Pyrazolidines: synthesis, reactivity, physical and biological properties

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Abstract

This review summarizes the available information of monocyclic pyrazolidines (tetrahydropyrazoles) according to the following plan: synthesis; chemical properties and reactivity; structure, spectroscopic and physical properties; biological properties and drugs; and catalysts. Special stress has been placed on synthetic methodologies due to the richness of the topic. A total of 613 structural formulae plus 33 catalysts and 277 references are part of the present work.

Keywords: Pyrazolidines, hydrazines, [3+2] dipolar cycloadditions, catalysts, redox reactions, biological properties
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1. Introduction

The universe of pyrazoles is very vast; a classification according to their oxidation degree is represented in Figure 1. In addition to general reviews that include several of these items,$^{1,2}$ we have devoted specific reviews to the following compounds: pyrazolidinones $^{7}$, pyrazoles $^{8,4,5,6,7,8}$ 3-pyrazolines $^{9,9}$ and 2-pyrazolines $^{10,10}$ The present review deals with the less oxidized structure, the pyrazolidines $^{11}$. We have published several papers on these compounds that will be cited in the corresponding sections.

This review concerns only compounds called pyrazolidines excluding fused derivatives, very numerous, that have other names ($^{12-17}$, Figure 2). Exceptionally, it also includes a compound with a three membered ring linking both nitrogen atoms (1,5-diazabicyclo[3.1.0]hexane). Derivatives with a C=O exocyclic double bond, called oxo or keto pyrazolidines $^{1,3}$ and $^{7}$, have been excluded also, so all the compounds reported here have three sp$^3$ carbon atoms in the ring except some structures with a C=C exocyclic bond.
Figure 1. The universe of pyrazole structures according to their oxidation degree.

Figure 2. IUPAC names of some fused pyrazolidines.

2. Reviews

There are numerous reviews dedicated, in most cases only partly to pyrazolidines. They are reported below in chronological order and with the corresponding titles:
1,3-Dipolar Cycloadditions Past and Future. Huisgen presented his original discovery of 1,3-dipolar cycloadditions including an unpublished result (section 4.2.1) and an example of the reduction of 2-pyrazolines to pyrazolidines, see Section 4.5.2.\(^\text{11}\)

Detection of Hindered Rotation and Inversion by NMR Spectroscopy. In this review Kessler reported a series of families presenting the title behaviors, amongst them briefly pyrazolidines. This topic is discussed in Section 6.10.\(^\text{12}\)

Nitrogen Inversion. Experiment and Theory. Lehn described in detail his studies on the nitrogen inversion of pyrazolidines including some new results that had never been published, see Section 6.10.\(^\text{13}\)

Intramolecular [4+2] and [3+2] Cycloadditions in Organic Synthesis. Oppolzer actualized Huisgen's review\(^\text{11}\) and included one of his works, a [3+2] cycloaddition leading to a pyrazolidine he classified as IIIb type.\(^\text{14}\)

Synthesis and Properties of Functionally-Substituted 1,2-Azolines.\(^\text{15}\) Motorina and Sviridova summarized all of the knowledge about isoxazolidines and pyrazolidines up to 1991.

Preparation of α,β-Unsaturated Ketones Bearing a Trifluoromethyl Group and Their Application in Organic Synthesis. Nenadjenko reported several examples of 3-trifluoromethyl-3-hydroxypyrazolidines and their dehydration to 2-pyrazolines, see our Sections 4.1.3 and 5.3.\(^\text{16}\)

All of the following reviews refer to selective reactions of different classes (our sections 4.1 and 4.2), one of the brightest topics related to pyrazolidines due to the presence of three correlative sp\(^3\) carbon atoms in their ring in addition to the regioselectivity of positions 3 and 5. Most of these reactions use specific catalysts that were optimized for the synthesis of pyrazolidines, they are reported at the end of the manuscript, numbered with a capital C, from \textbf{C1} to \textbf{C33}.

Asymmetric 1,3-dipolar cycloadditions. Pellisier provided a full review of these reactions up to 2007, including two schemes, 153 and 154, where the works of Kobayashi and Leighton were carefully described, see section 4.2.\(^\text{17}\)

Asymmetric 1,3-dipolar cycloadditions of acrylamides. An important summary of Huisgen 1,3-dipolar cycloadditions leading, amongst other compounds, to pyrazolidines and isoxazolidines, Section 4.2.1, was described in detail in its variants normal and asymmetric.\(^\text{18}\)

Synthesis of Cyclic Hydrazino α-Carboxylic Acids. Pyrazolidines are cyclic hydrazines. This review, although very limited, contains much useful information on the synthesis of the title compounds using different methodologies which are discussed in the corresponding sections, including double asymmetric induction.\(^\text{19}\)

Preparation of \(α,β\)-unsaturated-trifluoromethylketones and their application in the synthesis of heterocycles. In the field of pyrazoles and their derivatives, Figure 1, compounds bearing CF\(_3\) are of particular importance. For this reason, Nenadjenko has summarized, in an authoritative way, trifluoromethyl pyrazolidines. Note that these compounds bear in the same substituents, at positions 3 or 5, a CF\(_3\) and an OH group, C(OH)CF\(_3\).\(^\text{20}\)

Recent Developments in Pd-Catalyzed Alkene Aminoarylation Reactions for the Synthesis of Nitrogen Heterocycles. The review by Schultz and Wolfe covers many fields, but their section 3.1 is devoted to the synthesis of pyrazolidines.\(^\text{21}\)

Recent Developments in the Synthesis and Applications of Pyrazolidines. A Review. This review, published in 2013, is the only one exclusively devoted to pyrazolidines. The main difference with the present one is that bicyclic and oxo derivatives were included. Their part concerning "Applications" is very useful being divided into "As Therapeutic Agents", "As Peptide Mimics" and "Synthons for Diamine Ligands and Pyrazolines". We will use it in our manuscript.\(^\text{22}\)

Recent Advances in Catalytic Asymmetric Synthesis of Pyrazoline and Pyrazolidine Derivatives. Divided into two almost equal parts, "[3+2]-Cycloaddition reactions of hydrazones; 1,3-Dipolar cycloaddition reactions
of azomethine imines with alkenes\textsuperscript{23}, and “Asymmetric conjugate addition/cyclization cascade reactions”, it also includes bicyclic and oxo pyrazolidines.\textsuperscript{23}

1,3-Dipolar Cycloadditions of Azomethine Imines. The review by Nájera et al. contains abundant information about enantio-catalyzed 1,3-dipolar cycloadditions that yield pyrazolidines.\textsuperscript{24}

Metal-catalyzed \([3+2]\) cycloadditions of azomethine imines and Synthesis of Non-Racemic Pyrazolines and Pyrazolidines by \([3+2]\) Cycloadditions of Azomethine Imines. Svete, Pozgan et al. discussed the important aspect of metal-catalyzed synthesis of pyrazoles, 3-pyrazolines and pyrazolidines, including oxo and bicyclic pyrazolidines. Of particular relevance is tetrahydropyrazolo[1,2-\(a\)]pyrazol-1(5\(H\))-one (an oxo derivative of compound \textbf{12} reported in Figure 2).\textsuperscript{25,26}

3. Theoretical calculations on simple pyrazolidines

We will report in sections 4.2.b, 6.6 and 6.10a (summarized in section 6.11) a study we carried out purposely on compounds \textbf{11}, and \textbf{18} to \textbf{47} (Figure 3), Moreover, a selection of X-ray structures was also calculated, \textbf{48} to \textbf{52}, including the Refcodes from the Cambridge Structural Database (CSD))\textsuperscript{27} The results of that study are reported in Section 6.10.a.
Figure 3. Calculated pyrazolidines including in red the Refcodes\textsuperscript{27} of those whose X-ray structures have been determined.

4. Synthesis

4.1. From hydrazines and related compounds

4.1.1. With 1,3-dihalopropanes. This method, reaction of 53 and 54, is the oldest one and has been used by great names in Chemistry, in chronological order (Scheme 1) Michaelis,\textsuperscript{28} Wittig\textsuperscript{29} and Büchi.\textsuperscript{30} More recent papers correspond to the following references\textsuperscript{31,32,33,34,35,36,37,38,39,40,41}: 

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Scheme 1. Pyrazolidines prepared from hydrazines and 1,3-dihalopropanes.

In former times, the hydrazines were used as alkali-metal derivatives, for instance, the mono-sodium salt of 55,\textsuperscript{28,30} the di-lithium salt of 58,\textsuperscript{29} and the di-sodium salt of 58.\textsuperscript{31} In the case of 73, the starting compounds were azobenzenes reduced electrochemically to 73.\textsuperscript{38} In three other cases,\textsuperscript{42,43,44} azo compounds were used that, under the reaction conditions, were reduced to hydrazines. Pyrazolidine 87 was prepared by Varma from...
the corresponding hydrazine 75; other N-substituted pyrazolidines 78 were prepared by this author from hydrazine 76, although always as minor components of a mixture with 2-pyrazolines.\textsuperscript{39,40,41} Pyrazolidines 78 corresponds to $R^3 = H$, alkyl, aryl, and for \textbf{77} $X = \text{Cl, Br, I and OTs}$, and used microwave (MW) and ultrasound (US) methodologies.\textsuperscript{40,41} The syntheses of three pyrazolidines 32, 87 and 36 from hydrazines 69, 75 and 79 were reported by Nelsen and Hintz.\textsuperscript{45}

Epichlorohydrin 80 is a masked 1,3-dichloro-2-hydroxypropane that reacts with different hydrazines 55, 82, 58, 67, 75, 79, 85 and 86 to afford 4-hydroxypyrazolidines 81, 83, 84, 32, 87, 88, 36 and 89 (Scheme 2).\textsuperscript{46,47,48,49,50}

\begin{align*}
\text{Ph} & \quad \text{N-N} & \quad \text{H} & \quad \text{H} & \quad \text{Cl} & \quad \text{O} & \quad \text{OH} & \quad \text{Ph} \\
55 & & & & 80 & & & 81 \\
\text{Ph} & \quad \text{N-N} & \quad \text{H} & \quad \text{Me} & \quad \text{Cl} & \quad \text{O} & \quad \text{OH} & \quad \text{Ph} \\
82 & & & & 80 & & & 83 \\
\text{Ph} & \quad \text{N-N} & \quad \text{H} & \quad \text{Me} & \quad \text{Cl} & \quad \text{O} & \quad \text{OH} & \quad \text{Ph} \\
84 & & & & 80 & & & 84 \\
\text{Ph} & \quad \text{N-N} & \quad \text{Me} & \quad \text{R} & \quad \text{Cl} & \quad \text{O} & \quad \text{OH} & \quad \text{Ph} \\
69, R = \text{Me} & & & & 80 & & & 84 \\
75, R = \text{Et} & & & & & & & 84 \\
79, R = \text{i-Pr} & & & & & & & 84 \\
85, R = \text{Pr} & & & & & & & 84 \\
86, R = \text{Bn} & & & & & & & 84 \\
32, R = \text{Me} & & & & & & & 84 \\
36, R = \text{i-Pr} & & & & & & & 84 \\
38, R = \text{Pr} & & & & & & & 84 \\
89, R = \text{Bn} & & & & & & & 84 \\
\end{align*}

\textbf{Scheme 2}. Pyrazolidines prepared from hydrazines and epichlorohydrin.

2,2′-Bioxirane 90 reacts with hydrazines 67 and 58 like a 2,4-dihalobutane-1,3-diol to yield pyrazolidines 91 and 92, Scheme 3.\textsuperscript{51,52}

\begin{align*}
\text{R} & \quad \text{N-N} & \quad \text{H} & \quad \text{R} & \quad \text{Cl} & \quad \text{O} & \quad \text{OH} & \quad \text{Ph} \\
58 & & & & 90 & & & 91 \\
\text{R} & \quad \text{N-N} & \quad \text{Me} & \quad \text{R} & \quad \text{Cl} & \quad \text{O} & \quad \text{OH} & \quad \text{Ph} \\
67, R = \text{Ph} & & & & 90 & & & 91 \\
& & & & & & & 91, R = \text{Ph} \\
& & & & & & & 92, R = \text{Me} \\
\end{align*}

\textbf{Scheme 3}. Synthesis of pyrazolidines from 2,2′-dioxirane.

We have separated the acylhydrazines or hydrazides, RCONNH$_2$ and RCONHNR because, although their reactivity is similar, the resulting N-acylpyrazolidines 42, 94a/b, 96, 98, 101 and 103 have some characteristic properties. Moreover, the R substituents of the COR are, in most cases, typical of protein chemistry, CBz and Boc, 95 and 102 (Scheme 4). In almost all cases, 1,3-dibromopropane 56 was used with the exception of 100. The results are reported in Scheme 4 and correspond to the references.\textsuperscript{53,54,55,56,57,58,59,60,61,62}
Scheme 4. Pyrazolidines prepared from hydrazides.

4.1.2. By oxidation of 1,3-diaminopropanes. This procedure, although used much less than the preceding one, is the industrial method employed to prepare the parent pyrazolidine (11) in large amounts (framed, Scheme 5).

Scheme 5. Pyrazolidines prepared from 1,3-diaminopropanes.
Lüttringhaus and coworkers prepared 11 from the monochlorination of 1,3-diaminopropane (104) to afford 105 which, treated with NaOH, produced the desired compound.63 At about the same time, Wittig oxidized 1,2-diphenyl-1,3-diaminopropane (106) into 1,2-diphenylpyrazolidine (38) using MnO₉ or MeLi followed by I₂.64 The reaction was extended to other aryl groups (74, p-CH₃C₆H₄, m-CH₃C₆H₄, o-CH₃OC₆H₄ and p-C₂H₅OC₆H₄) from 107 by Daniels and Martin.65

Pasquet et al. published three papers where they proposed a mechanism for the process and the conditions to prevent the formation of pyrazoline 10 (through 109); they obtained 11 in 90% yield.66,67,68 The first clear proof of oxidative N-N coupling of secondary amidolithium compounds to yield pyrazolidines was reported by Mair.69

4.1.3. With α,β-unsaturated carbonyl compounds. This very frequently used procedure provides 3-hydroxypyrazolidines 110, the starting material being α,β-unsaturated carbonyl compounds. The literature results are presented in Schemes 6a and 6b.

Zelenin, Sviridova, Golubeva et al. made the greatest contribution to this method. In 1965 they prepared a large collection of pyrazolidines; for instance, 113 from hydrazides 111 and crotonaldehyde 112; compound 113 reacted with another molecule of 111 to afford 114; they also prepared pyrazolidines 117 and 119.70 The same group carried out a similar reaction and studied the ring-chain equilibrium 122a/122b.71 In a later paper, they studied the reactivity of hydrazide 111 and its anion 111⁻ with α,β-unsaturated aldehydes and then with acetophenones 125. Neutral molecule 111 and anion 111⁻ reacted differently, affording isomers 126 and 128 in different proportions.72

The natural evolution of organic chemistry led several authors in 2012 to report enantioselective synthesis of pyrazolidines. Vicario et al. described pyrazolidines 131-136, using catalysts C7 to C11, through an organocatalytic, enantioselective aza-Michael/hemiaminal-formation-cascade process from enals and 1,2-disubstituted hydrazides with excellent results, e.g., yields and ee (%) up to 99 and 92%, respectively.73 Pyrazolidines 139 and 140 were prepared simultaneously by Zang, Wang et al.74 and Córdova et al.75 reacting hydrazines 102 and 137 with cinnamaldehydes 138 using, as catalyst, C8 and other pyrrolidine catalysts. Córdova explained the resulting stereochemistry by a Michael hemiaminal cascade that favors 1,4-addition over 1,2-addition, and needs a protected hydrazine. Moyano et al., using Jørgensen-Hayashi catalysts, C8 and C10, also obtained very high yields and a single isomer 143 (dr > 30:1).76

In view of medicinal chemistry applications, a series of morpholine-connected pyrazolidine derivatives 146, 147 were prepared from the reaction between 144 and cinnamaldehyde (145) (see Section 7).77
Scheme 6a. Pyrazolidines prepared from hydrazines and α,β-unsaturated carbonyl compounds (first part).
Scheme 6b. Pyrazolidines prepared from hydrazines and α,β-unsaturated carbonyl compounds (second part).

Nenadjenko, Sanin and Balenkova initiated the use of trifluoromethyl-α,β-unsaturated ketones to prepare 5-trifluoromethyl-5-hydroxypyrazolidines 149. The presence of the CF₃ substituent strongly stabilizes these compounds, preventing dehydration. Compounds 150 to 152 represent some similar...
compounds prepared by these authors. Starting from semicarbazides and thiosemicarbazides, 5-trifluoromethyl-5-hydroxypyrazolidines 153-156 have been prepared.\(^7\) To determine the relative amounts of hydrazine and 1,1-dimethylhydrazine in a propellant, pyrazolidine 157 was prepared from the corresponding \(\alpha,\beta\)-unsaturated ketone (only hydrazine can react) and its proportion determined by GC-MS.\(^8\)

Exner et al. reacted hydrazobenzene (58) with benzaldehyde 158 to obtain compound 159 in which the OH group has been replaced by 58. In the presence of methanol or ethanol 160, the 5-alkoxy derivatives 161 were obtained.\(^9\) Other authors have described hydroxypyrazolidines 162-166 (the two last ones are pyrazolidinium quaternary salts),\(^10\) as well as the fluorinated derivatives 167 and 168 (\(R_F = CHF_2, CF_3, H(CF_2)_2, H(CF_2)_4, C_4F_9, C_6F_{13}\), only one diastereomer was obtained) (shown in Figure 4).\(^11\)

![Figure 4. Other 5-hydroxypyrazolidines.](image)

### 4.1.4. With \(\beta\)-diketones

This is a marginal section with a few examples concerning hydrazines 62 and 76 with \(\beta\)-diketones 169 that afford pyrazolidines 170 to 173. 3,5-Dihydroxypyrazolidines can be isolated even when both nitrogen atoms are non-substituted, e.g., 170 and 171 (Scheme 7).\(^8\) Reference 87, although reporting bicyclic pyrazolidines, describes a mechanistic proposal.

![Scheme 7. Pyrazolidines prepared from hydrazines and \(\beta\)-dicarbonyl compounds.](image)

### 4.1.5. Other methods involving hydrazines

The oldest methods to prepare pyrazolidines use hydrazines, either directly or through a more oxygenated form, and will appear in Sections 4.3 and 4.4. Here, we will report in Scheme 8 reactions involving hydrazines substituted in positions 1 and 2 with groups that can cyclize with the aid of a reagent.
Cyclization of an allyl precursor leads to the unexpected formation of the five-membered rings 174 with the trans-isomer as the main product. These products cannot arise from a ‘normal’ 5-exo-type cyclization. A large variety of cyclic α-hydrazino acid derivatives can be efficiently synthesized via this method.\textsuperscript{88}

Selenium-induced cyclization of alkenes containing bound nucleophiles continues to attract the attention of several research groups, as it represents an efficient synthesis of a wide variety of heterocyclic compounds. N-Alllyl-acetohydrazides readily result in organoselenium-induced cyclization reactions promoted by phenylselenenyl sulfate (PhSeOSO\textsubscript{3}H) to produce phenylseleno-N-acetyl pyrazolidines 177 as the thermodynamically-controlled products. A further interesting aspect of these cyclization reactions is that, in most cases, they are completely diastereoselective.\textsuperscript{89}

The authors reported that stirring the methoxycarbonyl-protected hydrazines 178 with 0.5 equivalents of concentrated sulfuric acid in dichloromethane at room temperature overnight, resulted in complete disappearance of the starting material and isolation of 179a/b in excellent yields.\textsuperscript{90}

The PhSeBr\textsubscript{2} induced cyclization of 2-(but-3-en-1-yl)-1,1-dimethylhydrazine has been studied. A 5-exo-trig ring closure occurred in each case and phenylselenylmethyl-pyrazolidines were obtained. They prepared a considerable number of compounds, amongst them 1,1-disubstituted pyrazolidinium quaternary bromides, 180.\textsuperscript{91}

Highly stereoselective synthesis of optically active pyrazolidines 182, and the prediction of the stereoselectivity, were accomplished by cyclization of optically active allenylhydrazine 181 with organic halides. The optimization procedure was achieved after screening several optically-active palladium catalysts, prepared \textit{in situ} from easily available chiral ligands and Pd(OAc)\textsubscript{2} [C4, C5, C6, C12, C13 and C14]. They also established a model with which the enantiopurities of the products and the diastereoselectivities of the reactions can be easily predicted.\textsuperscript{92,93}

Pd-catalyzed alkene difunctionalization was used by Wolfe\textsuperscript{94} to prepare 183 using as a catalyst Pd/S-Phos C25 (see ref.\textsuperscript{95} for a previous work by this author). An efficient and practical Pd-catalyzed intramolecular oxidative allylic amidation provides facile access to derivatives, in this way compound 185 was obtained pure from 184 in the trans form and with a \textit{dr} > 30:1, using molecular oxygen (1 atm) as the sole reoxidant of Pd.\textsuperscript{96} Similar results were reported almost simultaneously by Lalwani \textit{et al.}\textsuperscript{97}

Allylhydrazines react with phenylselenenyl sulfate, produced from the reaction of diphenyl diselenide and ammonium persulfate in the presence of trifluoromethanesulfonic acid, to afford phenylseleno-substituted pyrazolidines such as 3,3-dimethyl-1-phenyl-4-(phenylseleno)-pyrazolidine (186). The reaction was extended to other allylhydrazines.\textsuperscript{98}

Although paper\textsuperscript{99} concerns mainly isoxazolidines, it also contains an important contribution to the field of pyrazolidines: gold(I)-catalyzed enantioselective synthesis of pyrazolidines 188 from mono-Boc-protected homoallenic hydrazine 187, was achieved through an exhaustive optimization of catalysts [C15, C16, C17 and C18] and protecting groups. Chiral biarylphosphinegold (I) complexes C15 and C18 are suitable catalysts for the enantioselective addition of nitrogen nucleophiles to allenes.\textsuperscript{99}

Synthesis of enantio-enriched aza-proline derivatives 190 was accomplished through gold(I)-catalyzed cyclization of chiral α-hydrazinoesters bearing an alkyne group 189. Enantioenriched α-hydrazinoesters underwent ring closure by using Ph\textsubscript{3}PAuCl/AgBF\textsubscript{4} as a catalytic system. Under these conditions, 5-exo-dig cyclization was favored over 6-endo-dig, and aza-proline derivatives were obtained in good yields without epimerization at the stereogenic center. These results demonstrate the importance of the nature of the silver salt AgBF\textsubscript{4}, the hydrazine protecting group, and alkyne substitution on the yield and selectivity of the gold-catalyzed cyclization.\textsuperscript{100} Kerr \textit{et al.} reported an efficient diastereoselective (and diastereodivergent)
intramolecular annulation of hydrazones and 1,1-cyclopropanediesters allowing rapid access to structurally complex pyrazolidines.\textsuperscript{101,102}

The part containing pyrazolidines bearing CF\textsubscript{3} groups is well summarized in the Nenajdenko review of 2011.\textsuperscript{20}

Scheme 8. Pyrazolidines from \textit{N},\textit{N}'-disubstituted hydrazines.

4.2. By 1,3-dipolar cycloaddition from hydrazones
This section is as important as the previous one (4.1) for preparing pyrazolidines. The methods used belong to the Huisgen [3+2] cycloaddition family of reactions\textsuperscript{11,103}; but two variants must be distinguished ([3 + 2] and [3\textsuperscript{*} + 2], Scheme 9). Two excellent reviews on these reactions were published by Pellissier in 2007,\textsuperscript{17} and by Nájera, Sansano and Yus in 2015.\textsuperscript{24}

We reported in Scheme 9 the assumed reactivity of the phenylhydrazone of acetaldehyde 192 from 55 and 191. This compound exists in tautomeric equilibrium with a dipolar form 193 (an azomethine imine) that is less stable, but more reactive. Dipolar cycloaddition to styrene (194) affords two pyrazolidines 195 and 196 in different proportions depending on the reaction conditions. Protonation of 192 or 193 leads to a cation 197 that is also able to cycloadduct olefins to render, after losing a proton, the mixture of 195 and 196 in a different ratio. This last reaction has been called [3+2] by Schmidt, who points out that Hesse reported a previous example. Hamelin et al. consolidates the study depicted in Scheme 14, both neutral, and protonated variants.  

4.2.1. Neutral hydrazones, [3+2] cycloaddition. We will first report the uncatalyzed reactions gathered in Scheme 10, that correspond to references. Oppolzer, in 1970, using this procedure prepared pyrazolidines 200-204, compound 200 (R = Ph) was obtained by a three-component reaction between a hydrazine, paraformaldehyde and styrene. This was followed by Sucrow, who, in 1979 prepared pyrazolidines bearing four methoxycarbonyl groups 207, 208, 210 and 211 from dimethyl fumarate (206) and dimethyl maleate (209) and the azomethine imine 205. The reaction of phenylhydrazones 212 with methyl acrylate (213) and nitrostyrene [(E)-(2-nitrovinyl)benzene] (215) yields 4-methoxycarbonyl- 214 and 4-nitropyrazolidines 216, respectively. Grigg et al. reported that hydrazones of aldehydes or ketones undergo intermolecular cycloaddition to electron-negative olefins via azomethine imines, formed by a formal 1,2-prototropic shift, 192/193, providing the first clear analysis of these reactions. In this way, they prepared pyrazolidines 217-219. Cauquis and Chabaud prepared a series of pyrazolidines such as 222, 224 and 226a/b from azomethinimine 220 and different olefins: cis-2-butene (221), trans-2-butene (223) and 2,3-dimethyl-1,3-butadiene (225) for their study by mass spectrometry (section 6.6).
Scheme 10a. Uncatalyzed 1,3-dipolar cycloadditions [3+2] (first part).
Scheme 10b. Uncatalyzed 1,3-dipolar cycloadditions [3+2] (second part).
The search of pyrazolidines as peptidomimetics led Jones et al. to prepare a large collection of compounds with CO₂Me and CN substituents, 227-238. Deng and Mani discussed if the reaction of 239/240 with nitrostyrenes 241 to afford 242 occurs by a concerted [2+3] dipolar cycloaddition 243 or by a stepwise mechanism (aza-Michael) involving 244 and 245. In their first paper they concluded in a concerted mechanism, but, in a subsequent paper, taking into account the possible isomerization of pyrazolidines, they preferred the stepwise mechanism. This conclusion (see also) must be considered only provisional because other authors have rejected it. In particular, Wu et al., after examination of the stereochemistry and regioselectivity of the reaction 246 + 247 → 248, concluded that the mechanism is concerted; the metal salts Sc(OTf)₃, In(OTf)₃, Yb(OTf)₃, and Y(OTf)₃ could catalyze the 1,3-dipolar cycloaddition reaction.

Hu et al. have shown that basic conditions can also be used to carry out the [3+2] cycloadditions (we propose to name them [3⁻+2]); in this way 249⁻ reacts with 241 to afford the tetrabutyl ammonium salt 250⁻ that is protonated by water to yield the desired pyrazolidine 250. Pyrazolidines 251 to 253 were also obtained in basic conditions.

The lithium anions of phenylhydrazones also react with olefins to afford pyrazolidines; this paper, and a previous one, report the experiments of Hamelin to prove that the mechanism of Scheme 11 (pyrazolidines 255 and 256) corresponds to a [3+2] cycloaddition. 107 (4-Chlorophenyl)[(3S,5S)-5-phenyl-3-(trifluoromethyl)pyrazolidin-1-yl]methanone was obtained with a dr = 94/6 using Cu(OTf)₂ as catalyst. Finally, note that heterocyclic phenylhydrazone 254 reacts with trimethyl 1,1,2-ethylenetricarboxylate (257) to afford a pyrazolidine bearing three ester groups at positions 4 and 5, 258.

Scheme 11. Hamelin’s synthesis of poly-substituted pyrazolidines 255, 256 and 258.

The part concerning catalyzed [3+2] cycloadditions is, in general, more recent and was aimed at obtaining stereospecific pyrazolidines; Kobayashi was the precursor of these studies, using his catalysts C1, C2 and C3 combined with Zr(OPr)₄ to prepare optically active pyrazolidines. Scheme 12 summarizes the results reported in references.
In 2005, Leighton et al. developed highly diastereo- and enantioselective 1,3-dipolar cycloadditions of acylhydrazones 259 to enol ethers 260, catalyzed by a chiral silicon Lewis acid C26, to prepare pyrazolidines 261.\textsuperscript{124} They extended these studies in a subsequent paper,\textsuperscript{125} whereby, using similar reactants, 262 and 260, and a similar catalyst, C27, they obtained pyrazolidines 263. Furthermore, they proposed a mechanism to explain the role of the catalyst involving intermediates 265, 266 and 268. An asymmetric Brønsted acid-catalyzed cycloaddition using catalyst C19 led to enantioselective pyrazolidines 271 from N-acyl hydrazones 269 and alkenes 270 using as chiral catalyst Rueping catalyst C21.\textsuperscript{126}
Scheme 12b. Catalyzed 1,3-dipolar cycloadditions [3+2] (second part).

Jørgensen et al. described a catalytic asymmetric synthesis of 4-nitro-pyrazolidines 273 and 274 from 241 and 272 using their catalysts C30 to C33.127 Krause et al.128,129 reported an efficient, highly atom-economic synthesis, of hitherto unknown spirocyclic pyrazolidines 278 and 279 in a one-pot process. The gold-catalyzed three-component coupling of hydrazine 275, pentynol (276) and aldehydes 277 and 158 proceeds via cycloisomerization of the pentynol to an exocyclic enol ether and subsequent [3+2]-cycloaddition of an azomethine ylide. A library of 29 derivatives with a wide range of functional groups was created in up to 97% yields.

Four pyrazolidines were reported which belong to this section, although their stereochemistry was not always indicated. Starting from pyrazolidine 280 and using a catalyst related to C27 in five steps reached the alkaloid manzacidin C 281.130 Pyrazolidine 282 has a second molecule of hydrazine at position 5 similar to 114; the catalyst is related to C16.131 Pyrazolidines 283 and 284 were prepared using catalysts C28 and C29.132,133

4.2.2. Protonated hydrazones, [3^+2] cycloaddition. The first example of these reactions was described by Hesse in 1970 although he didn’t use Huisgen’s terminology. Protonated hydrazones 285 prepared in situ from R^1NHNNH_2 and R^2CHO react with olefins 270 to afford pyrazolidinium salts 286H^+ that, upon treatment with
NaOH, yield the free pyrazolidines $286$, $R^1 = \text{Ph, COMe, COBu, COPh, COAr}$; $R^2 = \text{H, Me, i-Pr, pentyl, Ph}$, $R^3, R^4 = \text{H, Me, Ph}$, Scheme 13.$^{105}$

Scheme 13. The first example of $[3^+2]$ pyrazolidine synthesis.

Hamelin et al. described these reactions in a fundamental paper using a wide collection of olefins (styrene, fumarate, maleate, cinnamate, crotonate, acrylate and acrylonitrile), to prepare twelve polysterminated pyrazolidines $287$-$298$ (Figure 5, $E = \text{CO}_2\text{Me}$).$^{108}$

Figure 5. Functionalized pyrazolidines.

When 1,1-dimethylhydrazine ($299$) is used as starting material, it reacts with benzaldehyde ($158$) and concentrated HCl to afford the protonated hydrazone $300a$ (not isolated) which reacts with methyl acrylate ($213$) and with styrene ($194$) to give analytically pure pyrazolidinium chlorides $301$-$303$ (Scheme 14); the authors reject structure $304$ based on $^1\text{H}$ NMR chemical shifts.$^{134}$ If cation $300b$ [from 1,2-dimethylhydrazine ($67$)] is used, the reaction with ethyl cinnamate ($305$) proceeds in the same way, yielding $306$ whose X-ray structure was used to establish its stereochemistry.$^{135}$

Rueping, Houk et al. have studied, experimental and theoretically, the reaction of hydrazones $307$ with ethyl vinyl thioether ($308$) to afford pyrazolidines $309$ (Scheme 15) in the presence of Kobayashi catalyst $C_2$, Leighton catalyst $C_{24}$, Tsogoeva catalyst $C_{16}$ and Rueping catalysts $C_{19}$ and $C_{21}$.$^{136}$ They developed a chiral Brønsted-acid-catalyzed highly-asymmetric $[3^+2]$ cycloaddition reaction; the reaction affords pyrazolidine derivatives in good yields, with high diastereoselectivities and excellent enantioselectivities. The cycloaddition reaction was also carried out with ethyl vinyl ether, and the corresponding pyrazolidine derivatives were synthesized with high enantioselectivities. Furthermore, Houk et al. carried out DFT calculations on the $[3^+2]$ cycloaddition mechanism. The alternative 1,3-dipolar $[3+2]$ cycloaddition pathway, with azomethine imine, is less favorable due to the endergonic isomerization from hydrazone to azomethine imine; in addition, they proved that the protonation of hydrazone by Brønsted acids is crucial for the catalytic efficiency.

Scheme 15. Synthesis using the [3+2] and [3+2] mechanisms.

The group of Vicario, Merino et al. studied this mechanism, again, with a different hydrazone, leading to a tricyclic pyrazolidine (15, Figure 2). In order to carry out theoretical calculations, they simplified the structure of catalyst C16 using instead 310 and 311 (Scheme 15). They employed Houk’s distortion model, reaching the
conclusion that the process is an apolar, concerted one in which all the events (bond breaking/bond formation) take place in a simultaneous way. Despite the polarity of the reacting groups, the overall charge transfer is not high enough for the process to be considered polar.\textsuperscript{137}

The three-component reaction between hydrazide \textsuperscript{312}, para-formaldehyde and styrene (\textsuperscript{194}) affords pyrazolidine \textsuperscript{313}\textsuperscript{138}; this publication also includes a discussion of the mechanism.

4.3. By reduction of pyrazolones and pyrazolidinones

4.3.1. Pyrazolones. This is a topic that was important in the past, but is now almost inactive, most of the publications originating from Jacquier’s laboratory (Montpellier, France). In Scheme 16 we have summarized the most relevant publications\textsuperscript{139,140,141,142,143,144,145}.

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\textbf{Scheme 16}. Reduction of pyrazolones to pyrazolidines.}
  \node (B) at (-3,-3) {\textbf{314}}; \node (C) at (3,-3) {\textbf{315}}; \node (D) at (-3,-6) {\textbf{318}}; \node (E) at (3,-6) {\textbf{319}}; \node (F) at (-3,-9) {\textbf{322}}; \node (G) at (3,-9) {\textbf{323}};
  \draw[->,thick] (B) -- node[above] {Na} (C);
  \draw[->,thick] (C) -- node[above] {Me} (D);
  \draw[->,thick] (D) -- node[above] {Ph} (E);
  \draw[->,thick] (E) -- node[above] {Me} (F);
  \draw[->,thick] (F) -- node[above] {Ph} (G);
  \draw[->,thick] (G) -- node[above] {Me} (B);
\end{tikzpicture}
\end{center}

Using this method, pyrazolidines \textsuperscript{315}, \textsuperscript{317}, \textsuperscript{319}, \textsuperscript{321}, \textsuperscript{323} and \textsuperscript{325} were prepared from the corresponding pyrazolones \textsuperscript{314}, \textsuperscript{316}, \textsuperscript{318}, \textsuperscript{320}, \textsuperscript{322} and \textsuperscript{324}. Note that compound \textsuperscript{316} is antipyrine, \textsuperscript{320} is thiopyrine [in this example, dihydrothiopyrine (\textsuperscript{321}) was also isolated when reducing it with lithium aluminium hydride (LAH)] and \textsuperscript{322} is pyramidon. The replacement of H by D to determine the mechanism can be found in references\textsuperscript{141 and 143}.4.3.2. Pyrazolidinones. Pyrazolidinones, being a degree more reduced than pyrazolones (Figure 1), are easier to reduce to pyrazolidines (Scheme 17).

In 1893, Knorr and Duden reported that the reduction of \textsuperscript{326} by Na/EtOH affords \textsuperscript{315} (R = H).\textsuperscript{139} In 1966, but using lithium aluminium hydride (LAH), Montpellier’s group obtained a mixture of 2-pyrazoline \textsuperscript{327} and pyrazolidine \textsuperscript{315} (R = H).\textsuperscript{141} In the same paper, the reduction of \textsuperscript{326} to afford 5-hydroxypyrazolidine \textsuperscript{328a} (in equilibrium with the open structure \textsuperscript{328b}) and pyrazolidine \textsuperscript{315} was also reported;\textsuperscript{141} replacing H by D the mechanism of the reductions was explored. The same year, Kornet reported the double reduction \textsuperscript{329} \rightarrow \textsuperscript{330},\textsuperscript{146} and the following year the synthesis of 1-methyl-pyrazolidine \textsuperscript{66} from \textsuperscript{331}.\textsuperscript{34} This author described in subsequent papers pyrazolidines \textsuperscript{332} and \textsuperscript{333}.\textsuperscript{147}

Using LAH, the reduction \textsuperscript{334} \rightarrow \textsuperscript{323}\textsuperscript{145} and the synthesis of pyrazolidines \textsuperscript{336/337} from \textsuperscript{335}, and \textsuperscript{340} were reported; the origin of the stereochemistry of C4-substituent in \textsuperscript{336}, \textsuperscript{337} and \textsuperscript{340} from \textsuperscript{338/339} was
determined. Reduction of any of 341/342 isomers with simultaneous acetylation affords 1-aryl-2-acetylpyrazolidine 343; the 4-methyl analogue 344 was reported in the same paper. Kornet is the author of the 345 → 1,4-dimethylpyrazolidine (346) reaction. Finally, Speckamp reported the reduction of 347 by sodium borohydride followed by treatment with ethanol in acid medium, to give the 3-ethoxypyrazolidine 348.

Scheme 17. Reduction of pyrazolidinones to pyrazolidines.
4.4. By reduction of pyrazoles and pyrazolium salts

Pyrazoles are resistant to reduction; only two exceptions have been reported (Scheme 18). In 1923, Thoms and Schnupp used Pd/H₂ to reduce 1-phenyl-1H-pyrazole (349) to 1-phenyl-pyrazolidine 57.¹⁴⁰ By preparative electrolysis, 4-hydroxy pyrazolidine 351 (E' = CO₂Et) was obtained from 4-hydroxy-1H-pyrazole 350.¹⁵²

![Scheme 18. Reduction of pyrazoles.](image)

Much more common is the reduction of pyrazolium salts. This field was explored by two groups, that of Jacquier in the 1970s (Montpellier, France)¹⁵³,¹⁵⁴,¹⁵⁵ and that of González Nogal in the 1990s (Valladolid, Spain).¹⁵₆,¹⁵₇,¹⁵₈

In Figure 6 are reported the pyrazolidines synthesized by the first group, 25, 26, 40/41, 317, 325, and the remaining ones from 352 to 361. A mechanism was proposed for the formation of these products, which were completed taking into account the incorporation of deuterium when LiAlD₄ is used as a reducing agent and (or) D₂O for the decomposition of the complexes.¹⁵⁵

![Figure 6. Pyrazolidines by reduction of pyrazolium salts, Montpellier results [153-155].](image)
In Figure 7 there are gathered the large number of pyrazolidines obtained by the second group, 362-383.156-158 The reducing agents were AlLiH₄ and NaBH₄ and the pyrazolidines 362-380 were obtained mixed with pyrazolines.156,157 The use of Grignard reagents leads to pyrazolidines with a supplementary methyl substituents, 381-383.158

Figure 7. Pyrazolidines by reduction of pyrazolium salts, Valladolid results [156-158].

4.5. By reduction of 1-, 2- and 3-pyrazolines
We will divide this section into four subsections, depending on the pyrazoline nature: 1-pyrazoline 109, section 4.5.1; 2-pyrazoline 10, section 4.5.2; 3-pyrazoline 384, section 4.5.3, and cations 385 and 386, and section 4.5.4 (Scheme 19).
4.5.1. 1-Pyrazolines. There is only a paper reporting the reduction of 1-pyrazolines 109, involving compounds 387 and 390 of Scheme 19.159 The results depend on the reducing agent and together with pyrazolidines 388 and 392, 2-pyrazoline 389 and diamine 391 are formed.
Scheme 19. Pyrazoline precursors and reduction of 1-pyrazolines.

4.5.2. 2-Pyrazolines. Different methods have successfully been used to reduce 2-pyrazolines 10 (Scheme 19) into pyrazolidines; the stereochemistry of pyrazolines is preserved in pyrazolidines (Scheme 20). Thus, Kost and Golubeva reduced 3,3,5-trimethyl-2-pyrazoline 393 with sodium in butanol into pyrazolidine 18.\textsuperscript{160} Polarography transforms 394 into 395.\textsuperscript{161} Crawford used Parr hydrogenation to carry out the synthesis of pyrazolidines 332 and 398, pyrazolidine 18 was also prepared by this method.\textsuperscript{33} Hesse used lithium aluminium hydride for the transformation 399 $\rightarrow$ 400.\textsuperscript{105}

Enantioselective synthesis was used by Carreira \textit{et al.} to prepare pyrazolidines 401-404.\textsuperscript{162,163} Barluenga \textit{et al.} reported the sequence 405 $\rightarrow$ 406 $\rightarrow$ 407 $+$ 408; the diastereo-selective reduction of C=N double bond being the key step.\textsuperscript{164} The regioselective reduction of the C=N double bond in 2-pyrazolines 409 using Superhydride (LiEt$_3$BH) gives pyrazolidines 410 with excellent levels of \textit{cis}-diastereoselectivity.\textsuperscript{165} Chiral 5,5-disubstituted-1H-pyrazoline-5-phosphonate 411 was treated with benzyl chloroformate (CbzCl) to give the protected pyrazolidine derivative 412 (97% ee).\textsuperscript{166}

In the field of peptidomimetics, NCbz pyrazolidines were prepared as proline surrogates.\textsuperscript{167} Some 2-pyrazolines proved to be extremely resistant to reduction using hydride reducing agents (NaCNBH$_3$, LiBH$_4$, LiAlH$_4$, BH$_3$, LiEt$_3$BH, Et$_3$SiH, and Bu$_3$SiH), catalytic reduction (H$_2$, Pd/C) or SmI$_2$; only limited success was achieved with NaBH$_4$ in refluxing methanol.\textsuperscript{168}
**Scheme 20. Reduction of 2-pyrazolines.**

### 4.5.3. 3-Pyrazolines

Reduction of 1-phenyl-2,3-dimethyl-3-pyrazoline (413) by catalytic hydrogenation affords the already reported pyrazolidine 317 (Scheme 21). The transformation 414 → 319 similarly proceeds using sodium borohydride. Nucleophilic addition of methanol to the double bond of 3-pyrazoline 415 affords the cis and trans pyrazolidines 416 and 417. Formic acid (Leuckart-Wallach reaction) has been used to reduce pyrazolines 418 and 419 into pyrazolidines 37 and 35. Hydrogenation of 420 furnished pyrazolidine 421 bearing two phenyl groups in the cis conformation.
Scheme 21. Reduction of 3-pyrazolines.

4.5.4. Pyrazolinium cations. This section includes the reduction of 3-pyrazolines 384 (Scheme 19) in the presence of Brønsted or Lewis acids, although cations 386 were not isolated (Scheme 22).
Pyrazolidine 354 was obtained from a mixture of pyrazoline-3, sodium borohydride and acetic acid in tetrahydrofuran; the pyrazolinium ion was formed and reduced without isolation by the hydride. A similar result was obtained using a Lewis acid, AlCl₃, with AlLiH₄, isolating pyrazolidine 319;¹⁷² and with I₂, which is transformed into IH during the process, pyrazolidines 25/26 and 358/359 were prepared.¹⁵⁵ Using sodium borohydride pyrazolidines 423 (30%) and 424 (70%) were obtained from the pyrazolinium salt 422.¹⁷³ Other pyrazolines, with interesting NMR properties, were prepared using the same procedure.¹⁷⁴

Addition of OH⁻ to type 386 cations resulted in 3-hydroxypyrazolidines 425-428,¹⁷⁵ and, starting from 429, pyrazolidines 430-431 were obtained.¹⁷³

![Scheme 23](image)

Scheme 23. Reduction of compound 432, related to cation 385, and zwitterion 434⁺.

There is an example of reduction of a type 385 cation (Scheme 19) due to Kost (Scheme 23) 432 → 433.¹⁷⁶ 2-[5,5-Dimethyl-3,3-bis(trifluoromethyl)-1-pyrazolin-l-yl]-1,1,1,3,3,3-hexafluoro-propan-2-ide (434⁺) has been reduced by Burger¹⁷⁷ and by Tipping to pyrazolidine 435, the radical 436 being postulated as intermediate (Scheme 23).¹⁷⁸

4.6. Non-conventional methods

4.6.1. From other heterocycles. We have reported in Scheme 24 a series of syntheses leading to pyrazolidines that have been prepared from other heterocycles, excluding those obtained from other pyrazolidines that we will discuss in the reactivity section 5.

Based on the sequence 437 → 438 → 439, a series of pyrazolidines 440 to 447 have been prepared.¹⁷⁹

The combination of a hetero-Diels–Alder reaction of 448 and 449 with ruthenium-catalyzed ring-opening cross metathesis (ROCM) renders new functionalized pyrazolidines 450 and 451.¹⁸⁰ For the first time, N,N’-unsubstituted pyrazolidines 453 have been prepared reacting 3-nitro-2-(trichloromethyl)-2H-chromene (452, X = Cl) and 3-nitro-2-(trifluoromethyl)-2H-chromene (452, X = F) with hydrazine (62).¹⁸¹
Scheme 24. Synthesis of pyrazolidines from other heterocycles.

Treatment of 6-aryl-1,5-diazabicyclo [3.1.0]hexane (51, Ar = p-MeC₆H₄) with Lewis acids affords an azomethine imine intermediate; in situ, reaction with carbon disulfide yields the inner salt 454. Insertion of benzoyl cyanide affords pyrazolidines 455;¹⁸² a similar reaction leads to 456.¹⁸³

4.6.2. Other reactions. Scheme 25 corresponds to two synthetic approaches to pyrazolidines that are rather unusual. The reaction of benzaldehyde azines 457 with tetracyanoethylene (TCNE, 458) yields a tetracyano
pyrazolidine 459 through a very complex and hypothetical mechanism. Alkylation of isatin 460-derived N-Boc-hydrazone 461 to afford 462, followed by a Pd-catalyzed carbo-amination reaction offers an entry to 3-spiro-pyrazolidyl-oxindoles 464 and 465.


5. Chemical Properties and Reactivity

5.1. Protonation, basicity and quaternization
Protonation of pyrazolidines just poses a problem at the site when the molecule lacks symmetry; otherwise, the result is without ambiguity, as is the case of 11H+, 23H+, 37H+ and 50 (Figure 3) as well as compound 306 of Scheme 14. A series of protonated asymmetric pyrazolidines were prepared by treatment with HCl/AcOEt and characterized by NMR, but the protonation site was not determined. Of similar structure to 306 was the pyrazolidine 468 prepared from 467 [Fmoc = 9-fluorenylmethoxycarbonyl; Fmoc-Osu = N-(Fmoc-oxy)-succinimide]]; in this case, the proton was attached to the NBoc, and 1H and 13C data were consistent with 468H+. Acetone reacts with 11H+ to afford the pyrazolidinium salt 466. Inverse deprotonation reactions were reported by Hesse concerning pyrazolidine 286 (Scheme 13).
Scheme 26. Protonation and quaternization of pyrazolidines.

Pyrazolidines, being cyclic hydrazines, their basicity does not differ from that of these compounds, a fact that has resulted in a lack of interest to determine the \( pK_a \) of pyrazolidines. However, the ring hinders the rotation about the N-N bond, typical of hydrazines. Note that only the gauche conformation is a minimum on the rotational curve of hydrazine,\(^{189,190}\) and few pyrazolidines can adopt such a structure. For instance, the dihedral angle between lone pairs of tetramethylhydrazine is 79° while that of pyrazolidine 12 is 12°.\(^{191,192}\)

Two authors have reported the \( pK_a \)s of hydrazines and pyrazolidine 11 at 25° (a)\(^{193}\) and at 35° (b)\(^{186}\): hydrazine 62 8.07 (a); 1,2-dimethylhydrazine 67 7.52 (a), 7.32 (b); pyrazolidine 11 7.60 (a), 7.25 (b). The hydrogen-bond acidity of 1-acyl-5-hydroxy-pyrazolidines like 122a (Scheme 6a) and related compounds is similar to that of phenol.\(^{194}\)

Quaternization of pyrazolidines has been reported in three papers, no \( \alpha \)-effect was detected.\(^{195}\) In the first one, quaternization of 469 took place on the N-methyl group 470 as expected.\(^{196}\) In Figure 4 it was reported that in the methylation of 5-hydroxy-2-isopropylpyrazolidine-1-carbaldehyde (162) to 166, again the isopropyl group was preferred to the formyl one.\(^{82}\) In Scheme 14 there are also reported several quaternary salts but they were not prepared by quaternization.

5.2. Reactions on the nitrogen atoms
The alkylation of pyrazolidines is straightforward, some examples are reported in Scheme 27, from Michaelis in 1893 (471 and 472)\(^{28}\) to Kornet in 1967 (473 and 474)\(^{34}\) and 1969 (475).\(^{147}\)
Scheme 27. Examples of N-alkylation of pyrazolidines.

Acylation (COMe, COR, COPh, COAr) of biochemical groups (Cbz, Boc), as well as tosyl and related groups, is very common, being one of the most studied reactions in pyrazolidine chemistry. Figure 8 reports the resulting compounds with the corresponding references.

Figure 8. Acyl, tosyl and phosphinate derivatives.

Examples of acetylation are compounds 476-479,28,105,197 and, of acylation, compound 480,198,199,200 including annelation leading to a bicyclic compound 481.201 Other results include peptidomimetics 482 and 483,61,162 benzoylation compounds 469,484 and double benzoylation 485,202 introduction of CO₂R groups using either ethyl chloroformate 48634 or 1H-imidazole carboxylates 487,142 introduction of CONHR groups using phosgene and heteroaryl amines (five- and six-membered rings) 488,203 tosyl 489,63 and phosphinyl groups 490.193
Addition of pyrazolidines to a double bond of heteroallenes has been mainly studied by Morgenstern et al. who have prepared the compounds 491-496 (R = Me, CH$_2$=CH-CH$_2$, Ph, Ar, 1-naphthyl) (Scheme 28). Reactions with other heteroallenes like isopropyl isocyanate, cyclohexyl isocyanate, and phenyl isothiocyanate have been reported.

Scheme 28. Addition of pyrazolidine 11 to isocyanates, isothiocyanates, carbon disulfide, carbodiimides and cyanogen bromide.

Related to these protecting groups are some deprotecting reactions. For instance, parent pyrazolidine 11 has been prepared by deprotection of diacyl-pyrazolidine CO-$i$-Bu, and Boc. It is possible to replace a protecting group by another, for instance, Alloc by Boc. It has been shown by Kost et al. that N-acyl pyrazolidines 497 react with reagents such as POCl$_3$/DMF, called the Golubeva synthesis related to the Vilsmeier-Haack reaction, to afford 3-methyl-1,2,3,4-tetrahydropyrimido[1,2-a]indole-10-aldehyde (498) (Scheme 29), and related compounds.

Scheme 29. Formation of indoles from N-acetyl pyrazolidines.

5.3. Reactions of the C-OH substituents and dehydration

There are two ways to transform OH to OR; the 4-hydroxy-pyrazolidines such as 36 are alkylated with alkyl halide to 4-alkoxy-pyrazolidines. Treatment of the dihydroxy derivative 91 (Scheme 3) with acetyl anhydride yields a di-O-Ac compound. On the other hand, 3-hydroxy-pyrazolidines react with alcohols to afford 3-alkoxy-pyrazolidines. 5-Hydroxy and alkoxy groups can be replaced by amino, hydrazino, and hydrazido groups (Scheme 6a). Particularly interesting is the reaction with D-tryptophan ethyl ester.
Scheme 30. Reaction of 5-hydroxypyrazolidine 113 with activated sp\(^3\) carbon atoms.

More original is the replacement of the OH groups by both sp\(^3\) and sp\(^2\) C atoms. Examples of the sp\(^3\) class are represented in Scheme 30. 5-Hydroxypyrazolidine 113 reacts with pyrazolinones to yield dimers 499 that exists as a mixture of tautomers a and b\(^{213}\); other pyrazolinones behave similarly.\(^{214}\) The same compound reacts with ethyl acetoacetate to afford compound 500.\(^{215}\) Similarly, using ethyl-2-oxocyclopentane-1-carboxylate, compound 501 was obtained.\(^{216}\) Finally, 113 reacts with 1-methylindolin-2-one to yield 502.\(^{217}\)

Rarer are reactions involving sp\(^2\) carbon atoms. One example is that of 113 reacting with the parent indole (other indoles and other 5-hydroxypyrazolidines were also studied) to afford 503.\(^{218}\)

Dehydration of 3- and 5-hydroxypyrazolidines to pyrazolines is an acid-catalyzed process where the OH group is protonated and leaves as water assisted by the adjacent N atom; the reason why 4-hydroxypyrazolidines are stable. The reaction is so easy that the CF\(_3\) group is often necessary to isolate the hydroxypyrazolidine. Several examples are gathered in Scheme 31.
Scheme 31. Pyrazolines from hydroxypyrazolidines.

When the hydroxypyrazolidine has no substituents on the nitrogen atoms, the reaction proceeds smoothly, e.g., the syntheses of 504 and 505.\textsuperscript{16,78,80} The same happens if one of the substituents is easy to remove, as in the case of Boc, compound 506.\textsuperscript{73} If the N atom adjacent to the OH group is substituted, 150 (R = Me), then the 2-pyrazoline 507 resulted after several double-bond migrations.\textsuperscript{16,78} Finally, $N,N'$-disubstituted compounds like 425 lead to the 3-pyrazoline 508.\textsuperscript{173}

Scheme 32. Hydroxypyrazolidine dimer.

Córdova et al. reported an interesting behavior of complex 509 formed by the reaction of 145 and Boc-NH-NH$_2$ (already used in Scheme 25, but not isolated) that, through an OH addition to a sp$^2$ carbon atom, dimerizes to 510 (Scheme 32).\textsuperscript{75}

5.4. Reactions of substituents on the carbon atoms of the pyrazolidine ring
These reactions correspond to classical organic chemistry and will be illustrated with a few cases exemplified in Figure 9.
Compound 511 was prepared by reduction of the corresponding nitro derivative. The reduction of 3-CH₂COMe with sodium triacetoxy borohydride or sodium tripivalyloxy borohydride affords 512 that was isolated as a hydrochloride and its structure determined by X-ray crystallography. Pyrazolidines 513-516 were prepared by the same group of authors by the reduction of the corresponding carbonyl compounds with NaBH₄ or LiAlH(OBu)₃; their structures were determined by X-ray crystallography to establish their relative R,S-configuration. They summarized these and similar results in a subsequent work.

5.5. Oxidation
This section reports reactions that are the opposite of those discussed in Sections 4.4 and 4.5. We will start with the oxidation of pyrazolidines to pyrazolines (Scheme 33). Oxidation to 1-pyrazolines requires both nitrogen atoms of the pyrazolidine to be unsubstituted, e.g., 11, 517 and 518 to afford 1-pyrazolines 109, 519 and 520, or the substituents easy to remove, e.g., the ethoxy carbonyl group of 521, depending on the experimental conditions, is eliminated giving 522 or not, yielding 523.

Oxidation to 2-pyrazolines requires that at least one N atom remains unsubstituted, as was the case for 57, 315, 289/290, 527, 529, 531/532 which were transformed into pyrazolidines 524, 327, 526, 528, 530, and 533 respectively. In the last example, due to the presence of a strong withdrawing group, NO₂, the reaction proceeds from 216 to the 2-pyrazoline 534, that then tautomerizes to the 3-pyrazoline 535.
Scheme 33. Oxidation of pyrazolidines to pyrazolines.

Although the oxidation of pyrazolidines to pyrazoles occurs via pyrazolines in a two-step process, in some cases, the oxidation directly renders pyrazoles (Scheme 34). Hamelin et al. reported the formation of pyrazoles 536 and 537 in the synthesis of intermediates 2-pyrazolidines 293 and 295, respectively. Compound 538 was stable under N₂ but, otherwise, it is oxidized to pyrazoline (not isolated) that loses HNO₂ to yield pyrazole 539.
Scheme 34. Pyrazoles from pyrazolidines (E = CO$_2$Me).

4-Hydroxypyrazolidines (Scheme 35) are oxidized to pyrazoles as in the 81 to 349 process.$^47$ The oxidation of 32 to 1-methyl-1H-pyrazole (541) involves presumably the 1,2-dimethyl-4-pyrazolinone (540).$^36$

Scheme 35. Oxidation of 4-hydroxypyrazolidines to pyrazoles.

A quantitative conversion of 542 into 543 (two tautomers) was obtained by oxidation with hydrogen peroxide in methanol.$^89$

The inverse reaction to the synthesis of pyrazolidines by reduction of pyrazolidinones (Section 4.3.b) is the C-OH to C=O oxidation (Scheme 36). Different oxidizing agents have been used to carry out this reaction, PCC for 135 $\rightarrow$ 544$^{73}$ and 545 $\rightarrow$ 546,$^{76}$ and COCl$_2$ for 36 $\rightarrow$ 547.$^{170}$ The vinyl group of 101 was oxidized with ozone to 548; this compound was the precursor of 48.$^{49}$
Scheme 36. Oxidation of OH and C=C groups to pyrazolidinones.

5.6. Reactions of N-substituents
This is a very common reactivity in heterocyclic compounds and only four examples will be given in Scheme 37.

Scheme 37. Reaction of N-substituents.

The art of using protecting groups is exemplified in the reactions 549 → 550 and 278 → 551. A bicyclic system that also involves the removal of a benzyl group was the result of treating 552 with titanium chloride to yield 553. Pyrazolidine 96 treated with two different acyl chlorides yielded first 554 and then 555.

5.7. Reduction to diamines: N–N bond breaking and ring opening
This reaction is the inverse of the synthetic method reported in Section 4.1.2. It constitutes one of the best ways to prepare 1,3-diaminopropanes 106, 556-559, 561 and 563 (Scheme 38). Hydrogen in the presence of Ni Raney was used for pyrazolidines 38, 195; hydrazine over Ni/Raney for pyrazolidines 511, 562; samarium(II) iodide, 421; and sodium in liquid ammonia for 560.
Scheme 38. Synthesis of 1,3-diaminopropanes.

5.8. Ring-chain tautomerism
3- or 5-Hydroxy or amino pyrazolidines always exist in equilibrium with open-ring structures having a carbonyl or an imino terminal bond; the position of the equilibrium depends on the substituents and on the media. Examples of these equilibria were reported in Schemes 6a, 77, 72 and 17. Most publications reporting these ring-chain equilibria were due to Zelenin and coworkers such as Golubeva and Sviridova. In their last paper, a detailed discussion of solvent effects on the equilibrium and the E/Z equilibrium, in the case of imines, was reported.

6. Structure, Spectroscopic and Physical Properties

Spectroscopic methods, in particular NMR and IR, but also, in former times, UV, are an essential part of most organic chemistry papers. Regarding pyrazolidines, in general, such methods are never used to identify new compounds and consequently, they will not be exhaustively commented upon.

The advances in these techniques and eventually the use of theoretical methods render the information provided by them, usually in the experimental part of the manuscript, of little use. When they prove interesting per se they will be cited, especially the use of \(^1\)H NMR, for studying dynamic processes will be discussed in detail in Section 6.10 “Conformational analysis and nitrogen inversion”. Note that there are no \(^{15}\)N NMR data.
6.1. UV spectra

As for their UV spectra (ethanol 95), pyrazolidines of Schemes 16 and 22 are divided into two groups, depending on whether there are methyl or phenyl groups fixed on the nitrogen atoms. In the first case, 1,2-dimethylpyrazolidines, whatever the nature of the substituents in position 3 and 5, the spectra have an ending absorption around 220 nm; those C-arylated, present phenyl bands in the 250 nm region. In the second case, 1-phenyl-2-methylpyrazolidines, a similar spectrum is always observed: an inflection point in the 230 nm region (ε ~ 3000) and a peak around 275 nm (ε ~ 5000); these data are similar to those of phenylhydrazine, 241 nm, ε = 1600, 283 nm, ε = 9300. Some papers where UV data are reported can be found in references. 

6.2. ESR and PES spectra

Nelsen et al. reported the electron spin resonance (ESR) spectra of the radical cations of pyrazolidines 23, 33 and 34, giving ESR splits in gauss (G) at room temperature. In another work of the same year, they added the parent compound 11 and 1,2-dimethyl-4,4-diethylpyrazolidine 564 (Figure 10). In this last work, they use the ESR data to deduce the trans conformation of these pyrazolidines, but in two different dispositions of the NR groups.

A subsequent publication on the ESR spectra of pyrazolidines 38, 565-567 use the data on the corresponding radical cations, hyperfine splits (g) to discuss their ring inversion. Replacement of H3/H5 protons by methyl groups, 566+ and 567+, yields 1:2:1 triplets for the remaining H4 protons; however, there are different values for the time-averaged splittings, 13.85 G for the cis isomer 566+ and 11.70 G for the trans isomer 567+. The larger proton splitting of 566+ probably indicates that the steric interactions between the 3 and 5-methyl groups with the phenyl substituents force them into positions with more pseudoequatorial character.

Although entirely different, we report also the work of Rademacher et al., on the use of photoelectron spectroscopy (PES) in the ultraviolet region (UPS) to study 1,2-diphenylpyrazolidine (38) in comparison to 1,2-diphenylhydrazine (58), Figure 11.
A similar picture of the n/π ionization bands can be found in the case of 1,2-diphenylpyrazolidine (38). However, the band splits are somewhat smaller. Accordingly, this is also possible that the φ angle has a slightly smaller value (this angle is defined as the lone pair–N–N–lone pair torsion angle, see section 5.1). This agrees well with a bisected position of the phenyl groups on an only slightly twisted five-membered ring corresponds to φ ≈ 130°. This conclusion is consistent with that reported in section 6.10.

6.3. IR spectra
Simple pyrazolidines have no interesting bands save the OH and NH stretching ones. The most interesting are the compounds of section 5.8, which present ring chain tautomerism, because, in the open ring compounds, there is a C=O band (in the case of aldehydes at 1718 cm⁻¹, 127b, Scheme 6a), and in the ring tautomers this band is absent.79,141,229

6.4. ¹H NMR spectra
From one of the pioneer publications in 1963⁵² to the most recent ones in 2024,²³⁵ the use of ¹H NMR spectroscopy has evolved considerably. In older times, the structural use of ¹H-¹H spin-spin coupling constants, SSCC, needed precise measurements of them that, in turn, required a careful analysis of the system that can be complex in molecules with multiple spin systems. Today, this is no longer the case and very few publications report rigorous analyses.

6.4.1. Ring-chain equilibrium. This fundamental question for the behavior of 3- or 5-hydroxy substituted pyrazolidines has been discussed in sections 4.1.c (122a/b, 124a/b, 127b), 4.3.b (328a/b) and 5.8 and will be discussed again in section 6.5.1. ¹H NMR is the method of choice to study these equilibria because tautomers are easily identified, and the equilibrium constant is easily measured.

6.4.2. Dynamic aspects: conformation and tautomerism. Finocchiaro et al. reported results on 1,2-diacylpyrazolidines 42 (Figure 3), 94a and 94b (Scheme 4) based on ¹H DNMR that will be discussed in detail in section 6.10 together with their dipole moments studies of section 6.7.²³⁷ The tautomerism between a pyrazolin-5-one and a 5-hydroxypyrazole was studied by ¹H NMR, the hydroxy tautomer being predominant.²¹₃,²¹₄

6.4.3. Pyrazolidines bearing fluorine substituted groups. In the complex field of pyrazoles (Figure 1), pyrazolidines occupy a small space; surprisingly the number of pyrazolidines bearing substituents of the CF₃ type and higher perfluorinated alkanes, like C₂F₅, are relatively much higher. This is probably related to the synthetic methods used to prepare pyrazolidines compared to more oxidized derivatives.
Some examples are depicted in Figure 12. Both isomers of \( \text{170} \) are easily distinguished because, in the \textit{cis} isomer, the protons \( H_A \) and \( H_B \) of the \( \text{CH}_2 \) group at position 4 are diastereotopic, while in the \textit{trans} isomer, they are enantiotopic.\(^{85}\)

![Figure 12. Some \( ^1\text{H} \) NMR data of fluorinated pyrazolidines.](image)

Major and minor isomers of the series \( \text{154} \) and \( \text{156} \) were assigned using \( ^1\text{H} \) NMR and crystallography (FANXUN, cf. section 6.9)\(^79\); compound \( \text{435} \) shows a spectrum consistent with its symmetry.\(^{178}\) Other compounds previously described also have \( \text{CF}_3 \) substituents, and their \( ^1\text{H} \) NMR spectra have been reported in the corresponding publications: \( \text{167},^{83} \text{168},^{84} \text{170}-\text{173},^{86} \) and \( \text{435}.^{178} \)

\textbf{6.4.4. Some interesting molecules.} We have selected six pyrazolidines in Figure 13 due to the interest of their \( ^1\text{H} \) NMR chemical shifts and coupling constants. Besides the parent pyrazolidine \( \text{11} \), a complex six-spin system that was not rigorously analyzed,\(^{201}\) 1,2-dimethyl-4-hydroxypyrazolidine (\text{32}) where the ABX was analyzed,\(^{36}\) and the spiranic ring \( \text{69} \) with its very simple spectrum\(^{35}\) are shown.

Compound \( \text{119} \) shows in both \( N \)-substituents the effect of the chirality of the C-5 carbon atom on the diastereogenic character of the methylene protons that become \( \text{AB} \) on the benzyl and \( \text{ABX}_3 \) on the ethyl group.\(^{71}\) Another spiranic pyrazolidine \( \text{388}^{159} \) and a zwitterion \( \text{454} \) were also selected in Figure 13.\(^{182}\)
Figure 13. $^1$H chemical shifts of some interesting molecules.

6.4.5. Some useful methods. Two methods have been used to determine the stereochemistry of 3,4 or 4,5-disubstituted pyrazolidines: the vicinal $^3J_{HH}$ SSCC because the trans is always larger than the cis (see, for instance, compound 32 in Figure 13), and Nuclear Overhauser Effect (NOE) proximity effects or the more modern NOESY version. This has been the case for compound 568, closely related to 403, 407 (after transformation into a bicyclic structure 569 by reaction with benzyl chloroformate and tetra-butyl ammonium chloride), and 410.

More detailed experiments showed how powerful this technique is when used for compounds 248 and 570.

Figure 14. NOE experiments.
6.5. $^{13}$C NMR spectra
We will consider four cases, leaving aside papers where $^{13}$C NMR was used only as a property of the compounds, often without assigning the signals: a) ring-chain equilibrium; b) dynamic aspects (conformation and tautomerism); c) $^{13}$C-$^{19}$F SSCC; d) some interesting molecules.

6.5.1. Ring-chain equilibrium. Although the C=O signal of b tautomers is different in aldehydes, ketones, esters and amides, it differs considerably in all cases from that of the C-OH group of the hydroxypyrazolidine, a tautomer. Besides if offers a way, taking some precautions, to determine the equilibrium by integration of the signals of both isomers.\cite{71,166,229}

6.5.2. Dynamic aspects: conformation and tautomerism. Finocchiaro et al. reported in 1977 a study of the conformation of diacylpyrazolidines \cite{42,94a,94b} that is consistent with the results obtained using dipole moments (Section 6.7) and $^1$H DNMR (section 6.4.2).\cite{237} Compounds 179a and 179b, Scheme 8, show in $^{13}$C NMR broad signals for the gem-dimethyl groups at position 3, this observation was related to their $^1$H NMR spectra.\cite{90} The stereochemistry of compounds 407/408, Scheme 20, was determined by several methods including $^{13}$C NMR.\cite{164} Although not directly related to the properties of pyrazolidines, the oxo/hydroxy prototropic tautomerism 499a/499b (Scheme 30) was studied by $^{13}$C NMR.\cite{213}

6.5.3. $^{13}$C-$^{19}$F SSCC. Pyrazolidines bearing groups with fluorine substituents, mainly CF$_3$, present interesting $^{13}$C-$^{19}$F coupling constants.\cite{79,121}

6.5.4. Some interesting molecules. We have gathered in Figure 15 four interesting molecules whose structures have been determined by $^{13}$C NMR spectroscopy.\cite{201,59,182,184}

![Figure 15. $^{13}$C chemical shifts of some interesting molecules.](image)

6.6. $^{19}$F NMR spectra
In the year 2000, Coe et al. reported the NMR spectra of 5-(perfluoroethyl)-3,4,5-tris(trifluoromethyl)pyrazolind-3-ol (167), both $^1$H and $^{19}$F in CDCl$_3$.\cite{83} Four of the five $^{19}$F signals were not assigned, only that of the CF$_2$ was assigned at $-111$ ppm, Figure 16. No decimal figures were given indicating that the signal was large. In molecule 167, all the carbon atoms were stereogenic; in the case of C5, that implies that the F atoms of the CF$_2$ group of the C$_2$F$_5$ group are anisochronous and enantiotopic; therefore, they appear as an ab system with a $^2$J$_{FF}$ geminal coupling constant. This, added to $^3$J$_{FF}$ couplings with the adjacent CF$_3$ group and $^4$J$_{FF}$ couplings with the CF$_3$ on C4, yield a very complex system for each fluorine atom that results in a broad signal. Important to note that none of the remaining signals appear split, indicating that 167 is not a mixture of compounds.

Thanks to GIAO calculations all the signals were assigned and the structure of the compound determined: it corresponds to the 3S,4R,5R, Figure 16.\cite{238}
There are data on $^{19}$F NMR on compound 168 (Figure 4)\textsuperscript{84} and on compound 435 (Scheme 23).\textsuperscript{178}

### 6.7. Dipole moments

Finocchiaro \textit{et al.} reported a conformational study of the $N,N$-diacylpyrazolidines 42, 94a and 94b based on $^1$H DNMRI (section 6.4.2) and on dipole moments (Figure 17 and Table 1).\textsuperscript{237}
Figure 17. Contour map of calculated dipole moments (D) as a function of the two internal rotation angles $\theta_1$ and $\theta_2$. Black dots refer to forms A, B, and C.

Table 1. Dipole moments of the pyrazolidines of Figure 17

<table>
<thead>
<tr>
<th>Pyrazolidine</th>
<th>Benzene 25 ºC</th>
<th>Benzene 50 ºC</th>
<th>(E)-1,2-dichloroethene</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>2.86</td>
<td>2.94</td>
<td>2.44</td>
</tr>
<tr>
<td>94a</td>
<td>3.10</td>
<td>3.15</td>
<td>2.39</td>
</tr>
<tr>
<td>94b</td>
<td>5.80</td>
<td>5.85</td>
<td>5.66</td>
</tr>
</tbody>
</table>

Due to kinetic restricted rotation about the amide bond, three diastereomeric forms are possible for the diacyl pyrazolidines; they are averaged through successive rotations by $\pi$ radians of each acyl group. The values of Figure 17 were calculated assuming 3.84 D for each amide group and the direction depicted there. For 42 and 94a the conformation should be C and for 94b freely rotating amide groups.\(^{237}\)

Hall, Katritzky et al. reported the calculated dipole moments of a peptidomimetic, showing that it is less polar than the triprolyl scaffold.\(^{57}\)

6.8. Mass spectrometry

In the mass spectra of pyrazolidines the main fragmentation corresponds to a 1,3-dipolar-retroaddition-like process giving back the protonated form of the azomethine imine used in their synthesis.\(^{239}\)
In the case of pyrazolidine 226b, fragmentation patterns A and B corresponding to the cations 571-574 are found for all pyrazolidines (Scheme 39). These two fragmentation patterns can be depicted assuming that the charge of the molecular ion is localized on N-2 carrying the methyl group. Path A can be considered as a double breakage of the C-3–C-4 and N-1–C-5 bonds in β of N-2 with rearrangement of one atom of hydrogen. Path B is due to a rupture of the N-1–C-5 bond at β of N-2 with formation of a quaternary ammonium followed by breaking off the N-2–C-3 bond with rearrangement of an atom of hydrogen.\(^{239}\)

The electron ionization mass spectra of six 1-thiocarbamoyl 492 and four 1-carbamoyl-pyrazolidines 491 were reported by Morgenstern (Scheme 28).\(^{240}\) Metastable ion analysis and exact mass measurements were used to determine the fragmentation pathways. The main fragmentation was the same for all the pyrazolidines; the most important reaction was the loss of the thiocarbamoyl or carbamoyl substituent with concomitant hydrogen atom migration from the (thio)carbamoyl nitrogen to the ring nitrogen giving rise to ionized pyrazolidine at 72 daltons. For all the compounds studied, \([M-2H]^+\) ion peaks formed by dehydrogenation of the original compounds were observed.

The mass spectrometric fragmentation of 19 substituted 3-amino-, 3-hydrazino-, and 3-hydroxypyrazolidines has been studied. In the gas phase these compounds exist partly as the acyclic tautomers b, Section 5.8.\(^{241}\)

### 6.9. X-ray molecular structures

We have gathered in Figure 18 all the structures of pyrazolidines as defined in the Introduction, excluding fused derivatives; exceptionally, we have included a compound with a three-membered ring linking both nitrogen atoms 51 (a derivative of 1,5-diazabicyclo[3.1.0]hexane). We have also excluded derivatives with C=O exocyclic double bonds, so all the compounds reported here have three sp\(^3\) carbon atoms in the ring.
Figure 18. Pyrazolidine X-ray structures.

There are four classes of compounds in Figure 18: a) number and reference already cited; b) number new, but reference already cited; c) number already cited, but reference new (from Figure 3), and d) number and reference new. The third class of pyrazolidines are \( 49: \text{Cl}^- \) and \( 49: \text{picrate}^- \), \( 50 \) and \( 580, 243 \) and \( 51, 244 \). To this last class belong \( 575, 245 576, 246 583, 247 586, 248 588, 249 593, 594 \) and \( 595, 250 600, 251 \) as well as \( 603 \) and \( 604, 252 \). There is a paper reporting the structures of aza-proline-containing peptides that are not gathered in the CSD.

An examination of the structures of Figure 18 reveals that only relative configurations are available. Let us be clear about what this “never absolute values” implied. It implied quite a lot. Firstly, the total absence of spontaneous resolution. Secondly, that no examples of chiral chromatography were attempted. Thirdly, that salts of pyrazolidines with chiral acids were prepared. Fourthly, indirectly related to solid-state, there are no solution \(^1\text{H}\) NMR experiments (section 6.4) using chiral solvents or chiral lanthanide-shift reagents.

In section 6.10.1 we discuss the theoretical calculations of the rings conformation of pyrazolidines depicted in Figure 3, \( 11-52 \) that include some X-ray structures \( 48-52 \).
6.10. Conformational analysis and nitrogen inversion

6.10.1. Ring analysis. The analysis of the conformation of the "nude" pyrazolidine ring, i.e., the five-membered ring without substituents, has been the objective of several studies, including those of Nelsen\textsuperscript{255,256} and Shipman.\textsuperscript{236} The most important contribution was that of Gaweda, Plazinska and Plazinski who, in 2020, reported the analysis of the conformation of saturated five-membered heterocycles, including the parent pyrazolidine (11), evaluated by MP2 calculations.\textsuperscript{257} They used the Altona-Sundaralingam pseudorotation wheel\textsuperscript{258} to classify the cis and trans isomers as twist envelopes. Note that the cis pyrazolidine is less stable than the trans.

These kind of studies was extended to all the neutral pyrazolidines of Figure 3 (11, 18-52) using the Cremer-Pople pseudorotation wheel.\textsuperscript{259} The computations were carried out at the B3LYP/6-311++G(d,p) level while the CREST program was used to search all possible stable conformers.\textsuperscript{260} The ring puckering has been calculated using the parameters (Q and φ) proposed by Cremer and Pople (CP). The numbering for the atoms of the pyrazolidine ring start with the two nitrogen atoms as previously used in the literature.\textsuperscript{257} Note that, in this publication, the corresponding \textsuperscript{1}H and \textsuperscript{13}C of the studied compounds were calculated and compared with the available experimental results.\textsuperscript{254}

Even with this limitation, the numbering could be clockwise and counterclockwise. Since this last decision is arbitrary and depends on how the molecule is presented, we have decided to calculate for each system the CP parameters both ways. In addition, we have considered the corresponding enantiomers since they show the same energy and conformational analysis programs as CREST only provides one of the enantiomeric conformations. Thus, for each conformation, four different sets of CP parameters are calculated with the same value of Q and four different values of φ. Each of this sets are located in one of the four quadrants delimited by the angles [18-108°], [108-198°], [198-278°] and [278-18°].

As an example of the different conformations obtained for these molecules, the five more stable conformations of 1,2-dimethyl-3-hydroxypyrazolidine (31) are represented in Figure 19; all of them have the two N-methyl groups in a trans disposition. Their CP parameters are shown in Figure 20.
A histogram of the $\phi$ values in all the minimum conformations obtained for 11, 18-52 (242 conformations) (Figure 21). The $^1T_2$ are the most abundant conformation in the first quadrant when all the conformations are considered (31% of the conformers). A similar conclusion is reached when only the most stable conformers for each molecule are analyzed (29% of the conformers are $^1T_2$). The population of other conformation is more dependent on the set used for the analysis, for instance, $E_2$ is the second most abundant conformation when all the conformers are considered (24%), but is the least one when the analysis is done with the most stable conformers (3%). The twist conformations (139 cases) are more abundant than the envelope ones (103 cases).
Figure 21. Histogram distribution of the conformers of all the minima obtained for 11, 18-52 in the first quadrant (18-108°).

6.10.2. Nitrogen inversion. $^1$H NMR studies were started simultaneously in Montpellier and Strasbourg in 1969-1970 on the conformation of monocyclic pyrazolidines. In the first place,\textsuperscript{153,154} and in the second one;\textsuperscript{13,261,262,263} although Lehn published a paper on bicyclic pyrazolidines in 1967.\textsuperscript{264} The main conclusion from the first group was that four of the five substituents adopt an alternate structure, \textit{e.g.}, up-down-up-down (the fifth is situated between an up and a down, and has no preference). They also reported the broadening of some signals when the temperature is lowered. Lehn \textit{et al.} results were more important because they measured some inversion barriers based on energetic considerations (Table 2), came to the conclusion that the inversion of the two adjacent nitrogens must be done successively, such that at least one of the nitrogens is always pyramidal.\textsuperscript{264}

These studies were long forgotten until Kostyanovsky developed them considerably (Table 2).\textsuperscript{170,242,265} In the case of 35 the \textit{up-down-up-down} conformation was blocked and in the case of 37 the barrier was too high to be measured by $^1$H NMR and was measured by classical kinetics after the enantiomers were separated by chiral chromatography (Chirasil-β-Dex chiral stationary phase) and then racemized.

Morgenstern observed that the protons of the CH\textsubscript{2} adjacent to the NH have different chemical shifts while those of the remaining CH\textsubscript{2} are isochronous; this phenomenon may be explained in terms of the hindered nitrogen inversion in the pyrazolidine ring on the NMR time scale.\textsuperscript{252} This conclusion should be considered with caution as only one proton is reported at 3.41 ppm, the other could be behind another signal; furthermore, it seems unlikely that NH inversion is blocked at room temperature.
Table 2. Nitrogen inversion barriers (kJ·mol⁻¹), coalescence temperature Tc (ºC)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Lehn</th>
<th>Kostyanovsky</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tc</td>
<td>ΔG‡</td>
</tr>
<tr>
<td>29</td>
<td>−45</td>
<td>46.4</td>
</tr>
<tr>
<td>34</td>
<td>75</td>
<td>67.7</td>
</tr>
<tr>
<td>35</td>
<td>No inversion b</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>55</td>
<td>69.2</td>
</tr>
<tr>
<td>37</td>
<td>c</td>
<td>114</td>
</tr>
<tr>
<td>45d</td>
<td>63.2</td>
<td></td>
</tr>
</tbody>
</table>

⁹ Estimated;  b conformation blocked;  c too high to be determined by NMR, separated by chromatography and racemized (kinetics treatment);  d this compound belong to section 6.10.3.

6.10.3. Amide group rotation. In sections 6.7, Figure 17,²³⁷ and 6.10.2, compound 45,²⁶⁴ some examples of N-COR pyrazolidine conformations were reported; these studies contain DNMR results. The impact of azaprole residue on peptide conformation was studied theoretically at the MP2/6-31+G** level by Che and Marshall;²⁶⁶ solvation effects were studied implicitly using the polarizable continuum model, and explicitly represented by interactions with a single water molecule. These kinds of studies were developed by Reddy et al. using NMR and circular dichroism.²⁶⁷

Mixed aryl and amide-substituted pyrazolidines were conformationally analyzed by Shipman et al.²³⁶ using the PMI (Principal Moments of Inertia) approach.²⁶⁸

6.11. Computational results
In the previous sections, 4.2.2, 6.6 and 6.10.1, we have reported results that involve different types of calculation: concerted mechanisms,¹³⁶,¹³⁷ geometries,²⁵⁴ NMR,²³⁸,²⁵⁴ etc. It is obvious that this section will be much more important in the future, since, with the exception of reference²⁵⁴ (Figure 3), structural studies are fragmentary, and cover few compounds. It is to be hoped that future publications on pyrazolidines will be accompanied by theoretical calculations. Non-concerted mechanisms also need to be supported by calculations.
7. Biological Properties and Drugs

Pyrazolidines are a class of saturated heterocyclic compounds with several representatives in the field of medicinal chemistry (Figure 22) and biochemistry (Figure 23).

![Chemical structures of pyrazolidines](image)

**Figure 22.** Some representative pyrazolidines in medicinal chemistry.

The compounds of Figure 22 were reported in the following original papers or reviews: 605, 606, 607, 608, 609, 610, 611, 612, and 613. Other publications due to Morgenstern (synthesis). Guilford Pharmaceuticals (immuno-suppressant) and Arribal Discovery (cannabinoids) were also described.

Another field of great importance concerns the use of pyrazolidines as azaprolines (613) (Figure 23). Many important peptide sequences contain proline since it confers conformational constraints to the peptide chain as the side chain cyclizes back to the backbone amide position. Thus, in an alpha helix, the possibility of forming hydrogen bonds with the previous turn is lost, and a kink will be introduced. Its activity is influenced by cis-trans isomerism. In epigenetics, proline isomerization is related to cis-trans isomerism. Only a limited number of peptidases are capable of hydrolyzing adjacent proline bonds.
There are two classes of azaprolines 613, the \( \alpha \) (1,2-dicarboxy) and the \( \delta \) (1,5-dicarboxy) (Figure 23). Azaproline analogs, \textit{i.e.}, pyrazolidine compounds 613, are more resistant to protease cleavage, and have many applications as enzyme inhibitors or receptor antagonists. The results in the literature suggest that some of the corresponding azapeptides have potential therapeutic utility in the treatment of degenerative diseases. Peptides containing azaproline residues with a \textit{cis}-amide conformation induce type IV \( \beta \)-turn mimetics.58,100,188,221,266,267,275,276,277 This conclusion was based on studies of peptide conformation.

8. Catalysts

In this review, several catalysts have been used. They are reported in Figure 24 with, in red, one or several references where they were used.
9. Conclusions

This review shows that the, seemingly minor, field of pyrazolidines encompasses a rich variety of results. The synthetic part is well developed and up-to-date, especially regarding enantioselective methods. The reactivity remains stuck in the past and needs a resurgence, for example, in the use of pyrazolidines as starting materials to prepare complex structures, whether organic or organometallic. The structure, spectroscopic and physical properties section shows that there is abundant information regarding solid-state, X-ray structures, however, in solution, most results are old and lack quality, and the gas-phase is almost unexplored, except for some recent calculations.
10. Acknowledgements

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Data availability
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Abbreviations
MW    Microwave
US    Ultrasound
B3LYP  Becke 3-parameter Lee Yang Parr
CCDC  Cambridge Crystallographic Data Centre
DNMR  Dynamic Nuclear Magnetic Resonance
GIAO  Gauge Invariant Atomic Orbital
Alloc  Allyloxycarbonyl
Boc   Tert-butyloxycarbonyl
Cbz   Benzoxycarbonyl
Fc    Ferrocenyl
Fmoc  9-Fluorenylmethoxycarbonyl
Fmoc-Osu  N-(Fmoc-oxy)-succinimide
Ns    Nosyl (4-nitrobenzenesulfonyl)
PCC   Pyridinium chlorochromate
Xc    Camphorsultam

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