Chemistry of Heterocyclic Compounds, Vol. 39, No. 4, 2003

METHODS FOR THE SYNTHESIS OF 3,4-2H-DIHYDROPYRROLES (Δ^1-PYRROLINES) AND THEIR CHEMICAL TRANSFORMATIONS. (REVIEW)

M.-G. A. Shvekhgeimer

Published data on the synthesis and chemical transformations of 3,4-2H-dihydropyrroles (Δ^1-pyrrolines) are analyzed and reviewed for the first time.

Keywords: 3,4-2H-dihydropyrroles (Δ^1-pyrrolines), synthesis, chemical properties.

For compounds of the pyrrole series there are three possible isomeric dihydro derivatives: 3,4-2H-dihydropyrroles (Δ^1-pyrrolines), 2,3-dihydropyrroles (Δ^2-pyrrolines), and 2,5-dihydropyrroles (Δ^3-pyrrolines). Of these three groups of compounds the Δ^1-pyrrolines are the most interesting as the subjects of various chemical transformations, such as synthons in the production of other heterocyclic systems and in particular various biologically active compounds (drugs, pesticides). The interest in Δ^1-pyrrolines arises from the fact that fragments of the pyrroline rings appear in the composition of important biologically active natural compounds such as alkaloids, steroids, hemes, chlorophylls.

A series of well developed methods for the production of Δ^1-pyrrolines from acyclic and also alicyclic or heterocyclic compounds have been described in the literature.

In 3,4-2H-dihydropyrroles there are several reaction centers, i.e., the C=N bond, the nitrogen atom, and the CH and CH_2 groups. Addition and cycloaddition involving the C=N bond have been studied most. There is less information on reactions accompanied by cleavage of the C=N bond with opening of the pyrroline ring. The literature contains little information on reactions at the nitrogen atom and with the hydrogen atoms at the carbon atoms of the heterocyclic ring.

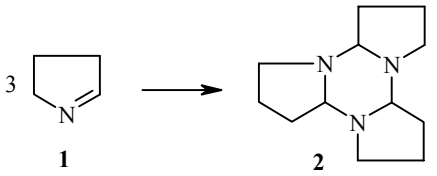
1. METHODS FOR THE PRODUCTION OF 3,4-2H-DIHYDROPYRROLES

The authors of almost all the papers on the production of Δ^1-pyrrolines from acyclic compounds have used bifunctional compounds (either diamines or compounds with two different functional groups) as starting materials. The production of Δ^1-pyrrolines from three-, five-, or six-membered heterocyclic compounds has been described. The possibility of synthesizing Δ^1-pyrrolines from alicyclic compounds was demonstrated.

It should be noted that the C=N bond in 3,4-2H-dihydropyrrole (**1**) enters readily into an addition reaction with the azomethine carbon atom of another molecule of **1**. The trimer **2** is formed in this way from three molecules of Δ^1-pyrroline:

A. N. Kosygin Moscow State Textile University, Moscow 117918, Russia; e-mail: office@msta.ac.ru.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 483-529, April, 2003. Original article submitted April 5, 2000; revision submitted January 31, 2003.

0009-3122/03/3904-0405$25.00



1 **2**

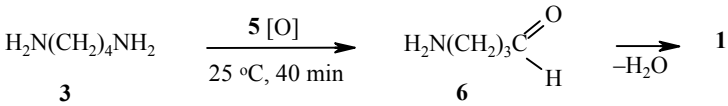
The formation of either the trimer **2** or mixtures during the production of the pyrroline **1** is determined by the reaction conditions and is not in most cases stated by the authors. For this reason in the present work the form of the obtained Δ^1-pyrroline (monomer, trimer, or their mixture) or of the compound used in the reaction is given in the form described by the author of the cited paper.

1.1. From Acyclic Compounds Containing NH_2 Groups

1.1.1. From Diamines

Of the compounds with two primary amino groups only 1,4-diaminobutane (putrescine) (**3**) and 1,8-diamino-4-azaoctane (spermidine) (**4**) have been used in the synthesis of Δ^1-pyrrolines.

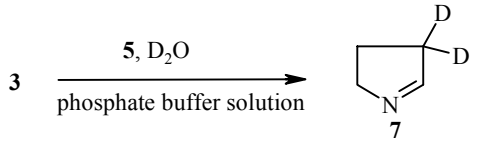
Under the conditions of enzymatic oxidation in the presence of diaminooxidase **5** at pH 5.7 [1, 2] or pH 7 [2] the diamine **3** is converted ito pyrroline **1** [1-5]. According to data from the authors in [2, 3], the process presumably includes the intermediate formation of the aldehyde **6**.



3 **6**

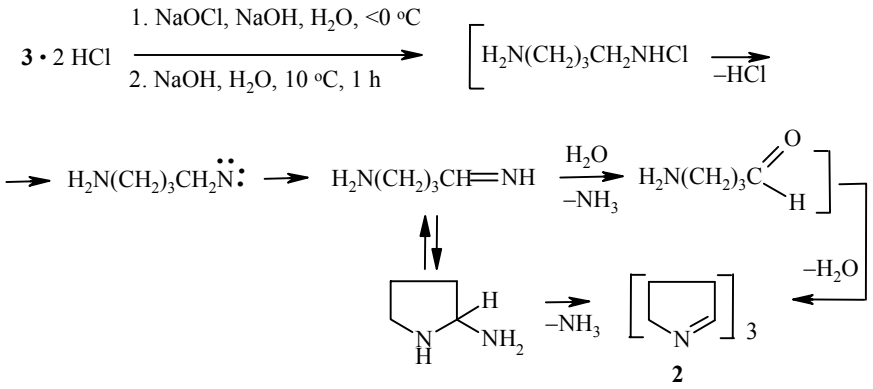
In the presence of compound **5** the diamine **3** with the C^{14} carbon isotope at position 5 is converted into a metabolite containing up to 94% of pyrroline **1** [6-8].

In the reaction of the diamine **3** with diaminooxidase **5** in a phosphate buffer and in D_2O the pyrroline **7** containing two deuterium atoms at position 3 is formed [9].

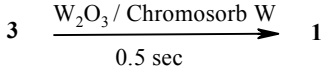


7

The trimer **2** was synthesized with a yield of 32% as a result of the reaction of the dihydrochloride of the diamine **3** with NaOCl and NaOH in water at low temperature followed by treatment of the reaction mass with aqueous sodium hydroxide. The authors propose the following scheme for the process [10]:



In the patent [11] a method was proposed for the production of pyrroline **1** from the diamine **3** over W_2O_3 in an inert atmosphere at 420-540°C with a contact time of 0.5 sec.



Temperature (°C), yield (%): 420, 55; 460, 63; 500, 73; 540, 70

The dehydrocyclization of the diamine **3** in the presence of various oxides, deposited on Chromosorb W, at various temperatures and with a contact time of 0.5 sec was investigated in [12] (Table 1).

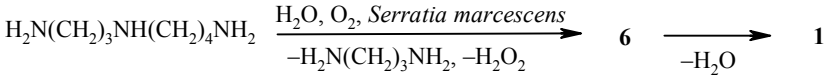
TABLE 1. Transformation of the Diamine **3** into Pyrroline **1**

Oxide	Content, %	Temperature, °C	Yield of **1**, %*
P_2O_5	1	300-500	1
WO_3	1	300	7
		500	57
P_2O_5+WO_3	0.98+0.02	300	2
		540	29
WO_3+SiO_2	0.98+0.02	300	14
		500	58
CuO	1	300	13
		500	49
NiO	1	300	2
		540	30
WO_3	1	500*[2]	71
WO_3	5	500*[2]	55
WO_3	1	500 (0.25 sec.)	25
WO_3	1	500 (0.7 sec.)	69
WO_3*[3]	5	540	58
WO_3*[3]	10	460	36
		500	71
WO_3*[3]	45*[4]	460	27
		500	85

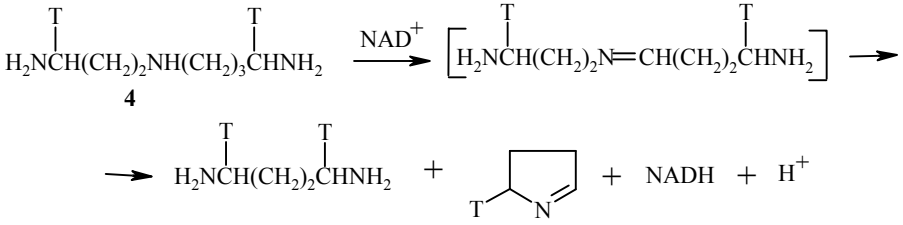
* The reaction products contain pyrrolidine and pyrrole.
*[2] In an atmosphere of helium.
*[3] The reaction was conducted in a flow-type regime.
*[4] On kaolin instead of Chromosorb.

It can be concluded from the data in [11, 12] that the highest yields of pyrroline **1** are obtained when the reaction is carried out over W_2O_3 or WO_3, deposited on Chromosorb W, in a helium atmosphere at 500°C or over WO_3 on kaolin at 540°C.

In the presence of an enzyme isolated from *Serratia marcescens* 1,8-diamino-4-azaoctane (**4**) is converted into a mixture of 1,3-diaminopropane and pyrroline **1**. In the authors' opinion [13, 14] the latter is formed from the intermediate amino aldehyde **6**.

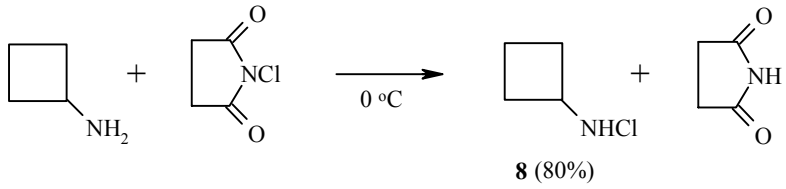


In a more recent paper [15] the cyclocondensation of compound **4**, containing tritium atoms at the two terminal carbon atoms, was realized by the action of the nicotinamideadeninenucleotide cation (NAD^+), and the following reaction scheme was proposed:



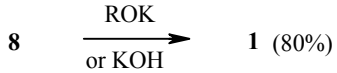
1.1.2. Recyclization of Aminocyclobutane

There are only two reports in the literature on the production of pyrroline **1** by the recyclization of alicyclic compounds. Both papers [16, 17] describe the transformation of aminocyclobutane into pyrroline **1**. This original method involves enlargement of the four-membered ring and insertion of the nitrogen from the amino group directly attached to the cyclobutane ring into the ring. In both papers the first stage of the process involves treatment of the aminocyclobutane with N-chlorosuccinimide to form the N-chloro derivative **8** [16, 17].



8 (80%)

The N-chloro derivative **8** was either treated with potassium alcoholates [16] or was brought into reaction with potassium *tert*-butoxide in the gaseous state (under vacuum) in a flow-type system [17].

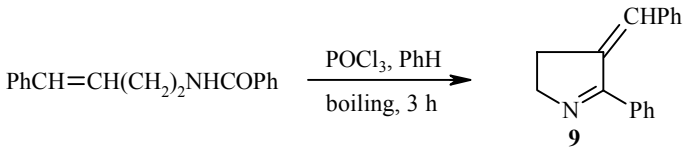


R = CMe_3, Ad-1

1.1.3. Cyclization of Primary Amines Containing Various Functional Groups

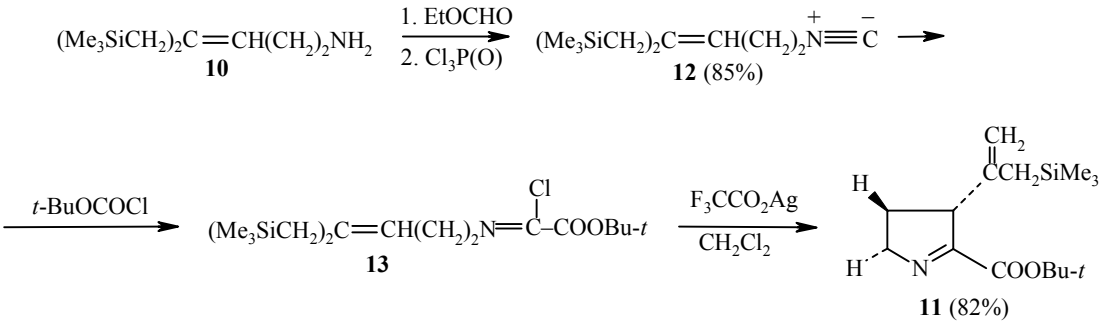
In this section we examine data from papers in which Δ^1-pyrrolines were obtained from bifunctional compounds containing a primary amino group and a different type of functional group (double bond, hydroxyl, aldehyde, ketone, carboxyl). It should be mentioned that in some cases the N-derivatives of amines and also the O-derivatives of aldehydes (acetals) or acids (esters) were used.

1.1.3.1. Cyclization of Unsaturated Amines. When 1-benzoylamino-4-phenyl-3-butene is heated with phosphorus oxychloride intramolecular cyclocondensation occurs, and Δ^1-pyrroline **9** is formed [18].



9

A more complicated path to the transformation of the unsaturated amine **10** into the Δ^1-pyrroline was described in [19]. The amine **10** was converted into the isonitrile **12**, which was brought into reaction with the acid chloride *t*-BuOCOCl. The ketoimino chloride **13** formed here was converted into Δ^1-pyrroline **11** by the action of silver triflate.



10

12 (85%)

13

11 (82%)

1.1.3.2. Cyclization of Amino Alcohols. 4-Aminobutanol (**14**) is the only representative of amino alcohols studied as starting compounds in the synthesis of Δ^1-pyrrolines. When the vapor of the amino alcohol **14** was passed over zeolite at 220-300°C, a mixture of pyrroline **1** (yield 1.1-3.7%), pyrrolidine **15** (yield 57%), and pyrrole (yield 8%) was obtained [20].

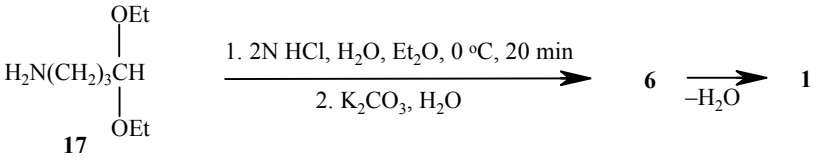
TABLE 2. The Transformation of $H_2N(CH_2)_4OH$ (**14**) over Catalysts Cu/Al_2O_3 or Cu/MgO

Catalyst	Temperature, °C	Ratio of products in catalysate, %			
		1	**15**	1-methylpyrrolidine	**16**
Cu/Al_2O_3	200	47	20	33	0
	225	42	45	13	0
	250	42	20	55	0
	275	10	9	71	10
	300	6	3	55	24
Cu/MgO	200	0	42	58	0
	225	0	62	38	0
	250	0	45	55	0
	275	0	45	55	0
	300	0	44	56	0

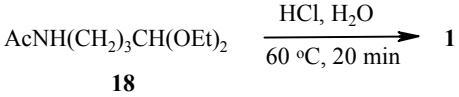
As a result of study of the cyclocondensation of the amino alcohol **14** under pulse chromatographic conditions over catalysts CuO, P_2O_5, WO_3, P_2O_5+WO_3, WO_3+SiO_2, or WO_3+CaO+B_2O_3 at temperatures in the range of 260-420°C it was established that pyrroline **1** is only produced with the best yields (2-10%) when 1% of CuO/Chromosorb W is used at 280-360°C. Pyrrolidine **15** (21-64%) and pyrrole (0.5%) are also formed under these conditions [21].

The authors of [22] realized the intramolecular cyclocondensation of the amino alcohol (**14**) in a quartz tube in the presence of methanol over catalysts Cu/Al_2O_3 or Cu/MgO at 200-300°C. It was found that three or four compounds were formed when Cu/Al_2O_3 was used as catalyst: pyrroline **1**; 1-methylpyrrolidine; 1,2-dimethylpyrrolidine (**16**). However, if Cu/MgO was used as catalyst, only pyrrolidine and 1-methylpyrrolidine were found in the reaction products (Table 2).

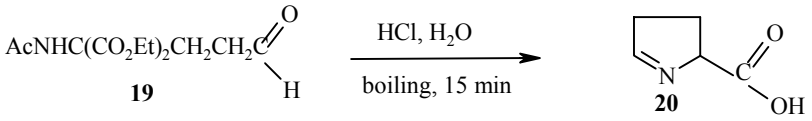
1.1.3.3. From Amino Aldehydes or Amino Ketones. Amino aldehydes and their derivatives have rarely been used as starting compounds in the synthesis of Δ^1-pyrrolines. The acetal **17** is converted into pyrroline **1** when treated with dilute hydrochloric acid. The reaction includes a stage with hydrolysis of the acetal to the amino aldehyde **6**, which undergoes intramolecular cyclization *in situ*, giving pyrroline **1** [23, 24].



Harsher conditions are required for the transformation of the N-acetyl derivative of the amino acetal **18** to pyrroline **1** by the action of hydrochloric acid [25].



Brief boiling of the aldehyde **19** in hydrochloric acid results in deacylation of the MeCONH group, hydrolysis of the ester groups, and partial decarboxylation of the $C(CO_2H)_2$. 5-Hydroxycarbonyl-3,4-2H-dihydropyrrole (**20**) is formed with a quantitative yield [26].



It should be noted that the literature contains a considerable number of papers describing the synthesis of Δ^1-pyrrolines by the cyclocondensation of compounds containing a ketone group (free or in the form of acetals) and a primary amino group (free or N-acylated).

The treatment of 2-bromohexan-5-one with gaseous ammonia in ethanol resulted in the production of 2,5-dimethyl-3,4-2H-dihydropyrrole (**21**) [27]. Clearly, at the first stage of the process the bromine atom is substituted by an amino group. The amino ketone **22** formed here undergoes intramolecular cyclocondensation and is converted *in situ* into the Δ^1-pyrroline **21**.

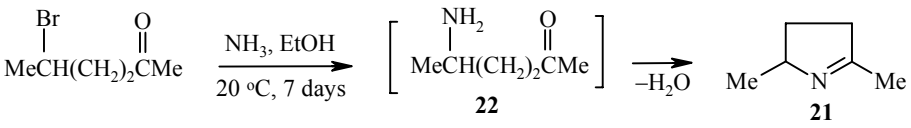
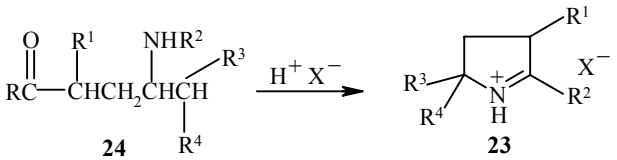


TABLE 3. Synthesis of Δ^1-Pyrrolines **23** from Amino Ketones **24**

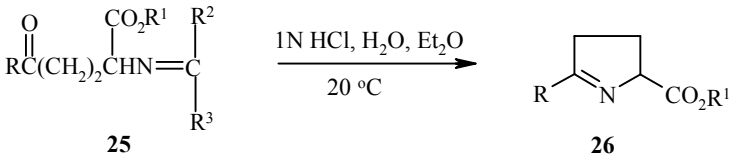
R	R^1	R^2	R^3	R^4		Reaction conditions	Yield, %	Reference
				23	**24**			
Me	Ac	Ac	CO_2Et	CO_2Et	CO_2H	Conc. HCl, boiling, 12 h	61	[28]
Me	Me	Ac	CO_2Et	CO_2Et	CO_2H	Conc. HCl, boiling, 12 h	61	[28]
Ph	H	Ac	CO_2Et	CO_2Et	CO_2H	Conc. HCl, boiling, 12 h	55	[28]
2-HOC_6H_4	H	Ac	CO_2Et	CO_2Et	CO_2H	Conc. HCl, boiling, 6 h	52	[29]
2-$MeOCH_2OC_6H_4$	H	CO_2Bu-*t*	H	CO_2Me	CO_2Me	Conc. HCl, MeOH, 20 °C, 12 h	82	[29]
Ph	H	CO_2Bu-*t*	H	CO_2Me	CO_2Me	CF_3CO_2H, 0°C, 0.5 h	89	[30]
C_6H_{13}	H	CO_2Bu-*t*	H	H	H	CF_3CO_2H, 20°C, 3 h	77	[31]
Ph	H	CO_2Bu-*t*	H	H	H	CF_3CO_2H, 20°C, 3 h	71	[31]

A series of salts of Δ^1-pyrrolines **23** were synthesized by the treatment of amino ketones **24**, containing Ac [28, 29] and CO_2Bu-*t* [30, 31] groups at the nitrogen atom, with strong acids (Table 3).



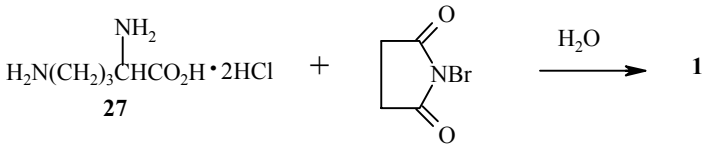
The reaction of (2*S*)-6,6-dimethyl-5-oxo-2-[N-(9-phenylfluorenyl)amino]heptanoic acid with trifluoroacetic acid in methylene chloride (boiling, 48 h) gives a 96% yield of the salt **23** (R = *t*-Bu, $R^1 = R^2 = H$, $R^4 = COOH$, $X = CF_3COO^-$).

Schiff bases containing a keto group at the γ position are also capable of entering into intramolecular cyclocondensation with the formation of Δ^1-pyrrolines. Thus, compounds **25** are converted by the action of dilute hydrochloric acid into derivatives of 3,4-2H-dihydropyrrole **26** even at normal temperatures [33, 34].



R, R^1, R^2, R^3, yield (%): Ph, Me,H, Ph, 100 (the keto group in the initial compound was in the form of $CO(CO_2H)_2$ O [33]; Me, Et, Ph, Ph, 67; Et, Et, Ph, Ph, 78 [34]

1.1.3.4. From Amino Acids or Their Esters. In this section two methods for the production of Δ^1-pyrrolines are examined, i.e., by the intramolecular destructive cyclocondensation of diamino acids [3, 35-40] or by two-component condensation of diethyl aminomalonate with α,β-unsaturated ketones [41]. In most of these papers [35-40] pyrroline **1** was synthesized by treating *DL*-ornithine hydrochloride (**27**) with N-bromosuccinimide.



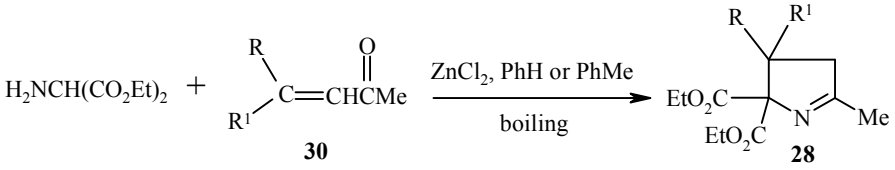
(Conditions), yield (%): (KI, H_2O, 20°C, 1 h; 100°C, 5 min), 80 [35]; (0°C, 1 h; 100°C, 5 min), 50-60 [36]; (n/i)* [37, 38]; (20°C, 1 h), n/i [40]

The authors of [40] reported on the synthesis of [2^{14}C]-3,4-2H-dihydropyrrole from *DL*-[2^{14}C]ornithine.

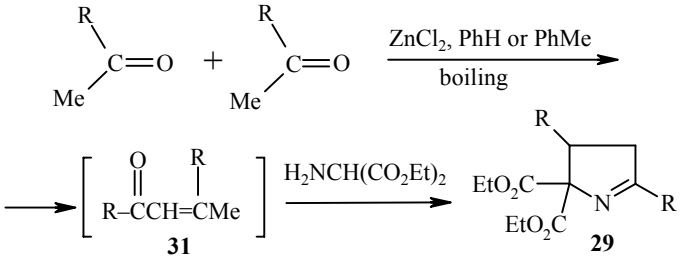
The pyrroline **1** was obtained by boiling the salt **27** with ninhydrin in water for 1 min (yield 22%) [35] and also by oxidative destructive cyclocondensation of *D*- or *L*-lysine in the presence of plant aminooxidase [3].

Two approaches were developed for the production of polysubstituted Δ^1-pyrrolines **28** and **29** from diethyl aminomalonate and unsaturated ketones. In the first the ready-made unsaturated ketones **30** were used, while in the second the unsaturated ketones **31** were produced at the first stage of the process from the respective saturated ketones and were brought into cyclocondensation with the aminomalonic ester *in situ*. It was found that the yields of the Δ^1-pyrrolines in the latter case were significantly lower [41].

* Here and subsequently, n/i = not indicated.

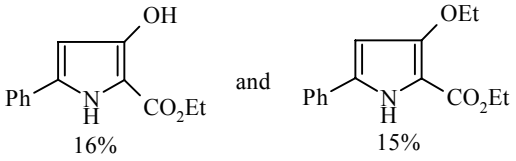


R, R[1], yield (%): Me, Me, 71; H, *i*-Pr, 77; H, 5-cyclohexenyl-2,2,6-trimethyl, 90; Me, CH_2=CH, 59



R, yield (%): Ph, 12; 3-pyridyl, 5

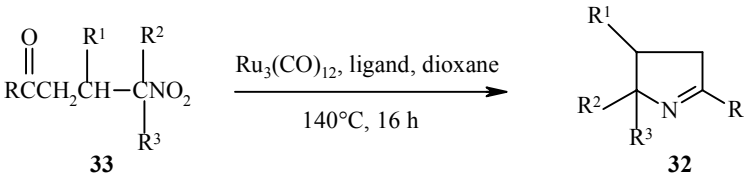
If R = Ph, the following compounds are also formed:



1.2. From Ketones Containing NO_2, CN, and N_3 Groups

In this section we examine data from papers on the synthesis of Δ^1-pyrrolines by the cyclization of bifunctional compounds containing a keto group and various nitrogen-containing groups other than amino groups.

Japanese authors [42] developed a method for the synthesis of derivatives of Δ^1-pyrroline **32**, involving cyclocondensation of the nitro ketones **33** in the presence of a ruthenium catalyst in an atmosphere of CO. 1,10-Phenanthroline (**34**), its derivatives, and certain other compounds were used as ligands (Table 4).



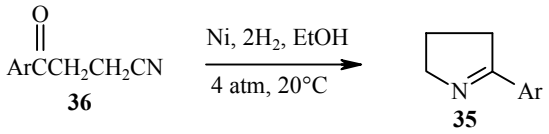
The authors of [42] consider that the zerovalent Ru-**34** complex is formed initially, after which deoxygenation of the nitro group occurs with the formation of a ruthenium-nitrene intermediate, which reacts with the carbonyl group, giving the derivative of 3,4-2H-dihydropyrrole **32** and a ruthenium-oxo complex. The ruthenium is reduced to the zerovalent state by the action of CO, thereby completing the catalytic cycle.

TABLE 4. Synthesis of Δ^1-Pyrrolines **32** by Catalytic Cyclocondensation of Nitro Ketones **33**

R	R^1	R^2	R^3	Ligand	Yield, %
Ph	H	Me	Me	**34**	91*
Ph	H	Me	Me*[2]	**34**	50
Ph	H	Me	Me*[2]	$PdCl_2(PPh_3)$ + $MoCl_2$ (instead of **34**)	23
Ph	H	Me	Me*[2]	$PdCl_2(PPh_3)$ + $SnCl_2$ (instead of **34**)	20
Ph	H	Me	Me*[2]	$PdCl_2(PPh_3)$ + $SnCl_2$ (instead of **34**)	46
Ph	H	Et	Et	**34**	81
Me	Ph	Me	Me	**34**	86
Me	H	Me	Ph	**34**	78
Ph	H	Me	Me	2,9-Dimethyl-4,7-diphenyl-**34**	21
Ph	H	Me	Me	2,9- Dimethyl -**34**	54
Ph	H	Me	Me	2,2[1]-Dipyridyl	62
Ph	H	Me	Me	Pyridine	9
Ph	H	Me	Me	N,N,N[1],N[1]-Tetramethyl-1,3-propanediamine	7
Ph	H	Me	Me	N,N,N[1],N[1]-Tetramethylethylenediamine	17
Ph	H	Me	Me	Triethylamine	4
Ph	H	Me	Me	1,2-Bis(dimethylphosphino)ethane	10
Ph	H	Me	Me	Triphenylphosphine	0

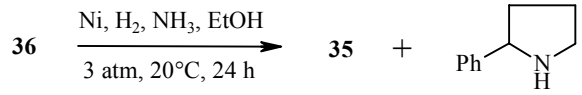
* Without **34** the yield was 2%; without $Ru_3(CO)_{12}$ the yield was 0%.
*[2] At 120°C.

Derivatives of pyrroline **35** containing aryl radicals at position 5 were synthesized with high yields as a result of hydrogenation of the respective β-keto nitriles **36** in the presence of Raney nickel catalyst until two moles of hydrogen had been absorbed [43].



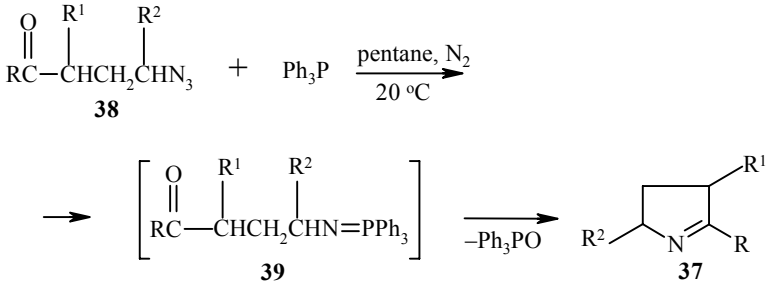
Ar, yield (%): Ph, 83; 4-$MeOC_6H_4$, 76; 3-$MeOC_6H_4$, 90; 1-naphthyl, 87

During hydrogenation under analogous conditions in the presence of ammonia without limiting the amount of hydrogen absorbed the keto nitrile **36** (Ar = Ph) is converted into a mixture of the pyrroline **35** (Ar = Ph) and 2-phenylpyrrolidine [44].



35, **36** Ar = Ph

The γ-azido ketones **38** are converted readily and, as a rule, smoothly into the pyrrolidines **37** by the action of triphenylphosphine. Clearly, at the first stage of the process the triphenylphosphine displaces a molecule of nitrogen from the azide group with the formation of the iminophosphines **39**, which then undergo an intramolecular Wittig aza-reaction *in situ* and are converted into the final compounds **37** [45, 46].

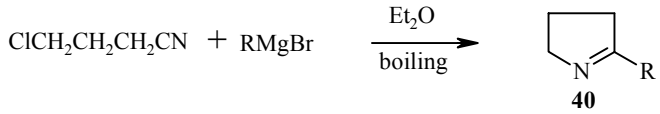


R, R^1, R^2, time (h), yield (%): Me, H, H, 10, 92; 4-BrC_6H_4, H, H, 18, 82; Me, Me, H, 12, 65; Me, Et, H, 12, 61 [45]; Ph, H, H, 14, 95; 4-MeC_6H_4, H, H, 14, 84; 4-ClC_6H_4, H, H, 14, 96 [46]

The keto azides **38** (R = Ph, 4-MeC_6H_4, $R^1 = R^2 = H$) are converted into the respective pyrrolines **37** (R = Ph, 4-MeC_6H_4, $R^1 = R^2 = H$) with yields of 79 and 81% by the action of tetrathiomolybdate when the reaction is carried out in acetonitrile at 25°C for 10 h under argon [47].

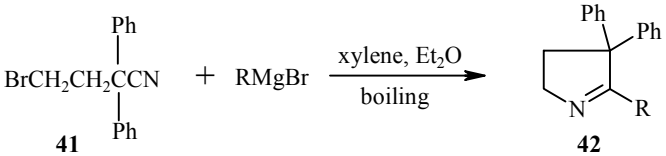
1.3. From Nitriles Containing Functional Groups Other than Keto Group

γ-Halo nitriles and Grignard reagents have most often been used for the production of Δ^1-pyrrolines. As a rule, the Δ^1-pyrrolines **40** are formed with low yields as a result of the reaction of 4-chlorobutyronitrile with Grignard reagents RMgBr [43, 48].



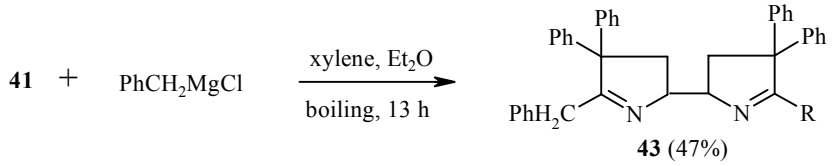
R, yield (%): 3-$MeOC_6H_4$, 46; 4-PhC_6H_4, 76; 9-phenanthryl, 28; 9-anthranyl, 14; 2-thienyl, 45; 1-naphthylmethyl, 22; 2-naphthylmethyl, 26; Me, 12; benzyl, 39 [43]; Et, n/i; C_5H_{11}, n/i; 1-naphthyl, n/i; Ph, n/i [48]

The two phenyl radicals at the α position to the nitrile group of compound **41** create specific steric hindrances for entry of the CN group into reaction with the Grignard reagents and subsequent cyclization to Δ^1-pyrrolines **42**. During the production of the pyrrolines **42**, therefore, the reaction mixture had to be boiled for a long time in a mixture of xylene and diethyl ether [49].



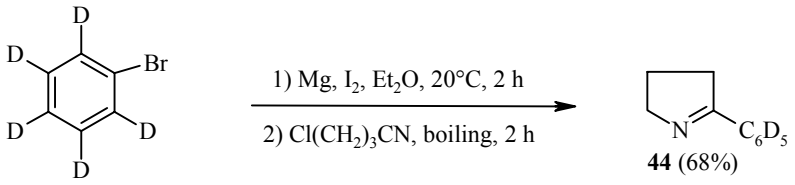
R, time (h), yield (%): Me, 10, 53; Ph, 8, 58; 2-MeC_6H_4, 17, 64; 2-ClC_6H_4, 16, 42; Et, 8, 65; Pr, 8, 22

The reaction of the nitrile **41** with benzylmagnesium chloride under analogous conditions takes place in a different direction, and the reaction product is compound **43** [49].



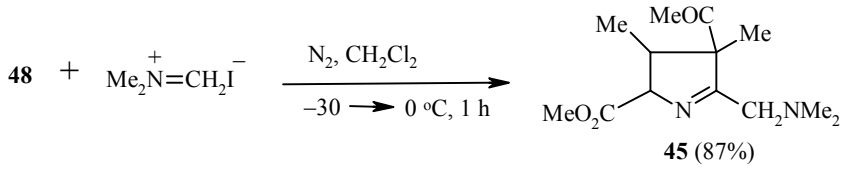
43 (47%)

As a result of treatment with magnesium in the presence of iodine and then with 4-chlorobutyronitrile pentadeuterobromobenzene is converted into 5-(pentadeuterophenyl)-2H-3,5-dihydropyrrole (**44**) [50].



44 (68%)

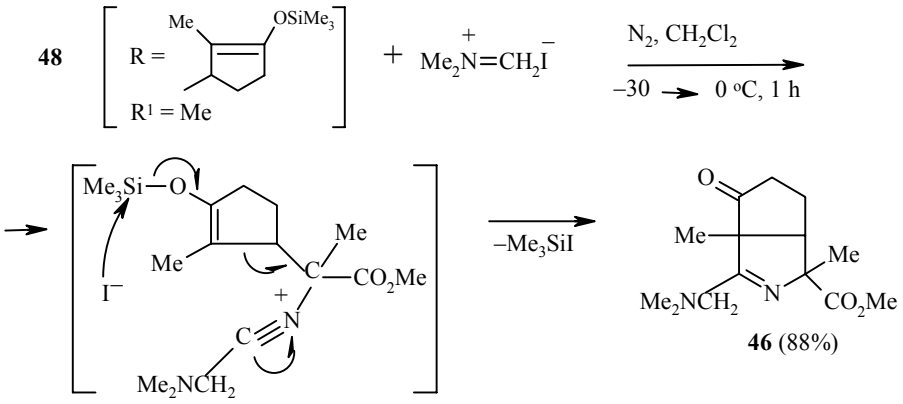
In [51] a method is described for the synthesis of various Δ^1-pyrroline derivatives of monocyclic (**45**), bicyclic (**46**), or spiro (**47**) compounds. All these compounds were obtained by the reaction of the compounds $RC(CN)(Me)CO_2R^1$ (**48**) with the immonium salt $Me_2N^+{=}CH_2I^-$ in an inert atmosphere. It was found that various derivatives of pyrroline **1** were formed, depending on the radical R in compounds **48**. Thus, if R was an acyclic radical Δ^1 pyrroline **45** was formed.



45 (87%)

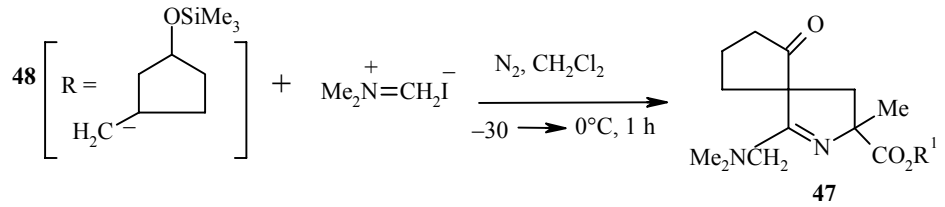
48 R = $Me_3SiOC(Me){=}C(Me)CH_2$, R^1 = Me

In the case where the radical R contained a cyclopentene fragment directly attached to the remainder of the molecule the reaction product was the bicyclic compound **46** [51].



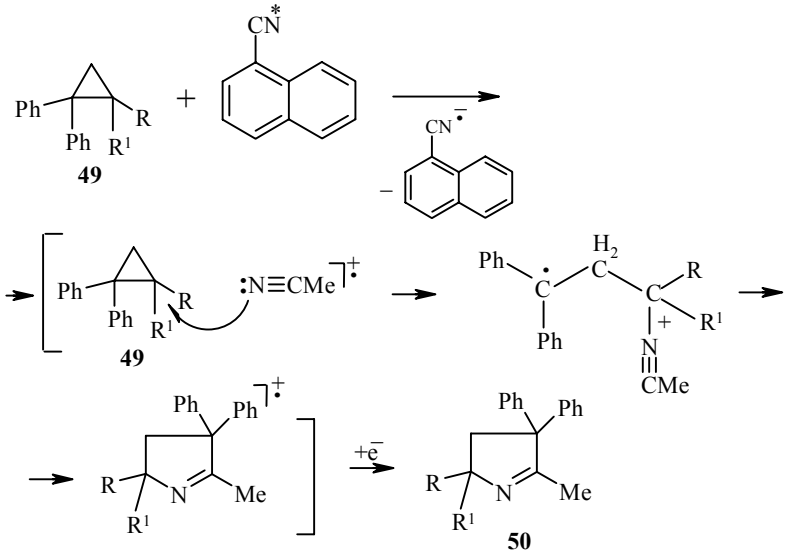
46 (88%)

Compounds with a spiro structure **47** are formed as a result of the treatment of compound **48**, containing a cyclopentylmethyl radical, with the salt $Me_2N^+{=}CH_2I^-$ [51].



R[1], yield (%): Me, 82; Et, 94

The authors of [52] developed an original method for the synthesis of Δ^1-pyrrolines. Derivatives of 3,4-2H-dihydropyrrole (**50**) were obtained as a result of the exposure of a mixture of the cyclopropane derivative **49** and acetonitrile to light with λ = 300 nm in the presence of 1-cyanonaphthalene. The following mechanism was proposed for this process:



R, R[1], time (h), yield (%): H, *t*-Bu, 40, 7; Me, Me, 83, 94

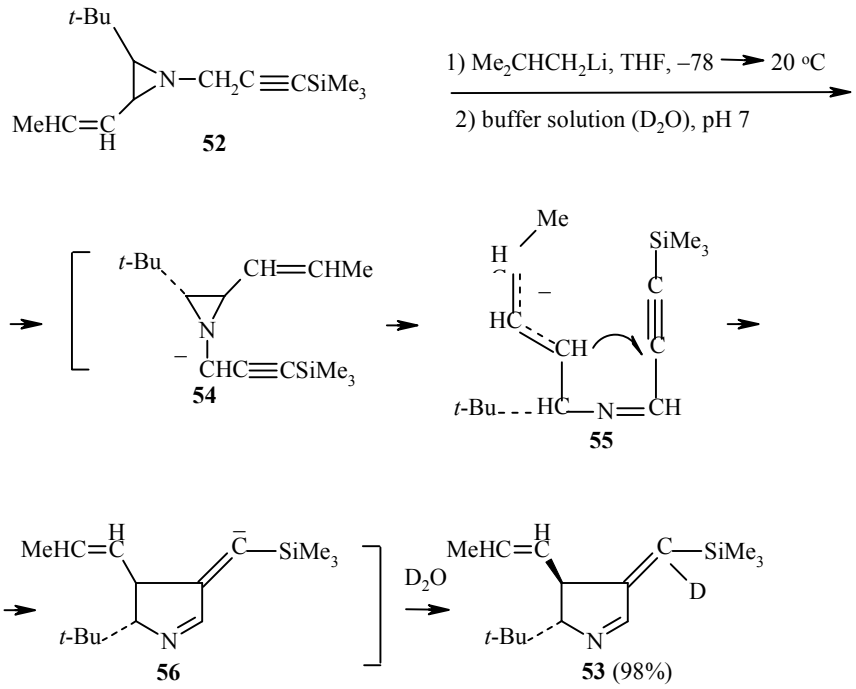
During irradiation of a mixture of compound **49** (R = H, R[1] = *t*-Bu) with acetonitrile 1-phenyl-3,4,4-trimethyl-1,2,3,4-tetrahydronaphthalene is also formed with a yield of 72% [52].

1.4. From Heterocyclic Compounds

1.4.1. From Three-membered Compounds

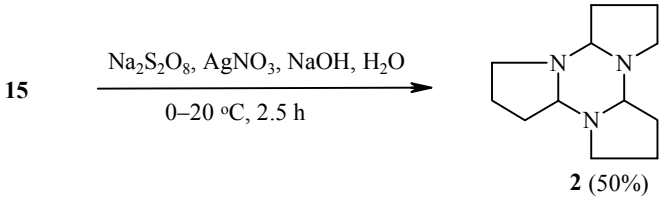
Of three-membered heterocyclic compounds only derivatives of aziridine have been used as starting compounds for the production of Δ^1-pyrrolines. Pyrroline **1** itself was synthesized by the reaction of N-(diethoxyphosphoryl)aziridine (**51**) with the dianion formed in the reaction of acetoacetic ester with 1,3-diketones in an acidic medium [53].

The transformation of compound **52** into Δ^1-pyrroline by the action of *sec*-butyllithium was explained by the authors of [54] by a reaction occurring through a number of consecutive stages. In their opinion the aziridine derivative **52** reacts with Me_2CHCH_2Li, being converted into the propargyl anion **54**, in which the aziridine ring is opened and the allyl anion **55** appears. Intramolecular cycloaddition then occurs in the latter with the formation of the anion **56**, treatment of which with D_2O gives the pyrroline derivative **53** [54].



1.4.2. From Five-membered Compounds

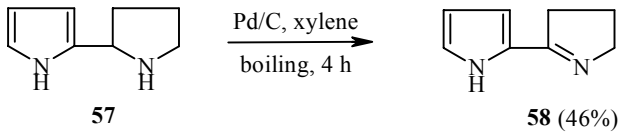
During the production of Δ^1-pyrrolines from five-membered heterocyclic compounds the pyrrolidine **15** or its derivatives with substituents at the carbon or nitrogen atoms are as a rule used as starting compounds. The amine **15** is converted by the action of sodium peroxydisulfate in the presence of silver nitrate in sodium hydroxide solution into 1,6,11-triazatetracyclo[10.3.0.0^{2,6}0^{7,11}]pentadecane – the trimer **2** [55, 56].



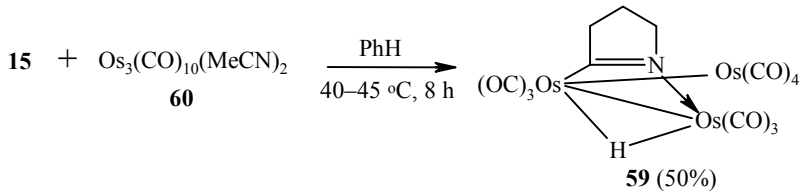
A mixture of pyrroline **1** and the trimer **2** was obtained as a result of the reaction of the amine **15** with $(PhIO)_n$ in deuterodichloromethane at 20°C for 24 h [57].

In [57] it was mentioned that the ratio of compounds **1** and **2** changes significantly when the reaction is carried out in various solvents: In methanol the equilibrium is displaced toward the formation of the monomer, and pyrroline **1** is mainly formed; in carbon tetrachloride the reaction product is mainly the trimer **2**.

On boiling in xylene in an inert atmosphere in the presence of Pd/C the pyrrolidine derivative **57** undergoes partial dehydrogenation, being converted into 2-(Δ^1-2-pyrrolinyl)pyrrole **58** [58].



The cluster **59**, formed under mild conditions from the amine **15** by the action of osmium bis(acetonitrile)decacarbonyl (**60**), contains a pyrroline **1** ring [59].

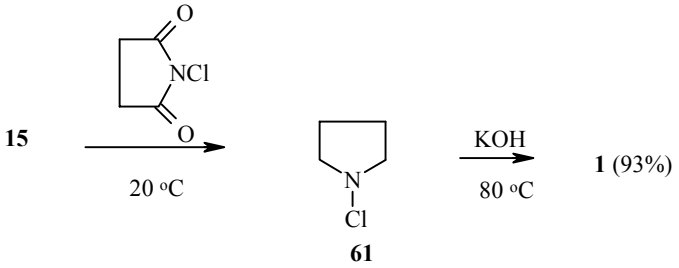


59 (50%)

A widely used method for the synthesis of pyrroline **1** and its derivatives is dehydrochlorination of the N-chloro derivatives formed by the action of N-chlorosuccinimide or *t*-BuOCl on the respective compounds of the pyrrolidine series.

It should be noted that pyrroline **1**, the trimer **2**, or their mixture is formed when the dehydrochlorination is carried out under various conditions.

3,4-2H-Dihydropyrrole was obtained in the form of the monomer **1** in a flow-type system under a vacuum of 10^{-2} mm Hg with successive passage of the amine **15** initially over N-chlorosuccinimide at 20°C and then over solid potassium hydroxide at 80°C in a stream of nitrogen [60].

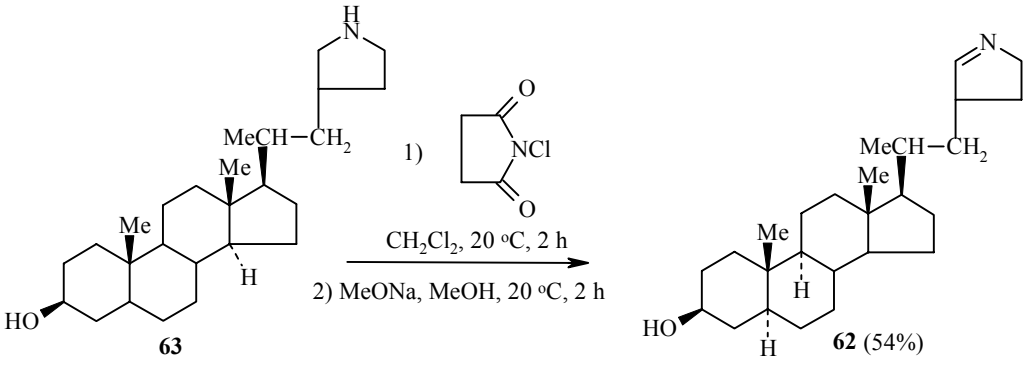


61

On the other hand the trimer **2** was obtained with a yield of 51% after dehydrochlorination of the chlorine derivative **61** with potassium hydroxide in boiling methanol for 30 min followed by distillation of the reaction products [61].

In [62] the chlorine derivative **61** was treated with sodium methoxide in methanol, and the ratio of compounds **1** and **2** was determined immediately after the reaction, after standing, and after distillation.

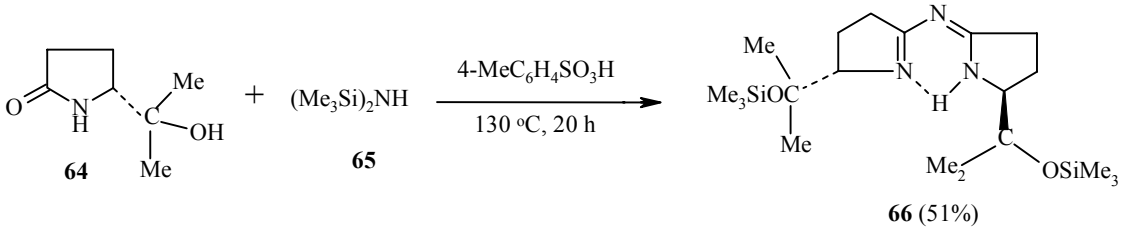
The new steroidal alkaloid **62** was synthesized from nor-23,26-imino-5α-cholestan-3β-ol (**63**) by the action of N-chlorosuccinimide and treatment of the chlorination product with sodium methoxide in methanol [63].



63 **62** (54%)

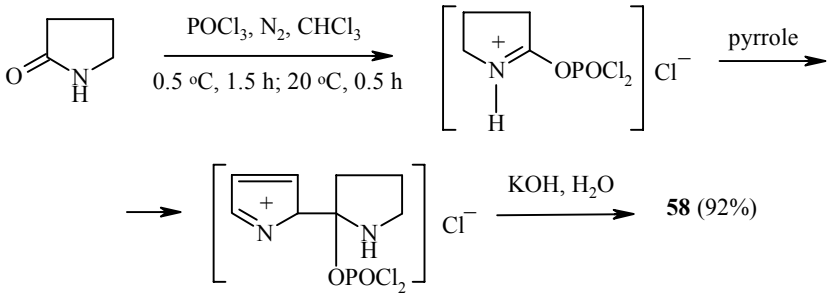
In a series of papers 2-pyrrolidone and its derivatives both with a free NH group and substituted at the nitrogen atom were used as starting compounds for the synthesis of Δ^1-pyrrolines.

5-(1-Hydroxy-1-methylethyl)-2-pyrrolidone (**64**) is converted into compound **66** when heated with hexamethyldisilazane **65** in the presence of *p*-toluenesulfonic acid in a sealed tube [64].

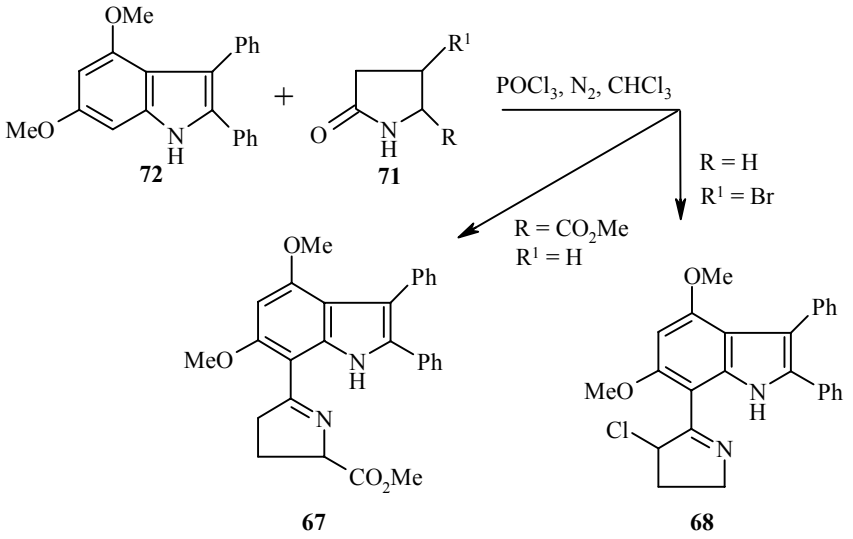


66 (51%)

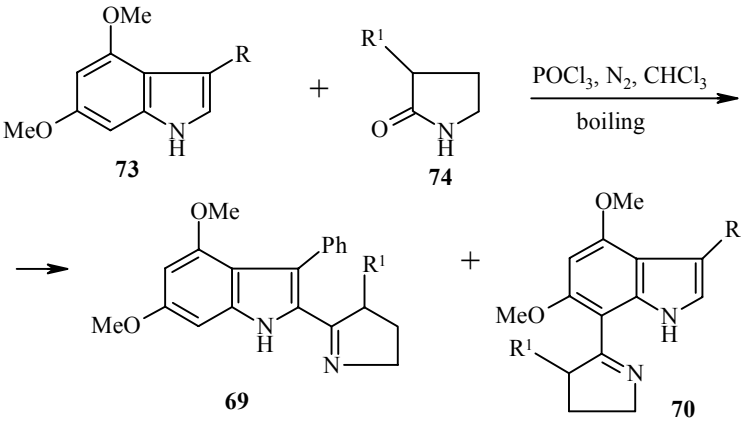
5-Substituted Δ^1-pyrrolines **58**, **67**-**69**, or **70** were synthesized by the reaction of compounds of the 2-pyrrolidone series with pyrrole or with indole derivatives [58-65]. Thus, 2-pyrrolidone reacts with pyrrole in the presence of phosphorus oxychloride at room temperature with the formation of compound **58** [58].



Interesting results were obtained during investigation of the reactions of pyrrolidone derivatives with compounds of the indole series. During the reaction of pyrrolidone derivatives **71** with 4,6-dimethoxy-2,3-diphenylindole **72** in the presence of phosphorus oxychloride it was found that in compounds **68** and **67** the radicals of the formed Δ^1-pyrroline derivatives were at position 7 of the indole ring, while the bromine atom in the initial **71** (R = H, R^1 = Br) was substituted by a chlorine atom (compound **68**) [65].

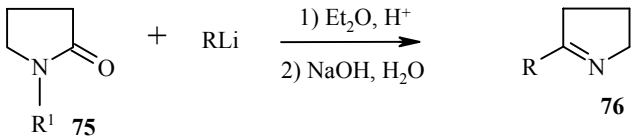


If, however, there is no substituent at position 2 of the indole derivative (compound **73**), the reaction takes place in a more complicated manner. As a result of the reactions with 2-pyrrolidone derivatives **74** two condensation products **69** and **70**, containing the Δ^1-pyrroline fragment at position 2 or 7 of the indole ring, are formed [65].

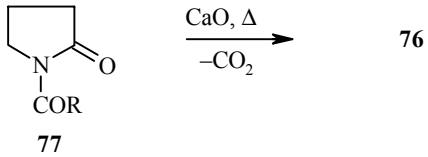


R, R^1, time (h), yield (%) of **69** and **70**: Me, H, 3, 12 and 36; 4-BrC_6H_4, H, 24, 5 and 30; 4-ClC_6H_4, H, 24, 5 and 30; 4-FC_6H_4, H, 24, 3 and 30; 4-ClC_6H_4, Br (in the reaction products R^1 = Cl), 2, traces, and 65; 4-BrC_6H_4, Br (in the reaction products R^1 = Cl); 2 (the reaction was carried out at 60°C), 0 and 65

In reaction with organolithium compounds RLi followed by treatment with strong acids and aqueous sodium hydroxide derivatives of 2-pyrrolidone **75** containing $CH{=}CH_2$ [66-68] or $SiMe_3$ [69] groups at the nitrogen atom are converted into Δ^1-pyrrolines **76** containing the radicals R from the organolithium compounds at position 5 (Table 5).



A more simple and effective method for the synthesis of Δ^1-pyrrolines **76**, developed by the authors in [70-72], is pyrolysis (heating over a naked flame) of the N-acyl derivatives of 2-pyrrolidone **77** in the presence of calcium oxide. This makes it possible to obtain the Δ^1-pyrrolines with higher yields than the method described above.



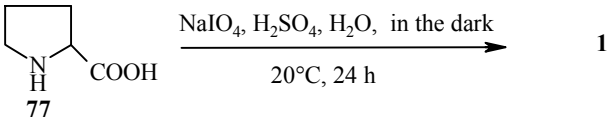
R, yield (%):3-pyridyl, 65-67 [70, 71]; Ph, n/i [71, 72], *t*-Bu, 40 [72]

Proline, its esters, and certain of its derivatives are good starting compounds for the production of Δ^1-pyrrolines.

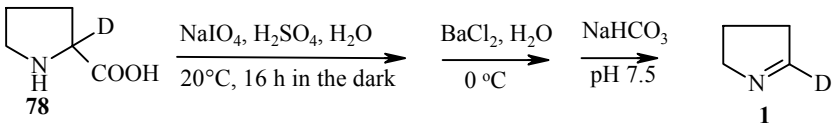
TABLE 5. Synthesis of Δ^1-Pyrrolines **76** from Derivatives of Pyrrolidone **75** and RLi

R	R^1	Reaction conditions	Yield, %	Reference
Pyridyl-3	$CH=CH_2$	1) Et_2O, hexane, -78°C, 2 h 2) conc. HCl, 0°C	25	[66]
		1) Et_2O, argon, -78°C, 5 h; 20°C, 18 h 2) $HClO_4$, EtOH, 20°C, 3 h	17	[67]
		1) Et_2O, -70°C, 2.5 h; -30°C, 0.5 h 2) 1 mol/l HCl (H_2O)	40	[69]
Pyridyl-2	$CH=CH_2$	1) Et_2O, hexane, -78°C, 2 h 2) conc. HCl, 0°C	28	[66]
3-Bromo-5-pyridyl-5	$CH=CH_2$	1) Et_2O, argon, -78°C, 5 h; 20°C, 18 h 2) $HClO_4$, EtOH, 20°C, 3 h	43	[67]
Me	$CH=CH_2$	1) Et_2O, argon, -78°C, 5 h; 20°C, 18 h 2) $HClO_4$, EtOH, 20°C, 3 h	15	[67]
		1) Et_2O, -20°C, 2 min 2) 1 mol/l HCl (H_2O)	55	[68]
Bu	$CH=CH_2$	1) Et_2O, -60°C → 0°C 2) 1 mol/l HCl (H_2O)	71	[68]
	$CH=CH_2$	1) Et_2O, argon, -78°C, 5 h; 20°C, 18 h 2) $HClO_4$, EtOH, 20°C, 3 h	37	[67]
i-Pr	$CH=CH_2$	1) Et_2O, -40°C, 50 min 2) 1 mol/l HCl (H_2O)	40	[68]
Ph	$CH=CH_2$	1) Et_2O, -15°C, 1 h 2) 1 mol/l HCl (H_2O)	79	[68]
$PhCH=CH_2$	$CH=CH_2$	1) Et_2O, -20°C, 10 min 2) 1 mol/l HCl (H_2O)	19	[68]
Ph	$SiMe_3$	1) THF	20	[69]
2-$MeOC_6H_4$	$SiMe_3$	1) THF	43	[69]

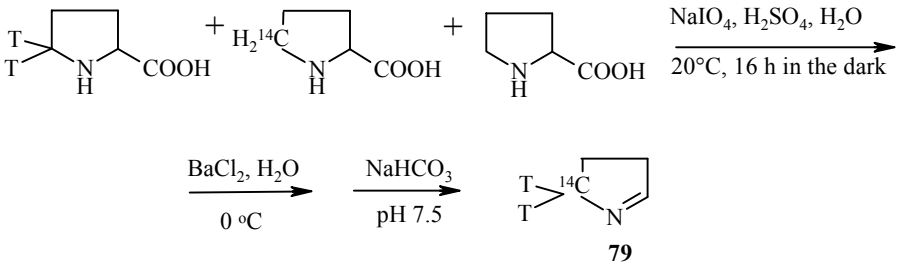
L-Proline was first converted into pyrroline **1** by the action of an aqueous solution of sodium metaperiodate and sulfuric acid in the dark at 20°C [73].



In more recent work [74] this method was improved and was used for the transformation of proline containing hydrogen and carbon isotopes. Thus, deuterated *DL*-proline **78** was converted as a result of a series of consecutive reactions into pyrroline **1** containing the deuterium atom at position 5 [74].



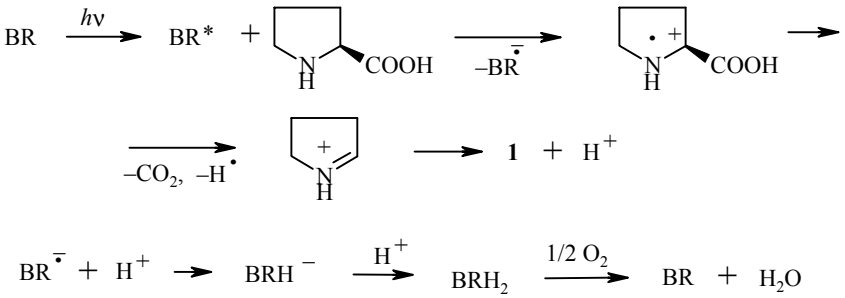
The corresponding Δ^1-pyrroline **79** was synthesized under analogous conditions from a mixture of *L*-proline containing two tritium atoms, *DL*-proline containing the C^{14} isotope, and proline [74].



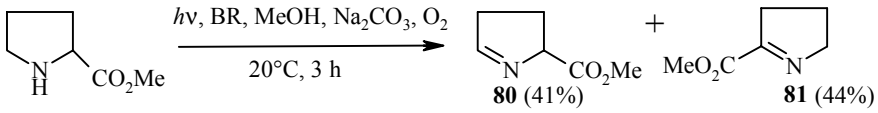
79

When treated with an aqueous solution of sodium hypochlorite at normal temperature for 1 h, proline hydrochloride is converted into pyrroline **1** (isolated in the form of the aurate with a yield of 73%) [75].

The pyrroline **1** is formed (yield 82%) during the photooxidative decarboxylation of proline in aqueous sodium hydroxide at 20°C for 5 h with exposure to an ICV 100-200 GS halogen lamp in the presence of a sensitizer [Bengal rose (BR)] [76].



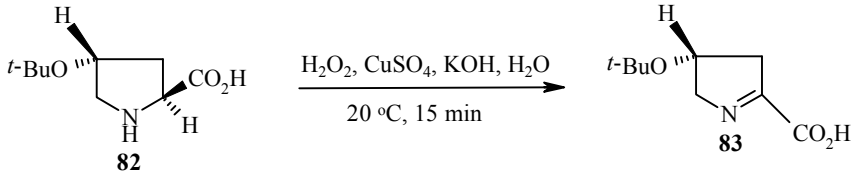
Under somewhat different conditions proline methyl ester is converted into a mixture of 2-methoxycarbonyl-3,4-2H-dihydropyrrole (**80**) and 5-methoxycarbonyl-2H-3,4-dihydropyrrole (**81**) [76].



80 (41%) **81** (44%)

If the hydrogen atom of the NH group in proline is substituted by COMe or COOBu-*t*, photooxidative decarboxylation does not occur [76].

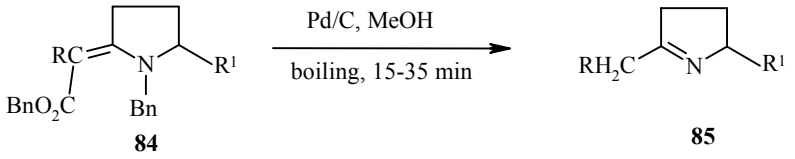
It is interesting that decarboxylation is not observed during treatment of the carboxylic acid **82** with hydrogen peroxide in the presence of copper sulfate in an alkaline medium. The reaction product is the pyrroline derivative **83** [77].



82 **83**

Several approaches have been developed for the synthesis of Δ^1-pyrrolines from derivatives of pyrrolidine containing substituents at the cyclic nitrogen atom.

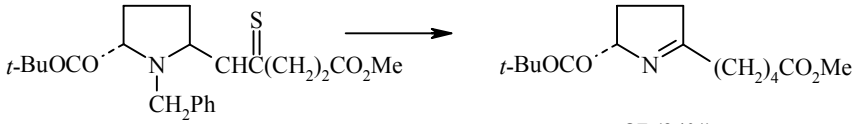
When boiled in methanol in the presence of Pd/C and cyclohexene, 2,5-disubstituted pyrrolidines **84** containing a benzyl group at the nitrogen atom are converted with high yields into the corresponding Δ^1-pyrrolines **85** [78, 79].



84 **85**

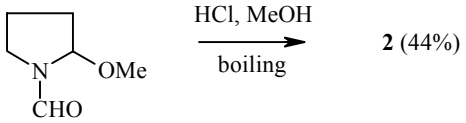
R, R^1, yield (%): C_6H_{13},CO_2Bu-*t*, 85; C_3H_7, C_7H_{15}, 70; C_3H_7, CO_2Bu-*t*, 87 [78];
$(CH_2)_3C(Me)OCH_2CH_2O$, CO_2Bu-*t*, 76 [79]

In the presence of a nickel catalyst the N-benzyl derivative **86** undergoes debenzylation and desulfurization, giving the Δ^1-pyrroline **87** [80].

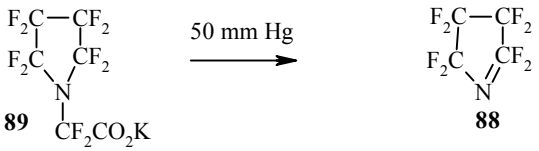


86 **87** (34%)

The trimer **2** is formed as a result of the action of heat on 1-formyl-2-methoxypyrrolidine with hydrogen chloride in methanol [81].

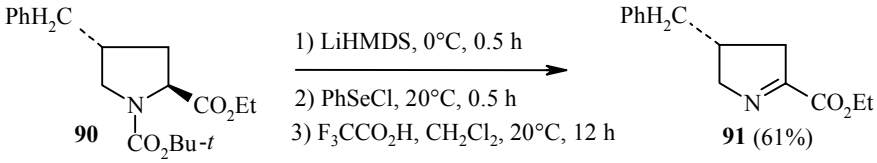


A method for the synthesis of perfluoro-Δ^1-pyrroline (**88**) by the pyrolysis of compound **89** under vacuum was patented [82].



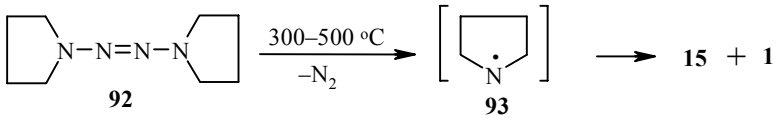
89 **88**

After lithiation compound **90** was treated with PhSeCl and then with trifluoroacetic acid. As a result the pyrroline derivative **91** was obtained [83].



90 **91** (61%)

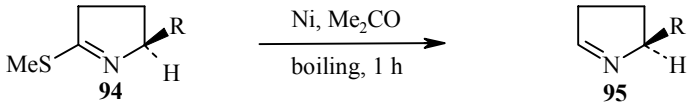
At high temperature the tetrazene **92** eliminates a molecule of nitrogen with the formation of the radical **93**. The latter disproportionates, giving the pyrrolidine **15** and the pyrroline **1** [84].



92 **93**

The action of zinc dust on pyrrole in hydrochloric acid (15-25°C, 1.5-2 h) gave a mixture of reduction products, from which the trimer **2** was isolated with a yield of 12% [85, 86].

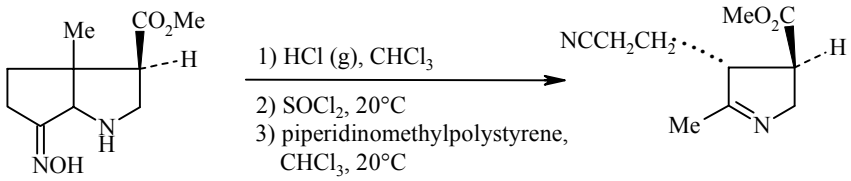
The lactim thioethers **94** are converted into Δ^1-pyrrolines **95** when heated with Raney nickel catalyst in acetone [87].



94 **95**

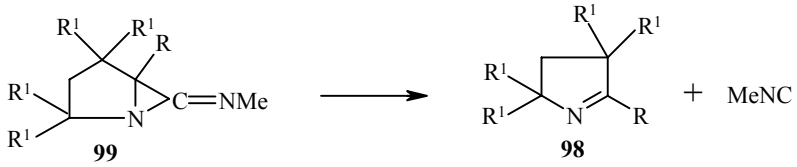
R, yield (%): CO_2Et, 40; CH_2OCOBu-*t*, 32

The production of Δ^1-pyrrolines from bicyclic heterocyclic compounds was reported in two papers [88, 89]. Thus, the derivative of 1-azabicyclo[3.3.3]octane (**96**) was converted in a three-stage synthesis into the Δ^1-pyrroline **97** [88].



96 **97**

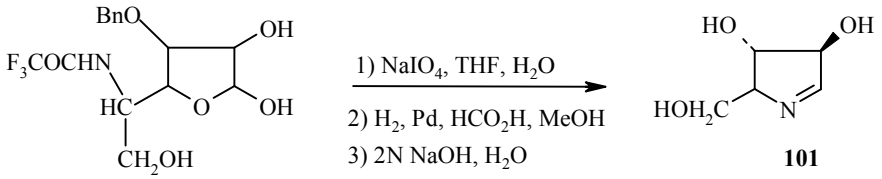
Whereas the transformation to the Δ^1-pyrroline **97** in the case of the bicyclic compound **96** takes place with retention of all the carbon atoms, the synthesis of Δ^1-pyrrolines **98** from derivatives of 2-azabicyclo[3.1.0]hexane is accompanied by elimination of the –C=NMe group with the formation of compounds **98** and methyl isocyanide [89].



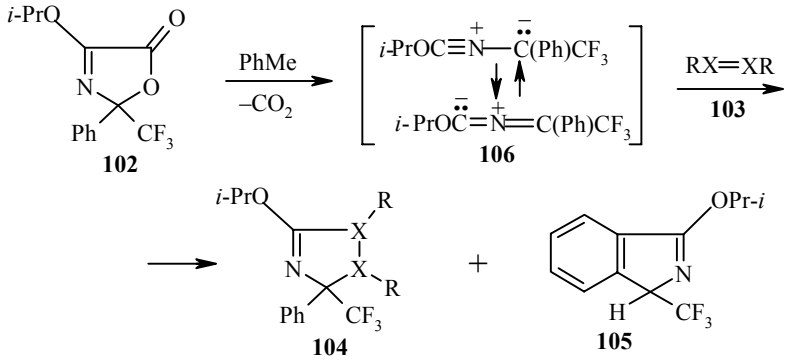
99 **98**

R, R^1, temperature (°C), time (h), yield (%): H, H, 90-95, 7, 67;
Me, H, 80-95, 7, 93; H, Me, 80-95, 27, 86

Δ^1-Pyrrolines can be obtained by the recyclization of other five-membered heterocyclic compounds. For example, the tetrahydrofuran derivative **100** is recyclized as a result of a series of consecutive reactions, giving 3,4-dihydroxy-2-hydroxymethyl-3,4-2H-dihydropyrrole (**101**) [90].

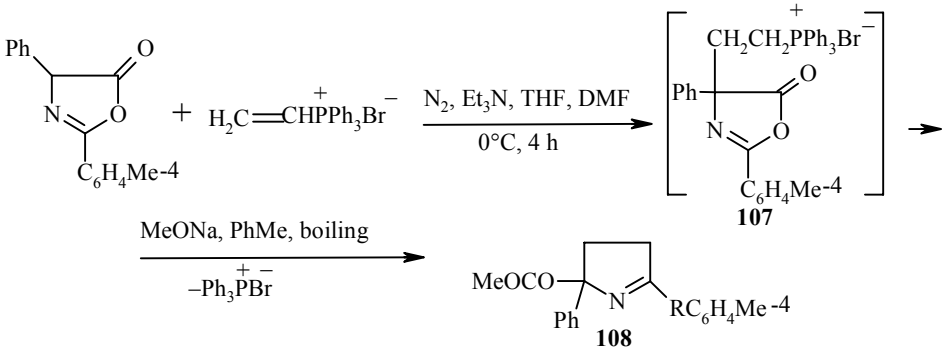


When the oxazolone derivative **102** was heated with unsaturated compounds in toluene mixtures of Δ^1-pyrrolines **104** and 1-isopropoxy-3-trifluoromethylisoindole (**105**) were obtained [91]. It is clear that compound **102** undergoes ring opening under the reaction conditions with the elimination of a molecule of CO_2, giving the nitrile ylide **106**, which enters into 1,3-dipolar cycloaddition with the dipolarophiles **103** *in situ* to form the adducts **104** and **105**.



R, X, °C, time (h), yield (%): CO_2Et, N, 158, l, 18.5 and 26.2; CO_2Me, CH, 155, 2.5, 23 and 58.6

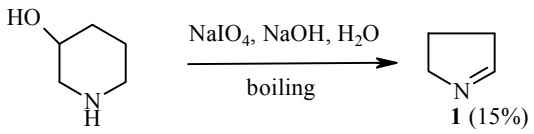
When heated with sodium methoxide in toluene compound **107**, formed as a result of the reaction of 2-(*p*-tolyl)-4-phenyl-5-oxazolone with the salt CH_2=CHP$Ph_3^+Br^-$, undergoes recyclization with the ejection of $Ph_3P^+Br^-$ and is converted into the Δ^1-pyrroline **108** [92].



1.4.3. From Six-membered Compounds

The number of publications in which the production of Δ^1-pyrrolines by recyclization of six-membered heterocyclic compounds is described is limited.

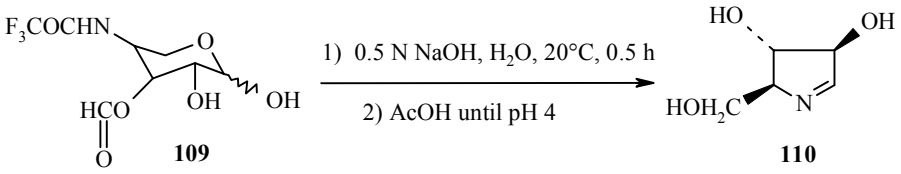
3,4-2H-Dihydropyrrole **1** is formed as a result of the action of heat on 3-hydroxypiperidine with sodium metaperiodate in an aqueous solution of sodium hydroxide [93, 94].



1 (15%)

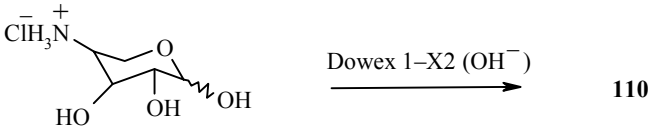
It was suggested [93] that the 3-hydroxypiperidine is converted under these conditions into 4-aminobutanal **6**, which changes into pyrroline **1** as a result of intramolecular cyclocondensation. It has been mentioned that 1-hydroxy-2-piperidone gives pyrroline **1** when heated (175-195°C) with polyphosphoric acid [95].

Of great interest are the numerous papers on the synthesis of Δ^1-pyrrolines by the recyclization of derivatives of sugars containing an amino group (both unsubstituted and acylated). The derivative of deoxyarabinose **109** is converted by the action dilute aqueous sodium hydroxide solution at room temperature into the Δ^1-pyrroline **110** with an excellent yield [96].



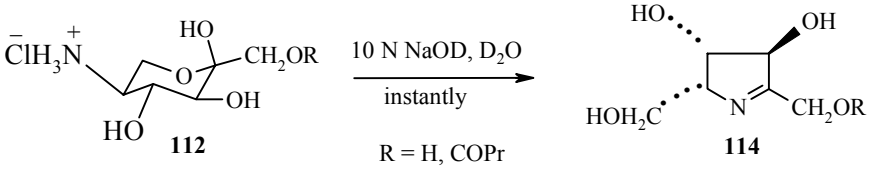
109 **110**

The same pyrroline is formed with a 90% yield as a result of ion-exchange chromatography of compound **111** [97].

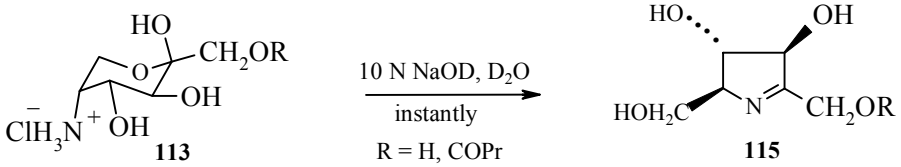


111 **110**

At room temperature in the presence of NaOD in D_2O the stereoisomers – the deoxyxylose derivative **112** or the deoxyarabinose derivative **113** – undergo very rapid recyclization to the Δ^1-pyrrolines **114** or **115** without change of configuration [98].



112 **114**

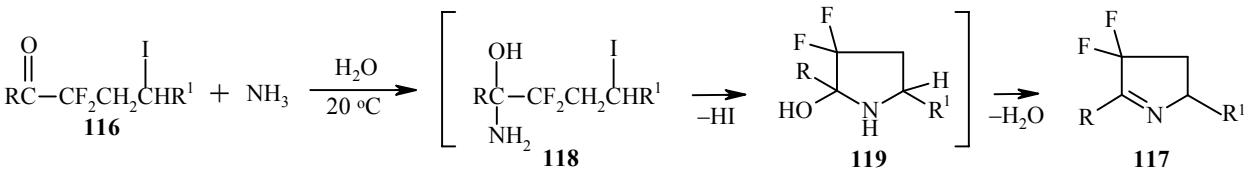


113 **115**

1.5. Other Methods

Individual papers describing single cases of the production of derivatives of pyrroline **1** that do not fit into the classification of methods for the synthesis of Δ^1-pyrrolines adopted above will now be discussed.

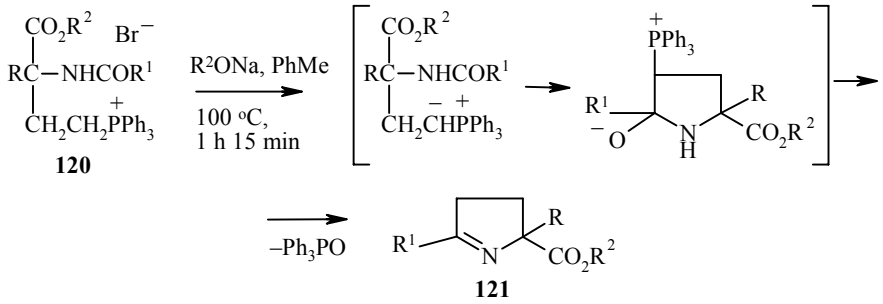
Treatment of the 4-iodo ketones **116** with an aqueous solution of ammonia gives the Δ^1-pyrrolines **117** [99, 100]. It is clear that the *gem*-amino alcohols **118** are formed at the first stage of the process. They enter into an intramolecular S_N2 reaction and are converted into hydroxypyrrolidines **119**. The latter eliminate a molecule of water *in situ*, giving the final products **117**.



R, R^1, time (h), yield (%): C_6H_{13}, $CONMe_2$, 12, 100 [99]; C_6H_{13}, $SiMe_3$, 24, 91; Bu, $SiMe_3$, 24, 93; Ph, $SiMe_3$, 24, 37 [100]

In the reaction of the ketone **116** (R = Ph, R^1 = $SiMe_3$) with ammonia 3-fluoro-2-phenylpyrrole is formed with a yield of 29% in addition to the pyrroline **117** (R = Ph, R^1 = $SiMe_3$) [100].

When heated with sodium alcoholates in toluene in an inert atmosphere the phosphine salts **120** enter into an intramolecular Wittig reaction and are converted into Δ^1-pyrrolines **121** according to the scheme [92]:



R, R^1, R^2, yield (%): Ph, Ph, Me, 72; Ph, 4-MeC_6H_4, Me, 92; Me, Ph, Et, 65

A series of 3,4,5-trisubstituted Δ^1-pyrrolines **122** were synthesized from compounds **123** and the alkenes **124** in the presence of CsF and triflates CF_3CO_2R. The salts **125** are clearly formed initially and are then converted into the dipoles **126**, which enter into cycloaddition with the alkenes **124** and form the adducts **122** (Table 6) [101].

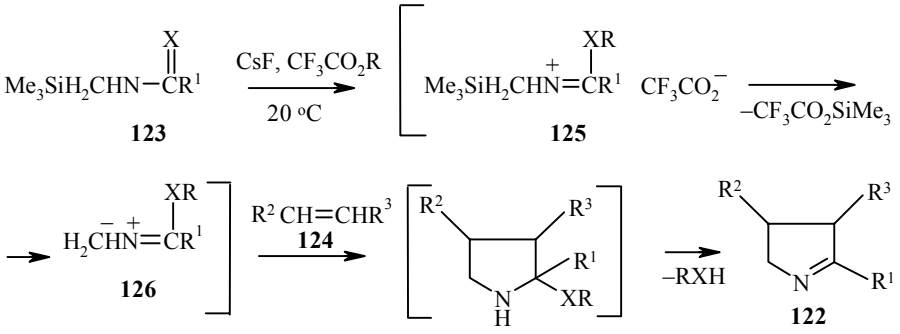


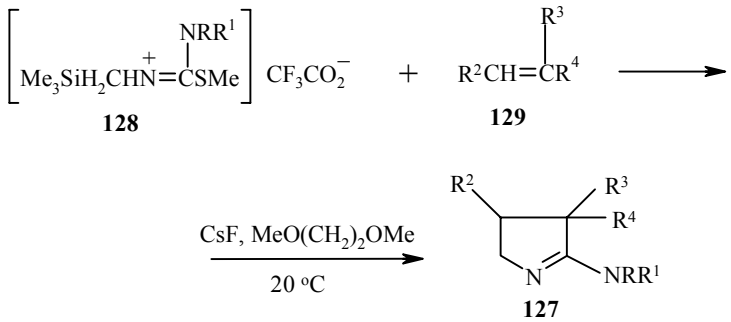
TABLE 6. The Synthesis of Δ^1-Pyrrolines **122** from Compounds **123** and Alkenes **124**

X	R	R^1	R^2	R^3	Reaction conditions	Yield, %
NH	Me_3Si	Ph	*trans*, CO_2Me	CO_2Me	MeCN, 15 h	67
NH	Me	Me	*trans*, CO_2Me	CO_2Me	MeCN, 12 h	73
NH	Me	Et	*trans*, CO_2Me	CO_2Me	MeCN, 12 h	63
NH	Me	Bu	*trans*, CO_2Me	CO_2Me	MeCN, 13 h	53
S	Me	Bu	*trans*, CO_2Me	CO_2Me	$MeO(CH_2)_2OMe$, 13 h	68
S	Me	Bu	*cis*, CO_2Me	CO_2Me	$MeO(CH_2)_2OMe$, 13 h	21
H	Me_3Si	Ph	*trans*, CN	CN	MeCN, 14 h	69
S	Me	Ph	*trans*, CN	CN	$MeO(CH_2)_2OMe$, 14 h	95
NH	Me	Me	*trans*, CN	CN	MeCN, 13 h	51
NH	Me	Et	*trans*, CN	CN	MeCN, 12 h	51
S	Me	Et	*trans*, CN	CN	$MeO(CH_2)_2OMe$, 13 h	70
NH	Me	Bu	*trans*, CN	CN	MeCN, 13 h	58
S	Me	Ph	H	CO_2Me	$MeO(CH_2)_2OMe$, 14 h	48
S	Me	Ph	H	COMe	$MeO(CH_2)_2OMe$, 14 h	63

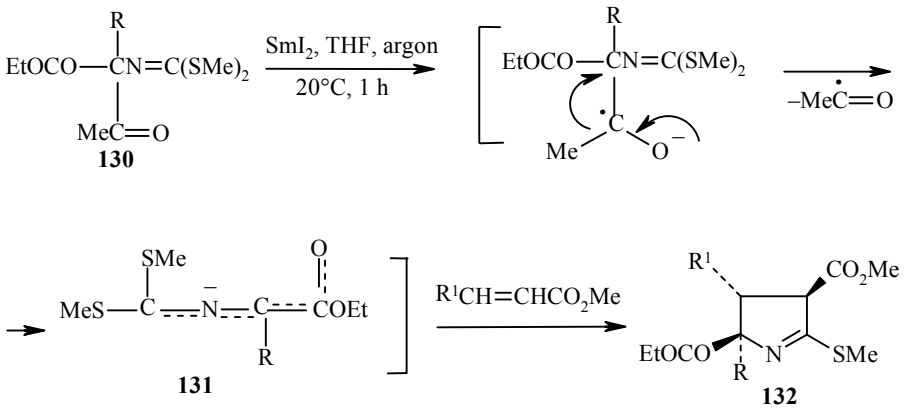
TABLE 7. The Synthesis of Δ^1-Pyrrolines **127** from the Salts **128** and Alkenes **129**

R	R^1	R^2	R^3	R^4	Reaction conditions	Yield, %
H	Ph	*trans*, CO_2Me	CO_2Me	H	20°C, 20 h	71
$(CH_2)_5$		*trans*, CO_2Me	CO_2Me	H	20°C, 20 h	38
$(CH_2)_5$		*trans*, CO_2Me	CO_2Me	H	Boiling, 10 h	52
H	Ph	*cis*, CO_2Me	CO_2Me	H	20°C, 20 h	52
$(CH_2)_5$		*cis*, CO_2Me	CO_2Me	H	Boiling, 10 h	35
$(CH_2)_2O(CH_2)_2$		*cis*, CO_2Me	CO_2Me	H	Boiling, 10 h	30
H	Ph	H	Cl	CN	Boiling, 5 h	31
$(CH_2)_2O(CH_2)_2$		H	Cl	CN	Boiling, 10 h	18

The respective Δ^1-pyrrolines **127** were synthesized by the reaction of the salts **128** with the alkenes **129** in the presence of CsF at room temperature (Table 7) [102].



In the presence of powdered SmI_2 in an inert atmosphere compound **130** is converted into the ylides **131**, which enter into reaction with the esters $R^1CH{=}CHCO_2Me$ *in situ*, giving high yields of the Δ^1-pyrrolines **132** [103].



R, R^1, yield (%): Me, Me, 90; Me, *t*-Bu, 85; Bn, Me, 80; Bn, *t*-Bu, 80

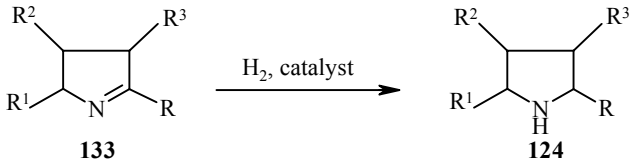
CHEMICAL TRANSFORMATIONS OF Δ^1-PYRROLINES

2.1. Addition to the C=N Bond

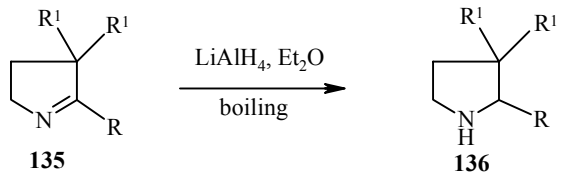
2.1.1. Hydrogenation and Reduction

The transformation of Δ^1-pyrrolines into the corresponding pyrrolidine derivatives has been described in many papers. The process takes place both by catalytic hydrogenation and by the action of chemical reducing agents.

Δ^1-Pyrrolines **133** were converted into pyrrolidine derivatives **134** by the action of molecular hydrogen in the presence of various catalysts (Table 8).



High yields of the reduction products **136** were obtained during the reduction of pyrroline derivatives **135** with lithium aluminum hydride in ether [43, 49].



R, R^1, time (h), yield (%): $PhCH_2$, H, n/i, 54; 9-phenanthryl, H, n/i, 94; 2-thienyl, H, n/i, 88 [43]; Me, Ph, 48, 83.5; Et, Ph, 25, 75.4; Ph, Ph, 26, 86.6; 2-ClC_6H_4, Ph, 15, 91.5 [49]

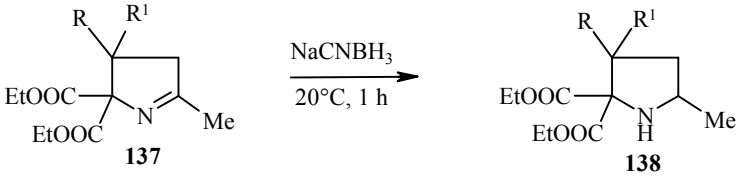
TABLE 8. Catalytic Hydrogenation of Δ^1-Pyrrolines

R	R^1	R^2	R^3	Hydrogenation condition	Yield, %	Reference
H	CO_2H	H	H	PtO_2, 25°C, AcOH, H_2O	73	[26]
Me	CO_2H	H	H	PtO_2, 20°C, 3 atm, 0.5 h	100	[28]
Me	CO_2H	H	Me	PtO_2, 20°C, 3 atm, 0.5 h	100	[28]
Ph	CO_2H	H	H	PtO_2, 20°C, 3 atm, 0.5 h	62	[28]
2-HOC_6H_4	CO_2H	H	H	PtO_2, 20°C	n/i	[29]
Me	CO_2Me	H	H	Pd/C, MeOH	n/i	[34]
Et	CO_2Et	H	H	Pd/C, EtOH	n/i	[34]
4-PhC_6H_4	H	H	H	Ni, 20°C, 4 atm, EtOH	85	[43]
$PhCH_2$	H	H	H	Ni, 20°C, 4 atm, EtOH	92	[43]
1-Naphthyl-methyl	H	H	H	Ni, 20°C, 4 atm, EtOH	87	[43]
H	H	H	H	PtO_2, 20°C, 8 h, EtOH	n/i	[73]
H	H	H	H	PtO_2, HCl, H_2O	n/i	[75]
CO_2H	T	*t*-BuO	T	Pd/$BaSO_4$, 100°C, 1 h, ampul*	23	[77]
C_7H_{15}	CO_2Bu-*t*	H	H	PtO_2, 20°C, 3 atm, 4.5 h	99	[78]
C_4H_9	C_7H_{15}	H	H	PtO_2, 20°C, 3 atm, 4.5 h	90	[78]
C_4H_9	CO_2Bu-*t*	H	H	PtO_2, 20°C, 3 atm, 4.5 h	96	[78]
$(CH_2)_4$–C(Me)(O)–$(CH_2)_2$O	CO_2Bu-*t*	H	H	PtO_2, 20°C, 2 h, EtOH	96	[79]

* In **133** R = CO_2H, R^1 = R^2 = R^3 = H; the reaction was conducted in an atmosphere of tritium.

5-(3-Pyridyl)-3,4-2H-dihydropyrrole or 5-phenyl-3,4-2H-dihydropyrrole was converted by the action of sodium borohydride in alcohol (20°C, 18 h) into 2-(3-pyridyl)pyrrolidine (yield 20%) or 2-phenylpyrrolidine (yield 16%) respectively [67].

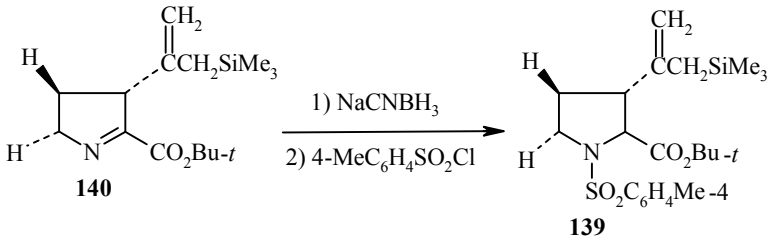
Various Δ^1-pyrrolines are reduced to pyrrolidine derivatives with high yields when sodium cyanoborohydride is used. Polysubstituted Δ^1-pyrrolines **137** are converted smoothly into compounds **138** by the action of sodium borohydride at room temperature [41].



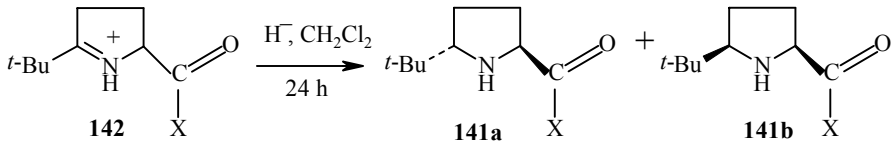
137 **138**

R, R^1, yield (%): Me, Me, 85; H, *i*-Pr, 78

The N-substituted pyrrolidine **139** was synthesized from Δ^1-pyrroline **140** by a two-stage method (without isolation of the product formed at the first stage of the process) by the action of sodium cyanoborohydride followed by treatment with *p*-toluenesulfonyl chloride [19].



A mixture of stereoisomers **141a**,**b** in various ratios is formed when the salts **142** are heated with borohydrides, and in nearly all cases 100% conversion of the salts **142** is observed [32].



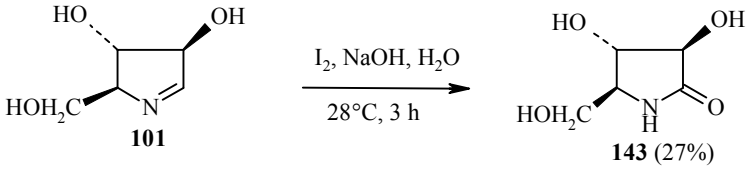
X, hydride, °C, solvent, **141a**:**141b** ratio: OH, $NaCNBH_3$, 66, THF, 43:57; OH, $Me_4NBH(OAc)_3$, 66, THF, 88:17 (100% conversion after 6 h); OH, $Me_4NBH(OAc)_3$, 0, THF, 66:33; OH, $Me_4NBH(OAc)_3$, -70, MeCN, 33:66; OH, $NaCNBH_3$, -40, MeCN, 50:50; OH, $Me_4NBH(OAc)_3$, 0, MeCN, 58:42; OH, $Me_4NBH(OAc)_3$, -40, MeCN, 54:46; NHMe, $Me_4NBH(OAc)_3$, 66, THF, 37:73; NHMe, $Me_4NBH(OAc)_3$, 0, MeCN, 50:50 (66% conversion after 96 h)

An original method for the reduction of 2-phenyl-3,4-2H-dihydropyrrole to 2-phenylpyrrolidine (yield 85%) involved the action of butylmagnesium chloride in the presence of Cp_2TiCl_2 at 25°C for 15 h [104].

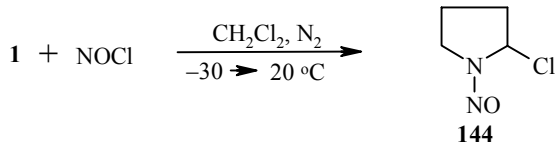
2.1.2. Reactions with Inorganic Compounds

The products from the addition of inorganic compounds to the cyclic C=N bond of Δ^1-pyrrolines have only been reported in two papers.

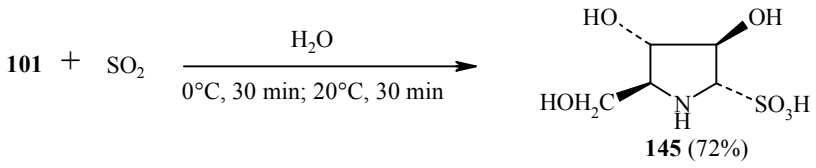
In the presence of sodium hydroxide and iodine Δ^1-pyrroline **101** adds a molecule of water and is converted without change of configuration into (3*S*,4*R*,5*R*)-3,4-dihydroxy-5-hydroxymethyl-2-pyrrolidone (**143**) [96].



3,4-2H-Dihydropyrrole **1** adds nitrosyl chloride at the C=N bond in an inert atmosphere and is converted into 2-chloro-1-nitrosopyrrolidine (**144**) [105].



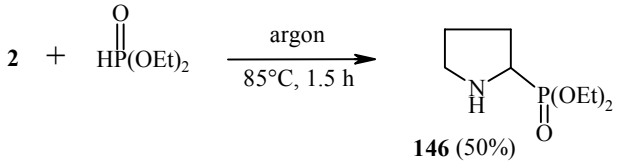
The product **145** from addition of sulfurous acid to the cyclic C=N bond of Δ^1-pyrroline **101** was obtained by passing sulfur dioxide into an aqueous solution of the pyrroline **101** [96].



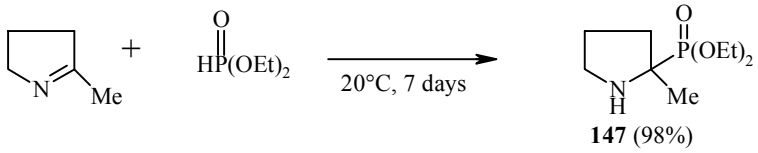
2.1.3. Reactions with Heteroorganic Compounds

The compounds of this type that have been studied most in reactions with Δ^1-pyrrolines are phosphorus-containing compounds.

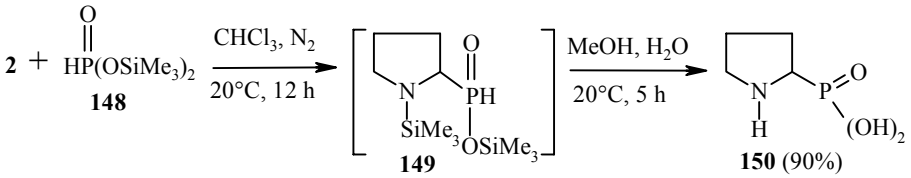
The reaction of the trimer **2** with diethyl phosphite was realized by heating in an atmosphere of argon, and as a result the addition product **146** was obtained [106].



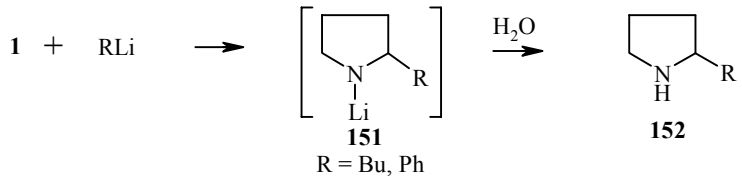
As shown recently, diethyl phosphite adds to 2-methyl-3,4-2H-dihydropyrrole even at room temperature, and the corresponding compound **147** is formed with a yield of 98% [107].



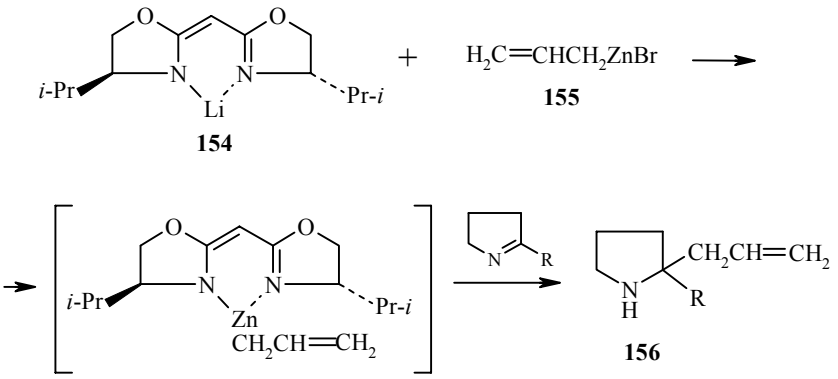
Bis(trimethylsilyl) phosphonite (**148**) also reacts with the trimer **2** at room temperature, giving the intermediate compound **149**. The latter is converted into compound **150** by treatment with aqueous methanol [108].



Butyllithium or phenyllithium reacts with the pyrroline **1** at 20°C to form the addition products **151**, which are converted by treatment with water into the pyrrolidine derivatives **152** [109].



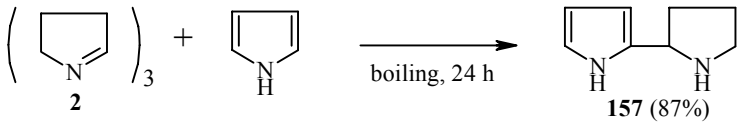
The reaction product obtained from compounds **154** and **155** was brought into reaction with pyrroline **1** or with 5-*tert*-butyl-3,4-2H-dihydropyrrole, and the pyrrolidine derivatives **156** were synthesized [110].



R, °C, time (h), yield (%): H, -30, 8, 54; *t*-Bu, 0, 20, 75

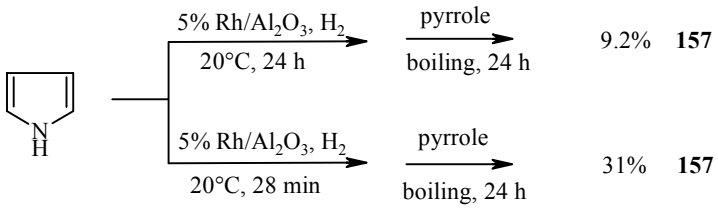
2.1.4. Reactions with Compounds of the Pyrrole Series

In this section all known published data on the reactions of pyrroline **1** with pyrrole, its homologs, or indole, leading to the corresponding 2-heterylpyrrolidines, are discussed. It should be noted that investigations in this regions have been concentrated into a single paper [96]. The reaction of pyrroline **1** with pyrrole was studied in greatest detail. 2-(2-Pyrrolyl)pyrrolidine (**157**) was obtained when the trimer **2** was heated for a long time with pyrrole [93].

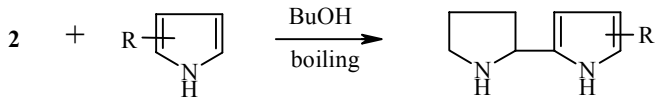


In cases where the pyrroline **1** was produced as a result of the transformation of some other heterocyclic compound and brought into reaction with pyrrole *in situ* the addition product **157** was formed with lower yields. Thus, the pyrroline **1** formed by heating $NaIO_4$ with 3-hydroxypiperidine in aqueous sodium hydroxide with heat was used in the reaction with pyrrole for 48 h at the boiling point of the mixture. As a result the addition product **157** was obtained with a yield of 20% [93].

When the pyrrolidine **15** was passed (0.3 ml/min) in a stream of hydrogen (30 ml/min) though a Pyrex tube containing Pd/C, the following results were obtained. Temperature, °C, yields (%) of pyrrole, pyrroline **1**, and compound **157**: 200, 0.8, 0; 240, 5.5, 7, 11; 320, 8, 12, 16; 350, 0.15, 30; 400, 0.24, 48 [96]. Low yields of the addition product **157** were observed when pyrrole was passed over the catalyst Rh/Al_2O_3 in a stream of hydrogen [93].



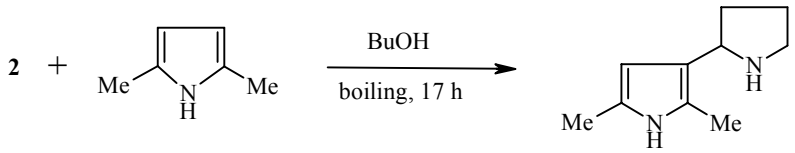
The trimer **2** reacts with 2-methylpyrrole or 3-methylpyrrole in boiling butanol with the formation of compounds **158**, in which the pyrrolidine radical is at position 5 of the pyrrole ring [93].



158

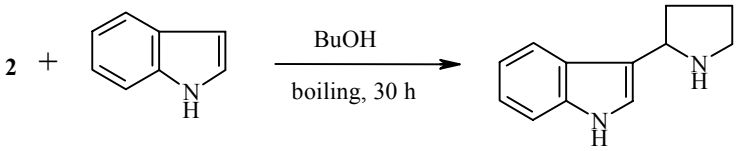
R, time (h), yield (%): 3-Me, 24, 72; 4-Me, 22, 33

If both α-positions in the pyrrole contain substituents, the reaction with pyrrole takes place at position 3. Thus, the product **159** was obtained by heating the trimer **2** with 2,5-dimethylpyrrole in butanol [93].



159 (40%)

The trimer **2** enters into reaction with indole with greater difficulty, and to obtain a satisfactory yield of the reaction product it is necessary to boil the reagents for a long time in butanol. As usual, the indole reacts at position 3 with the formation of the adduct **160** [93].



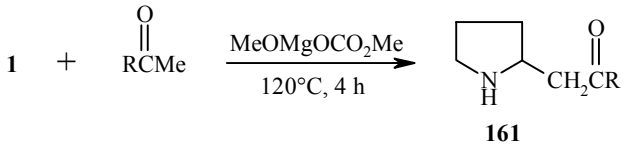
160

1-Methylcarbazole and carbazole do not react with pyrroline **1** under the investigated conditions [93].

2.1.5. Reactions with Methyl Ketones or β-Keto Acids

It seems logical to examine the reactions of Δ^1-pyrrolines with ketones RCOMe or β-keto acids $RCOCH_2COOH$ in one section (as addition to the C=N bond of pyrrolines) on account of the fact that the products of these reactions are formally adducts of methyl ketones and pyrroline **1**.

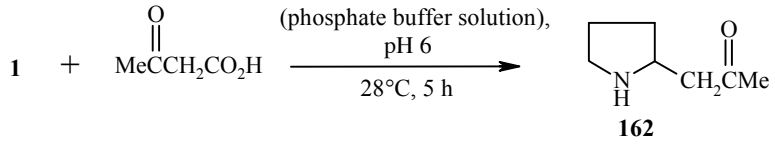
In 1974 a method was patented for the synthesis of 2-pyrrolidinylmethyl ketones **161** by heating pyrroline **1** with methyl ketones RCOMe in the presence of magnesium methylcarbonate in DMF in an atmosphere of carbon dioxide. The reaction was carried out in a stream of nitrogen in order to remove the methanol released during the reaction [111, 112].



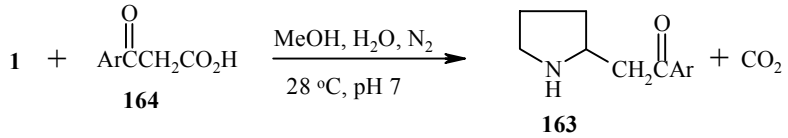
R = 2-fluorenyl [111]; 4-PhC$_6$H$_4$, 4-PhOC$_6$H$_4$, 4-PhCH$_2$C$_6$H$_4$, 4-PhSC$_6$H$_4$, 4-PhCH=CH–C$_6$H$_4$, 3-PhO(CH$_2$)$_4$C$_6$H$_4$, 4-(4-BrC$_6$H$_4$O)C$_6$H$_4$, 4-(4-MeOC$_6$H$_4$)C$_6$H$_4$, 4-(4-MeOC$_6$H$_4$O)C$_6$H$_4$, 4-Ph(CH$_2$)$_8$OC$_6$H$_4$, 2-Ph(CH$_2$)$_2$OC$_6$H$_4$, 4-Ph(CH$_2$)$_2$C$_6$H$_4$, adamantyl-1,4-C$_{12}$H$_{25}$C$_6$H$_4$, PhCH=C(Me)CH=CH$_2$ [112]

The experimental details of this reaction were described in greater detail in [113, 114]. The yields of the obtained compounds were given, and certain limitations of the process making it possible to obtain compounds **161** were described. R, yield, %: Ph(CH$_2$)$_2$C$_6$H$_4$, 63; 2-anthranyl, 65 [113]; 4-PhOC$_6$H$_4$, 34; (9-fluorenylidene)=C$_6$H$_4$-4, 27; 2-fluorenyl, 65; 4-PhCH$_2$C$_6$H$_4$, 63 [114].

In reaction with pyrroline **1** acetoacetic acid is decarboxylated, and compound **162**, i.e., the product from addition of acetone to the C=N bond of pyrroline, is formed [4].

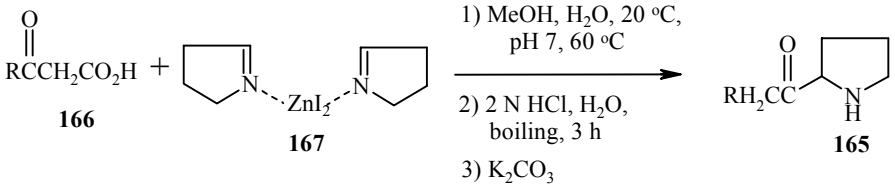


The synthesis of aryl 2-pyrrolinylmethyl ketones **163** by the condensation of pyrroline **1** with β-diketones **164**, taking place at 20°C and pH 7, was described in a series of papers [36, 40, 115-118]. The obtained compounds are the products from formal addition of the ketones ArCOMe to the C=N bond of pyrroline **1**.



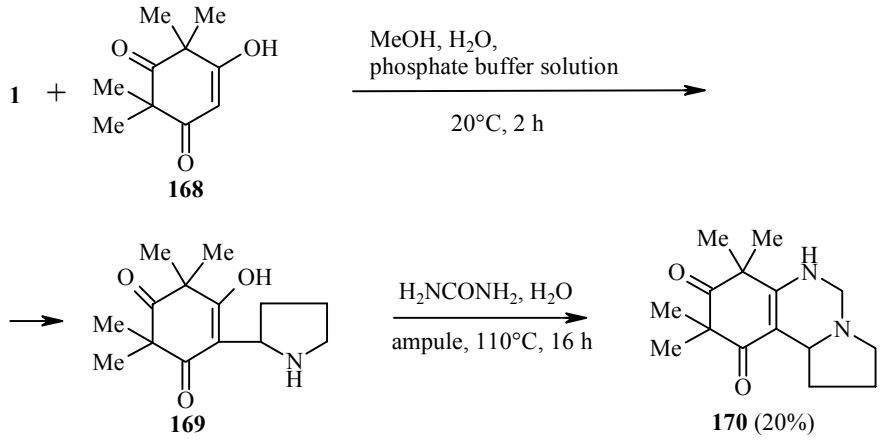
Ar, time (h), yield: Ph, 60, 53-65 [36, 115]; 4-MeOC$_6$H$_4$, 24, 88 [36]; 3,4-(MeO)$_2$C$_6$H$_3$, 24-38, 52-85 [36, 115, 117]; 3-MeO, 4-BnOC$_6$H$_3$, 46-60, 46 [40, 118]; 3-PhCO$_2$, 4-MeOC$_6$H$_3$, 40, 45.9 [116]; 4-BnOC$_6$H$_4$, 60, 61 [40]; Ph (in **1** T is at position 5, in Ph all the atoms are C^{14}), 60, n/i; 4-OHC$_6$H$_4$ (in **1** ^{14}C is at position 5, in 4-HOC$_6$H$_4$ T is at position 3), 60, n/i; 3-MeO, 4-HOC$_6$H$_3$ (in **1**, T is at position 5), 60, n/i [40]

The condensation products **165** were synthesized with high yields by the reaction of the β-keto acids **166** with the complex **167** at 20°C and pH 7 (phosphate buffer solution) followed by heating the reaction mixtures with dilute hydrochloric acid and the action of potassium carbonate [24].



R, yield (%): Me, 85; Ph, 88; 3,4-(MeO)C$_6$H$_3$, 92

The reaction of pyrroline **1** with the cyclic ketone **168** was described in [39]. It resulted led to the product **169** from addition of the diketone at the C=N bond of the pyrroline **1**. In reaction with urea the product was converted into the *Syncarpurea* alkaloid **170**.

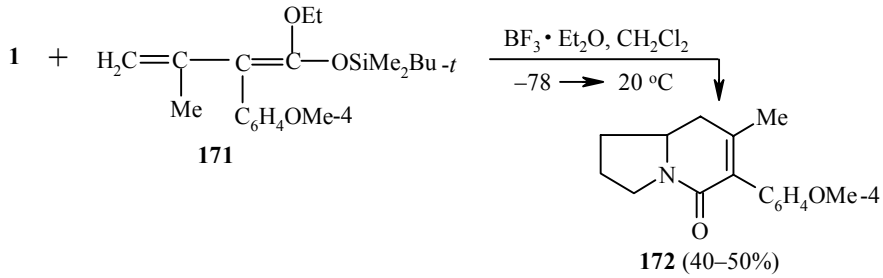


168 **169** **170** (20%)

2.1.6. Cycloaddition and Cyclocondensation

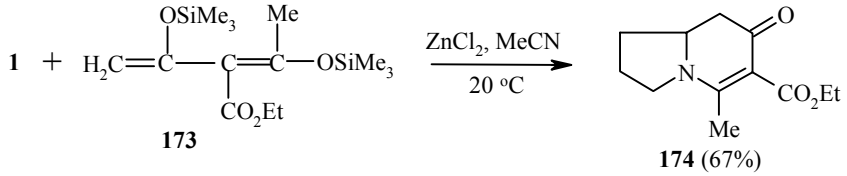
In this section we review published data on the reactions of Δ^1-pyrrolines with unsaturated polyfunctional compounds, leading to condensed systems containing a pyrrolidine ring.

In the presence of boron trifluoride etherate the pyrroline **1** enters into an aldiminodiene cyclocondensation with the diene **171** with the formation of the bicyclic compound **172** [119].



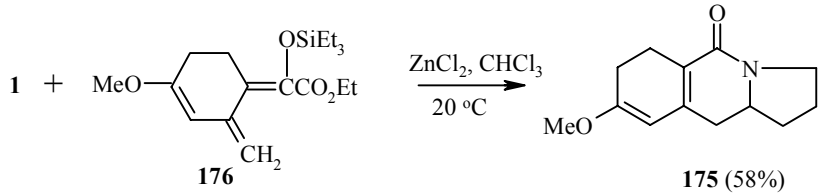
171 **172** (40–50%)

Cyclocondensation of pyrroline **1** with the diene **173** in the presence of zinc chloride gives 1-aza-2-methyl-3-ethoxycarbonylbicyclo[4,3,0]nonan-4-one (**174**) [119].

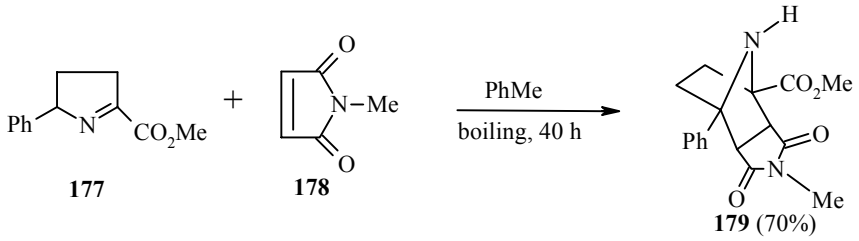


173 **174** (67%)

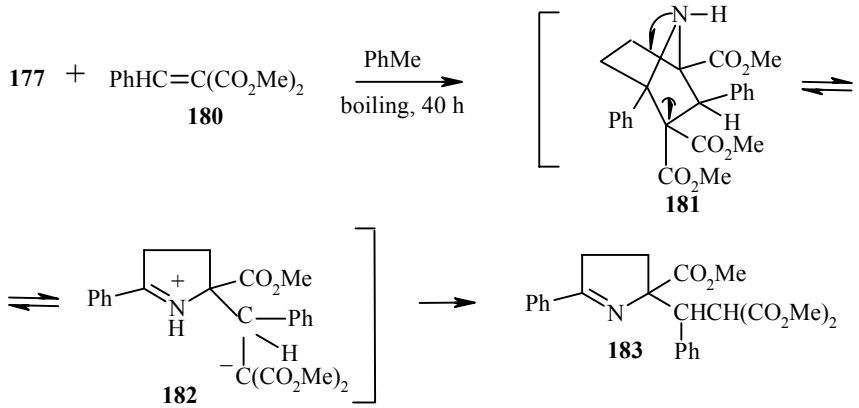
The tricyclic compound **175** was synthesized by the aldiminodiene cyclocondensation of pyrroline **1** with the cyclohexene derivative **176**, which contains two endocyclic double bonds [119].



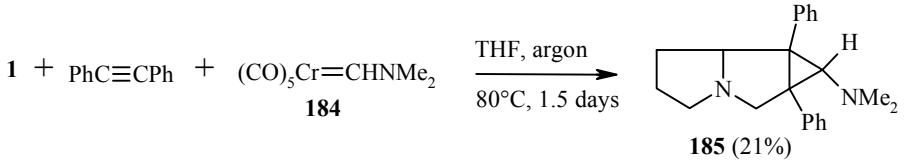
Δ^1-Pyrrolines (potential azomethine ylides) are capable of entering into 1,3-dipolar cyclocondensation with alkenes containing an activated double bond. For example, the Δ^1-pyrroline **177** gives the adduct **179** when heated with N-methylmaleimide **178** [33].



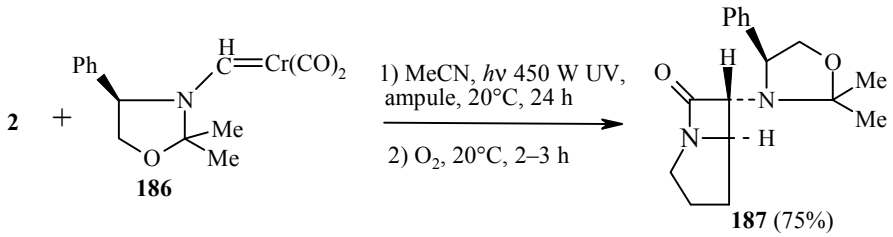
A more complicated picture is observed during the reaction of Δ^1-pyrroline **177** with the alkene **180**. Compound **181**, formed as a result of 1,3-dipolar cycloaddition, can be converted reversibly into the tautomer-dipole **182**, the prototropic rearrangement of which leads to the final compound **183** [33].



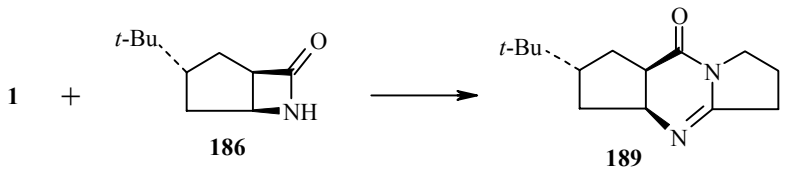
Compound **185** was synthesized by the prolonged action of heat on a mixture of pyrroline **1**, diphenylacetylene, and the carbene complex **184** in an inert atmosphere [120].



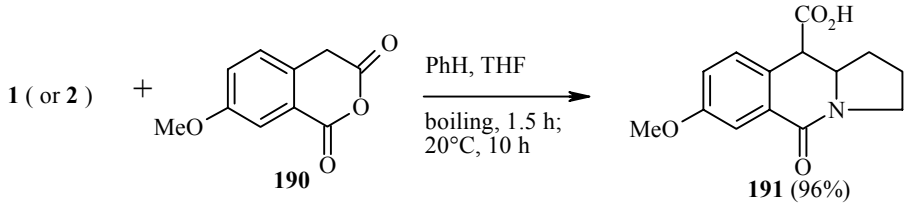
The cyclocondensation product **187** was obtained by irradiating a mixture of the trimer **2** and the carbene complex **186** with ultraviolet light followed by oxidation of the reaction mass [121].



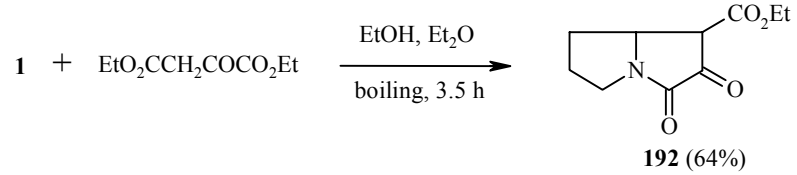
The pyrrolopyrimidine derivative **189** is formed in the reaction of pyrroline **1** with (1*R**,3*S**,5*S**)-3-*tert*-butyl-6-azabicyclo[3.2.0]heptan-7-one (**188**). The reaction takes place with retention of the configuration of the original lactam [122].



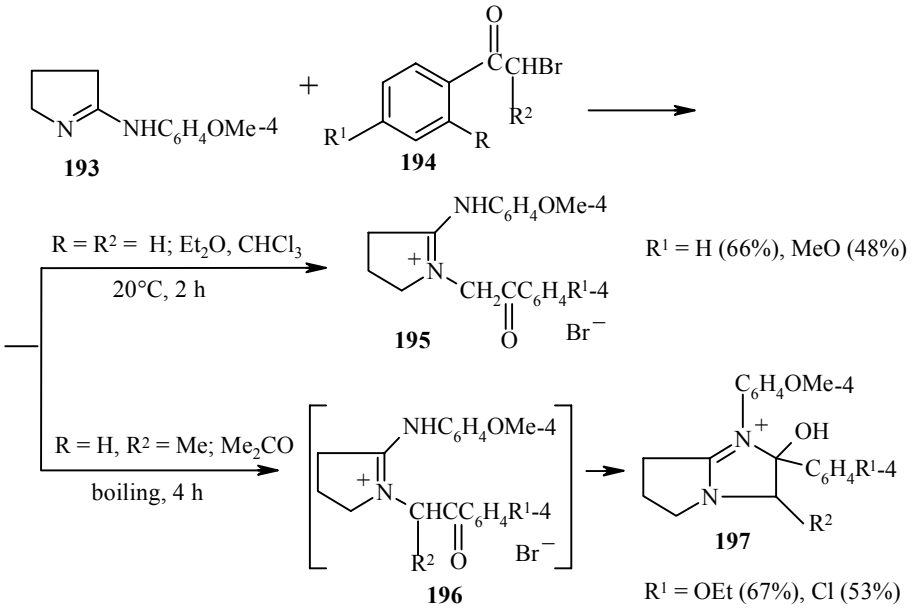
The cyclocondensation of pyrroline **1** with 7-methoxyisochroman-1,3-dione (**190**) takes place nonstereospecifically, and 7-methoxy-10-hydroxycarbonyl-1,2,3,5,10,10a-hexahydropyrrolo[1,2-*b*]isoquinolin-5-one (**191**) is formed as a 50:50 mixture of *cis* and *trans* isomers [123, 124].



1-Ethoxycarbonylpyrrolizidine-2,3-dione (**192**) (a synthon for the production of alkaloids of the *Senecio* group) is formed as a result of the cyclocondensation of pyrroline **1** with oxaloacetic ester without the use of condensing agents [125].



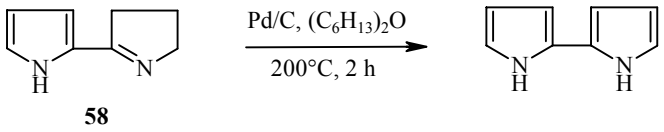
If the reaction of 5-(*p*-anisidyl)-3,4-2H-dihydropyrrole (**193**) with phenacyl bromides **194** (R = H) was carried out at 20°C, only alkylation with the formation of the corresponding salts **195** occurred. However, if the reaction of the Δ^1-pyrroline **193** with phenacyl bromides **194** (R = Me) was carried out in boiling acetone, the reaction did not stop at the alkylation stage, but the alkylation products **196** entered *in situ* into intramolecular nucleophilic cycloaddition, leading to compounds **197** [126].



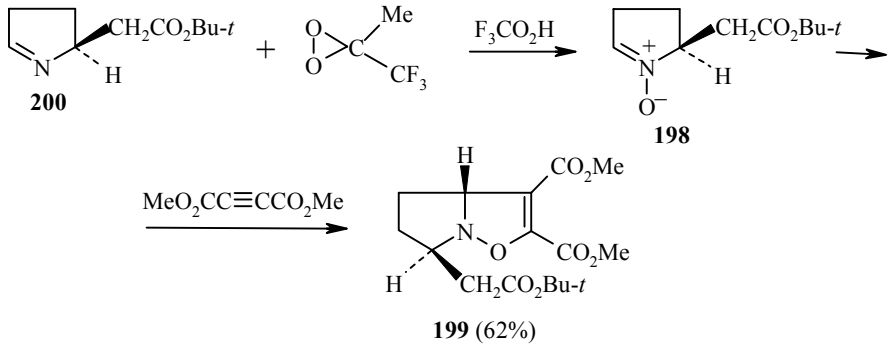
2.2. Other Reactions

2.2.1. Dehydrogenation and Oxidation

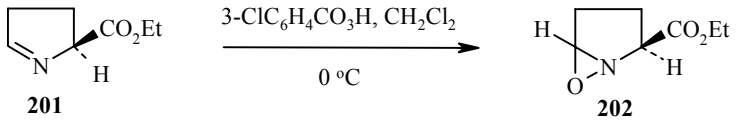
When heated in the presence of Pd/C, 2-(Δ^1-2-pyrrolinyl)pyrrole (**58**) eliminates a molecule of hydrogen and is converted into 2,2'-bipyrrole [58].



The attention of many investigators has been attracted to 1,3-dipolar cycloaddition as a convenient method for the synthesis of various heterocyclic compounds, including important natural compounds and, mainly, alkaloids [127]. Of considerable interest in this connection are the N-oxides of nitrogen-containing heterocycles and, in particular the N-oxides of Δ^1-pyrrolines. It is therefore surprising that only one paper has been devoted to the synthesis of Δ^1-pyrroline N-oxide (**198**) and its use in 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate. As a result the adduct **199** was obtained under very mild conditions [87].



The C=N bond in 2-ethoxycarbonyl-3,4-2H-dihydropyrrole (**201**) is easily oxidized during the action of the peroxy acid 3-$ClC_6H_4CO_3H$, resulting in the formation of compound **202** [87, 107].

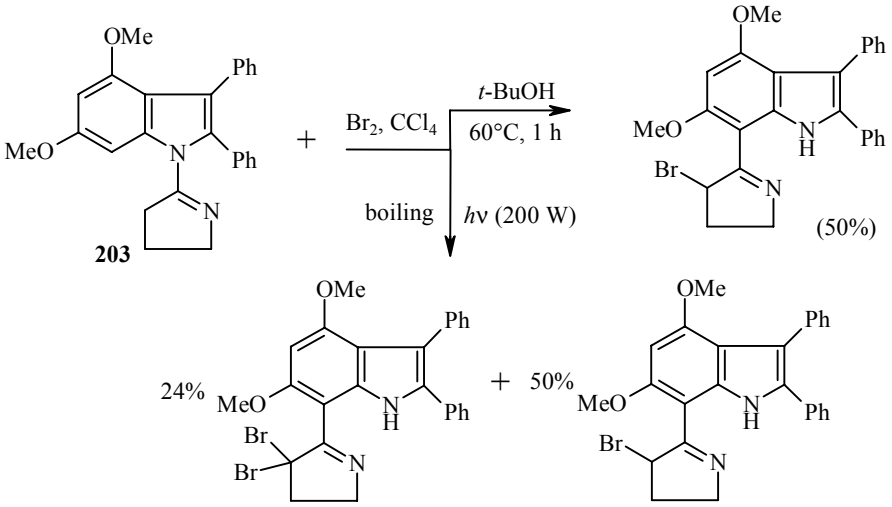


201 **202**

R, R^1, yield (%): CO_2Et, H, n/i [87]; $P(O)(OEt)_2$, Me, 57 [107]

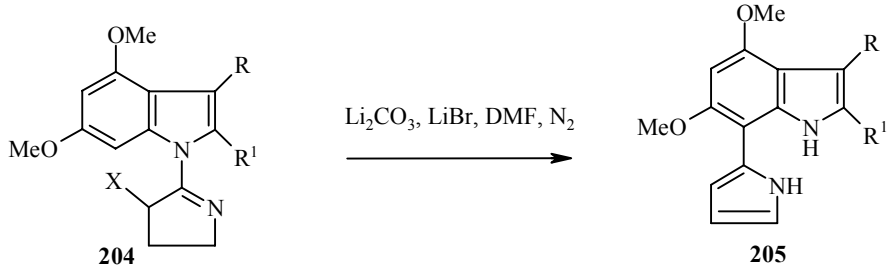
2.2.2. Halogenation and Dehalogenation

The Δ^1-pyrroline **203** is brominated by N-bromosuccinimide at position 4 of the pyrroline ring. The composition of the bromination products varies significantly with variation of the bromination conditions [65].



203

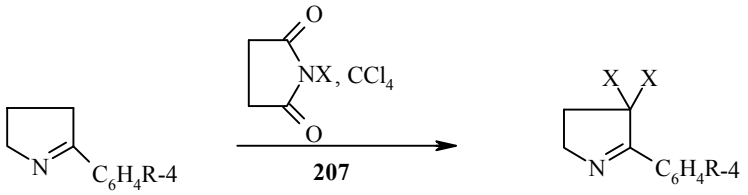
During the action of lithium carbonate and lithium bromide in an inert atmosphere the halogen derivatives **204** undergo dehydrobromination, resulting in the formation of the indole derivatives **205** with the pyrrole ring at position 7 [65].



204 **205**

R, R^1, X, °C, time (h), yield: Ph, Ph, Br, 90, 3, 85;
4-ClC_6H_4, H, Cl, 110, 2, 85; 4-BrC_6H_4, H, Cl, 110, 24, 85

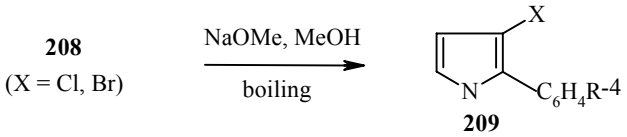
The halogenation of the pyrroline ring in the Δ^1-pyrrolines **206** by the action of N-halogenosuccinimides **207** gives high yields. If an excess of the halogenating agent is used, two hydrogen atoms at position 4 in the pyrroline ring are substituted by two atoms of the respective halogen, and compounds **208** are formed [46].



206 **207** **208**

R, X, (conditions), yield (%): H, Cl, (boiling, 10 min; 20°C, 7 h), 90; Me, Cl, (boiling, 10 min, 20°C, 14 h), 83; OMe, Cl,(boiling, 10 min; 20°C, 14 h), 86; Cl, Cl, (boiling, 10 min; 20°C, 12 h), 98; H, Br, (65°C, 48 h), 80; Me, Br, (boiling, 14 h), 88; OMe, Br, (boiling, 7 h), 99; Cl, Br, (65°C, 48 h), 79

The obtained dihalogen derivatives **208** were converted into 3-halogeno-2-arylpyrroles **209** by the action of sodium methoxide in boiling methanol [46].



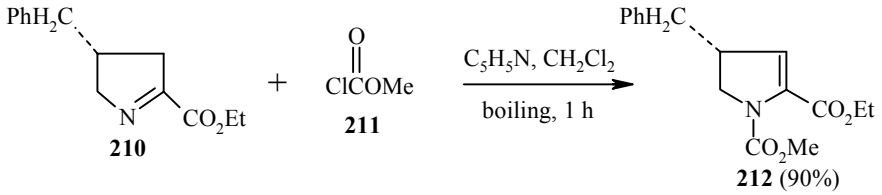
209

R, X, time (h), yield (%): H, Cl, 2, 95; Me, Cl, 3, 98; MeO, Cl, 3, 78; Cl, Cl, 4, 95; H, Br, 2, 85; Me, Br, 3, 82; OMe, Br, 3, 78; Cl, Br, 3, 87

2.3.3. Reactions with Carboxylic Acid Chlorides

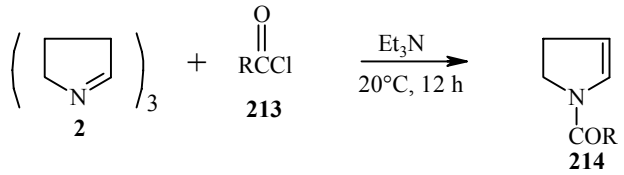
The reaction of Δ^1-pyrrolines with carboxylic acid chlorides leads to acylation of the pyrrolines at the cyclic nitrogen atom with isomerization of the double bond from position 1-2 to position 2-3.

Compound **212** is formed when ethyl 3-benzyl-3,4-2H-dihydropyrrole (**210**) is heated with chlorocarbonic ester **211** in the presence of pyridine [84].

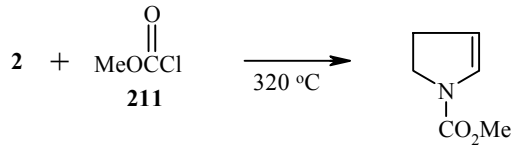


210 **211** **212** (90%)

In the presence of triethylamine the trimer **2** reacts with acid chlorides **213** at normal temperature, and the acylation products **214** are as a rule formed with good yields. However, if the reaction of the trimer **2** with chlorocarbonic ester was carried out without triethylamine, it was necessary to heat the reaction mixture above 300°C for successful reaction [128].

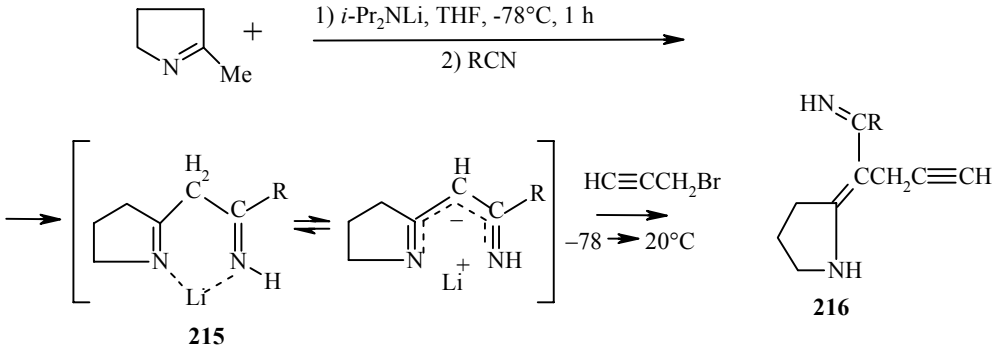


R, yield (%): MeO, 78; EtO, 79; $PhCH_2O$, 74; Cl_3CCH_2O, 39; Me, 71; $ClCH_2$, 57

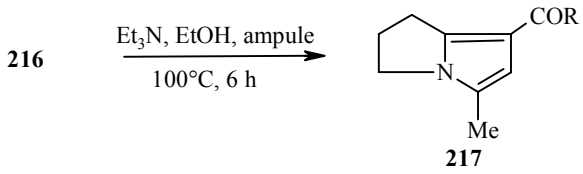


2.2.4. Reaction with Nitriles or Isonitriles

The lithium derivatives **215**, formed during the action of *i*-Pr_2NLi on 5-methyl-3,4-2H-dihydropyrrole and nitriles RCN, react with propargyl bromide, giving the condensation products **216**, which can be converted into the bicyclic compounds **217** by heating with triethylamine [129].

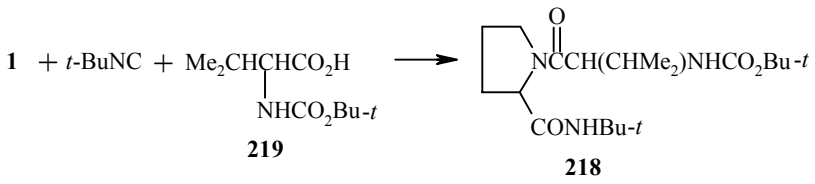


R= Ph, cyclohexyl, cyclopropyl, 2-thienyl, 2-furyl



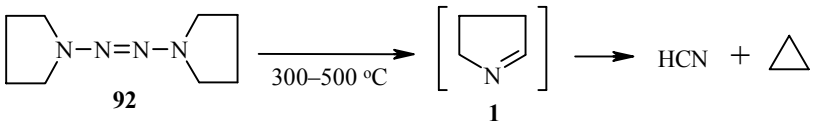
R, yield (%): Ph, 55; cyclohexyl, 71

The pyrrolidine derivative **218** was synthesized by the joint condensation of pyrroline **1**, *tert*-butylisonitrile, and N-*tert*-butoxycarbonylvaline (**219**) [130].



2.3. Reactions Accompanied by Cleavage of the Pyrroline Ring

The pyrroline **1**, formed during pyrolysis of the tetrazene **92**, decomposes under the experimental conditions and is converted into hydrogen cyanide and cyclopropane [84].

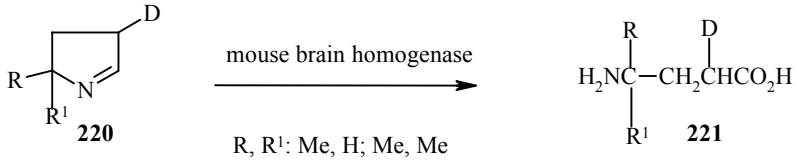


92 **1**

In the presence of enzyme systems the heterocyclic ring of Δ^1-pyrrolines undergoes oxidative cleavage with the formation of the corresponding γ-amino acids. Thus, under the influence of the enzyme system containing rabbit liver catalase in the soluble fraction the pyrroline **1** is converted into a mixture of γ-aminobutyric acid and 2-pyrrolidone [131].

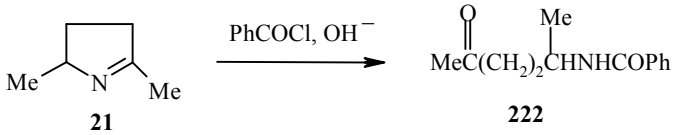
The pyrroline **1** deuterated at position 3 is converted in the presence of mouse brain homogenase into γ-aminobutyric acid containing the deuterium atom at position 2 [131].

The Δ^1-pyrroline **220** also reacts under analogous conditions with opening of the heterocyclic ring, giving the derivatives of γ-aminobutyric acid **221** [131].



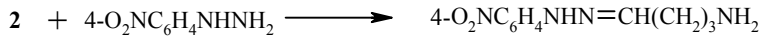
220 **221**

Under the conditions of the Schotten–Baumann reaction the pyrroline **21** is converted into the amino ketone benzoate **222** [27].



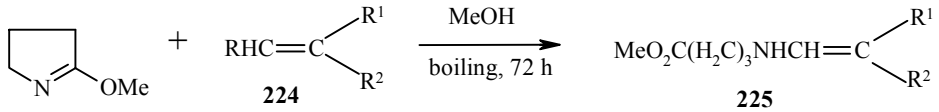
21 **222**

The reaction of the trimer **2** with 4-nitrophenylhydrazine gave the product from reaction of the hydrazine with the intermediately formed γ-butyraldehyde, i.e., the hydrazone **223** [10].



223

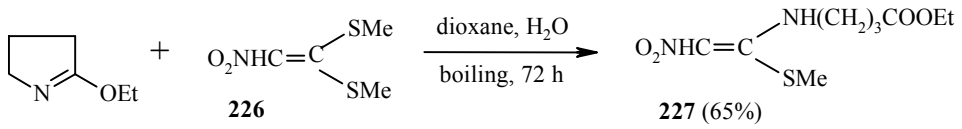
Interesting transformations were observed by the authors of [132] when 5-alkoxy-3,4-2H-dihydropyrroles were heated with 1,2,2-trisubstituted ethylenes in various solvents. Compounds **225** were produced by boiling 5-methoxy-3,4-2H-dihydropyrrole with alkenes **224** in methanol [132].



224 **225**

R, R^1, R^2, yield (%): NO_2, SMe, SMe, 43; EtO, COMe, COMe, 48;
EtO, COMe, CO_2Et, 38; EtO, CO_2Et, CO_2Et, 40

The reaction of 5-ethoxy-3,4-2H-dihydropyrrole with the alkene **226** in aqueous dioxane takes place in a different direction – with the formation of compound **227**.



REFERENCES

1. K. Hasse and H. Maisack, *Biochem. Z.*, **327**, 296 (1955).
2. K. Hasse and H. Maisack, *Naturwissenschaft*, **42**, 627 (1955).
3. P. J. Mann and W. R. Smithies, *Biochem. J.*, **61**, 89 (1955); *Chem. Abstr.*, **49**, 15992 (1955).
4. A. J. Clarke and P. J. Mann, *Biochem. J.*, **71**, 596 (1959).
5. P. S. Callery, M. S. B. Nayar, L. A. Geelhaar, M. Stogniew, and E. M. Jakubowski, *Biomed. Mass Spectrom.*, **7**, 525 (1980); *Chem. Abstr.*, **95**, 4071 (1981).
6. A. Ch. Andersson, S. Henningsson, L. Persson, and E. Rosengren, *Agents Actions*, **8**, 380 (1978); *Chem. Abstr.*, **89**, 160750 (1978).
7. A. Ch. Andersson, S. Henningsson, L. Persson, and E. Rosengren, *Acta Physiol. Scand.*, **102**, 159 (1978); *Chem. Abstr.*, **88**, 84973 (1978).
8. A. Ch. Andersson and S. Henningsson, *Agents Actions*, **10**, 104 (1980); *Chem. Abstr.*, **92**, 212962 (1980).
9. P. S Callery, M. S. B. Nayar, and L. A. Geelhaar, *Biomed. Mass Spectrom.*, **11**, 118 (1984); *Chem. Abstr.*, **101**, 19675 (1984).
10. A. Lüttringhaus, J. Jander, and R. Schneider, *Chem. Ber.,* **92**, 1756 (1959).
11. Ya. F. Oshis, A. A. Anderson, and M. V. Shimanskaya, USSR Inventor's Certificate 891658; *Ref. Zh. Khim.*, 17 N203P (1982).
12. Ya. F. Oshis, A. A. Anderson, and M. V. Shimanskaya, *Izv. Akad. Nauk LatvSSR, Ser. Khim.,* 67 (1987).
13. U. Bachrach, *Nature*, **194**, 377 (1962).
14. U. Bachrach, *J. Biol. Chem.*, **237**, 3443 (1962).
15. E. C. Woff, M. H. Park, and J. E. Folk, *J. Biol. Chem.*, **265**, 4793 (1990).
16. H. Bock and R. Dammel, *Chem. Ber.*, **120**, 1971 (1987).
17. J.-C. Guillemin and J.-M. Denis, *Tetrahedron*, **44**, 4431 (1988).
18. S. Sugasawa and S. Ushioda, *Tetrahedron*, **5**, 48 (1959).
19. T. Kercher and T. Livinghouse, *J. Org. Chem.*, **62**, 805 (1997).
20. A. A. Anderson, T. G. Andronikashvili, L. Ya. Laperashvili, Ya. F. Oshis, G. V. Tsitsishvili, M. V. Shimanskaya, and S. P. Yurel', *Application of Zeolites in Catalysis. Abstracts of All-Union Conference* [in Russian], Moscow (1981), p. 234.
21. Ya. F. Oshis, A. A. Anderson, and M. V. Shjimanskaya, *Izv. Akad. Nauk. LatvSSR, Ser. Khim.*, 408 (1981).
22. J. Kijenski, P. J. Niedzielski, and A. Baiker, *Appl. Catal.*, **53**, 107 (1989).
23. K. Yoshikawa, L. M. Libbey, W. Y. Cobb, and E. A. Day, *J. Food Sci.*, **30**, 991 (1965); *Chem. Abstr.*, **64**, 6933 (1966).
24. G. Baxter, J. C. Melville, and D. J. Robins, *Synlett*, 359 (1991).
25. K. Hasse and G. Schmid, *Biochem. Z.*, **337**, 480 (1963).
26. H. J. Vogel and B. D. Davis, *J. Am. Chem. Soc.*, **14**, 109 (1952).
27. G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

28. H. Gershon and A. Scala, *J. Org. Chem.*, **26**, 2347 (1961).
29. E. Kato, K. Yamamoto, Yo. Kawashima, T. Watanabe, M. Oya, T. Iso, and J. Iwao, *Chem. Pharm. Bull.*, **33**, 4836 (1985).
30. J. Ackermann, M. Matthes, and Ch. Tamm, *Helv. Chim. Acta*, **73**, 122 (1990).
31. A. Giovannini, D. Savoia, and A. Umani-Ronchi, *J. Org. Chem.*, **54**, 228 (1989).
32. E. Beausoleil, B. L'Archeveque, L. Belec, M. Atfani, and W. D. Lubell, *J. Org. Chem.*, **61**, 9447 (1996).
33. A. Mkairi and J. Hamelin, *Tetrahedron Lett.*, **28**, 1397 (1987).
34. A. Van der Werf and R. M. Kellogg, *Tetrahedron Lett.*, **32**, 3727 (1991).
35. W. B. Jakoby and J. Fredericks, *J. Biol. Chem.*, **234**, 2145 (1959).
36. J. E. Cragg, R. B. Herbert, F. B. Jackson, Ch. J. Moody, and I. T. Nicolson, *J. Chem. Soc., Perkin Trans. I*, 2477 (1982).
37. D. W. Lundgren, H. A. Lloyd, and J. Hankins, *Biochem. Biophys. Res. Commun.*, **97**, 667 (1980).
38. J. C. Richards and I. D. Spenser, *Tetrahedron*, **39**, 3549 (1983).
39. K. T. Okamoto and J. Clardy, *Tetrahedron Lett.*, **25**, 2937 (1984).
40. R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J. Chem. Soc.*, *Perkin Trans. I*, 825 (1984).
41. G. B. Itoua and J.-Y. Laronze, *Synthesis*, **353** (1987).
42. Y. Watanabe, J. Yamamoto, M. Akazome, T. Kondo, and T. Mitsudo, *J. Org. Chem.*, **60**, 8328 (1995).
43. J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1281 (1958).
44. E. Leete, M. R. Chedekel, and G. B. Bodem, *J. Org. Chem.*, **37**, 4465 (1972).
45. M. Vaultie, P. H. Lambert, and R. Carrie', *Bull. Soc. Chim. Fr.*, 83 (1986).
46. N. De Kimpe, K. A. Tehrami, Ch. Stevens, and P. De Cooman, *Tetrahedron*, **53**, 3693 (1997).
47. K. R. Prabhu, P. S. Sivanand, and S. Chandrsekaran, *Synlett*, **47** (1998).
48. P. M. Maginnity and J. B. Cloke, *J. Am. Chem. Soc.*, **73**, 49 (1951).
49. P. J. A. Demoen and A. J. Janssen, *J. Am. Chem. Soc.*, **81**, 6281 (1959).
50. S. Wagaw, R. A. Rennels, and S. L. Burchwald, *J. Am. Chem. Soc.*, **119**, 8451 (1997).
51. M. Murakami, N. Hasegawa, T. Nagatomi, and Yo. Ito, *Heterocycles*, **47**, 85 (1998).
52. J. P. Dinnocenzo, H. Zuilhof, D. R. Lieberman, T. R. Simpson, and M. W. Me Kechney, *J. Am. Chem. Soc.*, **119**, 994 (1997).
53. K. Osowska-Pacewicka and A. Zwierzak, *Synth. Commun.*, **28**, 1127 (1998); *Chem. Abstr.*, **128**, 294654 (1998).
54. J. Ahman, T. Jarevang, and P. Somfai, *J. Org. Chem.*, **61**, 8148 (1996).
55. Yu. Nomura, K. Ogawa, Yo. Takeuchi, and Sh. Tomoda, *Chem. Lett.*, 693 (1997).
56. K. Ogawa, Yu. Nomura, Yo. Takeuchi, and Sh. Tomoda, *J. Chem. Soc., Perkin Trans. I*, 3031 (1982).
57. M. Ochiai, M. Inenaga, Yo. Nagao, R. M. Moriarty, R. K. Vaid, and M. P. Duncan, *Tetrahedron Lett.*, **29**, 6917 (1988).
58. H. Rapoport and N. Castagnoli, Jr., *J. Am. Chem. Soc.*, **84**, 2178 (1962).
59. E. Rosenberg, Sh. E. Kabir, K. I. Hardcastle, M. Day, and E. Wolf, *Organometallics*, **9**, 2214 (1990); *Ref. Zh. Khim.*, 146226 (1991).
60. J.-C. Guillemin, J.-M. Denis, M. C. Lasne, and J.-L. Ripoll, *Tetrahedron*, **44**, 4447 (1988).
61. C. Schopf, Germ. Patent 1054088; *Chem. Abstr.*, **55**, 8439 (1961).
62. H. Poisel, *Monatsh. Chem.*, **109**, 925 (1978).
63. G. Piancatelli and A. Scettri, *Tetrahedron*, **32**, 1745 (1976).
64. U. Leutenegger, G. Umbricht, Ch. Fahrni, P. Matt, and A. Pfaltz, *Tetrahedron*, **48**, 2143 (1992).
65. D. StC. Black, M. C. Bowyer, and N. Kumar, *Tetrahedron*, **53**, 8573 (1997).
66. D. Spitzner, *Synthesis*, 242 (1977).
67. J. I. Seemzn, *Synthesis*, 498 (1977).
68. J. Bielawski, S. Brandange, and L. Lindblom, *J. Heteterocycl. Chem.*, **15**, 97 (1978).
69. B. L. Feringa and J. F. G. A. Jansen, *Tetrahedron Lett.*, **27**, 507 (1986).

70. B. P. Mundy and B. R. Larsen, *Synth. Commun.*, **2**, 197 (1972).
71. B. P. Mundy, B. R. Larsen, L. F. Me Kenzie, and G. Braden, *J. Org. Chem.*, **37**, 1635 (1972).
72. B. P. Mundy, K. B. Lipkowitz, M. Lee, and B. R. Larsen, *J. Org. Chem.*, **39**, 1963 (1974).
73. P. D. Bragg and L. Y. Hough, *J. Chem. Soc.*, 4050 (1958).
74. G. Grue-Sorensen and I. D. Spenser, *Can. J. Chem.*, **60**, 643 (1982).
75. K. Hasse, J. Hess, and H. W. Hornig, *Chem. Ber.*, **104**, 2420 (1971).
76. K. Endo, K. Hirayama, Yu. Aota, K. Seya, H. Asakura, and K. Hisamichi, *Heterocycles*, **47**, 865 (1998).
77. Yu. A. Zolotarev, E. V. Laskatelev, V. S. Kozik, E. M. Dorokhova, S. T. Rozenberg, Yu. A. Borisov, and N. F. Myasoedov, *Izv. Akad. Nauk. Ser. Khim.*, 1820 (1997).
78. K. Shiosaki and H. Rapoport, *J. Org. Chem.*, **50**, 1229 (1985).
79. J. S. Petersen, G. Pels, and H. Rapoport, *J. Am. Chem. Soc.*, **106**, 4539 (1984).
80. M. H. Howard, F. J. Sardina, and H. Rapoport, *J. Org. Chem.*, **55**, 2829 (1990).
81. K. Warning and M. Mitzlaff, German Patent 2636098; *Ref. Zh. Khim.*, 1 N235 P (1979).
82. T. Abe and H. Fukaya, Jpn. Patent 08165275; *Chem. Abstr.*, **125**, 221580 (1996).
83. J. Ezquerra, A. Escribano, and A. Rubio, *Tetrahedron Asymmetry*, **7**, 2613 (1996).
84. P. Rademacher, P. Heymanns, R. Münzenberg, H. Wöll, K. Kowski, and R. Poppek, *Chem. Ber.*, **127**, 2073 (1994).
85. L. Knorr and P. Rabe, *Berichte*, **34**, 3491 (1901).
86. L. H. Andrews and M. McElvain, *J. Am. Chem. Soc.*, **51**, 887 (1928).
87. P. de March, M. Figueredo, J. Font, T. Gallagher, and S. Milan, *J. Chem. Soc. Chem. Commun.*, 2097 (1995).
88. A. Eschenmoser and C. E. Wintner, *Science*, **196**, 1410 (1977).
89. H. Quasi, A. Fuss, and W. Nüdling, Eur. J. Org. Chem., 317 (1998).
90. H. Kayakiri, Sh. Takase, H. Setoi, I. Uchida, H. Terano, and M. Hashimoto, *Tetrahedron Lett.*, **29**, 1725 (1988).
91. N. Bojkova and H. Heimgartner, *Heterocycles*, **47**, 781 (1998).
92. F. Clerici, M. L. Gelmi, D. Pocar, and R. Rondena, *Tetrahedron*, **51**, 9985 (1995).
93. D. W. Fuhlhage and C. A. Van der Werf, *J. Am. Chem. Soc.*, **80**, 6249 (1958).
94. H. Mohrle, G. Troster, M. Linden, D. Mootz, and H. Wunderlich, *Tetrahedron*, 37, 2881 (1981).
95. G. Maio, P. A. Tardella, *Proc. Chem. Soc.*, 224 (1963).
96. H. Kayakiri, K. Nakamura, Sh. Takase, H. Setoi, I. Uchida, H. Terano, M. Hashimoto, T. Tada, and S. Koda, *Chem. Pharm. Bull.*, **39**, 2807 (1991).
97. Yo. J. Kirn and T. Kitahara, *Tetrahedron Lett.*, **38**, 3423 (1997).
98. Sh. Takayama, R. Martin, W. Jiangyue, K. Laslo, G. Siuzdak, and Ch.-H. Wong, *J. Am. Chem. Soc.*, **119**, 8146 (1997).
99. Z.-M. Qiu and D. J. Burton, *Tetrahedron Lett.*, **35**, 4319 (1994).
100. Z.-M. Qiu and D. J. Burton, *Tetrahedron Lett.*, **36**, 5119 (1995).
101. O. Tsuge, Sh. Kanemasa, and K. Matsuda, *J. Org. Chem.*, **51**, 1997 (1986).
102. O. Tsuge, T. Hatta, Yo. Kakura, H. Tashiro, H. Maeda, and A. Kakehi, *Chem. Lett.*, 945 (1997).
103. C. Alvarez-Ibarra, A. G. Csaky, I. L. de Silanes, and M. L. Quiroga, *J. Org. Chem.*, **62**, 479 (1997).
104. Sk. R. Amin and W. E. Crowe, *Tetrahedron Lett.*, **38**, 7487 (1997).
105. B. Rugewitz-Blackholm and M. Wiessler, *Liebigs Ann. Chem.*, 583 (1987).
106. E. W. Petrillo, Jr., and E. P. Spitzmiller, *Tetrahedron Lett.*, 4929 (1979).
107. S. Barbati, J.-L. Clement, C. Frejaville, J.-C. Bouteiller, P. Tordo, J.-C. Michel, and J.-C. Yadan, *Synthesis*, 2036 (1999).
108. X.-Yu. Jiao, M. Borloo, Ch. Verbruggen, and A. Haemers, *Tetrahedron Lett.*, **35**, 1103 (1994).
109. F. E. Scully, Jr., *J. Org. Chem.*, **45**, 1515 (1980).
110. M. Nakamura, A. Hirai, and E. Nakamura, *J. Am. Chem. Soc.*, **118**, 8489 (1996).

111. J. M. Grisar and G. P. Claxton, German Patent 2417782; *Chem. Abstr.*, **82**, 72580 (1975).
112. J. M. Grisar and G. P. Claxton, German Patent 2418480; *Chem. Abstr.*, **82**, 72794 (1975).
113. J. M. Grisar, G. P. Claxton, and K. T. Stewart, *Synthesis*, 284 (1974).
114. J. M. Grisar, G. P. Claxton, K. T. Stewart, R. D. MacKenzie, and T. Kariya, *J. Med. Chem.*, **19**, 1195 (1976).
115. R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J. Chem. Soc. Chem. Commun.*, 450 (1976).
116. V. K. Mangla and D. S. Bhakuni, *Indian J. Chem.*, **19B**, 931 (1980).
117. V. K. Mangala and D. S. Bhakuni, *Indian J. Chem.*, **19B**, 748 (1980).
118. K. Iwasa, M. Kamigauchi, N. Takao, and W. Wiegrebe, *J. Nat. Prod.*, **51**, 172 (1988); *Ref. Zh. Khim.*, 15E122 (1988).
119. S. J. Danishefsky and C. Vogel, *J. Org. Chem.*, **51**, 3915 (1986).
120. L. S. Hegedus and D. B. Miller, Jr., *J. Org. Chem.*, **54**, 1241 (1989).
121. L. S. Hegedus, R. Imwinkelried, M. Alarid-Sargent, D. Dvorak, and Y. Satoh, *J. Am. Chem. Soc.*, **112**, 1109 (1990).
122. Z. Szakonyi, F. Fulop, G. Bernath, and P. Sohar, *Magy. Kern. Foly*, **104**, 17 (1998); *Chem. Abstr.*, **128**, 192622 (1998).
123. F. T. Smith, J. De Ruiter, and D. A. Carter,*J. Heterocycl. Chem.*, **26**, 1815 (1989).
124. F. T. Smith and R. V. Atigadda, *J. Heterocycl. Chem.*, **28**, 1813 (1991).
125. B. M. Goldschmidt, *J. Org. Chem.*, **27**, 4057 (1962).
126. K. G. Nazarenko, V. A. Kovtunenko, A. M. Demchenko, and M. V. Kornilov, *Ukr. Khim. Zh.*, **62**, 42 (1996).
127. J. J. Tufariello, *1,3-Dipolar Cycloaddition Chemistry*, (Ed. A. Padwa), Wiley, New York, (1984), Vol. 2, Ch. 9.
128. G. A. Kraus and K. Neuenschwander, *J. Org. Chem.*, **46**, 4791 (1981).
129. J. Barluenga, M. Tomas, V. Kouznetsov, A. Suarez-Sobrino, and E. Rubio, *J. Org. Chem.*, **61**, 2185 (1996).
130. R. F. Nutt and M. M. Joullie, *J. Am. Chem. Soc.*, **104**, 5852 (1982).
131. P. S. Callery, L. A. Geelhaar, M. S. B. Nayar, M. Stogniew, and K. G. Rao, *J. Neurochem.*, **38**, 1063 (1982); *Chem. Abstr.*, **97**, 85941 (1982).
132. M. Anbazhagan, A. N. Dixit, and S. Rajappa, *J. Chem. Soc., Perkin Trans. I*, 2421 (1997).