction (HCO₂NH₄, Pd/C) of the ketoester moiety of dihydropyrrolizine 98 was nonselective, since the desired compound 99 was obtained along with the dechlorinated analogue. Chemoselective reduction of the keto group of 98 was performed by reduction of the corresponding tosylhydrazone with NaBH₃CN in 90% yield <1999T5145>. Compound 98 was synthesized by Suzuki coupling of triflate 100 with (4-chlorophenyl)boronic acid in the presence of Pd(PPh₃)₄ and 5.4 M aqueous potassium hydroxide in refluxing THF (Scheme 14). Under the Suzuki or other cross-coupling reaction conditions, analogues of triflate 100 without the ketoester substituent, the expected coupling compounds, were obtained in less than 10% yield <1999T5145>.



Scheme 14

In an attempt to oxidize the methyl group of danaidone 101 to the corresponding formyl group with ceric ammonium nitrate (CAN) in acetic or TFA, Rajaraman and Jimenez <2002T10407> obtained the nitration compound 102 as the major compound. However, scaling up under the same conditions gives a mixture of products. Even under refluxing reaction conditions, CAN could not give oxidation at the pseudobenzylic carbon atom of the deactivated dihydropyrrolizinone 102. Finally, the desired pseudobenzylic alcohol 104 was synthesized in two steps starting from 102; bromination under free radical conditions (NBS, 2,2'-azobisisobutyronitrile (AIBN), CCl₄, $h\nu$) afforded 103 which undergoes quantitative nucleophilic substitution in refluxing water leading to 104 (Scheme 15). When applied to the danaidone 101, this free radical bromination procedure resulted in the bromination of the pyrrole ring which is not deactivated as in 102.



Scheme 15

11.01.7 Ring Synthesis Classified by Number of Ring Atoms in Each Component

In this section, whatever the saturation level of the aza-bicyclic compound considered, we will focus only on the bond-formation step which leads to the azabicyclic skeleton of pyrrolizines and their derivatives. The reported routes will be classified according to the number of atoms in the newly formed bond, as already done in CHEC-II(1996) <1996CHEC-II(8)12> and shown in Figure 1. Not all of these modes were equally employed; the most popular are 1,8-; 1,2-; 2,3-; 3,4-; 1,8:2,3-; 1,2:3,4-; and 1,8:3,4-bond formations. Each of these modes will be described in this section; all other bond-formation modes will be discussed in Section 11.01.9.

11.01.7.1 1,8-Bond Formation

Despite the development of some new methods for this strategy of bicyclic system formation, the intramolecular C-acylation of pyrrole is still frequently employed. This reaction may be performed starting from N- β -cyanoethyl-pyrroles as well as starting from their acid, ester, and even amide analogues.



Figure 1 Various modes of bond formation.

When submitted to the Houben–Hoesch cyclization (dry HCl in Et₂O or THF), 2-aryl-1- β -cyanoethylpyrroles 105 have led to a series of 5-aryl-1,2-dihydropyrrolizin-1-ones 106. Some of the latter showed remarkable anti-inflammatory and/or analgesic activities on mice <2003CCL565>. Analogues 108 were also obtained following the same method starting from pyrrole derivatives 107 <2003JIC851>. This cyclization was already described with substrate 109 as selectively leading to danaidone 101 in good yield <1966JA1305>. More recently, Rajaraman and Jeminez <2002T10407> described this cyclization with variable yields (0–25%) in danaidone 101; pyrrole polymerization was suspected because of the difficulty in controlling the HCl concentration. For this reason, they employed the ester analogue 110 as substrate for this cyclization; thus, danaidone 101 was isolated in 75% yield using BBr₃ as catalyst, according to an earlier procedure described by Jefford *et al.* (Scheme 16) <1995HCA1511>.



Scheme 16

Sonnet *et al.* <2000BMC945> had already used this ester cyclization catalyzed with BBr₃, for the synthesis of 3-arylpyrrolizin-1-ones **112**, which were evaluated as potential aromatase inhibitors. This method could not be applied to the substrate **111b**, due to the sensitivity of the trifluoromethoxy group to boron tribromide. The corresponding dihydropyrrolizinone **112b** could be synthesized via the Vilsmeier cyclization; treatment of amide **113b** with phosphorus oxychloride in refluxing toluene led to an iminium ion which was isolated as its perchlorate salt **114b**. Treatment of the latter with sodium hydroxide afforded the expected product **112b**. The same authors had previously employed this Vilsmeier method for the cyclization of **113a** <1993H(36)2129> and, recently, Lisowski *et al.* <2004JME1448> prepared **112c** in 53% yield via the same procedure (**Scheme 17**).



a: R = Ph; **b**: R = 4-F₃C-O-C₆H₄⁻; **c**: R = 3-BnO-2-MeO-C₆H₃-

Sayah *et al.* <2000JOC2824> attempted direct cyclization of acid **115a** with phosphorus pentaoxide and isolated the expected compound **116** in poor yield (20%). They could improve the yield (57%) of this ring closure via the mixed anhydride **115b** which was isolated prior to its cyclization in the presence of BF₃·OEt₂ (Scheme 18).



Scheme 18

Vedejs and Little <2002JA748> developed a new route to leucoaziridinomitosene derivative **119** via intramolecular Michael addition using substrate **117b**. Preliminary attempts of tin–lithium exchange and subsequent intramolecular Michael addition from **117a** had led to a complex mixture due to the competition between indole C–H lithiation and tin–lithium exchange. Treatment of monodeuterated substrate **117b** with phenyllithium and quenching of the resulting Michael enolate with ethanol afforded **118a** in 78% yield along with 5% of **119** and 17% of the destannylated substrate. These results clearly show a great deuterium isotope effect that efficiently prevents the indole lithiation. A value of $k_{\rm H}/k_{\rm D} = ca$. 35 was found for the C-2 indole deprotonation. Achievement of this sequence starting from **117b** in the presence of phenylselenyl chloride allowed direct isolation of product **119** in 71% yield (**Scheme 19**). The presumed selenide intermediate **118b** was not observed. In this synthesis, the deuterium atom serves as a protecting group for the indole C(2)–H bond during the tin–lithium exchange; moreover, this blocking group is removed during the final spontaneous *syn*-elimination sequence <2004JOC1794>. A similar route was earlier developed by Ziegler and Belema utilizing the cyclization of an aziridinyl radical instead of the anionic species derived from **117** <1997JOC1083>.



Scheme 19

Tolstikov *et al.* <1989IZV1209> have previously described the synthesis of the benzo-annulated pyrrolizindione **122** starting from sulfonium salt **120**, via the corresponding sulfur ylide **121a**. The same group described a modified procedure where ylide **121a** was generated *in situ* by reacting Me₂S with diazoketone **121b** in the presence of $Rh_2(OAc)_4$ (**Scheme 20**) <2002IZV189>. Pyrrolam regioisomer **12** was synthesized in 87% yield via an intramole-cular Wittig reaction of *N*-(3-iodopropyl)succinimide <2004JOC6105>.



Padwa *et al.* <2001OL1781, 2004JOC33> succeeded in constructing the saturated pyrrolizinones **125** by photochemical-promoted intramolecular cyclization of thiolactams **123** leading to **124**. Treatment of the latter with Raney-Ni in ethanol afforded compound **125a**, while treatment with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) followed by Raney-Ni leads to bicyclic hexahydropyrrolizin-3-ones **125b** (Scheme 21).



Scheme 21

N-(3-Iodopropyl)succimide was subjected to intramolecular reductive cyclization with samarium iodide (3 equiv) in presence of Fe(DBM)₃ catalyst (where DBM = dibenzoylmethane enolate) to afford the corresponding hemiaminal **126** which smoothly undergoes partial dehydration leading to the pyrolam A regioisomer **12**. When applied to N-(3-iodopropyl)phthalimide, a similar sequence afforded pyrrolizinone **127** <1996TL2577>.



Benzo-annulated pyrrolizin-3-ones **129** were synthesized in good yields from *N-o*-benzoylated pyrroles **128** by an intramolecular Heck reaction (Scheme **22**) <2001JME4615>.



Scheme 22

(S)-Ketorolac 132, a nonsteroidal anti-inflammatory drug (NSAID), was synthesized in a two-step procedure based on an intramolecular oxidative coupling of pyrrole at the C-2 position with a chiral sultam enolate 130 leading to dihydropyrrolizine 131 as a 4.5:1 mixture of epimers (Scheme 23). Subsequent benzoylation, performed on the crude



reaction mixture of the coupling step, followed by hydrolysis afforded (*S*)-ketorolac in 38% overall yield and 90% ee <2005AGE609>. The best result was reached with ferrocenium hexafluorophosphate as oxidant, which is well known to convert enolates into radical species by single-electron transfer <2002EJO718>.

11.01.7.2 1,2-Bond Formation

Katritzky *et al.* <1997JOC4148> described the cyclization of pyrrole derivatives **133** via lithiation at the benzotriazol-1-ylmethyl group and subsequent intramolecular nucleophilic displacement of tosylate to give in good yields dihydropyrrolizines **65**, which lead to *3H*-dihydropyrrolizines **68** under treatment with malonate anion (see Section 11.01.5.3).

Reaction of compound 134, either with sodium carbonate or potassium *tert*-butoxide, leads in moderate yields to the enolized bicyclic compound 135 along with a dimer resulting from the oxidative coupling of the initial enolate of substrate 134 (Scheme 24) <2005T1693>.





Reaction of Weinreb *N*-vinylprolinamides 136 with organometallic reagents afforded ketoenamines 137 which were thermally cyclized to dihydropyrrolizines 138 in good yields (53–92%). The success of this cyclization requires an electron-withdrawing R^2 group (Scheme 25) <2002S2450>.



Scheme 25

Intramolecular Wittig reaction of keto-stabilized ylide 28 took place in refluxing toluene leading to the 1*H*dihydropyrrolizines 31 in the case of α -ketocarboxylic derivatives <2001T5873>, while trifluoroacetyl ylide 28c afforded exclusively the 3*H*-dihydropyrrolizine 30c (Scheme 26) <2006ARK55>.



Intramolecular 1,3-dipolar cycloaddition of unsaturated nitrones 139 has been shown to lead selectively to the fused ring regioisomer 140 when R^1 and/or R^2 are alkyl or phenyl substituents, while substrates with a monosubstituted carbon–carbon double bond gave mainly the bridged regioisomer <2001T8323, 2002EJO2080>. These cycloadditions also were studied with unsaturated nitrones 141 derived from indole nucleus. Similar substituent effects were observed; the benzo-annulated dihydropyrrolizines 142 are preferred regioisomers when the C=C is mono- or disubstituted (Scheme 27) <2000JOC8924>.



Photochemically promoted rearrangement of 2,3-dihydroisoxazoles 143 resulted in the isolation of azomethines 144 which undergo thermal rearrangement and cyclization leading to a mixture containing its tautomer 145 and dihydropyrrolizines 146. Regioisomer 146a was obtained in 63% yield when R = H and $R^1 = OMe$ (Scheme 28) <2003EJO1438>.



Scheme 28

Reaction of α -allenyl alcohol 147 with methanesulfonyl chloride and triethylamine in toluene at 190 °C, in a sealed tube, led to the tricyclic dihydropyrrolizin-4-one 149 in 35% yield. This transformation involves a domino mesylation/ σ [3,3] transposition/intramolecular Diels–Alder cycloaddition via diene 148 (Scheme 29) <2002CC1472>.



Scheme 29

Indoline and proline derivatives 150 and 151, on treatment with *c*-HexMgBr and MeTi(O-*i*-Pr)₃, underwent the intramolecular Kulinkovich cyclopropanation leading to annelated pyrrolizines 152 and 153, respectively, as mixtures of *cis*- and *trans*-diastereomers (Scheme 30) <2004CEJ785>.

Benzo-annulated dihydropyrrolizine 155 was quantitatively prepared via the Heck cyclization of 154 (Scheme 31) <2001TL7513>.