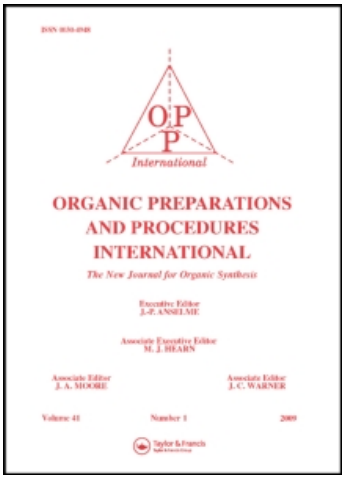


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE CHEMISTRY OF PYRAZOLIDINONES. A REVIEW

Rosa María Claramunt[a]; José Elguero[b]
[a] Departamento de Química Orgánica, Facultad de Ciencias, UNED, Ciudad Universitaria, Madrid, SPAIN [b] Instituto de Química Médica CSIC, Madrid, SPAIN

To cite this Article Claramunt, Rosa María and Elguero, José(1991) 'THE CHEMISTRY OF PYRAZOLIDINONES. A REVIEW', Organic Preparations and Procedures International, 23: 3, 273 — 320
To link to this Article: DOI: 10.1080/00304949109458208
URL: http://dx.doi.org/10.1080/00304949109458208

ORGANIC PREPARATIONS AND PROCEDURES INT., 23 (3), 273-320 (1991)

THE CHEMISTRY OF PYRAZOLIDINONES. A REVIEW

Rosa María Claramunt[†] and José Elguero*[††]

[†]Departamento de Química Orgánica
Facultad de Ciencias, UNED, Ciudad Universitaria
28040 Madrid, SPAIN

[††]Instituto de Química Médica
CSIC, Juan de la Cierva, 3
28006 Madrid, SPAIN

THE CHEMISTRY OF PYRAZOLIDINONES. A REVIEW

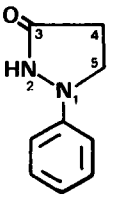
Rosa María Claramunt[†] and José Elguero*[††]

[†]Departamento de Química Orgánica
Facultad de Ciencias, UNED, Ciudad Universitaria
28040 Madrid, SPAIN

[††]Instituto de Química Médica
CSIC, Juan de la Cierva, 3
28006 Madrid, SPAIN

INTRODUCTION

Pyrazolidinones (described previously as pyrazolidones), like their most important derivative phenidone **1**, are an interesting although rather neglected class of heterocyclic compounds. Possibly their character-neither aromatic nor saturated (their hydroxy tautomer is a pyrazoline)-explains why the classical monographs on pyrazoles[1-5] contain so little information on these molecules.



1

A review by Dorn[6] constitutes the best available study on these compounds, particularly on the relationship between pyrazolidinones, aminopyrazolines, pyrazolinones (old pyrazolones) and aminopyrazoles. Two other important sources of information are a review on the chemistry of aminimides[7] which includes a thorough discussion of structures **4** and **5** and a book by Grashey[8] where the reactivity of "pyrazolidinium ylids" **5** is well studied. Finally there is a review on phenidone and some of its derivatives, their physico-chemical properties and applications.[9]

To illustrate the coverage of the pyrazolidinone field Table 1 represents statistics of the 149 references found in Chemical Abstracts between 1977 and 1989.

Table 1. Distribution of References Concerning Pyrazolidinones

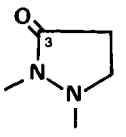
	Synth.	React.	Phys-chem. properties	Drugs	Photogr.	Others
Articles	14	19	19	12	7	--
Patents	10	--	--	16	42	10[a]

[a] Antioxidants, Electroplating, Inks, Dyes.

It is apparent that during this period the field of pyrazolidinones has expanded from purely academic interest to an area of industrial significance. Thus, some important results being quite recent, e. g. the Lilly work on synthetic antibacterial agents, an updating of the previous reviews seems useful.

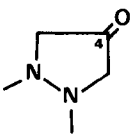
The main objective of this review is to survey the synthesis and reactivity of pyrazolidinones, both 3- and 4-pyrazolidinones, the latter ones being much less studied. Thiopyrazolidinones, iminopyrazolidines and the acetals derived from the 4-oxo group will be discussed only in relation to pyrazolidinones. The review will include a short summary of the physico-chemical properties of pyrazolidinones as well as some references concerning their applications.

Structures Included



Pyrazolidin-3-ones

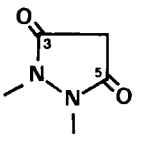
2



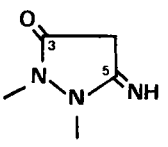
Pyrazolidin-4-ones

3

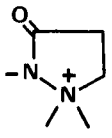
Structures Excluded



Pyrazolidin-3,5-diones

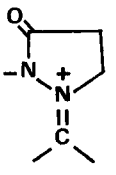


5-Imino-pyrazolidin-3-ones



Betaines

4



Azomethine Imines

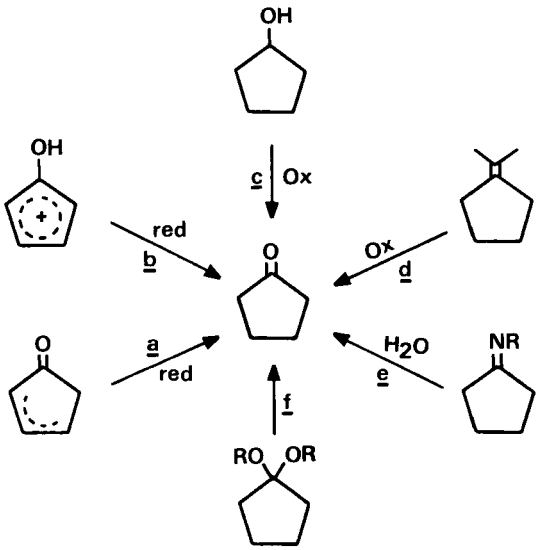
5

Dipolar compounds **4** and **5** have attracted much attention. Betaines **4** (also described in some publications as ylides) were known as 1,1-diR-pyrazolinium-3-oxides although their correct name is 1,1-diR-3-oxopyrazolidinium hydroxide inner salts. Still more confusion exists regarding compounds **5** which have been described as pyrazolidinium ylides, azomethineimides, 1-substituted ylidene pyrazolidin-3-one N,N-betaines and pyrazolidin-3-one azomethineimines, although it was always recognized that they are 1,3-dipoles -carbonyl stabilized azomethineimines-. The terms -ylide and -imide must not be used for these very polar compounds ($\mu \approx 8$ D for **5** and $\mu \approx 9$ D for the corresponding C=S derivative).

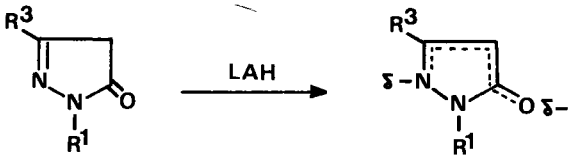
I. SYNTHESES

1. From Other Pyrazole Derivatives

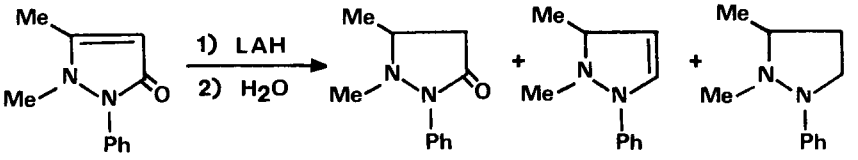
All the possibilities are represented in Scheme 1 where the nitrogen atoms have been omitted to cover both 3-and 4-pyrazolidinones. Although not a preparative method since it generally gives a mixture of products, the reduction of pyrazolinones (pathway a) has been much studied. The most frequently used reducing agent is lithium aluminium hydride (LAH) which only reduces 1,2-disubstituted Δ^3-pyrazolin-5-ones. Unsubstituted or 1-monosubstituted Δ^2-pyrazolin-5-ones are not reduced, due to the formation of a stabilized anion which prevents the reduction.[10]



Scheme 1

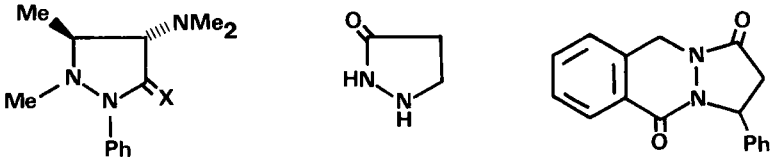


The reduction of antipyrine **6** (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) by means of LAH yields the 3-pyrazolidinone **7** in addition to compounds of further reduction, pyrazoline **8** and pyrazolidine **9**.[11] Investigation of the mechanism established that the hydrogen of the 3-position of **7** comes from LAH and that of the 4-position from the water of hydrolysis.[12]



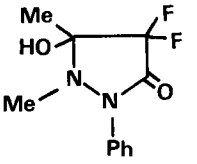
6 **7** **8** **9**

The reaction was generalized to thiopyrine,[13] pyramidon,[14] and thiopyramidon.[15] In the last two cases, the substituents of pyrazolidinone have the trans stereochemistry, as shown by ^1H NMR.



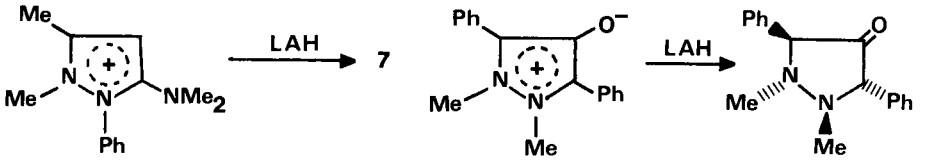
Catalytic hydrogenation has been successfully used to reduce pyrazolinones. Thus, pyrazolidinone itself **10** has been obtained from the parent pyrazolinone[16] and the tricyclic system **11** from the corresponding pyrazolinone,[17] showing that both Δ^2-and Δ^3-derivatives are reduced in these conditions. A related and rather curious reaction was reported by Barton et al.[18] Fluoroantipyrine reacts with CF_3OF to yield the

pyrazolidinone **12** which corresponds to a formal addition of HOF to the C_3-C_4 double bond.



12

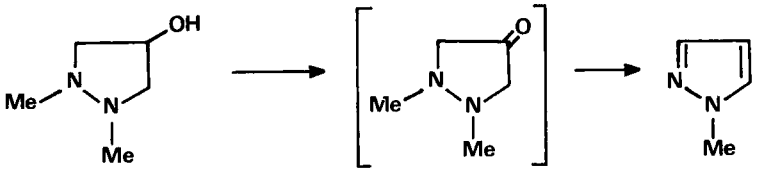
Of the same degree of oxidation as pyrazolinones are pyrazolium salts. Although the reduction of pyrazolium salts to pyrazolines is well-known,[5] the use of hydroxypyrazolium derivatives has been little explored. The only reported examples of pathway b are those shown in Scheme 2.



Scheme 2 **13**

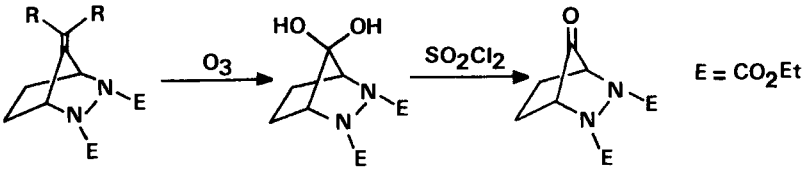
In both cases, the reaction should proceed through an intermediate Δ^3-pyrazoline which in turn is hydrolyzed to **7** or tautomerizes to **13**.[19]

There are no examples of oxidation of 1,2-disubstituted-3-hydroxypyrazolidines into pyrazolidin-3-ones, probably because in the absence of disubstitution at position 4 they dehydrate into Δ^3-pyrazolines. Oxidation of 1,2-dimethyl-4-hydroxypyrazolidine **14** by sodium dichromate seems to yield 1,2-dimethylpyrazolidin-4-one **15** (pathway c) although further oxidation is observed.[20]



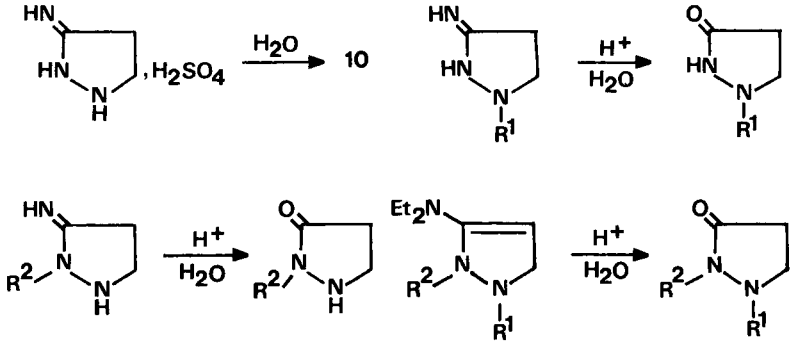
14 **15**

Oxidation of 4-methylenepyrazolidines (pathway d) leads to 4,4-dihydroxypyrazolidines[21] which can subsequently be dehydrated to pyrazolidin-4-ones (Scheme 3).[22]



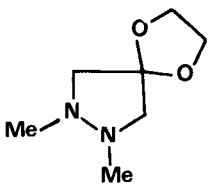
Scheme 3

The hydrolysis of 3-iminopyrazolidines (pathway e) to obtain pyrazolidin-3-ones is a very useful method which has been carefully studied (Scheme 4).[6]

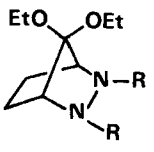


Scheme 4

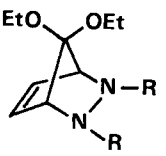
The hydrolysis of 3-iminopyrazolidine sulfate (readily available) is the best method to prepare pyrazolidinone **10**.[23,24] When there is a substituent at position 1 (R^1 = alkyl, aralkyl or aryl) or at position 2 (R^2 = aryl), acid hydrolysis leads to the corresponding pyrazolidinones.[25-29] The less common case[30] of 1,2-disubstituted derivatives, is identical. Finally, the hydrolysis of acetals (pathway f) failed in all reported attempts: acetals **16**[31] and **17**[21,32] are stable in acids.



16



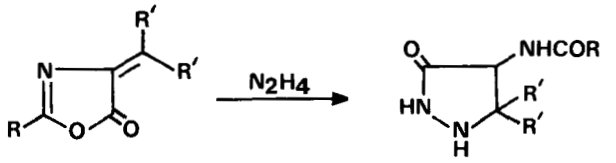
17a



17b

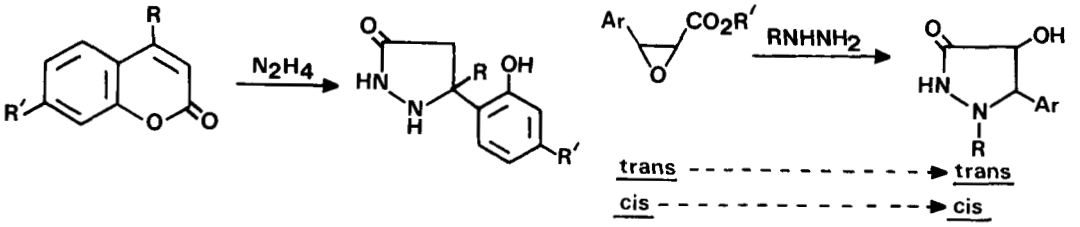
2. From Other Heterocycles

Amongst the very rich field of heterocyclic rearrangements, a few of them yield pyrazolidinones. Some require hydrazines as reagents and they proceed through steps very similar to section I.3 (below). The most interesting is Nálepa's use of unsaturated azlactones **18** to obtain 4-aminopyrazolidin-3-ones **19** (see also refs 36 and 225 for the reaction with pheylhydrazine).[33-35]



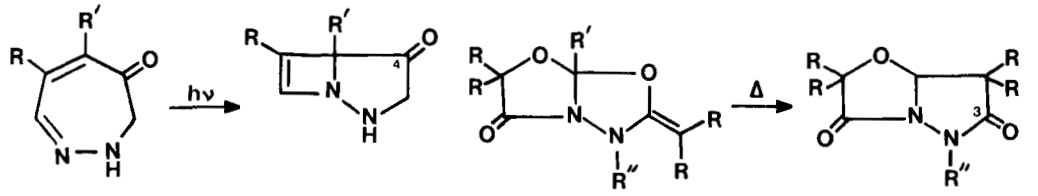
18 **19**

Related reactions using coumarins[37] or epoxyesters[38] are illustrated in Scheme 5.



Scheme 5

Rearrangement of diazepinones has been reported by Moore[39,40] and that of bicyclic oxazolidines by Market and Fahr[41] (Scheme 6).



Scheme 6

3. From α,β-Unsaturated Acid Derivatives and Hydrazines

The reaction between hydrazines and 1,3-difunctional compounds is the most common procedure to prepare "pyrazoles".[5] The simplicity of this method and the stability of the resulting products explain why "pyrazoles" (pyrazoles,

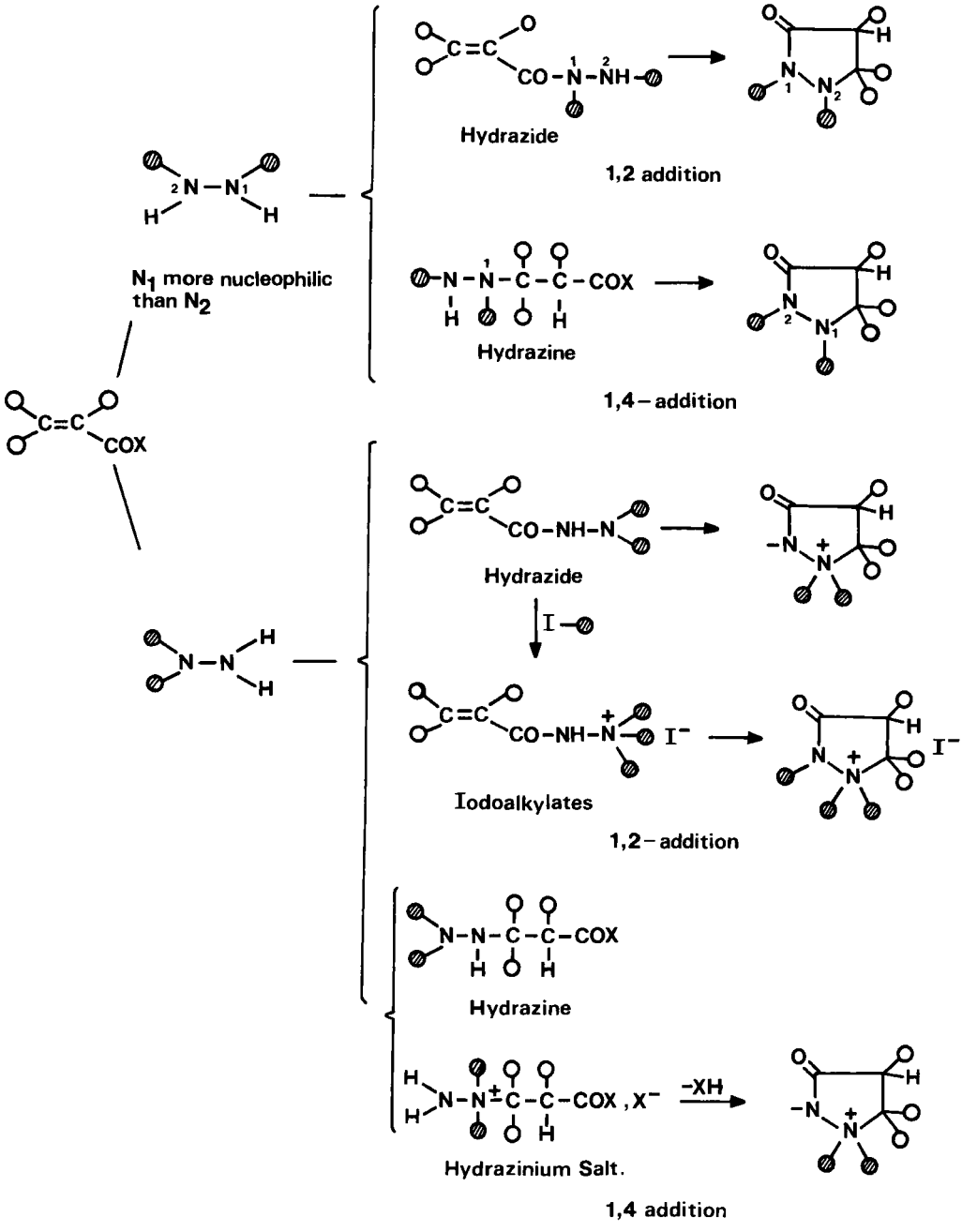
pyrazolinones, pyrazolines, pyrazolidinones and pyrazolidines) are so popular amongst chemists. We have already described synthesis of pyrazolidinones using hydrazines (section I.2 above) and we will encounter this reagent again (section I.4 below). The 1,3-difunctional compounds are generally the α, β-unsaturated acids or one of their derivatives (mainly esters, but also acyl chlorides, anhydrides or even amides). Although there is an abundant bibliography on this reaction, there are few mechanistic studies. The formation of pyrazolidin-3-ones from mono- or 1,2-disubstituted hydrazines is discussed in two references.[42,43] Baldwin used the example of the reaction between cinnamic acid and hydrazine to illustrate his rules.[44] The synthesis of betaines **4** from 1,1-disubstituted hydrazines was developed by Sokolova.[45,46].

It is difficult to systematize this reaction since it depends on so many factors:

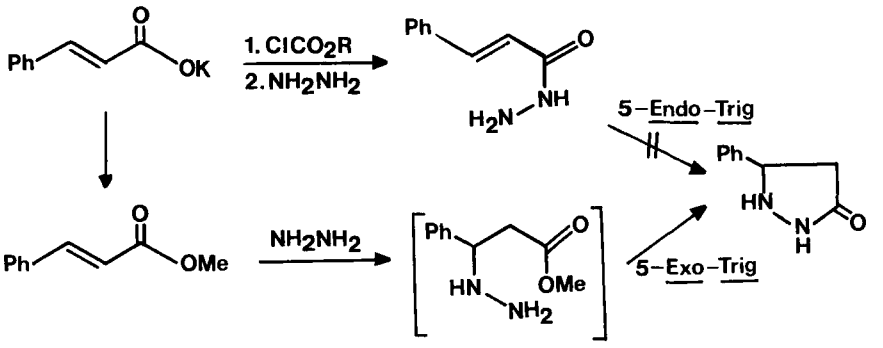
- the substituents on the carbon atoms
- the nature of the COX group (X = OH, OR, Cl, NH_2, etc.)
- the nature of the hydrazine: hydrazine itself, 1,2 or 1,1-disubstituted hydrazines
- the substituents on the nitrogen atoms (alkyl, aralkyl, aryl, acyl, etc.)
- the experimental conditions and, especially, the solvent polarity and the presence (or absence) of a base.

Scheme 7 represents an effort to present the available experimental evidence schematically, considering only the type of hydrazine. Hydrazine itself reacts with α,β-unsaturated esters to yield 4-R,[24] 5-R,[24,47,48] 4,5-R_2,[49] and 5,5-R_2 pyrazolidinones,[24] depending on the substituents on the double bond of the α,β-unsaturated ester. Unsubstituted pyrazolidinone **10** cannot be obtained from alkyl acrylates and hydrazine. As already pointed out, this was the reaction selected by Baldwin[44] to illustrate his rules (Scheme 8).

The forbidden 5-Endo-Trigonal cyclization of the hydrazide does not occur even at 200°C, whereas the 1,4-adduct (the hydrazine) cannot be isolated, so facile the allowed 5-Exo-Trigonal cyclization. As was pointed out by Anselme,[50]



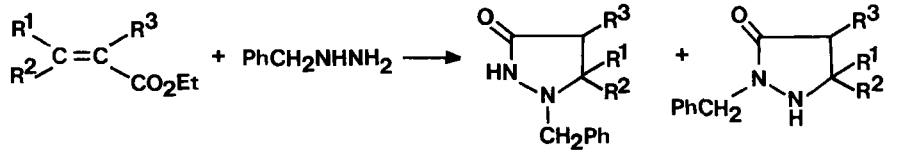
Scheme 7



Scheme 8

factors other than geometric and stereochemical considerations play a role in determining whether cyclization will occur readily, especially when heteroatoms are involved. Even using esters, formation of hydrazides is observed.[49] Finally, the reaction of hydrazine with cyanoacrylates does not yield 4-cyanopyrazolidin-3-ones but cyanoacetic acid arylidene hydrazides ($NCCH_2CONHN=CHAr$) by a retro-Knoevenagel reaction.[51]

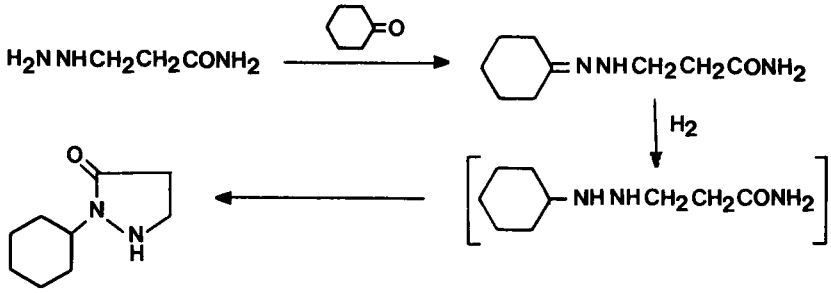
Methylhydrazine always yields 1-methylpyrazolidin-3-ones when reacted with acids[52,53] or esters.[54] Assuming that the N-methyl nitrogen is the most nucleophilic one (it is the nitrogen acylated by esters)[55] the final product corresponds to a 1,4-addition followed by ring closure of the hydrazine, in agreement with Baldwin's rules. In the case of benzylhydrazine, in which the difference of nucleophilicity between nitrogens should be small, both isomers are obtained. Scheme 9 summarizes the results obtained with different esters.[56]



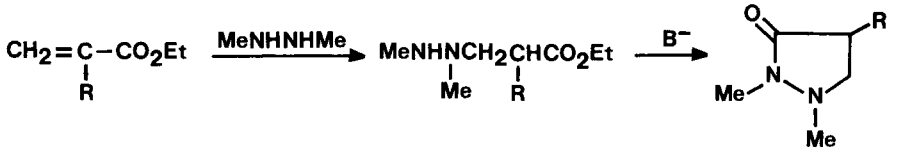
R^1	R^2	R^3	20	21
H	H	H	67%	33%
Me	H	H	40%	60%
Me	Me	H	---	100%
H	H	Me	44%	56%

Scheme 9

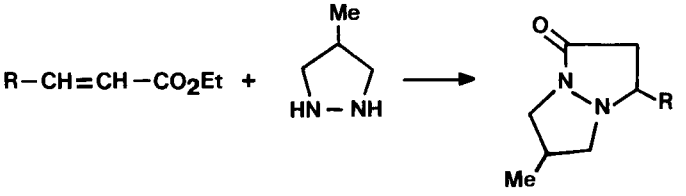
The results of Scheme 9 are still consistent with a mechanism which proceeds through two intermediate hydrazines, $PhCH_2NHNHC(R^1R^2)CH(R^3)CO_2Et$ and $PhCH_2N(NH_2)C(R^1R^2)CH(R^3)CO_2Et$, which cyclize into **21** and **20**, respectively. Steric effects between R^1, R^2 and the benzyl group explain the different ratios. The following synthesis of pyrazolidinones which probably involves an intermediate hydrazine is related to these monoalkyl and monoaralkylhydrazines.[23,57]



The reaction of 1,2-dimethylhydrazine with acrylic esters $CH_2=CRCO_2Et$ (R = H, Me, Ph) was studied by Kornet,[58,59] who had previously described the synthesis of 1,2-disubstituted pyrazolidinones from 1,2-diethylhydrazine. Although there is no problem of orientation, this case is interesting since the intermediate hydrazine was isolated.

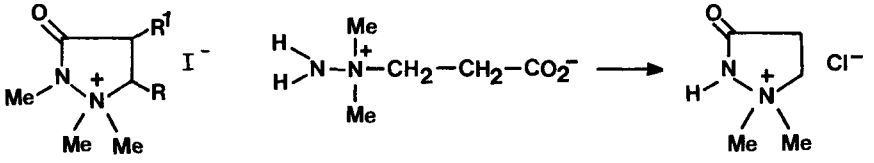


Kornet[58] extended the reaction of other 1,2-dialkylhydrazines (Et,Pr,i-Pr), which also works with 1,2-dibenzylhydrazine.[56] In the case of ethyl acrylate (R = H) the hydrazine resulting from the addition of **both** nitrogens $EtO_2CCH_2CH_2NR'NR'CH_2CH_2CO_2Et$ is formed.[58] Cyclic hydrazines behave like 1,2-dialkylhydrazines.[48]



The reaction between 1,1-dimethylhydrazine and α,β-unsaturated acid derivatives was studied in a remarkable series of papers published between 1964 and 1970 by Sokolova and coworkers.[45,46] The most important result is that the pyrazolidinone formed is always 1,1-disubstituted **4** and never 2,2-disubstituted. Since 1,1-dimethylhydrazine is acylated on the NH_2 nitrogen in spite of the NMe_2 nitrogen being more basic (a consequence of the instability of the $H_2N\text{-}N(Me)_2CO_2R$ salt)[55,60] the only possibilities are those illustrated in Scheme 7.

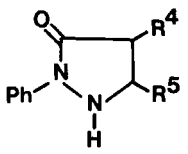
In most cases,[61-63] the betaine **4** was isolated, but in some cases the hydrazine, e.g. $Me_2NNHCH_2CH_2CO_2Me$,[64] is formed which cannot be cyclized. In other cases, the hydrazide $R\text{-}CH{=}C(R')CONHNMe_2$ is isolated,[65,66] but most importantly, it is possible to transform the hydrazide into the betaine **4** in spite of the fact that such transformation is a forbidden 5-Endo-Trigonal cyclization.[46,67] Only when there is a bulky substituent on the nitrogen and on the β-olefinic carbon, cyclization cannot occur.[68] The transformation hydrazine to betaine **4** is reversible (section II.3). Two other results worth noting and related to Scheme 7 involve the rearrangement of iodoalkylates of hydrazides into 1,1,2,-trisubstituted pyrazolidin-3-one iodides **22**.[69] Recently, the reactivity of 1,1-dimethylhydrazine towards acrylic acid was reexamined.[70] The authors isolated the zwitterion of hydrazinopropionate **23**, which by treatment with acetyl chloride yields the salt **24**. Thus both mechanisms of Scheme 7 are operative in the case of 1,1-dialkylhydrazines.



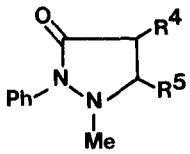
22 **23** **24**

The use of phenylhydrazine in the synthesis of pyrazolidinones was extensively studied in two publications.[42,43] In neutral medium, phenylhydrazine reacts at the more nucleophilic NH_2 group. The 1,2-addition leads to hydrazides $RR'C{=}C(R'')CONHNHPh$ and the reaction stops

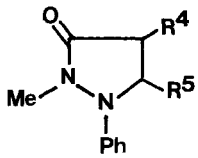
(phenylhydrazine is acylated exclusively on the terminal NH_2).[55] 1,4-Addition leads to hydrazines, which were not isolated, and subsequently to 2-phenylpyrazolidin-3-ones **25**. However, the most frequent reaction of phenylhydrazine is the formation of 1-phenylpyrazolidin-3-ones, such as phenidone **1**, by reaction with α,β-unsaturated esters in basic medium.[42,71,72] It has been postulated[25,42] that in this last case the reaction corresponds to a 1,4-addition by the N-phenyl nitrogen of the $Ph\text{-}N\text{-}NH_2$ anion. The reaction is general for aryl and heteroarylhydrazines.



25



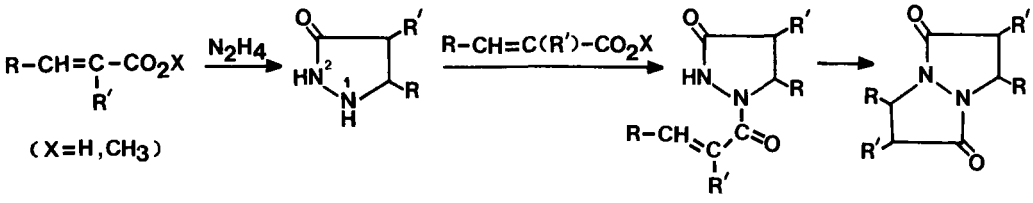
26



27

1-Phenyl-2-methylhydrazine behaves like phenylhydrazine;[42,43] in neutral medium, it reacts by the NH-Me nitrogen to yield 1-methyl-2-phenylpyrazolidin-3-ones **26** and hydrazides and in basic medium where Ph-N-NH-Me is formed, the isomeric 1-phenyl-2-methylpyrazolidin-3-ones **27** are formed; 1-phenyl-1-methylhydrazine yields only hydrazides due to steric hindrance.

Acylhydrazines, hydrazides, react in some cases with α,β-unsaturated acid derivatives to yield pyrazolidinones. For instance, hydrazine can react twice to form derivatives of pyrazolo[1,2-a]pyrazole (Scheme 10)[48] (see also ref 73).



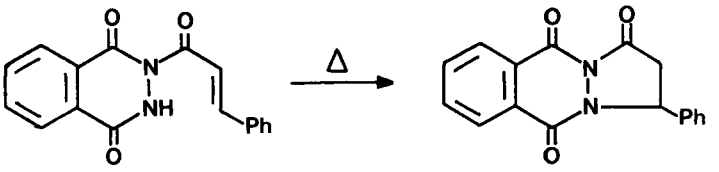
(X=H,CH_3)

28

Scheme 10

It can be observed that the most nucleophilic nitrogen, N_1 (section II.2.a), forms the hydrazide **28** which subsequently cyclizes. This 5-Exo-Trigonal cyclization was also observed

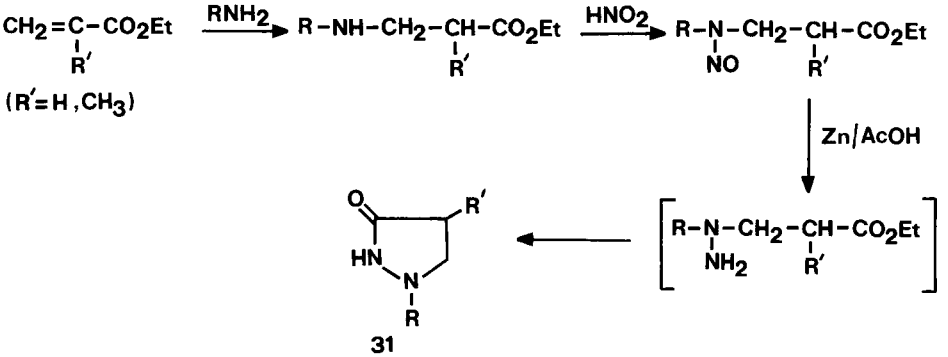
by Anselme[50] in the case of N-cinnamoylphthalhydrazide **29** which yields the tricyclic product **30**.



29 **30**

In summary, the formation of pyrazolidinones from hydrazines and α,β-unsaturated acids and their derivatives proceeds generally through a Michael addition followed by a 5-Exo-Trigonal ring closure. However, in some cases (1,1-dialkylhydrazines, acylhydrazines) the reaction goes through the hydrazide and forbidden 5-Endo-Trigonal pathway.

The synthesis of pyrazolidinones by reduction of N-nitrosamines is related to the preceding method, since it starts also from α,β-unsaturated esters and proceeds through a similar hydrazine (Scheme 11).



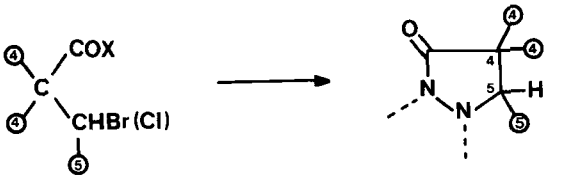
Scheme 11

A large variety of 1-R-pyrazolidin-3-ones **31** were prepared by this method with R = Me, cyclohexyl, benzyl, phenethyl and phenyl amongst other substituents.[25-27] Phenidone (R=Ph, R′= H) is conveniently prepared by this method.

4. From β-Haloacyl Halides (Pyrazolidin-3-ones) and 1,3-Dibromopropanones (Pyrazolidin-4-ones)

The second most used method to synthesize pyrazolidin-3-ones is by the reaction of β-haloacyl halides (in some cases β-halopropionic acids or esters) with hydrazines. The reaction proceeds through similar intermediates, hydrazines

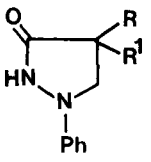
and hydrazides, as in the previous method (Scheme 7), but in this case it is possible to obtain 4,4-disubstituted pyrazolidinones, whereas previously there was always at least one hydrogen in that position.



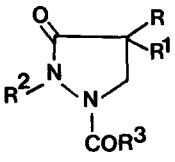
Scheme 12

Although the method could also serve to provide 5,5,-disubstituted derivatives (Scheme 12), in practice the method has been used to prepare C-unsubstituted or 4,4-disubstituted pyrazolidinones; only one reference[74] reports the synthesis of a 5-methyl derivative.

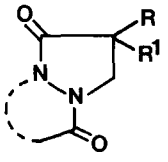
Bellasio, Testa and coworkers[16,75-78] have used this reaction (X = Cl) extensively to prepare 4,4-disubstituted pyrazolidinones. Concerning the orientation of the reaction, the most nucleophilic nitrogen, i.e. the one removed from the phenyl in phenylhydrazine and from the acyl in hydrazides (see section I.3), reacts with the acyl chloride to yield a hydrazide, which has been isolated in some cases. The pyrazolidinone results from the reaction of the less nucleophilic nitrogen with the CH_2Br or CH_2Cl group. In this way, compounds **32, 33** and **34** have been prepared.[75,77,16,76]



32

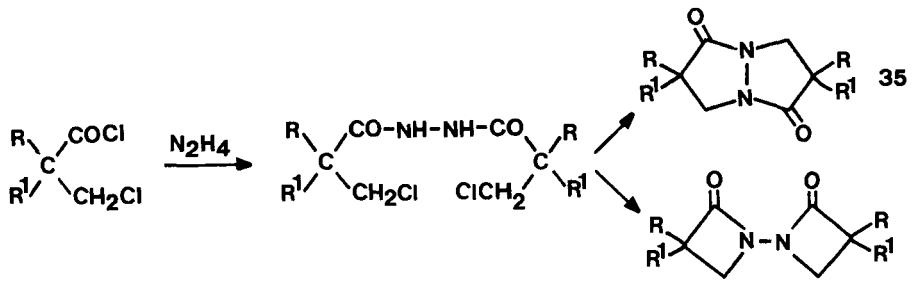


33

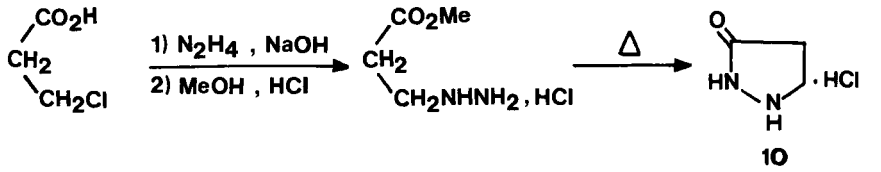


34

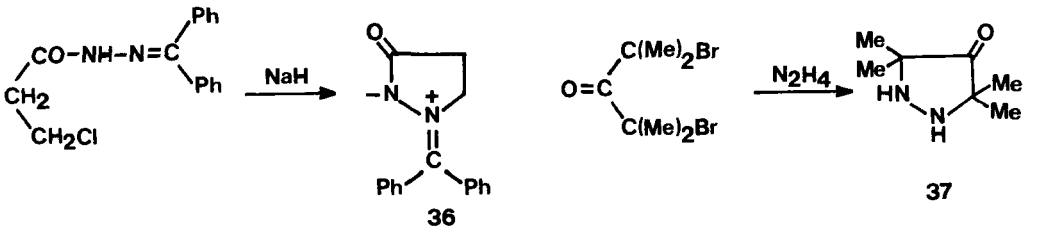
The reaction of hydrazine with β-chloropropionyl chloride yields, depending on the cyclization orientation, pyrazolo[1,2-a]pyrazoles **35** (compare with Scheme 10) or N,N'-bisazetidin-2-ones.[78]



This method has been successfully used with hydrazobenzene (1,2-diphenylpyrazolidin-3-ones),[74,79] with heterocyclic hydrazines and with pyrazolidinones.[73] Esters (X = OEt) and acids (X = OH, Scheme 12) can also be used. Thus, pyrazolidines were obtained by the reaction of hydrazine with β-bromopropionic esters[75] or with β-chloropropionic acid.[80] In this last case, an intermediate hydrazine was isolated.



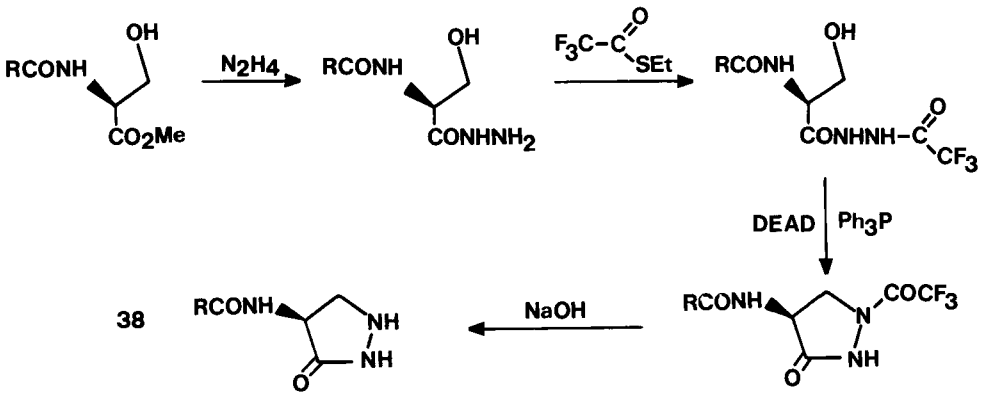
This method provided also an access to betaines **4** and to azomethineimines **5**. The betaines **4** are simply obtained using 1,1-disubstituted hydrazines (1,1-dimethyl, 1,1-diethyl and 1-aminopiperidine).[70] The cyclization of β-chloropropionylhydrazone of propiophenone yields **36** using sodium hydride in benzene.[81]



The much less studied pyrazolidin-4-ones **37** can be prepared by reacting 1,3-dibromopropanones and hydrazine.[82]

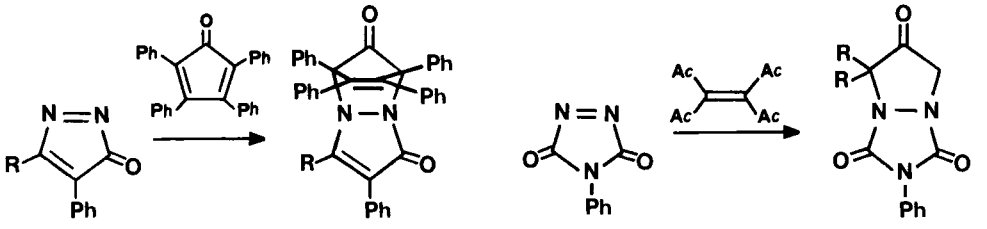
5. Miscellaneous

It is worth reporting here the first synthesis of a chiral pyrazolidin-3-one, **38**. Although it uses a β-hydroxyester and, for this reason, is related to the preceding section, it deserves special mention[83] (see also ref. 223).



Compound **38** is a key intermediate in the synthesis by the Lilly group of bicyclic pyrazolidinone antibacterial agents (section IV.2).

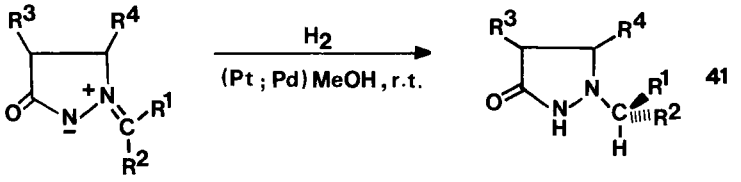
The reaction of azodicarbonyl compounds with some enones yields pyrazolidin-4-ones. Compounds **39**[84] and **40**[85] were prepared in this fashion. It is not known if the reaction is general and could be used to synthesize simpler compounds.



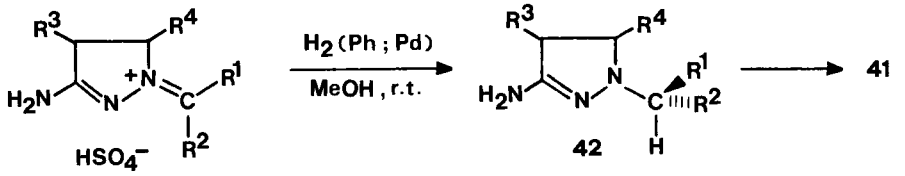
This section dealing with the synthesis of pyrazolidinones will conclude with the best and most efficient methods to obtain pyrazolidin-3-ones substituted at position 1 with an sp^3 carbon:

i) the hydrogenation of azomethinimines (section II.4.b) with or without their isolation. Compounds **41** may be obtained from reduction of a mixture of equimolar amounts of an N- of

unsubstituted pyrazolidin-3-one and a carbonyl compound (aldehydes including formaldehyde, ketones, ketocarbonic acids and monosaccharides but not ArCOR).

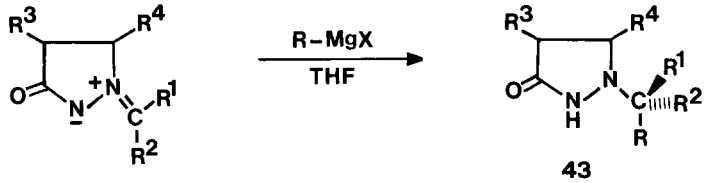


ii) the hydrogenation of the corresponding imines and subsequent hydrolysis of the amino derivatives **42** (section I.1).



In this case the reaction also works with ArCOR.

iii) the Grignard reaction of azomethineimines (section II.4.b) yields compounds **43**.



(R = alkyl, aryl or aralkyl)

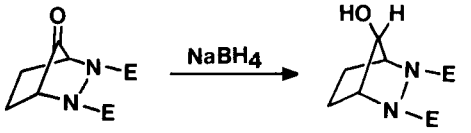
II. REACTIVITY

1. Transformation into Other Pyrazole Derivatives

a. Reduction

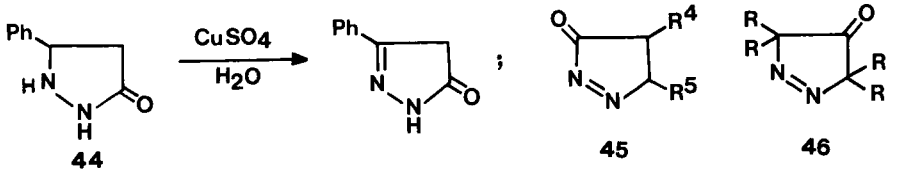
Reduction of pyrazolidin-3-ones has been reported by several authors. The most common result is the formation of pyrazolidines (C=O → CH_2). Thus, N-unsubstituted,[48] N-monosubstituted,[53,86] and N,N′-disubstituted pyrazolidin-3-ones[14,76,78,87,88] yield the corresponding pyrazolidines on treatment with lithium aluminium hydride. The same reagent transforms pyrazolidin-3-thiones into pyrazolidines.[13,15] In some cases, the reduction stops at the 3-hydroxypyrazolidine level which, in some cases, can be isolated[89,90] and others dehydrated to a Δ^2 or a Δ^3-pyrazoline.[11,14] A detailed discussion of the mechanism of reduction of pyrazolidinones

and pyrazolidones by LAH is to be found in references 12 and 90. Grignard reagents converted N,N'-disubstituted pyrazolidin-3-ones into 3-R Δ^3-pyrazolines.[91] Sodium borohydride reduced pyrazolidin-4-ones into 4-hydroxypyrazolidines.[22,92]



b. Oxidation

Oxidation of 1-substituted pyrazolidin-3-ones into 1-substituted-3-hydroxypyrazoles -which is at the origin of the properties of phenidone **1**- is a common and much studied reaction. The electrochemical oxidation of phenidone and its derivatives has been described several times;[93-99] a series of papers by Bellamy et al.[100-102] established the mechanism of the oxidation. When position 4 or 5 are disubstituted, thus preventing the oxidation to pyrazoles, dimers are usually formed. Chemical oxidants include $CuSO_4$,[47] MnO_2,[72] $K_3Fe(CN)_6$,[103-105] HgO,[106] $FeCl_3$,[107] Br_2, [108,109] and I_2.[108,110] In each instance, the experiments were carried out with 1-substituted pyrazolidin-3-ones, the only exception was compound **44** which, on oxidation, gave a pyrazolinone.[47]



44 **45** **46**

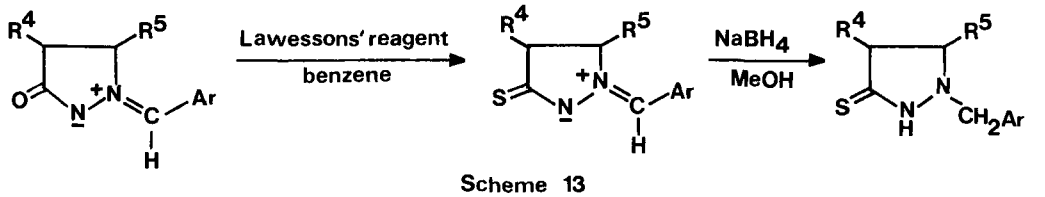
When the substituent is an alkyl group, in some cases the oxidation leads to an azomethineimine ($N\text{-}CHRR'\rightarrow\overset{+}{N}=CRR'$).[106,110] The use of bromine as the oxidizing agent gave brominated pyrazoles as side-products,[108,110] and if the formation of aromatic pyrazoles is prevented by disubstitution at position 4, 5,5'-linked dimers are obtained.[103] Oxidation of 2-substituted pyrazolidin-3-ones yields pyrazolinones.[23,111]

In some cases, oxidation of N,N'-unsubstituted pyrazolidinones takes place between both nitrogen atoms. In the case of pyrazolidin-3-ones, the intermediate Δ^1-pyrazolin-3-one **45** was not isolable (neither using yellow mercuric

oxide[112] nor lead tetraacetate[84]) and the reaction yielded olefins by loss of nitrogen and carbon monoxide. Manganese dioxide converted pyrazolidin-4-ones, such as **37**, into Δ^1-pyrazolin-4-ones **46**.[82]

c. Other Reactions of the Carbonyl Group

The carbonyl group of pyrazolidin-4-ones is very reactive. It adds methanol and water very rapidly.[22] The corresponding readily available acetals are completely inert toward hydrolysis (section I.1, formulae **16** and **17**).[21,22,31,32] Phosphorus pentasulfide (P_4S_{10}) transforms pyrazolidin-3-ones into the corresponding thiones.[113] Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] has been used[114] in the sequence of reactions depicted in Scheme 13.

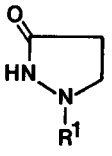


Scheme 13

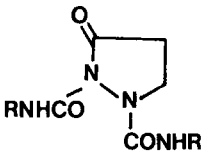
2. Reactions at the Ring

a. At Nitrogen

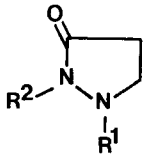
When both nitrogen atoms are free to react with electrophiles, reaction always occurs at N_1 first in agreement with the amidic character of N_2 and consistent with theoretical calculations (section III.1). We will consider first the cases where the reaction yields a neutral molecule. N,N'-Unsubstituted pyrazolidin-3-ones such as pyrazolidinone **10**, reacts with a wide variety of electrophiles to yield compounds such as **47** where R^1 is NO,[47] tosyl,[23] acetyl,[111] benzoyl,[111,115,116] CONHPh,[116] C(NH)OR,[116] $CSNH_2$,[117] 2-thiazolyl,[118] CH_2CO_2R[119] and $CH_2CH(CN)PO_3R$ (Michael addition).[120] Addition to β-nitrostyrenes at room temperature yields the kinetically controled N_1 substituted product (R^1 = $CHRCH_2NO_2$). These products rearrange on heating, via a retro-Michael reaction, to the thermodynamically stable N_2 adducts (**49**, R^1=H, R^2=$CHRCH_2$ NO_2).[114]



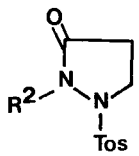
47



48

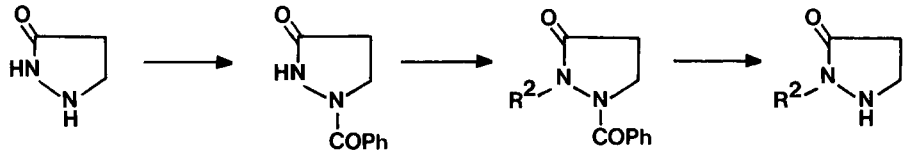


49



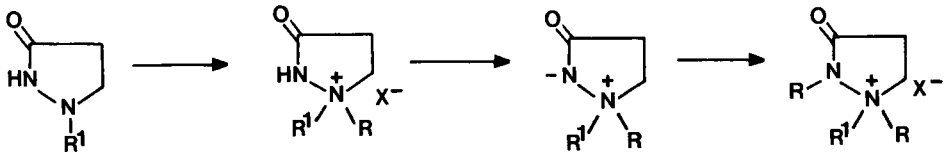
50

In some cases, two substituents are introduced simultaneously, as in **48**.[121] When N_1 is substituted, the reaction takes place on N_2 to yield **49**, where R^2 can be an alkyl group,[23,111,115] a CH_2NR_2 residue (Mannich reaction),[108,122] a tosyl group[123] or a CHR_2 substituent (Michael addition).[54] Compounds such as **50**, obtained in two steps (first tosylation, then alkylation), on treatment with sodium hydroxyde yielded pyrazolinones.[23,107,111] This is an alternate procedure to oxidation methods previously described (section II.1.b). The best method to prepare 2-alkylpyrazolidin-3-ones uses the sequence described in Scheme 14.[23]



Scheme 14

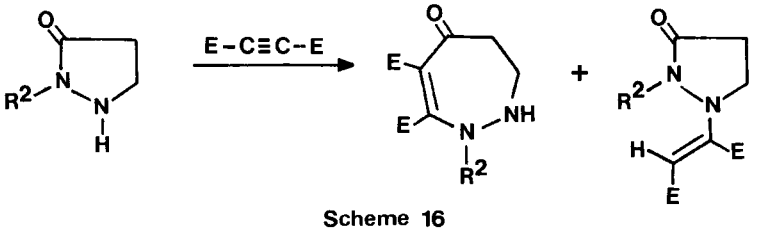
In other cases, salts were obtained, but the reactivity is the same. For instance, quaternary salts **51** have been prepared which on treatment with base yield the betaines **4**.[61,124] Betaines can be alkylated on N_2 (Scheme 15).[61] Compounds **52** can also be obtained by quaternization on N_1 of 1,2-disubstituted pyrazolidin-3-ones.[42] IR and ^1H NMR studies have been useful in determining that protonation of the pyrazolidinones occurred on N_1.[42,125]



51 4 52

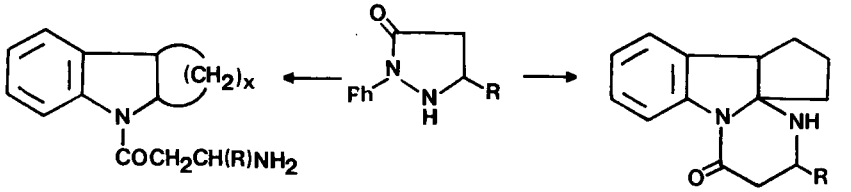
Scheme 15

Another very characteristic reaction of N,N'-unsubstituted pyrazolidin-3-ones is the formation of azomethineimines **5** by reaction with carbonyl compounds. Discovered by Godtfredsen and Vangedal,[47] this reaction has been studied intensively.[37,80,110,126-128] and constitutes an important step in the Lilly synthesis of antibacterial agents from **38** (sections II.5 and IV.2).[129-131] Ege et al.[132-134] studied the reaction of 2-substituted pyrazolidin-3-ones with dimethyl acetylenedicarboxylate (Scheme 16). Depending on the nature of R^2, 1,2-diazepin-5-ones or Michael adducts were obtained.



Scheme 16

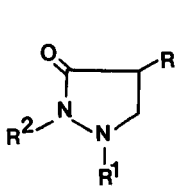
2-Phenylpyrazolidin-3-ones behave like cyclic phenylhydrazines in the Fisher indole synthesis;[135] compounds **53** and **54** have been prepared in this fashion.



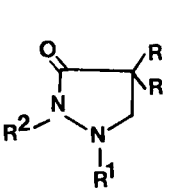
53 **54**

b. At Carbon

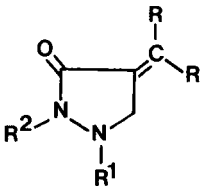
4,5-Diphenylpyrazolidin-3-one yielded 3,4-diphenyl-4-chloropyrazolinone upon treatment with chlorine,[136] but it is not know if the chlorination occurred before or after the oxidation step (section II.1.b). In a series of papers, Kornet et al.[59,88,91] explored the reactivity of the carbon atom at position 4 of 1,2-disubstituted pyrazolidin-3-ones. In basic medium, they obtained mono and dialkylated derivatives **55** and **56**, ethylidene derivatives **57** via aldol condensation and 4-acyl compounds **58** by reaction with esters.



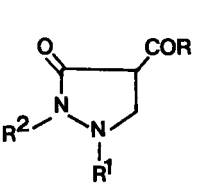
55



56

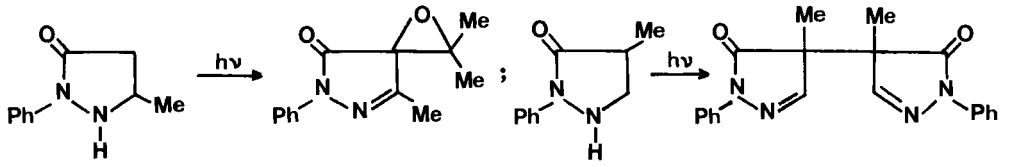


57



58

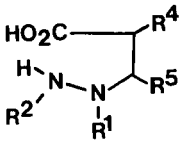
2-Phenyl-5-methylpyrazolidin-3-one gives a novel spiro-epoxide **59** on irradiation in acetone; the isomeric 2-phenyl-4-methylpyrazolidin-3-one undergoes oxidative dimerization to **60**.[137]



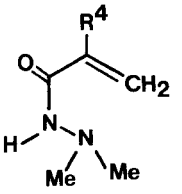
59 60

3. Ring Opening and Transformations

Ring opening between N_2 and C_3 of pyrazolidin-3-ones is the reverse reaction of synthesis from α,β-unsaturated acids and hydrazines (section I,3. Scheme 7). Thus, alkaline hydrolysis of 1-substituted[138] or 2-substituted derivatives[111] leads to β-hydrazinoacids **61** (R^1 or R^2 = H). Analogously, betaines **4** yield acrylic hydrazides **62** on heating by retro Michael addition (N_1-C_5 bond rupture)[52,67,139].

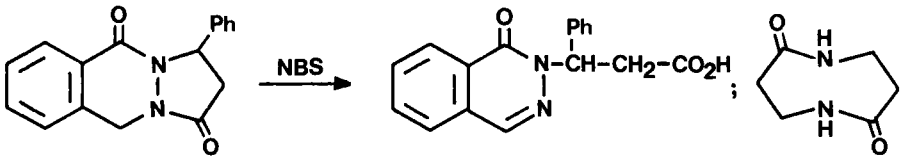


61



62

Like in β-lactam antibiotics, the alkaline ring opening of pyrazolidin-3-ones may be related to their antibacterial activity (section IV.2).[140] Another example of N_2-C_3 bond breaking is observed when compound **11** is treated with NBS.[17]



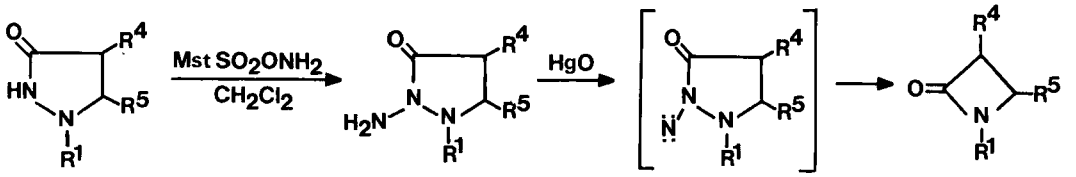
11 63 64

The only reported case of bond rupture between N_1 and N_2 is the synthesis of 1,5-diazacyclooctanes **64** by sodium/liquid ammonia reduction of compounds **35**.[78]

An important aspect of the reactivity of pyrazolidin-3-ones is their ring contraction to β-lactams. Discovered by Ege,[141] the photochemical rearrangement of 2-phenyl pyrazolidinones produced the first examples of an N-aminoazetidin-2-one **65**.[142]

65 66

A series of papers by Johnson and Hatch extended considerably the reaction: to other substituents at position 2, especially acyl groups,[143-145] to 1-substituted pyrazolidin-3-ones[146] or, even to unsubstituted derivatives (formation of the N-amino derivative **66**).[146] All these articles concern photochemical reactions, but in their last publication,[147] they use a chemical procedure (Scheme 17).



Scheme 17

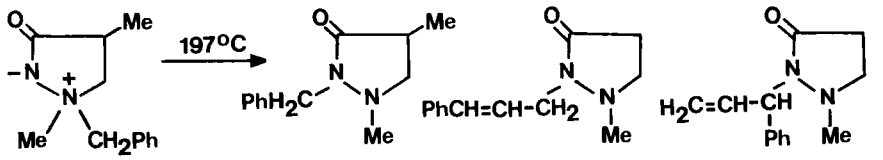
4. Reactions of Substituents

a. Pyrazolidinones

i) On Nitrogen

The most interesting reaction of substituents on nitrogen is the so-called Wawzonek rearrangement of betaines.

Discovered by Wadsworth[52] with **67**, it was extended subsequently to other N-benzyl[148] and N-allyl (or cinnamyl) substituents.[149,150]



67 **68** **69** **70**

The formation of products of [1,2] and [3,2] rearrangement, **69** and **70** respectively, has been observed with cinnamyl betaines.[149] The [3,2] derivative is formed by an intramolecular mechanism, whereas the mechanism of formation of the [1,2] product, **68**, is entirely radical in nature.[148] Ring closure involving both N-substituents leads to bicyclic [5,5] and [5,6] hydrazines.[222]

ii) On Oxygen

In addition to N-alkylation (section II.2.a) and C-alkylation (section II.2.b) is O-alkylation of pyrazolidin-3-ones. Several groups have been introduced: tetra-O-acetyl-α-D-glucopyranosyl,[151] benzyl,[152] CH_2CO_2R and similar groups,[71] and propargyl.[153] In some cases, the reaction is regio-selective,[151,152] in others the N- and the O-substituted products are formed simultaneously.[71,153]

b. Azomethineimines

i) Cleavage of the $\overset{+}{N}{=}C$ Bond

The inverse reaction of formation of azomethineimines (section II.2.a) has been observed; hydrolysis of azomethineimines yields the pyrazolidinone and the carbonyl compound.[121]

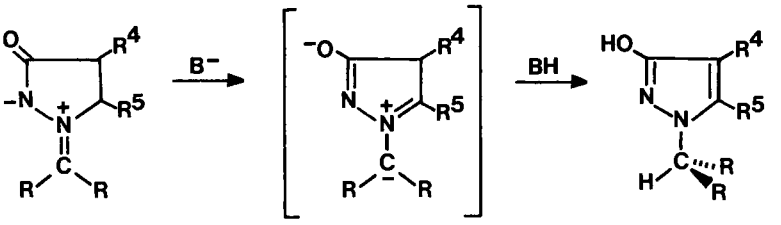
ii) Reduction of the $\overset{+}{N}{=}C$ Bond

As was summarized earlier (section I.5), one of the best methods for the preparation of 1-alkyl (or aralkyl) pyrazolidin-3-ones **41** is the reduction of azomethineimines. A series of papers has been devoted to this reduction. Most examples concern catalytic hydrogenation over platinum or palladium,[26,27,126,127,154] although sodium borohydride is equally efficient[81] (see also Scheme 13). Grignard reagents introduce

an alkyl, benzyl or aryl residue on the N-C carbon (section I.5).[155]

iii) Dorn Rearrangement

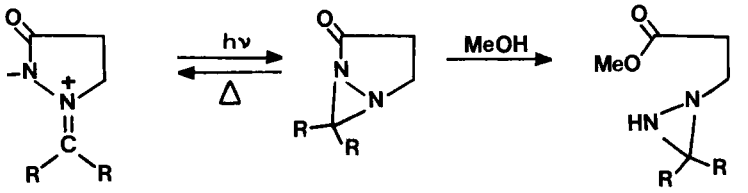
In basic medium, azomethineimines rearrange to 3-hydroxypyrazoles (Dorn rearrangement).[81,110]



The mechanism has been investigated using deuterium labelling experiments.[156] The method allows the preparation of 3-hydroxypyrazoles (pyrazolin-3-ones) in a one-pot procedure from substituted α,β-unsaturated esters.

iv) Photochemistry

One last aspect of the chemistry of azomethineimines concerns their photochemical behaviour. The reaction, first studied by Schulz and West[158-161] and then by Tomaschewski and Geissler,[162-166] can be summarized as shown in Scheme 18.



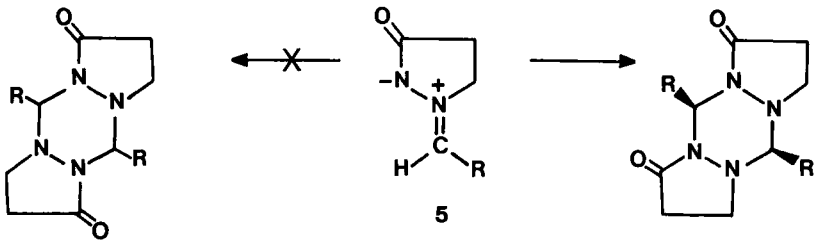
Scheme 18

In some cases, the azomethineimine dimerizes (section II.5)[161] and if the irradiation is carried out in the presence of oxygen and a sensitizer, fragmentation occurs (photooxidation).[159]

5. Dipolar Cycloadditions of Azomethineimines

a. Dimerization

The dimerization of azomethineimines **5**[154] and the proof that the dimer is "mirror symmetric" **71a** and not centrosymmetric **71b** has shed light on the general problem of the dimerization of 1,3-dipoles.[167,168] A three step mechanism, called ADD-ADD-EL (addition-addition-elimination), has been invoked to explain this unusual result.[168]

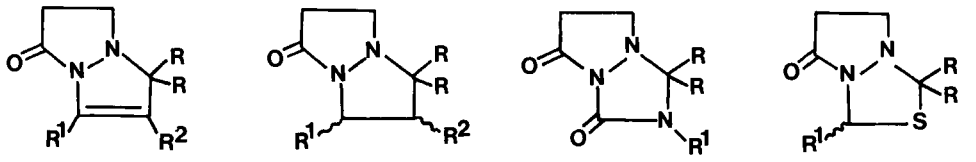


71b R = Ph, C_6H_4-OMe-4 71a

5

b. Reaction with CX Double and Triple Bonds

The 1,3-dipolar character of azomethinimines is exemplified in their reactions with double and triple bonds, to yield azapentalene derivatives. Discovered in Germany,[106,121,169-171] Jungheim and his group made use of this chemistry in the synthesis of antibacterial agents (section IV.2).[129,130,131,172-174]



72 73 74 75

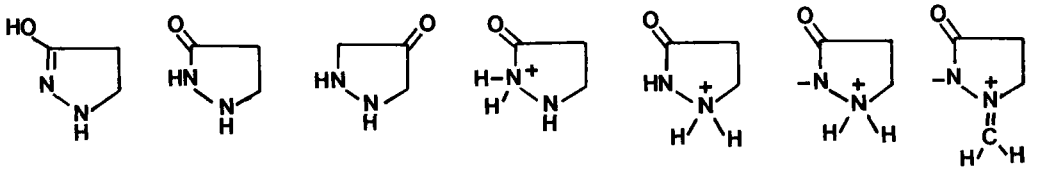
Conjugated triple bonds (generally R^1 = R^2 = ester) lead to derivatives of pyrazolo[1,2-a]pyrazole **72**,[106,129,130,172-174] whereas double bonds produce the corresponding dihydro derivatives **73**[169,170] (for the mechanism and stereochemistry see ref 171). Compounds **74** and **75** were prepared from isocyanates[121] and N-(alkoxycarbonylmethylthio) phthalimides,[131] respectively. When this review was nearly completed, the reaction of azomethine-imines with benzyl bromide was described.[224] The main products were a head-to-head dimer similar to **71a**, a ring-opened hydrazone and the 1-benzyl and 1,2-dibenzylpyrazolidinones.

III. PHYSICOCHEMICAL PROPERTIES AND STRUCTURE

1. Theoretical Methods

Only two papers deal specifically with theoretical calculations on pyrazolidinones **2-5**, one of which had its origin in the preparation of this review. The first dealt with semi-empirical calculations (MINDO/3 and CNDO/2) of **81** (all substituents equal to H); the authors noted the acceptable geometry obtained by MINDO/3 and the fact that the

charges obtained by CNDO/2 correspond to a polymethine type alternation.[175] Recently,[176] we have used INDO and AM1 methods to study the following seven molecules.



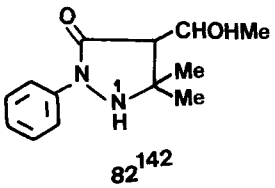
76 **10** **77** **78** **79** **80** **81**

The AM1 geometries are in reasonable agreement with the available X-ray determinations (section III.2.a), and the INDO energies correctly describe the tautomeric equilibria **76** ⇌ **10** and **78** ⇌ **79** (N_1-protonation, section II.2.a). Total charges (CNDO/2) in connection with ^{13}C chemical shifts (section III.2.b, Scheme 20, compounds **96**)[177] and bond orders (CNDO/2) in connection with bond lengths (section III.2.a, Scheme 18, compound **83**) have been discussed.[178]

2. Structural Methods

a. X-Ray Diffraction

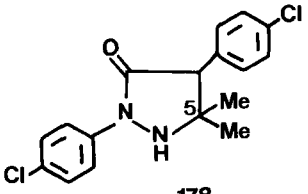
A surprisingly large number of structures of pyrazolidinones have been determined by X-ray diffraction as a result of the effort of two main groups, that of Kulpe, Seidel and Geisler (six structures; two more, concerning dimers **71a**, are in print) and that of Jungheim and his group (three structures) (Scheme 19). From this data, it is possible to evolve a reasonably good image of pyrazolidinones **2**, **3** and **5** (no data is available on betaines **4**).



82[142]

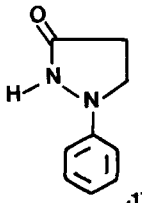
N_1: sp^3

2 independent molecules



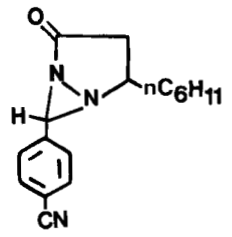
83[178]

puckered conformation (C_5 out of plane)



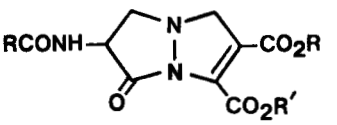
1[179]

half-chair (N–H···O intramolecular H bonds)



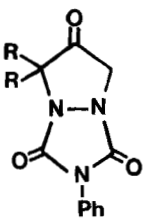
84[166,180]

trans – exo stereochemistry



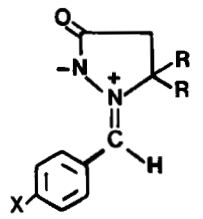
85[129,130]

three structures (only figures)



40[85]

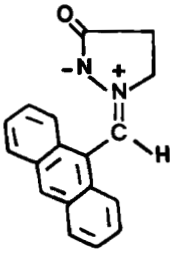
almost planar (twist envelope)



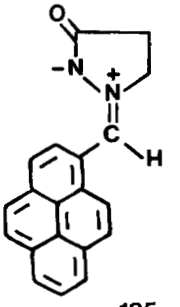
X = NO_2 , R = H , 86[181]

X = Cl , R = Me , 87[182]

X = OMe , R = H , 88[183]



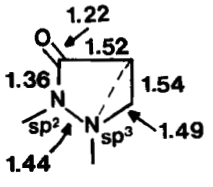
89[184]



90[185]

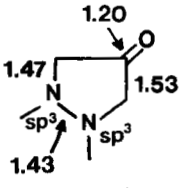
2 independent molecules

Scheme 19



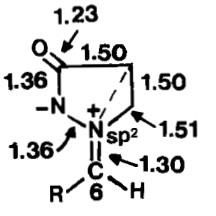
envelope

2



almost planar

3



slight envelope

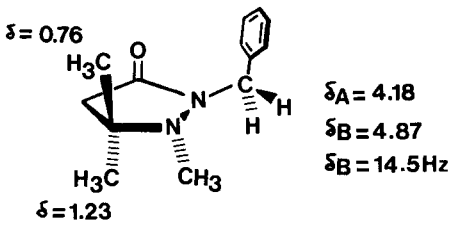
5

Azomethineimines **5** have been discussed in terms of a $\overset{\delta-}{O}=\overset{\delta+}{C}-\overset{\delta-}{N}=\overset{\delta+}{N}-\overset{\delta-}{C}$ form.[182] However, the $\overset{+}{N}=C$ is practically a Csp^2-N double bond[181] and the N-C=O part is nearly identical to that of **2**; only a definite shortening of the N-N bond length is observed. The configuration of the $\overset{+}{N}=C$ bond is always Z.

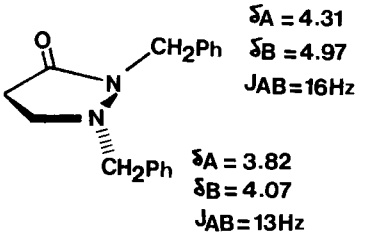
Another interesting aspect of the structure of azomethineimines **5** is the existence of relatively strong intermolecular hydrogen bonds between the C_6-H and either the carbonyl oxygen (compounds **86, 87** and **88**) or the negatively charged nitrogen atom (compounds **89** and **90**).[186]

b. NMR Spectroscopy

Pyrazolidinones are usually characterized by ^{1}H NMR[42] and more recently by ^{13}C NMR. For this reason there is a large amount of data, but very few publications dealing specifically with the NMR behavior of these compounds. The most significant publication studied the nitrogen inversion of pyrazolidin-3-ones by ^{1}H-NMR.[56] Even if the phenomenon is apparent on the cyclic protons of 1-methyl-2-phenyl-pyrazolidin-3-one **26** (R = R^1 = H), the investigation is more easily carried out on the methylene protons of N-benzyl derivatives. A series of ten compounds (1-benzyl, 2-benzyl and 1,2-dibenzyl) were studied at different temperatures and the activation energy corresponding to the inversion of the substituent at position 1 determined (the substituent at position 2 is nearly planar). Two of the 3-pyrazolidinones, 1,5,5-trimethyl-2-benzylpyrazolidin-3-one **91** and 1,2-dibenzylpyrazolidin-3-one **92** are depicted below.



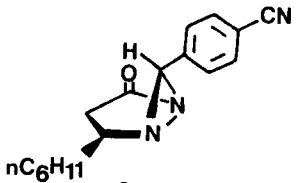
91 (Acetone-d_6, -93°C)



92 (Acetone-d_6, -81°C)

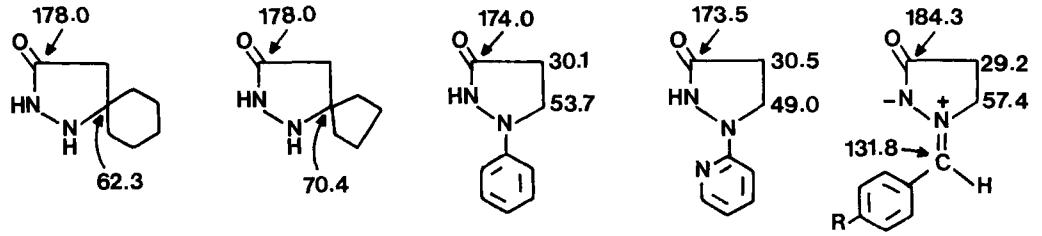
The anisochronism of methylene protons of the CH_2Ph substituent is observed at room temperature when there is a stereogenic center (monosubstitution at position 4 or 5).[56] This and the shielding of the 5-methyl substituent by the phenyl ring has been observed by other authors.[134] Conformational analysis using Karplus type relationships has been performed on pyrazolidin-3-ones.[187]

The stereochemistry of the exocyclic double bond of azomethineimines has been studied by Geissler et al.[188] Using the influence of the aromatic substituent on the methine proton, a conformation consistent with the X-ray structures (compounds **86-90**, Scheme 18) was deduced. The same authors[166] studied the exo-endo stereochemistry of bicyclic compounds **84** (and related structures) using ring current effects and lanthanide induced shifts. Here also these methods lead to an exo structure, which was definitely established later by crystallography (Scheme 18).



84

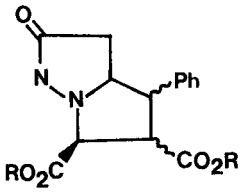
Carbon-13 chemical shifts of several pyrazolidinones are available. Some representative compounds are gathered in Scheme 20.



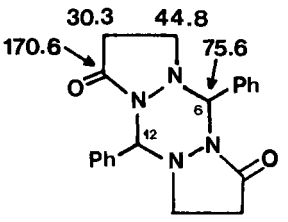
93[145] (CDCl3) **94**[145] (CDCl3) **1**[72] (DMSO-d6) **95**[72] (DMSO-d6) **96**[177] (DMSO-d6)

Scheme 20

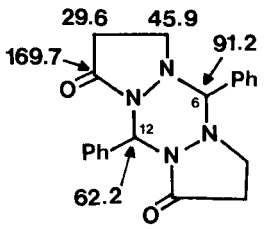
The four diastereoisomers of formula **97** have different ^{13}C chemical shifts (the C=O appears between 168 and 175 ppm).[170] A very interesting result concerns azomethineimine dimers, head-to-tail **71b** and head-to-head **71a** isomers.



97



71b



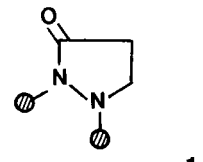
71a

The first one exhibits a normal spectrum,[161] but isomer **71a** shows two very different central carbons (averaged value, 76.7 ppm, near that of **71b**). Moreover, the ortho and meta carbons of the phenyl at C_6 are anisochronous ($\Delta G^{\ddagger}$ of the p-methoxy isomer = 16.3 kcal.mol^{-1})[167] suggesting an equatorial position on the hexahydrotetrazine ring.

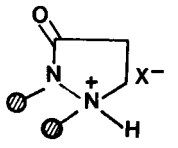
c. UV and IR Spectroscopies

The electronic spectra of 1-aryl and 2-arylpyrazolidin-3-ones have been studied with regard to the problem of protonation (section II.2.a). The 1-aryl isomers absorb at 245-250 nm with a shoulder at 285 nm whereas 2-arylpyrazolidinones show a single maximum at 265-270 nm.[42] The absorption of azomethineimines, as **96** was examined in connection with their photochemistry (section II.4.b.iv).[162]

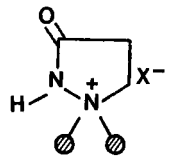
Most infrared studies of pyrazolidinones deal with the carbonyl absorption. Scheme 21 illustrates the most common cases.



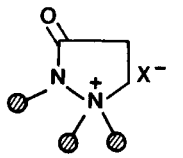
1685 - 1710 cm^{-1}
refs 42,125,189



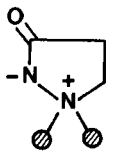
1730 - 1750 cm^{-1}
refs 42 , 125



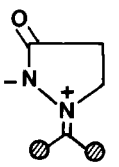
1730 - 1735 cm^{-1}
ref 70



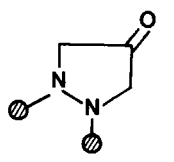
1740 - cm^{-1}
ref 42



1580 cm^{-1}
refs 52 , 190



1655 - 1685 cm^{-1}
refs 27, 191-193



1750 cm^{-1}
ref 19

Scheme 21

Association in pyrazolidin-3-ones plays an important role on the C=O frequency when there is an hydrogen atom at position 2.[189] The case of azomethineimines has been the only controversial one, since in the first publication[27] the assignments of C=O and C=N (now at 1600-1616 cm^{-1}) were inverted.[191] The most recent publication on this topic[193] contains much information about solvent and substituent effects on the C=O band.

d. Mass Spectrometry

No systematic study has been published on the behavior of pyrazolidinones under electron impact, although the method has been used to characterize these compounds.[79,145,146]

e. Others

In azomethineimines such as **96** where differences of conformation about the C-aryl bond exist between the solid state (X-Ray, section III.2.a) and in solution (UV, section III.2.c) photoacoustic spectroscopy proved useful to detect these conformational changes.[194]

3. Tautomerism

Pyrazolidin-3-ones, cyclic hydrazides, and pyrazolidin-4-ones, cyclic ketones, exist in the oxo form, as all structural methods discussed before amply support.

IV. APPLICATIONS AND IMPORTANT COMPOUNDS

1. Phenidone and Derivatives

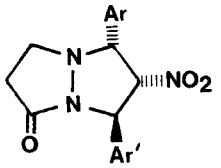
It is not commonly found that a compound such as phenidone **1** possesses important applications for both its biological properties and its industrial uses in photography. Its strong reducing properties (section II.1.b) are responsible for its uses,[195,196] which have not been improved significantly by substitution (mainly on the 4-position and on the 1-phenyl substituent). Its photographic uses discovered by Kendall[197] have been explored by most companies: Agfa-Gevaert,[198] Kodak,[96,199-201] Fuji (4-methyl)[202] and Konica (many derivatives)[203] as well as in Germany,[204] Poland[195,196] and the Soviet Union.[205] These compounds are know as "super-additive developers" and are especially useful for cinema films. The reaction responsible for their properties proceeds via radical and radical ions to 1-aryl-3-hydroxypyrazoles.

Reduction of Ag(I) and Pd(II) as well as complex formation with Rh (III) have been explored.[206,207]

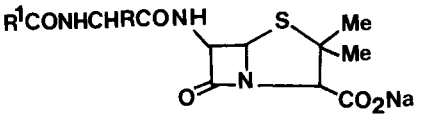
In 1978, Blackwell reported for the first time that phenidone inhibits both the cyclooxygenase (CO) and the lipoxygenase (LO) pathways of arachidonic acid (AA) metabolism.[208] Since then, phenidone has become the standard substance in AA metabolism. Among the most significant publications on this topic, a review on anti-rheumatic drugs[209] contains a discusion on phenidone and a series of papers published in 1989 shows the importance of phenidone as inhibitor of 15-LO (the m-CF_3 derivative is also a potent inhibitor),[72] of 5-LO[210-212] and of soybean LO.[213]

2. Other Important Pyrazolidinones

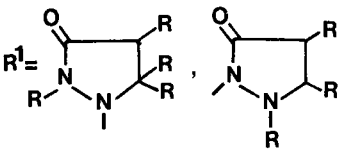
We have already described the Lilly research on bicyclic pyrazolidinone antibacterial agents.[83] Related bicyclic structures **98** were claimed to have antibacterial effects.[214] Bayer patented compound **99** carrying pyrazolidinone residues.[215]



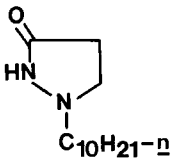
98



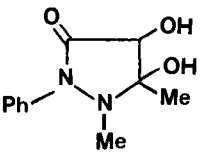
99



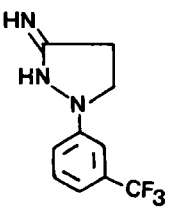
Compound **100**, 1-(n-decyl)-pyrazolidin-3-one (BW357U) is a potent, selective inhibitor of γ-aminobutyrate amino-transferase (GABA-T). BW357U produces marked anorexia in laboratory animals.[216] Analogs of BW357U were synthesized.[217] 2-(n-Decyl) (or n-dodecyl)-3-pyrazolidinones 1-acetic (or 1-propionic) acids have antimicrobial activity due to their surfactant properties.[218]



100



101



102

Antipyrine **6** is metabolized to dihydrodiol **101** by the epoxide-diol pathway.[219,220] Closely related to phenidone is the

compound BW755C **102** a very powerful LO and CO inhibitor,[221] which is effective in vivo and has served as a model for other iminopyrazolidines and pyrazolidinones.[72]

Acknowledgments.- We want to express our deep gratitude to Prof. Dr. Helmut Dorn (Akademie der Wissenschaften, Berlin, Germany); without his help, this review would not have been written. The last version was improved considerably by the referees and, especially, by the Editor of Organic Preparations and Procedures International.

REFERENCES

1. T. L. Jacobs, "Heterocyclic Compounds", R.C. Elderfield, Ed. John Wiley and Sons, N.Y. 1957. Vol. 5.

2. R. H. Wiley and P. Wiley, "The Chemistry of Heterocyclic Compounds", A. Weissberger, Ed. John Wiley and Sons, N.Y. 1964. Vol. 20.

3. A. N. Kost and I. I. Grandberg, Adv. Heterocycl. Chem., **6**, 347 (1966).

4. L. C. Behr, R. Fusco and C. H. Jarboe, "The Chemistry of Heterocyclic Compounds", A. Weissberger, Ed. John Wiley and Sons, 1976.

5. J. Elguero, "Comprehensive Heterocyclic Chemistry", A. R. Katritzky and C. W. Rees, Eds., Pergamon Press, Oxford, 1984. Vol. 5.

6. H. Dorn, Chem. Heterocycl. Comp. USSR, **17**, 1 (1981).

7. W. J. McKillip, E. A. Sedor, B. M. Culbertson and S. Wawzonek, Chem. Rev. **73**, 255 (1973).

8. R. Grashey, "1,3-Dipolar Cycloaddition Chemistry", A. Padwa, Ed., John Wiley and Sons, N.Y. 1984. Vol. I, p. 733.

9. M. Guzek and J. Maslowska, Sesz. Nauk-Politech Lodz, Technol. Chem. Spozyw., 53 (1984); Chem. Abstr. **103**, 6250.

10. J. Elguero, R. Jacquier, V. Pellegrin and V. Tabacik, Bull. Soc. Chim. Fr., 1974 (1970).

11. P. Bouchet, J. Elguero and R. Jacquier, Tetrahedron, **22**, 2461 (1966).

12. J. Elguero, R. Jacquier and D. Tizané, ibid., **27**, 133 (1971).

13. C. Dittli, J. Elguero and R. Jacquier, Bull. Soc. Chim. Fr., 4466 (1969).

14. C. Dittli, J. Elguero and R. Jacquier, ibid., 4469 (1969).

15. C. Dittli, J. Elguero and R. Jacquier, ibid., 4474 (1969).

16. E. Testa and L. Fontanella, Farmaco, Ed. Sci., **26**, 1017 (1971).

17. E. Toja, A. Omodei-Salé and G. Nathanson, Tetrahedron Lett., 111 (1976).

18. J. Airey, D. H. R. Barton, A. K. Ganguly, R. H. Hesse and M. M. Pechet, An. Quim., **70**, 871 (1974); Chem. Abstr., **83**, 163090.

19. J. Elguero, R. Jacquier and S. Mignonac-Mondon, Bull. Soc. Chim. Fr., 2807 (1972); J. Elguero and E. Henry, Unpublished results.

20. C. Dittli, J. Elguero and R. Jacquier, Bull. Soc. Chim. Fr. 1038 (1971).

21. N. P. Marullo, and J. A. Alford, J. Org. Chem., **33**, 2368 (1968).

22. N. P. Marullo, A. Bodine, J. L. Eggers and A. Sobti, Tetrahedron Lett., 3939 (1969).

23. H. Dorn, A. Zubek and G. Hilgetag, Angew. Chem. Int. Ed. Engl., **5**, 665 (1966).

24. H. Dorn and A. Zubek, Z. Chem., **7**, 150 (1967).

25. H. Dorn, A. Zubek and G. Hilgetag, Chem. Ber., **98**, 3377 (1965).

26. H. Dorn and A. Otto, Angew. Chem. Int. Ed. Engl., **7**, 214 (1968).

27. H. Dorn and A. Otto, Chem. Ber., **101**, 3287 (1968).

28. H. Dorn and A. Otto, ibid., **103**, 2505 (1970).

29. H. Dorn and D. Arndt, J. prakt. Chem., **313**, 1173 (1971).

30. H. W. Heine, L. M. Bachawski, S. M. Bonser and G. D. Wachob, J. Org. Chem., **41**, 3775 (1976).

31. C. Dittli, J. Elguero and R. Jacquier, Bull. Soc. Chim. Fr. 696 (1970).

32. E. L. Allred and C. Anderson, J. Org. Chem., **32**, 1874 (1967).

33. K. Nálepa, Monatsh. Chem., **98**, 1230 (1967).

34. K. Nálepa, Acta Univ. Palacki Olomuc, Fac. Rerum. Nat., **79**, 47 (1984); Chem. Abstr., **103**, 22554.

35. K. Nálepa, ibid., **88**, 223 (1987); ibid., **109**, 92955.

36. M. M. Kidwai and N. H. Khan, J. Nepal, Chem. Soc. **1**, 39 (1981); Chem. Abstr., **104**, 129822.

37. C. F. H. Allen and E. W. Magder, J. Heterocyclic Chem., **6**, 349 (1969).

38. C. Sabaté-Alduy, J. Bastide, P. Berçot and J. Lematre, Bull. Soc. Chim. Fr., 1942 (1974).

39. M. G. Pleiss and J. A. Moore, J. Am. Chem. Soc., **90**, 1369 (1968).

40. J. L. Derocque, W. J. Theuer and J. A. Moore, J. Org. Chem., **33**, 4381 (1968).

41. J. Markert and E. Fahr, Tetrahedron Lett., 769 (1970).

42. P. Bouchet, J. Elguero and R. Jacquier, Bull. Soc. Chim. Fr., 3502 (1967).

43. G. Coispeau and J. Elguero, ibid., 2717 (1970).

44. J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, Chem. Commun., 736 (1976).

45. T. A. Sokolova and N. P. Zapevalova, Usp. Khim. **38**, 2239 (1969); Chem. Abstr., **72**, 89403.

46. L. A. Ovsyannikova and T. A. Sokolova, Bull. Acad. Sci. USSR, Chem. Ser., 863 (1970).

47. W. O. Godtfredsen and S. Vangedal, Acta Chem. Scand., **9**, 1498 (1955).

48. H. Stetter and K. Findeisen, Chem. Ber., **98**, 3228 (1965).

49. R. Harada and H. Kondo, Bull. Chem. Soc. Jpn., **41**, 2521 (1968).

50. J.-P. Anselme, Tetrahedron Lett., 3615 (1977).

51. G. Geissler, M. Hippius and G. Tomaschewski, J. prakt. Chem., **324**, 910 (1982).

52. W. S. Wadsworth, J. Org. Chem., **31**, 1704 (1966).

53. M. J. Kornet, J. Pharm. Sci., **67**, 1471 (1978).

54. M. Tamura, Y. Matsushita, K. Yoshida and M. Ochiai, Tetrahedron, **44**, 3231 (1988).

55. P. Bouchet, J. Elguero, R. Jacquier and J.M. Pereillo, Bull. Soc. Chim. Fr., 2264 (1972).

56. J. Elguero, C. Marzin and D. Tizané, Org. Magn. Reson., **1**, 249 (1969).

57. H. Dorn, A. Zubek and K. Walter, Ann., **707**, 100 (1967).

58. M. J. Kornet and S. I. Tan, J. Heterocyclic Chem., **5**, 397 (1968).

59. M. Kornet and H. S. I. Tan, J. Pharm. Sci., **61**, 188 (1972).

60. R. F. Smith, A. C. Bates, A. J. Battisti, P. G. Byrnes, C. T. Mroz, T. J. Smearing and F. X. Albrecht, J. Org. Chem., **33**, 851 (1968).

61. T. A. Sokolova, A. I. Kol'tsov, N. P. Zapevalova and L. A. Ovsyannikova, Bull. Acad. Sci. URSS, Div. Chem. Sci., 1641 (1964).

62. N. P. Zapevalova and T. A. Sokolova, ibid., 865 (1966).

63. N. P. Zapevalova, L. A. Ovsyannikova and T. A. Sokolova, ibid., 149 (1967).

64. N. P. Zapevalova, L. A. Ovsyannikova and T. A. Sokolova, ibid., 2127 (1966).

65. A. I. Kol'tsov, ibid., 1318 (1965).

66. N. P. Zapevalova and T. A. Sokolova, ibid., 1398 (1965).

67. T. A. Sokolova, I. N. Osipova and L. A. Ovsyannikova, J. Org. Chem. USSR, **3**, 2202 (1967).

68. N. P. Zapevalova and T. A. Sokolova, Bull. Acad. Sci. USSR, Div. Chem. Sci., 2124 (1966).

69. T. A. Sokolova and I. N. Osipova, Proc. Acad. Sci. USSR, **193**, 500 (1970).

70. L. K. Dalton, S. Demerac and B. C. Elmes, Australian J. Chem., **33**, 1365 (1980).

71. G. B. Bennett, W. J. Houlihan, R. B. Mason and J. B. Roach, J. Med. Chem., **19**, 715 (1976).

72. J. Frigola, A. Colombo, J. Parés, L. Martínez, R. Sagarra and R. Roser, Eur. J. Med. Chem., **24**, 435 (1989).

73. D. S. Kemp, M. D. Sidell and T. J. Shortridge, J. Org. Chem., **44**, 4473 (1979).

74. A. Etienne, G. Arditti and S. Abbühl, Bull. Soc. Chim. Fr., 1475 (1971).

75. B. J. R. Nicolaus, L. Mariani, E. Bellasio and E. Testa, Gazz. Chim. Ital., **94**, 652 (1964).

76. E. Bellasio, G. Pagani, A. Ripamonti and E. Testa, Farmaco, Ed. Sci., **20**, 428 (1965).

77. E. Bellasio, A. Ripamondi and E. Testa, Gazz. Chim. Ital., **98**, 3 (1968).

78. E. Bellasio and G. Gallo, Farmaco, Ed. Sci., **25**, 295 (1970).

79. T. Okawara, R. Kato, N. Yasuda, T. Yamasaki and M. Furukawa, J. Chem. Res., Synop., 254 (1987).

80. J. C. Howard, G. Gever and P. H. L. Wei, J. Org. Chem., **28**, 868 (1963).

81. R. B. Greenwald and E. C. Taylor, J. Am. Chem. Soc., **90**, 5273 (1968).

82. R. J. Crawford and H. Tokunaga, Can. J. Chem., **52**, 4033 (1974).

83. L. N. Jungheim, R. J. Ternansky and R. E. Holmes, Drugs of the Future, **15**, 149 (1990).

84. C. W. Rees and M. Yelland, J. Chem. Soc., Perkin Trans. 1, 221 (1973).

85. A. M. Celli, D. Donati and M. Scotton, Tetrahedron, **45**, 7929 (1989).

86. M. K. Eberle, G. G. Kahle and S. M. Talati, ibid., **29**, 4045 (1973).

87. M. J. Kornet, J. Med. Chem., **9**, 493 (1966).

88. M. J. Kornet and H. S. I. Tan, J. Pharm. Sci., **61**, 235 (1972).

89. J. Elguero, R. Jacquier and D. Tizané, Bull. Soc. Chim. Fr., 1936 (1970).

90. J. L. Aubagnac, J. Elguero and R. Jacquier, ibid., 3758 (1971).

91. M. J. Kornet and S. I. Tan, J. Heterocyclic Chem., **6**, 325 (1969).

92. J. J. Tufariello and J. J. Spadaro, Tetrahedron Lett., 3935 (1969).

93. H. H. Adam and T. A. Joslin, J. Electroanal. Chem. Interfacial Electrochem., **58**, 393 (1975).

94. H. H. Adam and T. A. Joslin, ibid., **72**, 197 (1976).

95. H. H. Adam, B. D. Baigrie and T. A. Joslin, J. Chem. Soc., Perkin Trans. 2, 1287 (1977).

96. G. I. P. Levenson and P. J. Twist, J. Photogr. Sci., **26**, 44 (1978).

97. H. Raither and W. Jaenicke, Z. Phys. Chem., **111,** 193 (1978).

98. B. D. Baigrie and T. A. Joslin, J. Electroanal. Chem. Interfacial Electrochem., **87**, 405 (1978).

99. H. H. Adam, T. A. Joslin and B. Thomas, J. Photogr. Sci., **27**, 66 (1979).

100. A. J. Bellamy, D. I. Innes and P. J. Hillson, J. Chem. Soc., Perkin Trans. 2, 1599 (1982).

101. A. J. Bellamy, D. I. Innes and P. J. Hillson, ibid., 175 (1983).

102. A. J. Bellamy, D. I. Innes and P. H. Hillson, ibid., 179 (1983).

103. W. E. Lee, J. Org. Chem., **30**, 2571 (1965).

104. D. Vogel and W. Jaenicke, Ber. Bunsenges. Phys. Chem., **75**, 1297 (1971).

105. D. Vogel and W. Jaenicke, ibid., **75**, 1302 (1971).

106. H. Dorn and A. Otto, Tetrahedron, **24**, 6809 (1968).

107. H. Dorn and A. Zubek, J. prakt. Chem., **313**, 1118 (1971).

108. H. Dorn, A. Otto and H. Dilcher, ibid., **313**, 236 (1971).

109. V. M. Zolin and R. B. Zhurin, Chem. Heterocycl. Comp. USSR, 527 (1971).

110. H. Dorn and H. Graubaum, J. prakt. Chem., **316**, 886 (1974).

111. H. Dorn and D. Arndt, ibid., **313**, 1173 (1971).

112. R. H. Kent and J.-P. Anselme, Can. J. Chem., **46**, 2322 (1968).

113. U. Anthony, G. Borch, P. Klaeboe, K. Lestrup and P. H. Nielsen, Acta Chem. Scand., Ser. A, **35**, 767 (1981).

114. H. Dorn and Th. Kreher, Unpublished results.

115. H. Dorn and A. Zubek, Z. Chem., **8,** 218 (1968).

116. M. Neitzel and G. Zinner, Ann., 1907 (1980).

117. A. M. Richter and V. Mojjoukhine, J. prakt. Chem., **324**, 873 (1982).

118. N. P. Peet, S. Sunder and R. J. Barbuch, J. Heterocyclic Chem., **19**, 747 (1982).

119. R. J. Ternasky and S. E. Draheim, Tetrahedron Lett., **29**, 6569 (1988).

120. R. J. Ternansky and S. E. Draheim, ibid., **31**, 2805 (1990).

121. H. Dorn and A. Otto, Z. Chem., **12**, 175 (1972).

122. H. Dorn and H. Dilcher, J. prakt. Chem., **313**, 229 (1971).

123. V. N. Mikhailova and V. P. Yurevich, Zh. Obshch. Khim., **46**, 879 (1976); Chem. Abstr., **85**, 62996.

124. H. Dorn and H. Dilcher, J. prakt. Chem., **314**, 220 (1972).

125. B. E. Zaitsev, L. B. Preobrazhenskaya and R. B. Zhurin, Khim. Geterotsikl. Soedin., 676 (1972); Chem. Abstr., **77**, 113270.

126. H. Dorn and A. Otto, Z. Chem., **8**, 217 (1968).

127. H. Dorn and A. Zubek, ibid., **8**, 273 (1968).

128. G. Geissler, K. Angermüller, I. Behning, S. Fürneisen, W. Fust, M. Hippius, B. Müller, G. Schauer, H. Slezak and G. Tomaschewski, ibid., **21**, 356 (1981).

129. L. N. Jungheim and S. K. Sigmund, J. Org. Chem., **52**, 4007 (1987).

130. L. N. Jungheim, S. K. Sigmund and N. D. Jones, Tetrahedron Lett., **28**, 289 (1987).

131. T. A. Shepherd and L. N. Jungheim, ibid., **29**, 5061 (1988).

132. S. N. Ege, E. Y. Tsui, R. L. Spenser, B. E. Potter, B. K. Eagleson and H. Z. Friedman, Chem. Commun., 216 (1974).

133. S. N. Ege, M. L. Carter, R. L. Spenser, C. E. Nordman and H. Z. Friedman, J. Chem. Soc., Perkin Trans. 1, 868 (1976).

134. S. N. Ege, M. L. C. Carter, D. F. Ortwine, S. S. P. Chou and J. F. Richman, ibid., 1252 (1977).

135. M. K. Eberle and L. Brzechffa, J. Org. Chem., **41**, 3775 (1976).

136. L. A. Carpino, J. Am. Chem. Soc., **80**, 601 (1958).

137. S. N. Ege, C. J. Tien, A. Diesk, B. E. Potter and B. K. Eagleson, Chem. Commun., 682 (1972).

138. M. S. Henry and R. E. Ross, J. Photogr. Sci., **33**, 1 (1985).

139. L. A. Ovsyannikova, T. A. Sokolova and N. P. Zapevalova, Zh. Org. Khim., **4**, 459 (1968); Chem. Abstr., **68**, 104542.

140. J. M. Indelicato and C. E. Pasini, J. Med. Chem., **31**, 1227 (1988).

141. S. N. Ege, Chem. Commun., 759 (1968).

142. S. N. Ege, W. M. Butler, A. Bergers, B. S. Biesman, J. E. Boerma, V. I. Corondan, K. D. Locke, S. Meshinchi, S. H. Ponas and T. D. Spitzer, J. Chem. Soc., Perkin Trans. 1, 1111 (1983).

143. C. E. Hatch and P. Y. Johnson, Tetrahedron Lett., 2719 (1974).

144. P. Y. Johnson and C. E. Hatch, J. Org. Chem., **40**, 909 (1975).

145. P. Y. Johnson and C. E. Hatch, ibid., **40**, 3502 (1975).

146. P. Y. Johnson and C. E. Hatch, ibid., **40**, 3510 (1975).

147. P. Y. Johnson, N. R. Schnuff and C. E. Hatch, Tetrahedron Lett., 4089 (1975).

148. H. P. Benecke and J. H. Wikel, ibid., 3479 (1971).

149. K. Chantrapromma, W. D. Ollis and I. O. Sutherland, J. Chem. Soc., Perkin Trans. 1, 1029 (1983).

150. R. F. Smith, C. J. Aquino, L. A. Olson, J. M. Galante and S. C. Liptak, Tetrahedron Lett., **26**, 5663 (1985).

151. G. Wagner, B. Dietzsch and G. Fischer, Z. Chem., **13**, 295 (1973).

152. C. E. Hatch and P. Y. Johnson, Tetrahedron Lett., 2153 (1973).

153. R. Amstutz, A. Closse and G. Gmelin, Helv. Chim. Acta, **70**, 2232 (1987).

154. H. Dorn and A. Zubek, Z. Chem., **8**, 270 (1968).

155. H. Dorn and A. Graubaum, J. prakt. Chem., **318**, 253 (1976).

156. H. Dorn, Z. Chem., **14**, 231 (1974).

157. M. Schulz and G. West, J. prakt. Chem., **312**, 161 (1970).

158. M. Schulz and G. West, ibid., **315**, 711 (1973).

159. M. Schulz and N. Grossman, ibid., **318**, 575 (1976).

160. M. Schulz, G. West, U. Müller and D. Henke, ibid., **318**, 946 (1976).

161. M. Schulz, G. West and R. Radeglia, ibid., **318**, 955 (1976).

162. G. Tomaschewski, G. Geissler and G. Schauer, ibid., **322**, 623 (1980).

163. A. Klimakova, M. V. Koz'menko, G. Tomaschewski and M. G. Kuzmin, Khim. Vys. Energ., **14**, 149 (1980); Chem. Abstr., **93**, 70613.

164. G. Geissler, I. Menz, K. Angenmüller and G. Tomaschewski, J. prakt. Chem., **325**, 197 (1983).

165. G. Geissler, W. Fust, B. Krüger and G. Tomaschewski, ibid., **325**, 205 (1983).

166. G. Geissler, I. Menz, H. Köppel, M. Kretschner and S. Kulpe, ibid., **325**, 995 (1983).

167. H. Dorn, R. Ozegowski and R. Radeglia, ibid., **319**, 177 (1977).

168. H. Dorn and T. Kreher, Tetrahedron Lett., **29**, 2939 (1988).

169. H. Dorn, R. Ozegowski and E. Gründeman, J. prakt. Chem., **321**, 555 (1979).

170. H. Dorn, R. Ozegowski and E. Gründemann, ibid., **321**, 565 (1979).

171. H. Dorn, Tetrahedron Lett., **26**, 5123 (1985).

172. L. N. Jungheim, S. K. Sigmund and J. W. Fischer, ibid., **28**, 285 (1977).

173. L. N. Jungheim, C. J. Barnett, J. E. Gray, L. H. Horcher, T. A. Shepherd and S. K. Sigmund, Tetrahedron, **44**, 3119 (1988).

174. L. N. Jungheim, Tetrahedron Lett., **30**, 1889 (1989).

175. A. Melhorn, J. Fabian and S. Kulpe, J. prakt. Chem., **362**, 303 (1984).

176. J. Elguero and J. L. G. de Paz, Bull. Soc. Chim. Belg., in press.

177. R. Radeglia and H. Dorn, Z. Chem., **22**, 313 (1982).

178. F. Ganazzoli, A. Citerio and A. Albinati, Acta Crystallogr., Sect. C., **42**, 1181 (1986).

179. M. Sbit, L. Dupont, O. Dideberg, J. P. Snoeck and J. Delarge, ibid., **43**, 718 (1987).

180. S. Kulpe, I. Seidel, I. Menz, G. Geissler and G. Tomaschewski, Cryst. Res. Technol., **21**, 635 (1986).

181. S. Kulpe, I. Seidel, G. Geissler and G. Tomaschewski, ibid., **17**, 91 (1982).

182. S. Kulpe, I. Seidel, P. Leibnitz and G. Geissler, Acta Crystallogr., Sect. C., **39**, 278 (1983).

183. S. Kulpe, I. Seidel and G. Geissler, Cryst. Res. Technol., **17**, 1427 (1982).

184. S. Kulpe, I. Seidel and G. Geissler, ibid., **17**, 1419 (1982).

185. S. Kulpe, I. Seidel and G. Geissler, ibid., **18**, 339 (1983).

186. S. Kulpe and I. Seidel, Z. Phys. Chem., **264**, 25 (1983).

187. L. M. Kapkan, A. Yu. Chervinskii, T. M. Pekhtereva, Yu. I. Smirnov and A. F. Dmitruk, Teor. Eksp. Khim, **25**, 363 (1989); Chem., Abstr., **111**, 173279.

188. G. Geissler, M. Hippius and G. Tomaschewski, J. prakt. Chem., **324**, 903 (1982).

189. B. Y. Zaitsev, N. A. Andronova, R. B. Zhurin and L. B. Preobrazhenskaya, Chem. Heterocycl. Comp. USSR, 1568 (1970).

190. T. A. Sokolova and N. P. Zapevalova, Usp. Khim., **38**, 2239 (1969); Chem., Abstr., **72**, 89403.

191. S. Kulpe, Z. Chem., **20**, 377 (1980).

192. M. Siegmund, K. D. Schleinitz, I. Menz and G. Geissler, ibid., **21**, 188 (1981).

193. M. Siegmund, M. von Lowis, G. Geissler and I. Menz, J. prakt. Chem., **327**, 183 (1985).

194. G. Geissler, J. Lerchner, E. Hoyer, P. Sladky and S. Kulpe, ibid., **325**, 1033 (1983).

195. J. Maslowska and M. E. Guzek, Chromatographia, **17**, 426 (1983).

196. M. E. Guzek and J. Maslowska, J. Therm. Anal., **29**, 933 (1984).

197. J. D. Kendall, Brit. Pat., 650,911 (1951); Chem. Abstr., **46**, 144g.

198. J. F. Willems, Photogr. Process., Proc. Symp., 71 (1971); Chem. Abstr., **81**, 44046.

199. G. I. P. Levenson and M. G. Rumens, J. Photogr. Sci., **19** 135 (1971).

200. J. Reeman, ibid., **21**, 227 (1973).

201. R. J. Eubanks and L. K. Johnson, U.S. Pat., 4,835,285 (1989); Chem. Abstr., **111**, 194757.

202. S. Washizu, J. Yamaguchi, F. Shinozaki, A. Shimomura, T. Usami, T. Endo and K. Saeki, Ger. Offen., 3,835,062 (1989); Chem. Abstr., **111**, 222120.

203. A. Kamitakahara and K. Ogi, U.S. Pat., 4,840,879 (1989); Chem. Abstr., **111**, 222036.

204. W. Jaenicke and H. Kobayashi, Electrochim. Acta, **28**, 245 (1983).

205. V. L. Abritalin, R. B. Zhurin, T. G. Andreyanova, V. N. Ivina and V. M. Zolin, Zh. Nauchn. Prikl. Fotogr. Kinematogr., **20**, 89 (1975); Chem. Abstr., **83**, 123979.

206. S. Athanassiou and A. Fabrikanos, Chem. Chron., **1**, 260 (1972); Chem. Abstr., **79**, 70539.

207. A. Fabrikanos, G. Pallikaris and V. Havredaki, Chem. Ind. (London), 281 (1975).

208. G. J. Blackwell and R. J. Flower, Brit. J. Pharmacol., **63**, 360P (1978).

209. I. L. Bonta, M. J. Parnham, J. E. Vincent and P. C. Bragt, Prog. Med. Chem., **17**, 225 (1980).

210. M. J. DiMartino, C. E. Wolff, G. K. Campbell and N. Hanna, Agents Actions, **27**, 325 (1989); Chem. Abstr., **111**, 17376.

211. D. Riendeau, J. P. Falgueyret, D. J. Nathaniel, J. Rokach, N. Ueda and S. Yamamoto, Biochem. Pharmacol., **38**, 2313 (1989).

212. L. A. Marshall, J. Y. Chang, W. Calhoun, J. Yu and R. P. Carlson, J. Cell Biochem., **40**, 147 (1989).

213. J. Van der Zee, T. E. Eling and R. P. Mason, Biochemistry, **28**, 8363 (1989).

214. H. Dorn and R. Ozegowski, DDR Pat., 143,617 (1979); Chem. Abstr., **95**, 43100.

215. W. Schroeck, K. Metzger and H. B. Koenig, Ger Offen., 2,320,039 (1974); Chem. Abstr., **82**, 57676.

216. H. L. White, J. L. Howard, B. R. Cooper, F. E. Soroko, J. D. McDermed, K. J. Ingold and R. A. Maxwell, J. Neurochem., **39**, 271 (1982).

217. L. Yangzhi, L. Weiyi, L. Weiqin and P. Yinquan, Yiyao Gongye, **17**, 66 (1986); Chem. Abstr., **105**, 172347.

218. Y. Abe, S. Osanai and H. Tenmyo, Yakugaku, **27**, 230 (1978); Chem. Abstr., **89**, 191670.

219. M. Stafford, G. Kellermann, R. N. Stillwell and M. G. Horning, Res. Commun. Chem. Pathol. Pharmacol., **8**, 593 (1974).

220. M. G. Horning, C. M. Butler, M. Stafford, R. N. Stillwell, R. M. Hill, T. E. Zion, D. J. Harvey and W. G. Stillwell, Adv. Mass Spectrom. Biochem. Med., **1**, 91 (1976).

221. S. R. Challand, F. C. Copp, C. V. Denyer, K. E. Eakins, J. M. G. Walker, N. Whittaker and A. G. Caldwell, Eur. Pat. Appl., **22**, 578 (1981); Chem. Abstr., **95**, 62193.

222. F. O. H. Pirrung, F. P. J. T. Rutjes, H. Hiemstra and W. N. Speckamp, Tetrahedron Lett., **31**, 5365 (1990).

223. R. E. Holmes and D. A. Neel, ibid., **31**, 5567 (1990).

224. J. E. Dowling and J.-P. Anselme, Bull. Chim. Belges, **100**, 000 (1991)

225. K. Joseph, A. M. Tikdari and A. K. Mukerjee, J. Chem. Res., Synop., **404** (1990).

(Received October 24, 1990; in revised form February 4, 1991)