ISOXAZOLES

Part Two

This is the forty-ninth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR AND PETER WIPF, *Editors*

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ISOXAZOLES

Part Two

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The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry, and for this reason we initiated several years ago a parallel series entitled General Heterocyclic Chemistry, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

It is a major challenge to keep our coverage of this immense field up to date. One strategy is to publish Supplements or new Parts when merited by the amount of new material, as has been done, *inter alia*, with purines, pyrimidines, quinazolines and pyrimidines. This is also the case with *Condensed Isoxazoles*, which were last covered in Volume 17 published in 1962. Professors Grünanger and Vita Finzi have done a heroic job in covering almost 30 years of condensed isoxazole chemistry in the present volume, and efforts are currently underway to update further their coverage of both mononuclear and condensed isoxazoles.

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EDWARD C. TAYLOR

Preface

Part 1 of the present work on isoxazole chemistry appeared within this series (Vol. 49) in 1991. It was a complete, new reelaboration of the previous monograph published in 1962 by A. Quilico and G. Speroni, *Isoxazoles and Related Compounds* (Vol. 17 of this series). Owing to the huge development in the field of isoxazole derivatives in the last decades, from both synthetic and theoretical points of view, Part 1 was restricted to mononuclear isoxazoles and their hydrogenated counterparts (isoxazolines and isoxazolidines), with the notable exception of isoxazolones.

This second part is devoted to the chemistry of condensed isoxazoles: 1,2- and 2,1-benzisoxazoles and related compounds such as isoxazoles fused with carbocyclic or heterocyclic rings. Contrary to the previous part, each of the above cited groups was entrusted to different eminent specialists in that field. Each chapter illustrates the syntheses and reactions of these classes of compounds; physical properties are also included whenever they differ notably from those of the corresponding mononuclear isoxazoles already reported in Part 1. In order to facilitate the text writing and to avoid possible draft complications, references are collected at the end of each chapter, although this might be somewhat uncomfortable to the reader. Notwithstanding the advantages offered by computerization to text composition, the literature survey was ended, except for some items in Chapter 2, with Volume 115 of *Chemical Abstracts* (1991). We apologize for the long gap between literature deadline and publication year, and hope to update both Part 1 and Part 2 in the planned Part 3, which will include a chapter on isoxazolones. As a rule, patent literature has been evaluated only in those cases when the factual material therein has not subsequently appeared in the regular literature. An effort has been made to bring the chemical nomenclature in line with more recent IUPAC recommendations; nevertheless, sometimes the *Chemical Abstracts* names (e.g., 1,2-benzisoxazole) as well as some more commonly used names (e.g., 2-isoxazolines instead of 4,5-dihydro-1,2-oxazoles) have been utilized for the sake of simplicity.

We are greatly indebted to Dr. L. Toma and Dr. E. Magistrali for outstanding help in data collection and references control, to Mr. J. Dowling for critical supervision and language improvement of the whole text, and to the series editor Professor E. C. Taylor for constant advice.

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ISOXAZOLES

Part Two

This is the forty-ninth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

Chemistry of Heterocyclic Compounds, Volume 49
Paolo Grünanger, Paola Vita-Finzi
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CHAPTER 1

1,2-Benzisoxazoles

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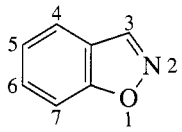
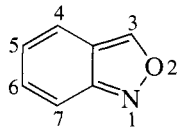
1.1. INTRODUCTION

The annulation of an isoxazole nucleus with a benzene ring gives rise to two bicyclic ring systems, **A** and **B**; only one of them, **A**, can properly be called a *benzisoxazole*, in that it has a formal benzenoid ring.



A



B

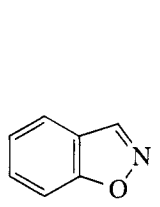
Each of these two compounds is known in the literature under several names.

Ring system **A** has been described as indoxazene, 1,2-benzisoxazole, 4,5-benzisoxazole, α,β-benzisoxazole, benzo[*d*]isoxazole (IUPAC nomenclature), and benzisoxazole. It is indexed in *Chemical Abstracts* as 1,2-benzisoxazole and numbered as shown in the figure; its ring index is 1123.

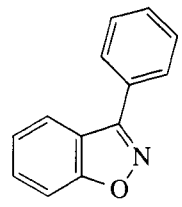
Ring system **B** has been described as anthranil, anthroxan, 2,1-benzisoxazole, 3,4-benzisoxazole, β,γ–benzisoxazole, benzo[*c*]isoxazole (IUPAC nomenclature), and benzpseudoxazole. It is indexed in *Chemical Abstracts* as anthranil and numbered as shown in the figure; its ring index is 1124.

This chapter deals only with ring system **A**, which henceforth will be named and numbered in accordance with the *Chemical Abstracts* system.

The first member of the family, 3-phenyl-1,2-benzisoxazole (**2**), was synthesized by Cathcart and Meyer a century ago,[1/892] and the parent compound, 1,2-benzisoxazole (**1**), was obtained by Conduché in 1908.[1/08]



1



2

This ring system was first reviewed by Quilico,[1/62] while a systematic coverage of the subject was made by Wünsch and Boulton[1/67] and updated 15 years later by Smalley.[1/81]

1.2. PHYSICOCHEMICAL PROPERTIES

The physicochemical behavior of 1,2-benzisoxazole and its derivatives was investigated early, especially with regard to establishing its correct structure However, extensive examination and recording of physicochemical properties have occurred only in more recent years. The subject has been briefly reviewed by Speroni.[2/62]

1.2.1. Infrared and Raman Spectra

A complete analysis and the attribution of the fundamental vibrations and of some overtones and combination vibrations of 1,2-benzisoxazole (**1**) have been performed in liquid and in solution.[1/80] Vapor spectra could not be recorded for **1** because of its decomposition at high temperature (see § 1.4.4).

If the molecule is considered to have a planar structure, it can be attributed to the C_s group of symmetry. In this case there are 36 fundamental vibrations, all of which are IR- and Raman-active, and which can be classified as 10 in-plane bending (γ) and stretching (δ) CH vibrations and 15 ring vibrations (ν_i) with A' symmetry; 5 deformation vibrations (γ CH) and 6 out-of-plane bending vibrations (Γ_i) with a A'' symmetry. The frequencies of the fundamental vibrations are

reported in Tables 1.1 and 1.2, while the original IR and Raman spectra are illustrated in the reference above cited.

For practical purposes the stretching frequency of the nuclear C=N bond is characteristic of the cyclic system, and it is mostly reported in the literature as the IR signature of 1,2-benzisoxazole derivatives. It has a medium to strong absorption that shows some variation according to the structure of the compounds. Some representative examples of this band are reported in Table 1.3. The C=N absorption band is lost in 2,3-dihydro-1,2-benzisoxazole derivatives as shown by the spectrum of 2-*t*-butyl-2,3-dihydro-1,2-benzisoxazole.[1/84]

In most cases reported IR spectra deal primarily with the assignment of significant side-chain functions, and are therefore not worth taking into account in this review. In other cases the reported absorptions have not been assigned, or the proposed designation is questionable. In Table 1.4 a few complete IR spectra of selected 1,2-benzisoxazole derivatives are reported; the assignments in brackets are those proposed by the authors.

The absorption frequency of the C=N bond does not seem to change after quaternization of the nitrogen, as shown by the $\nu_{C=N}$ of *N*-ethyl-1,2-benzisoxazolium fluoborate (ν = 1620 cm^{-1}).[1/65]

The C=N absorption frequency of polynuclear 1,2-benzisoxazole derivatives also seems to remain fairly constant.[2/80,4/87] However, in derivatives such as **3** the $\nu_{C=N}$ is reported to be as low as 1530 cm^{-1}.[2/77]

TABLE 1.1. ASSIGNMENTS OF FUNDAMENTAL C–H VIBRATIONS OF 1,2-BENZISOXAZOLE[a]

	Raman			IR Neutral solvents		DMSO	Acetone
Assignment[1/80]	ν (cm^{-1})	I	ρ	ν (cm^{-1})	ε	ν (cm^{-1})	(cm^{-1})
A′ symmetry							
ν CH isoxazole	3102	23	0.17	3096	9	—	—
ν_1 CH	3079	14	0.19	3078	13	—	—
ν_2 CH	—	—	—	3063	25	—	—
ν_3 CH	—	—	—	3055	19	—	—
ν_4 CH	—	—	—	3045	10	—	—
δ_1 CH	1259	46	0.18	1257	46	1258	—
δ CH isoxazole	1177	9	0.14	1173	90	1175	1175
δ_2 CH	—	—	—	1154	15	~1157	1157
δ_3 CH	1145	5	0.19	1141	46	1145	1145
δ_4 CH	1119	7	0.69	1116	50	1116	1116
A″ symmetry							
γ_1 CH	—	—	—	980 w (°)	—	—	—
γ_2 CH	—	—	—	~936s	—	—	945
γ_3 CH	888	3	0.75	886	101	886	886
γ CH isoxazole	—	—	—	873	100	—	—
γ_4 CH	—	—	—	752	422	763(°)	—

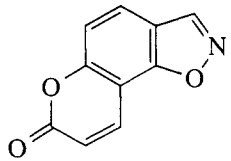
[a] Key: I = Intensity; ρ = depolarization factor; ε = apparent molar extinction coefficient; w = weak; s = shoulder; (°) = observed only in liquid sample.

TABLE 1.2. FUNDAMENTAL SKELETON VIBRATION OF 1,2-BENZISOXAZOLE[a]

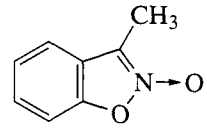
	Raman			IR Neutral solvents	
Assignment[1/80]	ν (cm^{-1})	I	ρ	ν (cm^{-1})	ε
A' symmetry					
ν_1	1613	13	0.45	1610	100
ν_2	1582	2	—	1585	14
ν_3	1514	36	0.25	1511	100
ν_4	1473	6	0.18	1470	71
ν_5	1432	45	0.19	1427	175
ν_6	1344	26	0.16	1341	55
ν_7	1306	7	0.26	1303	24
ν_8	1227	24	0.10	1227	105
ν_9	1003	38	0.05	1003	24
ν_{10}	934	22	0.06	933	101
ν_{11}	843	17	0.16	846	100
ν_{12}	763	100	0.05	764	94
ν_{13}	620	18	0.75	618	34
ν_{14}	534	28	0.20	532	11
ν_{15}	—	—	—	421	45
A″ symmetry					
Γ_1	—	—	—	744	362
Γ_2	—	—	—	667 (w)[a]	—
Γ_3	607	2	dp	604	141
Γ_4	562	3	0.75	556	6
Γ_5	—	—	—	394	41
Γ_6	260	4	0.75	256	29
	218	6	0.73	—	—

[a] See legend in Table 1.1 Footnote; dp = depolarized.

In a series of substituted 1,2-benzisoxazole-2-oxides, of which **4** is an example, the $\nu_{C=N}$ absorption occurred in the range 1570–1620 cm^{-1}, which is quite similar to that for 3,4-diphenylfuroxan (1575–1570 cm^{-1}), and the most characteristic absorptions were those in the ranges 1200–1240 and 1520–1590 cm^{-1}.[1/86,1/87]



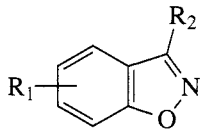
3

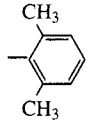
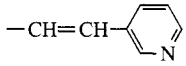


4

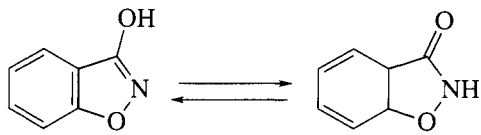
IR spectroscopy has been very useful in establishing the position of the tautomeric equilibrium in 1,2-benzisoxazolin-3-one. The enol form **5a** is preferred in the solid state as shown by the strong absorption at 3000–2500 cm^{-1}, the lack of carbonyl absorption and the C=N absorption at 1620 cm^{-1}. Both forms are

TABLE 1.3. IR DATA FOR THE C=N STRETCHING ABSORPTION OF SELECTED 1,2-BENZISOXAZOLE DERIVATIVES



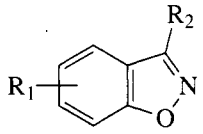
R_1	R_2	ν_{CN} (cm^{-1})	Phase	References
H	H	1607	CCl_4	1/65
4-OH	$-CH_3$	1613	Nujol	1/73
6-OCH_3,7-$COCH_3$	$-CH_3$	1595	CCl_4	2/80
6-OCH_2CHCH_2 (O)	$-CH_3$	1630	Nujol	2/87
H	$-C_6H_5$	1610	$CHCl_3$	3/84
H		1600	$CHCl_3$	3/84
6-OH,7-$COCH_3$	$-C_6H_5$	1630	$CHCl_3$	3/87
5-CH_3		1550	Nujol	4/84
6-OCH_3, 7-Cl		1620	Nujol	1/77
H	$-CHO$	1609	Nujol	1/82
6-OMe		1540	Nujol	1/74
H	$-CHBrCOOEt$	1600	Nujol	2/83
H	$-CHOHCOOEt$	1610	Nujol	2/83
H	$-OCH_2CH_2NMe_2$	1534	KBr	1/68
H	$-Cl$	1613	KBr	3/67

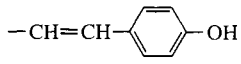
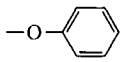
present in chloroform solution (OH absorption as above and carbonyl absorption at 1670 cm^{-1}).[2/67,1/69,1/71] Methylation with diazomethane gives both 3-methoxy-1,2-benzisoxazole ($\nu_{C=N}$ 1615 cm^{-1}) and 2-methyl-1,2-benzisoxazolin-3-one (ν_{CO} 1675 cm^{-1}).[1/71]



5a **5b**

TABLE 1.4. IR DATA OF SELECTED 1,2-BENZISOXAZOLE DERIVATIVES



R_1	R_2	ν (cm^{-1})	Phase	References
6-CH_3	$-CH_3$	2920 (CH), 1625 (C=N), 1604, 1575 (aromatic), 1346, 1391, 1256, 1152, 860, 800, 761, 638	Neat	1/79
H		1630 (CN), 1595, 1550 (C=C), 1510, 1475, 1440 (−O−C=N), 1385, 1335, 1280, 1230, 1105, 1015 (aromatic and isoxazole), 965 (HC=CH *trans*), 940, 830, 750 (aromatic)	KBr	2/79
H		2900(w), 1608(s), 1510(s), 1482(w), 1440(s), 1393(s), 1333(w), 1247(w), 1224(w), 911(m), 870(m), 747(s)	Neat	1/72
5-Cl	$-N_3$	2137(s), 1499(s), 1460(s), 1361(s), 1310(s), 1093(m), 930(m), 820(s), 752 (s), 717(m)	KBr	3/67
5-Cl		1527(s), 1460(s), 1366(s), 1316(m), 1193(m), 926(m), 820(m), 810(m), 763(s), 749(m), 690(m)	KBr	3/67

On this basis two kinds of derivatives obtained after alkylation or arylation can be recognized.[1/83,2/84] Accordingly, 3-chloro-1,2-benzisoxazole showed a sharp absorption at 1613 cm^{-1} ($\nu_{C=N}$),[3/67] while in a series of *N*-aryl derivatives of substituted 1,2-benzisoxazolin-3-one the absorption of the carbonyl function ranged from 1728 to 1753 cm^{-1}.[2/69]

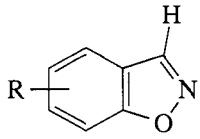
IR spectroscopy in solution at different dilutions has been used to support the attribution of the *E* or *Z* configurations of the isomeric α-oxyimino-1,2-benzisoxazole-3-acetic acid ethyl esters on the basis of the absorption frequency of the OH groups, which for the *Z* series indicates a bonded OH group as opposed to the free OH group of the *E* series.[2/83]

1.2.2. Ultraviolet Spectra

1,2-Benzisoxazole and its derivatives show only $\pi \rightarrow \pi^*$ transitions in the UV region in accordance with other heterocycles of this kind.

The UV spectrum of the parent compound has been reported by several authors.[1/41,1/65,1/79] In cyclohexane the band at 280 nm is clearly resolved into a fine structure.[1/41] Compared to the spectrum of the corresponding open com-

TABLE 1.5. UV DATA OF SELECTED 1,2-BENZISOXAZOLE DERIVATIVES



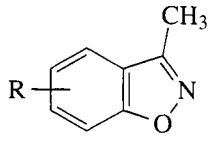
R	λ_{max}(nm)	log ε	Solvent	References
H	229	3.88	EtOH	1/79
	234	3.98		
	240	3.91		
	280	3.44		
H	235	4.00	EtOH	1/65
	243	3.91		
	280	3.46		
6-OCH_3	219	3.97	H_2O	2/73
	251	3.88		
	283	3.76		
	291	3.73		
5-OCH_3	236	3.92	H_2O	2/73
	306	3.54		
6-Cl	244	4.00	H_2O	2/73
	284	3.47		
5-Cl	236	3.95	H_2O	2/73
	293	3.50		
6-NO_2	275	4.18	H_2O	2/73
5,7-$(NO_2)_2$	255	4.15	H_2O (pH 3)	2/73
	305	3.61		

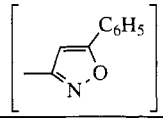
pound, salicylaldoxime, there is a hypsochromic shift of about 20 nm, which is indicative of the reduced electronic availability and the increased rigidity of the chromophore.

Calculations of $\pi \rightarrow \pi^*$ transitions with a variety of theoretical methods [including Pariser–Parr–Pople self-consistent field (PPP SCF) and modified CNDO-CI (complete neglect of differential overlap–configuration interaction)] are in good agreement with experimental data (see § 1.2.8).[3/69,1/70,2/71,2/72,1/78] The UV spectra of some 1,2-benzisoxazole compounds are reported in Table 1.5. From a comparison of 1,2-benzisoxazole and isoxazole spectral data, von Auwers first proposed the actual structure of this heterocycle.[1/24] The decomposition kinetics of 1,2-benzisoxazole and several substituted derivatives to the corresponding salicylonitriles have been followed using UV spectra that are fairly different for the two species, especially at pH 10.[2/73] On the basis of UV studies it has been found that 1,2-benzisoxazole derivatives are very weak bases, weaker than the corresponding isoxazoles (see § 1.2.9).[1/66]

Methyl substitution gives the expected slight bathochromic effect that seems higher when the methyl group is in position 6.[1/79] UV spectra allow better differ-

TABLE 1.6. UV DATA OF SELECTED 3-METHYL-1,2-BENZISOXAZOLE DERIVATIVES (EtOH)

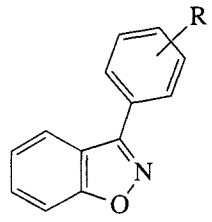


R	λ_{max}(nm)	log ε	References
H	231	3.85	1/79
	236	3.91	
	243	3.80	
	280	3.46	
	297(sh)	3.31	
H	236.5	3.92	4/69
	243.0	3.86	
	282.0	3.49	
	292.0(sh)	—	
H	235	3.89	3/71
	243	3.83	
	285	3.42	
	330	2.85	
5-CH_3	232	3.87	1/79
	237	3.92	
	243	3.83	
	289	3.51	
	297(sh)	3.36	
6-CH_3	240	3.98	1/79
	246(sh)	3.89	
	280	3.55	
	289(sh)	3.96	
4-OH	213	4.42	1/73
	242	3.39	
	292	3.36	
6-OH, 7-NH_2	228–232	4.03	4/87
	276–278	3.68	
6-OH, 7-$COCH_2COC_6H_5$	238	4.5	3/73
	285	4.5	
	370	4.6	
6-OH, 7-$N{=}CHC_6H_5$	225	4.41	4/87
	275	4.12	
	345	4.21	
6-OH, 7- 	230	4.13	3/87
	280	4.01	

entiation of 3-methyl-1,2-benzisoxazole and 1,2-benzisoxazole-3-acetic acid from the corresponding benzoxazole derivatives than do ^{1}H-NMR spectra.[4/69]

The spectral data of some 3-methyl-1,2-benzisoxazole derivatives are reported in Table 1.6.

TABLE 1.7. UV DATA OF SELECTED 3-PHENYL-1,2-BENZISOXAZOLE DERIVATIVES (EtOH)



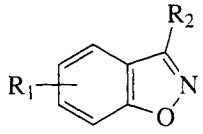
R	λ_{max} (nm)	log ε	References
3-NO_2	285	3.81	5/69
	224	4.29	
2-NHCHO	237(sh)	4.37	2/74
	246(sh)	4.29	
	291	3.90	
2-$NHCOCH_3$	235	4.32	2/74
	290	3.89	
2-NH_2, 5-Cl	225	4.33	2/74
	234	4.34	
	278	3.73	
	287(sh)	3.66	
	297	3.56	
	353	3.72	
2-NH_2	234	4.29	2/74
	277	3.63	
	284	3.63	
	295	3.65	
	332	3.66	

Even if a sound comparison is made difficult by the lack of sufficient data, substitution with a phenyl ring in position 3 seems to bring about the expected bathochromic and hyperchromic effect. Some UV spectral data of 3-phenyl-1,2-benzisoxazole derivatives are reported in Table 1.7.

The effect of other substituents on the various positions of the 1,2-benzisoxazole ring is reported in Table 1.8. In a series of 2-(1,2-benzisoxazolyl-3) acrylonitriles, UV spectra have been used to establish the *E* and *Z* configurations of the products obtained.[3/83] UV spectra have been used at different pH to evaluate the pK_a values of 4- and 6-hydroxy-1,2-benzisoxazole-3-carboxylic acid (see § 1.2.9).[1/75]

The spectral data of selected *O* and *N* derivatives of 1,2-benzisoxazolin-3-ones are reported in Table 1.9. Usually the *N*-alkyl and *N*-aryl derivatives show a bathochromic shift with respect to the corresponding *O*-alkyl and *O*-aryl derivatives. The *N* derivatives also show a higher ε. The spectra of some of these derivatives are reproduced in Böshagen and Geiger's work.[2/69]

TABLE 1.8. UV DATA OF SUBSTITUTED 1,2-BENZISOXAZOLES



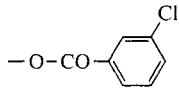
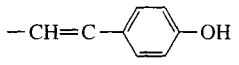
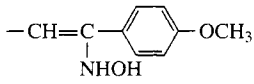
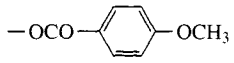
R_1	R_2	λ_{max} (nm)	log ε	Solvent	References
H	−OH	278	3.51	CH_3OH	2/69
		282	3.51		
		289	3.54		
H	−OH	236	3.70	CH_3OH	2/67
		274(sh)	3.39		
		278	3.50		
		282	3.50		
		288.5	3.53		
H	$-OCH_3$	236	3.76	CH_3OH	1/71
		273(sh)	3.45		
		278	3.57		
		282	3.57		
		288	3.58		
H	$-OCOC_6H_5$	279	3.70	CH_3OH	2/69
		289(sh)	3.51		
H		281	3.71	CH_3OH	2/69
		289(sh)	3.65		
H	$-OCOOCH_3$	279	3.50	CH_3OH	2/69
		289	3.45		
H	$-CH_2COOH$	237.5	3.78	EtOH	4/69
		244.0	3.67		
		283.0	3.40		
		293(sh)	—		
H		230	4.18	EtOH	2/79
		255	4.05		
		285	4.12		
		3.22	4.47		
5-CH_3		220	—		2/86, 5/87
		269	—		
		313	—		
5-Cl	−OH	291	3.47	$CHCl_3$	2/69
		295	3.47		
		302	3.46		
5-Cl	$-OCO-C_6H_5$	287	3.65	CH_3OH	2/69
		301(sh)	3.48		
5-Cl		268	4.35	CH_3OH	2/69
		302(sh)	3.72		
5-Cl	$-OCOOCH_3$	291	3.37	CH_3OH	2/69
		301	3.31		

TABLE 1.8 (*continued*)

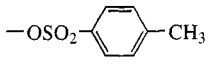
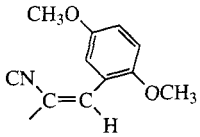
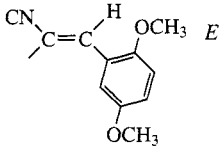
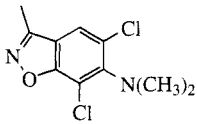
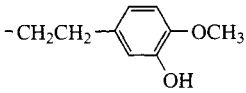
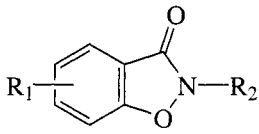
R_1	R_2	λ_{max} (nm)	log ε	Solvent	References
5-Cl		293 301(sh)	3.61 3.54	CH_3OH	2/69
5-Cl	 *E*	315 390	4.15 3.96	EtOH	3/83
5-Cl	 *E*	288 380	4.03 3.83	EtOH	3/83
5,7-Cl_2,6-$N(CH_3)_2$		218 323	3.75 3.13	EtOH	5/71
4-OH, 6-OCH_2COONa		259	4.01	H_2O	3/81
4-OH	−COOH	306 325	3.41 3,72	H_2O (pH 2) H_2O (pH 13)	1/75
6-OH	−COOH	289 312	3.93 4.07	H_2O (pH 3) H_2O (pH 10)	1/75

TABLE 1.9. UV DATA OF SELECTED 1,2-BENZISOXAZOLIN-3-ONE DERIVATIVES (CH_3OH)



R_1	R_2	λ_{max} (nm)	log ε	References
H	$-CH_3$	242(sh) 254(sh) 287 294	3.73 3.45 3.73 3.73	1/71
H	$-CH_2-CH=CH_2$	244(sh) 255(sh) 289 295	3.76 3.50 3.72 3.73	1/71

TABLE 1.9 (*continued*)

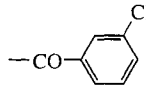
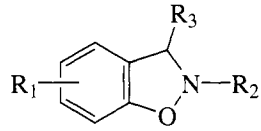
R_1	R_2	λ_{max} (nm)	log ε	References
H	$-COCH_3$	299	3.71	2/69
		309	3.69	
H		307	3.60	2/69
		315(sh)	3.59	
H	$-COOCH_3$	296	3.72	2/69
		306	3.70	
5-Cl	$-COCH_3$	312	3.65	2/69
		322	3.62	
5-Cl	$-COOCH_3$	309	3.64	2/69
		319	3.61	

TABLE 1.10. UV DATA OF 2,3-DIHYDRO-1,2-BENZISOXAZOLE DERIVATIVES



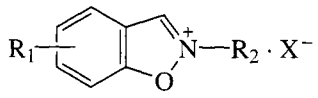
R_1	R_2	R_3	λ_{max} (nm)	log ε	Solvent	References
H	$-C_2H_5$	H	280	3.34	H_2O (pH 5–12)	4/67
			276	3.21	H_2O(pH1)	
			269	3.24		
5-NO_2	H	$-CH_2COOH$	232	4.06	EtOH	4/71
			309	3.87		
5-NO_2	H, HCl	$-CH_2COOH$	230	3.93	EtOH	4/71
			318	3.93		
5-NO_2	H	$-CH_2COOCH_3$	231	3.93	EtOH	4/71
			320	3.99		
5-NO_2	$-COCH_3$	$-CH_2COOH$	233.5	418	EtOH	4/71
			302	3.92		

The UV spectra of a few 2,3-dihydro-derivatives are known; they are reported in Table 1.10. There are no reported UV spectral data for 1,2-benzisoxazole-2-oxides.

UV spectra have been reported for only two 1,2-benzisoxazolium salts, and the data are shown in Table 1.11. Even if comparison is difficult because of the limited amount of data available, quaternization of nitrogen seems to induce a strong bathochromic shift in the spectra.

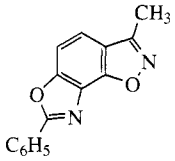
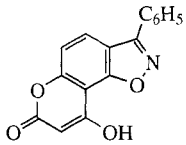
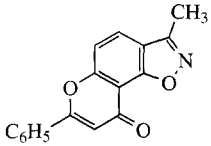
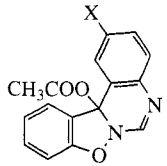
Finally, the data for a few polynuclear condensed 1,2-benzisoxazole derivatives are reported in Table 1.12. In a series of 9(*H*)-oxopyrano[2,3-*g*]1,2-benzisoxazoles, three maxima have been observed in all cases around 220, 265, and 320 nm. The former has been attributed to the isoxazole moiety acting as an independent chromophore.[3/73]

TABLE 1.11. UV DATA OF 1,2-BENZISOXAZOLIUM SALTS (H_2O)



R_1	R_2/X	λ_{max} (nm)	log ε	References
H	$-C_2H_5/BF_4^-$	258	4.12	1/65
		297	3.46	
7-OH	$-C_2H_5/BF_4^-$	307	3.42	3/74
		248	3.94	
		214	3.30	

TABLE 1.12. UV DATA OF SELECTED POLYCYCLIC 1,2-BENZISOXAZOLES

Compound	λ_{max} (nm)	log ε	Solvent	References
	220 250 280	4.19 4.30 4.43	EtOH	4/87
	240 280 305	4.10 3.86 3.91	EtOH	3/87
	220 264(265) 294(303–306)	4.10 4.39 4.25	EtOH	3/73, 3/87
	X=H; 230(sh) 286 X=Cl; 286	3.97 3.56 3.80	*i*.PrOH *i*.PrOH	2/74 2/74

1.2.3. Nuclear Magnetic Resonance Spectra

In the presence of condensed benzene and isoxazole rings, 1,2-benzisoxazole derivatives give NMR spectra that have the characteristics of both nuclei and generally lack original features. Perhaps for this reason NMR studies on this heterocyclic system are much less numerous than those concerning parent benzene and isoxazole rings.

1.2.3.1. PMR Spectra

The chemical shifts and coupling constants of the protons of 1,2-benzisoxazole have been analyzed as a five-spin system that absorbs in the aromatic region. Coupling constants of the benzenoid ring reflect normal aromaticity and have the usual values, following the well-known pattern $J_o > J_m > J_p$.

The hydrogen in position 3 shows long ring interring couplings only along well-defined patterns. Thus, following the well-known straight zigzag route, H3 couples with H7 with a coupling constant of 1.16 Hz, while the 3,4 coupling constant is definitely smaller (0.03 Hz).[3/72] Substitution of H3 with a methyl eliminates this interring interaction and results in a substantially simplified spectrum.[3/72] In fact, the PMR spectra of 3-substituted-1,2-benzisoxazoles can be treated like those of substituted benzene and do not need to be discussed in detail. This is exemplified in Table 1.13, where the spectra of a number of selected derivatives are reported.

In a study on heteroaromatic compounds the theoretical ring current contributions to diamagnetic anisotropy and proton shielding in 1,2-benzisoxazoles have been calculated.[5/67] More recently the diamagnetic susceptibility and ^{1}H- and ^{13}C–NMR chemical shifts have been calculated and found to agree with experimental data.[1/85]

3-Substituted 1,2-benzisoxazoles are of special interest, and for this reason the PMR spectra of a few derivatives are reported in Tables 1.14 and 1.15. Table 1.16 shows the ^{1}H-NMR data of a few 2,3-dihydro-1,2-benzisoxazoles.

The PMR spectra of 1,2-benzisoxazole-2-oxides show patterns similar to those of the corresponding 1,2-benzisoxazole derivatives, with only a slight upfield shift of the 3-methyl resonance with respect to the parent compound (δ 2.37 and 2.43, respectively). The coupling constants also remain similar to those of substituted benzenes (J_o = 7.0–8.0; J_m = 1.8–3.0; J_p = 0.5–1.0 Hz).[1/86,1/88]

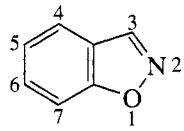
On the other hand, there is, as expected, a sharp deshielding effect of the quaternized nitrogen of 1,2-benzisoxazolium salts on the hydrogen or methyl in position 3 (Table 1.17). No details on coupling constants are available.

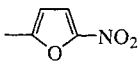
The *N*-methyl chemical shift in the spectrum of 2-methyl-1,2-benzisoxazolium perchlorate has been used with that of the corresponding isoxazolium compound and those of other similar heterocyclic compounds to evaluate the donating effect of the heteroatom. From these studies the donating order in the ground state for quaternized azoles has been found to be $NCH_3 > S > O$.[4/74]

In a series of *O*- and *N*-acyl derivatives of 1,2-benzisoxazolin-3-ones no difference in the aromatic region of the two series of compounds has been found.[2/69] The same happens for 2-methyl- and 3-methoxy-1,2-benzisoxazole; in this case N–CH_3 and O–CH_3 signals have been found at δ 3.63 and 4.12, respectively.[1/71]

The configuration of a series of isomeric oximes like **6a** and **6b** has been established on the basis of the deshielding effect of the hydroxyl group on the proton in position 4. In fact, while in the *Z* series (**6b**) the aromatic protons

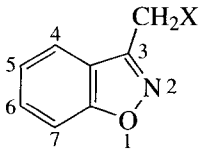
TABLE 1.13. PMR DATA OF SELECTED 1,2-BENZISOXAZOLES [δ, TMS = 0, J (Hz)][a]



3	4	5	6	7	Solvent	References
8.8(s)•		7.0–7.7			Neat	1/65
8.86(s)•		7.11–7.75			CCl_4	1/79
8.85	7.69	7.25	7.47	7.58	Neat	3/72
8.87						2/78
8.97(d)•	NO_2	9.64(d)•	NO_2	9.10(dd)•	$(CD_3)_2CO$	4/79
CH_3(2.43)$^+$	7.44	7.19	7.45	7.47	Neat	3/72
CH_3(2.43)$^+$	7.18(d,8)*	6.62(dd,2,8)*	OMe (3.8)$^+$	6.70(d,2)*	CCl_4	5/79
CH_3(2.68)$^+$	8.61(d,2)*	NO_2	8.46(dd,9,2)*	7.65(d,9)*	$CDCl_3$	4/77, 7/77
CH_3(2.41)$^+$	7.32(d,8)*°	6.95(d,8)*°	CH_3(2.31)$^+$	7.14(s)•	CCl_4	1/79
CH_3(2.65)$^+$	OH	6.74(q,8,1)*°	7.42(t,8)*	7.04(q,8,1)*°	—	1/73
CH_3(2.41)$^+$	7.05(d,8)*	6.15(d,8)*	OMe(3.85)$^+$	Br	CCl_4	5/79
CH_3(2.75)$^+$	7.95(s)•	Br	OMe(4.07)$^+$	7.08(s)•	TFA	5/79
CH_3(2.26)$^+$	7.43(d,9)*	7.06(d,9)*	OMe(4.06)$^+$	$COCH_3$(2.73)$^+$	CCl_4	2/80
CH_3(2.50)$^+$	7.5(d)°	6.8(d)°	OH (13.2)$^+$	$COCH_3$(2.9)$^+$	$CDCl_3$	3/73
CH_3(2.52)$^+$	7.72(d,9)*	6.92(d,9)*	OH(11.85)$^+$	CHO(10.50)$^+$	$CDCl_3$	2/77
CH_3	7.76(d,2)*	CH_3	8.23(d,2)*	NO_2	$CDCl_3$	7/77
CH_3	NO_2	CH_3	7.68(d,11)*	7.52(d,11)*	$CDCl_3$	7/77
CH_3	7.92(s)•	NO_2	OH	6.95(s)•	$CDCl_3$	6/83
CH_3(2.68)$^+$	7.56(d,9)*	6.95(d,9)*	OH	NO_2	$CDCl_3$	6/83
CH_3	NO_2	Cl	7.74(d,11)*	7.70 (d,11)*	$CDCl_3$	7/77
CH_3	8.89(d,2)*	NO_2	8.36(d,2)*	NO_2	$CDCl_3$	7/77
CH_3(2.53)$^+$	7.63(s)•	Br	OH(14.0)$^+$	$COCH_3$(2.87)$^+$	CCl_4	2/80
CH_2-CH_3	7.62(d,8)*	6.36(d,8)*	OH	$COCH_3$(2.88)$^+$	—	5/77
C_6H_5		7.10–7.95			$CDCl_3$	3/84
C_6H_5(7.5)$^+$	8.0(q,8)*		OH(6.9)$^+$	$COCH_3$(2.5)$^+$	—	3/87
	7.24(d,2)*	CH_3(2.25)$^+$	7.56(dd;2,8)*	7.6(d,8)*	$CDCl_3$	4/84
	7.8 (d)•	6.9(d)•	OMe(3.9)$^+$	Cl	$CDCl_3$	1/77
	7.67(m)•	7.67(m)•	7.67(m)•	8.83(m)•	$CDCl_3$	5/69
OH		7.15–7.95			$CDCl_3$	1/71
NH_2	7.95(d,9)*	7.25 (m)•	7.48(m)•	7.48(m)•	d_6-DMSO	2/89
NH_2	OH	6.57(d,9)*	7.30(dd,9)*	6.85(d,9)*	d_6-DMSO	2/89
COOH	OH(9.6)$^+$	6.78(d,8)*	7.66(t,8)*	7.20(d,8)*	$(CD_3)_2CO$	1/75
COOMe	NH_2	6.47(d,8)*	7.34(t,8)*	6.89(d.8)*	$CDCl_3$	1/75

[a]*Key*: • multiplicity; $^+\delta$ of the substituent; *multiplicity and coupling constants (Hz); ° the attribution of these signals has not been proved.

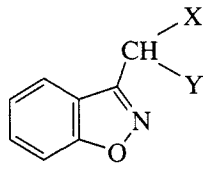
TABLE 1.14. PMR DATA OF SELECTED 3-α-MONOSUBSTITUTED 1,2-BENZISOXAZOLES [δ, TMS = 0, J (Hz)][a]



X	CH_2	4	5	6	7	Solvent	References
Br	4.85(s)•		7.00−7.84 (m)•			$CDCl_3$	4/72
Br	4.84(s)•	8.67(d,2)*	NO_2	8.44(dd,9,2)*	7.68(d,9)*	$CDCl_3$	4/72
OH	4.94(s)•	6.87−7.45(m)•	OMe(3.73)+		6.87−7.45(m)•	$CDCl_3$	4/72
COOH	4.27	8.93(d,2)*	NO_2	8.53(dd,2,10)*	7.98(d,10)*	d_6-DMSO	4/78
COOH	4.08(s)•	OMe(3.97)+	6.75(d,9)*	7.73(d,9)*	Br	$CD_3OD/CDCl_3$	4/72
COCl	4.59 (s)•		7.2−7.9(m)•			$CDCl_3$	2/82
COOMe	4.08(s)•	Br	OH	7.03(d,9)*	7.98(d,9)*	$CD_3OD/CDCl_3$	4/72
SO_2NH_2	4.84(s)•	7.82−8.02(m)•		7.35−7.80(m)•		d_6-DMSO	3/82
SO_2NH_2	4.93	8.50(dd,1,2)*	SO_2NH_2	8.17(dd,2,10)*	7.97(dd,1,10)*	d_6-DMSO	4/78
$-SO-C_6H_5$ ‖ NH	4.87(s)•		7.2−8.2(m)•			$CDCl_3$	4/82
	6.0(s)•	7.95(d)•	7.55(dd)•	Cl	8.05(d)•	d_6-DMSO	3/89

[a]*Key*: • multiplicity; + δ of the substituent; *multiplicity and coupling constants (Hz).

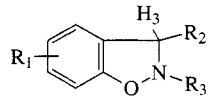
TABLE 1.15. PMR DATA OF SELECTED 3-α,α′-DISUBSTITUTED 1,2-BENZISOXAZOLES [δ, TMS = 0, J (Hz)]



X	Y	CH	Solvent	References
Br	Br	6.94[a]	$CDCl_3$	4/72
OMe	OMe	5.78	$CDCl_3$	1/82
=O		10.47	$CDCl_3$	1/82
$=N-SOC_6H_5$		9.28	$CDCl_3$	1/82
C_6H_{11}	COOEt	3.98	$CDCl_3$	6/87
Br	COOEt	5.84	$CDCl_3$	2/83
OH	COOMe	5.76	$CDCl_3$	2/83
NH_2	COOH	6.07	D_2O/DCl	4/72

[a] 5-Methoxy derivative.

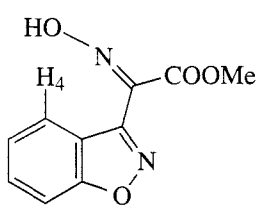
TABLE 1.16. PMR DATA OF SELECTED 2,3-DIHYDRO-1,2-BENZISOXAZOLES (δ, TMS = 0)



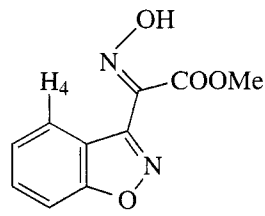
R_1	R_2	R_3	H_3	Solvent	References
H	H	CH_2-CH_3 (2.8,q;1.1,t)[a]	4.1(s)	CCl_4	4/67
H	H	$C(CH_3)_3$(1.23,s)[a]	3.96(s)	$CDCl_3$	1/84
H	CH_3(1.70,d)[a]	CH_2-CH_3	4.65(q)	$CDCl_3$	2/88
5-NO_2	CH_2COOH	H(9.13,s)	5.28(t)	d_6-DMSO	4/71
5-NO_2	CH_2COOMe	H	5.20(t)	$CDCl_3$	4/71
5-NO_2	CH_2COOH	$COCH_3$(2.23,s)[a]	6.10(t)	d_6-DMSO	4/71

[a] Chemical shift and multiplicity of the substituent.

cluster between 7.82 and 6.89 δ, in the *E* series (**6a**) proton 4 is further deshielded (δ = 8.11 ppm) and appears as an isolated doublet.[2/83]

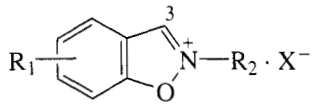


6a (*E*)



6b (*Z*)

TABLE 1.17. PMR DATA OF SELECTED 1,2-BENZISOXAZOLIUM SALTS
[δ, TMS = 0, J (Hz)]



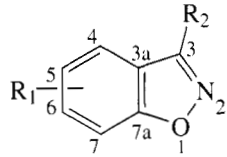
R_1	R_2	X^-	3	Solvent	References
H	CH_3(4.60,s)[a]	BF_4^-	CH_3(3.18,s)[a]	$(CD_3)_2CO$	4/77
5-NO_2	CH_3(4.70,s)[a]	BF_4^-	CH_3(3.30,s)[a]	$(CD_3)_2CO$	4/77
H	CH_2–CH_3(4.90,q)[a]	BF_4^-	H 9.80(s)[b]	CH_3CN	1/65
5-NO_2	CH_2–CH_3(4.90,q)[a]	BF_4^-	H 10.00(s)[b]	CH_3CN	4/67
H	$C(CH_3)_3$(2.02,s)[a]	ClO_4^-	H 9.98(s)[b]	CD_3NO_2	8/84

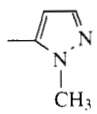
[a] Chemical shift and multiplicity of the substituent (printed in italics in ethyl derivatives).
[b] Multiplicity.

1.2.3.2. ^{13}C-NMR Spectra

The ^{13}C-NMR spectrum of the parent compound shows no major deviation from that expected on the basis of benzene and isoxazole spectra.[2/78] It has been found not to be diagnostic in distinguishing between the 1,2-benzisoxazole and its isomer, anthranil. Some ^{13}C-NMR data are reported in Table 1.18; those

TABLE 1.18. ^{13}C-NMR CHEMICAL SHIFTS (ppm) OF 1,2-BENZISOXAZOLE DERIVATIVES (TMS = 0, DMSO-d_6)

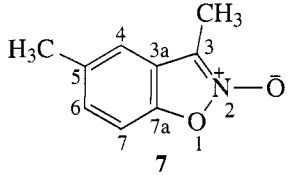


R_1	R_2	3	4	5	6	7	7a	3a	References
H	H	147.1	124.3	123.0	130.6	109.9	162.7	122.2	2/78
H	H	146.1	123.6	121.9	129.9	109.5	162.1	121.2	1/88
H	CH_3	154.8	123.1	121.2	129.6	109.4	162.7	122.2	1/88
4,6-$(CH_3)_2$	CH_3	154.6	132.7	126.0	140.7	107.6	164.4	119.0	1/88
5-Cl	OH	165.0	120.8	127.5	130.6	111.8	162.0	116.3	3/79
5-$COCH_3$	OH	167.0	123.3	132.6	130.3	110.3	165.3	115.0	3/79
6-OCH_3		152.1	122.2	114.9	162.4	92.9	165.8	113.4	1/89
6-OCH_3, 7-Cl		148.7	120.7	113.3	157.0	102.2	159.5	114.6	1/90

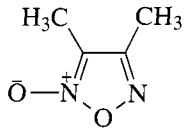
of ring-substituted compounds allow easy assignment of the substituted position.

As with ^{1}H-NMR, ^{13}C-NMR chemical shifts of 1,2-benzisoxazole have also been calculated by theoretical methods and found to comply with the experimental values.[1/85]

The ^{13}C-NMR spectra of variously substituted 1,2-benzisoxazole-*N*-oxides like **7** contain a high field signal (around 118 ppm) for the carbon at the 3 position that is quite close to that of the corresponding carbon signal in the ^{13}C spectra of furoxanes **8** (around 114 ppm).[3/80]



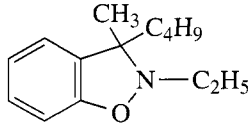
7



8

The N—O dipole causes a charge polarization in the ring through its "push–pull" character. The effect of the dipole is however largely localized on the isoxazole ring and is particularly marked on the carbon atoms in positions 3 and 7a. The presence of substituents does not have a marked effect on ^{13}C resonance.[1/88]

Finally, in the ^{13}C spectrum of **9**, apparently the only 2,3-dihydro-1,2-benzisoxazole for which such a spectrum has been reported, the signal of the quaternary carbon appears at 69.60 δ ($CDCl_3$).[2/88]



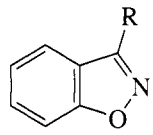
9

1.2.3.3. Other NMR Spectra

The ^{15}N and ^{14}N chemical shifts of 1,2-benzisoxazole (Table 1.19) have been reported in comparison with those of other isomeric benzazoles.[2/78,3/78,5/84]

The ^{14}N chemical shift was found to provide a simple and unambiguous argument for benzenoid and quinoid structures and can be used to discriminate between 1,2-benzisoxazole and anthranil [(δ($MeNO_2$) = +8 (±1)].[2/78] The ^{15}N chemical shift was also able to discriminate between isomeric benzisoxazoles.[3/78,5/84] It has also been found in several azole rings that have been examined, including 1,2-benzisoxazole and its isomer. There is a simple correlation between nitrogen shift and calculated π-charge densities, which can be used in the estimation of one of the parameters from the other.[3/78]

TABLE 1.19. ^{15}N AND ^{14}N CHEMICAL SHIFTS (ppm) OF 1.2-BENZISOXAZOLE COMPOUNDS ($MeNO_2$ EXTERNAL REFERENCE)



		Chemical shifts		Half-height width	
R	Solvent	^{15}N [$^2J(^{15}N-^1H)$]	^{14}N	(Hz)	References
H	Neat	—	$+27 \pm 1$	1250 ± 25	2/78, 3/78
H	DMSO	−3.2 (14.6)	—	—	5/84
H	$CDCl_3$	−0.2	—	—	1/88
CH_3	$CDCl_3$	−9.0	—	—	1/88

The introduction of an exocyclic oxygen, as in 3-methyl-1,2-benzisoxazole-2-oxide, shifted the ^{15}N resonance to −59.5 ppm with a large shielding of 50.5 ppm compared with the corresponding 3-methyl-1,2-benzisoxazole.[1/88]

1.2.4. Mass Spectra

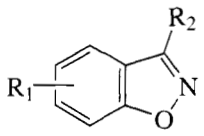
Mass spectral data for 1,2-benzisoxazole derivatives are scanty. Thus the mass spectra of the parent compound and its 3,5-dimethyl-substituted derivatives were partially reported by Doppler et al. in 1979 but not interpreted.[1/79]

A few years before Maquestiau et al. had shown, on the basis of metastable ion analysis, that 1,2-benzisoxazole, like benzoxazole, isomerized to *o*-cyanophenol before degradation, with a loss of CO(28) and HCN(27).[2/75] This finding rationalized the loss of carbon monoxide, which was otherwise difficult to explain. However the authors reported only an unidentified mass spectrum which does not correspond to the one reported by Doppler.

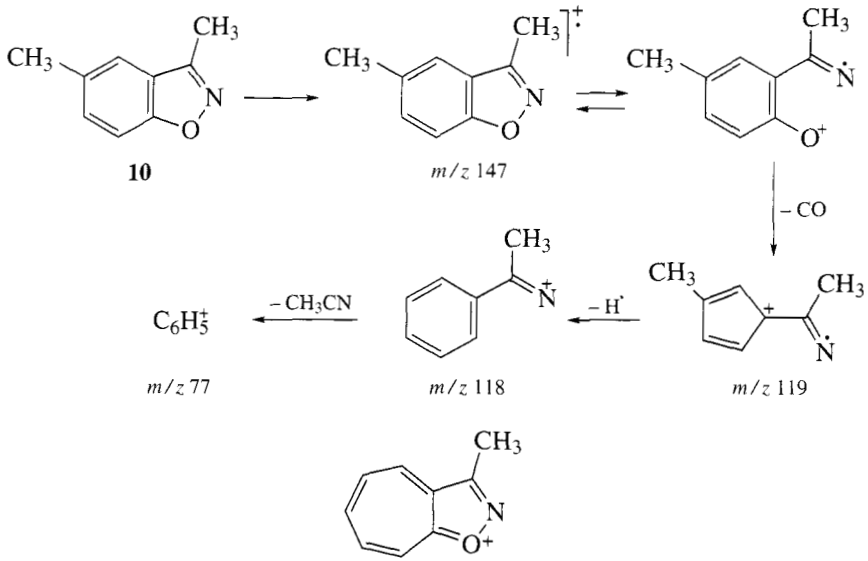
Later on, the mass spectrum of 1,2-benzisoxazole was again examined under chemical ionization conditions (methane-d_4 as CI reagent gas) by mass-analyzed ion kinetic energy (MIKE) spectrometry.[1/84] The loss of mass 27 (HCN) was shown to be favored over that of 28 (CO), and it was confirmed that the latter corresponds to the loss of carbon monoxide. However in this case also no complete mass spectrum was reported.

More recently, the mass spectrum of 3,5-dimethyl-1,2-benzisoxazole (**10**) (Table 1.20), as well as spectra of other 3,5-dialkyl analogs, have been reported and analyzed.[2/90] On the basis of metastable peaks, the fragmentation has been considered to proceed through cleavage of N–O linkage followed by carbon monoxide and acetonitrile expulsion. The peak at m/z 146 has been attributed to

TABLE 1.20. MASS SPECTRA OF 1,2-BENZISOXAZOLE AND 3,5-DIMETHYL-1,2-BENZISOXAZOLE



R_1	R_2	*m/z* (relative intensity)	References
H	H	119(M^+,95); 105(5); 91(100); 64(59); 63(55); 38(38)	1/79
5-CH_3	CH_3	147(M^+,100); 132(9); 118(51); 105(20); 91(13); 78(96); 77(49); 63(22); 51(64); 39(33).	1/79, 2/90



11

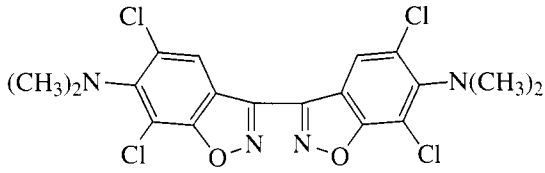
an azulene-like structure (**11**) whose stability explains the relatively low abundance of lower fragmentation ions.

In general the spectra of 5-alkyl-substituted 3-methyl-1,2-benzisoxazole are similar to those of the corresponding benzoxazoles. The differences are mainly due to the relative abundance of the ion peak and reflect the lability of the O–N bond. However when the substituent in position 3 is larger than a methyl group,

the fragmentation pattern depends on the relative positions of the alkyl group and the heterocyclic nitrogen atom and, as a consequence, the two heterocyclic rings can easily be distinguished.

The spectra of some substituted 3-phenyl-1,2-benzisoxazoles have been partially reported, and in all cases a significant $[M–CO]^+$ peak is present. In the case of 3-(2,6-dimethylphenyl)-1,2-benzisoxazole a large $[M-1]^+$ peak has been found.[3/84]

The spectrum of the dimeric compound **12** shows an unprecedented $[M^+–2NO]$ peak, which also constitutes the base peak.[5/71] As will be discussed later, such fragmentation is typical of 1,2-benzisoxazole-2-oxides and could cast some doubts on the structure of **12**.



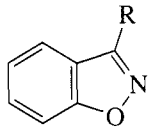
12

Mass spectral data for compound **12**: 460(M^+, 28); 444(M^+–O,19); 400(M^+–2NO,100); 230(M^+/2,61); 213(M^+/2-OH,90); 204(M^+/2-CN,78); 44[$N(CH_3)_2^+$, 28].

The spectra of two 3-alkylamino derivatives of 1,2-benzisoxazole have been reported (Table 1.21).[1/72]

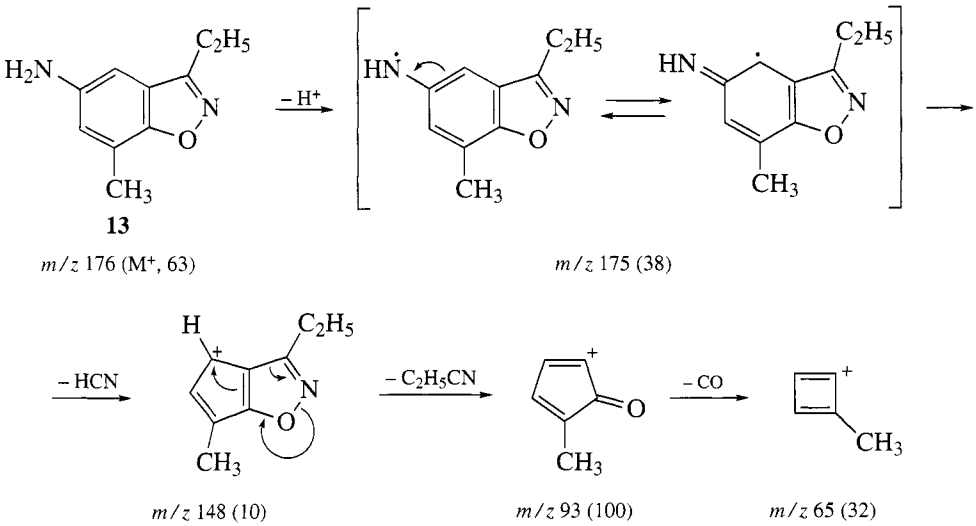
In a series of 1,2-benzisoxazoles substituted in the phenyl ring, the fragmentation pattern has been shown to be controlled by the substituents.[3/73,2/77,5/78] Thus

TABLE 1.21. MASS SPECTRA OF 3-ALKYLAMINO-1,2-BENZISOXAZOLES



R	*m/z* (relative intensity)	References
—N△	161(10); 160(M^+,90); 133(8);132(10); 105(8); 104(12); 91(8); 90(11); 64(12); 63(15); 42(100).	1/72
$NHCH_2CH_2Cl$	198(34); 196(M^+,100); 161(29); 148(31); 147 (78); 134(42); 119(39); 118(86); 91(45); 90 (46)	1/72

in a series of amino and sulfanilamido 1,2-benzisoxazoles such as **13**, the following fragmentation pattern has been suggested (Scheme 1.1).[5/78]

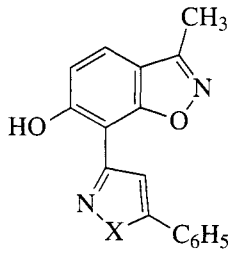


Scheme 1.1

For 3-methyl-6-hydroxy-7-formyl-1,2-benzisoxazole (**14**) and the corresponding 7-acetyl derivative the fragmentation shown in Scheme 1.2 has been proposed.[3/73,2/77]

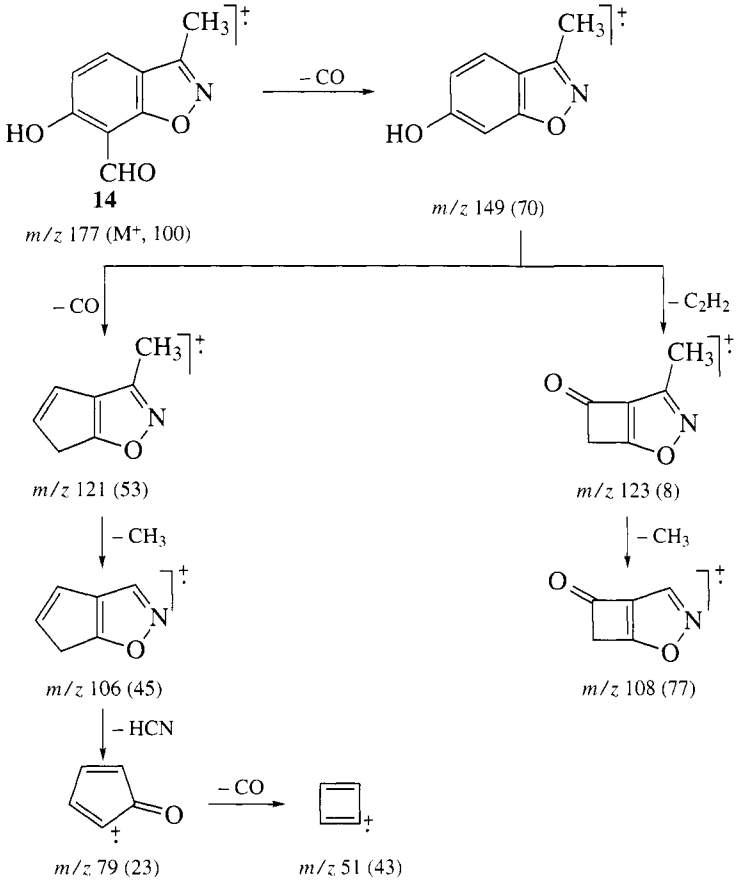
In 1981 Kallury et al., after examining the mass spectra of some substituted 1,2-benzisoxazoles, proposed that the ring isomerizes to a benzoxazole prior to fission, as this rearrangement is more pronounced with simple derivatives such as **15** (Scheme 1.3).[4/81] The reasons for this proposal lay in the ubiquitous presence of $[M–CH_3CN]^+$ and $[M–CH_3CO]^+$ ions and in the well-known thermal and photochemical isomerizations of 1,2-benzisoxazoles (see § 1.4.4).

In the same study it was found that the degradation pattern of compounds **16** and **17** mostly resemble 5-phenylisoxazole and 1,2-diphenylpyrazole, respec-

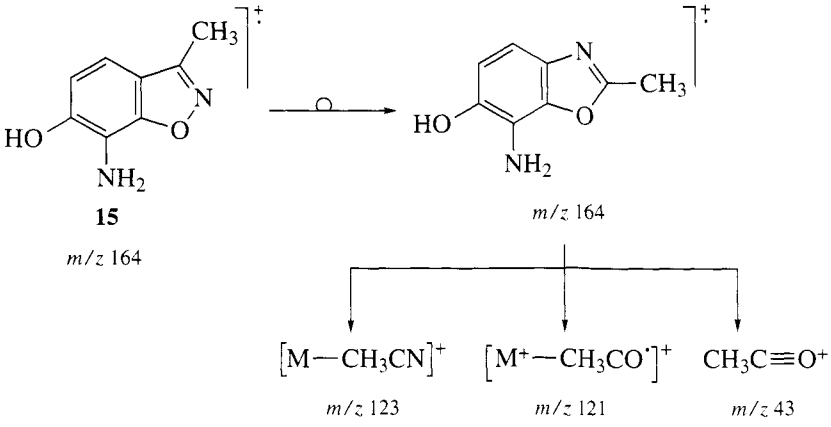


16, X= O

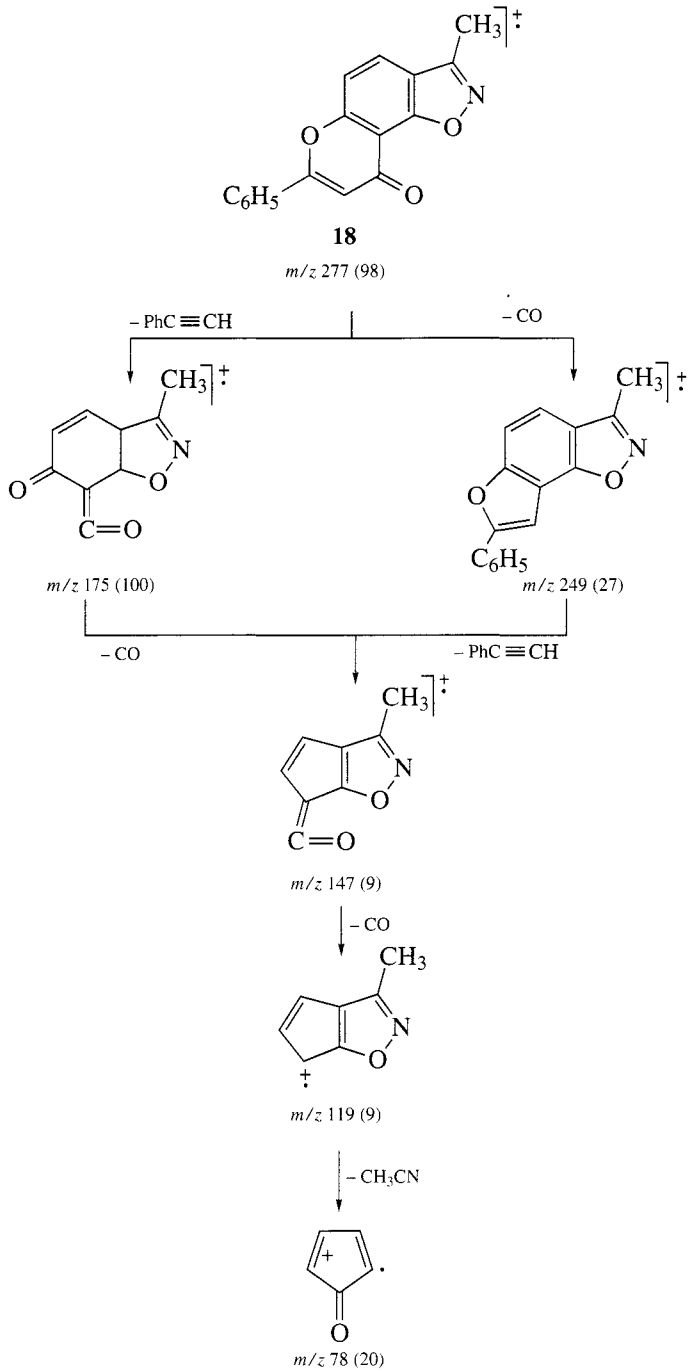
17, X= NC_6H_5



Scheme 1.2



Scheme 1.3

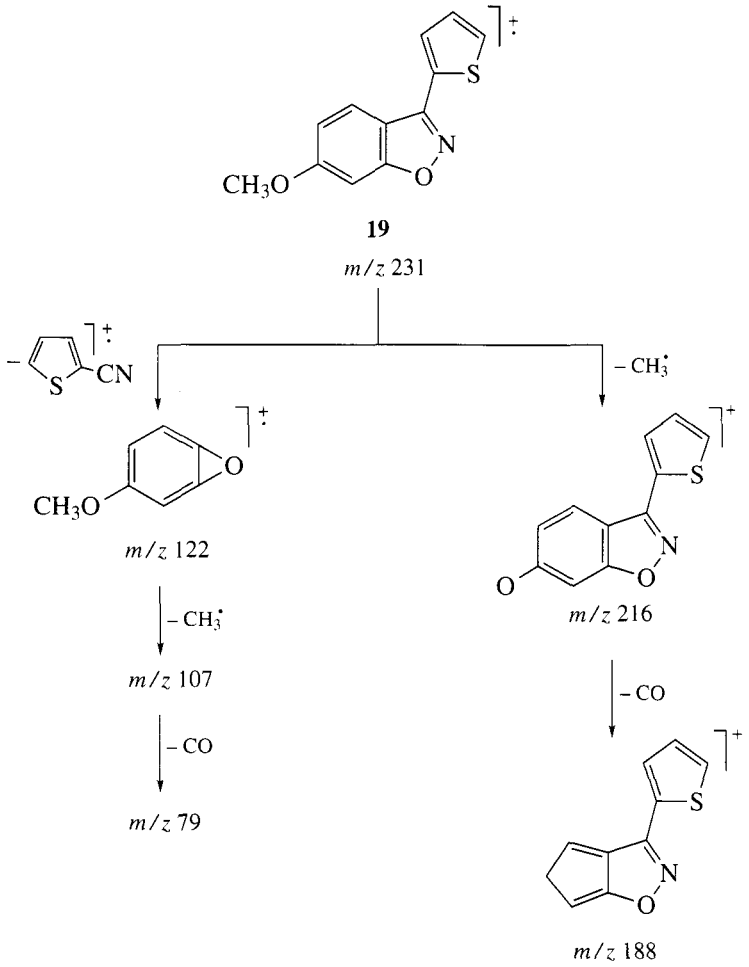

CH3
N
O
O
C6H5
O
18
m/z 277 (98)
– PhC≡CH
– CO
CH3
N
O
O
C=O
m/z 175 (100)
CH3
N
O
O
C6H5
m/z 249 (27)
– CO
– PhC≡CH
CH3
N
O
C=O
m/z 147 (9)
– CO
CH3
N
O
m/z 119 (9)
– CH3CN
O
m/z 78 (20)

Scheme 1.4

tively, indicating that the isoxazole and pyrazole moieties are more prone to rearrangement than the 1,2-benzisoxazole ring.

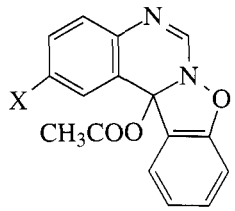
The greater tendency of the isoxazole nucleus to survive fragmentation with respect to the substituted benzene ring is confirmed by the spectra of some condensed polynuclear derivatives of 1,2-benzisoxazole such as **18** (Scheme 1.4).[3/73] This compound is fragmented mainly through Diels–Alder fission of the γ-pyrone nucleus, which is typical of flavones.

However, in the case of 6-methoxy-3-(2-thienyl)-1,2-benzisoxazole (**19**), the mass spectrum is characterized by the cleavage of both the nitrogen–oxygen bond and the substituted phenyl ring (Scheme 1.5).[1/89]



Scheme 1.5

The mass spectra of compounds **20** and **21** have been reported but not interpreted.[2/74]

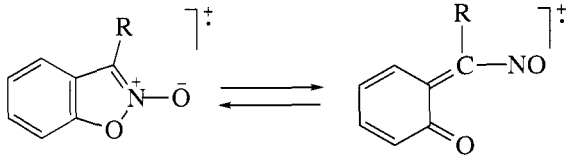


20, X= H
21, X= Cl

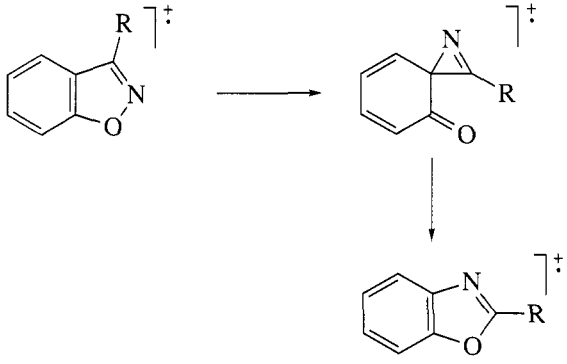
The mass spectra of 1,2-benzisoxazole *N*-oxides have been studied in detail, and several of them have been fully reported.[2/85,1/86,1/87]

The presence of substituents in position 3 causes considerable differences in the observed fragmentation patterns. On the other hand, phenyl substituents do not seem to influence skeletal fragmentation.[2/85]

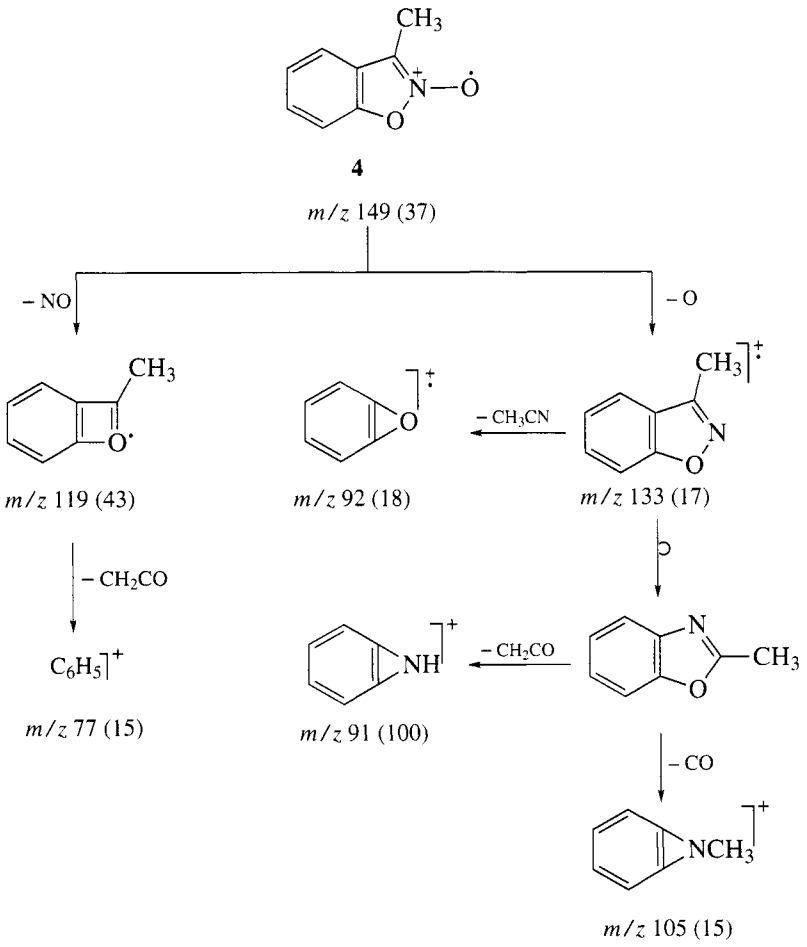
The fragmentation pattern of such compounds is characterized by peaks at $[M^+-16]^+$ and $[M^+-30]^+$ corresponding to a loss of oxygen and of a nitroso group that probably occurs through an impact-induced isomerization to a valence bond isomer that can easily eliminate NO.



In this case, too, an isomerization of the deoxygenated species to benzoxazole through an intermediate aziridine ring has been postulated on the basis of the photochemical and thermal behavior of 1,2-benzisoxazoles.



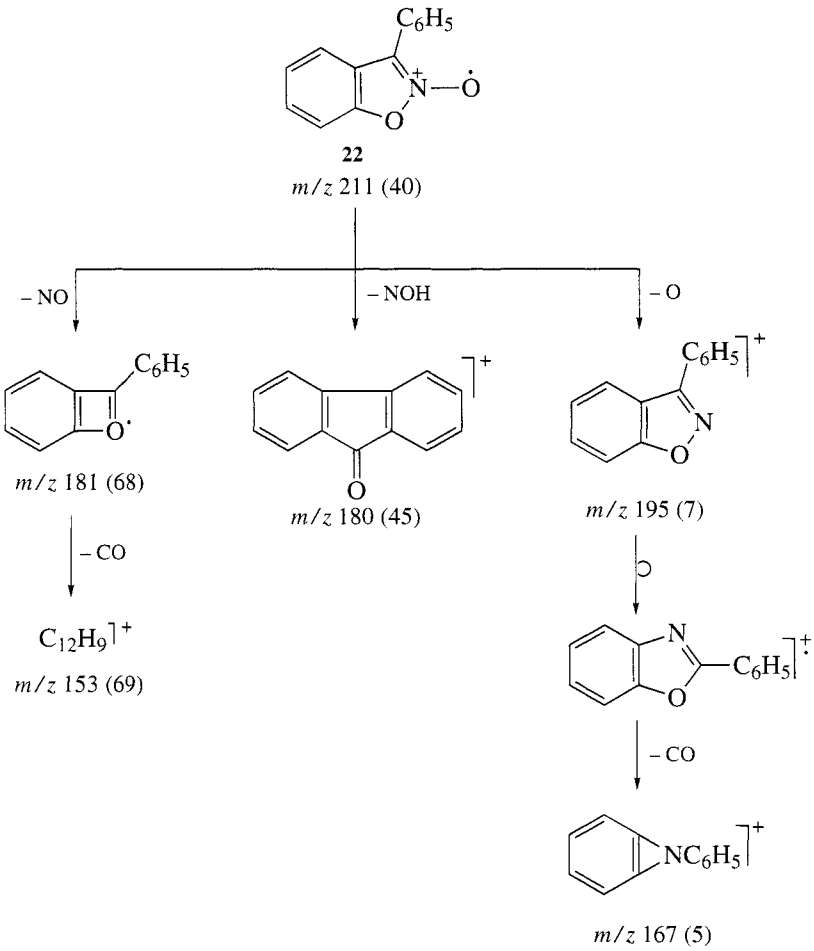
The proposed fragmentation pathways of 3-methyl- and 3-phenyl-1,2-benzisoxazole-*N*-oxides (**4** and **22**) are depicted in Schemes 1.6 and 1.7, respectively.



Scheme 1.6

1.2.5. Other Spectra

The He(I) photoelectron spectra of 1,2-benzisoxazole have been obtained and assigned by means of a combination of heteroatom effects and ab initio molecular orbital calculations.[1/78] The experimental ionization potentials (IPs) and assigned orbitals are reported in Table 1.22.



Scheme 1.7

TABLE 1.22. EXPERIMENTAL IONIZATION POTENTIALS AND ASSIGNED ORBITALS (ENERGY, ε_i) OF 1,2-BENZISOXAZOLE

IP	$-\varepsilon_i$ (eV)	Assignment
9.20	10.22, 10.29	π,π
11.27	13.28, 13.34	LP_N,π
12.15	14.07, 14.81	σ,π
13.15	15.42	σ
13.68	15.85	σ
14.53	17.13, 17.42	σ,σ
15.18	18.68, 18.79	σ,π
16.97	19.61, 20.40	σ,σ
19.34	22.81, 23.17	σ,σ

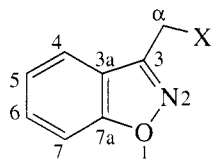
1.2.6. Crystal and Molecular Structure

There are only a few examples of X-ray structures of 1,2-benzisoxazole compounds, derivatives **23** and **24** are among these (Table 1.23).[3/88,3/90]

The 1,2-benzisoxazole ring appears to be planar, and there are indications of extensive electron delocalization within this system. Bond distances and angles compare with those found in similar compounds.

The crystal structure of compound **25** has been resolved and the 2-*R* configuration has been attributed on its basis, but no crystallographic data have been reported; [9/84,10/84] the same is true for the antipsychotic drug Risperidone **26**.[4/88]

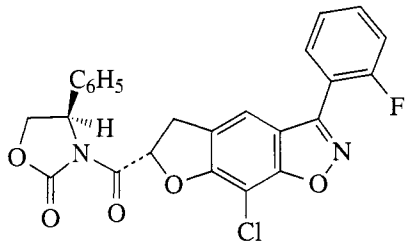
TABLE 1.23. SELECTED BOND LENGTHS (Å) AND ANGLES FOR COMPOUNDS **23** AND **24** WITH E.S.D[a] IN PARENTHESES



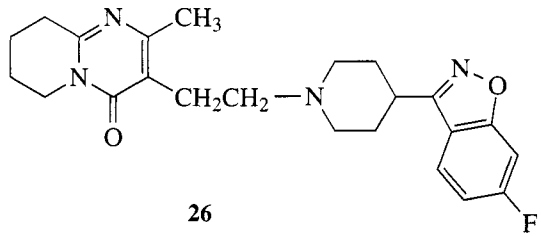
23, X = SO_2NH_2
24, X = COOH

	Bond length			Degrees	
Bond	**23**	**24**	Angle	**23**	**24**
O1-N2	1.412(2)	1.418(2)	N2−O1−C7a	107.4(2)	107.1(1)
N2-C3	1.299(3)	1.297(2)	O1−C7a−C3a	109.8(2)	109.9(2)
C3-C3a	1.433(3)	1.434(2)	O1−C7a−C7	126.6(2)	126.4(2)
C3-Cα	1.488(3)	1.497(3)	C7−C7a−C3a	123.6(2)	123.7(2)
C3a-C4	1.405(3)	1.402(2)	C7a−C7−C6	115.9(2)	115.4(2)
C4-C5	1.371(4)	1.375(3)	C7−C6−C5	121.9(2)	122.3(2)
C5-C6	1.416(4)	1.407(3)	C6−C5−C4	121.7(3)	121.1(2)
C6-C7	1.358(4)	1.376(3)	C5−C4−C3a	116.6(2)	117.7(2)
C7-C7a	1.389(3)	1.394(2)	C4−C3a−C3	135.8(2)	136.4(2)
C7a-C3a	1.378(3)	1.384(3)	C3a−C3−Cα	128.5(2)	128.2(2)
C7a-O1	1.366(3)	1.364(2)	C3a−C3−N2	111.1(2)	111.1(1)
Cα-Sβ	1.792(2)	—	C3−N2−O1	107.7(2)	108.0(2)
Cα-Cβ	—	1.511(3)	N2−C3−Cα	120.3(2)	120.6(2)
			C7a−C3a−C4	120.3(2)	119.8(2)
			C7a−C3a−C3	104.0(2)	103.9(1)
			C3−Cα−Cβ	—	113.3(2)
			C3-Cα-Sβ	110.8(2)	—

[a] Estimated standard deviation

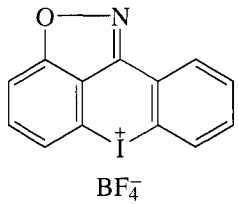


25

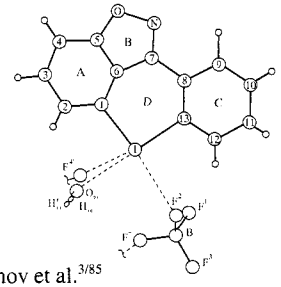


26

TABLE 1.24. BOND LENGTHS (Å) AND ANGLES (DEGREES) OF COMPOUND **27**



27



After Batsanov et al.[3/85]

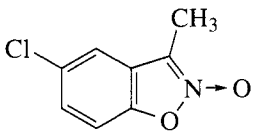
Bond	Å	Bond	Å	Bond	Å
I–C1	2.094(2)	C5–C6	1.385(4)	C7–C8	1.462(4)
I–C13	2.128(3)	C6–C1	1.384(4)	C8–C9	1.403(4)
C1–C2	1.376(4)	C6–C7	1.424(4)	C9–C10	1.387(4)
C2–C3	1.410(4)	C7–N	1.311(4)	C10–C11	1.379(4)
C3–C4	1.378(5)	N–O	1.422(3)	C11–C12	1.391(4)
C4–C5	1.390(4)	O–C5	1.359(4)	C12–C13	1.390(4)
				C13–C8	1.400(4)

Bond angle	Degrees	Bond angle	Degrees	Bond angle	Degrees
C1IC13	95.6(1)	C5C6C1	119.4(2)	C7C8C13	122.1(2)
IC1C2	123.8(2)	C1C6C7	135.6 (3)	C13C8C9	117.7(2)
IC1C6	115.9(2)	C5C6C7	105.0(2)	C8C9C10	120.9(3)
C2C1C6	120.4(2)	C6C7C8	125.7(2)	C9C10C11	120.0(3)
C1C2C3	118.1(3)	C6C7N	111.0(2)	C10C11C12	120.8(3)
C2C3C4	123.5(3)	C8C7N	123.3(2)	C11C12C13	118.8(3)
C3C4C5	115.7(3)	C5ON	108.3(2)	IC13C8	124.9(2)
C4C5C6	122.9(2)	ONC7	106.8(2)	IC13C12	113.3(2)
C4C5O	128.2(3)	C7C8C9	120.2(2)	C8C13C12	121.7(2)

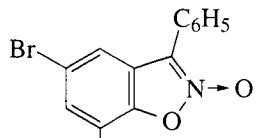
The only other structure reported is that of the cyclic iodonium derivative **27**, which has been resolved as the tetrafluoroborate monohydrate by X-ray crystallography.[3/85] The main bond lengths and angles found are reported in Table 1.24.

Rings A, B, and C are planar, and the dihedral angles between them are small (1.5°–3.6°). Ring D has an indistinct chair conformation with a 4.6° flexus of the C1–C19 line. Thus on the whole the molecule is found to be almost planar. The geometry of ring B has been found to be close to that observed in 3,4,5-trisubstituted isoxazoles[17/74] with the C7–N bond longer and C6–C7 shorter than the standard C=N double bond and C_{sp^2}–C_{sp^2} single bonds, respectively. The geometry of benzene ring C hardly differs from the ideal geometry, and C7–C8 bond length indicates a weak π-conjugation of ring C with ring B.

The 1,2-benzisoxazole-2-oxides have been more widely studied. The structures of 5-chloro-3-methyl-1,2-benzisoxazole-2-oxide (**28**) and of 5,7-dibromo-3-phenyl-1,2-benzisoxazole-2-oxide (**29**) have been reported.[5/82,3/86] The bond lengths and angles of compound **28** are shown in Figure 1.1.

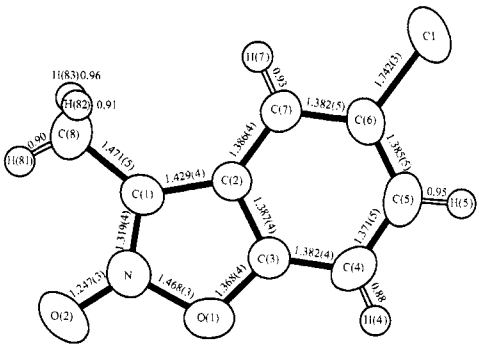


28

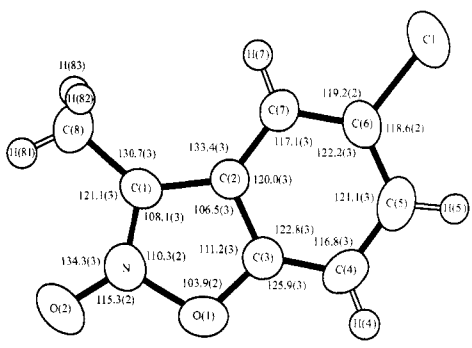


29

In both compounds the 1,2-benzisoxazole moiety appears to be planar. In general the bond distances and angles do not appear to deviate significantly from those reported for compound **27**, even if the distance N–O1 seems longer than



(*a*)



(*b*)

Figure 1.1. Bond lengths (*a*) and angles (*b*) of compound **28**. (After Chiari and Viterbo).[5/82]

that of other compounds with a similar isoxazole ring. The distance N–O2 appears to be comparable to that of the furoxans, a class of compounds that bears many similarities to 1,2-benzisoxazole-2-oxides. The two N–O bonds in the isoxazole ring are quite different in length; the exocyclic N–O is comparable with that of a nitro group and is shorter than that of the cyclic N–O. As far as the phenyl ring of **29** is concerned , it is turned in such a way that it forms a dihedral angle of 42.3° with the plane of the isoxazole ring.[3/86]

1.2.7. Dipole Moments

The dipole moment in benzene at 25°C of 1,2-benzisoxazole (μ=3.03 D) has been reported.[1/43] It is in good agreement with values calculated (Table 1.25) using a variety of theoretical methods (see § 1.2.8).[1/60,2/65,2/72,1/78]

The dipole moment of 1,2-benzisoxazole-2-oxide has been calculated (μ = 4.98 D),[23/87] but its experimental value is not known.

1.2.8. Theoretical Calculations

1.2.8.1. Electron Density, Reactivity, and Ionization Potentials

The π-electron density distribution and π-bond order of 1,2-benzisoxazole have been calculated by a variety of theoretical methods.[1/60,2/65,1/70,2/72,1/78] The results are reported in Table 1.26. The calculated ground-state π-electron densities consistently indicate that the C5 and C7 positions are the most nucleophilic, as the latter have the higher charge density.

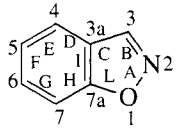
Therefore electrophilic substitution mainly in the 7 position would be predicted. This prediction is not borne out by experiments, as most electrophilic substitutions take place in 5 position and, in only a few cases, both in the 5 and 7 positions (see § 1.4.5).

TABLE 1.25. CALCULATED AND OBSERVED DIPOLE MOMENTS OF 1,2-BENZISOXAZOLE (D)

Observed	Calculated	Method[a]	References
3.03	—	—	1/43
	3.1	MO-LCAO[a]	1/60
	2.83	H[b]	2/65
	4.10	LCGO[c]	1/78
	3.71	CNDO-CI	2/72

[a] Molecular orbital–linear combination of atomic orbitals.
[b] Modified Hückel method.
[c] Linear combination of Gaussian orbitals.

TABLE 1.26. CALCULATED GROUND-STATE π-ELECTRON DENSITIES AND π-BOND ORDERS OF 1,2-BENZISOXAZOLE



O1	N2	C3	C3a	C4	C5	C6	C7	C7a
0.15	−0.39	0.22	−0.04	0.04	−0.02	0.04	−0.03	0.04
0.098	−0.310	0.222	−0.054	0.020	−0.024	0.036	−0.041	0.053
1.742	1.317	0.904	1.025	0.989	1.021	0.981	1.048	0.972
1.707	1.284	0.928	1.054	0.982	1.022	0.986	1.044	0.992
1.831	1.231	0.901	1.055	0.967	1.040	0.961	1.069	0.945
1.7952	1.1442	0.9924	1.0854	0.9744	1.0198	0.9643	1.0385	0.9859

A	B	C	D	E	F	G	H	I	L	Method	References
0.79	0.82	0.47	0.59	0.70	0.64	0.69	0.61	0.57	0.47	MO-LCAO	1/60
—	—	—	—	—	—	—	—	—	—	H[a]	2/65
0.328	0.794	0.504	0.566	0.720	0.613	0.710	0.587	0.563	0.432	PPP-SCF I	1/70
0.371	0.791	0.509	0.557	0.727	0.606	0.722	0.569	0.565	0.448	PPP-SCF II	1/70
—	—	—	—	—	—	—	—	—	—	CNDO-CI	2/72
—	—	—	—	—	—	—	—	—	—	LCGO	1/78

[a] Modified Hückel method

This has also been found for 3-methyl-1,2-benzisoxazole, which is nitrated exclusively in the 5 position: such a substitution has been explained assuming that in this system the orbital term prevails over the coulumbic one and that the frontier orbital coefficients at position 5 are larger than at position 7.[4/77]

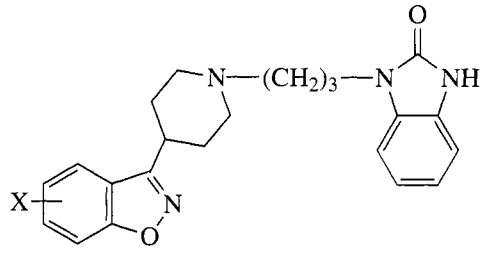
Calculations have indicated that excitation in the lowest $^1(\pi,\pi^*)$ and/or $^3(\pi,\pi^*)$ state induces a decrease in the π-bond orders of the O–N–C linkage of 1,2-benzisoxazole and favors bond lability, thus explaining the known photochemical isomerization into benzoxazole and ring cleavage to salicylonitrile.[1/70]

The highest occupied orbital energy, which corresponds to chemical ionization potentials, and the lowest vacant orbital energy, which represents electron affinity, have also been evaluated, together with the total π energy. They are reported in Table 1.27.

TABLE 1.27. CALCULATED IP (IONIZATION POTENTIAL), HIGHEST OCCUPIED ENERGY (ε_{HOMO}),LOWEST VACANT ORBITAL ENERGY (ε_{LUMO}), AND TOTAL π-ENERGY (E_π) OF 1,2-BENZISOXAZOLE (eV)

IP/-ε_{HOMO}	$-\varepsilon_{LUMO}$	$-E_\pi$	Method	References
−9.31	−1.44	−337.17	PPP-SCF I	1/70
−9.85	−1.66	−338.10	PPP-SCF II	1/70
−9.33	—	—	CNDO-CI	2/72
−9.20	—	—	LCGO	1/78
−9.237	—	—	VI-1	2/71
−9.323	—	—	VI-2	2/71

The ε_{LUMO} (lowest unocuppied molecular orbital) energy of compounds **30–33**, which are potent neuroleptics, has also been calculated and successfully correlated to the biological activity;[7/87] it has been used to model the binding to the dopamine receptor.[6/88]



30, X = 5,6-$(OCH_3)_2$
31, X = 6-OCH_3
32, X = H
33, X = 6-F

The atomic charge distribution (net charge), π-bond orders and ε_{HOMO} and ε_{LUMO} energies have been calculated for a series of 1,2-benzisoxazole-2-oxides. The data concerning the parent compound and its 3-methyl derivative are reported in Table 1.28. The dipolar nature of N–O functionality is evident, while the π-bond order suggests some partial double-bond character of the dipole The substituents do not seem to have much effect on the polarity of N−O bonds.

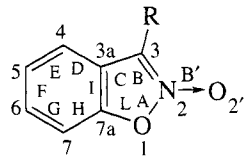
Charge distribution predicts the susceptibility of positions C7 > C4 > C5 toward electrophiles. In this case, too, the experimental results are at variance with predictions, in fact, 3-methyl-1,2-benzisoxazole-3-oxide gives only the 6-nitro derivative (see § 1.4.5). However, when the intermediacy of a protonated form was considered in the light of the strongly acidic media employed, the results suggested that the C6 position of 3-methyl-1,2-benzisoxazole-2-oxide was the activated one.[23/87]

1.2.8.2. Other Calculations

The photoelectronic spectrum, electronic spectrum and dipole moment of 1,2-benzisoxazole have been calculated.[1/60,2/65,3/69,1/70,2/71,2/72,1/78] The results are generally in agreement with the experimental values (Table 1.29) (see § 1.2.2 and § 1.2.7).

The ^1H chemical shifts of a series of *O,N*-heterocycles have been shown to correlate with the total charge ($\sigma + \pi$) calculated for the corresponding carbon atom: 1,2-benzisoxazole is one of these heterocycles and the chemical shift of its C3 proton perfectly fits the correlation.[2/72]

TABLE 1.28. CALCULATED ATOMIC CHARGE DISTRIBUTION (NET CHARGE), π-BOND ORDERS AND ε_{HOMO} AND ε_{LUMO} OF 1,2-BENZISOXAZOLE-2-OXIDE AND 3-METHYL-1,2-BENZISOXAZOLE-2-OXIDE[23/87]



π-electron densities and π-bond orders	R=H	R=CH_3
O1	−0.163	−0.174
N2	0.378	0.342
O2′	−0.382	−0.397
C3	−0.068	−0.117
C3a	0.016	−0.007
C4	−0.009	−0.003
C5	−0.002	−0.002
C6	0	0.004
C7	−0.024	−0.029
C7a	0.156	0.162
A	0.219	0.209
B	0.784	0.778
B′	0.492	0.452
C	0.377	0.368
D	0.615	0.616
E	0.699	0.695
F	0.648	0.648
G	0.674	0.673
H	0.645	0.641
I	0.603	0.604
L	0.279	0.288
ε_{HOMO}	−10.47 (eV)	−10.02 (eV)
ε_{LUMO}	1.69 (eV)	1.78 (eV)

TABLE 1.29. CALCULATED AND EXPERIMENTAL UV SPECTRUM OF 1,2-BENZISOXAZOLE

Calculated		Experimental		
$\Delta E_{\pi n}$ (eV)	Method	λ (nm)	ΔE (eV)	References
—	—	245	5.06	1/41, 2/65
—	—	280	4.43	
4.83	H[a]	—	—	2/65
4.36	CNDO−CI	—	—	2/72
4.59	PPP−SCF I	—	—	1/70
5.01	PPP−SCF II	—	—	1/70

[a] Modified Hückel method.

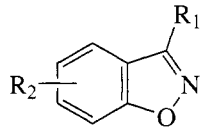
1.2.9. Basicity

1,2-Benzisoxazole is a very weak base (Table 1.30). On the basis of UV spectral data it has been concluded that it is a weaker base than isoxazole.[1/66]

The pK_a of a series of substituted 1,2-benzisoxazole-3-carboxylic acids has been measured and, as expected, is dependent on the electronic properties of the substitutent.[2/73] In the case of 4- and 6-hydroxy-1,2-benzisoxazole-3-carboxylic acid the pK_as of both functions have been evaluated through UV spectroscopy (Table 1.30).[1/75]

In general the pK_as of substituted 1,2-benzisoxazole-3-carboxylic acids are comparable to those of the corresponding *o*-nitrobenzoic acids, which underlines the electron-withdrawing effect of the 1,2-benzisoxazole nucleus.[3/75]

TABLE 1.30. pK_a (CONJUGATED ACID) OF SELECTED 1,2-BENZISOXAZOLE DERIVATIVES



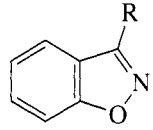
R_1	R_2	pK_{a1}	pK_{a2}	References
H	H	−4.2	—	4/77
H	H	−4.7	—	2/73
H	5-CH_3	−4.03	—	4/77
CH_3	H	−2.69	—	4/77
C_6H_5	H	−4.31	—	1/66
COOH	6-NO_2	1.57	—	2/73, 3/75
COOH	5-NO_2	1.77	—	2/73, 3/75
COOH	6-Cl	1.86	—	2/73, 3/75
COOH	H	1.97	—	2/73, 3/75
COOH	6-OCH_3	2.03	—	2/73, 3/75
COOH	4-OH	0	11	1/75
COOH	6-OH	1.3	8	1/75

1.2.10. Miscellaneus Data

1,2-Benzisoxazole and its methyl derivatives are colorless liquids that can be distilled, while the corresponding 3-phenyl homolog is a crystalline solid.

Some physicochemical data concerning 1,2-benzisoxazole derivatives are listed in the literature;[2/62,1/67] a few selected data are reported in Table 1.31.

TABLE 1.31. PHYSICOCHEMICAL DATA OF SELECTED 1,2-BENZISOXAZOLE DERIVATIVES



R	b.p. (°C/mm Hg)	m.p. °C	d_4 (t)	n_D (t)	MR_D (cm^3)	EM_D (cm^3)	μ(D)	References
H	84(11)	—	1.1750 (16)	1.56423 (16)	32.97	−0.20	3.03[a]	1/24, 1/43
CH_3	92.5(11)	—	−1.1260 (19.9)	1.55098 (19.9)	37.70	−0.09	—	1/26, 1/27
C_6H_5	181(13)	83−84	1.1241 (89.9)	1.59279 (89.9)	57.78	1.50	—	1/24

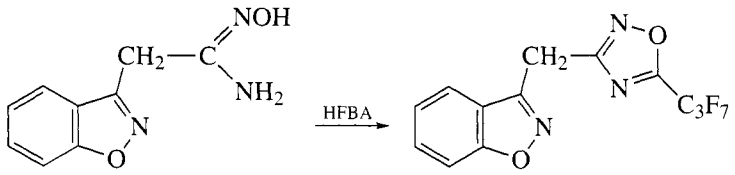
[a] Benzene solution at 25°C.

1.2.11. Analytical methods

Thin-layer chromatography on silicagel plates has been reported in most of the papers concerning the synthesis, detection, and isolation of 1,2-benzisoxazoles. In a particular study a systematic search for developing solvents for thin-layer silicagel preparations was performed on a number of heterocyclic compounds, including 1,2-benzisoxazole.[8/87]

More sophisticated and quantitative methods have been developed mainly with the purpose of studying the pharmacokinetics of potential drugs.

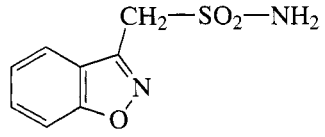
Thus amidoxime **34** (PF-257) has been examined in plasma with a gas chromatographic method after derivatization with heptafluorobutyric anhydride (HFBA) to form 3-[(5-*n*-heptafluoropropyl-1,2,4-oxadiazol-3-yl)methyl]-1,2–benzisoxazole (**35**).[6/78]



34 **35**

Zonisamide (**23**), an effective antiepileptic, is one of the many antiepileptic drugs that has been analyzed through HPLC (high-performance liquid chromatography), using a microbore column on EtOAc solution obtained from

serum. The isocratic conditions used in the case of monomedication with **23** had to be changed because of interference with other drugs.[9/87,10/87,8/88,20/90,9/91] The same drug and its metabolites have been analysed with tandem mass spectrometry, which is capable of rapidly identifying molecules with characteristic substructures without prior separation.[7/88]

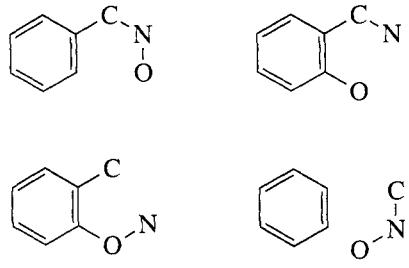


23

More recently, an enzyme immunoassay (EIA) method has been developed for the same drug.[4/90] This method, that uses competing antibodies to Zonisamide, has the advantage over HPLC in its simplicity and speed and in the fact that it requires no special equipment.

1.3. METHODS OF PREPARATION

Most of the methods used to obtain the 1,2-benzisoxazole nucleus rely on ring closure of a suitable benzene derivative. The following general pathways can be singled out:



The first two approaches involve ring closure of oxyimino derivatives with the formation of 7a–1 or 1–2 bonds; the starting materials can be obtained from the easily accessible carbonyl compounds. These methods are the most useful ones and have been widely employed to synthesize a large variety of 1,2-benzisoxazole derivatives.

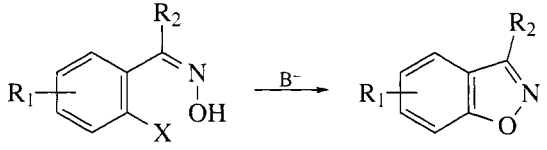
The third approach, which makes use of *O*-arylhydroxylamine derivatives to form the 2–3 bond, is less common but has been found to be the method of choice for obtaining 1,2-benzisoxazoles that carry 2′,6′-disubstituted aryl groups in position 3.

Only a few examples involving concomitant formation of the 7a–1 and 3–3a bonds via cycloadditions have been reported.

In addition, the reaction of 4-hydroxycoumarins with hydroxylamine has become a very useful method for obtaining 1,2-benzisoxazole-3-acetic acids that, in turn, can be manipulated to open the way to a large variety of corresponding 3-substituted derivatives.

1.3.1. Formation of Bond 7a–1

The base-promoted intramolecular displacement reaction for formation of the 7a–1 bond is one of the most useful methods for obtaining 1,2-benzisoxazole derivatives (Scheme 1.8):



Scheme 1.8

Group X is usually a halogen but can also be a nitro, a diazo, a methoxy function, and so on.

1.3.1.1. From 2-Halobenzoyl Derivatives

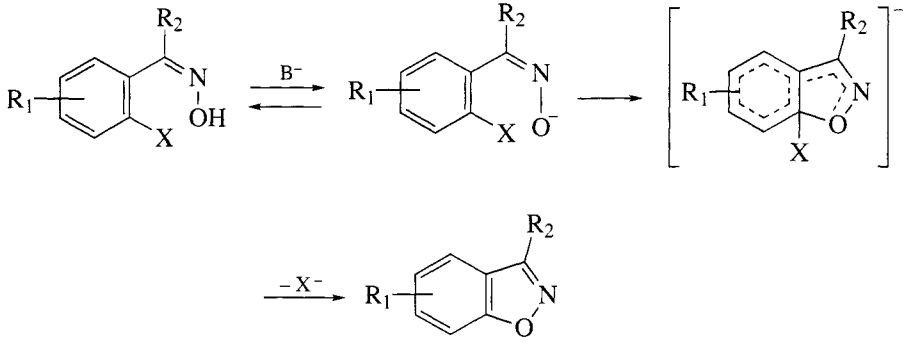
Base-promoted ring closure of 2-halogenated benzophenone oximes has been used since 1892, when 3-phenyl-1,2-benzisoxazole (**2**; Scheme 1.8: R_1=H, R_2=C_6H_5) was obtained by the action of hydroxylamine on 2-bromobenzophenone in an alkaline medium.[1/892]

This kind of reaction may lead to the cyclic final product either directly or via the isolated oxime. This approach has been extended to a variety of 2-halophenyl ketones, where R_2 is an alkyl, substituted or unsubstituted aryl, heteroaryl, and so on.[1/894,1/895,3/08,1/25,1/28,1/39,2/39,2/41,3/65,2/70,5/72,1/77, 6/77,7/78,5/81,6/82,11/84,4/85,5/85,20/86,3/89]

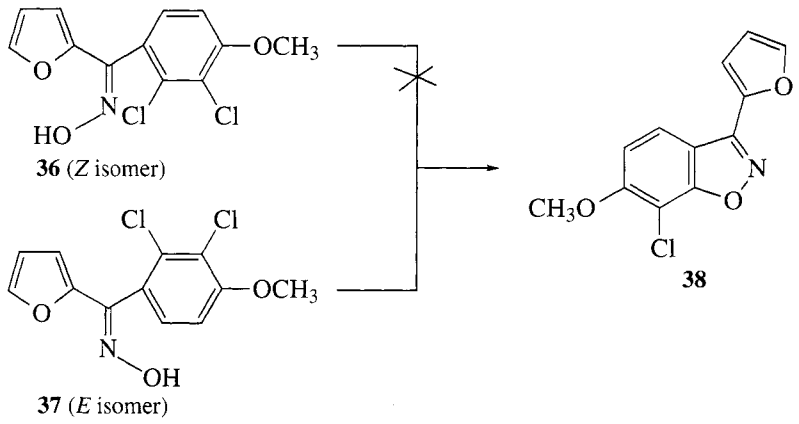
Bases of different strengths such as aqueous Na_2CO_3, KOH, or NaH in DMF have been used to effect cyclization of the intermediate oximes.

The formation of 1,2-benzisoxazoles proceeds by attack at the 2 position of the benzene ring by the oxime anion followed by elimination of halide ion.

The proximity of the displacing group is, of course, important in assisting the reaction; accordingly the configuration of the oxime is critical, and only one of the two *E*/*Z* isomers undergoes prompt cyclization.[2/24,1/25,2/25,1/28,6/82]



This fact has been used to establish the configuration of isomeric oximes such as **36** and **37**.[1/77] However, in these cases the possibility of oxime isomerization under the reaction conditions used should be taken into account.[1/90]

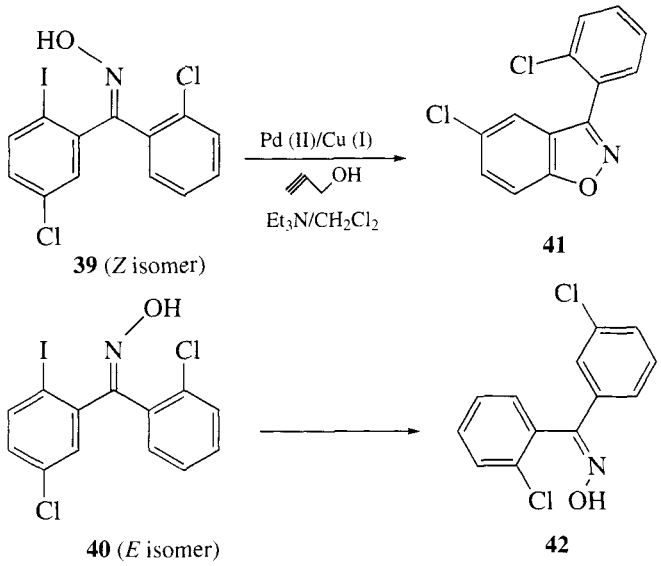


36 (*Z* isomer)

37 (*E* isomer)

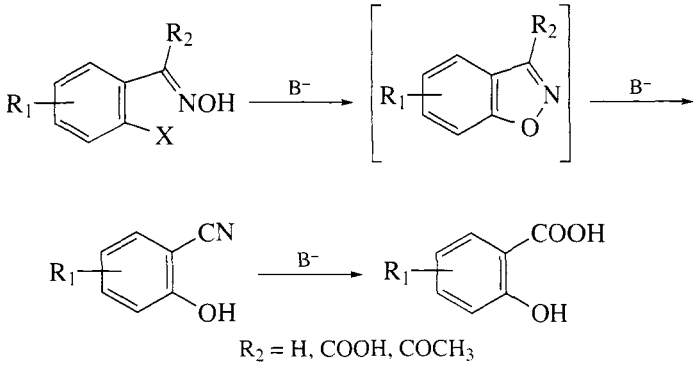
38

Another example of the influence of oxime configuration on reactivity is provided by the isomeric 2′,5-dichloro-2-iodobenzophenone oximes (**39** and **40**). In an attempt to displace the iodo group with propargyl alcohol in an alkaline medium, the Z isomer (**39**) was readily converted into the corresponding 1,2-benzisoxazole (**41**) while the *E* isomer (**40**), under the same conditions, was reduced to **42**.[11/84] Other examples of the influence of oxime configuration on cyclization have been reported.[6/71,7/71] This method of synthesis is also interesting in that it emphasizes the different reactivity of halo derivatives to cyclization. The iodo compounds are in fact more easily cyclized than the corresponding bromo and chloro derivatives.[2/892,1/893,1/894,2/08, 2/24,1/25,2/41,1/56] The fluoro derivatives are reported to give the highest yields in cyclization.[1/39,3/41,6/71,7/71]



However, it has also been reported that cyclization of 2-chloro-2′-fluorobenzophenone oximes under basic conditions is not selective, and mixtures of 3-(2-chlorophenyl)- and 3-(2-fluorophenyl)-1,2-benzisoxazoles have been obtained.[6/82]

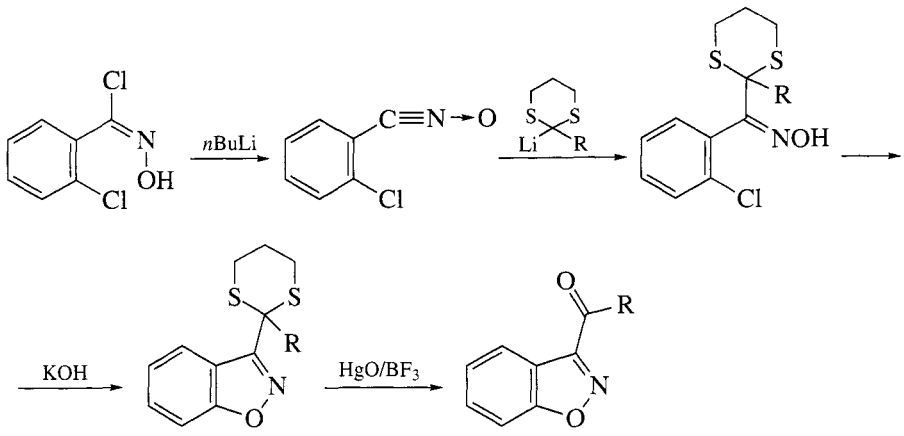
This synthetic method is unsuitable when the substituent (R_2) is hydrogen, an acyl, or a carboxylic group. In this case the base used as a cyclizing agent promotes the abstraction or extrusion of the R_2 group, which is followed by cleavage of the ring (see § 1.4.5) into salicylnitriles or salicylic acid derivatives.[3/892,2/893,3/893,4/893] For example, 2-chloro-5-nitrobenzaldehyde oxime (Scheme 1.9: R_1 = 5-NO_2, R_2 = H, X = Cl) and 2-bromophenylglyoxylic acid



Scheme 1.9

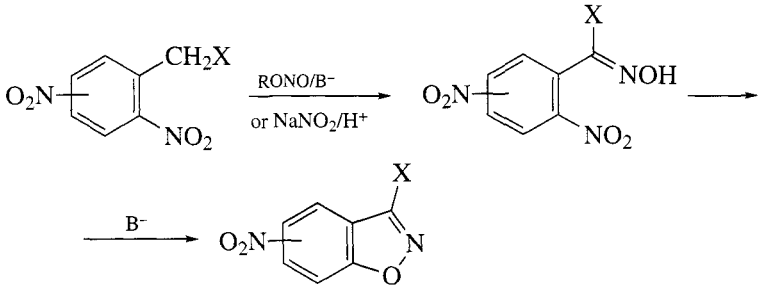
oxime (Scheme 1.9: R_1 = H, R_2 = COOH, X = Br) give the corresponding salicylic acids as final products.

For this reason the route proposed by Yamamori et al.,[5/81] which consists of cyclization of 2-substituted 1,3-dithian-2-yl-*o*-chlorophenylketoximes, is particularly interesting in that it allows the synthesis of 3-acyl-1,2-benzisoxazoles in excellent yields, as depicted in the following reaction sequence.



1.3.1.2. From 2-Nitrobenzoyl Derivatives

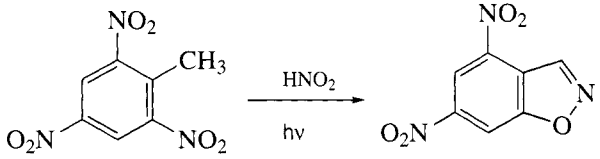
2-Nitrobenzophenone gives 3-phenyl-1,2-benzisoxazole when treated with hydroxylamine;[3/893] other similar compounds do not, however, react in the same way.[2/893,3/893] This kind of reaction has indeed found synthetic application, mainly when the phenyl ring is substituted with a second nitro group, as in the cyclization of 2,6- and 2,5-dinitrophenylacetic acid derivatives (Scheme 1.10: X = $COOCH_3$ CONHR).



Scheme 1.10

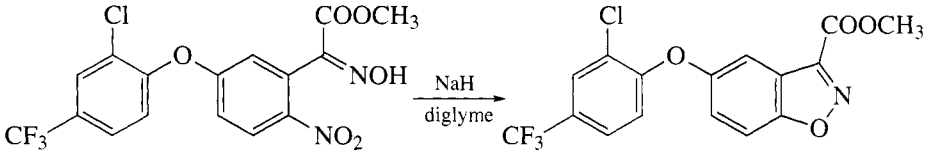
In this case the requisite oxime can conveniently be obtained by nitrosation with an alkyl nitrite in the presence of sodium alkoxide or with nitrous acid.[1/09,1/19,1/50,2/50,1/58,1/64,8/71,6/72,1/75,3/75] The reaction has been extended to obtain 3-acyl (Scheme 1.10: X = $COCH_3$; COC_6H_5), 3-alkyl (X = CH_3), and 3-arylamide (X = CONHR) derivatives of 1,2-benzisoxazoles.[1/12,2/19,8/71]

The reported formation of 4,6-dinitro-1,2-benzisoxazole (**43**) by photonitrosation of trinitrotoluene may proceed in a similar fashion.[4/79]



43

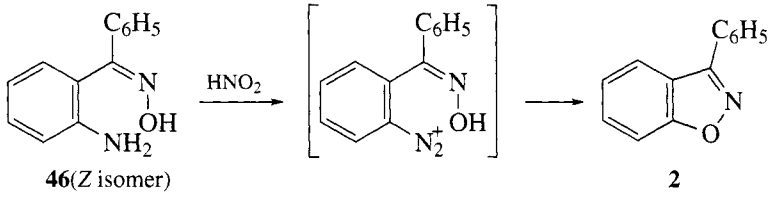
Recently the NaH-promoted cyclization of compound **44** has been reported.[9/88]



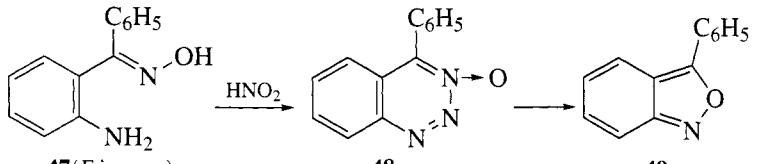
44 **45**

1.3.1.3. From Other 2-Substituted Benzoyl Derivatives

2-Aminobenzophenone oxime, when treated with nitrous acid, gives 3-phenyl-1,2-benzisoxazole (**2**) via the diazonium salt.[5/893,2/27] Here, too, the stereochemistry of the oxime has been found to be critical, as the high-melting-point *Z* isomer **46** is cyclized while the *E* form **47** gives 3-phenyl anthranil (**49**), possibly through the intermediacy of the benzotriazine oxide **48**.[2/27]

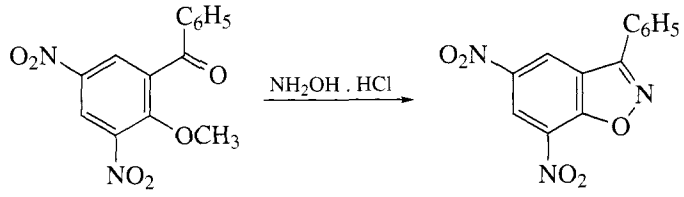


46(*Z* isomer) **2**



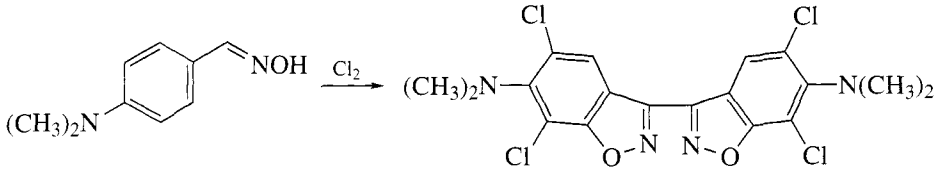
47(*E* isomer) **48** **49**

When properly activated, hydroxyl and methoxy groups can also be eliminated as happens in 3,5-dinitro-2-methoxybenzophenone (**50**), which, when treated with hydroxylamine, gives 5,7-dinitro-3-phenyl-1,2-benzisoxazole (**51**) in quantitative yield; [1/25] the corresponding 3,5-dinitro-2-hydroxybenzophenone oxime also cyclized in water.[1/25]



50 **51**

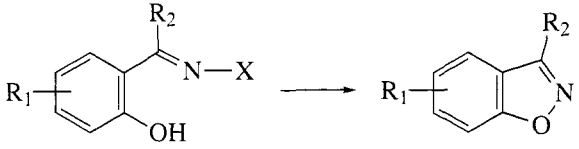
Finally, chlorination of *p*-dimethylaminobenzaldoxime (**52**) is reported to give the dimeric compound **12**, although in very poor yields. The mechanism suggested by the author would require that the 1,2-benzisoxazole ring be formed through an unprecedented elimination of hydrogen from the *ortho* position.[5/71]



52 **12**

1.3.2. Formation of Bond 1–2

Formation of 1,2-benzisoxazoles from 2-hydroxyderivatives has been widely utilized; 1,2-benzisoxazole itself has been synthesized by pyrolysis of salicylaldoxime acetate (Scheme 1.11: $R_1 = R_2 = H$; $X = OCOCH_3$).[1/26] The reaction can be written formally as an intramolecular nucleophilic attack by the hydroxy group, or its anion, followed by displacement of a suitable leaving group from the nitrogen.



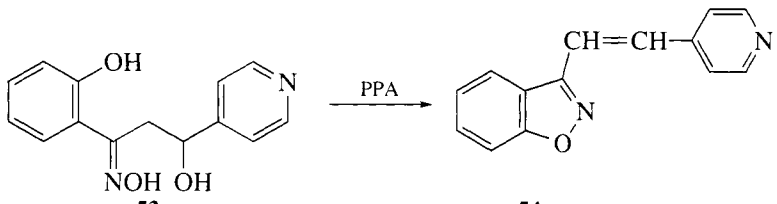
Scheme 1.11

The reaction has been effected by thermal decomposition of the appropriately substituted 2-hydroxybenzoyloxime acetate (X = $OCOCH_3$), often under reduced pressure.[1/26,1/27,3/27,1/29,1/36,2/56,6/67,2/68] The presence of silica gel or Al_2O_3 has been reported to be advantageous.[3/70] Milder conditions can be used with stoichiometric amounts of dilute alkali,[1/27] sodium carbonate in boiling triglyme,[6/77,6/79] or boiling pyridine.[3/77,7/77,4/84,21/84,2/87] Benzoyl (X = $OCOC_6H_5$),[1/38] trichlorocarbamoyl (X = $OCONHCOCCl_3$),[7/79,4/83] ethoxycarbonate (X = $OCOOC_2H_5$),[2/60,3/62] and hydrosulfate derivatives (X = OSO_3H)[1/65,8/77] can be also used. In the latter case the product can be conveniently obtained using hydroxylamine-*O*-sulfonic acid; this is actually one of the best ways to obtain 1,2-benzisoxazole.[1/65] However, the mechanism proposed for formation of the 1–2 bond in this reaction has been called into question (see § 1.3.3).[2/76]

The reported synthesis of substituted 1,2-benzisoxazoles by the action of thionyl chloride on 2-hydroxyacetophenone oximes and salicylaldoximes follows the same reaction pathway.[9/77]

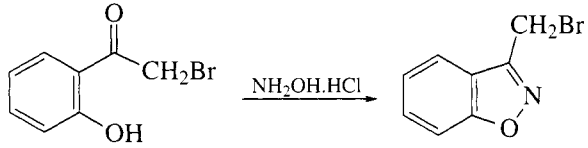
The micellar effects on the concurrent hydrolysis and intramolecular nucleophilic cyclization of 2-hydroxyacyloximes have been studied.[6/81]

Direct cyclization of oxyimino derivatives (X = OH) by means of silica gel,[11/87] sulfuric acid,[1/44] and polyphosphoric acid[1/74] has been reported. In the latter case dehydration of the starting material (**53**) can occur, leading to the corresponding chromanone derivative (**54**).



53 **54**

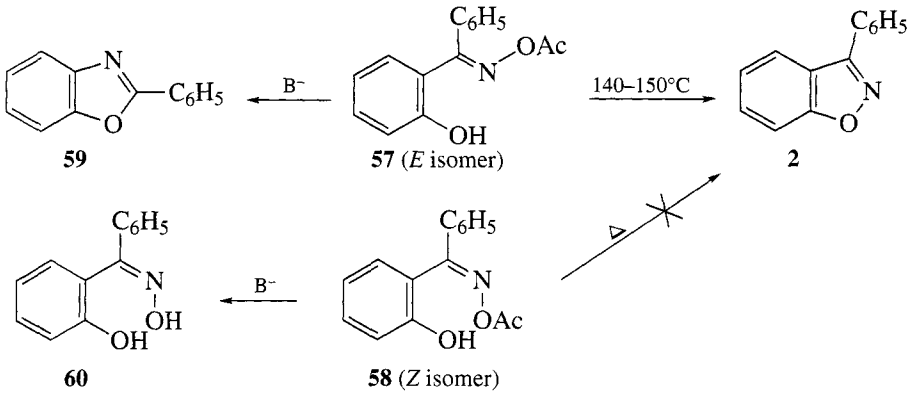
In a few cases boiling carbonyl derivatives in the presence of hydroxylamine led to the formation of the 1,2-benzisoxazole nucleus directly.[5/73,3/81,21/90] Thus treatment of **55** with hydroxylamine hydrochloride gave, in a remarkable one-pot synthesis, 3-bromomethyl-1,2-benzisoxazole (**56**) (see § 1.4.7.2).[21/90]



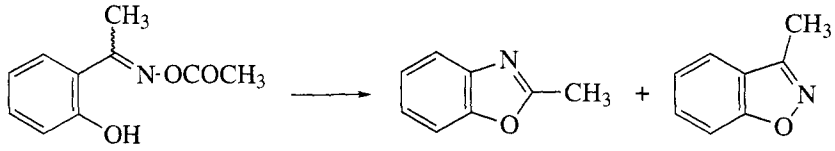
55 **56**

This synthetic method is related to the one used to obtain 1,2-benzisoxazoles from other heterocycles (see § 1.3.5).

The influence of the configuration of the oxime and oxime derivatives on the course of cyclization has been investigated in particular for acetates (Scheme 1.11: X = $OCOCH_3$). Only the *E* isomer of the acetate of 2-hydroxybenzophenone oxime (**57**) gives 3-phenyl-1,2-benzisoxazole (**2**); the *Z* isomer (**58**) gives only traces of the cyclic compound under the same conditions.[1/36,1/38] When the reaction is performed under basic conditions (e.g., 10% NaOH), the *Z* isomer is simply hydrolized to the oxime **60** while the *E* isomer undergoes a Beckman–like rearrangement that eventually leads to the corresponding benzoxazole **59**.

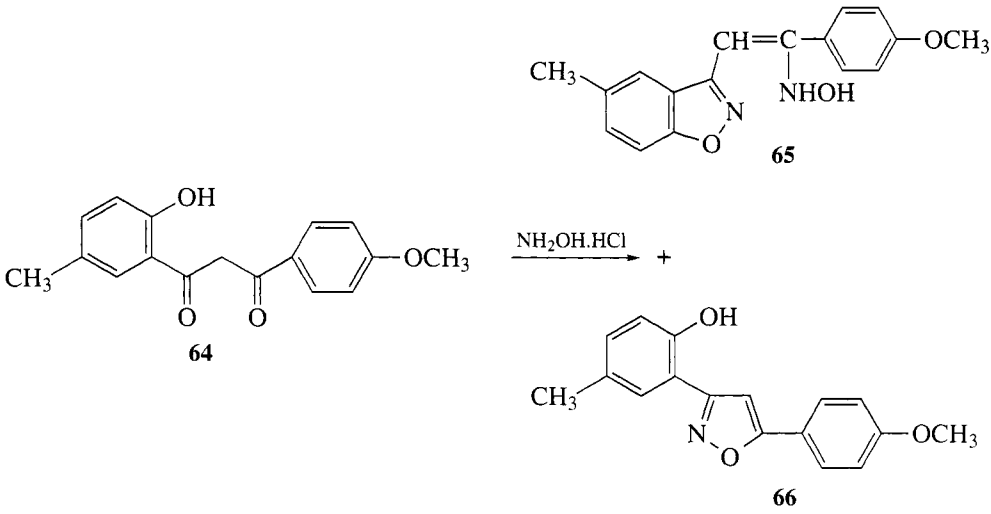


This kind of rearrangement has been shown to occur under a variety of conditions,[1/38,1/55,3/71,8/72,1/73,2/79,4/83,10/88,1/89] and its incidence also depends on the reaction conditions,[4/69,3/71] as shown by the cyclization of 2-hydroxyacetophenone oxime acetate (**61**).[4/69]



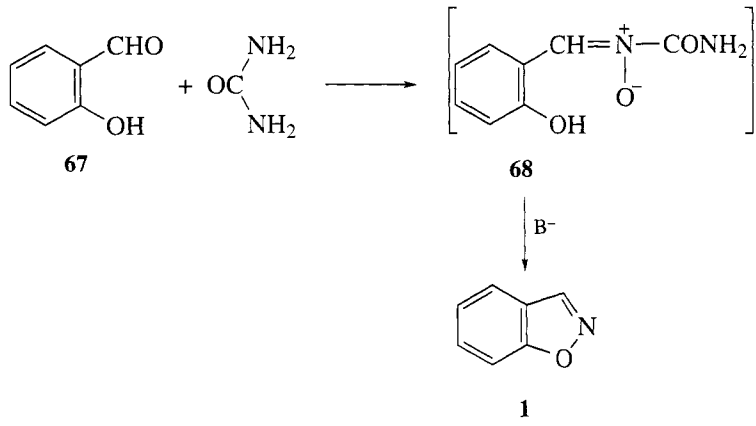
10% NaOH	90%	10%
Na_2CO_3	90%	10%
160°C	50-80%	50-20%

Reaction conditions seem important also where there are concurrent ring closures;[5/73,2/86,5/87] thus 2-hydroxy-5-methyl-4′-methoxydibenzoylmethane (**64**) gives different ratios of **65** and **66** depending on the dielectric constant of the reaction medium.[2/86]



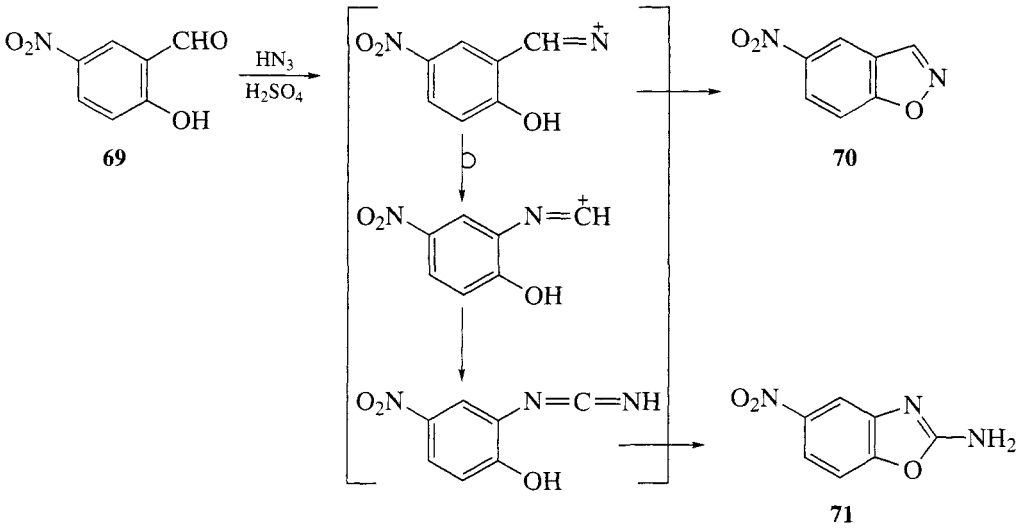
A number of reactions lead to 1,2-benzisoxazoles, possibly through a 1–2 bond formation, whose mechanism is however still obscure or unproven.

The oldest such reaction is the Conduché reaction[1/08] where salicylaldehyde (**67**) is condensed with hydroxyurea to give the proposed intermediate **68** and eventually 1,2-benzisoxazole (**1**) by addition of a stoichiometric quantity of alkali.

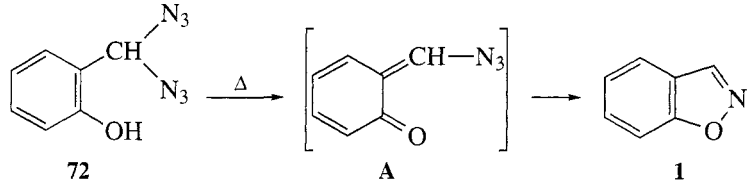


The structure of the intermediate in this reaction has tentatively been assigned as that of **68**,[1/67] although an oxaziridine intermediate has also been proposed.[1/08]

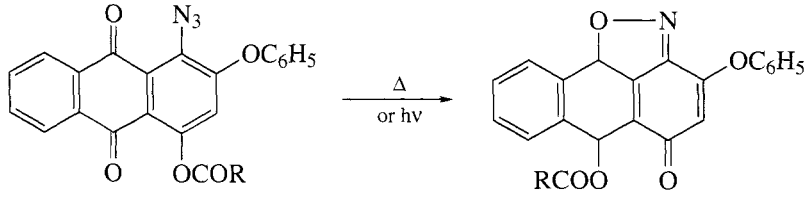
Salicylaldehyde derivatives can be transformed into substituted 1,2-benzisoxazoles by treatment with hydrazoic acid in sulfuric acid.[2/58,1/59] In this reaction 2-aminobenzoxazoles are obtained as by-products. The following mechanism has been proposed:



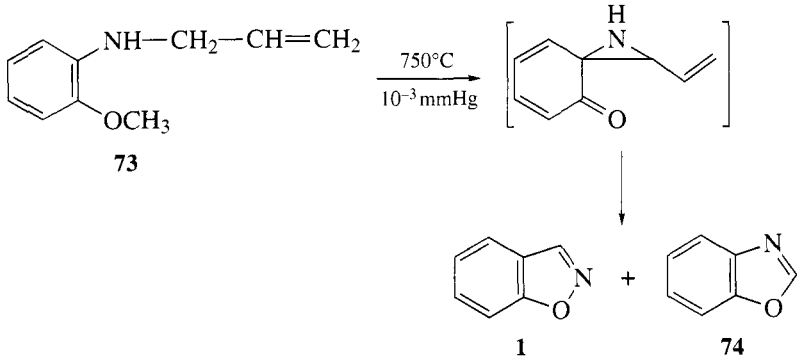
Another venerable preparation of **1** is reported to occur on boiling 2-hydroxytolylbisazide (**72**) in acetic acid; in this case as well the nature of the proposed intermediate (**A**) is uncertain.[3/25]



Recently a synthesis of 1,2-benzisoxazole derivatives from azides has been reported that seems to support the previous mechanism.[15/91]



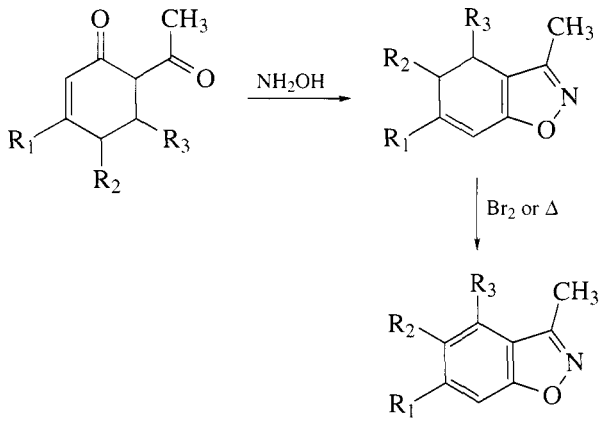
Pyrolysis of 2-methoxy-*N*-allylaniline (**73**) has been reported to produce a mixture of benzisoxazole **1** and benzoxazole **74**.[6/85]



73 **1** **74**

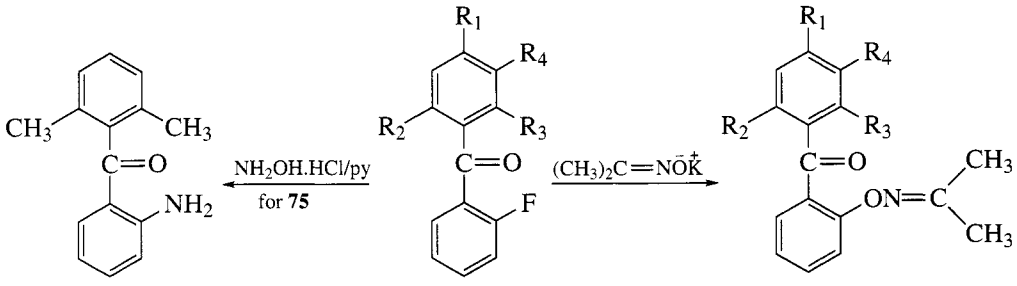
7-Amino-1,2-benzisoxazole has been claimed as the product of the reaction of 2-hydroxy-3-nitrobenzaldehyde with hydrazine.[7/82] However, no evidence for this assignment has been presented.

At the end of this section it is convenient to mention a reaction that can give 1,2-benzisoxazoles through oxidation of the corresponding 4,5-dihydroderivatives obtained from the reaction of substituted 6-acetylcyclohexenones with hydroxylamine; the reaction has been also extended to cinnamoyl cyclohexanones.[7/72,1/76,10/77,4/80,5/80,4/86]



1.3.3. Formation of Bonds 2–3 or 3–3a

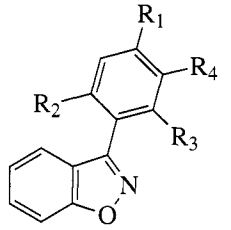
There are only a few examples of 2–3 ring closure.[2/76,3/84] The most interesting one, reported by Shutske,[3/84] involves an intramolecular *trans* oximation. A similar reaction pathway had previously been proposed in the synthesis of 1,2-benzisoxazole from salicylaldehyde and hydroxylamine-*O*-sulfonic acid.[2/76]



77

75, $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$
76, $R_1 = OCH_3$, $R_2 = H$
$R_3 = R_4 = Cl$

78, $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$
79, $R_1 = OCH_3$, $R_2 = H$
$R_3 = R_4 = Cl$

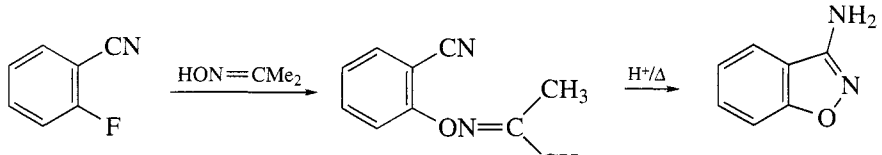


80, $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$
81, $R_1 = OCH_3$, $R_2 = H$, $R_3 = R_4 = Cl$

The method of Shutske[3/84] seems valuable for obtaining derivatives carrying 2′,6′-disubstituted phenyl groups, which are inaccessible by the usual synthetic methods. As an example, treatment of **75** with hydroxylamine in pyridine gives only 12% of **77** along with unchanged starting material. Compound **77** is probably formed through a nucleophilic substitution by hydroxylamine followed by reduction by the same reagent.

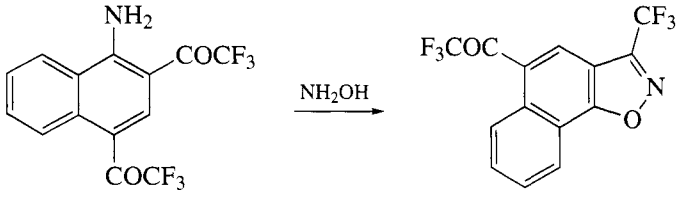
Unlike what was previously reported on the cyclization of 2-chloro-2′-fluorobenzophenone oximes, which, under basic conditions, affords a mixture of 3-(2-chlorophenyl)- and 3-(2-fluorophenyl)-1,2-benzisoxazoles,[6/82] this method is highly selective. In fact, 3-(2,3-dichloro-4-methoxyphenyl)-1,2-benzisoxazole (**81**) is obtained in a 73% yield from 2,3-dichloro-2′-fluoro-4-methoxybenzophenone (**76**).[3/84]

This approach has also been used by the same author to achieve a clean and rapid synthesis of 3-amino-1,2-benzisoxazole (**84**) starting from 2-fluorobenzonitrile (**82**).[2/89]



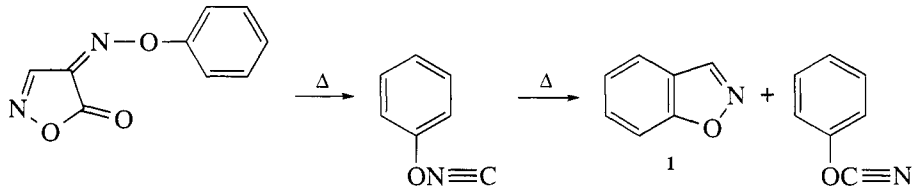
82 **83** **84**

A similar aromatic nucleophilic N–O exchange has been described in the synthesis of 5-trifluoroacetyl-3-trifluoromethylnaphth[2,1-*d*]isoxazole (**86**) from 2,4-bis(trifluoroacetyl)-1-naphthylamine (**85**) with hydroxylamine, although the reported yields are modest.[5/90]



85 **86**

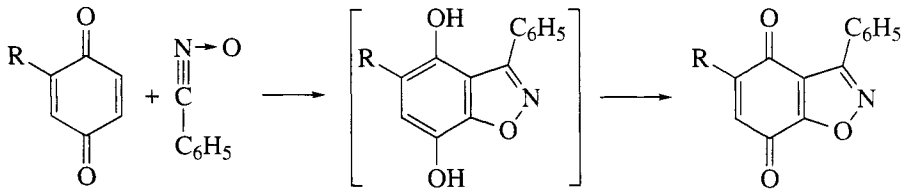
Although an example of 3–3a bond formation has been reported,[12/84] it is of little synthetic interest. Pyrolysis of isoxazolone **87** gives 1,2-benzisoxazole (**1**) and the isomeric phenylcyanate (**89**), possibly through the isocyanate (**88**).



87 **88** **89**

1.3.4. Formation of Two Bonds

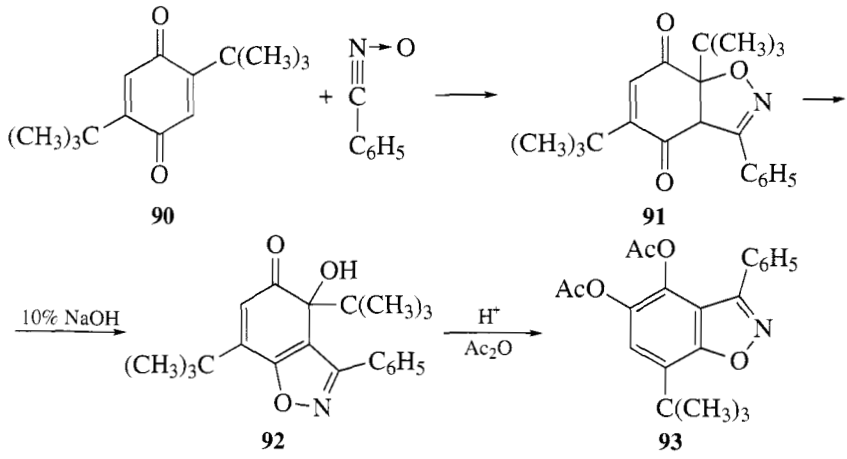
1,3-Dipolar cycloaddition of nitrile oxides with substituted *p*-benzoquinones gives the corresponding 4,7-dihydroxy-1,2-benzisoxazoles, which are readily oxidized to the more stable isoxazoloquinone derivatives.[3/50,13/84,14/91]



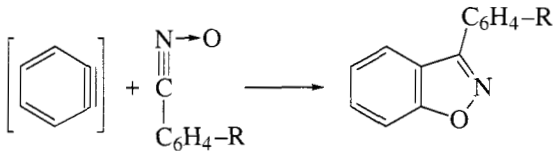
This reaction has been studied in terms of frontier molecular orbital (FMO) theory by the ab initio self-consistent field (SCF) method, and the site selectivity and regioselectivity have been predicted.[13/84]

More recently a direct synthesis of 1,2-benzisoxazole derivatives through the same kind of reaction has been described.[14/84] The reaction proceeds through the

expected cycloaddition, but then an acid-promoted elimination of isobutane affords the substituted 1,2-benzisoxazoles, as shown for the synthesis of **93**.

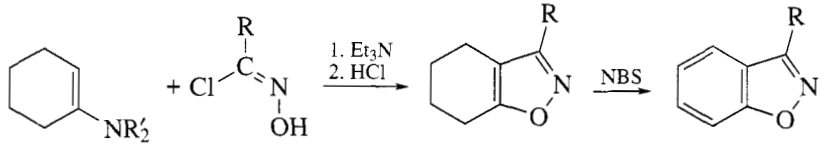


1,3-Dipolar cycloaddition of nitrile oxides with benzyne gives 3-substituted-1,2-benzisoxazoles directly.[2/64,5/69]



However, while Quilico claims a 53% yield,[2/64] in the other case the reported yields are quite low.[5/69]

1,2-Benzisoxazoles have also been obtained by aromatization with *N*-bromosuccinimide[2/66] of the hexahydro- and tetrahydro-1,2-benzisoxazoles, which are, in turn, obtained by 1,3-dipolar cycloaddition of nitrile oxides to enamines.[1/63,3/64,2/66]



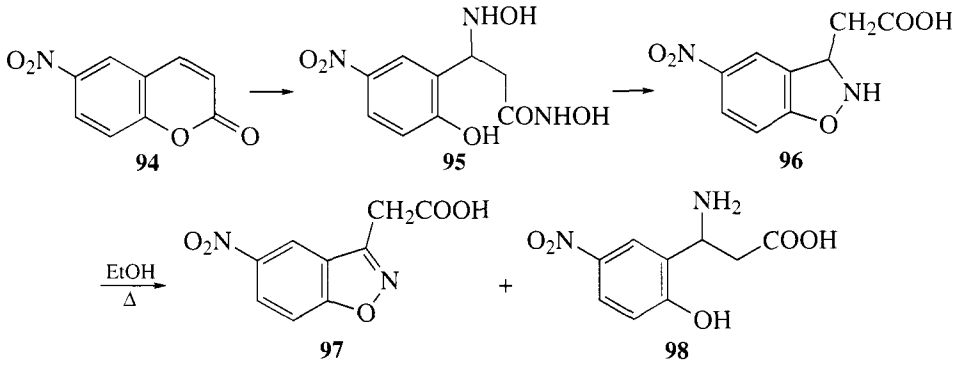
The recently reported synthesis of 1,2-benzisoxazole derivatives through anodic electrolytic oxidation of 2,4,6-tri-*tert*-butylphenol[6/69] has been shown to be incorrect, as the final product has been shown to be the corresponding benzoxazole.[7/69]

1.3.5. From Other Heterocycles

An early report[1/13] proposed a 1,2-benzisoxazole structure for a by-product of the reaction of 6- and 7-methylcoumarin with hydroxylamine; although the evidence presented was inconclusive.

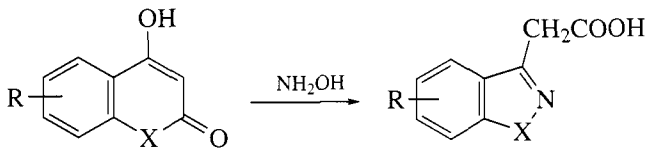
Later on the reaction was carefully reinvestigated,[4/71] and it was shown that the original assignment was correct. The reaction proceeds through an addition of hydroxylamine, a possible disproportionation of the intermediate, and a final cyclization of the oxidized product to 1,2-benzisoxazole. The reaction pathway illustrated below (**94–98**) shows the reaction of 6-nitrocoumarin (**94**), where it was possible to isolate the 1–2 adduct **95** and the 5-nitro-1,2-benzisoxazolin-3-acetic acid (**96**); these are probably both intermediates to **97** and to the β-aminoacid **98**. As a matter of fact, when it was boiled in ethanol **96** gave equimolecular amounts of **97** and **98**.

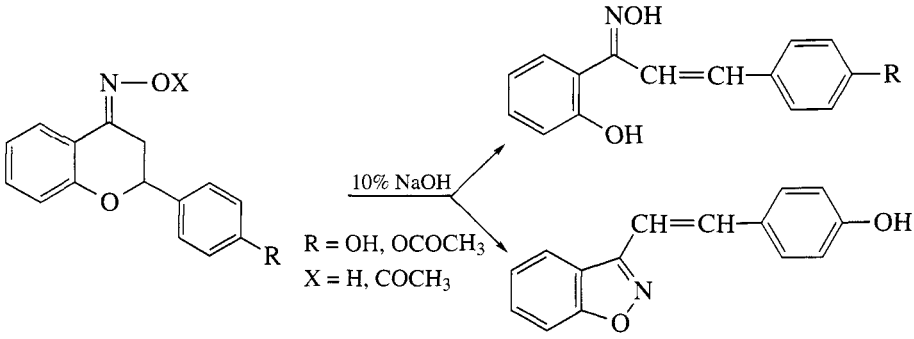
Unsubstituted coumarin gave 3-(2-hydroxyphenyl) isoxazolin-5-one instead of 1,2-benzisoxazolin-3-acetic acid.



When 4-hydroxycoumarin is used, 1,2-benzisoxazole-3-acetic acid is the major product of the reaction.[4/69]

This reaction has been extended to substituted 4-hydroxycoumarins and to the corresponding thiocumarins, and represents a convenient synthetic route to 1,2-benzisoxazole- and 1,2-benzisothiazole-3-acetic acid derivatives, which have been widely exploited because of their high reactivity (see § 1.4.5 and 1.4.7).[9/71,9/72,3/76,7/85,7/91]



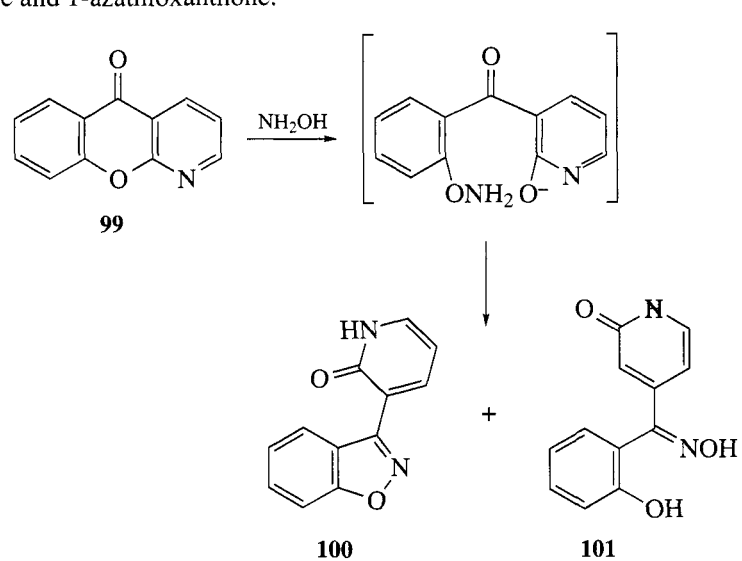


Scheme 1.12

The same reaction has also been used to synthesize 1,2-benzisoxazole-3-acetic acid labeled with ^{14}C in position α or β of the side chain starting from 4-hydroxy [3-^{14}C] coumarin and from 4-hydroxy[2-^{14}C] coumarin, respectively. [11/88] Labeled positions were determined by mass spectrometry and were in agreement with the proposed reaction scheme. [11/88]

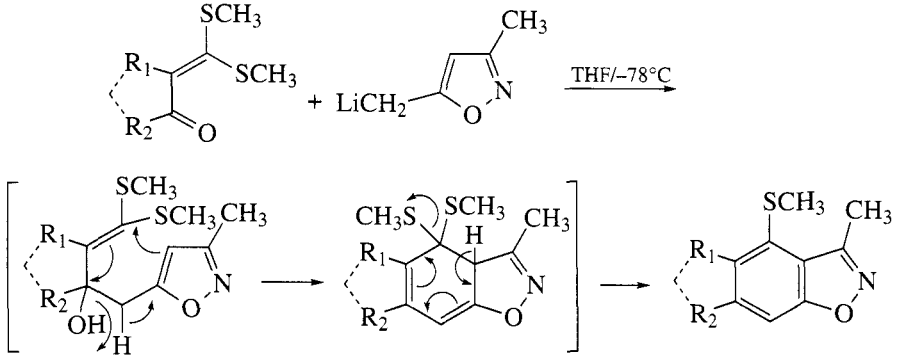
4-Hydroxyflavone oxime (Scheme 1.12: R = OH; X = H) and its monoacetate (R = OH; X = $COCH_3$) and diacetate (R = $OCOCH_3$; X = $COCH_3$), treated with 10% NaOH, similarly give the corresponding 1,2-benzisoxazole derivative,[2/79] while analogs with different R groups consistently give the intermediate oxime of 2′-hydroxychalcones. These can be cyclized to the corresponding 1,2-benzisoxazole compounds with standard methods.

1-Azaxanthone (**99**), when treated with hydroxylamine in alkaline solutions, affords a mixture of **100** and **101**. In stronger basic conditions (NaH/DMF) **100** becomes the only product. A similar result has also been observed using 3-azaxanthone and 1-azathioxanthone.[4/75]



99 **100** **101**

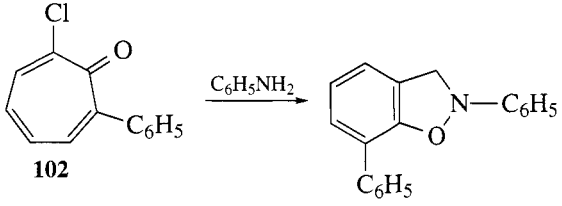
A very particular case of preparation of 1,2-benzisoxazole derivatives is the recently reported cycloaromatization of α-oxoketene dithioacetals with 3-methyl-5-lithiomethylisoxazole.[12/88] The reaction has been extended to many different substituted analogs.



1.3.6. 2,3-Dihydro-1,2-benzisoxazoles

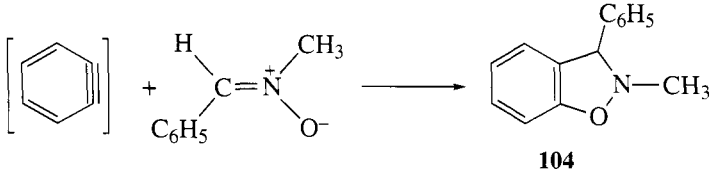
2,3-Dihydro-1,2-benzisoxazoles, also known as 1,2-benzisoxazoline derivatives, cannot be obtained by reduction of the corresponding 1,2-benzisoxazoles and are usually prepared by direct synthesis.

Although a compound like **103** was reported to have been obtained by the action of aniline on α-chlorotropone **102**,[2/59] the first useful synthesis of these compounds in good yields was reported by Huisgen et al.[4/62,8/69]



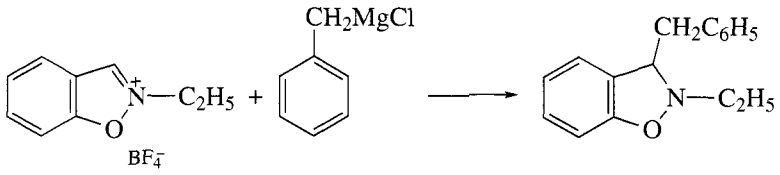
102 **103**

The method consists of a 1,3-dipolar cycloaddition of nitrones to benzyne as shown in the case of **104**.



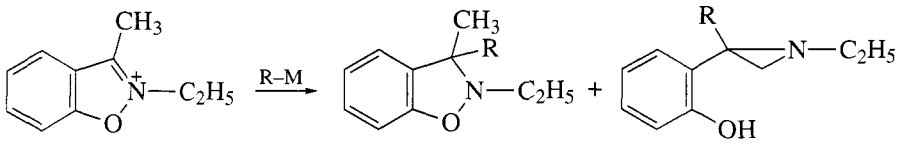
104

These compounds can also be obtained by addition of Grignard reagents to *N*-alkyl-1,2-benzisoxazolium salts.[5/74]



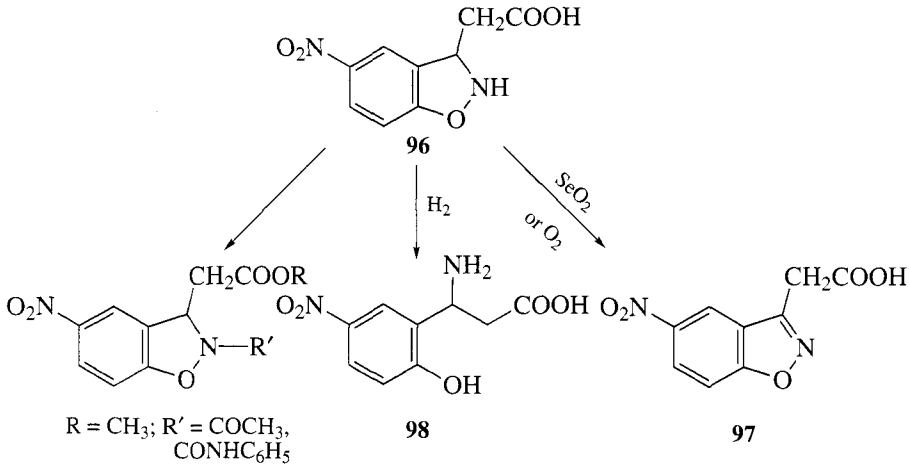
105 **106**

More recently this reaction has been extended to organometallic compounds,[2/88] but in some cases it is complicated by the concurrent formation of aziridines (see § 1.4.6).

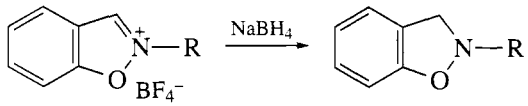


107

5-Nitro-1,2-benzisoxazolin-3-acetic acid (**96**) has been obtained as one of the products of the reaction of 6-nitrocoumarin with hydroxylamine (see § 1.3.5).[4/71] This compound can be derivatized and oxidized (**97**), but reduction with H_2/Pd(C) results in cleavage to β-amino-β-(2-hydroxy-5-nitrophenyl) propionic acid (**98**).



Unlike 1,2-benzisoxazoles, *N*-alkyl-1,2-benzisoxazolium salts can be reduced under controlled conditions to the corresponding 2,3-dihydro-1,2-benzisoxa-



105, R = C_2H_5 **108**, R = C_2H_5

109, R= *t*.C_4H_9 **110**, R = *t*.C_4H_9

zoles. Thus the *N*-ethyl derivative **105** was transformed into **108** by reduction with $NaBH_4$.[4/67]

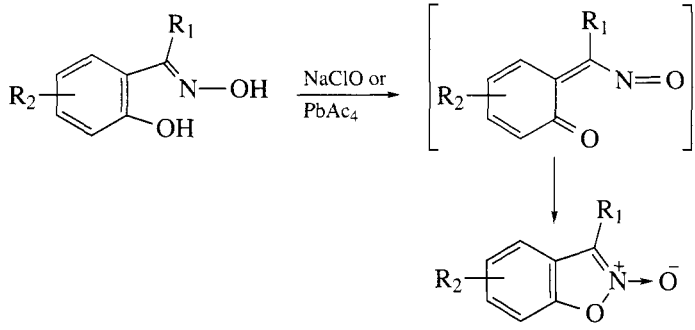
The method has been successfully applied to the synthesis of 2-*tert*-butyl-2,3-dihydro-1,2-benzisoxazole (**110**)[1/84] and 3-methyl-2-ethyl-2,3-dihydro-1,2-benzisoxazole.[2/88]

1.3.7. 1,2-Benzisoxazole-*N*-oxides

Until 1980 1,2-benzisoxazole-*N*-oxides were unknown; they cannot be obtained by direct oxidation of 1,2-benzisoxazoles, and only in that year did Boulton and Tsoungas succeed in synthesizing the first members of the series by oxidation of 2-acylphenol oximes with lead tetracetate.[3/80]

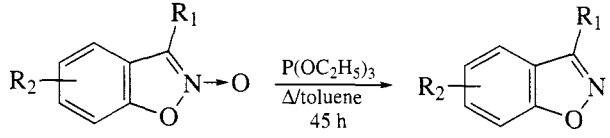
The oxidant was then successfully substituted with sodium hypochlorite[1/86] and the reaction applied to a variety of 2-acylphenol oximes. The parent compound 1,2-benzisoxazole-*N*-oxide, however, remained elusive.

The following mechanism has been proposed for the reaction:



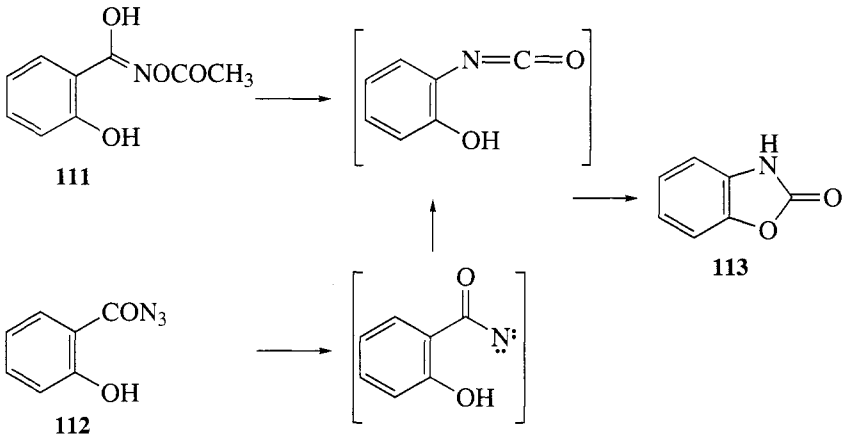
Accordingly, the configuration of the starting oxime seems to be of little importance.[1/86]

These compounds are stable crystalline solids and can be reduced to 1,2-benzisoxazoles, albeit under quite compelling conditions.[3/80]

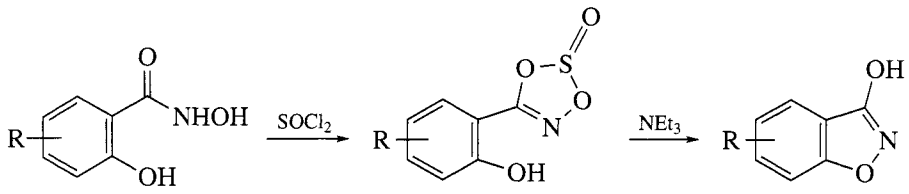


1.3.8. 1,2-Benzisoxazolin-3-ones

Reaction of compound **111** with alkali or heating the azide **112** in benzene does not provide the 1,2-benzisoxazolin-3-one or its 3-hydroxy tautomeric form because a rearrangement to benzoxazolinone **113** similar to that discussed before occurs (see § 1.3.2).[4/27]



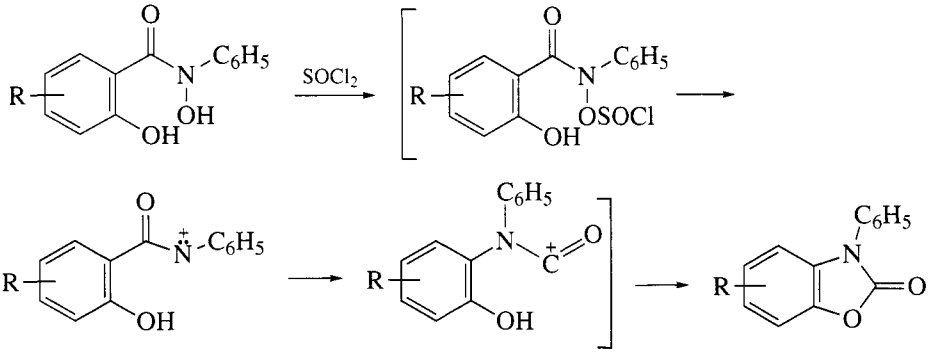
1,2-Benzisoxazolin-3-ones can, however, be obtained by reaction of thionyl chloride with salicyloylhydroxamic acids, followed by treatment with triethylamine.[2/63,2/67]



Thionyl chloride can be substituted by phosgene, [3/68] and, according to Friary and Sunday,[3/79] this two-step procedure can be simplified using carbonyldiimidazole followed by acidification.

The reported application of this reaction to *N*-phenylsalicyloylhydroxamic acids, to give *N*-phenyl-1,2-benzisoxazolinones,[9/77] has been proved to be incorrect; the compounds obtained are the *N*-phenylbenzoxazolinones derived from Lossen-like rearrangement of an acylnitrenium ion formed in the reaction.[8/78]

Infrared studies of the tautomeric nature of 1,2-benzisoxazolin-3-ones, indicate that the enol tautomer is present in the solid state, while both keto and enol tautomers are present in $CHCl_3$.[1/71] Methylation of the parent compound produces a 3–1 mixture of 3-methoxy and 2-*N*-methyl derivatives.[2/67,1/71]

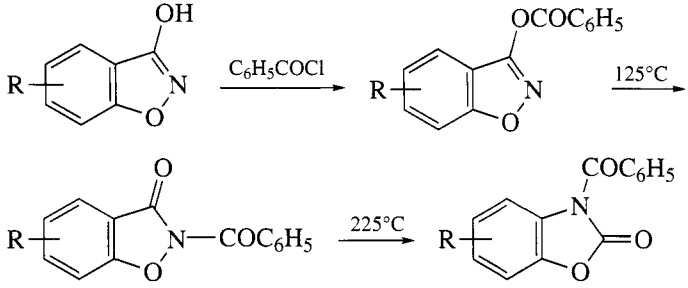


Accordingly, alkylation of 1,2-benzisoxazolin-3-ones with ethylenic chloridrine affords a 2–1 mixture of *O*- and *N*-alkyl derivatives.[5/83]

In other cases, however, the *O*-alkyl derivative seems to be the only product formed.[11/77,9/78,10/78,7/81,5/86] The small quantity of *N*-alkyl isomer formed is probably transformed into the isomeric 1,3-benzoxazin-4-one by a base-catalyzed reaction (see § 1.4.5).[9/78]

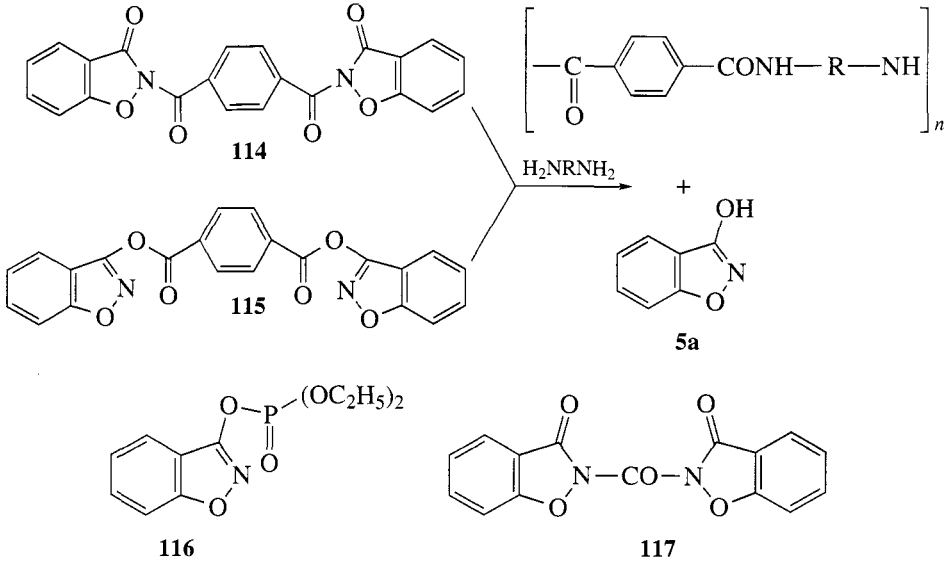
On the other hand, it has been reported[2/84] that alkylation with ethylene oxide or epichlorohydrin gives only *N*-alkyl-1,2-benzisoxazolin-3-ones, as indicated by IR spectroscopy. However, the possible isomerization of the compounds has not been taken into account by the authors.

Acetylation with acetic anhydride gives only the *O*-acetyl derivatives.[2/67] The same happens with other acylating reagents.[11/78,6/80] In any case it has been shown that *O*-acyl derivatives are labile forms that can be rearranged by heating into *N*-acyl-1,2-benzisoxazolin-3-ones and, under more severe conditions, into the isomeric *N*-acyl benzoxazolinones.[2/69,4/70,8/81]



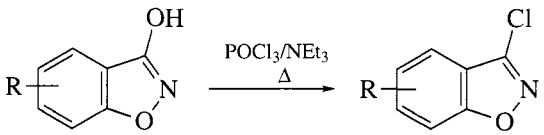
1,2-Benzisoxazolin-3-one is a very good leaving group and *N*-acyl and *O*-acyl derivatives such as **114** and **115** are susceptible to aminolysis under mild conditions and have been used for polyamide synthesis.[8/81]

In the same framework compound **116** has been used as an activating agent[8/85,9/85] and **117** as a condensing agent for peptide synthesis.[1/83]



Phosphates and thiophosphates of 3-hydroxy-1,2-benzisoxazoles are reported in a series of patents as insecticidal and acaricidal agents.[10/72,11/72,12/72]

3-Hydroxy-1,2-benzisoxazoles are easily and quantitatively transformed into the 3-chloro derivatives, which are useful starting materials for other 3-substituted 1,2-benzisoxazoles (see § 1.4.5).[3/67]



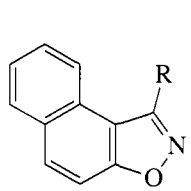
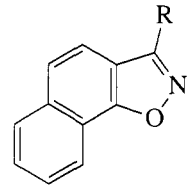
1.3.9. Polynuclear Condensed 1,2-Benzisoxazoles

Polynuclear condensed 1,2-benzisoxazoles are usually obtained by closing the 1,2-benzisoxazole ring with one of the methods previously reported, or by building up the condensed nucleus on a preexisting 1,2-benzisoxazole structure.

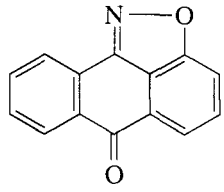
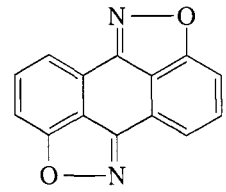
1.3.9.1. 1,2-Benzisoxazole Condensed with Hydrocarbons

Few examples of 1,2-benzisoxazole derivatives containing condensed hydrocarbon rings are known.

Naphth[1,2-*d*]isoxazoles and naphth[2,1-*d*]-isoxazoles have usually been obtained from the corresponding acetylated oximes of 1- and 2-acylnaphthols by the action of alkali.[3/27,1/44,2/66,12/77,7/80,8/80,5/90]

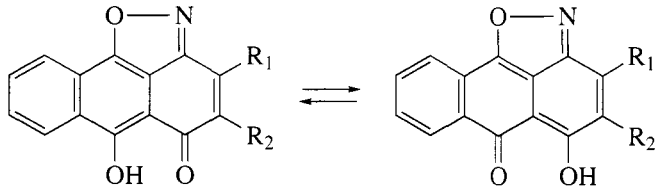



Compounds **118** and **119** were obtained from 1-chloro and 1,5-dichloro anthraquinones after treatment with hydroxylamine hydrochloride in ethanol.[1/10]

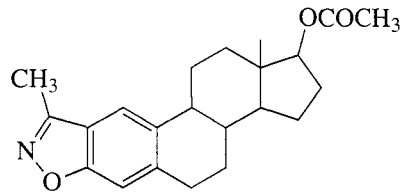



118 **119**

Similar derivatives have recently been synthesized and shown to exist in equilibrium with the tautomeric form (see § 1.4.8.2).[6/90]



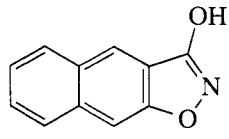
Treatment of 2-acetylextradiol with hydroxylamine and benzenesulfonyl chloride in dilute potassium hydroxide gave the benzisoxazole **120**.[3/71]



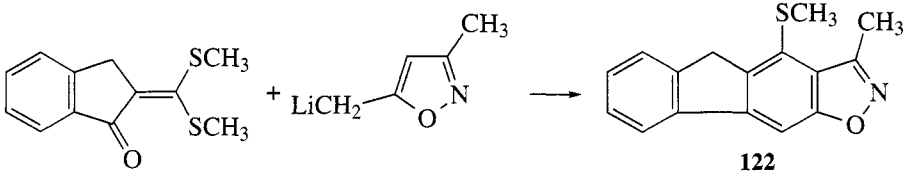
120

3-Hydroxy-naphth[2,3-*d*]isoxazole **121** was obtained with the general method of Böshagen.[2/67]

Hydrocarbon-condensed 1,2-benzisoxazoles such as **122** can be obtained by cycloaromatization of α-oxoketene dithioacetals following a previously discussed method (see § 1.3.5).[12/88]



121



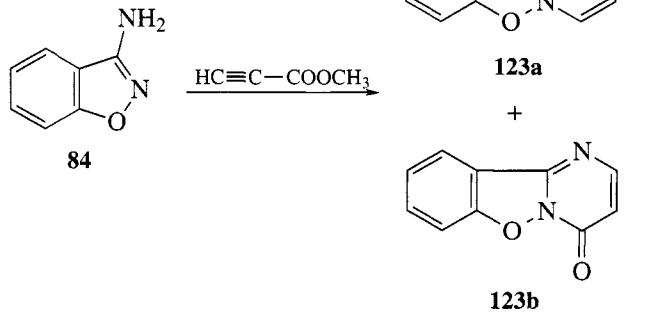
122

1.3.9.2. 1,2-Benzisoxazole Condensed with Other Heterocycles

Several polynuclear heterocyclic systems containing the 1,2-benzisoxazole nucleus are known. They are usually obtained by building up the condensed heterocycle on the preexisting, appropriately substituted 1,2-benzisoxazole.

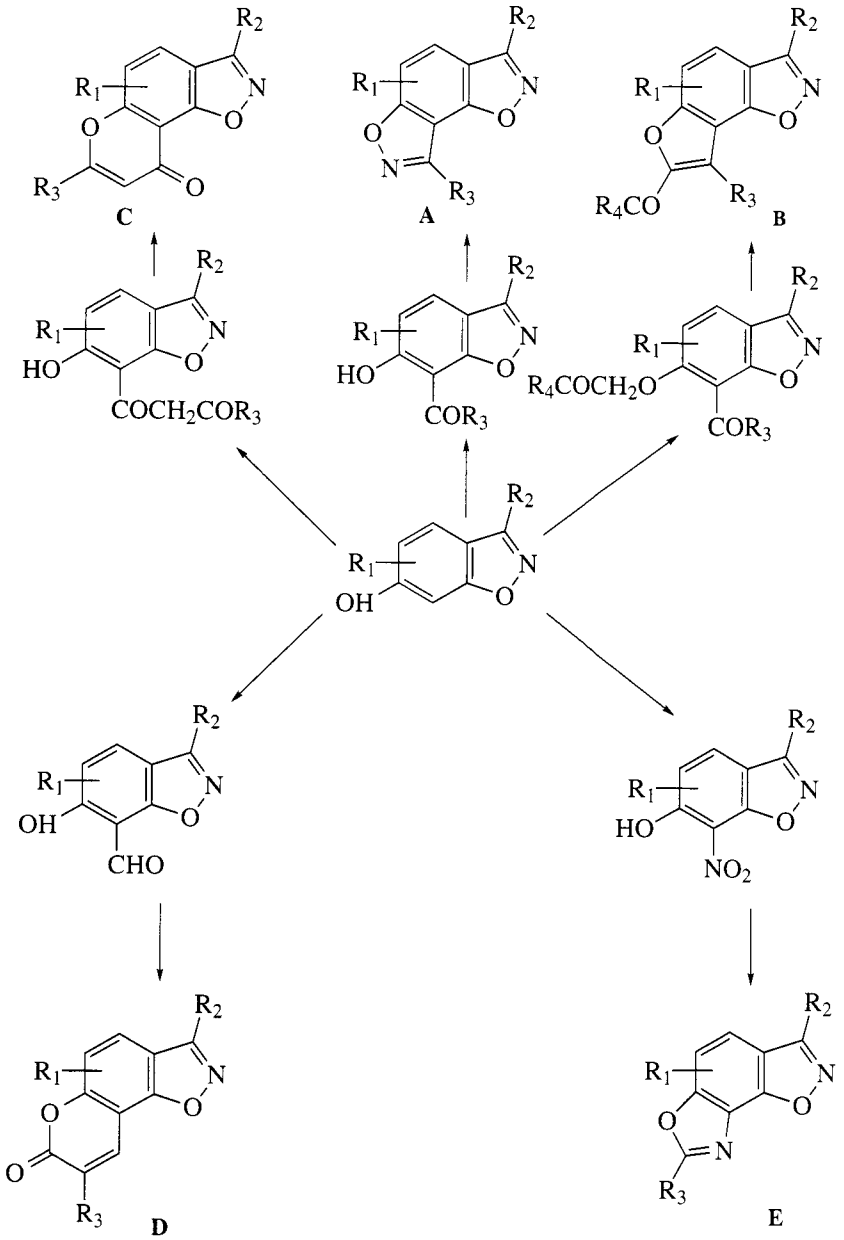
Thus manipulation of 6-hydroxy-1,2-benzisoxazole derivatives through standard methods that do not interfere with the isoxazole nucleus has allowed the synthesis of a series of isoxazolo[6,7-*d*]1,2-benzisoxazoles (**A**);[5/77,9/80] furano[6,7-*d*]1,2-benzisoxazoles (**B**);[5/77,2/80,6/86] 9(H)-oxopyrano[2,3-*g*]1,2-benzisoxazoles (**C**);[3/73,6/73,13/77,3/87] 7(*H*)-oxopyrano[2,3-*g*]1,2-benzisoxazoles (**D**);[2/77,3/87] and oxazolo[5,4-g]1,2-benzisoxazoles (**E**).[4/87]

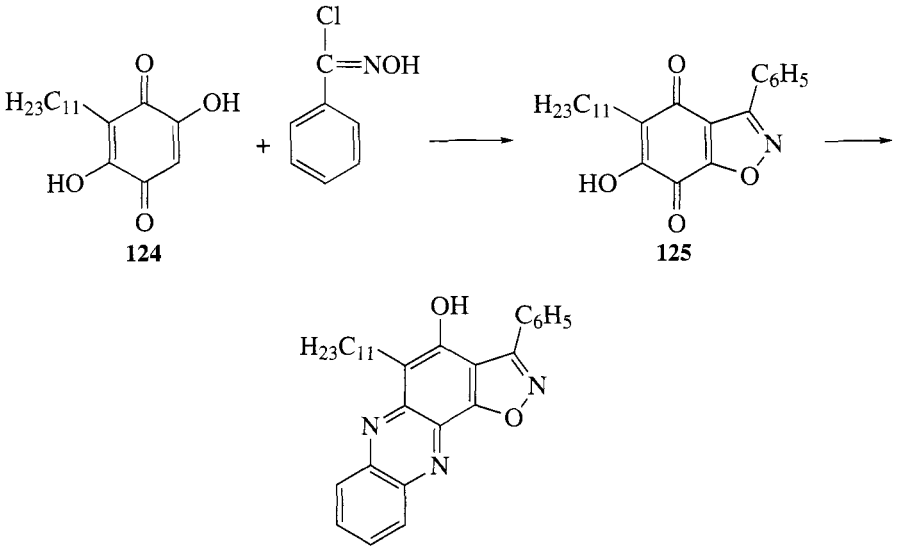
Condensation of methyl propiolate with 3-amino-1,2-benzisoxazole (**84**) gives the regioisomeric 2-oxo-2H-pyrimido- (**123a**) and 4-oxo-4H-pyrimido[1,2-*b*]- benzisoxazoles (**123b**).[15/72]



84 **123a** + **123b**

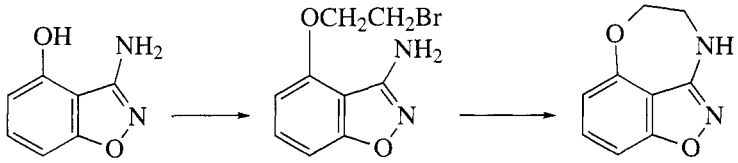
Tetracyclic 1,2-benzisoxazoles such as **126** were synthesized from the corresponding diones (**125**), obtained by cycloaddition of benzonitrile oxide on embelin (**124**).[14/91]


R2
R1
O
N
O
R3
O
C
A
B
R4CO
HO
COCH2COR3
COR3
R4COCH2O
OH
CHO
NO2
D
E



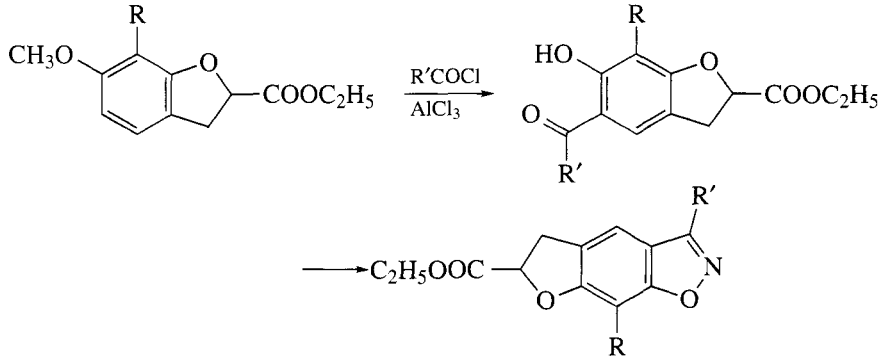
124 **125** **126**

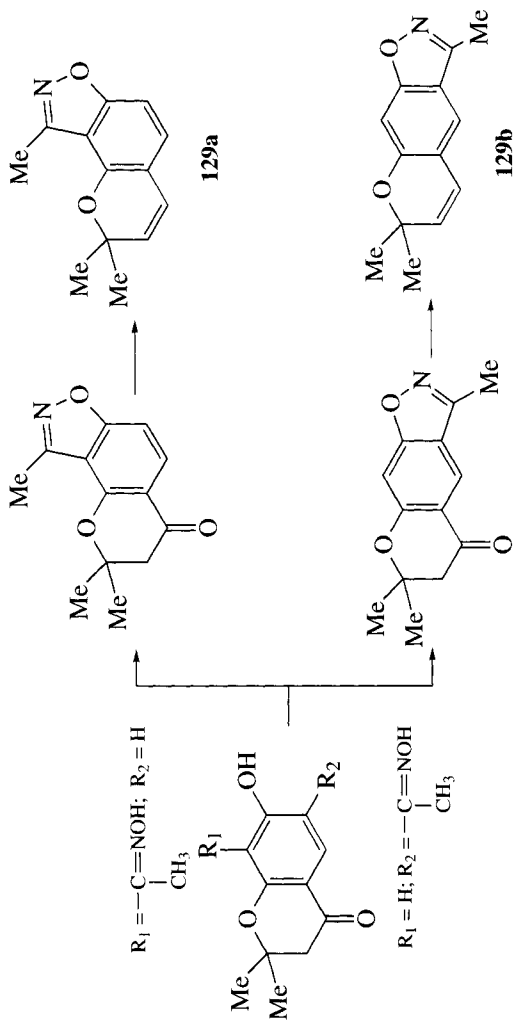
Manipulation of 3-amino-4-hydroxy-1,2-benzisoxazole (**127**) has led to 4,5-dihydroisoxazolo [3,4,5-*ef*][1,4]benzoxazepine (**128**).[4/89]



127 **128**

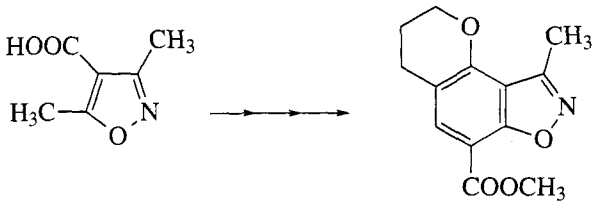
A series of 5,6-dihydrofuro[3,2-*f*]-1,2-benzisoxazole-6-carboxylic acids endowed with saluretic activity has been prepared by construction of the 1,2-benzisoxazole ring on suitably substituted dihydrobenzofuranes by the usual synthetic methods.[6/84,9/84,15/84,7/86]




Me
N
O
Me
Me
O
O
129a
129b
$R_1 = -C(=NOH)-CH_3$; $R_2 = H$
$R_1 = H$; $R_2 = -C(=NOH)-CH_3$
OH
R_1
R_2

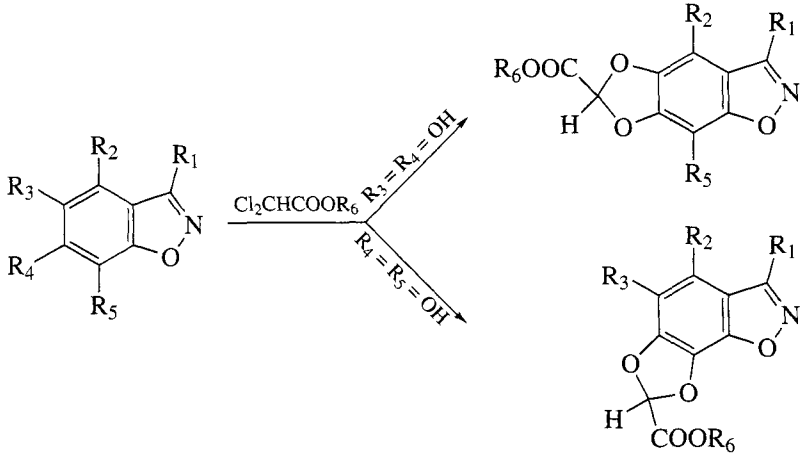
A similar approach, in which the isoxazole ring is constructed on a preexisting heterocycle, has been followed to obtain 2(*H*)-pyrano[2,3-*e*]- and 7(H)-pyrano[3,2-*f*]-1,2-benzisoxazole derivatives, **129a** and **129b** respectively.[5/89]

The same approach has been used to obtain annulated 1,2-benzisoxazole **130** starting from a simple isoxazole derivative.[6/89]

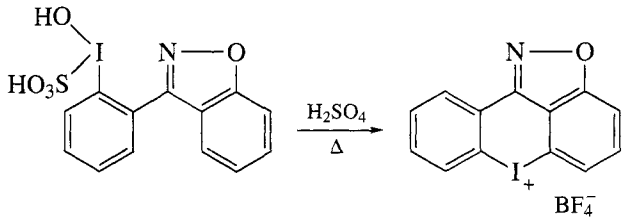


130

1,3-Dioxolo[4,5-*f*]-1,2-benzisoxazoles and 1,3-dioxolo[4,5-*g*]-1,2-benzisoxazoles have been prepared in order to evaluate their diuretic activity.[8/86,13/91,2/92]

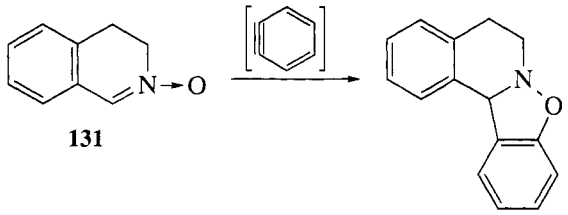


A very unusual polycyclic 1,2-benzisoxazole **27** was obtained by Tolstaya et al.;[10/85] its structure was proved by X-ray crystallography.[3/85]



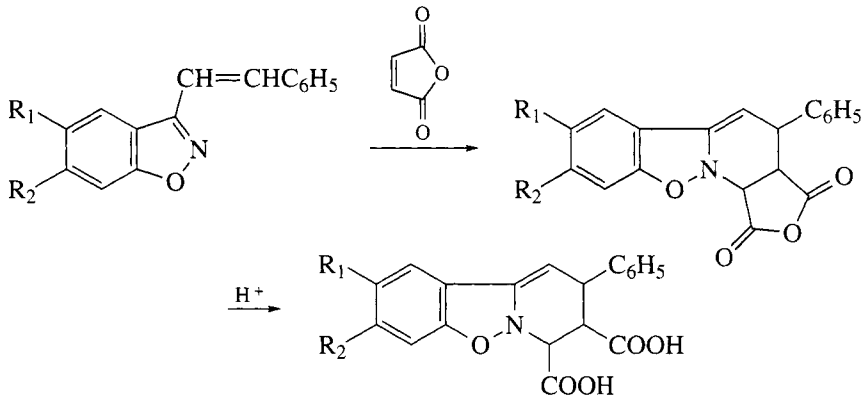
27

In some polynuclear molecules the 2,3-dihydro-1,2-benzisoxazole moiety is present. One such structure is **132**, which has been obtained by reaction of dihydroisoquinoline oxide (**131**) with benzyne.[8/69]

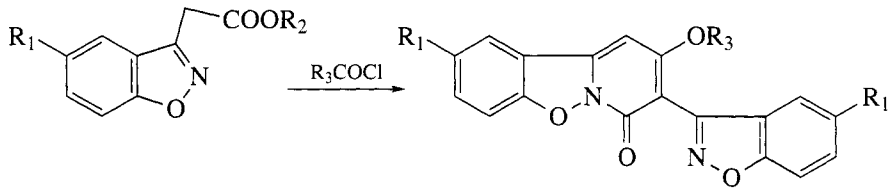


131 **132**

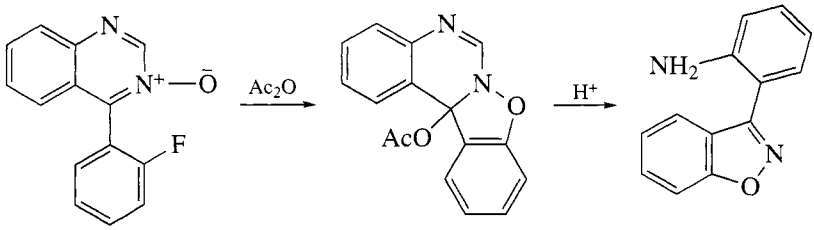
The reduced 1,2-benzisoxazole nucleus is also present in compounds obtained by reaction of styryl derivatives with maleic anhydride; subsequent hydrolysis of the adducts gave the corresponding dicarboxylic acids.[7/80]



Similar compounds were also obtained by dimerization of the corresponding 1,2-benzisoxazole-3-acetic acids with acyl chlorides.[2/82]

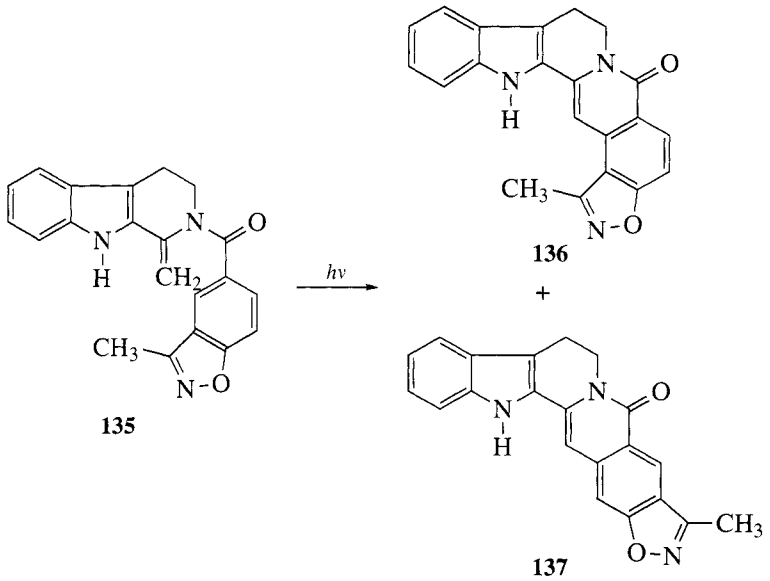


Upon treatment with acetic anhydride 4-(2-fluorophenyl)quinazoline 3-oxides such as **133** undergo intramolecular nucleophilic displacement of fluoride to yield 1,2-benzisoxazolo[2,3-*c*]-quinazolines such as **20**. These compounds are hydrolized with acids to 3-(2-aminophenyl)-1,2-benzisoxazoles (**134**).[2/74]



133 20 134

Finally, the isomeric compounds **136** and **137** have been obtained by irradiation of **135** in a synthesis of yohimbine.[10/80] It is interesting to note that in this case the 1,2-benzisoxazole ring was used as a protected and easily hydrolizable form of the 2-hydroxyacetophenone system. It is also noteworthy that no photochemical isomerization to benzoxazole has been reported (see § 1.4.4).



135 136 137

1.4. CHEMICAL PROPERTIES

Whereas 3-alkyl- and 3-aryl-1,2-benzisoxazoles are fairly stable, 3-unsubstituted derivatives are quite unstable toward bases and, to a lesser extent, acids, properties that are shared by the corresponding 3-acyl and 3-carboxy derivatives. Under these conditions, as well as with a variety of reducing agents, the isoxazole ring is cleaved. In general, the reactivity of 1,2-benzisoxazole is dictated, as with isoxazole, by the weak N–O bond.

The chemistry of the substituents on the phenyl ring is similar to that of the corresponding benzene derivatives, and, taking into account the stability of the isoxazole ring in the reaction conditions used, they can be induced to undergo standard aromatic substitution reactions.

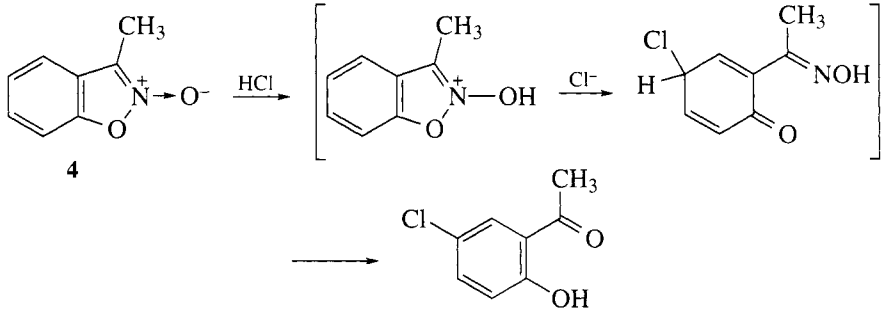
1.4.1. Protonation and Acid Stability

1,2-Benzisoxazole derivatives are weak bases; in general, they are weaker bases than the corresponding noncondensed isoxazoles.[2/73,4/77] They can therefore be dissolved in strong acids, but so far no stable crystalline salts have been described. The 2,3-dihydroanalogs, on the other hand, are sufficiently basic to give isolable salts.[4/67,4/71]

Whereas 3-alkyl- and 3-acyl-1,2-benzisoxazoles are quite stable toward acids, 3-alkoxycarbonyl- and 3-carboxylic acids and their hydrolizable derivatives are broken down to the corresponding salicylic acids.[1/12,2/29,1/48,4/50,1/58] The 3-hydroxy derivatives are particularly unstable, being cleaved to give the corresponding acylhydroxamic acids, which, in turn, can undergo Beckmann rearrangement when heated.[2/29]

1,2-Benzisoxazole is isomerized to salicylonitrile by hydrochloric acid and aluminum trichloride.[5/50]

3-Methyl-1,2-benzisoxazole-2-oxide (**4**) is cleaved by hydrochloric acid to give 2-hydroxy-5-chloroacetophenone (**138**) as a consequence of nucleophilic attack by chloride ion during ring opening.[1/87]

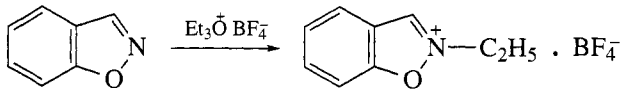


4 **138**

1.4.2. Quaternization and Metal Complexation

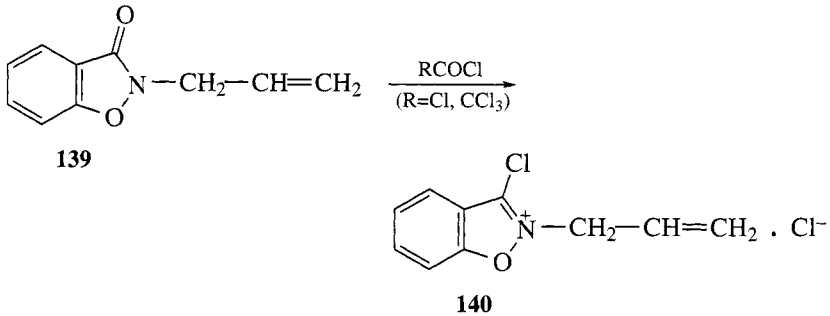
The nitrogen atom in 1,2-benzisoxazoles may be easily quaternized. Dimethyl- and diethylsulfate,[1/31,2/55,1/61,6/74] benzyl chloride,[5/62] and methyl-2,4-dinitrobenzensulfonate[3/66] have been employed for this purpose; reaction with triethyloxonium tetrafluoroborate[1/65] would seem to be the method of choice for the preparation of *N*-ethyl derivatives.

A variety of salts has been obtained, including iodides, chlorides, perchlorates, trichloromercurates, tetrachloroferrates, and tetrafluoroborates.[1/31, 2/55,1/61,5/62, 1/65,3/66,6/74,8/84]



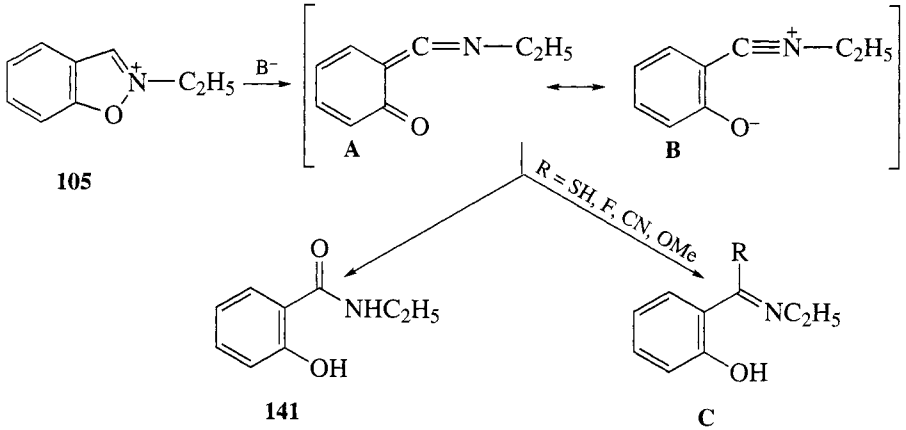
1 **105**

More recently, *N*-allyl-3-chloro-1,2-benzisoxazolium chloride (**140**) has been prepared by treating the carbonyl derivative **139** with phosgene or trichloromethylchloroformate.[12/78,9/79]



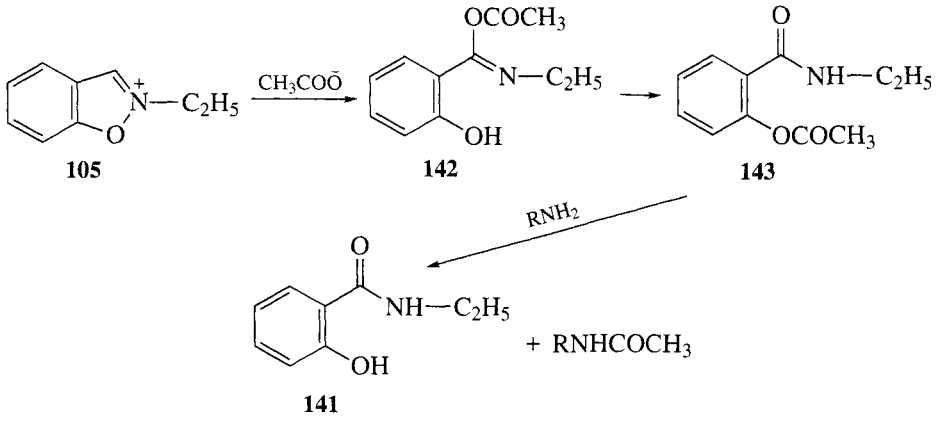
139 **140**

The chemistry of 1,2-benzisoxazolium compounds has been extensively studied by Kemp and Woodward, who have shown that these derivatives easily undergo a general, base-catalyzed transformation into a resonance-stabilized, highly electrophillic intermediate such as **A**.[1/65] Naphth[1,2-*d*]isoxazolium cations behave in a similar way.[12/87] In the absence of reactive anions, the final product is *N*-ethylsalicylamide (**141**); when other nucleophiles are present, a variety of compounds with the general structure **C** can be obtained.[4/67,7/74]

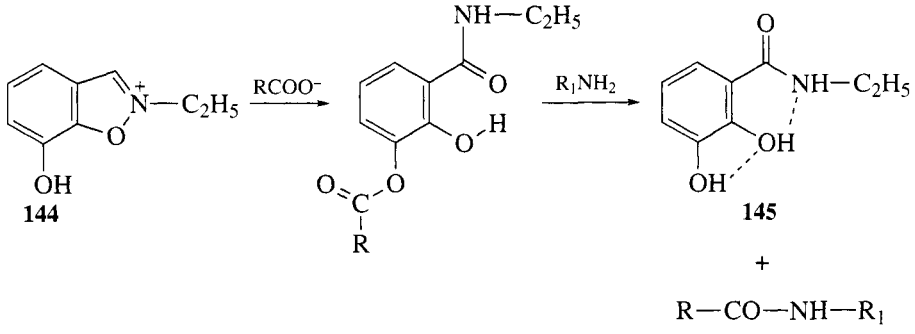


105 **A** **B** **141** **C**

Accordingly, the reaction of 1,2-benzisoxazolium salts such as **105** with an aqueous solution of acetate ion leads to high yields of *O*-acetyl-*N*-ethyl-salicylamide (**143**), through the unstable intermediate **142**. Compound **143** is an activated ester and can easily react with an amino group,[4/67] a property that has led to the use of 1,2-benzisoxazolium salts, such as **144**, as condensing agents for the synthesis of peptides.[4/67,7/67,3/74,7/74,8/74]

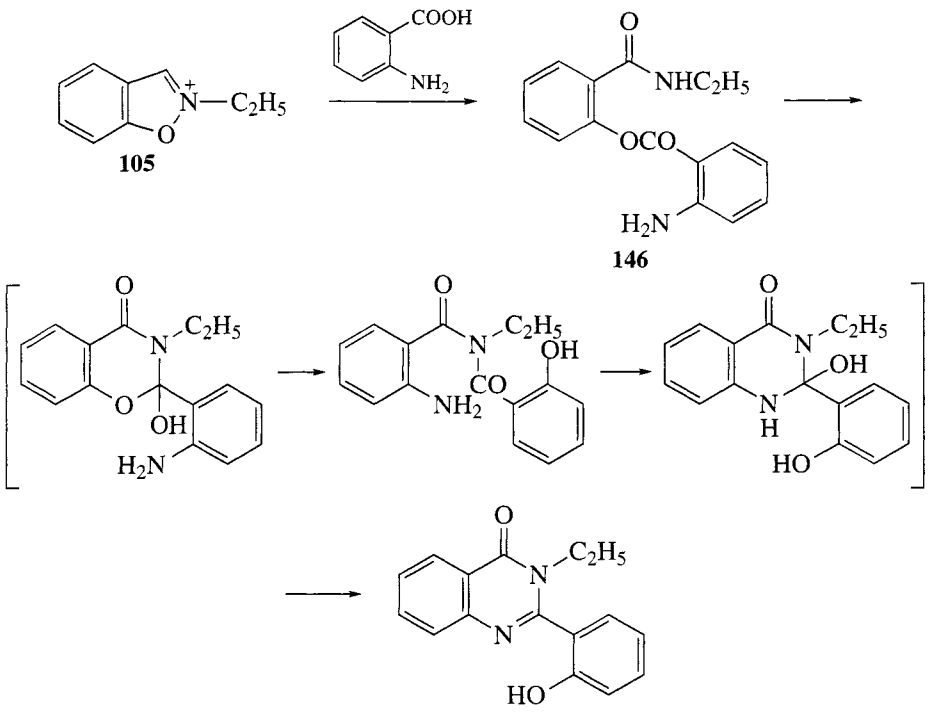


At a pH in the range of 4.5–5.0, in the presence of carboxylate ions, peptides can be obtained in almost quantitative yield and without racemization.



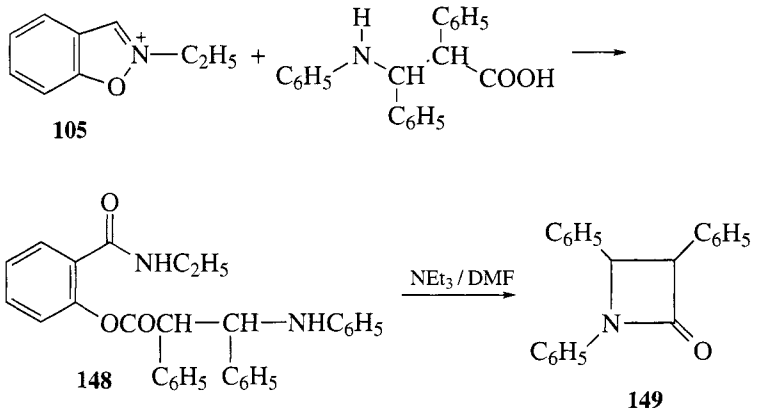
The advantage of 1,2-benzisoxazolium salts over the corresponding isoxazolium species seems to lie in the stabilizing effect of the condensed benzene ring. This allows, for instance, a substantial contribution of structure **B**, which should be more reactive than the ketoketenimines derived from isoxazolium salts.[1/65] This class of compounds has found wide use in peptide chemistry.[4/68,8/70,9/81,10/81,16/84,11/85,13/87,14/87]

When **105** was treated with anthranilic acid, it gave the expected ester **146** accompanied by 3-ethyl-2-(*o*-hydroxyphenyl)-4-quinazolone (**147**).[7/73] The latter compound is believed to arise from **146** by an oxygen-to-nitrogen migration followed by intramolecular reaction of the resulting imide.



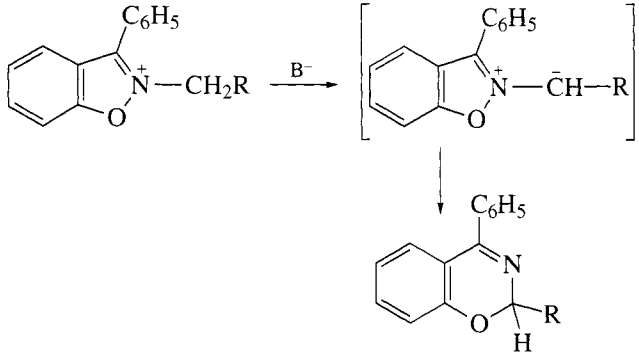
105 146 147

Interestingly, the same reagent with *erythro*-β-anilino-α,β-diphenylpropionic acid gave the corresponding activated ester **148**, which on treatment with triethylamine in DMF, gave a mixture of *cis* and *trans* β-lactam **149**.[5/75]

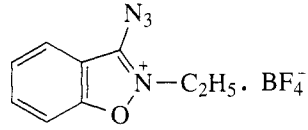


105 148 149

It has been reported that strong bases promote the rearrangement of 3-phenyl-1,2-benzisoxazolium salts to dihydrooxazines,[1/31,5/62] possibly through an ylide intermediate.

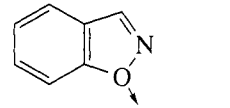


2-Ethyl-3-azido-1,2-benzisoxazolium tetrafluoroborate (**150**) has been employed to study the kinetics of the diazo transfer reaction.[9/74,10/74]



150

Finally, there is only one reported example of complexes of 1,2-benzisoxazole with metals; the pentacarbonyl complex of 1,2-benzisoxazole with tungsten (0) (**151**), for which ^{1}H-NMR and IR spectra have been recorded.[13/72]



151 W $(CO)_5$

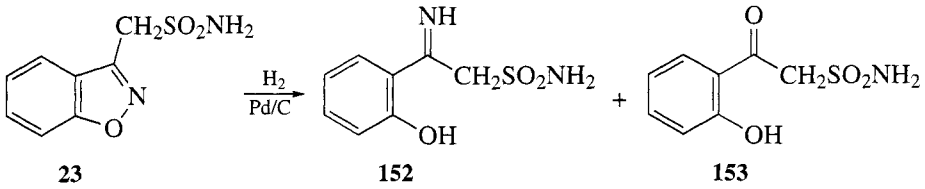
1.4.3. Reduction and Oxidation

Several reagents have been used to reduce 1,2-benzisoxazole derivatives, many of which lead to ring cleavage.

Catalytic hydrogenation with catalysts such as Pd or Raney Ni usually cleaves the isoxazole ring, leading to the corresponding ketimine and/or carbonyl compounds, depending on the reaction conditions.[1/27,4/69, 10/71,4/76,10/79,3/82]

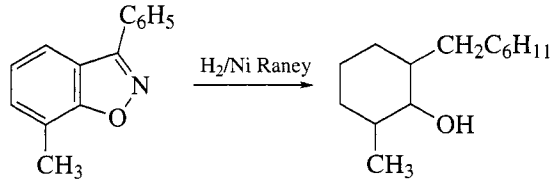
3-Sulfamoylmethyl-1,2-benzisoxazole (**23**), when reduced in ethanol, gave ω-sulfamoyl-2-hydroxyacetophenone imide (**152**) and ω-sulfamoyl-2-hydroxyacetophenone (**153**).[3/82]

It has nevertheless been reported that 6-nitro-1,2-benzisoxazole-3-carboxylic acid can be reduced to the corresponding amino derivative using hydrogen and Raney Ni without cleavage of the ring.[1/53] In another instance, however, the same



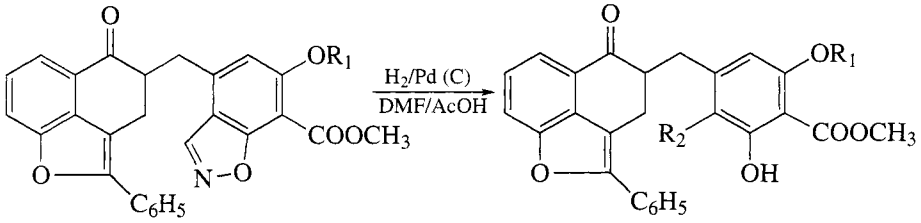
23 **152** **153**

catalyst led to complete reduction of 7-methyl-3-phenyl-1,2-benzisoxazole to alcohol **154**.[2/56]



154

Surprisingly, while compound **155** (R_1 = Ac) was reduced as expected to the hydroxyaldehyde **156** (R_2 = CHO), compound **157** (R_1 = H) instead gave the corresponding nitrile **158** (R_2 = CN) under the same conditions.[10/71]



155, R_1 = Ac
157, R_1 = H

156, R_1 = Ac, R_2 = CHO
158, R_1 = H, R_2 = CN

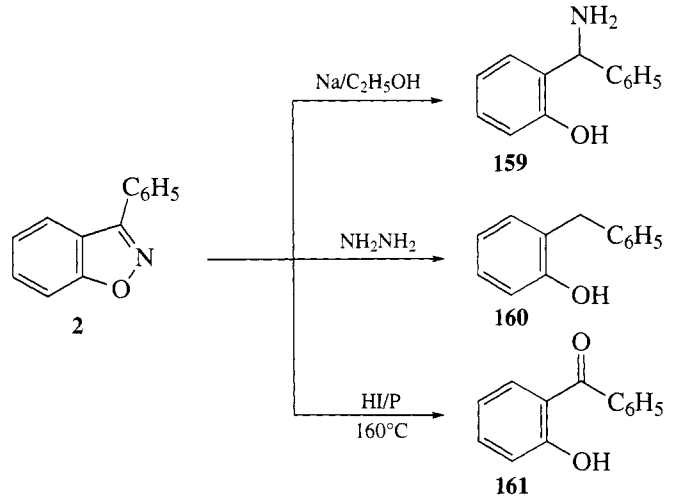
Reduction of 3-phenyl-1,2-benzisoxazole (**2**) with sodium in ethanol also gave ring cleavage but led to isolation of the amino derivative **159**.[2/894,1/896,1/39]

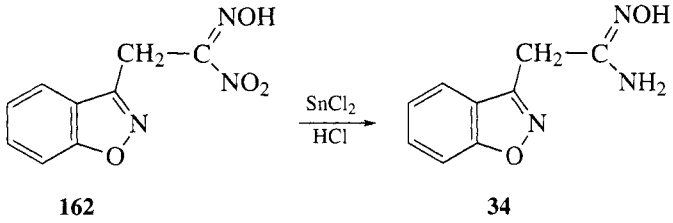
The same substrate gave 2-hydroxydiphenylmethane (**160**) after treatment with hydrazine hydrate[1/39] and 2-hydroxybenzophenone (**161**) with HI/P.[1/896]

Stannous chloride reduces nitro groups, as in nitrolic acid **162**,[8/75] without cleaving the ring, and this reagent has been widely used in 1,2-benzisoxazole chemistry.[1/26,3/27,1/29, 2/29,1/75,3/75,7/75,7/78,6/83]

There have been some reports of the introduction of a chlorine atom into the benzenoid ring during $SnCl_2$/HCl reduction.[3/27,1/29]

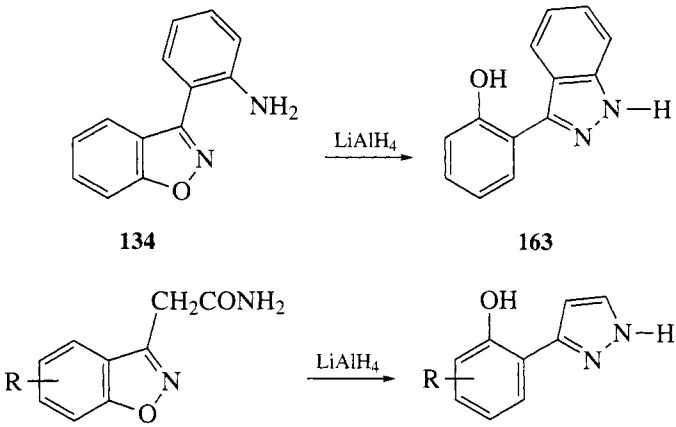
Metal hydrides exhibit a dual behavior: in some cases the 1,2-benzisoxazole ring is cleaved, and in other circumstances the isoxazole ring survives. 1,2-Benzisoxazol-3-ones are cleaved to salicylamide derivatives by $NaBH_4$.[2/67]





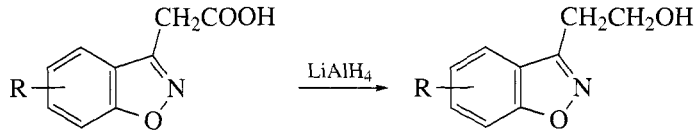
162 34

The amino derivative **134** is transformed into 3-(2-hydroxyphenyl)indazole(**163**) by treatment with $LiAlH_4$ or NaH[2/74] and primary amides of 1,2-benzisoxazole-3-acetic acids are transformed into 3-(2-hydroxyphenyl) pyrazole derivatives.[6/75]

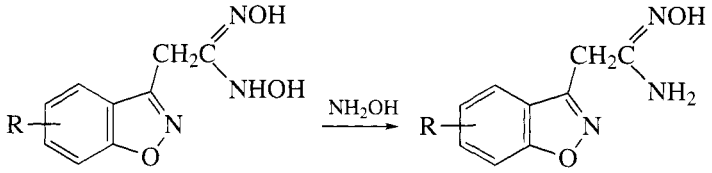


134 163

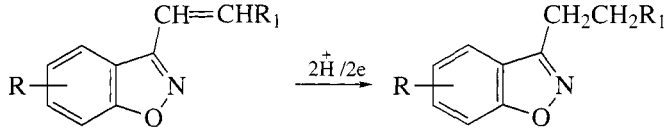
However, in these two cases the 1,2-benzisoxazole ring was likely opened by the action of metal hydrides acting as strong bases (see § 1.4.5). Conversely, 1,2-benzisoxazole-3-acetic acids are reduced to the corresponding alcohols by $LiAlH_4$.[6/75,7/75]



Hydroxylamine reduction of hydroxamic acid oximes containing a 1,2-benzisoxazole nucleus gives the corresponding 3-acetamidoximes, leaving the isoxazole ring unchanged.[13/75]

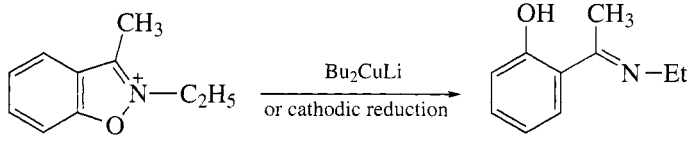


It has been reported that polarographic reduction of some 3-substituted 1,2-benzisoxazoles selectively reduces the double bond of the side chain.[13/78]



As already mentioned (see § 1.3.6), 1,2-benzisoxazolium salts can be reduced to 2,3-dihydro-1,2-benzisoxazoles by $NaBH_4$[4/67] under carefully controlled conditions.

In contrast, reductive cleavage of the isoxazole ring, to give the enamino derivative **164**, was observed when **107** was treated with lithium dialkylcuprates.[9/86]

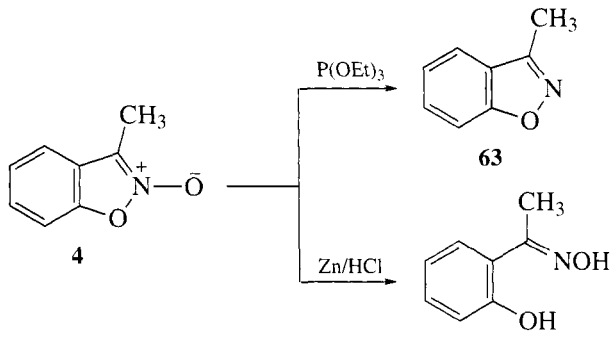


107 **164**

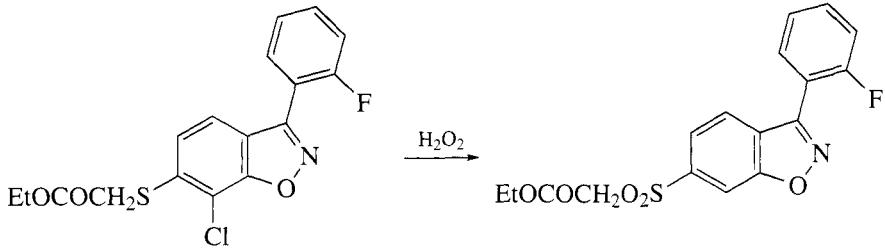
Cathodic reduction effects the same transformation.[13/88]

It has been reported that reduction of *N*-methyl 3-amino-6-nitro-1,2-benzisoxazolium iodide with Adam's catalyst gives the corresponding *N*-methyl-3,6-diamino-1,2-benzisoxazolium salt without ring opening.[1/61]

Reduction of 3-methyl-1,2-benzisoxazole-2-oxide (**4**) with triethylphosphite gives the corresponding 1,2-benzisoxazole derivative **63**, while reduction with Zn and HCl gives 2-hydroxyacetophenone oxime (**165**).[1/87]

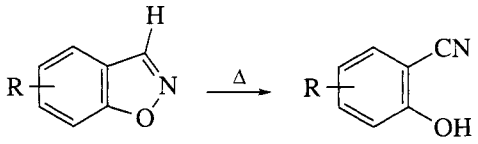


As discussed previously (see § 1.3.7), direct oxidation of the 1,2-benzisoxazole ring is not feasible. This property makes it possible to carry out selective oxidation of substituents on the 1,2-benzisoxazole ring. For example, 4-methyl-1,2-benzisoxazoles can be oxidized to the corresponding aldehydes in workable yield by Thiele's method.[11/71] As part of a study of potent antihypertensive compounds that contain a 1,2-benzisoxazole nucleus, it has been observed that **166** can be safely oxidized with H_2O_2 to the corresponding sulfone **167**.[12/85]

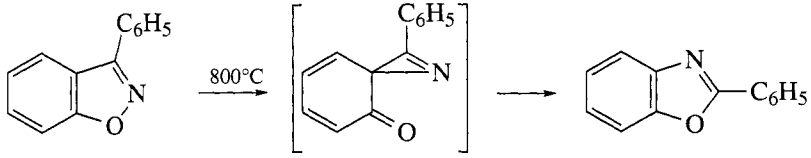


1.4.4. Thermolysis and Photolysis

On heating, usually above their melting temperatures, 3-unsubstituted 1,2-benzisoxazole derivatives decompose to the corresponding salicylonitriles.[3/29]

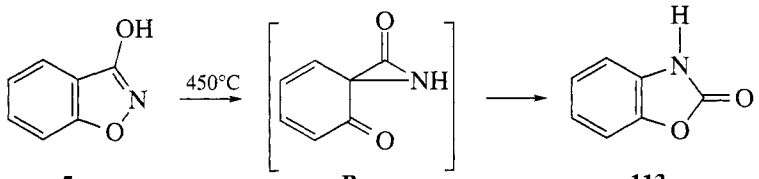


When pyrolyzed at 800°C at low pressure (0.1–1 mmHg), 3-phenyl-1,2-benzisoxazole (**2**) is converted to 2-phenylbenzoxazole (**59**).[14/78] A spiroazirine intermediate, of the type proposed in other isoxazole–oxazole rearrangements, may be involved in this transformation.[5/76]



2 **A** **59**

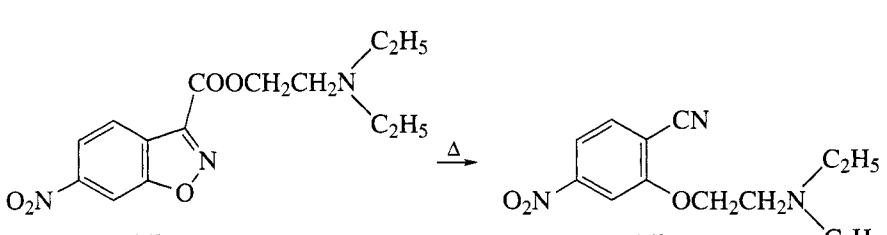
3-Hydroxy-1,2-benzisoxazole (**5a**) also undergoes a clean thermal isomerization to benzoxazolinone (**113**), presumably with the intermediacy of a spiroaziridine.[1/69]



5a **B** **113**

The multistep thermal rearrangement of *N*- or *O*-acylated 3-hydroxy-1,2-benzisoxazoles to the isomeric acylated benzoxazol-2-ones[2/69,4/70] has been discussed (see § 1.3.8). This rearrangement has also been studied by thermal analysis.[11/79]

Esters of 1,2-benzisoxazole-3-carboxylic acids (**168**) have been reported to undergo rearrangement to 2-cyanophenyl ethers (**169**) on prolonged heating in dry toluene.[1/52]

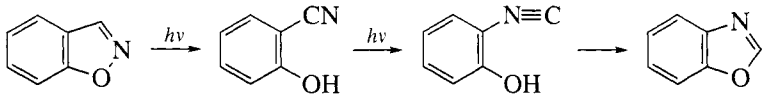


168 **169**

Photochemical studies both parallel and support the findings of 1,2-benzisoxazoles thermolysis. Photolysis of 1,2-benzisoxazole derivatives unsubstituted in

the 3 position gives a mixture of the corresponding benzoxazoles and 2-hydroxybenzonitriles.[4/66]

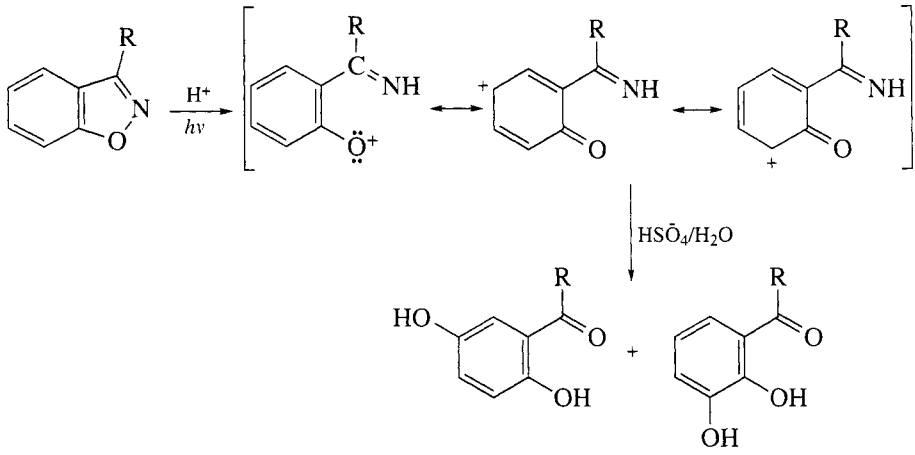
Low-temperature irradiation experiments have shown that the isonitrile **170b** is an intermediate in the conversion of **1** to the benzoxazole (**74**) and suggest that it can be produced photochemically from the nitrile **170a**. No azirine intermediates have been detected in these studies. It is shown that the conversion of **1** to benzoxazole (**74**) involves a π–π^* excited singlet and the conversion of **1** to **170a** via a n,π^* triplet.[8/73,11/74,12/74]



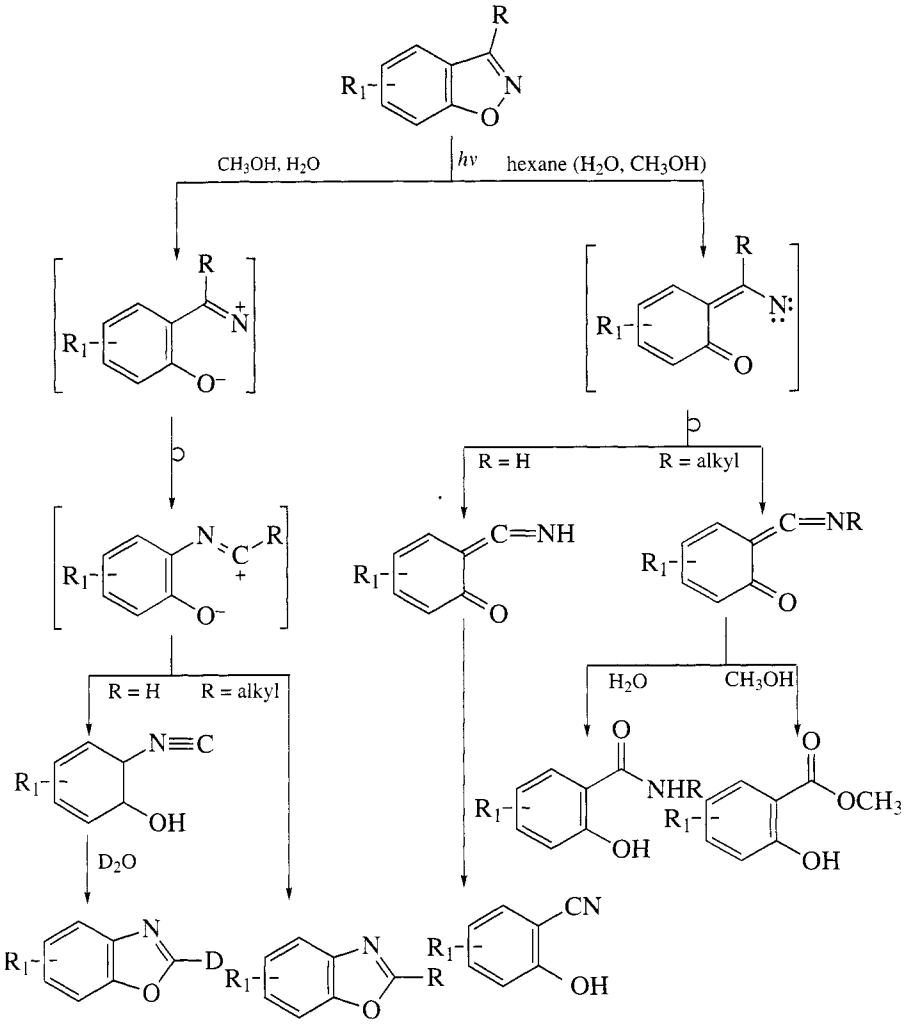
1 **170a** **170b** **74**

In another study, several methyl derivatives of 1,2-benzisoxazole were examined to assess the solvent dependence of ring fission. In water and methanol the substrates were quantitatively transformed into the corresponding benzoxazoles, while in acetonitrile and hexane (with low concentrations of water and methanol), 1,2-benzisoxazole gave only 2-hydroxybenzonitrile and 3-alkyl substituted analogs gave salicylamides and salicyl esters according to Scheme 1.13.[13/74]

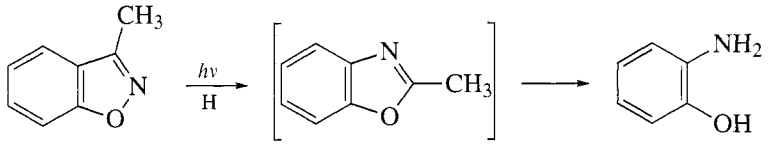
A mixture of 2,5- and 2,3-dihydroxybenzocarbonyl compounds was obtained on photolysis of 1,2-benzisoxazole and its 3-methyl derivative in concentrated sulfuric acid. The products are thought to arise from HSO_4^- trapping of the carbocations that result from photolysis of the protonated form of 1,2-benzisoxazoles.[12/71]



Irradiation of 3-methyl-1,2-benzisoxazole (**63**) in dilute sulfuric acid (0.5 – 9*M*) in methanol and water leads only to 2-aminophenol (**171**), probably via benzoxazole **62**.[1/79]

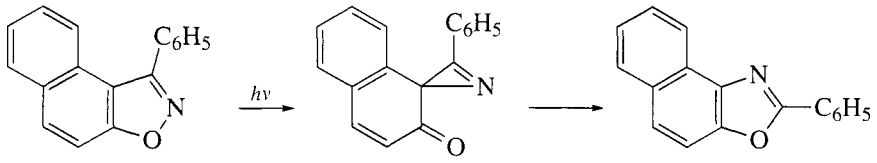


Scheme 1.13



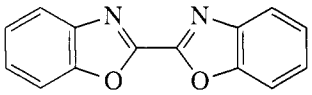
63 **62** **171**

The photolysis of naphthisoxazoles such as **172** has been studied by IR and UV spectroscopy and has shown that previously undetected spiroazirines such as **173** are indeed among the intermediates of photoisomerization of the benzisoxazole nucleus to the benzoxazole **174**.[8/73,11/74,12/74,12/77]



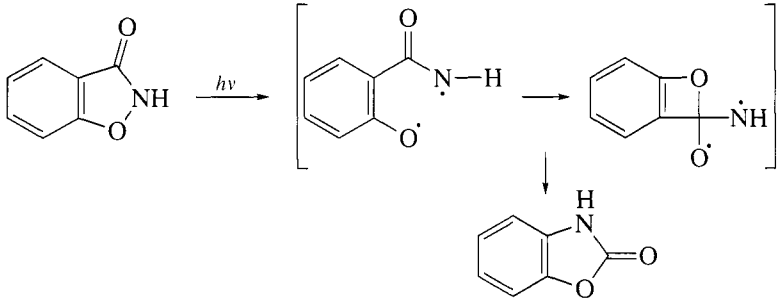
172 **173** **174**

When 1,2-benzisoxazole was irradiated in air-saturated ethanol, the usual photoisomerization was accompained by dimerization of benzoxazole to 2,2′-dibenzoxazole (**175**).[14/74]



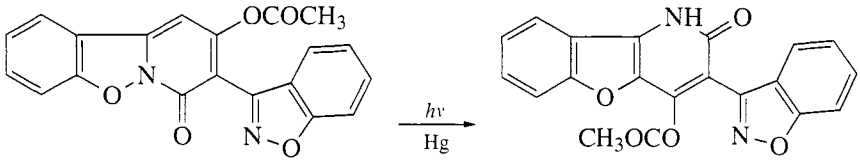
175

1,2-Benzisoxazolin-3-one derivatives also are photoisomerized to the corresponding benzoxazolinones. In this case the authors were unable to detect any aziridone or 2-hydroxyarylisocyanate intermediates and suggested a mechanism involving a diradical species. Sensitization studies indicated that the rearrangement occurs predominantly from the triplet state (IP).[1/71]



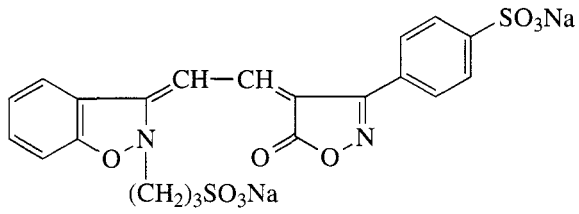
A case has been reported, however, in which irradiation of 1,2-benzisoxazole derivatives did not produce any benzoxazole isomer.[10/80]

Photolysis of 4-oxo-4*H*-benzisoxazolo[2,3-*a*]-pyridines such as **176** has been reported to give benzofuro[3,2-*b*]-pyridine derivatives such as **177**.[8/82]



176 **177**

Several cyanine and merocyanine dyes containing the 1,2-benzisoxazole nucleus as in **178** have been prepared as photosensitizers.[6/76,17/84,10/86]



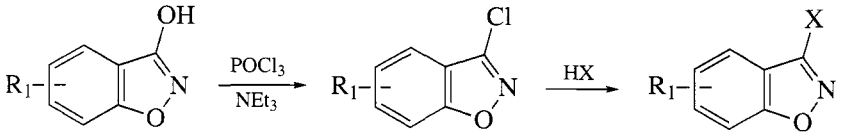
178

1.4.5. Reactions with Nucleophiles

Reaction of nucleophiles with 1,2-benzisoxazole derivatives may involve the substitution of suitably positioned halogens, usually those at the 3 and 3α positions, cleavage of the isoxazole ring, and/or transformation of 1,2-benzisoxazole nucleus into another cyclic system.

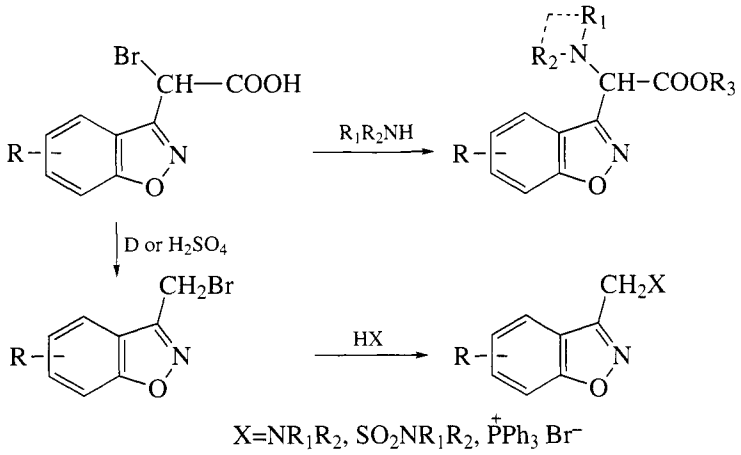
1.4.5.1. Reactions without Ring Cleavage

Substituted 3-chloro-1,2-benzisoxazoles[3/67] represent good substrates for nucleophilic substitution and are precursors to a variety of derivatives.[1/68,9/69,10/69,1/72,11/86]



X = OR_2, NR_3R_4, NHR_5, N_3

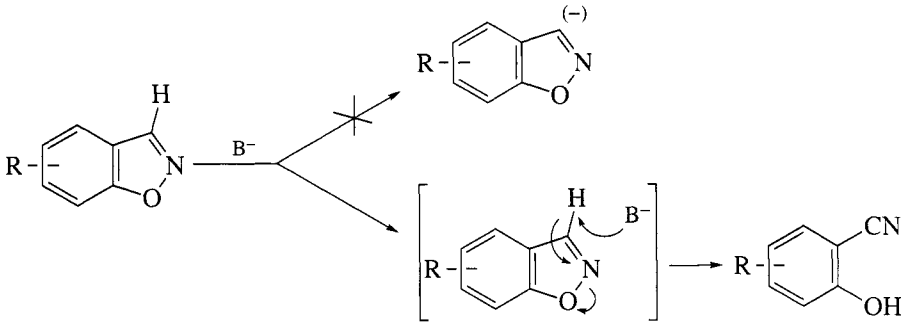
Replacement of the halogen with an azido group (X = N_3) followed by thiosulfate reduction permits the preparation of 3-amino derivatives.[3/67] An alternative method, which the aforementioned one supersedes, involves Curtius degradation of 1,2-benzisoxazole-3-carboxylic acid azide.[2/28,2/29] The 3-amino 1,2-benzisoxazole derivatives are aromatic amines and can be diazotized.[2/29,5/50,1/53] The α-bromo-substituted 1,2-benzisoxazole-3-acetic acid and its derivatives are highly reactive and have been used to obtain a variety of pharmacologically interesting compounds.[4/72,3/76,7/83,15/87] These acids are readily decarboxylated to give 3-bromomethyl derivatives in good yield.[4/72] The latter have been used in the preparation of other derivatives.[4/72,3/76,12/79,9/82]



1.4.5.2. Reactions with Ring Cleavage

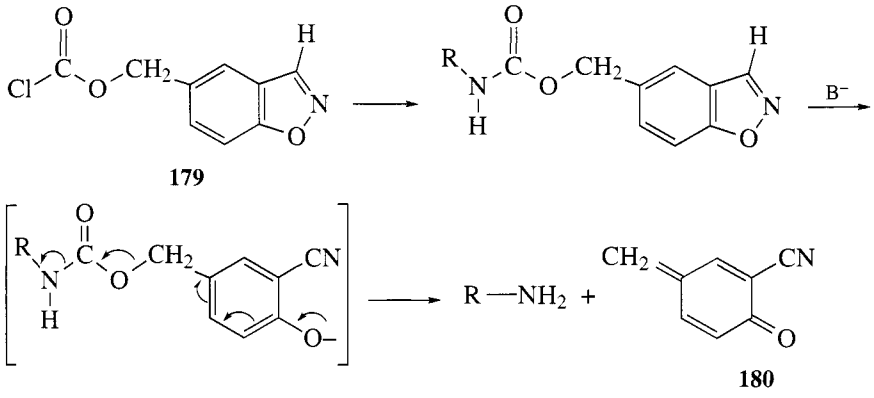
Whereas 3-alkyl- and 3-aryl-substituted 1,2-benzisoxazoles are fairly stable toward bases, 3-unsubstituted, 3-acyl-, and 3-carboxy-analogues are easily cleaved.

3-Unsubstituted compounds mainly give the corresponding salicylonitriles.[3/25,3/27,2/29,3/29] Ring cleavage was regarded to take place through initial formation of a 3-carbanion,[1/60] but further investigations showed that a concerted E2 elimination occurs.[2/73,9/73]



The ease of cleavage of these 3-unsubstituted derivatives has been exploited in the design of a new urethane-type protecting group for amino groups (**179**).[9/75]

The phosphate-protecting group 5-hydroxymethyl-1,2-benzisoxazole (BIM) (**181**) has been developed according to the same principle. BIM derivatives (**182**) are reasonably stable under the conditions of conventional DNA synthesis and are cleaved by treatment with Et_3N at room temperature to the phosphoric acid salts and **180**.[10/82] Unlike derivatives of **179**, no intermediates such as **A** are formed from **182**; a base-promoted, concerted decomposition occurs.[10/82]



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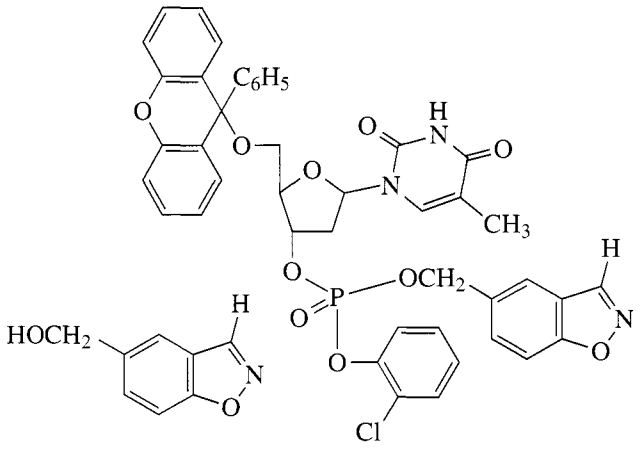
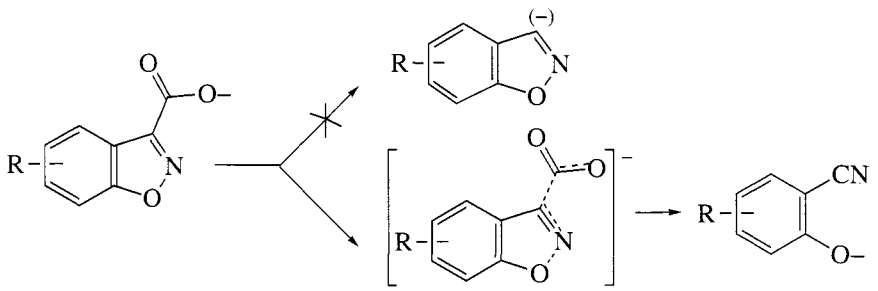
180



181 **182**

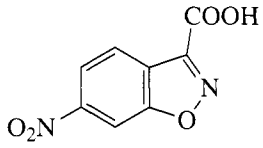
3-Acyl-1,2-benzisoxazole derivatives are cleaved by alkali to salicylonitriles.[1/12]

The decomposition of 3-carboxylic acids was found to involve a concerted loss of carbon dioxide rather than a stepwise process involving a carbanion.[2/29, 3/29,5/70,1/75,3/75]



The rate of decarboxylation and the pK_a values of the acids are influenced by the nature of the substituents on the phenyl ring.[1/75,3/75]

The rate of decarboxylation of 6-nitro-1,2-benzisoxazole-3-carboxylic acid (**183**) has been found to depend dramatically on solvent effects. A rate acceleration occurs when the medium is changed from water to dipolar aprotic solvents. The latter are thought to stabilize the transition state, unlike protic solvents, which are thought to stabilize the carboxylate anion by hydrogen bonding.[5/70,1/75,3/75,15/78,11/80,16/87]

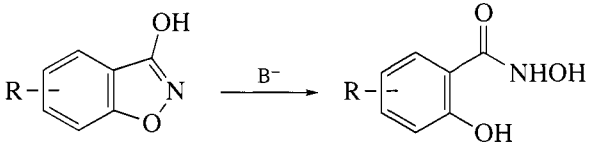


183

In fact, decarboxylation of **183** is catalyzed by cationic or zwitterionic micelles,[6/70,13/71,10/73,10/75,11/82,12/86,28/89,4/91,6/91,11/91] polisoaps,[14/77,10/91] phenylethylenimines,[7/76,13/79] cycloheptaamylose,[6/72] crown ethers,[11/75,16/78,17/78,14/79,15/79,12/80] and antibodies.[5/91] This lability has led to the wide use of **183** as a kinetic probe under a variety of reaction conditions.[13/80,14/80,15/80,16/80,11/81,12/81,8/83,9/83,18/84,13/85,13/86,14/86,17/87,14/88,11/91]

Unlike the 3-carboxylic acids from which they are derived, the corresponding hydrazides and azides are fairly stable.[3/29] The esters are similarly stable except during hydrolysis; the acids decompose as reported above.[1/12,2/29,1/49,1/50,1/53]

While 3-amino derivatives are quite stable toward bases, 3-hydroxy compounds are quickly decomposed to the corresponding 2-hydroxybenzhydroxamic acids by boiling alkali.[2/29,3/29]

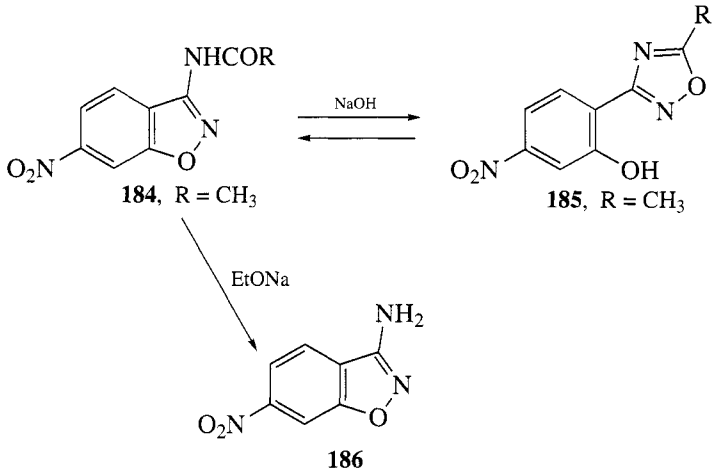


Ring opening of 1,2-benzisoxazolium salts has already been discussed in detail (see § 1.4.2).

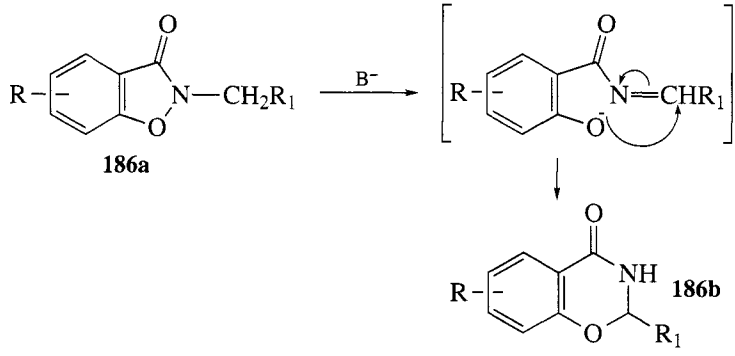
1.4.5.3. Reactions with Ring Transformation

1,2-Benzisoxazoles that bear an electron-withdrawing substituent on the benzenoid ring, usually in the 3 position, undergo ring transformations in the presence of bases. Whether the reaction goes through an initial opening of the isoxazole ring or through a concerted mechanism is in most cases not known.

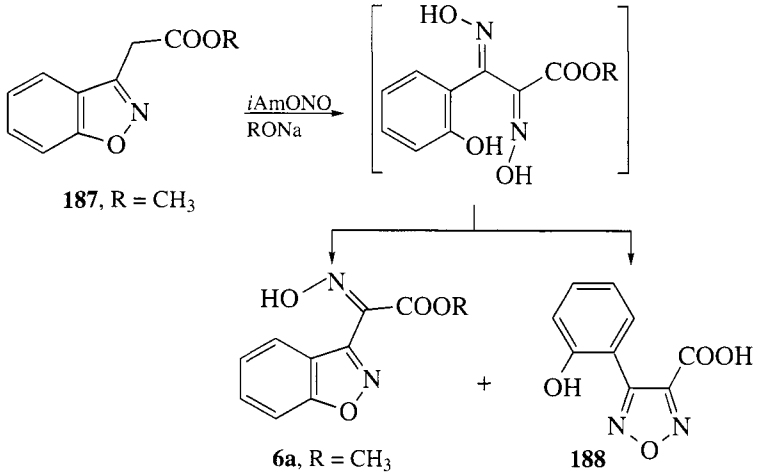
3-Amido derivatives such as **184** (R = CH_3) were reported to form oxadiazoles such as **185** (R = CH_3).[3/29] Later on, however, it was shown that these compounds are in equilibrium and that under certain conditions simple hydrolysis of the 3-amido group can occur.[11/73]



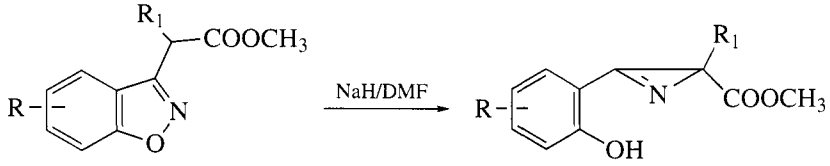
During alkylation of 1,2-benzisoxazolin-3-one derivatives **186a** (see § 1.3.8), which mainly affords *O*-alkyl derivatives, the small quantity of *N*-alkyl derivative produced is reported to undergo a base-induced ring expansion to 1,3-benzoxazin-4-ones **186b** when the R_1 group has proper electron-withdrawing properties (R_1 = COOH, COC_6H_5).[9/78]



The reaction of isoamyl nitrite and sodium alkoxide with 1,2-benzisoxazole-3-acetic acid esters (**187**) gives 4-(2′-hydroxyphenyl) furazan-3-carboxylic acid (**188**), possibly through the intermediacy of a vicinal bisoxime derivative, as well as oxime **6a**.[2/83]

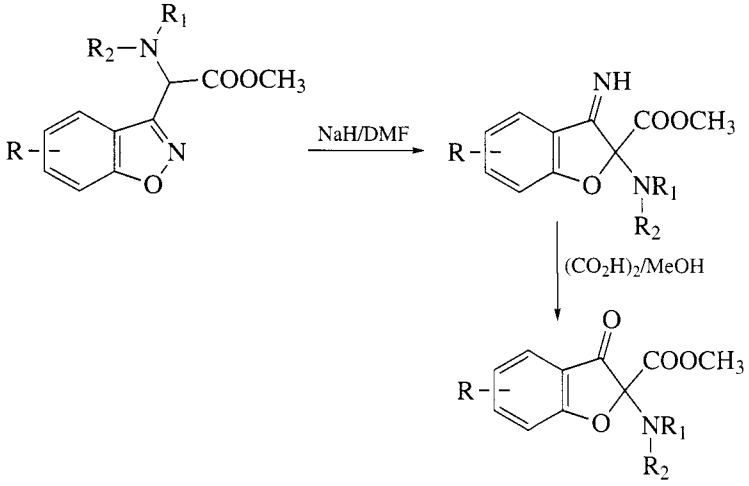


Treatment of α-monosubstituted-1,2-benzisoxazole-3-acetic acid esters with strong bases affords 2*H*-azirines. The product is believed to arise from a Neber-like rearrangement of the initially formed α-carbanion.[14/85,15/85,15/88]



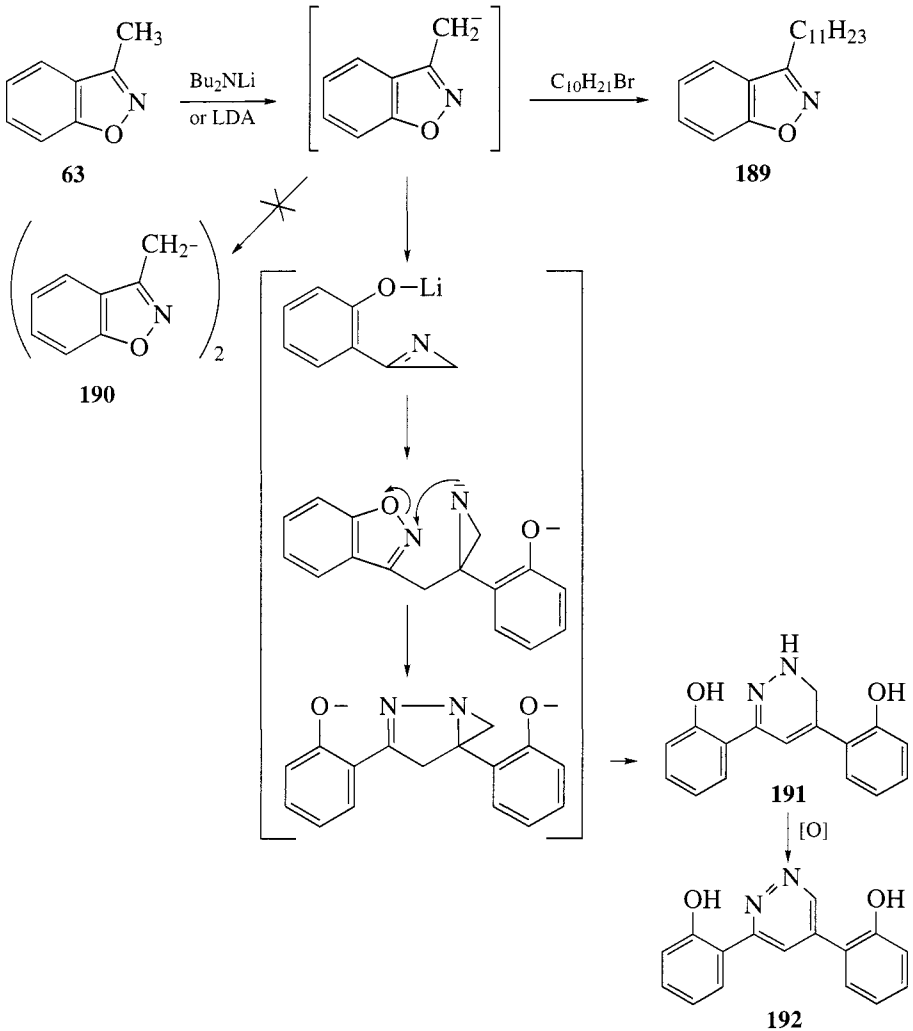
R_1 = CH_3, $CH_2C_6H_5$, OCH_3, OC_6H_5, SC_6H_5, cyclohexyl

When the α-substituent is an alkylated amine, the reaction takes a different course and 2,3-dihydrobenzo[*b*]furan derivatives are obtained.[15/86,15/88]

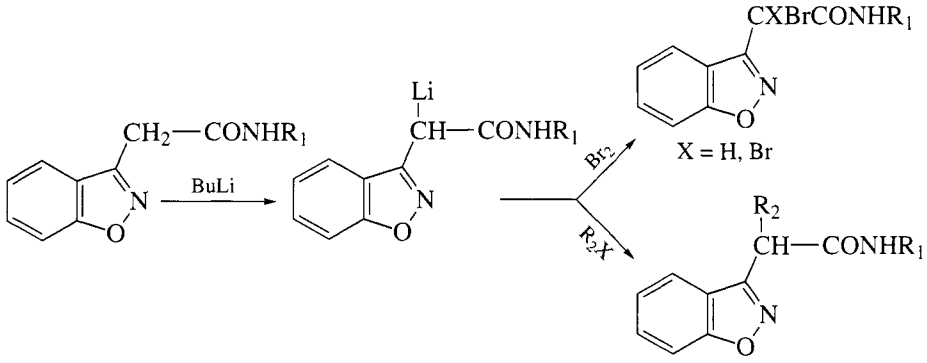


1.4.6. Metallation and Base-Promoted Condensations

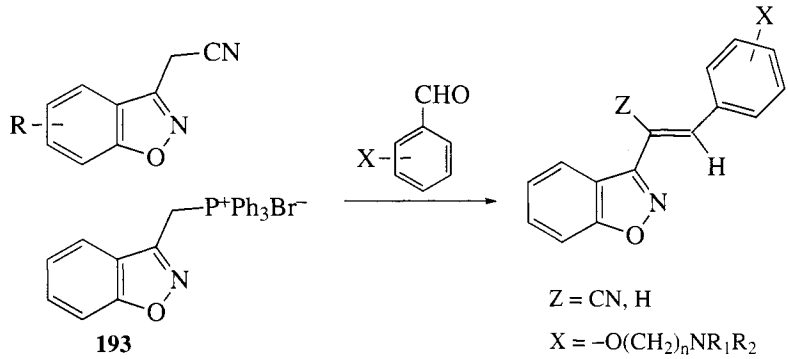
Few examples of metallated 1,2-benzisoxazoles have been reported. Treatment of 3-methyl-1,2-benzisoxazole (**63**) with lithium di-*n*-butylamide or lithium diisopropylamide (LDA) results in deprotonation of the methyl group.[2/81,7/89] In the presence of 1-bromodecane a satisfactory (52%) yield of 3-undecyl-1,2-benzisoxazole (**189**) could be obtained.[7/89] Although it has been erroneously reported that in the absence of an electrophile, the anion dimerizes to give **190**[2/81] rearrangement involving an azirine intermediate affords pyridazine **192**.[7/89]



Metallation with *n*-butyllithium occurs more readily when the 3-methyl group is substituted with electron-withdrawing groups. This method has been used to brominate and alkylate some amides of 1,2-benzisoxazole-3-acetic acid.[7/85]

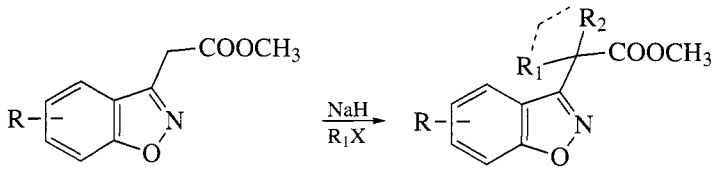


The methyl group of **63**, for which a pK_a of 35 has been reported,[2/81] does not give the corresponding anion on treatment with NaH in dimethoxyethane, a transformation that occurs readily with the corresponding 1,2-benzisoxazole-3-acetic acid derivatives.[7/84,6/87] Thus, several derivatives of pharmacological interest have been synthesized from substituted 1,2-benzisoxazole-3-acetonitrile using Knoevenagel's reaction conditions, with ammonium acetate in acetic acid or piperidine in toluene.[9/82,12/82,13/82,14/82,3/83] The corresponding compounds without the cyano group were prepared from the ylide derived from phosphonium salt **193**.[3/83] NMR spectra show that *trans* compounds are predominantly obtained.[3/83]



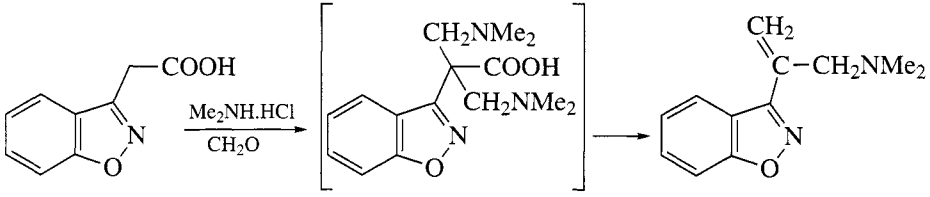
193

1,2-Benzisoxazole-3-acetic acid esters can be mono- or dialkylated with alkyl halides and NaH in DMF.[7/84,6/87]



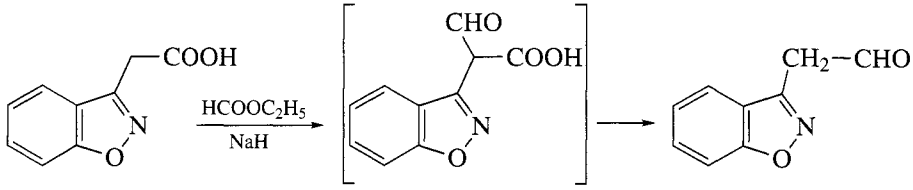
R_1, R_2 = H, CH_3, C_6H_{11}, cyclopentyl, cyclohexyl

Under Mannich reaction conditions the product of partial elimination (**194**) was obtained. The reaction proceeds similarly with other substituted 1,2-benzisoxazole-3-acetic acid derivatives.[18/78]



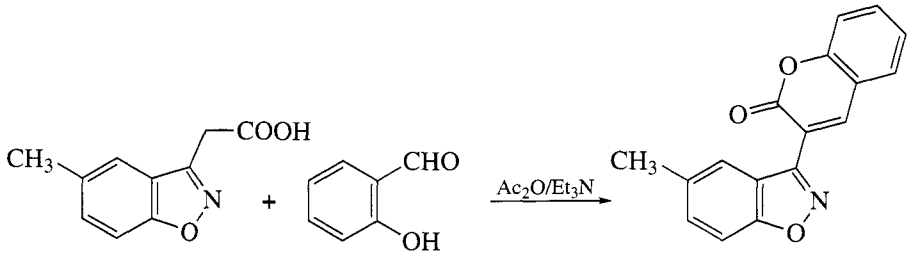
24 **194**

Under the same conditions 3-methyl-1,2-benzisoxazole did not react. Acid **24** also reacts with ethyl formate and sodium hydride to give 1,2-benzisoxazole-3-acetaldehyde (**195**), which results from the decarboxylation of the intermediate **A**.[8/75,4/78]



24 **A** **195**

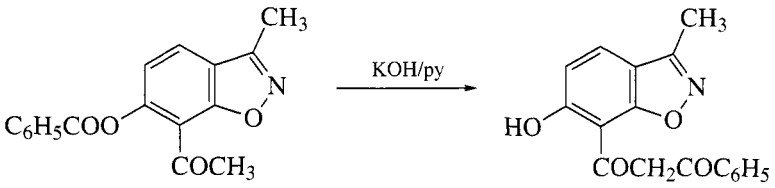
A base-promoted condensation of 1,2-benzisoxazole-3-acetic acid derivatives such as **196** with salicylaldehyde has been reported.[16/79]



196 **197**

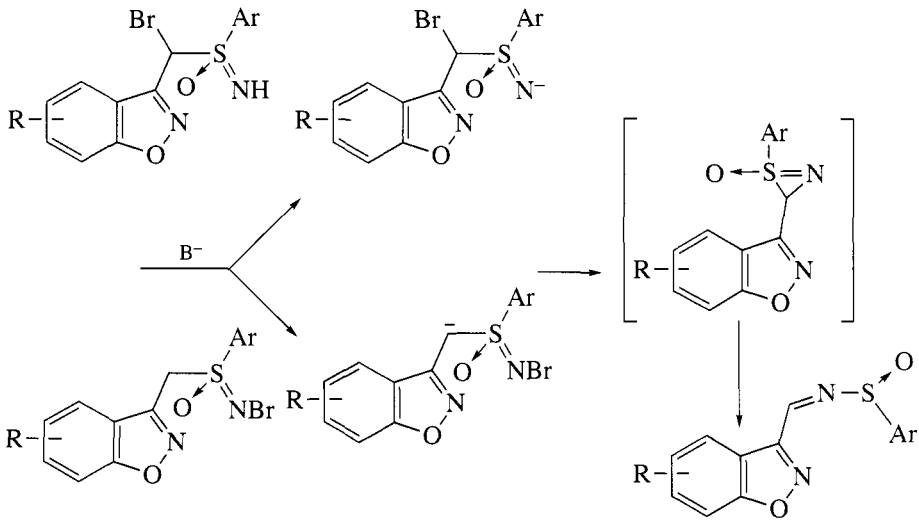
These results show that the hydrogens of the α-methylene group of compounds such as **24** are highly reactive, revealing the properties of a malonic methylene; thus it can be stated that the C=N bond behaves like a masked carbonyl group.

An interesting base-promoted intramolecular acylation has been described for a series of 7-acetyl-6-acyloxy-3-substituted-1,2-benzisoxazole derivatives exemplified by **198**.[16/85]



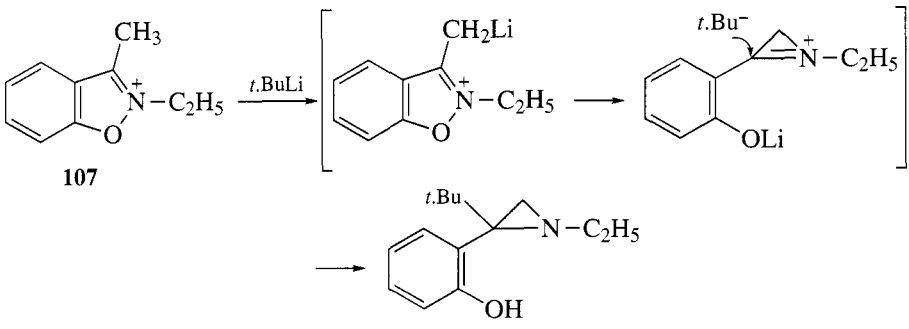
198 **199**

Base-induced chain rearrangement of α- and *N*-halo derivatives of *S*-aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides gives the corresponding *N*-sulfinylimines.[17/80,1/82,15/82]



The proposed mechanism involves a thiazirin *S*-oxide intermediate.[1/82]

Finally, the action of BuLi (or *t*.BuLi) on 1,2-benzisoxazolium salts gives, besides the 2,3-dihydro-1,2-benzisoxazoles (see § 1.3.6), the corresponding aziridine, possibly through initial lithiation of the exocyclic methyl group.[2/88] While the use of butyllithium results in an equimolecular mixture of benzisoxazoline and aziridine, *tert*-butyllithium causes aziridine **200** to predominate.

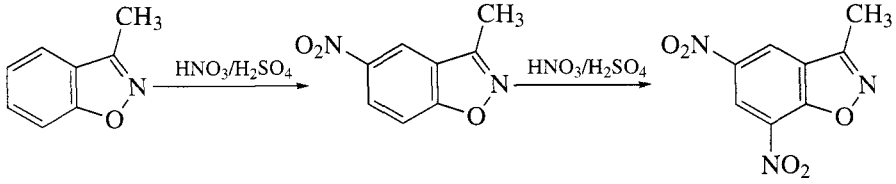


107 **200**

1.4.7. Electrophilic Substitution

1.4.7.1. Nitration

Nitration of 1,2-benzisoxazole exclusively affords 5-nitro-1,2-benzisoxazole.[1/26] Accordingly, 3-methyl-1,2-benzisoxazole (**63**) is nitrated only in the 5 position to give **201**. No other isomers could be detected in the reaction mixture by TLC (thin-layer chromatography) or ^{1}H-NMR analysis.[3/77,4/77,7/77] The 3-ethyl homolog behaves in the same way. Further reaction gave 3-methyl-(**202**) and 3-ethyl-5,7-dinitro-1,2-benzisoxazole, products whose structures were determined by NMR spectroscopy or direct synthesis.[7/77]

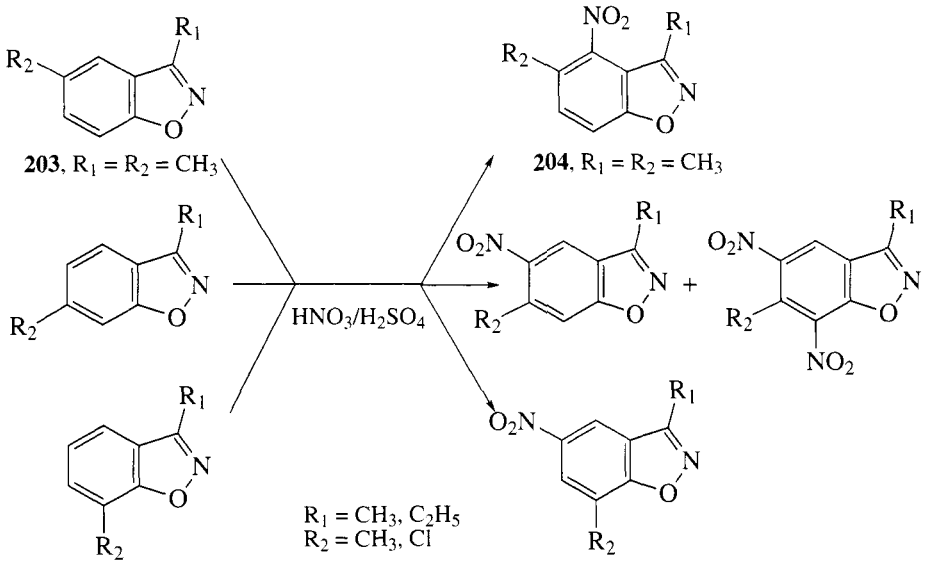


63 **201** **202**

The kinetics of nitration of **63** and of the corresponding *N*-methyl quaternary salts have been studied to identify the species that undergo nitration.[4/77] It was found that in 80–90% sulfuric acid nitration of the free base occurs, while at a higher sulfuric acid concentration the corresponding conjugated acid is the nitrated species. It is interesting that these results contradict theoretical calculations, which would suggest nitration at position 7 (see § 1.2.8). On this basis the authors have proposed that nitration of 1,2-benzisoxazole is not charge-controlled but probably frontier orbital–controlled.[4/77]

When unoccupied, the 5 position is the preferred position for electrophilic attack.[1/26,3/27,2/41,1/53] Products substituted in the 6 or 7 position have been reported when the 5 position is blocked.[1/26,1/27,2/41] However, these reports have been

proved generally incorrect by a careful study in which the structures of the nitro derivatives were confirmed by ^{1}H-NMR and/or synthesis.[7/77] For instance, it was found that the product of nitration of 3,5-dimethyl-1,2-benzisoxazole (**203**; $R_1 = R_2 = CH_3$) is not, as already reported,[1/26] the 7-nitro- but the 4-nitro-3,5-dimethyl-1,2-benzisoxazole (**204**; $R_1 = R_2 = CH_3$).[7/77]



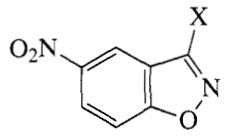
3-Phenyl-1,2-benzisoxazoles seem to behave similarly. However, in this case the possibility of a 4′ nitration of the 3-phenyl ring gives mixtures of mono- and dinitrated products that have not been separated or acceptably characterized.[2/892,1/39,2/56]

1,2-Benzisoxazole-3-carboxylic acid and its esters, 1,2-benzisoxazole-3-acetic acid esters and 3-(β-acetoxyethyl)1,2-benzisoxazole, are nitrated in position 5.[1/75,3/75,7/75]

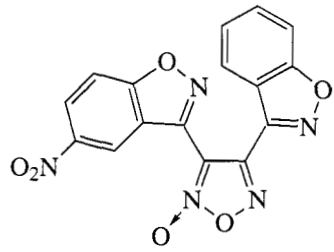
3-Hydroxy- and 3-chloro-1,2-benzisoxazole follow an identical path.[18/80]

X = OH, Cl, COOR, CH_2COOR, $CH_2CH_2OCOCH_3$

Nitration of 1,2-benzisoxazole-3-acetic acid is, however, more complex, giving—besides the expected 5-nitro derivative—a substantial quantity of side products, including the side-chain-substituted nitro derivatives **205** and **206** and the furoxane **207**.[4/78]



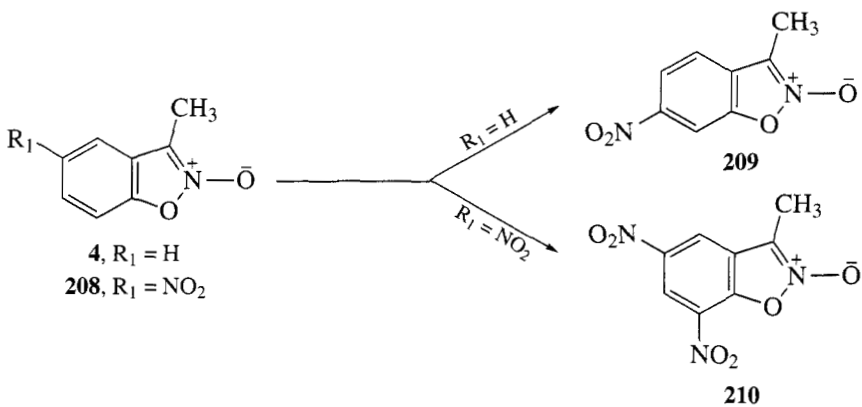
205, X = $CH(NO_2)_2$
206, X = $C(NO_2)_3$



207

When other powerfully activating substituents are present in the phenyl ring, the substitution pattern may become more complicated. Thus 3-phenyl-7-methoxy-1,2-benzisoxazole is reported to give only the corresponding 4-nitro derivative,[5/50] while 3-methyl-6-*n*-butoxy-1,2-benzisoxazole gives the 5-nitro and the 7-nitro derivatives.[6/83]

1,2-Benzisoxazole-2-oxides show quite a different pattern of nitration; the 6-nitro derivative **209** was obtained by nitration of the corresponding 3-methyl-1,2-benzisoxazole-2-oxide (**4**) and 3-methyl-5,7-dinitro-1,2-benzisoxazole-2-oxide (**210**) by nitration of 3-methyl-5-nitro-1,2-benzisoxazole-2-oxide (**208**).[1/87]



4, $R_1 = H$
208, $R_1 = NO_2$

209

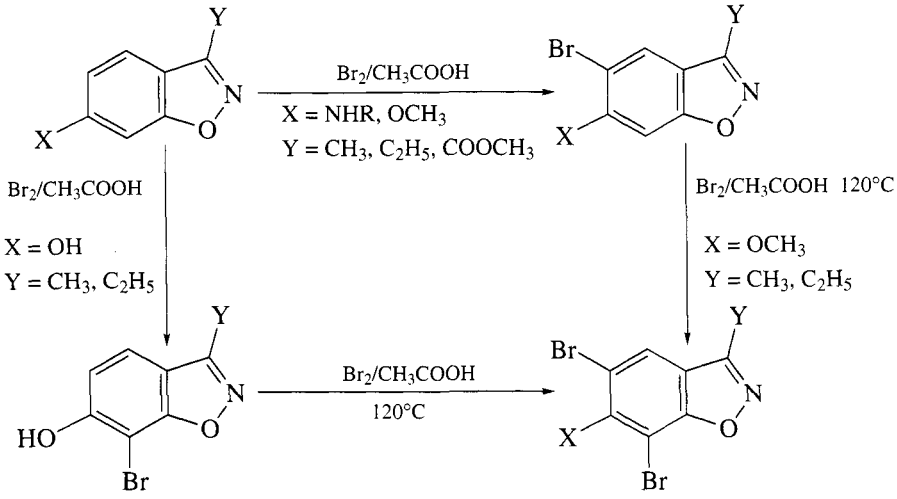
210

1.4.7.2. Halogenation

Whereas 3-phenyl-1,2-benzisoxazole is reported to undergo bromination in the 5 position,[1/39] 3-methyl-1,2-benzisoxazole (**63**) and 3-bromomethyl-1,2-benzisoxazole were not brominated by an excess of bromine under standard conditions.[3/76]

When the phenyl ring is suitably activated, bromination readily occurs. Thus 6-acetamido- and 6-benzoylamido-1,2-benzisoxazole-3-carboxylic acid methyl

esters were transformed into the 5-bromo derivatives,[1/53] much like 3-alkyl-6-methoxy-1,2-benzisoxazoles.[5/79]

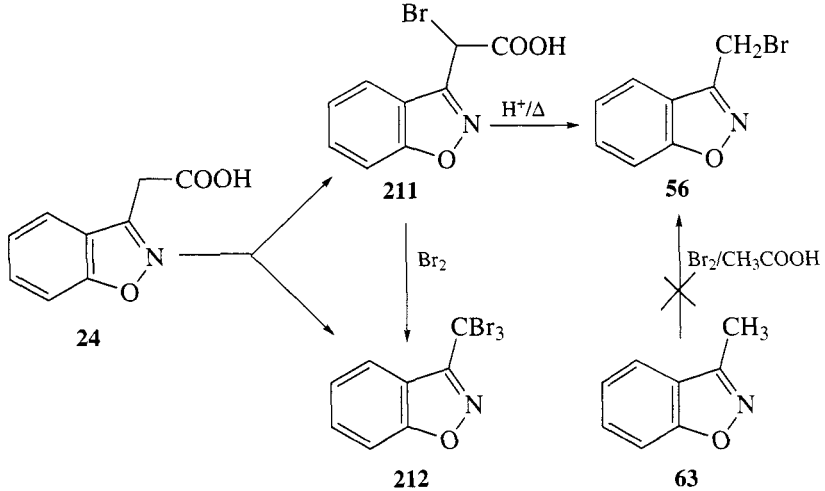


Under the same conditions 3-alkyl-6-hydroxy-1,2-benzisoxazoles gave the 7-bromo derivatives. At higher temperatures both 6-hydroxy and 6-methoxy compounds gave the corresponding 5,7-dibromo derivatives.[5/79]

α-Bromination of 1,2-benzisoxazole-3-acetic acid and its derivatives occurs readily without formation of ring-substitution products.[4/72,3/76,7/83]

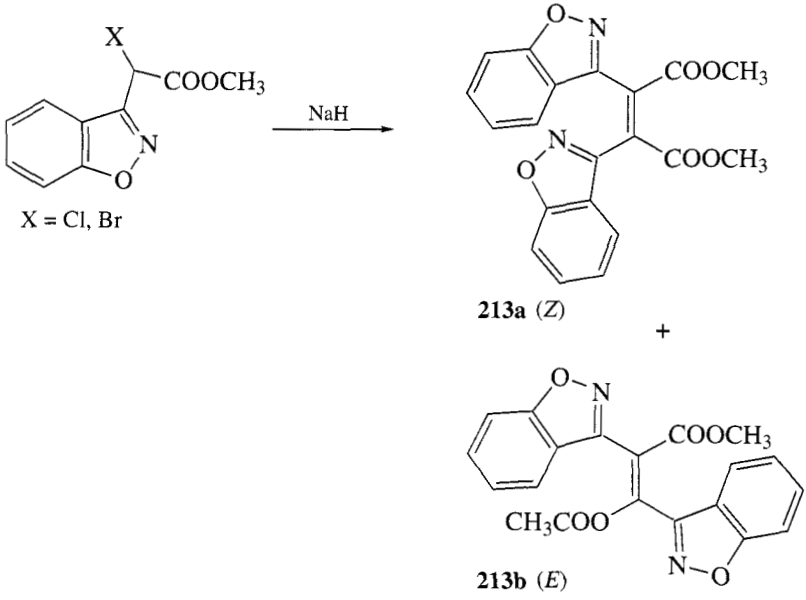
When 1,2-benzisoxazole-3-acetic acid **24** is brominated with an excess of bromine, 3-tribromomethyl-1,2-benzisoxazole (**212**) is obtained.[3/76]

Decarboxylation of the α-bromoacid **211** smoothly gives the 3-bromomethyl derivative (**56**), which cannot be obtained by direct bromination under the same

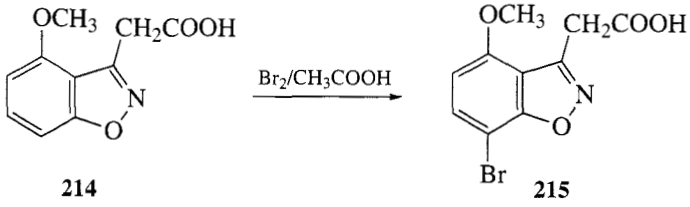


conditions but that was recently obtained by a one-pot synthesis (see § 1.3.2).[21/90] Bromination of the methyl ester of **24** with an excess of bromine gives only the monobromo derivative.[3/76]

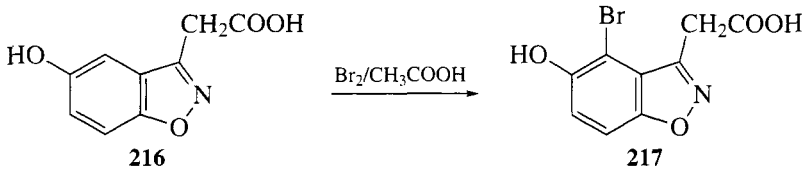
Chlorination under the same conditions gives the corresponding α-chloro derivatives.[4/78] The esters of α-halo-1,2-benzisoxazole-3-acetic acid, treated with strong bases such as NaH, give the *Z* and *E* forms of the corresponding ethylenedicarboxylates (**213a** and **213b**) in approximately 5:1 ratio.[15/88]



Attempted chlorination or bromination of **24** with an excess of *N*-chlorosuccimide (NCS) or *N*-bromosuccinimide (NBS) gives only the corresponding 3-trichloromethyl and 3-tribromomethyl derivatives of type **212**, while reaction with ICl in CH_3COOH at room temperature afforded α-iodo-1,2-benzisoxazole-3-acetic acid.[15/74]



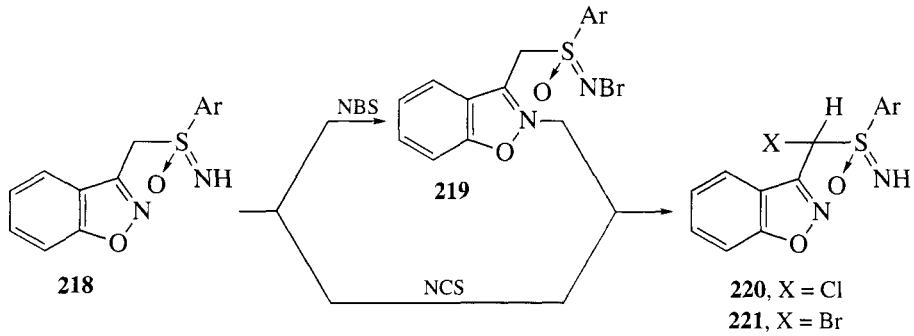
214 **215**



216 **217**

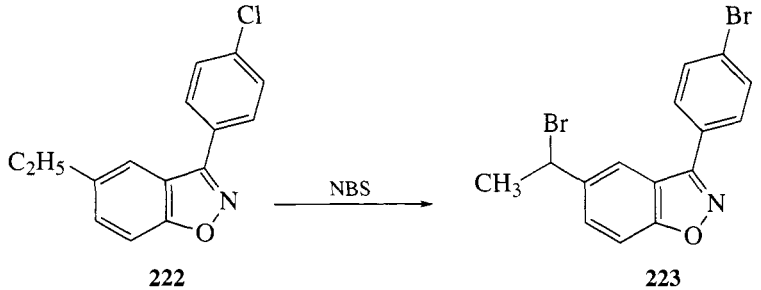
In this case too, when the phenyl ring is activated by substituents, ring bromination occurs, as shown for **214** and **216**.[4/72]

In a manner reminiscent of the reactivity of **24** toward electrophiles, *S*-aryl-*S*-[(1,2-benzisoxazol-3-yl)methyl] sulfoximides such as **218** undergo halogenation by *N*-bromo- or *N*-chlorosuccinimide. It has been shown that bromination proceeds via a facile *N*-bromination followed by a bromine transfer reaction of the resulting *N*-bromosulfoximide **219**, while chlorination proceeds directly.[4/82]



218 **219** **220**, X = Cl
221, X = Br

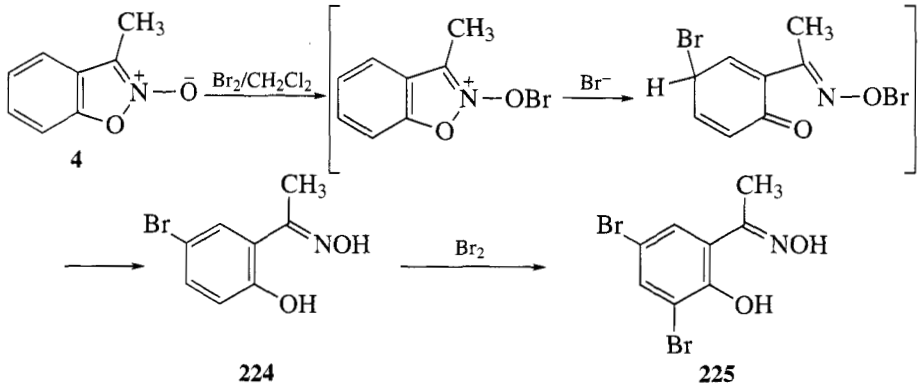
NBS has also been used to convert alkyl-3-aryl-1,2-benzisoxazoles (**222**) to the corresponding α-bromo derivatives (**223**).[6/79]



222 **223**

Bromination of 3-methyl-1,2-benzisoxazole-2-oxide (**4**) takes an unexpected course, providing the dibromo oxime **225** according to the following proposed

pattern:[1/87]

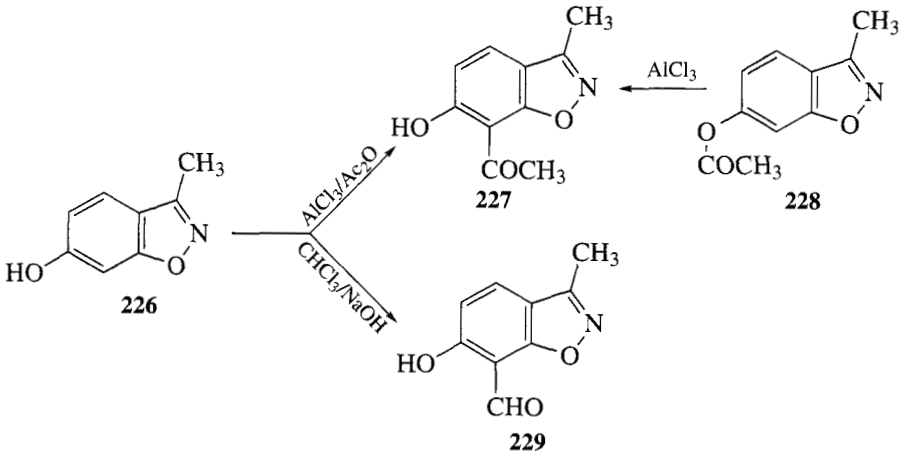


2-Ethyl-7-hydroxy-1,2-benzisoxazolium tetrafluoroborate gives a monochloro derivative when heated in boiling sulfonyl chloride .[7/74]

1.4.7.3. Acylation

1,2-Benzisoxazoles are acylated with difficulty, and only in some cases has it been possible to isolate small amounts of acyl derivatives.[5/50]

More recently, 3-alkyl-6-hydroxy-1,2-benzisoxazoles (**226**) have been converted under Friedel–Crafts conditions to the corresponding 7-acyl derivatives (**227**).[5/77] Accordingly, Fries rearrangement has been reported to proceed smoothly from **228** to **227** in the presence of $AlCl_3$ at 140°C,[3/73] a reaction that has been extended to other acyl derivatives.[3/87] The Reimer–Tiemann reaction has also been succesfully applied to some substrates (**226**); in this case, too, the reaction is regiospecific and only 7-derivatives (**229**) are obtained.[2/77]

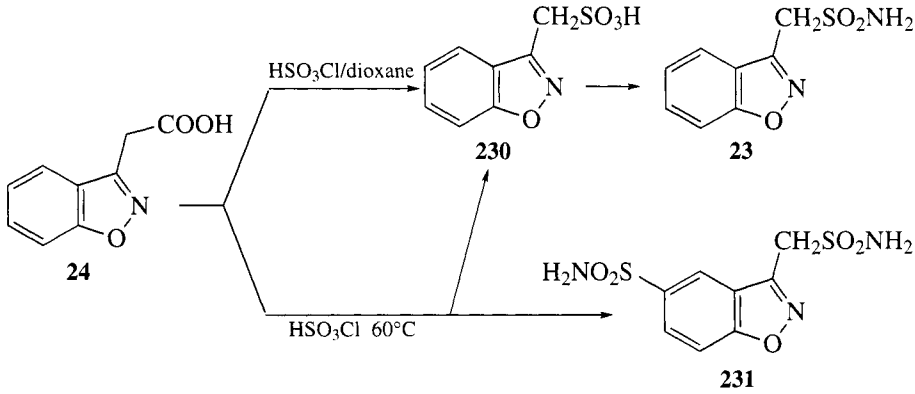


It is clear that in all these cases the reactivity is due to the hydroxyl group at the 6 position and is probably independent of the presence of the condensed isoxazole group.

1.4.7.4. Sulfonation

The products of the reaction of 3-phenyl-1,2-benzisoxazole with 40% oleum have not been identified; lower concentrations of SO_3 have given no reaction.[2/894]

Chlorosulfonation of 1,2-benzisoxazole-3-acetic acid (**24**) with a mixture of chlorosulfonic acid and dioxane in CH_2Cl_2 gives the 1,2-benzisoxazole-3-methanesulfonic acid (**230**), which can easily be converted into the corresponding amide **23**. Reaction at 60°C with an excess of chlorosulfonic acid and subsequent amination gave a more complex mixture, as 5-ring substitution also occurs (**231**). Similar results were obtained with the corresponding esters and nitriles.[4/78]



Sulfonation in 30% oleum of 2-ethyl-7-hydroxy-1,2-benzisoxazolium tetrafluoroborate gives the corresponding 4- or 6-sulfonic acid in high yields.[7/74]

1.4.8. Other Reactions without Ring Cleavage

Besides the typical ring opening reactions (see § 1.4.3 and § 1.4.4) and nucleophilic and electrophilic reactions (see § 1.4.5 and § 1.4.7) that have already been examined there are reactions, usually standard ones, that involve substituents on the side chains of the 1,2-benzisoxazole ring. They can be used to manipulate the 1,2-benzisoxazole for synthetic purposes and are useful insofar as they do not interfere with the stability of the 1,2-benzisoxazole ring. Some of them have already been examined, such as the selective reduction of nitro groups (see § 1.4.3) or the selective halogenation of α-methylene of 1,2-benzisoxazole-

3-acetic acids (see § 1.4.5.1). This chapter will review a few reactions that could not be conveniently included in the preceding sections.

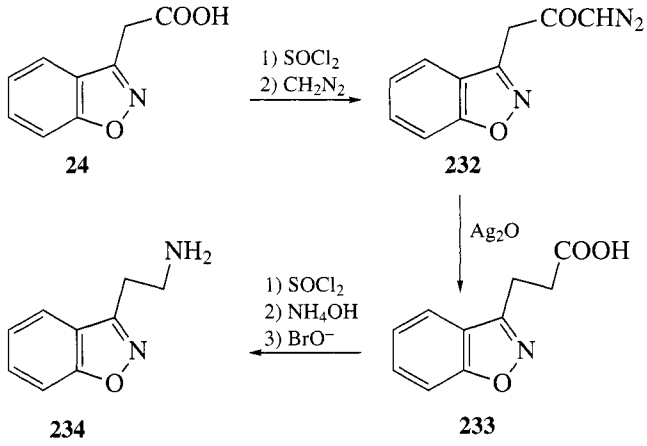
1.4.8.1. Carboxylic Acids and Their Derivatives

It has already been mentioned that 1,2-benzisoxazole-3-carboxylic acids are quite unstable and readily undergo decarboxylation and ring cleavage (see § 1.4.5).

The corresponding esters can be saponified,[2/29,3/29,16/86] transesterified,[2/29,1/52,2/53] and transformed into amides,[1/12,2/28,12/91] and hydrazides.[2/29,3/29,1/61] The latter compounds can be converted into the corresponding azides[2/29,3/29,1/61] and these give, by standard reactions, amines, ureas, and urethanes.[2/28,1/29,2/29,3/29,1/61] Some 3-carboxylic acid esters have interesting biological properties.[16/86]

Unless they are substituted in the α position, 1,2-benzisoxazole-3-acetic acids are stable (see § 1.4.5) and undergo standard reactions. They have been esterified and the esters converted into the corresponding amides and hydrazides.[4/69,4/71,9/71,12/73,13/73,6/75,7/83,10/83,7/84,17/85]

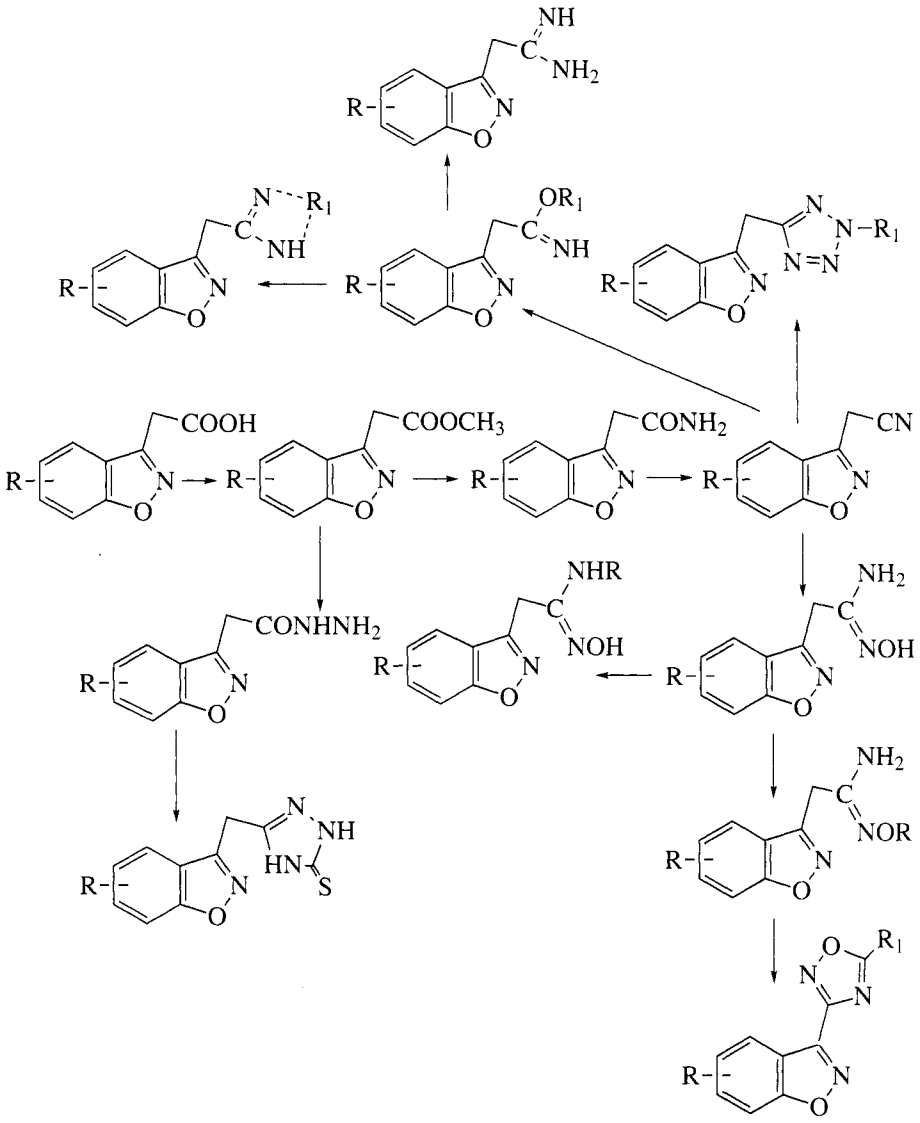
Homologation through the Arndt–Eistert reaction of 1,2-benzisoxazole-3-acetic acid (**24**) gives the corresponding 3-propionic acid **233**. This can be converted into the amide and transformed, through the Hoffman reaction, into β-(1,2-benzisoxazol-3-)ethyl amine (**234**). This compound is of interest because of its isosteric relationship with tryptamine.[6/75,7/75]



24 **232** **234** **233**

1,2-Benzisoxazole-3-acetamide and its higher homologs can be converted into the corresponding nitriles.[13/73,3/76]

Derivatization and transformation of 1,2-benzisoxazole-3-acetic acid has been thoroughly studied by the Dainippon group, which has obtained a variety of derivatives; some of these have been shown to possess interesting pharmacological properties (see § 1.5.1).[14/73,3/76]



Nitriles can be transformed into the corresponding amidines without any difficulty.[7/78]

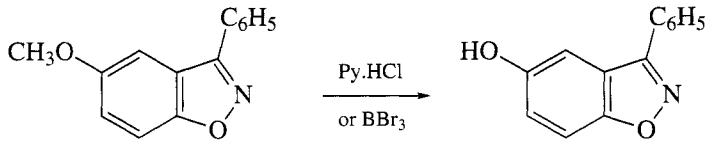
1.4.8.2. Hydroxy Groups

Hydroxy-substituted 1,2-benzisoxazoles can be alkylated and acylated in the usual way[3/27,6/75] with a variety of alkyl and acyl groups (see § 1.3.8 for the chemistry of 3-hydroxy compounds).

Alkylation of hydroxyoxoanthraisoxazoles leads to the alkoxy derivatives of both tautomers.[6/90] Similar mixtures result from the acylation reaction, but the nature of the final product is dependent on the reaction temperature (see § 1.3.9.1).[6/90]

Alkoxy derivatives show β-blocking,[15/77,20/80,17/86,2/87,18/87] diuretic,[21/80,11/83] and other[16/77,18/86] interesting pharmacological properties.

Alkylation of 3-hydroxymethyl-5-hydroxy-1,2-benzisoxazole with methyl iodide and NaOH selectively gives the 5-methoxy derivative.[4/72] Demethylation of methoxy derivatives, as shown for **235**, has been effected in good yield with pyridine hydrochloride or BBr_3 without cleavage of the ring.[6/82]



235 **236**

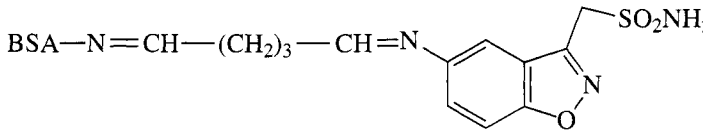
The hydroxy derivatives of 1,2-benzisoxazole can easily be transformed into the corresponding halo compounds without any difficulty.[3/67,4/72,7/75]

1.4.8.3. Amino Groups

The amino group in the phenyl ring of 1,2-benzisoxazole compounds behaves like that of aromatic amines and can be diazotized.[1/26,3/27,2/29,5/50,1/53,4/72,18/80] The diazonium salts, which in some cases are stable enough to permit isolation, undergo standard reactions.[3/27,2/29] They can be coupled with phenols and aromatic amines,[1/26,3/27,1/53] decomposed to the corresponding hydroxy compounds, [3/27,1/29,4/72,1/75] and substituted under Sandmeyer reaction conditions.[2/29,7/78]

The amino group in position 3 can be also diazotized and, at least in some cases, transformed to give the corresponding 3-hydroxy compounds.[2/29,3/29] Acylation occurs without any difficulty.[1/26,1/29,2/29,1/53]

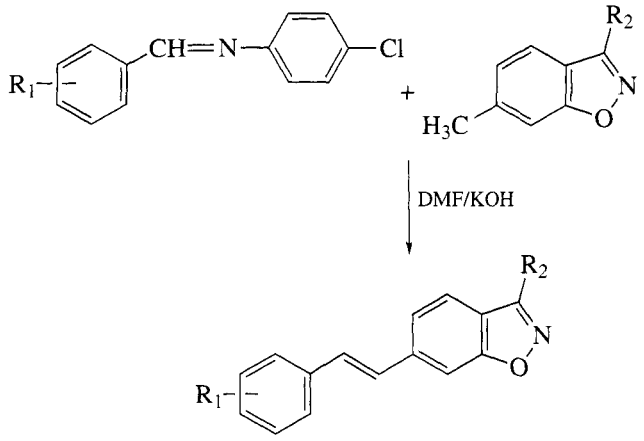
Recently, a protein–hapten conjugate (**237**) of 5-amino-3-sulfomoylmethyl-1,2-benzisoxazole and bovine serum albumin (BSA) has been obtained through a five-carbon linker for use in immunoassays.[19/87]



237

1.4.8.4. Alkyl and Aryl Groups

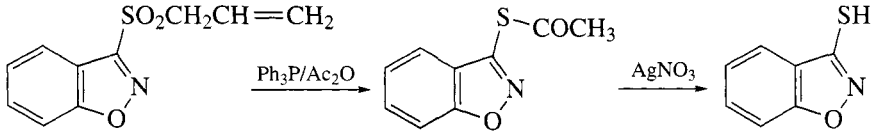
Several stilbene derivatives obtained by reaction of 3-(*p*-toluyl)- or 6-methyl-1,2-benzisoxazole with Schiff bases of *p*-chloroaniline have been synthesized as fluorescent whiteners for polyester textiles.[19/78,8/79,17/79,21/79,13/81,14/81]



1.4.8.5. Sulfonyl Groups

Sulfonic acids can be converted into the corresponding chlorides with $POCl_3$ and then into amides.[2/894,4/78]

The 3-allylsulfoxide **238** has been used to synthesize the corresponding 3-mercapto derivative **240**.[20/78]



238 **239** **240**

1.4.8.6. Carbonyl Groups

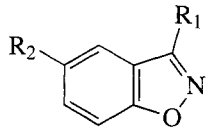
Carbonyl groups give the usual reactions with nucleophiles, apparently without any difficulty. Most of the compounds containing this group are already reported (see § 1.3.9).

6-Hydroxy-7-acetyl-1,2-benzisoxazole substituted in position 3 smoothly gives Schiff bases with tubercolostatic activity.[19/80]

1.5. BIOLOGICAL PROPERTIES

1.5.1. Pharmacological Activity

Because of its isosteric relationship with the indole nucleus, 1,2-benzisoxazole has enjoyed wide use as a carrier for pharmacophoric moieties in the search for potential drugs. Thus 1,2-benzisoxazole analogs of tryptophan (**241**),[4/72] tryptamine (**234**),[6/75] serotonin (**243**),[7/75] gramine (**242**),[6/75] and auxine (**24**)[4/69] have been synthesized and evaluated for their biological action. Several hundred 1,2-benzisoxazole derivatives have been synthesized and screened, most of them by drug companies.



23, $R_1 = CH_2SO_2NH_2$, $R_2 = H$

24, $R_1 = CH_2COOH$, $R_2 = H$

34, $R_1 = CH_2C(=NOH)NH_2$, $R_2 = H$

234, $R_1 = CH_2CH_2NH_2$, $R_2 = H$

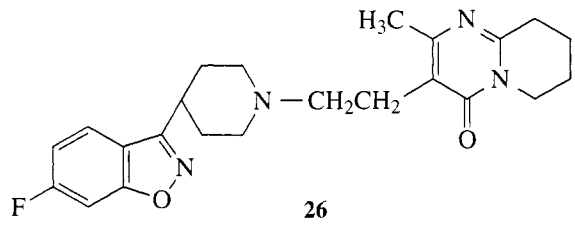
241, $R_1 = CH_2CHNH_2COOH$, $R_2 = H$

242, $R_1 = CH_2N(CH_3)_2$, $R_2 = H$

243, $R_1 = CH_2CH_2NH_2$, $R_2 = OH$

247, $R_1 = OP(=S)(OC_2H_5)_2$, $R_2 = Cl$

Of the many compounds studied, only a few have emerged as candidates for clinical use. 1,2-Benzisoxazole-3-methanesulfonamide (**23**; zonisamide) is a potent antiepileptic drug;[12/79,22/80] 6-fluoro-1,2-benzisoxazole derivative **26** (Risperidone) is a potent antipsychotic agent with thymosthenic properties,[4/88] and its analog **250** (HRP 913) is a potent dopamine antagonist with antipsychotic properties;[12/83] 1,2-benzisoxazole-3-acetamidoxime **34** (PF-257) is a psychotropic agent with seemingly new properties;[16/74,8/76] the acrylonitrile derivative **245** (SX-284) specifically inhibits acetylcholine release from the vagus nerve and is a valuable antispasmodic agent,[16/82] as is the basic ester **246** (SX-810).[19/86] The phosphate **247** (Bay 52957) is a potent insecticide,[8/67] and the acyloxyacetic acid derivative **248** (HP-522) is a high-ceiling diuretic with uricosuric action,[21/80] like its cyclic analog **249** (A-56234).[16/88]



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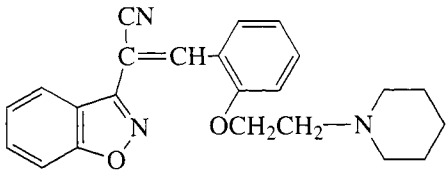

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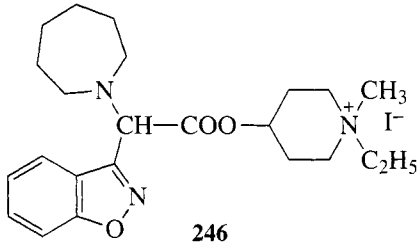

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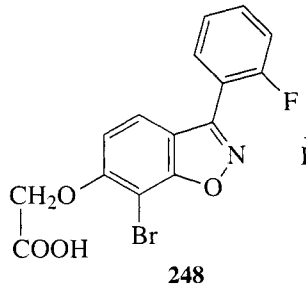

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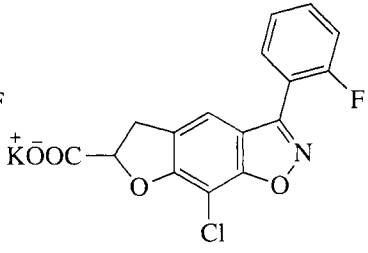

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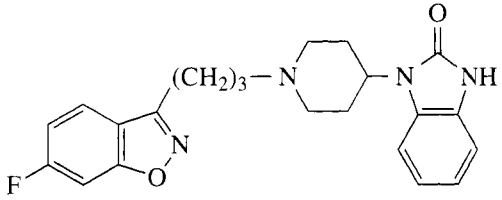

250

Table 1.32 reports the biological and pharmacological activities observed in 1,2-benzisoxazole derivatives.

TABLE 1.32. BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY OBSERVED IN 1,2-BENZISOXAZOLE DERIVATIVES

Biological or Pharmacological activity	References
Analgesic	21/82, 14/83, 5/88, 8/89, 12/89, 22/89, 23/89, 11/90
Analeptic	11/69
Antiallergic	16/77, 21/78, 2/91

(*continued*)

TABLE 1.32. (*continued*)

Biological or Pharmacological activity	References
Anticonvulsant	7/84, 21/89
Anthelmintic	12/69, 19/90
Antifungal	17/77, 18/77, 10/78, 22/78, 19/79, 4/84, 19/84, 20/84
Antifouling	20/84
Antihypertensive	15/83, 16/83, 17/83, 19/85, 20/85, 7/86, 18/88, 19/88, 20/88, 10/89, 11/89, 22/89, 23/89
Antiepileptic	12/79, 22/80
Antiinflammatory	10/69, 14/71, 12/75, 6/79
Antimicrobial	19/77, 5/78, 19/79, 20/87, 22/87
Antipsychotic, neuroleptic	17/82, 18/82, 12/83, 18/83, 5/85, 11/86, 20/86, 4/88, 3/89, 10/89, 11/89, 25/89, 27/89, 9/90, 13/90, 22/90, 3/91, 1/92
Antiserotoninergic	7/75, 9/76, 16/86, 6/88, 22/88, 17/90, 18/90, 1/91
Auxinic	4/69, 9/71, 15/90, 8/91
β-blocking	15/77, 20/80, 5/83, 17/86, 2/87, 18/87
Cholinomimetic	14/72
CNS depressant	11/78
Diuretic, uricosuric	20/79, 21/80, 6/82, 19/82, 20/82, 11/83, 15/84, 4/85, 8/86, 16/88, 16/89, 17/89, 18/89, 26/89, 14/90, 16/90, 13/91, 2/92
Enzyme induction	7/90
Enzyme inhibition	7/78, 9/89, 15/89, 24/89, 8/90
Gastric motility stimulant	21/87, 14/89
Herbicidal	17/85, 5/86, 18/86, 9/88, 21/88, 13/89, 20/89, 7/91
Hypoglycemic	19/89
Insecticidal – acaricidal	8/67, 9/70, 10/72, 11/72, 12/72, 4/73
Insect chemosterilizing	1/72
Local anesthetic	1/68
Oral antidiabetic	5/72
Psychotropic	14/73, 16/74, 8/76
Sedative analgesic	3/62
Spasmolytic	9/82, 13/82, 14/82, 16/82, 3/83, 7/83, 10/83, 19/86, 15/87, 10/90, 12/90
Trypanocidal	1/61
Tuberculostatic	1/54, 19/80, 6/83, 17/88

1.5.2. Toxicology

Few studies of the toxicology of 1,2-benzisoxazole compounds have been published. In one of them the aquatic toxicology of 1,2-benzisoxazole and several other heterocyclic molecules were related to hydrophobicity and molecular connectivity.[13/83] In another one the subacute inhalation toxicity of 3,6-dimethyl-1,2-benzisoxazole was found to be undetectable.[7/70] Some 1,2-benzisoxazole derivatives are among the many chemicals tested for oral toxicity in house mice and for mutagenicity.[18/79,18/85]

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CHAPTER 2

2,1-Benzisoxazoles*

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*This chapter is dedicated to the Sage of Puttaparthy on his 70th birthday.

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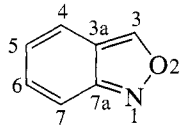
2.1. INTRODUCTION

This chapter discusses the chemistry of 2,1-benzisoxazoles (**1**), covered previously in the 17th volume of this series about 30 years ago. Furthermore, three excellent reviews are available on this subject.[1/67,1/81,1/84] The topic has also been discussed more recently.[1/91] 2,1-Benzisoxazoles have also been referred to as "anthranils," as they were erroneously considered to be anhydrides of anthranilic acid. 1,2-Benzisoxazoles or indoxazenes, which are closely related, yet different, are not discussed in this chapter. 2,1-Benzisoxazoles that are fused to other heterocyclic rings have been discussed in another chapter of this volume. About 240 known 2,1-benzisoxazoles were listed in 1967. References up to the end of 1993 have been included in this chapter based on *Chemical Abstracts* (CAS Registry No. 271-58-9) and other primary journals.



1

Anthranil, azoopianic acid, was obtained more than a century ago but was not identified as such. 5,6-Dimethoxy-2,1-benzisoxazole was the first compound of this class to be prepared.[1/881] Many classic names appear in the early literature.[1/896,1/899,1/01,2/01,1/02,1/03,2/03,3/03,4/03,1/04,1/06,1/07,1/08,1/09,2/09,3/09,4/09,5/09,1/10,2/10,1/24,1/28] The parent compound itself was made by the reduction of *o*-nitrobenzaldehyde with tin and acetic acid.[1/882] The use of ^{18}O-labeled *o*-nitrobenzaldehyde has shown[1/60] that the oxygen atom of the 2,1-benzisoxazole ring comes from the nitro group and that the aldehydic oxygen atom is lost in the reaction.

Interest in this class of compounds stems from the fact that they provide an easy route to *o*-aminobenzophenones, which serve as key intermediates in the synthesis of many important tranquilizers and have been used in treatment of

cancer even by oral administration. 5-Chloro-3-phenyl-2,1-benzisoxazole stands out in this regard.

The lively debate on the cyclisation of *o*-substituted aryl azides has also been covered in this chapter, with special reference to aromatic *o*-azido carbonyl compounds. Much work has been done in recent years on isoxazolequinones and anthraisoxazolones[1/92] and these are also covered in detail. Data on IR, UV, NMR, mass, and Raman spectra of 2,1-benzisoxazoles have also been tabulated in this chapter.

2.2. PHYSICOCHEMICAL PROPERTIES

The 10-π electron 2,1-benzisoxazole system is sensitive to both heat and light, and has a planar structure (as shown by X-ray crystallographic studies[1/62]). The molecule is aromatic,[1/90] has a resonance energy of 32 kcal/mol, and has been given an aromaticity index ($I_{5,6}$) of 54 showing substantial aromatic character for this *ortho*-quinonoid structure.[1/87] It has a dipole moment of 3.06 D, and electron density calculations on it have been recorded. The He(I) Photoelectron spectrum of 2,1-benzisoxazole has been recorded.[1/78] Vertical ionization potentials have been measured, and assignments made are shown in Table 2.1 and the population analysis is shown in Table 2.2.

TABLE 2.1. IONIZATION POTENTIALS OF 2,1-BENZISOXAZOLES

IP	ε_i	Assignment
8.50	8.89	π
9.96	11.29	π
10.82	12.34, 12.73	π, $\sigma(LP_N)$
12.42	14.59, 15.04	σ, π
13.30	15.25, 15.58	σ, σ
14.55	17.23, 17.42	σ, σ
15.00(sh)	—	—
15.85	18.75, 18.80, 19.42	π_L, σ
16.84	20.43	σ
18.48	22.66, 22.94	σ, σ
19.7	24.79	σ

TABLE 2.2. POPULATION ANALYSIS

	O2	N1	C3	C4	C6
$1s + 2s$	3.8045	3.6656	3.0336	3.0457	3.0447
$2p_\sigma$	2.8764	2.1576	1.8456	2.0973	2.0955
$2p_\pi$	1.6951	1.2515	0.9789	0.9865	1.0107
Total	8.3761	7.0748	5.8582	6.1294	6.1509

(*continued*)

TABLE 2.2. (*continued*)

	C6	C7	C3a	C7a
$1s + 2s$	3.0525	3.0401	2.9828	2.9749
$2p_\sigma$	2.1127	2.0832	1.9920	1.9327
$2p_\pi$	0.9678	1.0196	1.0909	0.9989
Total	6.1330	6.1429	6.0728	5.9065

2.2.1. Infrared and Raman Spectra

IR spectra of 2,1-benzisoxazoles show strong absorption at 1640 cm^{-1}. The parent unsubstituted compound shows an absorption at 3128 cm^{-1} due to the stretching vibration of the C–H bond. The bands at 1110 and 798 cm^{-1} are attributed to the isoxazole ring, as are the strong absorptions at 1640 cm^{-1} and at 751 cm^{-1}. Anthraisoxazolones often show absorptions at 1660 cm^{-1} due to the carbonyl group and at 1640 cm^{-1} due to the carbon–nitrogen double bond.

Absorptions in the Raman spectrum of 2,1-benzisoxazole have been completely characterized.[1/80] Assignments were made for 6-CH stretching vibrations and 1-CH bending vibration. In addition, 15 fundamental stretching vibrations of the ring and 5 bending vibrations of the benzisoxazole ring were characterized, as shown in Tables 2.3 and 2.4.

TABLE 2.3. FUNDAMENTAL FREQUENCIES OF 2,1-BENZISOXAZOLE RING[a]

	Raman spectrum			IR spectrum (neutral solvents)	
	ν (cm^{-1})	I	ρ	ν (cm^{-1})	ε
			A'		
ν_1	1640	9	0.53	1640	123
ν_2	1556	5	0.64	1554	12
ν_3	1519	7	0.45	1517	74
ν_4	1455	100	0.07	1456	31
ν_5	1411	20	0.11	1405	9
ν_6	1380	11	0.27	1381	77
ν_7	1358	11	0.14	1355	10
ν_8	1238	2	0.74	1236	14
ν_9	981	11	0.15	978	41
ν_{10}	922	13	0.08	920	41
ν_{11}	869	5	0.15	873	89
ν_{12}	750	30	0.04	751	682
ν_{13}	603	13	0.64	603	15
ν_{14}	535	21	0.12	534	7
ν_{15}	401	5	0.41	399	63

TABLE 2.3. (*continued*)

	Raman spectrum			IR spectrum (neutral solvents)	
	ν (cm^{-1})	I	ρ	ν (cm^{-1})	ε
			A″		
Γ_1				~741(sh)	
Γ_2				645(w)	
Γ_3	593	2	0.72	591	66
Γ_4	~543(sh)			541	15
Γ_5	436	2	0.75	432	132
Γ_6	260	1	0.63	254	44
	212	3	0.75	—	—

[a]Key: I = intensity, ρ = depolarization factor, ε = molar extinction coefficient, sh = shoulder, w = weak.

TABLE 2.4. FUNDAMENTAL FREQUENCIES OF THE CH VIBRATIONS OF 2,1-BENZISOXAZOLE[a]

	Raman spectrum			IR spectrum			
Vibrational band	ν (cm)$^{-1}$	I	ρ	Neutral ν (cm)$^{-1}$	Solvent ε	DMSO ν (cm)$^{-1}$	Acetone ν (cm)$^{-1}$
				A′			
$\nu_{\text{CH isox}}$	3130	2	0.19	3128	16		
$\nu_{1\text{-CH}}$	—	—	—	—			
$\nu_{2\text{-CH}}$	3070	7	0.20	3067	23		
$\nu_{3\text{-CH}}$	—			3055	21		
$\nu_{4\text{-CH}}$	—			~3051sh			
$\delta_{1\text{-CH}}$	1257	2	0.54	1253	12	1259(sh)	
$\delta_{\text{CH isox}}$	1113	2	0.51	1110	257	1110	1113
$\delta_{2\text{-CH}}$	1157	9	0.14	1149	14	1156	1156
$\delta_{3\text{-CH}}$	1142	4	0.64	1137	14	1140	1141
$\delta_{4\text{-CH}}$	~1137	3	—	1131	14	1133	1135
				A″			
$\nu_{1\text{-CH}}$				947	6		
$\nu_{2\text{-CH}}$	905	7	0.40	904	17	904	
$\nu_{3\text{-CH}}$	—			~897(sh)	848(w)	848(w)	
$\nu_{\text{CH isox}}$	—			798	179	820(s)	814
$\nu_{4\text{-CH}}$	—			728	234	741	735

[a]Key: I = intensity, ρ = depolarization factor, ε = molar extinction coefficient, sh = shoulder, w = weak, s = strong.

In the infrared spectrum of 2,1-benzisoxazole two intense absorptions are observed at 3128 and 3108 cm^{-1}. The former is attributed to the isoxazole ring and the latter, to an overtone. Four absorptions are observed between 3000 and

3080 cm^{-1}. While the peak at 3012 cm^{-1} is a combination band, those at 3067, 3055, and 3051 cm^{-1} are assigned to the C–H stretching vibration, which is similar to values in aromatic compounds pointing toward the absence of notable interactions between the six membered aromatic ring and the five membered heterocyclic ring.

By analogy with other benzo-fused heterocycles and *o*-substituted benzenes, 2,1-benzisoxazole is expected to give rise to absorptions between 1260 and 1050 cm^{-1}. In this region, the IR and Raman spectra show analogous bands at 1255 ± 2, 1152 ± 3, 1139 ± 2,and 1123 ± 8 cm^{-1} that are due to the bending vibrations of the benzene ring. The bending deformation of the isoxazole ring is located at 1110 cm^{-1}. The bending vibrations were sensitive to polar solvents, which is an additional argument in favor of these assignments. Out-of-plane C–H deformation in (*A″* type) were seen at 947, 904, 897(sh), 846, 798, and 728 cm^{-1}.

The Raman spectrum enables the assignment of ring vibrations to 15 different sets of frequencies that are medium or strongly polarised and are linked with type A′ modes: 1697 ± 14, 1569 ± 13, 1517 ± 3, 1444 ± 9, 1422 ± 11, 1362 ± 18, 1332 ± 26, 1233 ± 6, 992 ± 11, 928 ± 6, 856 ± 13, 757 ± 7, 611 ± 9, 534 ± 1, and 411 ± 10 cm^{-1}.

Symmetry type *A″* vibrations were seen at 741(sh) and 645(w). In Raman spectrum two weak depolarized bands were observed at 593 and 436 cm^{-1} with a shoulder at 543 cm^{-1}. The lowest frequency out of the plane ring movement is assigned to the 215 cm^{-1} peak, although no absorption exists in that region in the IR spectrum, due to limitations of the spectral range of the apparatus used.

2.2.2. Ultraviolet Spectra

UV spectra of 2,1-benzisoxazoles are characterized by bands at 343–387 nm (sensitive to substituents) and at 254–258 nm and at 249–253 nm (show little variation). Anthraisoxazolones are characterized by multiple absorptions in some cases going beyond 550 nm.

2.2.3. Nuclear Magnetic Resonance Spectra

The ^{1}H-NMR spectrum of 2,1-benzisoxazole has been described in a previous review.[1/67] Interesting use has been made of ^{1}H-NMR spectral data for establishing the structures of the nitration products of 2,1-benzisoxazoles.[2/81] Nitration of 5-chloro-2,1-benzisoxazole was shown to lead to attack at the C4 position as evidenced by the fact that the protons at C6 and C7 appeared at δ 7.16 and δ 7.53 respectively, both seen as AB doublets with coupling constants, J = 9.5 Hz. The C3 proton was seen as a singlet at δ 9.43.

5-Chloro-3-phenyl-2,1-benzisoxazole, on the other hand, underwent nitration at C7 and not at C4. Thus it was shown by ^{1}H-NMR data that the C4 and C6

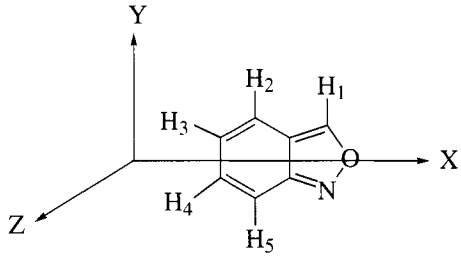
protons appeared at δ 8.23 and δ 8.43, respectively, both as doublets with a *meta* coupling constant, $J = 1.5$ Hz only. In this case, an additional nitro group entered at the C4′ position of the phenyl group, which was evident from AABB doublets at δ 8.50 ($J = 8.5$ Hz) and δ 8.21($J = 8.5$ Hz).

Nitration of 5-chloro-6-methyl-3-(4-phenyl)-2,1-benzisoxazole was shown to yield 3-(4′-nitrophenyl)-5-chloro-6-methyl-7-nitro-2,1-benzisoxazole; AABB doublets were observed for the 3-(4′-phenyl) moiety. In addition, the methyl group that appeared as a doublet ($J = 1.0$ Hz) in the starting material, due to the proton at C7, now appeared as a singlet in the product, thus lending further evidence that nitration occurred at the C7 position.

Nitration of 3-carbomethoxy-6-nitro-2,1-benzisoxazole was similarly shown to give the 4,6-dinitro derivative based on the fact that two signals were observed at δ 8.30 ($J = 1$ Hz) and δ 8.66 ($J = 1$ Hz), due to the protons at C5 and C7, which were *meta*-coupled to each other.

The ^{1}H-NMR spectrum of anthranil has been studied in the nematic phase.[14/84] Thus a solution of about 6 mol% of anthranil in a mixture of 69 mol% *N*-(*p*′-methoxybenzylidene)-*p*-*n*-butylaniline (MBBA) and 31 mol% *N*-(*p*′-ethoxybenzylidene)-*p*-*n*-butylaniline (EBBA) was studied at 20.5°C. The final spectral, geometric and order parameters for anthranil from the NMR spectrum in the mixture of MBBA and EBBA are given in Table 2.5.

TABLE 2.5. SPECTRAL, GEOMETRIC AND ORDER PARAMETERS FROM NMR SPECTRUM OF ANTHRANIL IN MBBA/EBBA MIXTURE



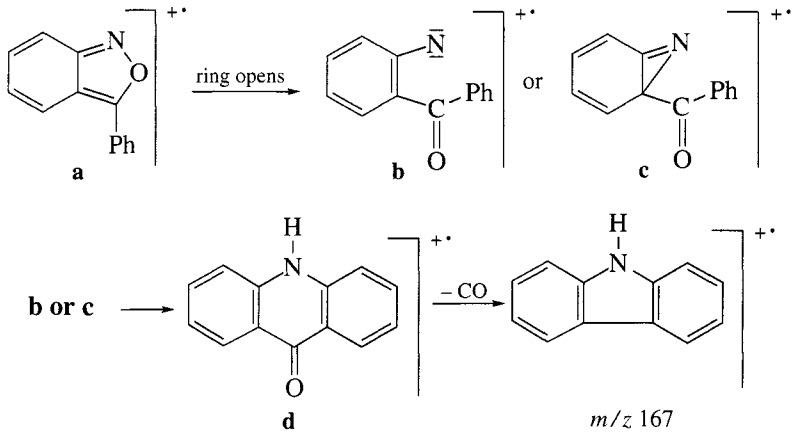
Parameter	Value (Hz)	Parameter	Value
D_{12}	634.05 ± 0.05	r_{12}/r_{34}	1.287 ± 0.003
D_{13}	-118.17 ± 0.12	r_{13}/r_{34}	2.146 ± 0.004
D_{14}	38.48 ± 0.09	r_{14}/r_{34}	2.487 ± 0.004
D_{15}	2.36 ± 0.09	r_{15}/r_{34}	2.226 ± 0.006
D_{23}	-574.35 ± 0.12	r_{23}/r_{34}	1.008 ± 0.001
D_{24}	23.60 ± 0.08	r_{24}/r_{34}	1.751 ± 0.001
D_{25}	23.82 ± 0.07	r_{25}/r_{34}	2.060 ± 0.004
D_{34}	205.31 ± 0.06	r_{35}/r_{34}	1.757 ± 0.003
D_{35}	-78.22 ± 0.09	r_{45}/r_{34}	1.007 ± 0.001
$\nu_2 - \nu_1$	488.38 ± 0.16	S_{xx}	0.1633 ± 0.0009
$\nu_3 - \nu_1$	589.60 ± 0.04	S_{yy}	-0.0261 ± 0.0001
$\nu_4 - \nu_1$	538.24 ± 0.08	S_{zz}	0.1372
$\nu_5 - \nu_1$	467.38 ± 0.09	S_{xy}	-0.0418 ± 0.0004

A ^{15}N-NMR study[16/84] of 2,1-benzisoxazole in 0.5*M* DMSO solution with 0.01 $Cr(acac)_3$ showed the observed ^{15}N nuclear nitrogen shielding to be +7.5.

2.2.4. Mass Spectra

Apart from the molecular ion peak, the mass spectrum of the parent 2,1-benzisoxazole is characterized by loss of carbon monoxide and hydrogen cyanide. Eight different 3-phenyl-2,1-benzisoxazoles with substituents at the 5 or 6 position have been investigated.[1/89] The unsubstituted compound in this case (R = H) showed the molecular ion peak, followed by loss of CO and then H^+; loss of C_6H_4N to leave behind $[C_7H_5O]^+$, *m/z* 105; and elimination of C_7H_7N to give $[C_6H_4O]^+$, *m/z* 92; and the phenyl cation fragments characterized its mass spectrum. These fragments, according to the authors, are significantly different from those of the parent 2,1-benzisoxazole molecule. The mass spectrum of 3-phenyl-2,1-benzisoxazole is best understood by comparison to that of 9(10*H*)-acridone. Similarities are strong, and many fragments are identical. Even in linked scans (*B/E*), there is close correspondence and the similarities extend to doubly charged ions. However, there are differences between the two spectra. In the case of the 3-phenyl-substituted compound the $PhCO^+$ peak appears with 10.1% abundance, whereas acridone shows it with only 0.2% abundance. Furthermore in the 3-phenyl case, the peaks at *m/z* 92, 77, 64, and 51 are due to abundant ions, whereas in the acridone case these are feeble (< 5%).

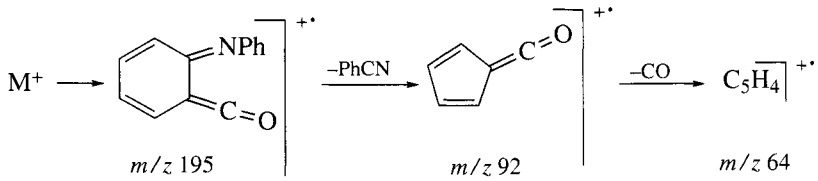
The fragmentation pattern of 3-phenyl-2,1-benzisoxazole is shown in Scheme 2.1.



Scheme 2.1

The molecular ion peak (**a**) is observed at *m/z* 195. It undergoes ring opening to the nitrene (**b**) or the benzazirine (**c**). It then recycles via nitrene insertion into the phenyl ring, forming acridone (**d**), which is similar to the known thermal

rearrangement reaction of the 3-phenyl compounds of this class. This reaction could also alternatively occur via the benzazirine. The observed successive losses of CO, H^+, and HCN are, according to the authors, well documented. Scheme 2.2 explains the loss of C_7H_5N and the subsequent loss of CO via N–O bond cleavage and phenyl radical migration, suggested also for simple isoxazoles. 5,6-Substituted-2,1-benzisoxazoles lose H, and CO is lost from both M^+ and $[M–H]^+$



Scheme 2.2

Thus the authors summarise that invariably a prominent molecular ion peak is observed and so also are abundant ions at m/z 77 $[C_6H_5]^+$ and m/z 51 $[C_4H_3]^+$. The ion at m/z 105 is almost always present with an abundance of 8.8–29.7%. $[C_7H_5O]^+$ loss is seen in R = H (20.9%) but is minor in R = NO_2, CO_2Et. The $[M–CO]^+$ is variable in R = H and zero in R = 5-NO_2 or 5-CO_2Et.

Rotation around C3 and C4, seen in the simple isoxazoles after the initial ring fission of isoxazoles by N–O cleavage, cannot occur in 2,1-benzisoxazoles. Similarly, in the case of 3-alkyl-2,1-benzisoxazoles[8/91] cyclization to acridone observed in the case of 3-phenyl-2,1-benzisoxazoles also cannot occur. In 3-alkyl-substituted compounds, the ketenimine pathway followed by loss of CO and alkyl cyanide is suggested. The fragments for the 3-methyl compound, shown below, are similar to the case of *N*-alkylanthranilic acid:

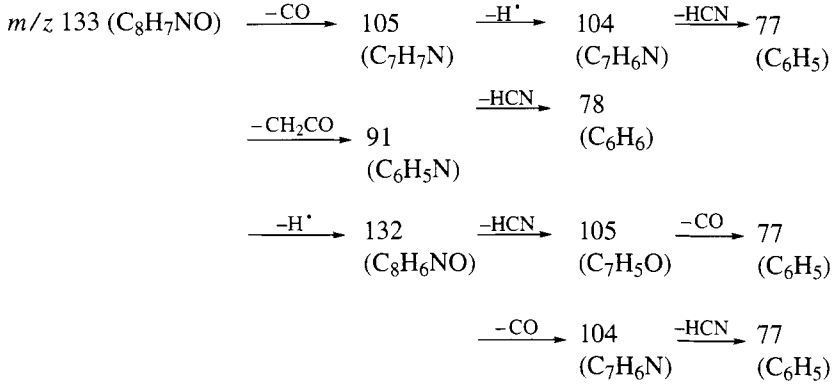


TABLE 2.6. ABUNDANCES (%) OF MOLECULAR IONS AND MAJOR DAUGHTERS IN EI-MASS SPECTRA OF 3-ALKYL-2,1-BENZISOXAZOLES

Ion	Abundances for alkyl substitutents as					
	3-Me	3,4-Me_2	3,7-Me_2	3-Et	3-Pr^i	3-Bu^t
M	68.4	100.0	100.0	100.0	100.0	38.6
M−H$^\cdot$	3.9	9.9	29.1	12.1	8.4	—
M−CO	10.2	21.5	11.9	—	16.0	—
M−CO−H$^\cdot$	55.8	62.9	35.7	84.0	83.1	—
M−ketene	13.4	7.1	20.5	8.4	—	19.7
M−alkene	—	—	—	41.5	31.9	8.9
M−alkene−CO	—	—	—	47.6	50.6	22.2
M−Me$^\cdot$	1.8	5.2	18.1	14.7	61.1	100.0
M−Me$^\cdot$−CO	11.9	23.4	42.4	43.6	24.9	43.0
Alk C$^+$O	100.0	89.7	40.2	36.3	—	—
Alk$^+$	—	—	—	48.9	39.7	33.3

Main loss of CO occurs in 3-alkyl-2,1-benzisoxazoles. For this to occur, the N−O bond must break and migration (from O to N) must follow to give the ketenimine (found in high abundance) from which CO loss can occur. Abundances of molecular and daughter ions in the mass spectra of some 3-alkyl-2,1-benzisoxazoles are shown in Table 2.6.

In the case of the 3-methyl-substituted compound, H loss, CO loss, and a combination of the two are observed. M−CH^+ loss is minor in the 3-methyl and 3,4-dimethyl compounds, and is observed to the extent of 18% in the 3,7-dimethyl compound. In the case of the 3-ethyl compound, M−$C_2H_4^{+\cdot}$ is observed and it loses CO. The 3-isopropyl compound parallels that of the corresponding anthranilic acid and loss of Me$^\cdot$ (α-cleavage) and C_3H_6 occurs as expected. The 3-*tert*-butyl-substituted compound shows methyl loss. No direct loss of CO occurs and α-cleavage of Me is followed by CO loss. It is also stated by the authors that, in general, the alkyl groups of these isoxazoles fragment in ways that suggest carbene reactions.

CI-MS of 2,1-benzisoxazoles has also been discussed. CH_4−CI generates $[M+H]^+$. Promotion at O and N is also possible. Preferential loss of mass 28 from these ions is shown in the MIKE (mass-analyzed ion kinetic energy) spectrum. CD_4-CI-MS confirmed that mass 28 is CD and not H_2CN^+ or C_2H_4.

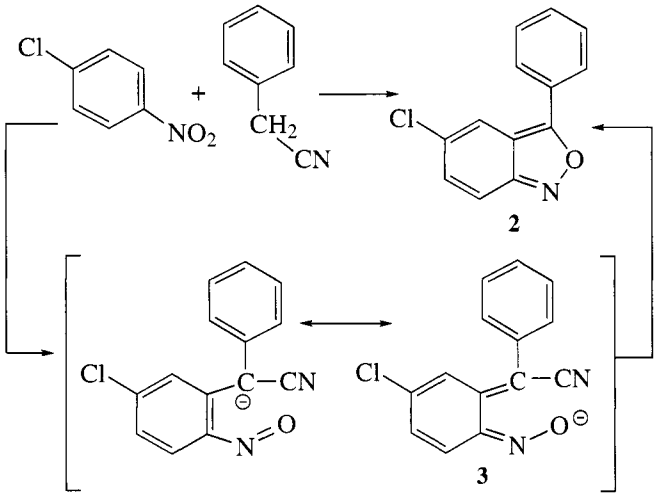
2.3. SYNTHETIC METHODS

2.3.1. Approaches Based on Intermolecular Reactions

2.3.1.1. Base-Catalyzed Condensation of Active Methylene Substrates and Halonitroarenes (Davis–Pizzini Reaction)

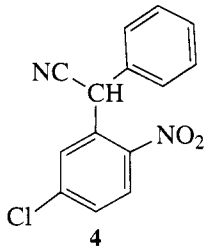
Halonitroarenes condense readily in the presence of base with benzyl cyanides, diethyl malonate, and ethyl cyanoacetate.[2/60,2/62] Thus *p*-chloroni-

trobenzene and benzyl cyanide in the presence of methanolic alkali give 5-chloro-3-phenyl-2,1-benzisoxazole (**2**). The reaction proceeds via an *o*-quinonoid intermediate **3**, which has been isolated in some cases (Scheme 2.3).[2/60,2/62]



Scheme 2.3

2,4-Dichloronitrobenzene on reaction with benzyl cyanide, sodium hydroxide, and benzyltriethylammonium chloride yields 5,7-dichloro-2,1-benzisoxazole as the major product. The use of NAH–DMSO brings about replacement of the chlorine, *ortho* to the nitro group, by the carbon nucleophile to give α-(5-chloro-2-nitrophenyl)benzylcyanide (**4**) along with other products.[1/76]

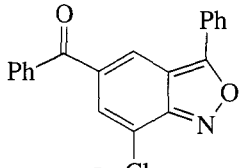


4

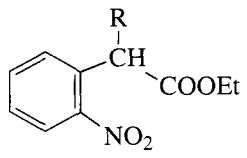
The use of 2-chloronitrobenzene, however, leads to a nucleophilic substitution. Reaction of 4-benzoyl-2-chloronitrobenzene with benzyl cyanide has been observed to give 5-benzoyl-7-chloro-3-phenyl-2,1-benzisoxazole (5).[1/77]

With the sodium salt of malonic ester or ethyl cyanoacetate and 2-chloronitrobenzene, nucleophilic replacement of the chlorine atom is observed. On

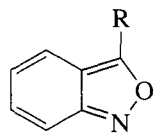
distillation, the product (**6**) gives the benzisoxazole **7**. In the case of ethyl cyanoacetate, the yield of 7 is low.[1/61]



5

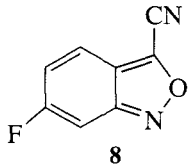


6 R = CN or COOEt



7

p-Aminobenzylcyanide fails to react with *p*-chloronitrobenzene, but isoxazole formation does occur if the amino group is protected.[2/77] Treatment of 2,5-difluoronitrobenzene with ethyl cyanoacetate affords 3-cyano-6-fluoro-2,1-benzisoxazole (**8**) in 26% yield.[1/68]



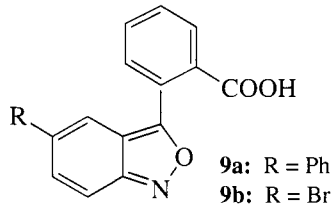
8

5-Chloro-3-phenyl-2,1-benzisoxazole, in particular, and related compounds in general, have been the subject of many patents in recent years. Production on a 12-kg scale has been described.[1/82] A German patent[1/83] describes the method and apparatus for producing thixotropic reaction masses. The 2′-carboxylic acid derivative has been synthesized,[2/84] and 5-chloro-3-(3′-chloro/3′-methoxy-4′-methoxy) and 2′-substituted phenyl-5-chloro-3-phenyl-2,1-benzisoxazoles have been prepared.[1/85,2/87] 5-Chloro-3-(4-chlorophenyl)-2,1-benzisoxazole has been used in the preparation of a new benzodiazepinone. In addition to the German patent,[2/85] a more recent one[2/90] describes the preparation of 5-chloro-3-phenyl-2,1-benzisoxazole in 230-kg quantities by Bechamp reduction. 5-Chloro-3-phenyl-2,1-benzisoxazole induced 39.4% inhibition of melanoma and other implant tumors in mice. 3-Phenyl-2,1-benzisoxazoles are useful in treatment of cancer and can be administered in oral, parenteral, or suppository formulations.

5-Chloro- and 5-bromo-3-phenyl-2,1-benzisoxazoles were also prepared during the synthesis of a new benzodiazepinone.[2/80]

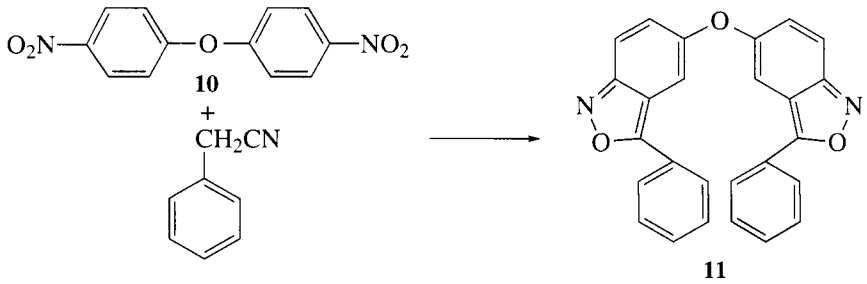
Recently 3-(*o*-carboxyphenyl)-5-phenyl-2,1-benzisoxazoles (**9a**) were synthesized[3/87] for evaluation of their potential agricultural utility. These workers also prepared 5-bromo-3-(*o*-carboxyphenyl)-2,1-benzisoxazole (**9b**) from 4-bromonitrobenzene and *o*-carboxyphenylacetonitrile in methanolic KOH containing THF at 0–5°C and converted it into the methyl ester under mild conditions. Recently, the reaction of *p*-chloronitrobenzene and benzylcyanide

was carried out in the presence of alkali metal alkoxides to prepare benzisoxazoles useful as intermediates for production of medicines and agrochemicals.[3/85] Thus a butanol solution of *p*-chloronitrobenzene and benzyl cyanide was added dropwise to sodium butoxide in butanol at 35°C and the resulting solution was maintained at room temperature for 6 h to give the isoxazole in 90% yield. Antiinflammatory derivatives of 3-aryl-2,1-benzisoxazoles were prepared recently.[1/88]



9a: R = Ph
9b: R = Br

Another typical preparation is that of 5,5′-oxy-bis(3-phenyl-2,1-benzisoxazole) (**11**). Thus to 150 g of sodium hydroxide in 750 ml of absolute methanol and 80.5 g of benzyl cyanide, 97.5 g of the nitro compound **10** was added slowly. The product was washed with methanol and crystallized from toluene to give 39.4% yield of the benzisoxazole (Scheme 2.4).[2/76]



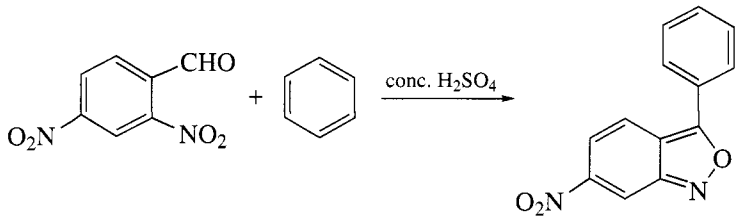
11

Scheme 2.4

2.3.1.2. Condensation of Nitrobenzaldehydes and Arenes (Kliegel–Tânâscescu Reaction)

Nitrobenzaldehydes (e.g., *o*-nitrobenzaldehyde, 2,4-dinitrobenzaldehyde) undergo a condensation reaction with benzene, toluene, and many other arenes in the presence of concentrated sulfuric acid to give 3-phenyl-2,1-benzisoxazoles **12** (Scheme 2.5). The reaction was first documented in 1908 but later extensively studied.[2/08,1/26,1/27,2/27,3/27,2/28,3/28,1/31,1/33] Use of naphthalene and fluoro-, chloro-, bromo-, and iodobenzene gave similar results.[1/59,3/60,4/60,5/60] Although the

proposed mechanism was severely criticized,[4/27,4/28,1/29,2/29,1/34] the actual mechanism of this reaction has not yet been established and it is clearly a complex one.



12

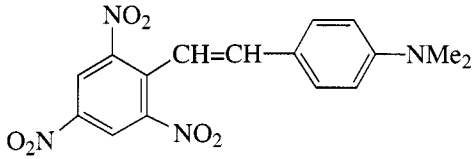
Scheme 2.5

Aniline underwent a reaction in the presence of $POCl_3$ with *o*-nitrobenzaldehyde to give 3-(*p*-aminophenyl) derivative with halogenation at the 5-position.[1/64] Use of zinc chloride gave in addition to the isoxazole, triarylmethanes as a by-product.[1/32,1/36,1/37] Phenols and *N,N*-dimethylaniline also underwent a similar reaction[2/04,2/06,1/53] in the presence of hydrogen halides in acetic acid or ether. Anisole and dimethoxybenzenes react similarly.[1/72] Recently, the condensation of 2,4-dinitrobenzaldehyde with naphthalene has been found to give 3-naphthyl-6-nitro-2,1-benzisoxazole.[2/88]

2.3.2. Approaches Based on Intramolecular Reactions

2.3.2.1. From o-Nitrobenzyl Compounds

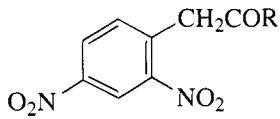
During photolysis of the *o*-nitrostilbene derivative **13,** a small quantity of 4,6-dinitro-2,1-benzisoxazole was obtained .[1/55]



13

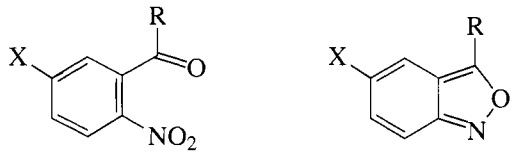
2,1-Benzisoxazoles were prepared from 2,4-dinitrophenylacetic acids and acetones **14** by treatment with concentrated sulfuric acid; the acyl moiety was lost in the reaction. 5-Chloro-3-phenyl-2,1-benzisoxazole was prepared from *o*-nitrobenzhydrol by reaction with thionyl chloride in chloroform, which introduces a chlorine atom at the 5 position.[2/64] Fluorosulfonic acid-catalyzed cyclization of (*o*-nitrophenyl)succinic anhydride gives a mixture of 4-hydroxy-

2-quinolone and anthranil-3-acetic acid and not a mixture of 1-hydroxyindole and 2-hydroxy-2-indoline-3-carboxylic acid. [4/70]



14

Using triethylphosphite, *o*-nitrobenzophenones were converted (Scheme 2.6) into 3-phenyl-2,1-benzisoxazoles.[1/70] The reaction with *o*-nitrobenzophenone (**15a**) was carried out under an atmosphere of nitrogen at 100°C for 12 h and at 120°C for 4 h. Work up and elution from alumina gave the product (**16a**) in 56% yield. 5-Chloro-2-nitroacetophenone similarly gave 5-chloro-3-methylanthranil (**16b**) in 37% yield, while *o*-nitrochalcone (**15c**) also gave the corresponding anthranil. The expected isoxazole was not obtained in the reaction with *o*-nitrobenzoate and ethyl anthranilate; instead, the corresponding phosphoramidate and its *N*-ethyl derivative were obtained as the products. *o*-Nitroacetophenone also gave only the phosphoramidate. Newer insights could be obtained by reinvestigating the mechanism of these reactions in detail. *o*-Nitrobenzaldehyde (**15d**) and benzene in the presence of concentrated sulfuric acid gave the 3-phenyl derivative.



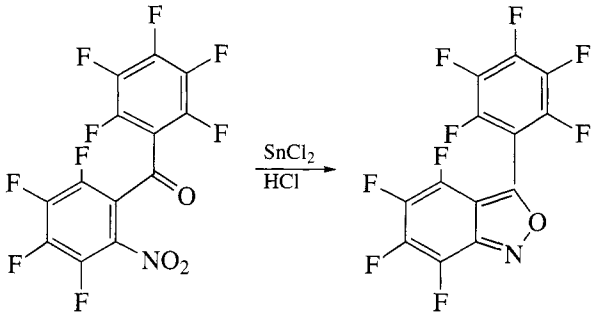
15a: X = H; R = Ph
15b: X = Cl; R = Me
15c: X = H; R = – CH=CH–Ph
15d: X = H; R = H

16

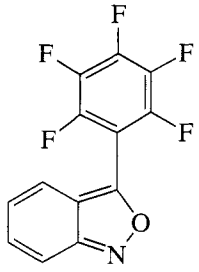
Scheme 2.6

Nonafluoro-3-phenylanthranil was prepared by reduction of 2-nitrononafluorobenzophenone with stannous chloride in hydrochloric acid (Scheme 2.7).[1/71]

3-Pentafluorophenylanthranil (**17**) was similarly obtained by zinc–ethanol–ammonium chloride reduction of 2,3,4,5,6-pentafluoro-2′-nitrobenzophenone, whose structure was, in addition to other evidence, supported by ^{19}F-NMR spectral studies. The latter compound was also prepared by thermolysis of the corresponding carbinol.[2/66]

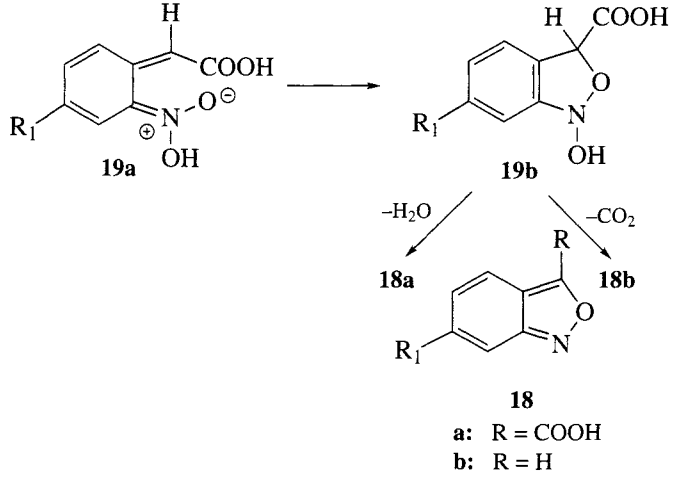


Scheme 2.7

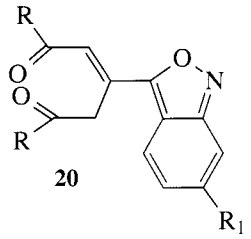


17

Treatment of *o*-nitrophenylacetic acids with concentrated sulfuric acid (120–30°C; 2 h) gave the anthranil 3-carboxylic acids **18a** and the decarboxylated anthranil **18b**. Involvement of the *aci*-nitro form (**19a**) of the starting material was invoked to explain the rapid conversion of these benzyl systems into benzisoxazoles under basic, acidic, and thermal conditions via the dihydroanthranil intermediate **19b**.[1/70]



3-(2-Benzoyl-1-phenacylidene-ethyl)-6-nitro-2,1-benzisoxazole (**20a**), 6-nitro-3-(1,3-dipivaloylpropen-2-yl)-2,1-benzisoxazole (**20b**), and 3-(2-benzoyl-1-phenacyliden-ethyl)-2,1-benzisoxazole (**20c**) were characterized and their mass spectra recorded.[1/73]



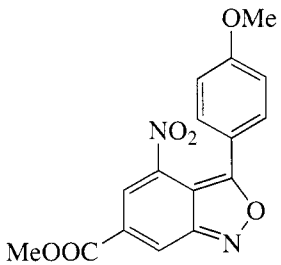
20

20a: R = Ph; $R_1 = NO_2$
20b: R = *t*-Bu; $R_1 = NO_2$
20c: R = Ph; $R_1 = H$

6-Methoxycarbonyl-3-(4-methoxyphenyl)-4-nitro-2,1-benzisoxazole (**21**) was prepared in 47% yield by the Wittig route.[2/73] In addition to signals that could be attributed to the methoxycarbonyl group, the methoxy group, and the aromatic protons of the 3-phenyl substituent, the ^{1}H-NMR spectrum of **21** showed the aromatic protons of the benzisoxazole ring at δ 8.35 and δ 8.68.

3-Benzoyl-2,1-benzisoxazoles were obtained during acid-catalyzed rearrangement of carbinol **22** to 2-arylisatogen and *cis*- and *trans*-stilbene.[5/75]

During the electrochemical reduction of *threo* and *erythro* carbinols **23**, the corresponding benzisoxazole was isolated as a minor product.[1/69]



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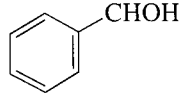

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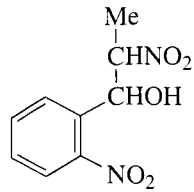
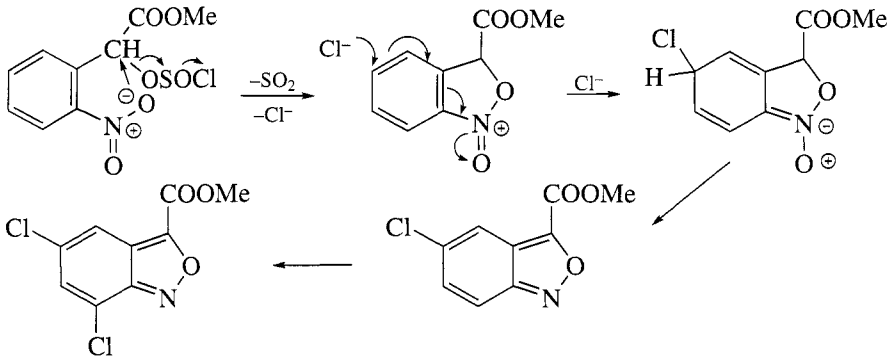


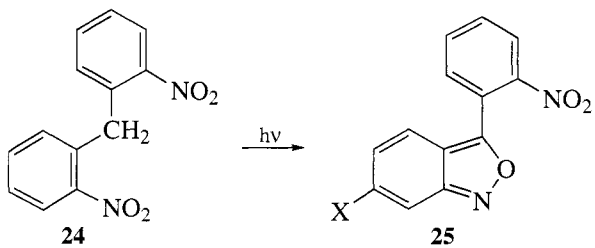
23

Reaction of methyl-*o*-mandelate with $SOCl_2$ depends critically upon the reaction conditions.[1/79] At room temperature only the sulfite ester is produced, but in pyridine at −80°C, the α-chloro compound is obtained. The latter is unaffected by boiling thionyl chloride but on prolonging the reaction (12 h) in chloroform the dichlorobenzisoxazole is obtained (via the 5-chloro compound) (Scheme 2.8).



Scheme 2.8

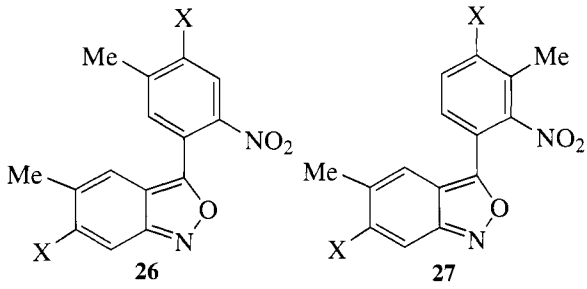
Photochemical reactions of 2,2′-dinitrodiphenyl methanes (**24**) have been intensively studied. It has been shown that 2,1-benzisoxazoles are often encountered among the products of these reactions. In some cases this provides a route to anthranils, which are otherwise difficult to prepare, even in small amounts. Thus 3-(2′-nitrophenyl)-2,1-benzisoxazoles **25** were prepared in 45–50% yields by photolysis in ethanolic H_2SO_4.[1/74,5/76]



24 **25**

Involvement of a biradical intermediate was suggested that could undergo spontaneous conversion to the dihydroanthranil. The same intermediate was also invoked to explain the cyclization of *o*-nitrophenylacetic acids. Irradiation of 5,5′-dimethyl-2,2′-dinitrodiphenylmethanes in propan-2-ol gave small quantities (3–5%) of the benzisoxazoles **26**, whereas in acidic ethanol these were obtained as major products (36–51% yields).[2/82]

The benzisoxazoles cited above were obtained along with diazepinone oxides, acridones, and diazepinone dioxides. These have also been shown to be photoproducts of the irradiation of benzisoxazoles. Thus irradiation of 3-(2′-nitrophenyl)-2,1-benzisoxazoles in acidified ethanol[2/83] using a high-pressure mercury quartz lamp (125 W) for 20 h afforded dibenzo[*c*, *f*][1,2]diazepin-11-one-5-oxide (32%), acridone (18%), and traces of dibenzo[*c*, *f*][1,2]-diazepin-11-one-5,6-dioxide (1%). 5,3′-Dimethyl-2-2′-dinitrodiphenylmethane on photoreaction in acidified ethanol gave benzisoxazoles **27**.[3/83]



Small amounts of 3-(2′-nitrophenyl)-2,1-benzisoxazoles were also obtained in the photolysis of 2,2′-dinitrodiphenylcarbinols along with a number of other photoproducts.[3/84]

To investigate whether the absence of a nitro group on the 3-phenyl substituent would help in improving the yield of the benzisoxazoles, photolysis of 2-nitrodiphenylmethane in isopropanol and acidified aqueous ethanol was studied.[4/84] However, the major products were the benzoic acids; the benzisoxazoles were obtained in only 14–23% yield.

2,1-Benzisoxazoles have also been prepared from 4,4′-difluoro/diiodoacridones and 2,2′-dinitrodiphenylmethanes.[3/90] More recently, 2,1-benzisoxazoles have been prepared from acetyl and benzoyl esters of 2,2′-dinitrodiphenylcarbinols in neutral and basic media.[2/91,3/91]

Nitrodiphenylmethane anions of α-(2-nitrophenyl)deoxybenzoin on reaction with sodium methoxide and methanol underwent disproportionation and intramolecular cyclization to give 3-phenyl-2,1-benzisoxazoles.[10/81]

3-Substituted-4,6-dinitroanthranils **29** are obtained by CuBr–CCl_4 oxidation of anionic σ complexes of 1,3,5-trinitrobenzene (**28**).[4/90] On the other hand, dinitrotrifluoromethylbenzene complexes gave alkylation products. (Table 2.7).

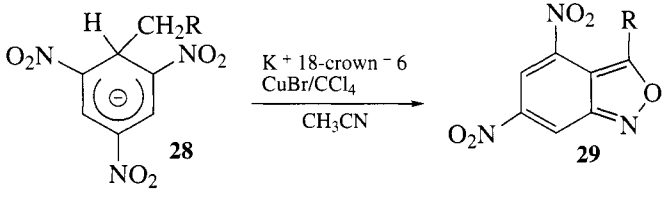
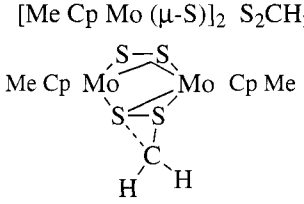


TABLE 2.7 3-SUBTITUTED-4,6-DINITROANTHRANILS

	R	Yield (%)	m.p. (°C)
a	COMe	62	143–144
b	COEt	70	120–121
c	COPh	65	163–164
d	CO(cyclopropyl)	54	110–112
e	COOEt	63	73
f	Ph	30	158–159

The parent 2,1-benzisoxazole was prepared by reduction of *o*-nitrobenzaldehyde with hydrogen using soluble molybdenum(IV) dimers with sulfido ligands **30**.[1/86]

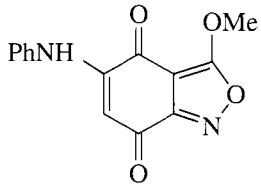


30

2.3.2.2. *From o-Amino Carbonyl Compounds*

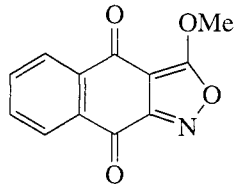
o-Aminobenzophenones are often prepared by reduction of 2,1-benzisoxazoles themselves. However, Caro's acid-based oxidation of *o*-aminoketones gave the corresponding nitroketones, where the 2,1-benzisoxazoles have been implicated as intermediates and occasionally even isolated. Thus 3-methoxy- and 3-diethylamino-2,1-benzisoxazole-7-carboxylic acids were also prepared.[1/75]

Phenyl iodosoacetate [PhI(OCOMe)$_2$] was used to prepare 2,1-benzisoxazole, and 3-methyl and 3-phenyl-2,1-benzisoxazoles.[3/73] With *o*-aminobenzophenone, lead tetracetate oxidation gave only the azo compound. However, isoxazole formation was observed in the quinone series to give **31**.[2/74]



31

Lead tetraacetate oxidation of 3-amino-2-methoxycarbonyl-1,4-naphthoquinone gave the naphtho-[2,3-*c*]isoxazole-4,7-dione (**32**) in excellent yields.[4/85]

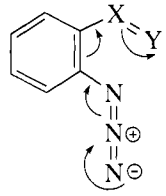


32

2.3.2.3. *From o-Azido Carbonyl Compounds*

2,1-Benzisoxazoles were synthesized[2/53] by the thermal or photochemical cyclization of aryl *ortho*-azidocarbonyl compounds as early as 1953.

It is assumed that the carbonyl group provides neighboring–group assistance and a "bridged" rather than a "free" nitrene is involved in the reaction. Most assisted thermal cyclizations require relatively much lower temperatures and are often successfully carried out between 50 and 120°C. One of the liveliest debates in recent years has centred around the exact mechanism of this reaction. In addition to the carbonyl group, neighboring group assistance is provided by other *ortho* substituents, notably azo and nitro groups, which, at 393 K in decalin, react 21, 180 and 738 times, respectively, faster than the parent phenyl azide. On the other hand, substrates with *o*-acetyl or benzoyl groups react only 287 and 70 times faster, respectively. The activation energy in the case of the acetyl substituent is a fairly low value of 26.1 ± 1.1 kcal/mol. A cyclic transition state was suggested for this reaction and a representation of it was depicted.[6/60] An electrocyclic mechanism (**33**) was suggested for this cyclization, which was later generalized.[2/68]



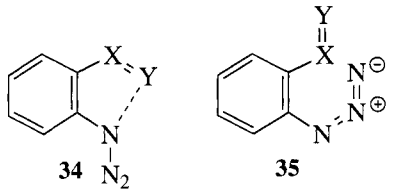
33

This concerted electrocyclic mechanism requires coplanarity of the reacting groups, and substituents that reduce this coplanarity are expected to diminish the rate of reaction. Thus, whereas 2-acetylazidobenzene reacts 287 times faster than phenylazide, the corresponding 3-methyl and 6-methyl derivatives reacted a mere 5.1 and 10.5 times faster.

On the basis of studies on substituted *o*-azidobenzophenones, the universal applicability of the electrocyclic mechanism has been questioned and an alternative 1,3-dipolar cycloaddition pathway suggested.[2/72] Many aromatic and heteroaromatic azides are known to form stable 1,3-dipolar cycloadducts retaining all three of the azido nitrogens. It has been suggested that the loss of nitrogen might occur in a fast step subsequent to the initial slow adduct formation and that a spectrum of possible mechanisms could exist. The electrocyclic mechanism was accepted only for the *ortho*-nitro substituents, as the kinetic data for the acetyl substituent had not been published at that time. All workers agree that a "free" singlet nitrene is involved only in the formation of carbazole.

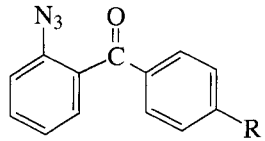
A main point of the debate is at what stage the nitrogen molecule departs. Does the bond between the carbonyl oxygen atom and the inner nitrogen atom of

the azide group first form **34**, or does attack of the terminal nitrogen atom on the carbonyl carbon atom of **35** occur first?



34 **35**

The electron-donating group *para* to the carbonyl group in *o*-azidobenzophenones **36** were observed to increase the rate of reaction as shown below:



36

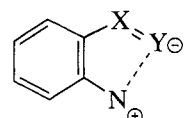
R	=	OMe	Me	H	Br	NO_2
Relative rate	=	0.62	0.92	1	1.01	1.60

The discussion in this chapter is restricted to the *ortho* carbonyl substituental, though kinetic data on many other substituents are also available. It was assumed that the 4′-substituent in 4′-substituted *o*-azidobenzophenones do not have any effect on the phenyl ring carrying the azido group.[2/72] This assumption itself has been questioned, as also the rather small rate enhancements observed.

During studies on the cyclization of *o*-azidostilbenes, which reacted 31.5 times faster than phenylazide, a new mechanism was advanced based on the assumption that charge separation in the transition state of the reaction is much more important than in the parent azide itself. Unlike the other mechanisms, this one alone explains the observed rates of enhancement provided by the various *ortho* substituents, specifically.

$$N{=}N \;>\; NO_2 \;>\; COR \;>\; RN{=}C(R)$$

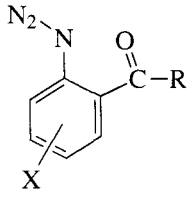
The more the transition state resembles the charge-separated structure **37**, the faster the reaction proceeds. The rate enhancement is provided by electrostatic attraction between the positive charge on the nitrogen atom and the negative



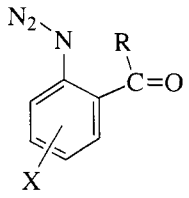
37

charge on the oxygen atom. This mechanism does not rely on the delocalization energy of the heterocycle (isoxazole ring, in the present case), which had been suggested earlier as the driving force of the reaction. More recently the original suggestion regarding the delocalization energy concept has itself been withdrawn.

While advancing arguments against the 1,3-dipolar cycloaddition pathway, two dramatic cases have been mentioned. Cyclization of 1-azidoanthraquinone to anthra[1,9-*cd*]isoxazole-6-one has been observed to occur 7385 times faster than the reaction of phenylazide. No such rate enhancement is anticipated on the basis of the cycloaddition pathway. *o*-Pivaloylphenyl azide similarly reacts 61.7 times faster than phenylazide. In this case as well, no such rate acceleration can be foreseen via the cycloaddition pathway. More recently Hammett correlations of the cyclization reaction of five substituted *ortho*-azidobenzophenones have been studied.[3/88] These show only a single infrared carbonyl band, suggesting the presence of the required conformation **36a** rather than conformation **36b**.



36a



36b

Rates of pyrolysis of 1-azidoanthracene-9(10*H*)-one, 1-azido-9*H*-fluoren-9-one, and 1-azidoanthracene-9,10-dione in nitrobenzene relative to azidobenzene were studied recently.[2/92] No isoxazole formation was observed in the case of the azidofluorenone, and the lack of neighboring-group participation was attributed to the large distance between the carbonyl oxygen and the inner azido nitrogen atom.

It is stated that the data argue against the proposal that the transition state is stabilized by electrostatic attraction. Much larger neighboring-group assistance is observed in the other azides due to the "locked conformation" **36a**, than in freely rotating groups such as the benzoyl. The results were interpreted in terms of an electrocyclic mechanism in which the transition state is "early" and N···O bond formation is less advanced than the other changes in bonds.

The authors state that interpretations of this type are essential to an understanding of this special kind of neighboring-group effect, which, they claim, is not well understood at all. A group such as acetyl would be at a disadvantage compared to a symmetrical nitro group insofar as conformational equilibrium of this type is concerned. They thus emphasized the importance of the "locked conformation" in the enhanced neighboring-group effects observed.

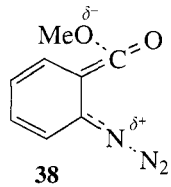
It has been shown that the first-order rate constants for pyrolysis of azidobenzenes in decalin solution are lower than previously reported ones, and that the published data on neighboring-group effects require revision. The new values of

rate enhancements produced by various *ortho* substituents suggested are phenylazo, 30160; nitro, 1060; acetyl, 413; and formyl, 28.8. The authors found that addition of the free-radical inhibitor [2,6-di-*t*-butyl-4-methylphenol (dbmp)] yielded reproducible rates even with compounds that otherwise did not. This inhibitor was added to the hot solvent just prior to the addition of the azide. Interestingly, lower relative rate constants and activation energy values were obtained for methyl-2-azidobenzoate, which gives no cyclic product. These azides do exhibit some small stabilizing effect on the pyrolysis transition state, but its nature remains uncertain despite much speculation.

Substituents studied included the 5-chloro, 5-ethoxycarbonyl, 5-fluoro, 4-methyl, 5-methyl, and 5-nitro groups. The authors concluded that electron-attracting groups acting on the azide group assist the reaction, whereas electron-donating groups retard the rate of the reaction. No correlation was found when the azido group and the carbonyl groups were considered in isolation. It has been proposed that a similar cancellation of the effects of the substituents must have led to the rather small differences in rates observed in the study on *o*-azidobenzophenones, implying that the assumption that the 4′ substituent has no effect on the azide-bearing benzene ring is really untenable.[3/88]

The two electrocylic mechanisms differ in that the inner nitrogen atom in the first case is either neutral or negatively charged, while in the second case it carries a positive charge.[2/68,5/85] The loss of nitrogen in the first case occurs "earlier" than in the second case. 5-Nitro and 5-ethoxycarbonyl-substituted *ortho*-azidobenzophenones were observed to bring about a marked rate acceleration. Recent data support the electrocyclic mechanism but do not rule out the charge separation mechanism altogether, as the *para*-ethoxycarbonyl or the nitro group could increase the positive charge on the nitrogen atom in the transition state, which could then explain the rate enhancement.

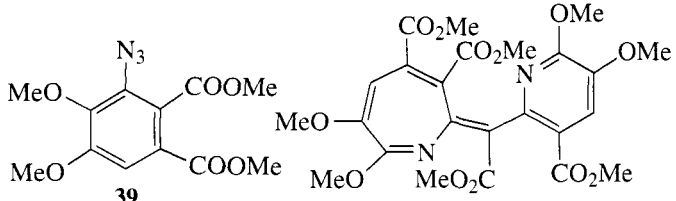
Attempts have been made to explain the rather exceptional lack of assistance observed for *o*-methoxycarbonyl and other ester substituents that have been compared to the linear nitrile group in which no rate enhancement is observed.[2/78] Accordingly, the methoxyl group separates somewhat from the carbonyl group in the transition state, providing a ketene-like structure **38** which resembles the linear nitrile group.



38

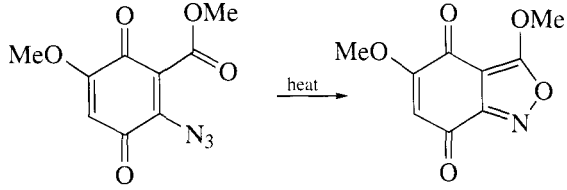
In the author's own laboratory, thermolysis of azido-*m*-hemipinate **39** did not lead to any detectable isoxazole ring formation. Instead, a most remarkable ring

expansion to an azaheptafulvalene and a concomitant ring extrusion reaction led to the synthesis of a new methyl azaheptafulvalenepyridyl acetate (**40**).[1/93]



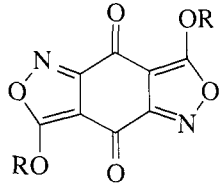
39 **40**

In this context, quite surprisingly in the quinone series the isoxazole ring formation of **42** from azido carboxylates such as **41** occurs very readily. [2/67] This has been exploited to prepare new isoxazolequinones in excellent yields.[2/89]



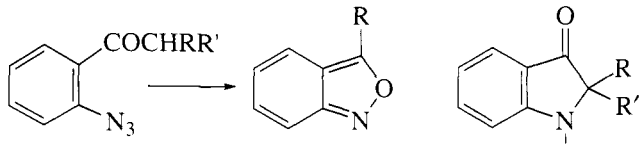
41 **42**

The diisoxazole quinone **43** has been prepared similarly.[3/78,8/80]



43 R = Me or Et

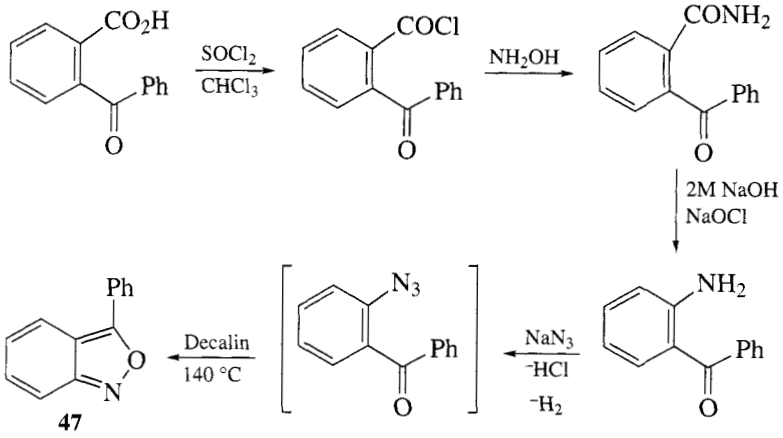
2,1-Benzisoxazoles **45** were obtained along with 1,2-dihydro-3*H*-indol-3-ones **46** upon thermolysis or spray vacuum pyrolysis of *o*-azidophenylalkyl ketones **44**.[2/86]



44 **45** **46**

Triplet quenching studies on 4-nitro-substituted *o*-azidobenzamide, a possible photoaffinity labeling agent, showed that the yield of anthranil increased from 21% to 38% in the presence of 0.2*M* isoprene and that a singlet nitrene was involved.[2/79]

A student preparation of 3-phenylanthranil **47** has been described starting from dry *o*-benzoylbenzoic acid and reacting it with thionyl chloride in chloroform in a water bath (Scheme 2.9).[3/72] Hydrogen chloride was removed, benzene added and distilled off in vacuum. The acid chloride thus obtained was taken up in dry benzene, concentrated ammonium hydroxide added, and the product washed with hot water. A Hoffmann bromoamide rearrangement was then carried out by heating with 2*M* NaOH–NaOCl for half an hour in a water bath. The amine thus obtained was diazotized and converted into the azide using sodium azide. The azide was not crystallized but thermolyzed in decalin at 140°C (25 min), followed by a petroleum ether wash and an ethanol crystallization to give 3-phenylanthranil, m.p. 53–54°C.



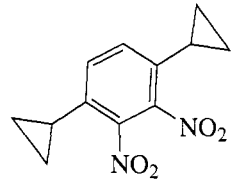
Scheme 2.9

2.3.2.4. *From o-Nitro/o-Nitrosophenylcyclopropanes*

Nitrosoacylbenzenes constitute useful starting materials for the preparation of 2,1-benzisoxazoles. However, they were relatively inaccessible before they were prepared from cyclopropylnitrobenzenes. Thus cyclization of the appropriate *o*-nitrosopropiophenone with dry HCl in an inert solvent led to anthranils.[4/73]

The *o*-nitroso compounds underwent deoxygenation more easily than did the corresponding *o*-nitro compounds. This provides a simple route to 3-ethylanthranils, as these *o*-nitroso compounds are easily available from the corresponding *o*-nitrophenylcyclopropanes.

Dicyclopropyldinitrobenzene (**48**) reacted with H_2SO_4 at 30–35°C, leading to the formation of only one anthranil ring.[2/75] However, in the case of nitrodicyclopropylbenzene (**49**), H_2SO_4 attacked the cyclopropyl ring adjacent to the nitro group. Mercuric acetate, on the other hand, brought about ring opening of the cyclopropyl ring further removed from the nitro group to give the mercury adduct, which reacted with bromine in chloroform. Treatment with sulfuric acid (–20°C) gave the corresponding *o*-nitroso propiophenone **50**, which, in turn, could be reduced to the 6-substituted 3-ethylanthranil **51**, using sodium bisulfite (Scheme 2.10).



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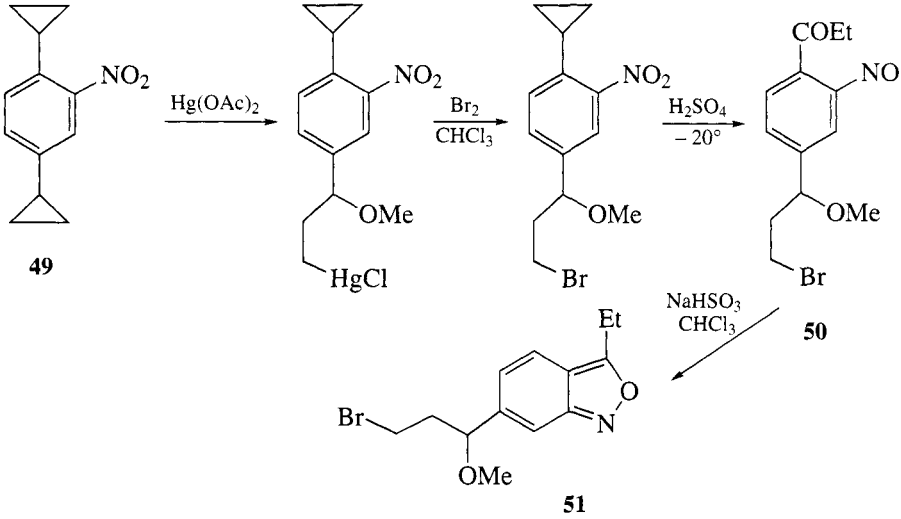


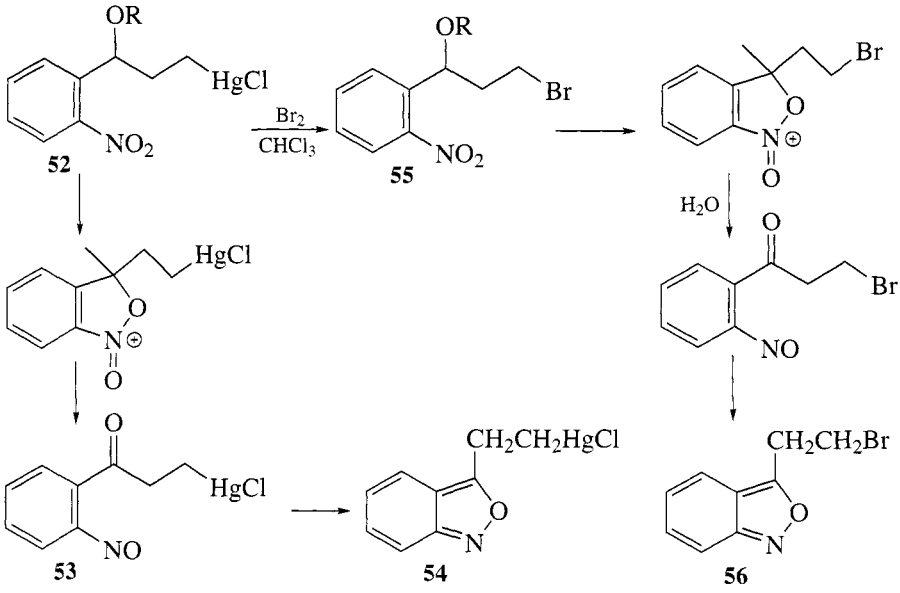
49 **50** **51**

Scheme 2.10

The reaction of phenylhydrazine in toluene in the ratio 1:1 gave up to 95% of the anthranil and traces of the azoxy compound.[3/79] The latter became the major product when phenylhydrazine was used in excess.

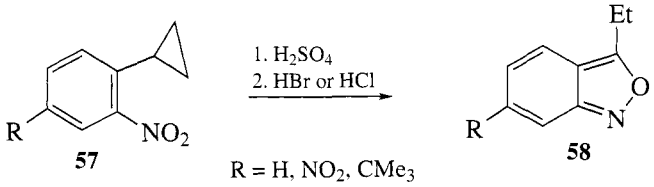
Cyclization of *o*-nitrosopropiophenones to anthranils in HBr–benzene or HCl–methanol was studied later.[3/76] The reactions were complex and the yields low. The products identified included 5-bromo-, 5-chloro-, and 5-methoxy-3-ethyl-2,1-benzisoxazoles. In addition, the corresponding *o*-nitro-, and *o*-amino-propiophenones and the azoxy compound were also identified.

Reaction of the mercury adducts **52** of arylcyclopropanes with concentrated sulfuric acid (Scheme 2.11) gave 84–85% yields of the mercurated (nitrosobenzyl)propanone **53**, which, on treatment with sodium bisulfite, gave the benzisoxazole **54** in 60% yield. On the other hand, bromine in chloroform gave **55**, which, on treatment with H_2SO_4 followed by $NaHSO_3$ reduction, gave the isoxazole **56**.[3/89]



Scheme 2.11

Benzisoxazoles **58** were obtained in 56% yields by reaction of the benzisoxazolium sulfates derived from nitrophenylcyclopropanes **57**.[5/90] The corresponding 5-bromo compound was obtained in 4% yield in this reaction.



Treatment of nitrophenylcyclopropane with H_2SO_4 followed by HCl gave the 5-chloro compound in 64% yield. Similarly, the dinitro analog gave 5-chloro-6-nitro and 4-chloro-6-nitro-3-ethyl-2,1-benzisoxazole in 32% yield and chloro-6-nitro and 4-chloro-6-nitro-3-ethyl-2,1-benzisoxazole in 32% and 17% yields, respectively.

2.3.3. From Nitrotoluenes

2.3.3.1. 2,1-Benzisoxazoles as Intermediates in the Conversion of o-Nitrotoluenes into Anthranilic Acid

The conversion of *o*-nitrotoluene into anthranilic acid, in 10.4% yield, using potassium hydroxide-water-2-methoxyethanol (9 h; 100°C, in dark) has classical relevance.[1/07] Anthranil has been regarded as an intermediate in this conversion. Although the yield is low, the mechanism of this reaction warrants further elucidation. ^{18}O-enriched water was used to show that one oxygen comes from the solvent.[5/73] Simultaneous oxidation of a methyl group (to a carboxylic acid) and the reduction of a nitro group to an amino group take place in this reaction without the formal involvement of either an oxidizing or a reducing agent. 2,1-Benzisoxazole has been postulated as an intermediate in the gas-phase version of this reaction.

2.3.3.2. 2,1-Benzisoxazoles as Intermediates in the Decomposition of TNT

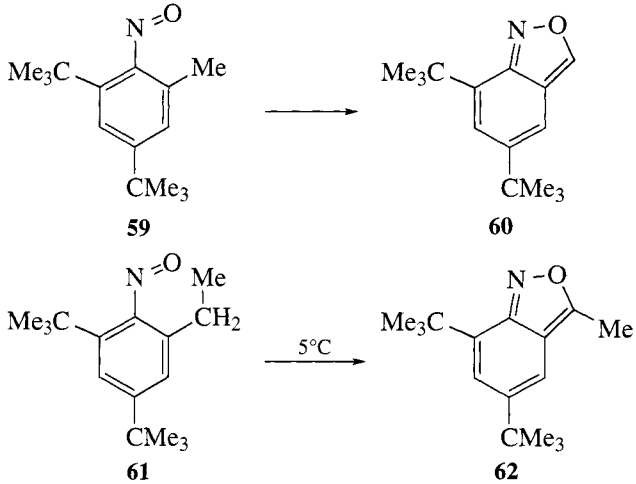
4,6-Dinitroanthranil is one of seven sharply melting products of the photo or thermal (controlled) degradation of TNT,[3/86] where 25 discrete species were identified along with large amounts of a telomeric or polymeric material of indefinite composition ("explosive cake"). It has been stated[4/88,2/93] that the initial process in the decomposition of TNT may involve benzisoxazole formation, which could have a catalytic effect on the decomposition, particularly at lower temperatures. At higher temperatures $C-NO_2$ cleavage becomes significant.

In the gas phase, anthranil formation from *o*-nitrotoluene has the fastest rate up to 950°C. At this temperature the $C-NO_2$ cleavage predominates. Thus $C-NO_2$ homolysis is favored in the gas phase when the temperature is high. The cyclization decomposition channels dominate at lower temperatures. However, in the condensed phase reactions can be strongly affected by near-neighbor interactions; for example, $C-NO_2$ homolysis could be assisted by hydrogen atom transfer to produce HONO rather than NO_2 and a concerted process involving both C–H and $C-NO_2$ homolysis might determine the rate constant. Arrhenius factors for condensation of *o*-nitrotoluene to 2,1-benzisoxazoles, determined on the basis of shock tube data (E_a = 42.5, 49.5 ± 1.3, and 51.520 kcal/mol at 300–350, 400–450, and 797–907°C, respectively), are smaller than those for $C-NO_2$ homolysis. The relatively low A factor suggests that a tight transition state exists, which is expected of a cyclic activated complex collapsing to a closed ring. $\Delta S^{\#}$ is −15 cal/deg for *o*-nitrotoluene compared to 20 and 14.5 cal/deg for 3-nitrotoluene and 4-nitrotoluene. The latter decompose by $C-NO_2$ cleavage, which produces a positive $\Delta S^{\#}$. Thermal conversion of 2-nitrotoluene to 2,1-benzisoxazoles is also supported by relative energies determined by ab

initio SCF-MO (self-consistent field-molecular orbital) methods. Anthranil formation is an exothermic process, whereas endothermic reactions predominate at higher temperatures.

2.3.4. Miscellaneous Methods

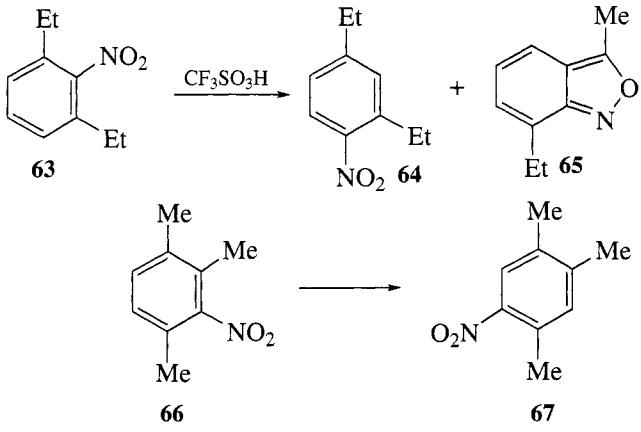
1. Unlike the corresponding *o*-nitrotoluene, 3,5-di-*tert*-butyl-2-nitrosotoluene (**59**) in boiling benzene gives 50% yield of 5,7-di-*tert*-butylanthranil (**60**) along with the corresponding amine.[4/78,12/82] Evidently, as steric hindrance increases, cyclization becomes easier and the nitroso compound **61**, prepared from the corresponding amine by *m*-chloroperbenzoic acid oxidation in methylenedichloride, undergoes cyclization to the benzisoxazole **62** even at 5°C in 59% yield.



59 **60**

61 **62**

2. A 1,3 shift of the nitro group of 1,3-diethyl-2-nitrobenzene (**63**) in trifluoromethanesulfonic acid gives rise to the 4-nitro compound **64**, along with 7-

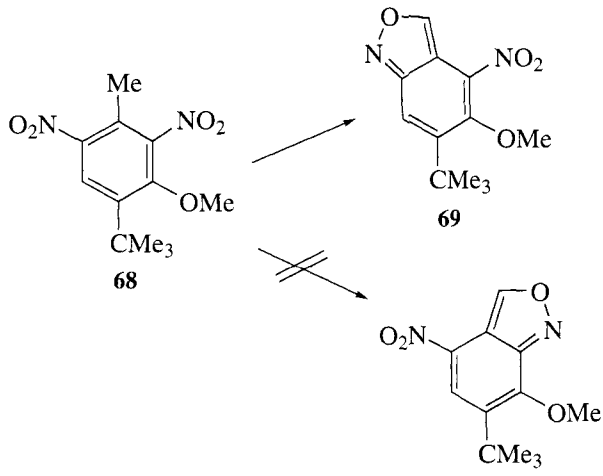


63 **64** **65**

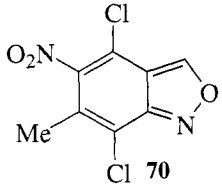
66 **67**

ethyl-3-methylanthranil (**65**). Similarly, 1,2,4-trimethyl-3-nitrobenzene (**66**) gives the 5-nitro isomer (**67**).[6/90,7/90] It appears that if the rearrangement involves a 1,3 shift, the nitro group should be between two alkyl groups.[7/90] On the other hand, cyclization to an anthranil is significant only when one of the alkyl substituents is an ethyl group.

3. 6-*Tert*-butyl-5-methoxy-4-nitroanthranil (**69**) was isolated during photolysis of 4-*tert*-butyl-3-methoxy-2,6-dinitrotoluene (**68**) ("musk ambrette") in methanolic alkali.[4/79] Reaction occurs with the less hindered C6 nitro group, which is presumably closer to coplanarity with the ring.



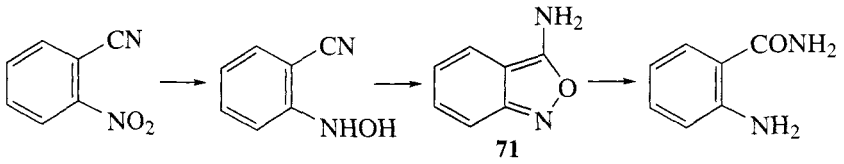
4. 2,5-Dichloro-3,6-dimethyl-1,4-dinitrobenzene on warming with fuming sulfuric acid (60%) gave 4,7-dichloro-6-methyl-5-nitroanthranil (**70**) in moderate yields.[4/72]



70

5. During studies on the herbicidal properties of Alachlor, its rat metabolite, 2,6-diethylnitrosobenzene, was shown to be a mutagen in the Ames *Salmonella* test. Thermal decomposition of this nitrosobenzene (i.e. 2,6-diethylnitrosobenzene) gave 3-methyl-7-ethylanthranil along with (2,6-diethylphenyl)hydroxylamine.[9/87]
6. Rearrangement of 2,2′-dipropionylazoxybenzenes led to 3-[1-alkoxy-1-(2-propionylamino)]benzo[*c*]isoxazoles in yields of 80–96% .[4/83]

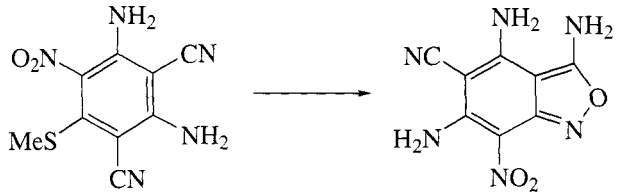
7. 3-Amino-2,1-benzisoxazole (**71**) was obtained (Scheme 2.12) in the catalytic reduction of *o*-nitrobenzonitrile to *o*-aminobenzamide.[1/65]



71

Scheme 2.12

8. 3,4,6-Triamino-7-nitro-2,1-benzisoxazole-5-carbonitrile (**73**) was prepared in 65% yield by reaction of hydroxylamine with 2,4-diamino-6-methylthio-5-nitroisophthalonitrile (**72**), the product of K_2CO_3-catalyzed condensation of 1,1-bis(methylthio)-2-nitroethene and malonitrile dimer.[6/85]



72 **73**

9. 3-Amino-2,1-benzisoxazoles were also synthesized from *o*-halobenzonitriles (Table 2.8) by treatment with NH_2OH and NaOMe.[6/84]

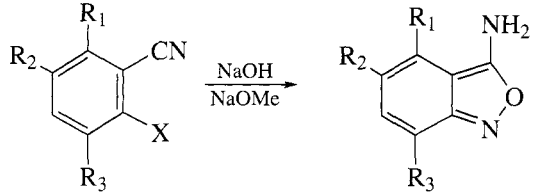
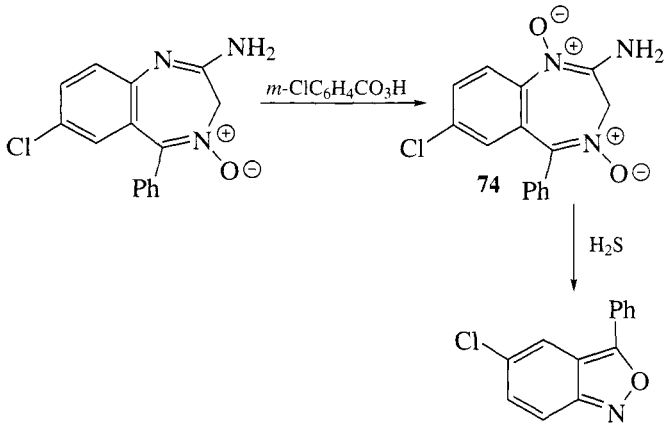


TABLE 2.8. SUBSTITUTED 3-AMINO-2,1-BENZISOXAXOLES FROM *o*-HALOBENZONITRILES

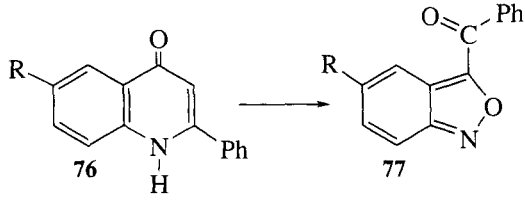
	R_1	R_2	R_3
a	H	NO_2	H
b	H	CN	H
c	H	H	CN
d	H	NO_2	NO_2
e	H	CN	NO_2
f	Cl	H	H

10. 5-Chloro-3-phenyl-2,1-benzisoxazole (**75**) was prepared, in 49% yield, by the reduction, with H_2S, of the 1,4-benzodiazepine-1,4-dioxide **74**, which had been obtained by *m*-chloroperbenzoic acid oxidation of 7-chloro-2-amino-5-phenyl-3*H*-1,4-benzodiazepine-4-oxide.[3/77]

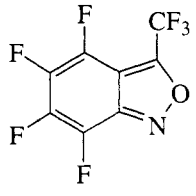


75

11. A novel, mild, and essentially one-pot synthesis of 3-benzoyl-2,1-benzisoxazole and its 5-methyl derivative relies on rearrangement of 2-phenylquinoline-4(1*H*)-ones **76** to give the corresponding 3-benzoyl-2,1-benzisoxazoles.[4/91] Treatment with methanolic aqueous sodium hydroxide and an excess of sodium dichloroisocyanurate followed by acidification gave 3-benzoyl-2,1-benzisoxazoles **77** in yields of 30%. On the basis of X-ray crystallographic data, the authors also determined the structure of 3-benzoyl-5-methyl- 2,1-benzisoxazole, to which an incorrect structure had been previously assigned.



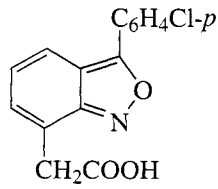
12. Perfluoro-3-methyl-2,1-benzisoxazole (**78**), along with other products, has been prepared, in 14% yield, by reaction of pentafluoronitrobenzene with 2*H*-pentafluoropropene and cesium chloride.[5/91]



78

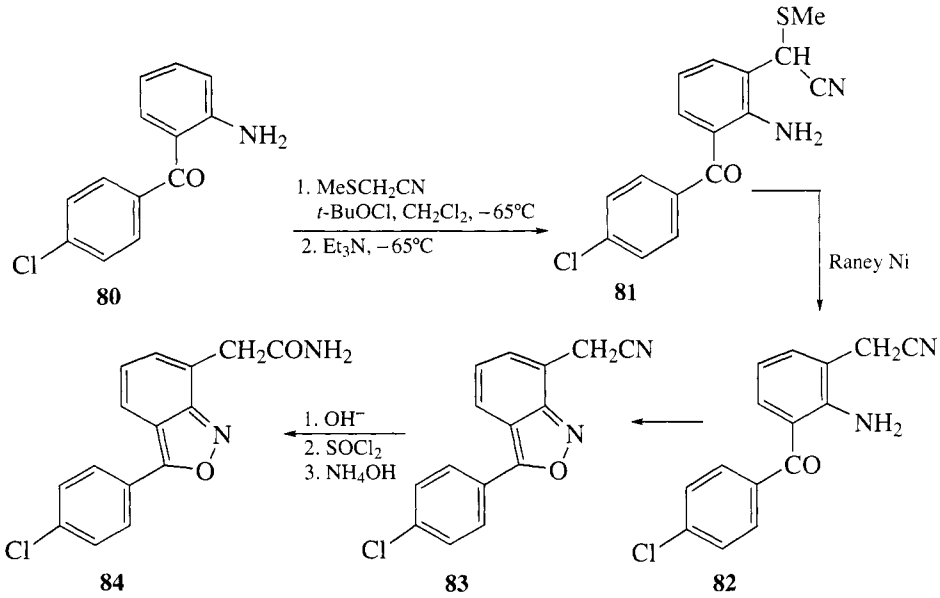
A mechanism for the formation of the benzisoxazole ring in this reaction has been proposed. Accordingly, the anion is formed first and it is highly unlikely that a nitro group migrates intramolecularly. Involvement of a nitro group from another molecule is invoked to explain how the original nitro group is displaced by a fluoride ion.

13. An antiinflammatory 3-aryl-2,1-benzisoxazoles, namely, 3-(4-chlorophenyl)-2,1-benzisoxazole-7-acetic acid (**79**), were shown to be as effective as indomethacin against *Mycobacterium butyricum*–induced arthritis in rats.[1/88]



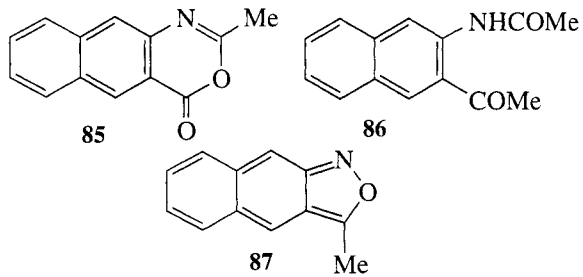
79

During further screening and evaluation of potential nonsteroidal antiinflammatory drugs with minimal or no gastrointestinal irritation, pro-drugs were tested,[8/90] which could be metabolically converted into 'amnefac' (sodium salt of 2-amino-3-benzoylbenzene acetate), a clinically employed drug. 7-Methyl-3-phenyl-2,1-benzisoxazole and 3-(4-chlorophenyl)-7-methyl-2,1-benzisoxazole were thus synthesized by peroxyacetic acid oxidation of the corresponding 2-aminobenzophenones. More drastic conditions gave the nitro derivatives. Bromination of the methyl substituents with *N*-bromosuccinimide, followed by displacement with cyanide anion and basic hydrolysis, gave 2,1-benzisoxazole-acetic acids.[8/90] 3-(4-Chlorophenyl)-2,1-benzisoxazole-5-acetamide was prepared from the reaction of 4′,5-dichloro-2-nitrobenzophenone with diethyl sodiomalonate followed by hydrolysis and decarboxylation of the product to give 3-(4-chlorobenzoyl)-4-nitrobenzene acetic acid.[8/90] Treatment of the corresponding acid chloride with hydroxylamine followed by Sn–HCl reduction gave the benzisoxazole-5-acetamide.[8/90] A synthetic route to 3-(4-chlorophenyl)-2,1-benzisoxazole-7-acetonitrile is depicted in Scheme 2.13. 4′-Chloro-2-aminobenzophenone (**80**) was converted into 2-amino-3-(4-chlorobenzoyl)-α-(methylthio)-benzene acetonitrile (**81**) by treatment with methyl- thioacetonitrile and *tert*-butoxychloride in dichloromethane at −70°C followed by reaction with triethylamine. Desulfurization with Raney nickel gave the corresponding benzene acetonitrile **82**, which was cyclized to the 3-(4-chlorophenyl)-2,1-benzisoxazole-7-acetonitrile (**83**) using sodium perborate in acetic acid. The acetonitrile was then converted into the acetic acid and via the acid chloride into the amide **84**. Although it was 2-amino-3-(4-chlorobenzoyl) benzene acetamide, which possessed a therapeutic index one order of magnitude greater than indomethacin, many 2,1-benzisoxazoles were prepared.[1/88,8/90]



Scheme 2.13

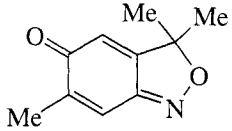
14. On treatment with methylmagnesium iodide, naphthoxazine **85** was converted to acetonaphthalene **86**. Hydrolysis of **86** gave the amine (89%), which was diazotized, treated with NaN_3 and the resulting azide thermolyzed in refluxing octane to give the linear benzannulated anthranil, naphthisoxazole **87**.[4/77]



15. Formyl-1,4-benzoquinone, on treatment with hydrazoic acid, gave an adduct that was converted into 2,1-benzisoxazole-4,7-quinone by the action of MnO_2.[4/87] Using stannous chloride dihydrate in THF–MeOH solution at room temperature, 4,7-dimethoxy-2,1-benzisoxazole was prepared from 2,5-dimethoxy-6-nitrobenzaldehyde in 32% yield. Under similar conditions, the 3-methyl derivative was prepared from the corresponding nitroacetophenone in 65% yield.[5/89]

2.3.5. Synthesis of Reduced 2,1-Benzisoxazoles

1,3-Dihydro-2,1-benzisoxazoles **89** have been obtained during the reduction of *o*-nitrobenzophenone and from the reduction of quinonoid compounds **88**.[1/63]



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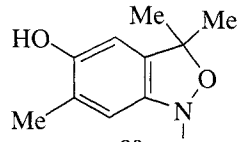
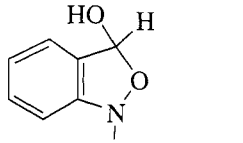


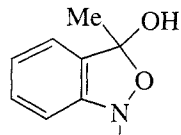
89

Acid-catalyzed rearrangement of *o*-nitrobenzylalcohol to *o*-nitrosobenzaldehyde involves Bamberger's "Argentobenzaldehyde" (2,1-benzisoxazolin-3-ol) **90**.[5/78]

2,1-Benzisoxazolin-3-ol **91** at 130°C is known to give *N,N'*-dimethylindigo.[6/78]



90 C_6H_4-NO_2-*o*

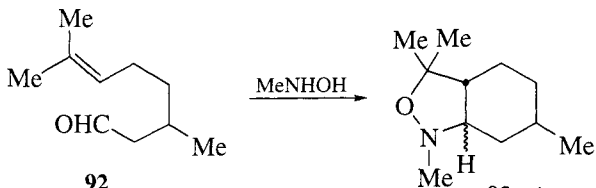


91

2-Acylcyclohexanones give a mixture of tetrahydro-1,2- and 2,1-benzisoxazoles. Although the 1,2-isomer predominates, it may be removed by capitalizing on the relative ease of its decomposition in alkali.[3/64]

2-Cyanocyclohexanones form 3-amino-4,5,6,7-tetrahydro-2,1-benzisoxazoles, which could also be prepared from 2-chlorocyclohexanone by reaction with KCN. 3-Unsubstituted-4,5,6,7-tetrahydro-2,1-benzisoxazoles are cleaved by alkali to give pimelates.[1/25]

The stereochemistry of hexahydro-2,1-benzisoxazoline formation by intramolecular nitrone–olefin cycloadditions has been studied.[2/71] The major products were shown to be 7-aza-8-oxa-bicyclo[4.3.0]nonane(3a,4,5,6,7,7a-hexahydro-2,1-benzisoxazoline, hydrindan). Condensation of (+)-citronellal (**92**) with *N*-methylhydroxylamine gave isomers **93** and **94** in ratios ranging



92

93, *cis*
94, *trans*

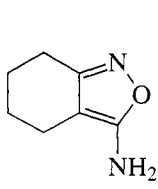
from 97:3 at 25°C to 87:13 at 138°C and in which the *trans*-fused isomer predominated. Interconversion of the isoxazolidines occurred in the temperature range 180–300°C when the thermodynamically more stable *cis*-fused isomer predominated. The preparation of 1,3,3a,4,5,6,7,7a-octahydro-1,3,3,6-tetramethyl-2,1-benzisoxazole has been discussed.[8/78]

A two-step synthesis of 5-aminoisoxazoles has been developed on the basis of reaction of the nitrosyl chloride adducts of various olefins with cyanide ion in acetonitrile. A high yield of 3,4-cyclohexeno-5-aminoisoxazoles (**95**) has been obtained on treatment of dimeric 1-nitroso-2-chlorocyclohexane with inorganic cyanide in refluxing acetonitrile. The reaction is catalyzed by triethylamine, and a mechanism has been suggested.[4/69]

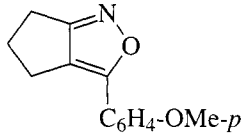
4,5,6,7-Tetrahydro-2,1-benzisoxazoles have been discussed in a seminal paper.[8/78] The regiospecific synthesis of isoxazoles and yields of earlier processes have been considerably improved. Cyclohexanone oxime was treated in succession with (1) *n*-BuLi (2 equivalents.) at 0°C, (2) ethyl formate, and (3) hydrochloric acid–dioxane at reflux, to afford 3,4-tetramethyleneisoxazole in 22% yield. These initial results were encouraging. Use of the corresponding dimethylamide [$HCON(Me)_2$ or $ArCONMe_2$] resulted in an 87% conversion following cyclization in a solution of sulfuric acid in aqueous THF.

Treatment of the dilithio derivative of cyclohexanone oxime with *N,N*-dimethylbenzamide afforded the 3-phenyl-2,1-benzisoxazole in 67% yield when 2 equiv of amide were added and in 64% yield, when 1 equiv of the amide was used, compared to yields of 31% and 15% when methyl benzoate (1 and 2 equiv, respectively) was employed. *N,N*-dimethyl-*p*-anisamide and cyclopentanone oxime gave the highly strained isoxazole **96** in 67% yield, a marked improvement over an earlier report of 15% yield.[6/76]

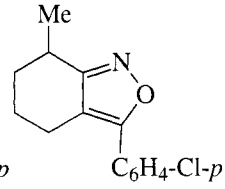
(*E*)-2-Methylcyclohexanone oxime and *N,N*-dimethyl-*p*-chlorobenzamide gave the isoxazole **97** in 64% yield after recrystallization.[8/78]



95

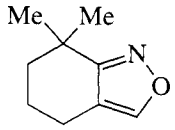


96

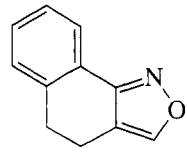


97

Similarly, 2,2-dimethylcyclohexanone oxime and α-tetralone–oxime gave the corresponding isoxazoles **98** and **99** in yields of 85% and 87%, respectively.[7/78]



98

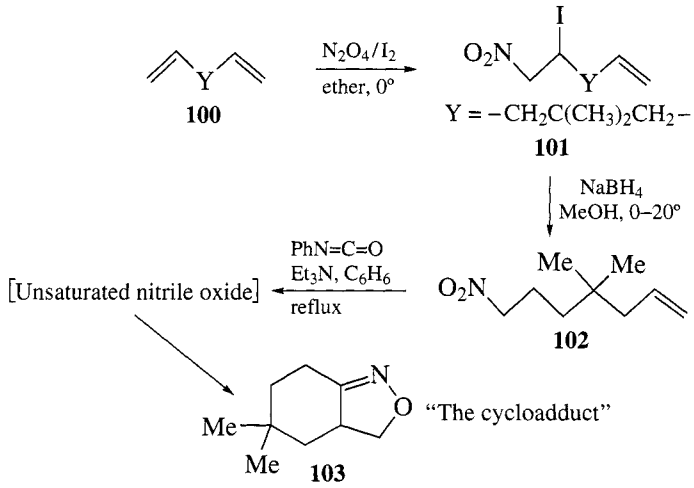


99

When 2,2-dimethylcyclohexanone oxime was used as a substrate and 1.5*M* H_2SO_4 was used for cyclization (instead of 3*M* H_2SO_4), the yield of **98** was reduced to 35% and the product was accompanied by a mixture of two 5-hydroxyisoxazoline diastereomers in a 1:1 ratio (35%).[7/78] Both could be dehydrated to the isoxazoles with trifluoroacetic acid. The authors stated that "the most difficult step in the cyclization process must be the final dehydration to the heteroaromatic system, a somewhat unexpected and surprising result."

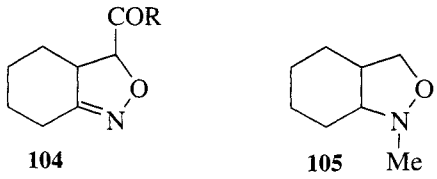
Bistetrahydroanthranil were prepared in 59% yield using diethyl oxalate and the dianion from cyclohexanone oxime.[3/75]

4,5,6,7-Tetrahydro-3-phenyl-2,1-benzisoxazole on reaction with *N*-bromosuccinimide gives 3-phenyl-2,1-benzisoxazole. Addition of nitrogen dioxide–iodine to the nonconjugated diene **100** in ether at 0°C gave **101**, which, on treatment with sodium borohydride in methanol at 0–20°C, gave 4,4-dimethyl-7-nitro-1-heptene (**102**) in 72% yield. Dehydration with phenylisocyanate, Et_3N and benzene under reflux gave the cycloadduct **103** in 91% yield via the nitrile oxide (Scheme 2.14).[4/69]



Scheme 2.14

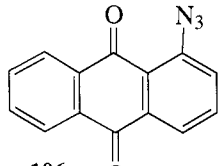
3-Acyl-3,3a,4,5,6,7-hexahydro-2,1-benzisoxazoles (**104**) are obtained on reaction of 1-nitrocyclohexene with acylsulfonium ylides.[5/72]



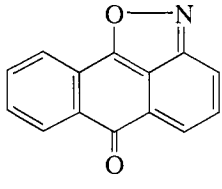
The octahydro derivative **105** was obtained by 1,3-dipolar cyclization of nitrones.[2/59]

2.3.6. Synthesis of Anthraisoxazolones

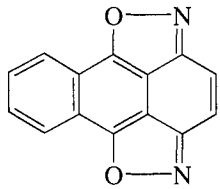
Anthraisoxazolone (**107a**) is easily prepared by thermolysis of azidoanthraquinone **106**. This cyclization is believed to occur via a nonnitrene pathway.[1/92] The anthraisoxazolones **107b**, have also been prepared by hypobromite oxidation[1/16,1/21,5/28] of aminoanthraquinones, although the azide thermolysis route is the most commonly employed one.



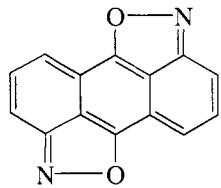
106



107a



107b

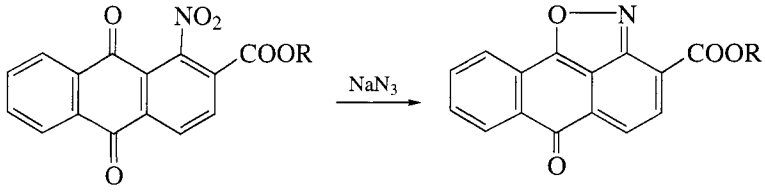


107c

1-Azido-2-aryloxyanthraquinones on heating in boiling benzene/toluene gave 3-aryloxyanthra[1,9-*cd*]isoxazole-6-ones. On the other hand, reaction in dimethylformamide–bromobenzene gave 5,6-phthalylphenothiazines.[3/80] The energy of activation for isoxazolone formation was calculated to be 104.5 kJ/mol, while that for phenoxazine formation was 122.1 kJ/mol. Attention was drawn to the fact that the activation energy for this isoxazole formation differs little from the activation energy for the analogous transformation of unsubstituted 1-azidoanthraquinones.

It appears that phenoxazine formation starts only after the initial azide completely disappears and the isoxazolone has accumulated. Compared to the activation energy of 159 kJ/mole for azirine formation, which is close to the N–O bond dissociation energy, the low value of energy of activation for the transformation of isoxazole into the phenoxazine can be attributed to the high strain in the annulated isoxazole ring and it has been conjectured that N–C bond formation takes place before N–O bond cleavage.

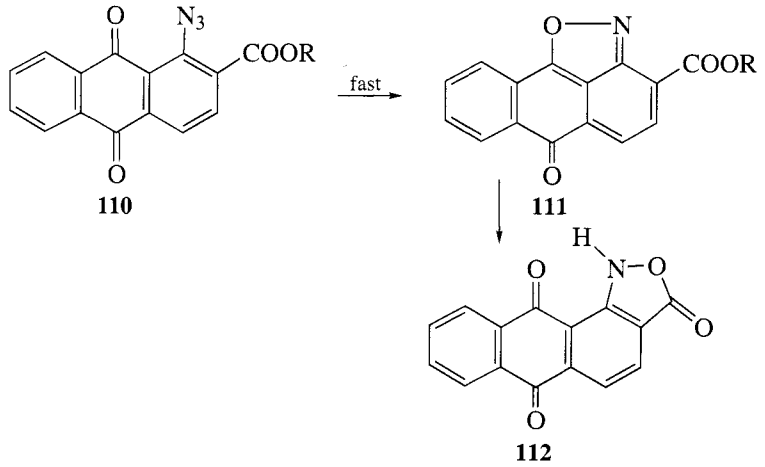
A series of 6*H*-anthra[1,9-*cd*]isoxazol-6-ones were prepared by thermolysis of the corresponding 1-azidoanthraquinones.[3/82] Anthraisoxazolones were also prepared by thermolysis of 1-azido-2-substituted benzoylanthraquinones.[5/83] An interesting preparation (Scheme 2.15) involved displacement of a nitro group adjacent to an *ortho*-alkoxycarbonyl group **108** by azide ion, leading directly to the anthraisoxazolone **109**.[6/83]



108 **109**

Scheme 2.15

Phase transfer catalysis with 18-crown-6 or dicyclo-18-crown-6 gave 65–85% yields of the anthraisoxazolones.[6/83] Boiling 1-azido-2-alkoxycarbonylanthraquinones (**110**) was observed to lead to the formation of only the 3-alkoxycarbonylanthra-[1,9-*cd*]-6-isoxazolones (**111**).[6/83] The corresponding 2-carboxylic acids led to the 1,3-dihydroanthra-[1,2-*c*]-isoxazole-3,6,11-trione (**112**). According to the author the latter compound is formed through the anthra[1,9-*cd*]-6-isoxazolone in a fast step. A slow, concerted step then leads to the trione (**112**).



110 **111** **112**

Thermolysis of 1-azido-2-arylthioanthraquinones in boiling toluene gave 3-arylthioanthra[1,9-*cd*]isoxazole-6-ones.[5/84] When the reaction was conducted in

diethylformamide, the corresponding 5,6-phthalylphenothiazines were obtained via the nitrene intermediate.

Melting points of anthra[1,2-*c*]isoxazole and anthra[1,2-*c*; 5,6-*c'*]diisoxazoles have been tabulated earlier. These included 3-methyl, 7-nitro-, and 7,8,9,10-tetrachloro derivatives of 6*H*,11*H*-6,11-dioxoanthra[1,2-*c*]isoxazole. The diisoxazoles listed included 6*H*,12*H*-6,12-dioxoanthra[1,2-*c*; 5,6-*c'*]diisoxazole; 6*H*,12*H*-6,12-dioxoanthra[1,2-*c*; 7,8-*c'*]-diisoxazole and 5-chloro; 5-bromo-; 5-nitro-; 5-methoxy-; 3-nitro-5-chloro-; 7-chloro-; 7-*N*=*N*-C_6H_4–NMe_2-*p*-; 10-azido- and 10-*N*=*N*–Ph_3 derivatives of 6*H*-6-oxo anthra[1,9-*c*,*d*]isoxazole as well as 5-chloroanthra[1,9-*c*,*d*; 5,10-*c'*,*d'*]diisoxazole and anthra[1,9-*c*,*d*; 4,10-*c'*,*d'*] diisoxazole.

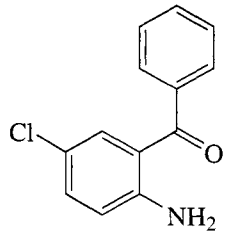
2.4. CHEMICAL PROPERTIES

2.4.1. Simple Ring Opening Reactions

2,1-Benzisoxazoles readily undergo cleavage of the heterocyclic ring under a variety of conditions. As stated earlier, they are sensitive to both heat and light, and apparently pure samples may contain small amounts of the corresponding *o*-aminocarbonyl compound. The most significant of these reactions is reductive cleavage of the N–O bond to 2-aminobenzophenones, key intermediates in the production of many commercially important 1,4-benzodiazepines like Valium, Librium, and flurazepam. A number of reducing agents have been used for this purpose. H_2–Pd or Pt, [1/39,4/59,2/62,2/67,4/68,3/71,4/71,2/76,7/77] nickel, [3/87] sodium dithionite, [1/62] iron, [1/42,1/46,7/72,8/72,4/74,4/75,3/76,7/77,11/83] zinc, zinc and acid (HCl or acetic acid), [1/05,1/56,] $CaCl_2$ [2/33] NH_4Cl,[1/02,1/32,1/36,1/64] Sn–HCl, $SnCl_2$–HCl,[2/02,2/06,1/45,1/52] $FeSO_4$–NH_4OH, [2/882.8/09] have all been successfully used. More recent reports cite the use of Ni–Al alloy, [8/87] hydrazine in warm ethanol, [4/80] electrolytic reduction, [1/69] iodotrimethylsilane, [13/84] thionyl chloride, [5/79] and even phenylhydrazine.[2/67,3/71] Reaction of 5-chloro-3-phenyl-2,1-benzisoxazole with dimethyl sulfate followed by reduction with Fe–HCl led to ring opening to give 5-chloro-2-(methylamino)benzophenone.[7/83] While advocating the use of aluminum iodide, the authors[4/89] state "that classical methods require high temperatures and catalytic reduction requires expensive palladium or platinum and moreover other functional groups cannot be tolerated as they get reduced. Thionyl chloride introduces chlorine, which lead to less active benzodiazepines." They point to the high selectivity, low cost, mild conditions, and excellent yields obtained with aluminum iodide.

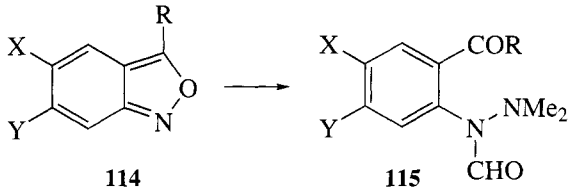
Oxidative ring opening is also possible using dichromate-sulfuric acid,[3/08,2/56,8/77] chromic anhydride–glacial acetic acid,[7/72,4/74,1/76,7/77] potassium permanganate,[1/10] nitric acid,[6/75] and nitrous acid.[1/10]

A procedure for the Bechamp reduction of 5-chloro-3-phenyl-2,1-benzisoxazole for the manufacture of 2-amino-5-chlorobenzophenone (**113**) has been documented.[2/90]



113

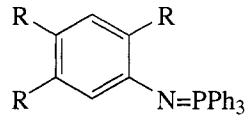
Benzisoxazoles are frequently synthesized using Vilsmeier cyclization. In one such instance, 3-phenyl-5-chloro-2,1-benzisoxazole (**114**), when treated with the Vilsmeier reagent, unexpectedly gave 2-benzoyl-5-chloro-*N*,*N*-(dimethylamino)formanilide (**115**) (Table 2.9).[5/87]



114 **115**

2.4.2. Nitrenoid Reactions

Iminophosphoranes such as **116** have been prepared from 2,1-benzisoxazoles.[3/74] No inter- or intramolecular aza-Wittig reactions were observed.



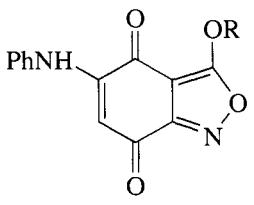
116

TABLE 2.9. FORMATION OF **115** BY REACTION OF 2,1-BENZISOXAZOLES WITH VILSMEIER REAGENT

R	X	Y	Time (h)	Temperature °C	Yield (%)
Ph	Cl	H	4	r.t.	92
Ph	Br	H	4	r.t.	90
Ph	Cl	Me	3.5	r.t.	95
C_6H_4-OMe-*o*	Cl	H	5	r.t.	85
Ph	NO_2	H	4	100	88

More recently, γ-cyano-methylidenebutenolides have been prepared by a highly stereoselective thermal rearrangement of readily accessible benzisoxazoles and naphthisoxazolequinones in solution and in the solid state.[6/91,3/93] A mechanism similar to the one generally accepted for the acid-catalyzed ring contraction of azido-1,4-quinones has been proposed. Rearrangement of an intermediate vinylogous nitrene is presumed to give a ketene intermediate, which gives the observed (*Z*)-butenolides following *o*-acylation. Alkylidene butenolides serve as precursors for physiologically active butenolides such as tetronomycin.[6/89]

Heating 3-methoxy-5-arylamino-2,1-benzisoxazoles (**117**) in chlorobenzene (110°C; 40–60 min) gave alkylidenebutenolide **118** in nearly quantitative yield. Only the (*Z*)-isomer of the butenolide was obtained stereoselectively. 3-Methylisoxazolequinone at 179°C (in dichlorobenzene, 5.5 h) gave the corresponding (*Z*)-butenolide in excellent yields.[3/93]



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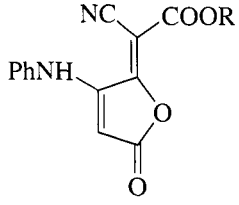
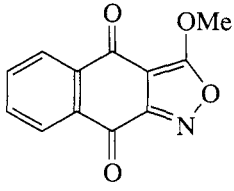


118

Naphtho[2,3-*c*]isoxazole-4,7-dione (**32**) did not afford any butenolide even after heating in refluxing chlorobenzene for 96 h. Only a mixture of *N*-methylisoxazolonequinone and other degradation products was obtained. When heated at 150°C for 2 h, **32** was converted, in 65% yield, to *N*-methylisoxazolonequinone (**119**) prompting the authors to suggest that this could be a useful route to such compounds.[3/93]



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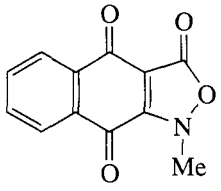
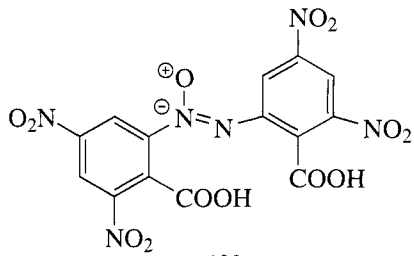


119

2.4.3. Substitution and Addition Reactions

2,1-Benzisoxazole forms a picrate[1/51], a hexachlorostannate[5/03] and an adduct with mercuric chloride.[1/882,3/03,4/03,2/08,7/09,1/51,2/53,4/60,5/60,2/64]

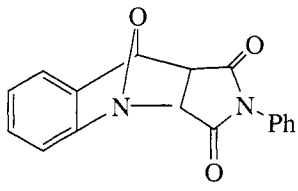
1. *Electrophilic Substitutions.* Halogenation of 3-methyl-2,1-benzisoxazole, attempted in the early part of this century,[6/09] was later reinvestigated, at which time it was determined that chlorination of the 4,5-double bond had occurred. On treatment with alkali or on steam distillation, this product was converted to 5-chloro-3-methyl-2,1-benzisoxazole.[1/66] In a similar fashion, bromination of the parent 2,1-benzisoxazole gave the 5-bromo derivative.[2/65] Nitration of the parent 2,1-benzisoxazole gave the 5- and 7-nitro isomers. Later it was found that the 5-chloro compound gave only the 4-nitro derivative.[2/81] However, if a phenyl ring was present at position 3, dinitration occurred, and in addition to nitration at the 7-position, nitration also occurred on the phenyl substituent. 3-Carbomethoxy-6-nitro-2,1-benzisoxazole underwent further nitration to give the 4,6-dinitro derivative.[2/81] 5-Chloro-6-methyl-3-phenyl-2,1-benzisoxazole gave, on nitration, 3-(4′-nitrophenyl)-5-chloro-6-methyl-7-nitro-2,1-benzisoxazole. However, nitration of 6-nitro-2,1-benzisoxazole brought about cleavage of the isoxazole ring and conversion to azoxybenzene **120**, possibly via the dinitro derivative.[2/81]



120

A haloalkoxy substitution reaction has been carried out on 6-nitro-2,1-benzisoxazole-3-carboxylic acid; treatment with sodium hypochlorite in methanolic alkali gave 6-chloro-7-methoxy-2,1-benzisoxazole-3-carboxylic acid.[1/66]

2. *Diels-Alder Reaction.* Conflicting reports exist concerning Diels–Alder adduct formation involving 2,1-benzisoxazole and maleic anhydride.[1/43,6/60] Reaction with *N*-phenylmaleimide gives a Diels–Alder adduct that can be hydrolyzed and dehydrated to give acridinic acid.[3/59] Although 2,1-benzisoxazole does not react with DMAD, both the 6-nitro and 5-chloro derivatives formed 1,4-cycloadducts.[2/81] It has been concluded that benzisoxazole shows both benzenoid and diene character. The Diels–Alder product from anthranil and *N*-phenylmaleimide was identified later as



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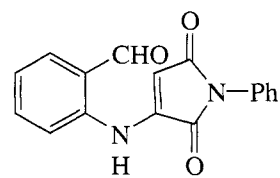
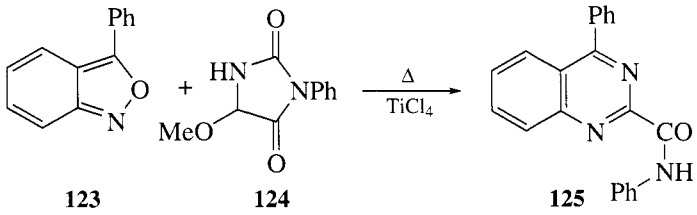


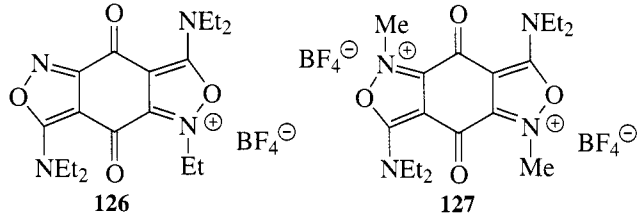
122

the *exo* product and not *endo*, as claimed earlier. Refluxing in xylene gave (2-formylanilino)-*N'*-phenylmaleimide[4/67] (**121**), contradicting the earlier reports, while further heating (20 h) gave *N*-phenylacridinimide **122**. [4+2]-Cycloaddition of 2,1-benzisoxazole with 3-substituted-5-alkoxyimidazoline-2,5-diones followed by the loss of carbon dioxide gave quinazoline derivatives; for instance, 3-phenyl-2,1-benzisoxazole (**123**) in dioxane in the presence of titanium tetrachloride and methoxyphenylimidazolinedione (**124**) gave diphenylquinazolinecarboxamide (**125**).[13/90]



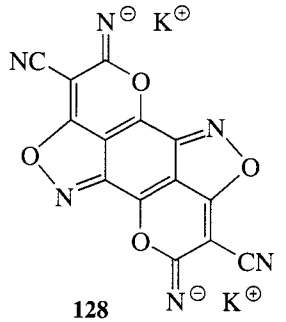
123 **124** **125**

3. *Reactions of 3,7-Dialkoxy-4H,8H-benzo[1,2-c,5-c']diisoxazole-4,8-diones.* The trialkyloxonium tetrafluoroborate salts ("Meerwein's salts") of 3,7-dialkoxy diisoxazole-4,8-dione underwent replacement of the alkoxy groups with *N*-nucleophiles. Reaction with primary and secondary amines gave the 7-dialkylamino compounds, which, on reaction with triethyloxonium tetrafluoroborate, allowed alkylation of a nitrogen of one of the isoxazole rings to give **126**. When trimethyloxonium tetrafluoroborate was used, alkylation of the nitrogen atoms of both isoxazole rings occurred to give **127**.[7/80]



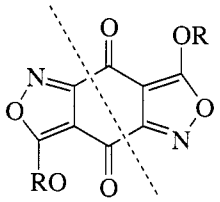
126 **127**

Reactions of diisoxazole **43** with carbon nucleophiles such as malononitrile, cyanoacetophenone, ethyl cyanoacetate, and some nitrogen nucleophiles have been reported.[3/81] Potassium and alkyl ammonium salts of propanedinitrile or ethyl cyanoacetate prepared *in situ* attacked **43** at the C3 and C7 to give substitution products. Reaction of malononitrile with **43** led to the dipotassium salt **128**. The structure of this dye is similar to that of quino[2,3-b]acridonequinone, from which a dipotassium salt has been prepared.[3/81]



128

Sterically crowded aliphatic primary and secondary amines, such as, *tert*-butylamine, diisopropylamine or even tertiary amines like triethylamine in methanol, effected symmetrical splitting of the tricyclic diisoxazole **43** to ammonium salts of the cyanomalonic dialkyl ester (**129**).[5/80]



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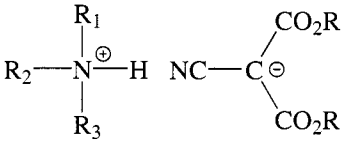
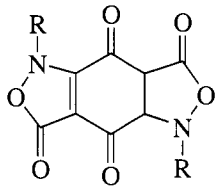


129

With KOH, the cyanomalonic acid dialkyl esters were obtained. Alkylation of **43** with dimethyl sulfate, diethyl sulfate, trimethyloxonium tetrafluoroborate, or triethyloxonium fluoroborate gave the *N*-alkyl derivatives **130**, which, on reaction with hydrazine hydrate, gave the hydrazone **131**, whereas 1,1-dimethylhydrazine gave the 3,7-dimethylhydrazone.[6/80]



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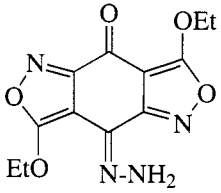

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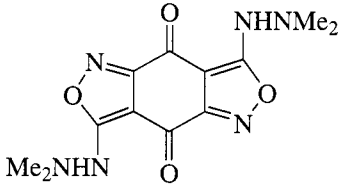


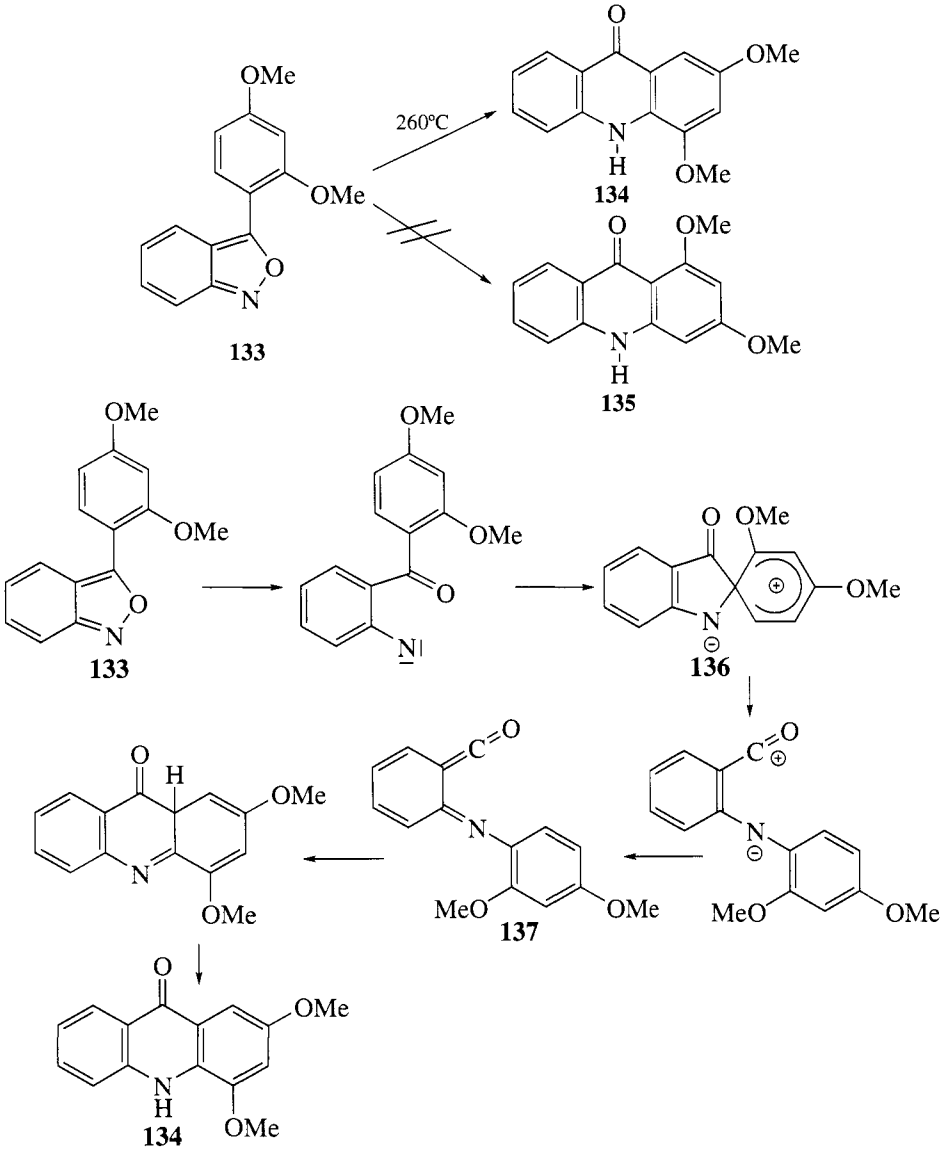
132

The diisoxazole (**43**) was treated with acids to obtain the vinylogous dicarboxylic acid, which, on reaction with PCl_5, gave the dichloro compound. This further reacted with various *N*-nucleophiles. Salts were prepared using alkali hydrogen carbonate, diisopropylthiophenolate, triethylamine, and pyridine.

2.4.4. Rearrangement Reactions

2.4.4.1. Rearrangement to Acridones

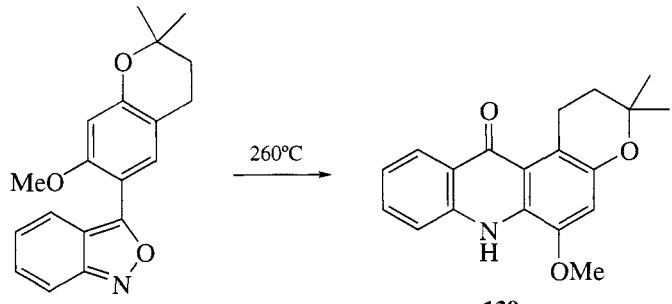
Thermolysis of 3-(2,4-dimethoxyphenyl)-2,1-benzisoxazole (**133**) led to the unexpected 1,3-dimethoxyacridone (**134**) and not to the expected dimethoxyacridone **135**.[3/68]



Scheme 2.16

A mechanism has been suggested in which a nitrene-like intermediate is captured to give spirocycle **136**. Rearrangement to ketene **137** followed by cyclization affords **134** (Scheme 2.16).

3-(7-Methoxy-2,2-dimethyl-6-chromanyl)-2,1-benzisoxazole (**138**) at 260°C similarly gave **139**.



138 **139**

5-Chloro-3-(4-methoxyphenyl)anthranil on heating with $POCl_3$ gave a 3:1 mixture of two dichloro-2- and 3-methoxyacridones.

An in-depth study of the azidobenzophenone–anthranil–acridone transformation has been published.[10/83]

Manganese acetate oxidation of *o*-aminobenzophenones bearing methoxy groups on the receptor ring took place without rearrangement, and both acridones were obtained, although the yields were low. However, caution must be exercised while interpreting these results.[6/72]

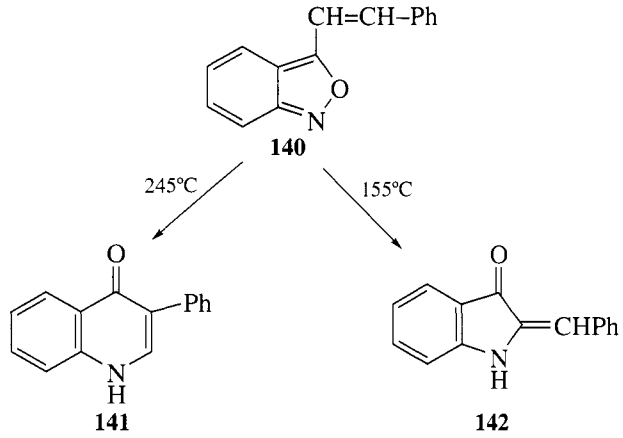
Some photochemical anthranil–acridone conversions have also been reported in which the aromatic ring is substituted, thereby precluding detection of potential rearrangement products.[3/68] When unsubstituted anthranils are irradiated in methanol or in the presence of *sec*-amines, acridone formation is suppressed and azepines are formed instead.[3/68] Yet another competing reaction in this case could be photochemical conversion to 2-arylbenzoxazoles.

2.4.4.2. Rearrangement to Quinolones

When heated at 110°C, *o*-azidophenylstyrylketones give the corresponding 2,1-benzisoxazoles **140**. Ring opening of the latter to a presumed nitrenoid intermediate is followed by rearrangement to 3-aryl-4-quinolones **141** at 245°C or to the arylideneindoxyl **142** at 155°C.[9/78]

2.4.4.3. Rearrangement to Indole Derivatives

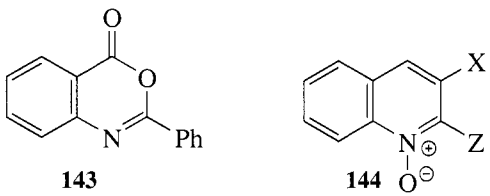
Spray vacuum pyrolysis of 3-methyl-2,1-benzisoxazoles in boiling xylene gave indigotin derivatives.[2/86] The 3-isopropyl derivative gave, in 19% yield, 2,2-



dimethyl-1,2-dihydro-3*H*-indol-3-one. Under basic conditions (NaH–DMF; NaH–THF; NaOMe; NaOH) *o*-azido-aryl-*s*-ketones gave 2,2-dialkyl-1,2-dihydro-3*H*-indole-3-ones.[5/69] Similarly, a 17% yield of 2,2- diethoxycarbonyl-1,2-dihydro-3*H*-indole-3-one was obtained from *o*-azidobenzoyl esters. Ethyl *o*-azidobenzoylphenylacetate gave a mixture of 3-[α-(ethoxycarbonyl)benzoyl]-2,1-benzisoxazole and indoxyl.[2/86] 2,2-Dialkylindoxyls have been prepared from *o*-azidoketones using NaH–DMF or, more efficiently, with alcoholic-NaOH.[6/79]

A mechanism has been suggested for the conversion of 3-benzoyl-2,1-benzisoxazoles to 2-phenyl-4*H*-3,1-benzoxazin-4-one (**143**).[3/70]

The ring expansion of anthranil to quinoline-1-oxides **144** has been carried out using a variety of active methylene compounds.[3/67]



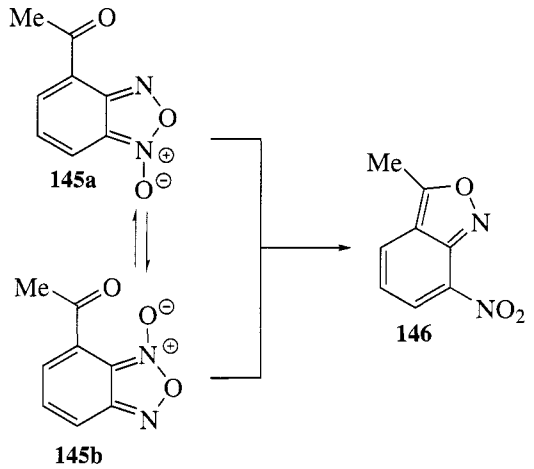
However, the involvement of carbene or ketene intermediates suggested earlier has been discounted.[7/60] Some of the examples studied are collected in Table 2.10.

TABLE 2.10. PREPARATION OF QUINOLINE-1-OXIDES BY REACTION OF ANTHRANIL WITH ACTIVE METHYLENE COMPOUNDS

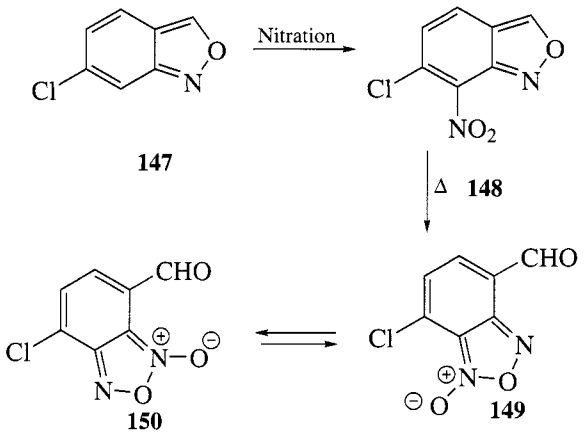
Active methylene compound	Product from anthranil	Yield (%)
Malononitrile	2-Amino-3-cyanoquinoline-1-oxide	99
Ethyl cyanoacetate	1-Hydroxy-3-cyano-2(1*H*)quinolone	97
Diethyl malonate	1-Hydroxy-3-carbomethoxy-2(1*H*)quinolone	80
Cyanoacetamide	2-Amino-3-carbonylquinoline-1-oxide	98
Phenylsulfonylacetonitrile	2-Amino-3-phenylsulfonylquinoline-1-oxide	82

2.4.4.4. Boulton–Katritzky Rearrangement

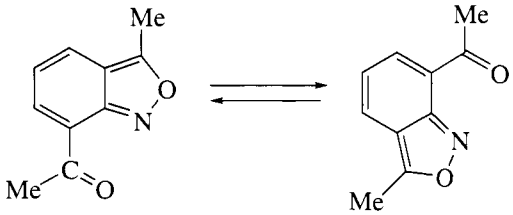
It has been observed that on heating, 4-acetylbenzofuroxan (**145a,b**) undergo rearrangement to 3-methyl-7-nitro-2,1-benzisoxazole (**146**).[4/64] Reactions of this type are now commonly referred to as the "Boulton–Katritzky rearrangement."[3/69] Only examples of this reaction where a 2,1-benzisoxazole is involved have been included in this chapter.



Nitration of 6-chloroanthranil (**147**) gave 6-chloro-7-nitroanthranil (**148**). On heating, this compound rearranged to 7-chloro-4-formylbenzofurazan oxide, which can be represented by two equilibrating structures **149** and **150**.[2/70]



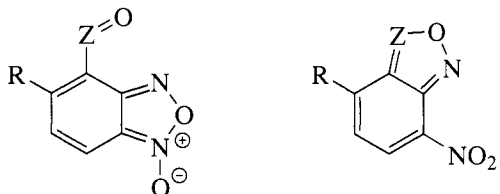
Valence tautomerism in 7-acetyl-3-methyl-2,1-benzisoxazole (**151**, **152**) was shown by spectroscopic studies to be a relatively slow process.[5/71]



151 152

Although its ^{1}H-NMR spectrum in deuterochloroform at 0–20°C gave only one peak, indicating that the two methyl groups were equivalent; at other temperatures two peaks were obtained, indicating that equivalence of the methyl groups is purely coincidental. The NMR spectrum in hexadeuterobenzene, on the other hand, gave a wide separation of the two methyl groups. Increasing the temperature by 150°C brought these two methyl singlets together by only 0.32 ppm, indicating that there is a rather high energy barrier to interconversion of the two identical valence tautomers.

The behavior of 10 different nitro-, nitroso-, and acylbenzofuroxans e.g. **153a** (R = Me, OMe, PhNH–, O-, Z = NO; R = H, Z = HC, MeC) during Boulton–Katritzky rearrangement to the isomeric nitrobenzofuroxans and 2,1-benzisoxazoles **153b** is dependent on the nature of the substituents.[5/68,9/90] In each case the final product was that with the lower IR vibrational frequency of the unsubstituted N in the heterocyclic ring.

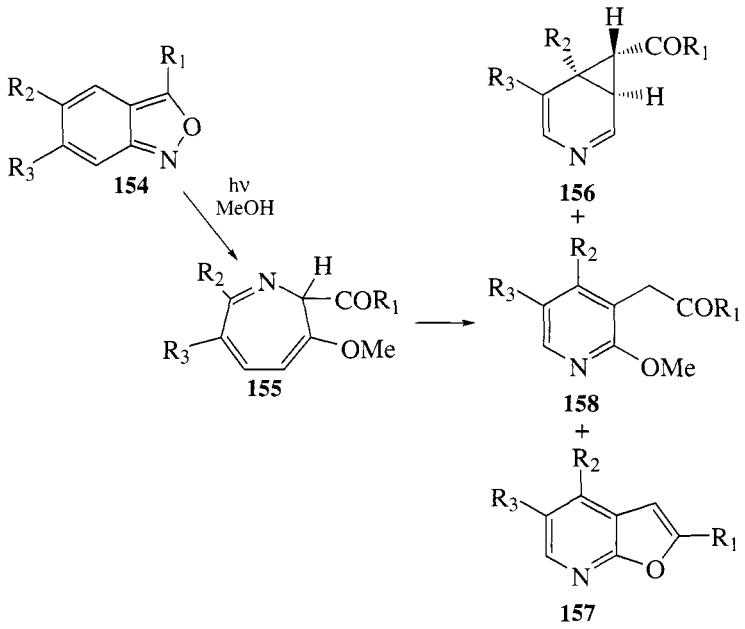


153a 153b

The Boulton–Katritzky rearrangement of 2,1-benzisoxazoles, benzofuroxans, and related systems has been reviewed.[4/81,4/93]

2.4.5. Photochemical Reactions

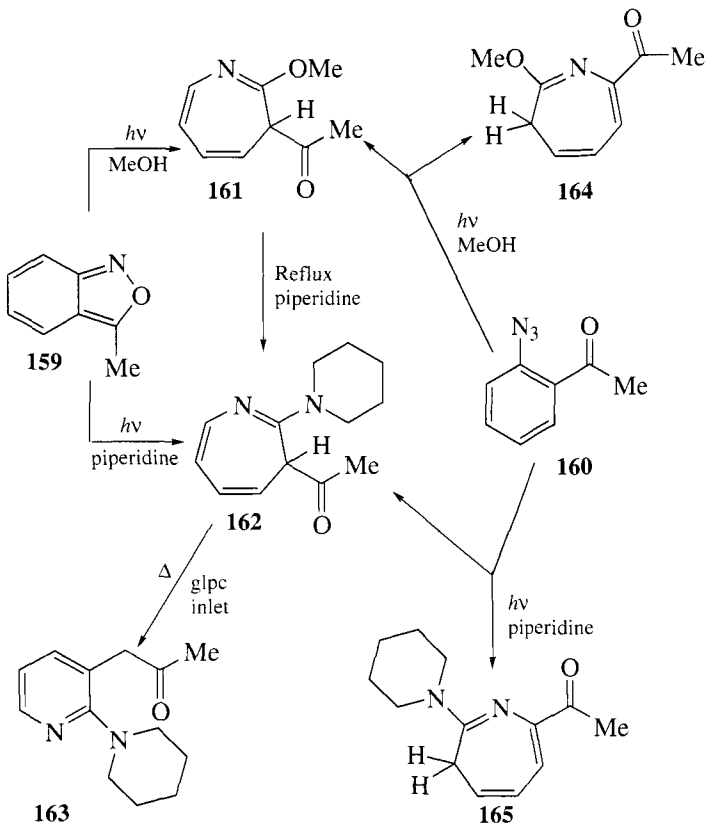
Ring expansion of anthranils (**154**) to 3*H*-azepines (**155**) occurs on photolysis in methanol.[2/69] Formation of a dihydropyridinocyclopropane (**156**), a pyridine **158**, and small amounts of a furanopyridine **157**, which are all quite obviously ring extrusion products, was also noted. Pyrolysis of 3-benzoyl-2-methoxy-3*H*-azepines also resulted in ring contraction to pyridines, an effect that was also observed after heating in decalin at 250°C for 2 h.



In a comparison of the photolysis of 3-methyl-2,1-benzisoxazole (**159**) and 2-azidoacetophenone (**160**) it was observed that on thermolysis the latter is converted exclusively into the former, while on photolysis the corresponding 3*H*-azepines are obtained.[6/71] Photolysis of **159** afforded 3-acetyl-2-methoxy-3*H*-azepine (**161**), in 58% yield, in addition to 2-aminoacetophenone, whose low yield (3%) is indicative of a predominantly singlet pathway. Photolysis of **159** in piperidine gave 3-acetyl-2-piperidino-3*H*-azepine (**162**) along with a trace of 7-acetyl-2-piperidino-3*H*-azepine (**165**). The piperidine derivative (**162**) underwent a rapid thermal rearrangement in the injection port during GLPC analysis to give 3-acetonyl-2-piperidinopyridine (**163**).

Examination of the photochemical reactions of 2-azidoacetophenone (**160**) in methanol suggested the presence of the isomeric methoxy-3*H*-azepine **164**, which could not be isolated successfully. On photolysis in piperidine, **160** gave, in addition to 3-acetyl-2-piperidino-3*H*-azepine, 7-acetyl-2-piperidino-3*H*-azepine (**165**), suggesting that only one of the possible benzazirines was formed during the photolysis of **159**, whereas in the case of photolysis of **160**, the other isomeric benzazirine was also formed. Quantum yields in the anthranil and azidoacetophenone photolyses were 0.16 ± 0.03 and 0.63 ± 0.04, respectively. Triplet photosensitisation occurred with acetophenone, xanthone, and 3-methoxy acetophenone, giving 2-aminoacetophenone as the major product.

Fission of the N−O bond of 2,1-benzisoxazoles during photolysis in acidic medium has been observed to give various products.[7/71,9/71,10/72] Thus 3,5-diphenylanthranil yields 5-(*p*-chlorophenyl)-2-aminobenzophenone along with minor



quantities of 2-amino-3-chloro-5-phenylbenzophenone on photolysis in concentrated HCl. Similarly, 5-halo-3-phenyl-2,1-benzisoxazoles give 3,5-dihalo-2-aminobenzophenones in 49% yields.[7/79] In sulfuric acid replacement by a hydroxyl group occurs along with migration of halogen to give 2-amino-6-halogeno-5-hydroxybenzophenones in 25–35% yields.[7/79] It has been shown that singlet nitrenium ions are involved in the photolysis of 3-methylanthranil in concentrated H_2SO_4 solution.[11/79] Photolysis of anthranils in sulfuric acid gives 3′- and 5′-substituted 2-aminoacylbenzenes. The various products are shown in Table 2.11.[9/71,10/72]

In concentrated HCl (Table 2.12), photolysis of 3-phenylanthranil gave 2-amino-5-chlorobenzophenone (75%) and 2-amino-3-chlorobenzophenone (8.4%). In parallel experiments with HBr, the reactions were presumed to take place via a triplet pathway.[7/79]

Potential irreversible chymotrypsin inhibitors such as the *N*-*o*-azidobenzoyl-L-phenylalanine ethyl ester (**166**) have been studied.[8/71] Photochemical activation

TABLE 2.11. PHOTOLYSIS OF 2,1-BENZISOXAZOLES IN H_2SO_4

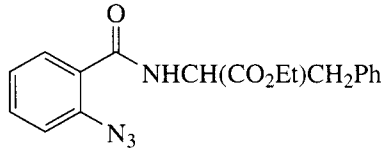
Substrate	Solvent	Reaction type	*p*-Product	Yield (%)	*o*-Product	Yield (%)
2,1-Benzisoxazole	H_2SO_4 98%	*hν*	2-AcNH-5-AcO benzaldehyde (after acetylating work up)	82	2-AcNH-3-AcO benzaldehyde	2
o-Azidobenzaldehyde	H_2SO_4 98%	Δ	2-AcNH-5-AcO benzaldehyde	28	2-AcNH-3-AcO benzaldehyde	2
3-Me-2,1-benzisoxazole	H_2SO_4 98%	*hν*	2-NH_2-5-OH acetophenone	87	2-NH_2-3-OH acetophenone	6
o-Azidoacetophenone	H_2SO_4 98%	Δ	2-NH_2-5-OH acetophenone	67	2-NH_2-3-OH acetophenone	9
o-Azidoacetophenone	Dioxan-H_2O-H_2SO_4 3:3:1	*hν*	2-NH_2-5-OH acetophenone	21	2-NH_2-3-OH acetophenone	3
3,4-Dimethylanthranil	H_2SO_4 98%	*hν*	2-AcNH-5-AcO-6-Me-acetophenone	67	2-NH_2-3-OH-6-Me-acetophenone	trace
2-N_3-6-Me-acetophenone	H_2SO_4 98%	Δ	2-AcNH-5-AcO-6-Me-acetophenone	63	2-NH_2-3-OH-6-Me-acetophenone	trace
3,6-Dimethylanthranil	H_2SO_4 98%	*hν*	2-NH_2-3-Me-5-AcO-acetophenone	55	—	—
2-N_3-3-Me-acetophenone	H_2SO_4 98%	Δ	2-NH_2-3-Me-5-AcO-acetophenone	62	—	—
3,5-Me_2-2,1-benzisoxazole	H_2SO_4 98%	*hν*	2-AcNH-5-Me-acetophenone	2-AcNH-6-CH_2OAc acetophenone		2-AcNH-6-Me acetophenone
2-N_3-5-Me-acetophenone	H_2SO_4 98%	Δ	2	13		28
2-N_3-5-Me-acetophenone	Dioxan–H_2O–H_2SO_4 3:3:1	*hν*	25	1		2
2-N_3-5-Me-acetophenone	MeCN–H_2O–H_2SO_4	*hν*	32	Trace		Trace
2-N_3-5-Me-acetophenone	H_2O–H_2SO_4	*hν*	37	Trace		Trace

TABLE 2.12. PHOTOLYSIS OF 3-PHENYL-2,1-BENZISOXAZOLES IN CONC. HCl AND CONC. HBr

Substrate: 3-Ph-2,1-benzisoxazoles	Photolysis (benzophenone yields, %)					
	In concentrated HCl		In concentrated HBr			
	2-NH_2	2-NH_2,5Cl	2-NH_2, 3-Cl	2-NH_2	2-NH_2, 5-Br	2-NH_2, 5-Br_2
Unsubstituted	—	75	8.4	9.9	42.4	8.8
5-Chloro	—	—	49.3	48.2	4.2	—
5-Phenyl	30.2[a]	—	2.8	31.9	41	—

[a] 5-(p-Chloro)phenyl.

led to the formation of 2-methoxy-3*H*-azepine-3-*N*-methylcarboxamide (**167**), which was characterized by its ^{1}H-NMR spectrum.



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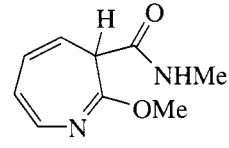
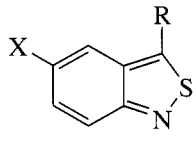


167

2.4.6. Miscellaneous Reactions

2,1-Benzisoxazoles were heated with phosphorus pentasulfide and imidazole to afford 2,1-benzisothiazoles **168**.[9/72,1/75] Heating 2,1-benzisoxazoles with ammonium acetate in sulfolane alone yielded tricycloquinazoline **169** in 51% yield.[6/73]



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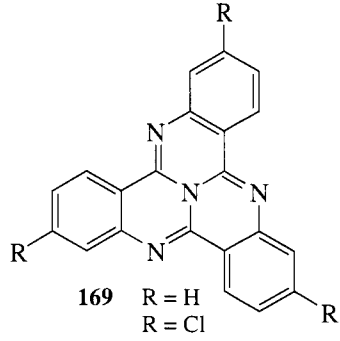
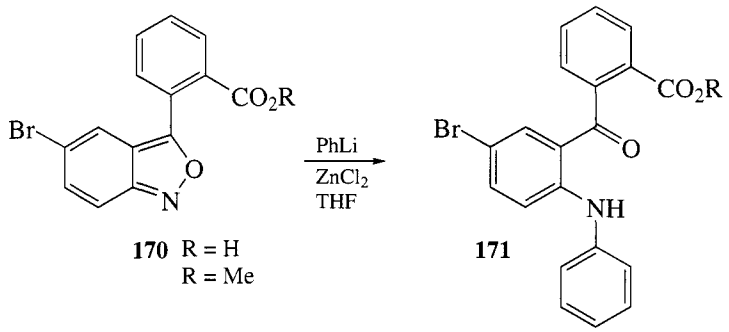


169 R = H
R = Cl

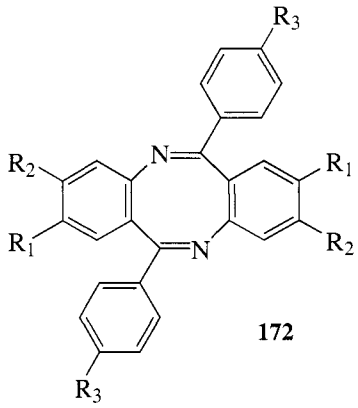
On reaction of 2,1-benzisoxazoles **170** with phenylzinc chloride (derived from phenyllithium and anhydrous zinc chloride) in THF with catalytic nickel acetylacetonate led, in addition to the usual N–O bond rupture, to formation of 2′-anilino-5′-bromo-2-carbomethoxybenzophenone (**171**).[3/87]



170 R = H
R = Me

171

Unlike the 7-formyl derivative, 4-formyl-2,1-benzisoxazole has been shown to yield dihydropyridines under Hantzsch's reaction conditions.[4/86] Lawesson's reagent has been used to convert 3-aryl-2,1-benzisoxazoles into dibenzo[*b*, *f*]-[1,5]diazocines **172**.[4/82] Table 2.13 shows the yields obtained in this reaction.



172

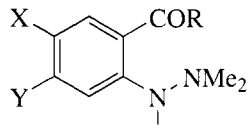
TABLE 2.13. CONVERSION OF 3-ARYL-2,1-BENZISOXAZOLES INTO DIBENZO-[*b*,*f*]-[1,5]DIAZOCINES USING LAWESSON'S REAGENT

R_1	R_2	R_3	Time (h)	Yield (%)
Cl	H	H	2	82
Br	H	H	2	78
Cl	H	OMe	3	79
NO_2	H	H	3	67
Cl	Me	H	2	74

TABLE 2.14. PREPARATION OF 2-AROYL-*N,N*(DIMETHYLAMINO)FORMANILIDES USING VILSMEIER REAGENT

R_1	X	Y	Time (h) (*T*)	Yield (%)
Ar	Cl	H	4 (r.t.)	92
Ar	Br	H	4 (r.t.)	90
Ar	Cl	Me	3.5 (r.t.)	95
$MeOC_6H_4$	Cl	H	5 (r.t.)	85
Ph	NO_2	H	4 (100°C)	88

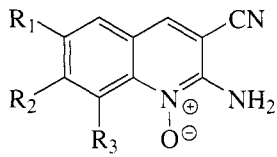
Tetrahalo derivatives of **172** have also been obtained from 3,5-dihalo-2-aminobenzophenones.[6/88] 2-Aroyl-*N,N*(dimethylamino)formanilides **173** have been obtained by reaction of 2,1-benzisoxazoles with the Vilsmeier reagent.[5/87] The results obtained are shown in Table 2.14.



173

Cyclopropane adducts have been prepared by the reaction of 2,1-benzisoxazoles with diazomethane.[9/79] Reaction of 6-nitro-2,1-benzisoxazoles with diphenyldiazomethane and phenyldiazomethane has been used to prepare 7-diphenylmethane derivatives and cyclopropanobenzisoxazoles.[5/82] 5-Nitro-2,1-benzisoxazoles also react with excess $N_2CHCOOR$.[7/82]

A base-catalyzed reaction of 2,1-benzisoxazoles with arylidenemalononitriles in the presence of triethylamine gives 2-aminoquinoline-3-carbonitrile-1-oxides **174** in good yields (Table 2.15).[7/85]



174

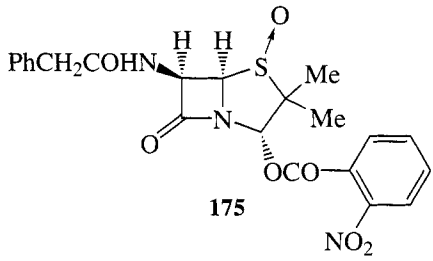
TABLE 2.15. YIELDS OF 2-AMINOQUINOLINE-3-CARBONITRILE-1-OXIDES

	R_1	R_2	R_3	Yield (%)
a	H	H	H	80
b	NO_2	H	H	70
c	H	NO_2	H	73
d	H	NO_2	Me	62
e	Cl	H	H	60

TABLE 2.16. REDUCTION OF *o*-NITROBENZOATES

Starting materials	Reduction	Yield (%)
(1*S*,5*R*,6*R*)-2,2-Dimethyl-6-phenylacetamide penam-3-α-yl-*o*-nitrobenzoate-5-oxide	Corresponding alcohol	91
Cholest-5-en-3-β-yl-*o*-nitrobenzoate	Cholesterol	82
2-Naphthol-*o*-nitrobenzoate	2-Naphthol	89
Oestrone-*o*-nitrobenzoate	Oestrone	92

The use of *o*-nitrobenzoates as protecting groups relies on the formation of anthranils from *o*-nitrobenzoates by Zn–NH_4Cl reduction, a reaction which has been employed in β-lactam (**175**) chemistry.[7/73]



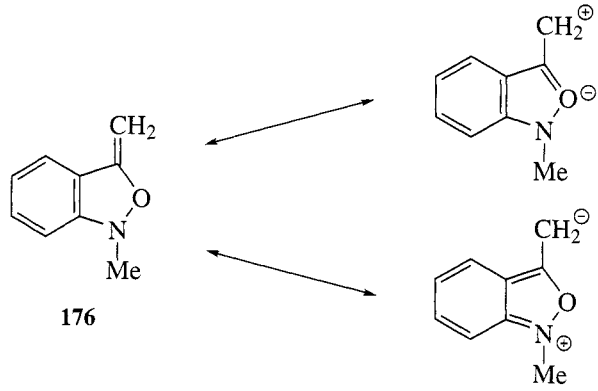
175

The substrates used are shown in Table 2.16.

Thermolysis of 3-phenylazoanthranils effects their rearrangement to benzotriazinones, presumably via initial ring opening to the nitrene followed by cyclization.[6/69]

2.4.7. Reactions of Anthranilium Salts

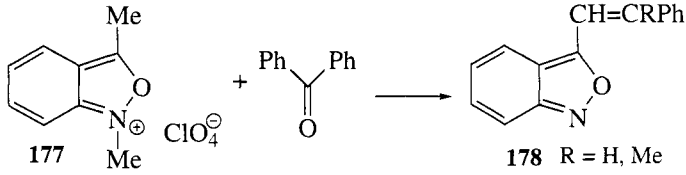
The acidity of the C3 protons in 3-methyl-2,1-benzisoxazolium salts (**176**) suggested their use as new active-methyl compounds.[6/78] These had been used



176

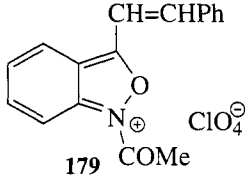
earlier as synthons for both the highly strained benzoazetinone and the tranquillizer Valium. The nucleophilic behavior of the 3-methyl groups in these salts **177** has also been used. Resonance structures of the anhydro base clearly show the negative charge on the C3 substituent atom.

The perchlorate salts **177** condensed with aromatic aldehydes and ketones to form highly colored styryl derivatives **178**.



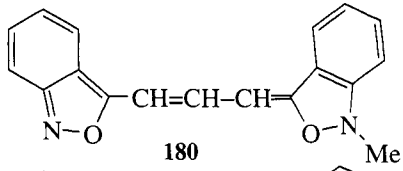
177 **178** R = H, Me

3-Methyl-2,1-benzisoxazoles can be made to participate in condensation reactions although the use of a strongly acidic medium such as $HClO_4$–Ac_2O is required. The condensation may occur via the *N*-acetyl derivative to give **179**.[6/78]

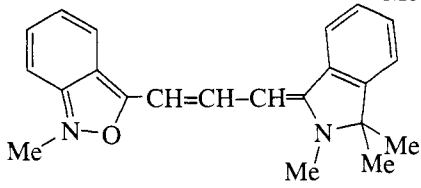


179

Cyanine dyes **180** and **181** were prepared from triethyl orthoformate and Fischer's aldehyde, respectively, to illustrate the utility of 3-methyl-2,1-benzisoxazoles as dye-forming reagents.[6/78]

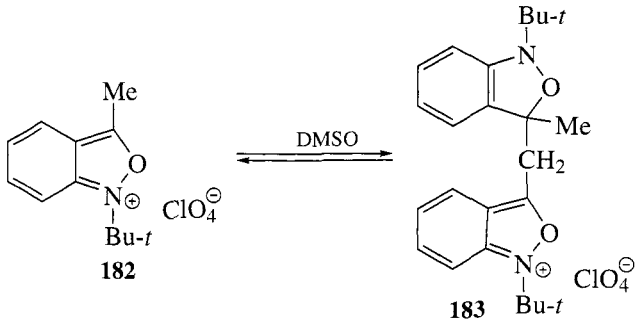


180

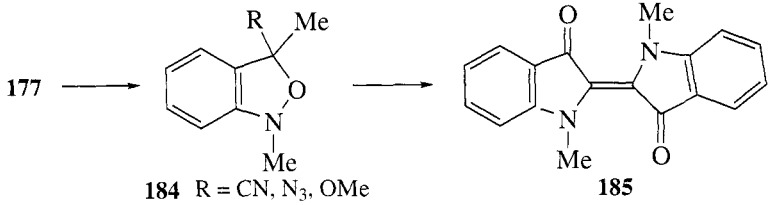


181

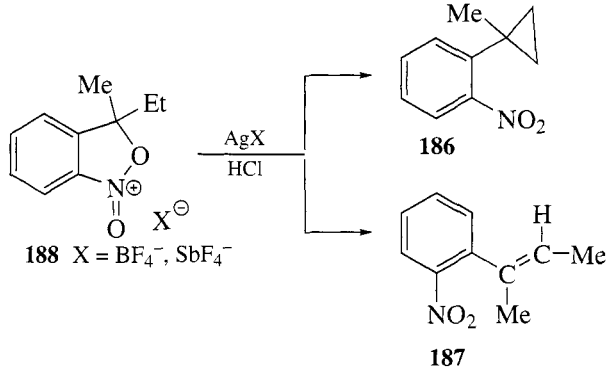
Addition of water to a solution of the perchlorate salt of *N-tert*-butyl-3-methyl-2,1-benzisoxazole (**182**) in DMSO resulted in dimerization to **183**, which was shown by NMR to exist in equilibrium with its monomer.[6/78]



The perchlorate salt **177**, on reaction with cyanide, azide, or methoxide ion, afforded 3-substituted benzisoxazolines **184**, which rearranged on heating to give the *N,N'*-dimethylindigo (**185**).[6/78]



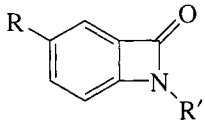
N-Oxo-5,5-dialkyl[3,4]benzo[1,2]oxaazoline salts (**188**) were prepared from 1-methyl-1-(*o*-nitrophenyl)cyclopropane (**186**) and 1-methyl-*o*-nitrostyrene (**187**).[4/76] These light-yellow-colored crystals have good solubility in nitromethane, acetonitrile, liquid sulfur dioxide, trifluoroacetic acid, dimethylsulfoxide, and dimethylformamide, and are insoluble in nonpolar organic solvents.



The IR spectra of these salts exhibit two intense bands at 1570 and 1650 cm^{-1} (for hexafluoroantimonates) and at 1575 and 1665 cm^{-1} (for tetrafluoroborates).

Anthranilium salts were prepared from the corresponding anthranils by treatment with trialkyl orthoformates and a variety of Lewis acids. Treatment of 5-chloro-1-(2-chloroethyl)-3-phenyl-2,1-benzisoxazolium tetrafluoroborate with ethanolic ammonia gave, in 40% yield, 7-chloro-5-phenyl-1,2-dihydro-3*H*-1,4-benzodiazepine.[9/72]

Alkylaminobenzophenones were prepared in yields of 53–78% from 2,1-benzisoxazolium salts.[13/84] On reaction with triethylamine, anthranilium salts undergo ring opening and then recyclize to *N*-alkylbenzazetinones **189** that are stabilized by the presence of tertiary alkyl groups.[12/84]



189 R = H, Br
R′ = Et, $CHMe_2$, CMe_3, 1-adamantyl

In the presence of base, 3-unsubstituted anthranilium salts react with alcohols to give adducts that rearrange to produce esters.[12/84]

2.4.8. Reactions of Anthraisoxazolones

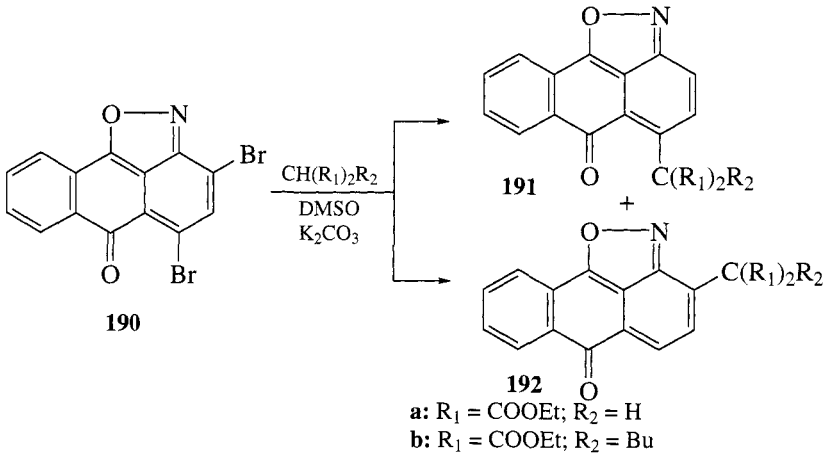
Anthra[1,9-*cd*]isoxazole-6-ones are heteroanalogs of 1,10-anthraquinone and undergo replacement of their halogen atoms, especially those at the 3 and 5 positions, by nucleophiles and hydride donors.[1/92] Moreover, the isoxazole ring undergoes ready cleavage, leading to the observation of some unusual reactions.[1/92]

2.4.8.1. Substitution Reactions

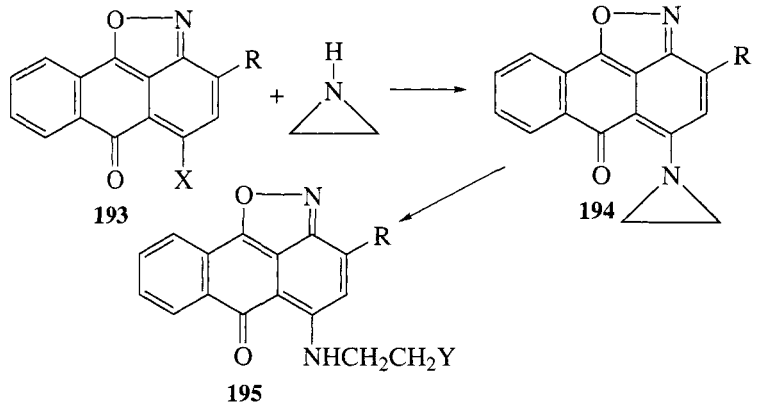
On reaction of 3-chloroanthra[1,9-*cd*]isoxazole-6-ones with methoxide ion, substitution occurs at the 3 position. When alkoxides derived from other alcohols (e.g., *n*-propoxide) are employed, the chlorine atom is not displaced and nucleophilic replacement of the hydrogen at the 5 position results.[10/90] 5-Chloroanthra[1,9-*cd*]isoxazol-6-ones react 100 times faster than 1-fluoro-9,10-anthraquinone in amination reactions.[1/92]

Anthra[1,9-*cd*]isoxazol-6-ones, on reaction with amines in acetonitrile, gave mainly the product of nucleophilic substitution at the 5 position. In the presence of Cu^{2+}, Ag^{+}, Co^{2+}, or Ni^{2+} cations in acetonitrile or nitromethane, the amines gave mainly the products of replacement of the hydrogen at the 3 position.[1/92] Evidence for the involvement of a free radical in these reactions was obtained when the reaction was conducted in an ESR spectrometer cell.[12/84]

The anthraisoxazolones **190** reacted with carbanion nucleophiles derived from malonic and alkylmalonic esters, acetoacetic ester, and acetylacetone to give 5-substituted anthraisoxazolones **191** or 3,5-disubstituted anthraisoxazolones **192** in ratios that were dependent on the number of molar equivalents of the carbanion.[1/92]

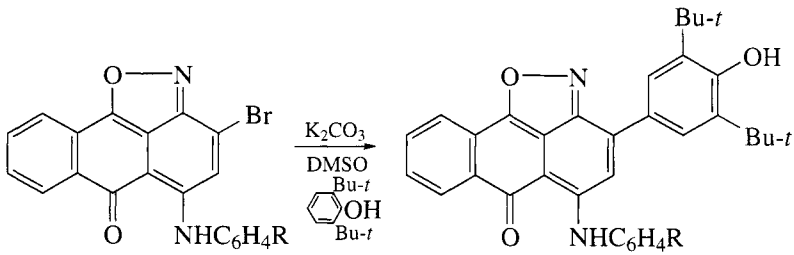


Reaction of 5-haloanthraisoxazolones **193** with aziridines led to substitution of halogen to give the aziridinyl derivatives **194**.[7/84] On reaction with HY (Y=Cl, Br), the aziridine ring was cleaved to give **195**. The corresponding substituted anthraquinones were obtained on reductive ring cleavage of the isoxazole ring with NH_2–NH_2 and Pd/C.

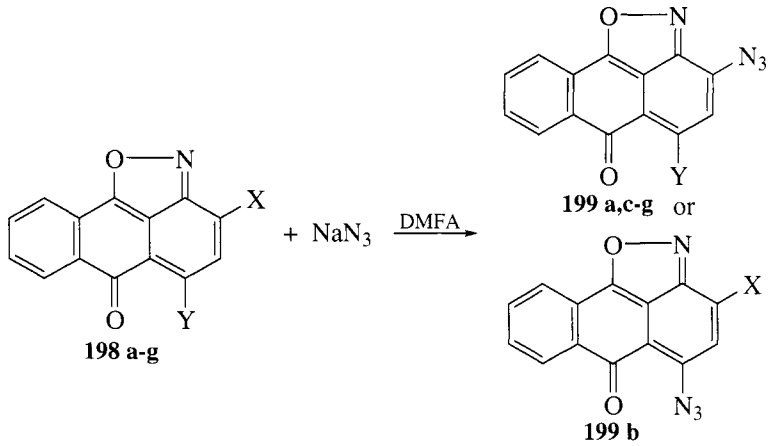


When treated with K_2CO_3, DMSO, and 2,6-di-*tert*-butylphenol, 6*H*-6-oxo-3-bromo-5-arylaminoanthra[1,9-*cd*]isoxazoles **196** gave 6H-6-oxo-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-arylaminoanthra[1,9-*cd*]isoxazoles **197** in good

yields.[10/84] The products were stable to prolonged heating in refluxing *o*-dichlorobenzene and, perhaps as a result of the steric hindrance of the *tert*-butyl groups, the well-known 'carbazole'-type reactions of the precursors to nitrobiaryl were not observed. Reduction with sodium borohydride required conditions much more drastic than those commonly used for other compounds of this class.

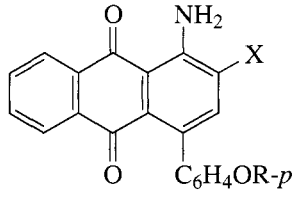


6*H*-6-Oxo-3(5)halogenoanthra[1,9-*cd*]isoxazoles **198a-g** react with sodium azide in DMF, but not with KF–DMSO or KF–DMF, to give either the 3-azido **199a,c-g** or the 5-azido[9/86] derivative **199b**. Treatment of **198a** with KF-CH_3CN-18-crown ether-6 resulted in the formation of the 5-fluoro derivative.

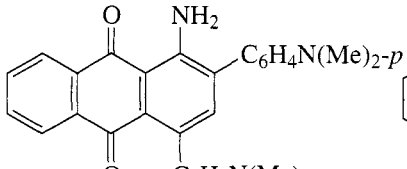


	X	Y		X	Y
a	Cl	H	**e**	Br	OC_6H_4Bu-*tert*-*p*
b	Br	NHC_6H_4Me-*p*	**f**	Br	OC_6H_4Me-*p*
c	Br	NHC_6H_4OEt-*p*	**g**	Br	OPh
d	Br	OCH_2Ph			

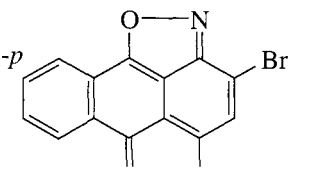
The reactivity of halogens in the 3 and 5 positions toward nucleophiles in 6*H*-6-oxoanthra[1,9-*cd*]isoxazoles was exploited as a means to effect arylation reactions.[6/87] In the presence of $AlCl_3$ and alkylphenylethers, it led to the formation of 1-amino-2-chloro-4-(4-alkoxyphenyl)anthraquinones (**200**). On the other hand, $AlCl_3$ and dimethylaniline led to 1-amino-2,4-di(4-dimethylaminophenyl) anthraquinone (**201a**). Both these reactions led to the reduction of the heterocyclic ring.



200

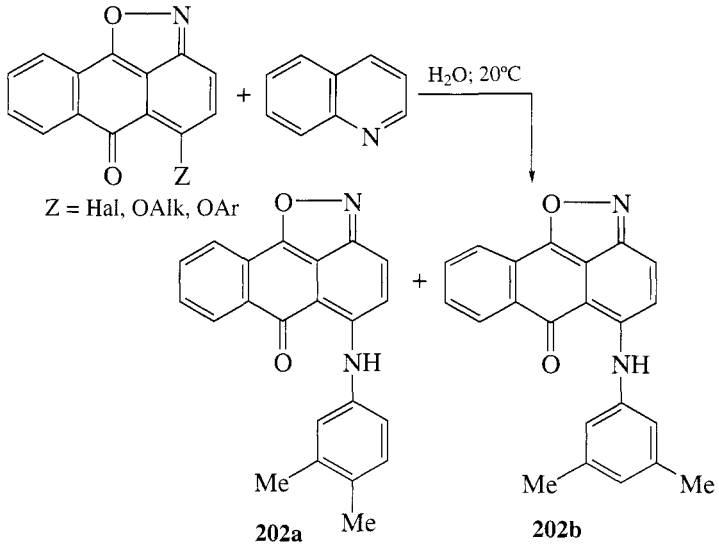


201a



201b

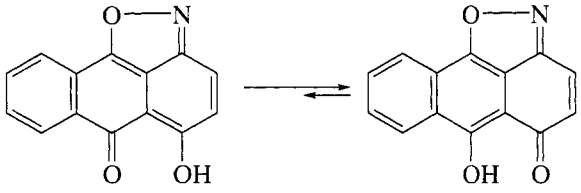
If both the reactive positions in the initial substrate are occupied by a halogen, its arylation is not accompanied by reductive cleavage of the isoxazole ring. Thus, with 6*H*-6-oxo-3,5-dibromoanthra[1,9-*cd*]isoxazole and phenetole and $AlCl_3$, only the bromine atom at the 5 position is displaced by phenetole to give **201b**, and both the bromine atom at position 3 and the isoxazole ring survive the reaction.



202a **202b**

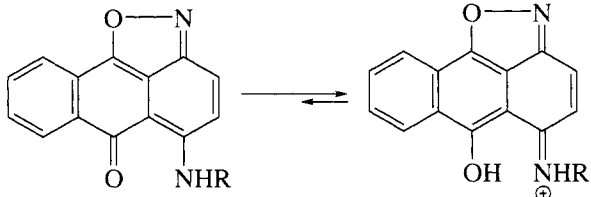
The reaction of 6*H*-6-oxo-5-haloanthra[1,9-*cd*]isoxazoles with quinolines in water, for which no mechanism has been suggested, gives **202a,b**.[5/86,5/93]

6*H*-6-Oxoanthra[1,9-*cd*]isoxazoles **203** show a tendency to tautomerize to the thermodynamically more stable 9,10- or 1,4-anthraquinone structure **204**.[1/92]



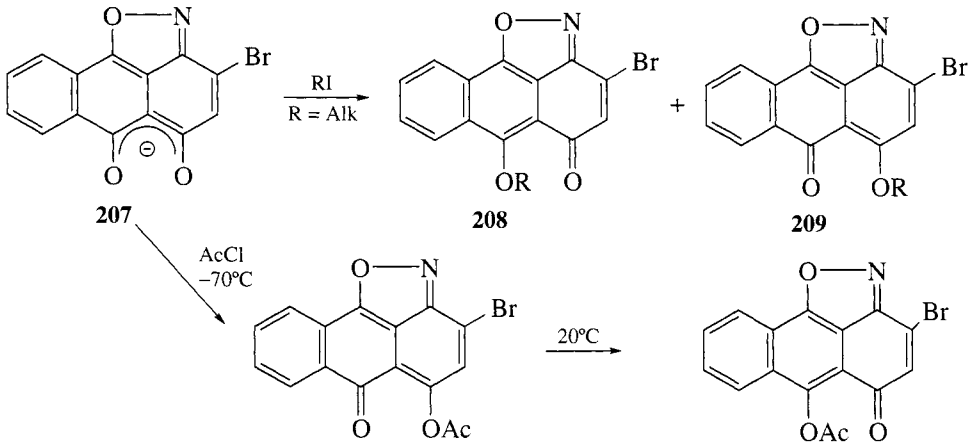
203 **204**

Similarly, aminoanthraisoxazolones **205** are protonated at the carbonyl group to give **206**.[1/92]



205 **206**

Alkylation of anions **207** derived from hydroxyanthraisoxazolones leads to a mixture of isomers **208** and **209**. Acetylation at low temperatures gives the 5-acyloxy compound; subsequent isomerization to the 6-acyloxy compounds **210** occurs upon warming to room temperature.[11/90]

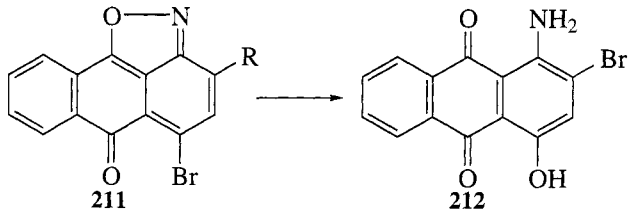


207 **208** **209**

210

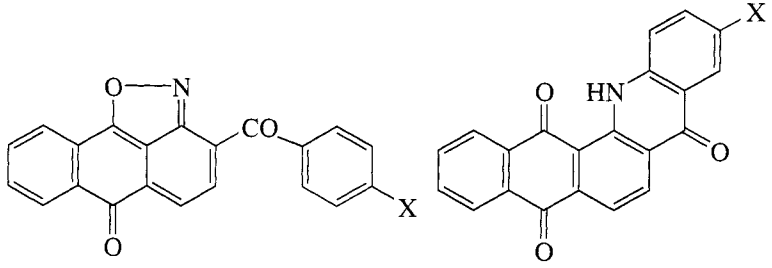
2.4.8.2. *Ring-Opening Reactions*

Ring-opening reactions leading to the 1-sulfoximido and 1,5-disulfoximido derivatives have been recorded.[3/82] On treatment with 90% H_2SO_4 the sulfoximines yielded the amines. Anthra[1,9-*cd*]isoxazolones **211** on treatment with H_2SO_4 underwent hydroxylation at the 5 position followed by migration of bromide to give **212**.[6/82]



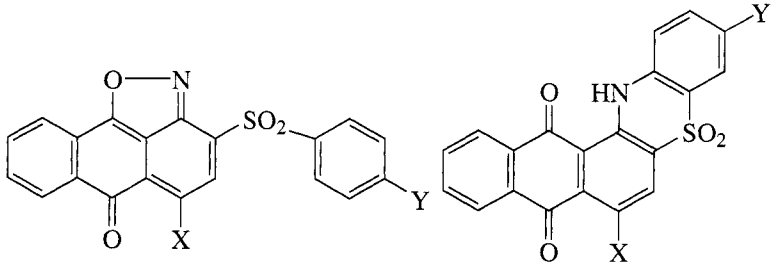
211 **212**

3-Aroylanthra[1,9-*cd*]isoxazol-6-ones (**213**) on being heated for 6–8 h[5/83] in *o*-dichlorobenzene gave **214**.



213 **214**

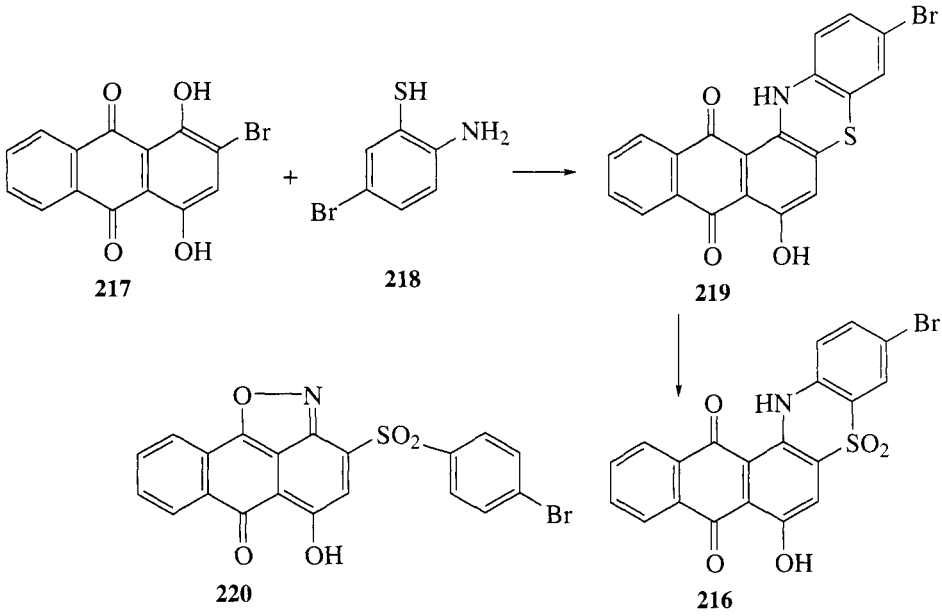
3-Arylsulfonylanthra[1,9-*cd*]isoxazolones **215** isomerise on prolonged boiling in nitrobenzene to naphtho[2,3-*b*]phenothiazine-7,13-dione-*S*,*S*-dioxides **216**. Kinetics of the reaction of 3-[2,4,6-trideuterophenoxy]-*s*-hydroxyanthra[1,9-*cd*]-6-isoxazolone compared with the unlabeled compound showed no



215 **216**

difference in rate, indicating that N–C bond is formed in a non-rate controlling step. If a spiro intermediate were involved, then the substituent *para* to the group Z would occupy the *para* position in the final product.[5/85]

To establish the position of the substituents more precisely, the authors compared the products obtained from the isoxazolones with the isomeric phenothiazines synthesized by alternative routes. Thus the phenothiazine **219** synthesized from **217** and **218** on oxidation gave 6-hydroxy-3-bromonaphtho[2,3-*b*]phenothiazine-7,12-dione-*S*,*S*-dioxide (**216**), which was identical with the product obtained by recyclisation of the isoxazolone **220**.

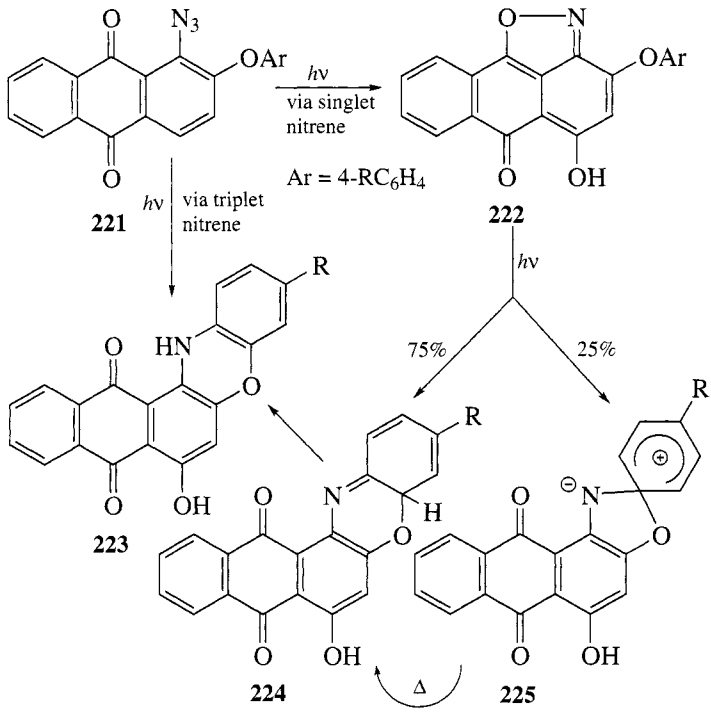


217 **218** **219** **220** **216**

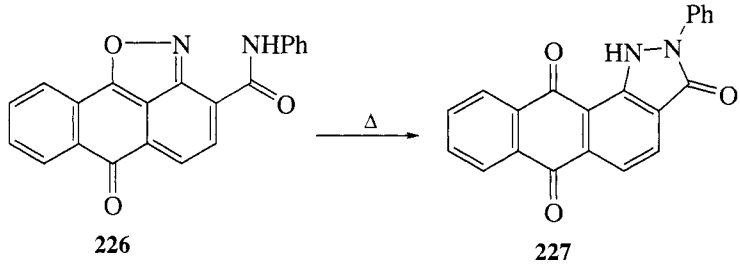
Unlike the cyclization of 2-azidodiphenylsulfones, where both the spiro intermediate and direct insertion of nitrene into the C–H bond are involved, it was claimed that only the former is involved in these reactions, which are more selective because of the favorable geometry for the formation of the spiro intermediate.

The photolysis of 1-azido-2-aryloxyanthraquinones (**221**) proceeds through a singlet nitrene to give 3-aryloxyanthra[1,9-*cd*]-6-isoxazolones (**222**). Photorearrangement of this latter compound led to naphtho[2,3-*a*]phenoxazine-8,13-diones (**223**) through the intermediacy of the diene **224**; as minor product the spiro compound **225** was isolated, which on heating at 80°C was converted to the intermediate **224** and finally to the phenoxazine **223**. Photolysis of **221** from the triplet excited state gave the phenoxazine **223** directly.[6/86]

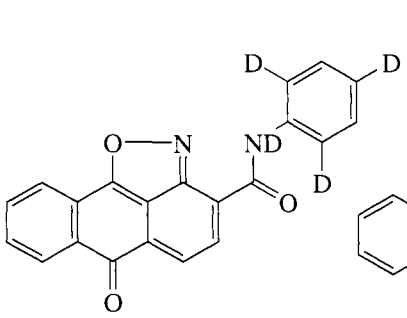
Pyrazoline formation is believed to involve the intermediacy of singlet nitrenes. This isomerization can occur via the nonnitrene pathway in DMSO, DMF at 20–40°C in the presence of alkali.



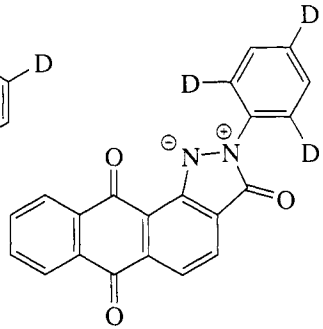
The 3-phenylaminocarbonyl derivative **226** gave mainly 1*H*-2-phenylanthra[1,2-*d*]pyrazoline-3,6,11-trione (**227**) when heated in *o*-dichlorobenzene. Surprisingly, when the reaction was conducted in a mixture of *o*-dichlorobenzene and bromobenzene, considerable amounts of the 1-amino compound were obtained.[7/84]



3-(2,4,6-*N*-Tetradeuterophenylaminocarbonyl)anthra[1,9-*c*,*d*]-6-isoxazolone (**228**) isomerized to **229** when heated in *o*-dichlorobenzene at 175°C. No difference in rate was observed compared to the unlabeled compound, which, according to the authors, pointed toward the involvement of the ylide **229**.

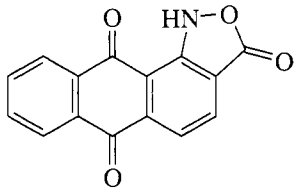


228



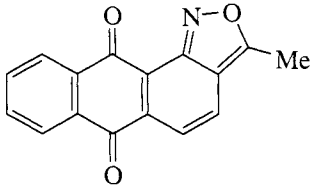
229

Thermolysis of anthraisoxazolones in cumene and *p*-cymene led to insertion of a nitrene intermediate into the C–H bond and also to reduction.[5/81]. 3-[(Alkylamino)carbonyl]-6-oxo-6*H*-anthra[1,9-*cd*]isoxazoles on reflux in *o*-dichlorobenzene gave 73–93% yields of anthrapyrazolines and the corresponding amines[8/85]. Thermolysis of 3-alkoxycarbonylanthraisoxazolones gave **230**.[8/84]

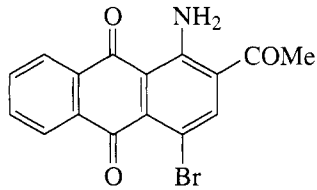


230

Ring opening of **231** to **232**, described in a recent patent, occurs in two steps, and involves reaction with H_2SO_4–$FeSO_4$ followed by reaction with NaBr. 4-Chloro-1-aminoanthraquinones were obtained from 3-substituted 6*H*-6-oxo-anthra[1,9-*cd*]isoxazolones on being refluxed with HCl–AcOH.



231

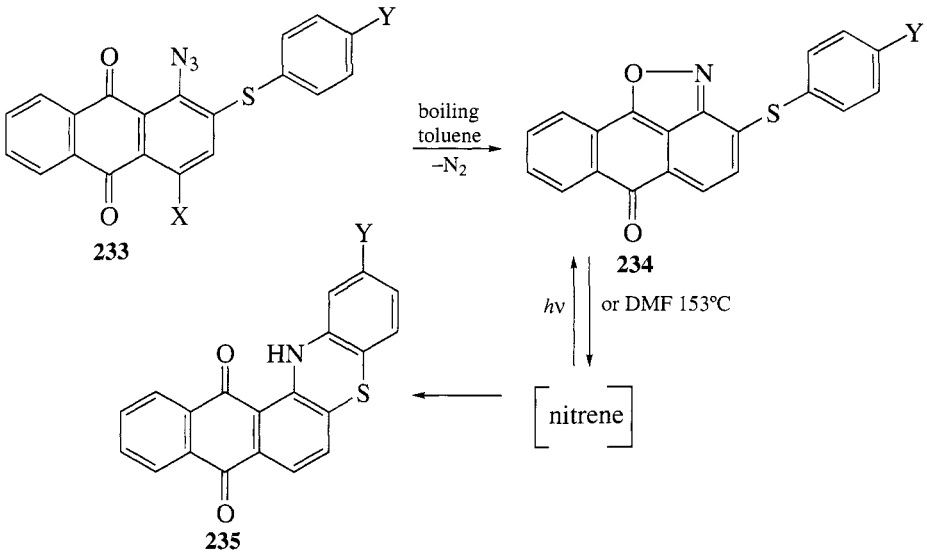


232

Either 3-, 5-halo, or 3,5-dihalosubstituted anthraisoxazolones of this type react with alkoxy and alkylbenzenes to give aminoanthraquinones.[6/87,5/88] The reaction with phenoxides and alkoxides has been shown to involve replacement

of halogen or a hydrogen atom depending on the attacking anion and the halogen in the starting material.[10/90]

Thermal and photochemical cyclization of 1-azido-4-acyloxy-9,10-anthraquinones to 6-acyloxy-5-oxo-5*H*-anthra[1,9-*cd*]isoxazoles occurs with migration of the acyl group to the 6 position. Similarly, 3-phenoxy(phenylthio)-6-acyloxy-5-oxo-5*H*-anthra[1,9-*cd*]isoxazoles undergo thermal isomerisation to the corresponding naphtho[2,3-*a*](phenothiazine)-7,12-diones via a reverse acyl transfer. 1-Azido-2-arylthioanthraquinones **233** in boiling toluene led to 3-arylthioanthra[1,9-*cd*]isoxazol-6-ones **234**. However, in DMF, either thermally or photochemically, 5,6-phthalylphenothiazines **235** were obtained. The latter serve as dyes for polyester fibers (Scheme 2.17).

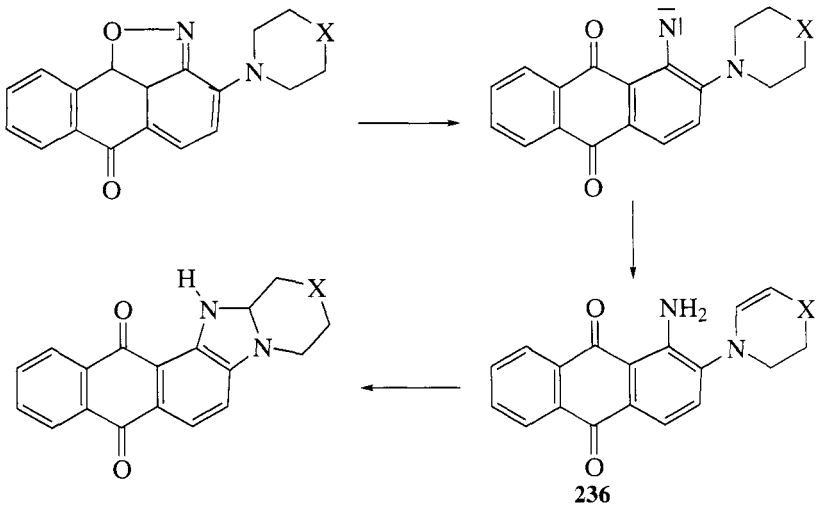


Scheme 2.17

Kinetics of the thermal transformations of 3-phenylthioanthraisoxazolones have been studied. For the formation of these compounds from the azides, the values are: rate constant, k = 3.91–11.88 × 10^{-4} s^{-1} at 94–106°C, $\Delta E^{\neq}$ ~106 kJ/mol^{-1}; ΔH = 102.8 kJ/mol^{-1}; ΔS = −31.8 J deg^{-1} mol^{-1} at 120°C. The corresponding values for phenothiazine formation are k = 2.88–5.43 × 10^{-4} s^{-1} at 138–146°C; ΔE = 114.9 kJ/mol^{-1}; ΔH = 111.4 kJ/mol^{-1} and ΔS = − 43.9 J deg^{-1} mol^{-1} at 120°C. A negative ΔS for the last reaction and a ΔE lower than the dissociation energy of the N−O bond both indicate that the N−C bond is formed prior to the N−O bond cleavage.[11/81]

In some cases during the course of these reactions it is possible to isolate products **236** which are formed as a result of extraordinary and rare intramolecu-

lar α,β-dehydrogenation of nitrenes (by the nitrogen atom). These further cyclise to imidazolines (Scheme 2.18).



Scheme 2.18

2.5. USES

Because of the facile reductive cleavage of the isoxazole ring, 2,1-benzisoxazoles (e.g., 5-chloro-3-phenyl-2,1-benzisoxazoles) have served as a ready source for *o*-aminobenzophenones, which are key intermediates in the synthesis of quinazolinones and 1,4-benzodiazepines. *N*-Alkyl-2,1-benzisoxazolium salts are useful synthons for the well-known tranquillizers, Valium and Librium. 3-Phenylanthranils are useful in the treatment of cancer. Interest in these compounds is evident from the number of patents filed in recent years. Derivatives of substituted benzisoxazole-4,7-diones have been shown to be potent radiosensitizers *in vitro*.[7/91] Anthraisoxazolones are precursors to many synthetic dyes, fluorescent whitening agents, and liquid crystalline materials. Many benzisoxazoles are useful in the production of conducting polyquinolines, electroactive heterocyclic polymers, and photothermographic materials.[1/78,7/81,9/81,10/82,11/82,11/84,10/85,11/85,7/86,8/86,7/87,12/90,2/91] However, their synthetic potential has not yet been fully realized. The field abounds in many mechanistic problems and a large number of rearrangement reactions, which, in particular, have yet to be rationalised. It would thus be reasonable to expect discoveries of new reactions and synthetic strategies. Anthranils have been implicated as intermediates in discussions on environmental problems, which augurs well for the future.

3-(4-Chlorophenyl)-2,1-benzisoxazole-7-acetic acid has been shown to be as effective as indomethacin against *Mycobacterium butyricum*–induced arthritis in

rats.[1/88] During studies on potential pro-drugs that could be metabolically converted into amnefac, a clinically used nonsteroidal antiinflammatory drug with minimal or no gastrointestinal irritation, it was shown that 3-(4-chlorophenyl)-7-methyl-2,1-benzisoxazole had a higher therapeutic index than indomethacin.[8/90]

Topical treatment with 2,1-benzisoxazole in both mothers and in off spring following the administration of [^{3}H]-thymidine to pregnant mice during late organogenesis assisted in the latter's action as an initiator for skin.[13/82] This transplacental-initiating capacity could be used in the bioassay of tumor promoters.

APPENDIXES

2.I TABLES ON IR SPECTRA OF 2,1-BENZISOXAZOLES AND ANTHRAISOXAZOLONES

TABLE 2.IA. IR SPECTRA OF 2,1-BENZISOXAZOLES

Compound	ν (cm)$^{-1}$	References
1. 3-Phenyl	1636	1/89
2. 6-Chloro-3-phenyl	1634	1/89
3. 5-Chloro-3-phenyl	1633	1/89
4. 5-Fluoro-3-phenyl	1648	1/89
5. 6-Methyl-3-phenyl	1643	1/89
6. 5-Methyl-3-phenyl	1643	1/89
7. 5-Nitro-3-phenyl	1636	1/89
8. 4-Formyl	2800, 1680(C=O), 1630, 1400, 1080, 820	4/86
9. 5-Chloro	1625(C=N), 1480, 1370, 1075	2/81
10. 4-Nitro-5-chloro	1629(C=N), 1520, 1320(NO_2)	2/81
11. 3-(4′-Nitrophenyl)-5-chloro-7-nitro	1625(C=N), 1590(NO_2), 1515, 1330, 1100	2/81
12. 3-(Carbomethoxy-4,6-dinitro	3100, 1725(C=O), 1630(C=N), 1560(NO_2), 1530(NO_2), 1370(NO_2), 1350(NO_2), 1115	2/81
13. 3-(*o*-Carboxyphenyl)-5-phenyl	2400–3000(OH), 1715(sh), 1685(C=O), 1635(C=N)	3/87
14. 5-Bromo-3-(*o*-carboxyphenyl)	1710(C=O), 1630(C=N)	3/87
15. 5-Bromo-3-(*o*-carbomethoxyphenyl)	1720(C=O), 1630(C=N)	3/87
16. 3-[α-Ethoxy(carbonyl)-benzyl]	1720(C=O)	2/86
17. 5-(2-Methyl-1,3-dioxolan-2-yl) 3-(4-diphenylene-2-yloxyphenyl	1505, 1430, 1320	8/86
18. 3-[4-(4-Phenoxyphenyl)phenyl]-5-bromo	1595, 1495, 1260	9/85
19. 3-[4-(4-Phenylphenoxy)phenyl]-5-bromo	1600, 1505, 1255	9/85
20. 3-[4-(4-Phenoxyphenoxy)phenyl]-5-bromo	1495(sh), 1485, 1225	9/85
21. 5-[*p*-2-Methyl-1,3-dioxolan-2-yl) phenyl-3-phenyl	1620(C=N), 1500, 1330(NO_2)	8/81
22. 9-[5-Phenyl-2,1-benzisoxazolyl)-9-[4′-(2-methyl-1,3-dioxolan-2-yl)-phenyl]fluorene	3170(Ar,C=H), 2990, 2890(CH_2), 1645 (C=N), 1560, 1525, 1500, 1475, 1445, 1370, 1250, 1040, 800, 740, 680	7/81
23. 7-Methoxy-3,4,5,6-tetramethyl	1635, 1570, 1535	3/70
24. 6-Nitro-2,benzisoxazole-3-Carboxylic acid	3505, 1695, 1548, 1523, 1275	1/70

TABLE 2.IA. (*continued*)

Compound	ν (cm)$^{-1}$	References
25. 5,5′-Oxybis(3-phenyl-)	1640, 1470, 1265, 1215	2/76
26. 3-(4-Methoxyphenyl)-4-nitro	1730(ester)	2/73
27. 3-Methoxy-2,1-benzizoxazole-7-Carboxylic acid	1751	1/75

28. 3-Substituted 4,6-dinitro-2,1-benzisoxazoles

Substituent	ν (cm^{-1}) Sym. NO	Asym. NO_2	C=O	References
a. Acetyl	1345	1550	1720	4/90
b. Benzoyl	1350	1550	1595	4/90
c. Propanoyl	1350	1550	1725	4/90
d. Cyclopropyl-CO	1345	1545	1735	4/90
e. Ethoxycarbonyl	1345	1545	1735	4/90
f. Phenyl	1345	1540	1605	4/90

29. 3,5-Disubstituted-2,1- benzisoxazole-4,7-quinones

Substituent at 3 Position	Substituent at 5 Position	ν (cm)$^{-1}$	References
Me	OMe	1680, 1661	2/74
Me	NHPh	1692, 1629, 1612	2/74
Me	NHAr(*o*-Me)	1690, 1629, 1611	2/74
Me	NHPh(*m*-Me)	1691, 1628, 1610	2/74
Me	NHPh-*p*-Cl	1689, 1614, 1604	2/74
o-Me	NHAr	1710, 1680, 1605	2/74
NMe_2	NHAr	1658, 1605	2/74
NHMe	OMe	1650, 1630	2/74
NHEt	OMe	1656, 1603	2/74
NMe_2	OMe	1660, 1605	2/74
NH_2	OMe	1670, 1640, 1620	2/74
1-Piperidinyl	OMe	1660	2/74
1-Morpholinyl	OMe	1669	2/74
NMe_2	NHEt	1660, 1630	2/74
N Me_2	1-Piperidinyl	1655, 1605	2/74
1-Piperidinyl	NMe_2	1645, 1630	2/74
NH_2	NHPh	1668, 1620	2/74
NMe_2	NMe_2	1658, 1620	2/74
NHCH-Me	NHPh	1635, 1610	2/74
1-Morpholinyl	NHPh	1653, 1638	2/74
NHCH(benzyl)CO_2Et	HNPh	1728, 1665, 1612	2/74

30. Substituted 3,7-dialkylamino-4*H*,8*H*-benzo[1,2-*c*:4,5-*c*′]diisoxazole-4,8-diones

Substituent	ν (cm^{-1}) C=O	C=C	C=N	N–H	References
a.	1670,	1585,	1520		5/80
b. 1-Piperidinyl	1680,	1595,	1518		5/80
c. $NHCH_2Ph$	1668,	1625,	1530,	3300	5/80
d. NEt_2	1670,	1590,	1520		5/80
e. $NHCH_2CH_2OH$	1675,	1610,	1532,	3430, 3380	5/80
f. NH-*n*-Bu	1663,	1622,	1530,	3300	5/80

TABLE 2.IA. (*continued*)

Substituent	ν (cm^{-1}) C=O C=C C=N N–H	References
g. NH-*i*-Pr	1663, 1615, 1523, 3300	5/80
h. NH-C_6H_{11}	1660, 1615, 1525, 3310	5/80
i. 1-Morpholinyl	1675, 1580, 1520	5/80
31. 1,5-Dimethyl-3,4,7,8-tetrahydrobenzo[1,2-*c*: 4,5-*c*′]diisoxazole-3,4, 7,8-tetrone (KBr)	1765, 1674, 1560	6/80
32. 1,5-Diethyl-3,4,7,8- tetrahydrobenzo[1,2-*c*: 4,5-*c*′]diisoxazole-3,4,7,8-tetrone (KBr)	1766, 1669, 1569	6/80
33. 3,7-Diethoxy-4*H*,8*H*-benzo[1,2-*c*: 4,5-*c*′] diisoxazole-8-hydrazone-4-one (KBr)	3260, 1688, 1584, 1511	6/80
34. 3,7-Bisdimethylhydrazino-4*H*,8*H*-: benzo[1,2-*c*: 4,5-*c*′]diisoxazole-4,8-dione (KBr)	3440(br), 1673, 1628, 1510	6/80
35. Bisdiisopropylammonium 3,7-bis(2-propanedi nitrile-2-ylidene)(3*H*,7*H*)benzo[1,2-*c*: 4,5-*c*′] diisoxazole-1,5-diamide.	2200, 2177, 1655, 1500	3/81
36. Bis-*tert*-butyl ammonium 3,7-bis(2-propanedi nitrile-2-ylidene)(3*H*,7*H*) benzo[1,2-*c*: 4,5-*c*′] diisoxazole-1,5-diamide (KBr)	2207, 2180, 1648, 1510	3/81
37. Bis-potassium-3,7-bis-2-propanedinitrile-2-ylidene(3*H*,7*H*) benzo-[1,2-*c*: 4,5-*c*′] diisoxazole-1,5-diamide (KBr)	2210, 2185, 1652, 1518	3/81
38. Bisdiisopropylammonium 3,7-bis(3-oxo-3-phenyl-propanenitrile-2-ylidene)(3*H*,7*H*) benzo [1,2-*c*: 4,5-*c*′]diisoxazole-1,5-diamide (KBr)	2190, 1680, 1475	3/81
39. Bispotassium-3,7-bis(ethyl cyanoacetate-ylidene)(3*H*,7*H*) benzo[1,2-*c*: 4,5-*c*′]diisoxazole-1,5-diamide (KBr)	2198, 1672, 1490	3/81
40. Bispotassium-3,7-bis-(phenylsulfonylimino) (3*H*,7*H*)benzo[1,2-*c*: 4,5-*c*′]diisoxazole-1,5-diamide (KBr)	1662, 1530	3/81
41. Bissodium-3,7-bis(4-methylphenyl-sulfonylimino-(3*H*,7*H*) benzo[1,2-*c*: 4,5-*c*′]–diisoxazole-1,5-diamide(KBr)	3580, 3470, 1665, 1526, 1500	3/81
42. Bispotassium-3,7-bis(4-chlorophenyl-sulfonylimino)(3*H*,7*H*)benzo-[1,2-*c*: 4,5-*c*′] diisoxazole–1,5-diamide (KBr)	1665, 1520	3/81
43. Bisdiisopropylammonium-3,7-dioxo-(3*H*,7*H*)-benzo-[1,2-*c*: 4,5-*c*′]diisoxazole-4,8-diolate (KBr)	477 (NH_2), 1692(C=O), 1603(C=C), 1512(C=N)	8/82
44. Bistetraethylammonium-3,7-dioxo-(3*H*,7*H*)-benzo-[1,2-*c*: 4,5-*c*′]diisoxazole-4,8-diolate (KBr)	1705(C=O), 1610(C=C) 1510(C=N)	8/82
45. Bistriethylmethyl-ammonium-3,7-dioxo-(3*H*,7*H*)benzo[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-dione (KBr)	1703(C=O), 1610(C=C), 1510(C=N)	8/82
46. Bis-(*N*-methylpyridinium)-3,7-dioxo-(3*H*,7*H*)-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-diolate (KBr)	3600, 1687(C=O), 1613(C=C)	8/82

TABLE 2.IA. (*continued*)

Substituent	ν (cm^{-1}) C=O C=C C=N N–H	References
47. *N*-ethylpyridinium-4,7-dioxo-(4*H*,7*H*)-benzo-[1,2-*c*: 4,5-*c*′]diisoxazole-3-ethoxy-8-olate (KBr)	3060(Ar–H), 1713, 1686(C=O), 1609, 1579(C=O), 1506, 1483(C=N)	8/82
48. Bispyridinium-3,7-dioxo-(3*H*,7*H*)-benzo-[1,2-*c*: 4,5-*c*′]diisoxazole-4,8-diolate (KBr)	060(Ar–H), 1680(C=O), 623(C=C), 1518(C=N)	8/82
49. Magnesium-3,7-dioxo-(3*H*,7*H*)-benzo[1,2-*c*: 4.5-*c*′]-diisoxazole-4,8-diolate (KBr)	1695(C=O), 1585(C=C), 1510(C=N)	8/82
50. 3,7-Bis(diethylamino)-1-ethyl-4,8-dioxobenzo-[1,2-*c*: 4,5-*c*′]diisoxozole-1-iumtetrafluoroborate	1689(C=O), 1628(C=C), 1050(BF_4)	5/80
51. 3,7-Bis(diethylamino)-1,5-diethyl-4,8-dioxo-(4*H*,8*H*)-benzo[1,2-*c*: 4,5-*c*′]diisoxazole-1.5-ium-bistetrafluoroborate	1700(C=O), 1640(C=C), 1030 (BF_4)	5/80
52. 3,7-Diethoxy-(4*H*,8*H*)-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-dione (KBr)	1715(C=O), 1600(C=C), 1585(C=N), 1010, 970	3/78
53. 3,7-Dipiperidino(4*H*,8*H*)-benzo-[1,2-*c*: 4,5-*c*′]–diisoxazole-4,8-dione (KBr)	2950, 2920, 2860(C–H), 1665(C=O), 1580(C=C)	3/78
54. 3,7-Diamino-(4*H*,8*H*)-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-dione (KBr)	3410(NH_2), 3380(w), 3290(m), 3230(w), 3170(w), 3120, 1680 (C=O),1625(C=C,C=N), 1100, 970 (s,C–O)	3/78
55. 3,7-Dimethoxy-(4*H*,8*H*)-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-dione (KBr)	1690(C=O), 1580(C=O), 15 14(C=N)	8/80
56. *N*-Acetyl-2,1-benzisoxazolone ($CHCl_3$)	3040(w), 1786(s), 1704(s), 1613(w), 1477(m), 1464(s), 1379(s), 1350(m),1332(s), 1299(w), 1153(w), 1112(w),1074(w), 1042(w), 980(m.b)	1/72
57. 1-*tert*-Butyl-2,1-benzisioxazolin-3-one	3410, 2270, 1715	5/77
58. 6-Methyl-3a,5-cyclohexadieno[4,5-*d*] isoxazolino-3,7-dione-*N*-oxide	1800(vs), 1680(vs), 1650(vs) 1605(s), 1530(w), 1460(w), 1420(w), 1370(w), 1300, 1270(sh), 1250(vs), 1170(s)	6/77
59. *N*-Oxo-5,5-dialkyl[3,4]benzo[1,2]-oxoazoniaolines	3120(ArC–H), 1570, 1650, 665 (SbF_6), 3120(ArC–H), 1575, 1665, 1050(BF_4)$^-$	4/76
60. 1,3-Dimethyl-2,1-benzisoxazolium perchlorate (KBr)	1630, 1500, 1420, 1090, 755	6/78
61. *N*-*tert*-Butyl-3-methyl-2,1-benzisoxazolium perchlorate (KBr)	1625, 1450, 1090, 760	6/78
62. 3-Formyl-1-methyl-2,1-benzisoxazolium perchlorate-*p*-nitrophenylhydrazone	3175(NH),-1620(C=N), 1090 (ClO_4)	6/78
63. *N*-Acetyl-3-(*p*-*N*,*N*-Dimethylaminostyryl)-2,1-benzisoxazolium perchlorate	1724(C=O), 1080(ClO_4)	6/78
64. 3-Azido-1,3-dimethyl-2,1-benzisoxazoline	2083 (N_3)	6/78

TABLE 2.IB. IR SPECTRA OF ANTHRAISOXAZOLONES

3(5)-Alkoxy-6-oxo-6H-anthra[1,9-c,d]isoxazole

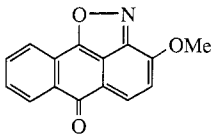
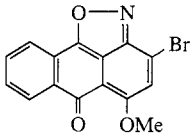
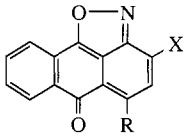
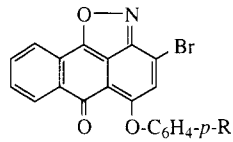
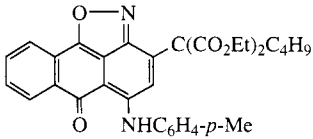
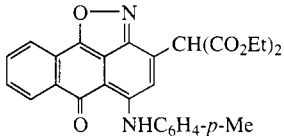
Compound			C=O	C=N	References
	a		1660	1639	10/90
	b		1665	1635	10/90
	c	R = Me X = H	1665	1630	10/90
	d	R = *n*-Pr X = Cl	1660	1633	10/90
	e	R = *n*-Bu X = Br	1660	1630	10/90
	f	R = *n*-Pr X = Br	1670	1640	10/90
	g	R = *n*-Bu X = Br	1665	1665	10/90
	h	R = *n*-Pr X = H	1665	1630	10/90
	i	R = *n*-Bu X = H	1675	1642	10/90
3-Dimethylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one			1634	1669	9/82
3-Diethylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one			1638	1669	9/82
3-Piperidinonthra[1,9-*c*,*d*]-isoxazole-6-one			1642	1671	9/82
3-Amylaminonthra[1,9-*c*,*d*]-isoxazole-6-one			1640	1673	9/82
3-Diethylamino-5-chloronthra-[1,9-*c*,*d*]-isoxazole-6-one			1639	1668	9/82
5-Diethylaminonthra[1,9-*c*,*d*]-isoxazole-6-one			1632	1671	9/82
5-*N*-amyl-*N*-benzylaminonthra-[1,9-*c*,*d*]]-isoxazole-6-one			1627	1663	9/82
N-Amylaminonthra[1,9-*c*,*d*]-isoxazole-6-one			1629	1632	9/82

TABLE 2.IB. (*continued*)



6H-6-Oxo-3-bromo-5-aryloxyanthra[1,9-c,d]isoxazoles

R	C=O	C=N	References
tert-Butyl	1645	1676	9/82
Me	1645	1670	9/82
H	1642	1675	9/82
Diethyl-2-{6*H*-oxo-3-bromoanthra-[1,9-*c*,*d*]isoxazole-5-yl)propanedioate	1660 1720 1735	1635	9/82 9/82
6*H*-6-Oxo-3,5-di(butylmalonyl)anthra-[1,9-*c*,*d*]isoxazole	1640 1710 1750		9/82
	1690 1720	1620	4/85
	1650 1700 1720	1620	4/85
6*H*-6-Oxo-3-bromo-4-(4′-ethoxy phenyl)-anthra[1,9-*c*,*d*]-isoxazole	1650		6/87
6*H*-6-Oxo-3-bromo-5-benzyloxy anthra-[1,9-*c*,*d*]isoazole	1672	1645	9/86
6*H*-6-oxo-5-fluoroanthra-[1,9-*c*,*d*]-isoxazole	1670	1650	9/86

3-Azido-5-substituted 6H-6-oxo-anthra[1,9-c,d]isoxazole

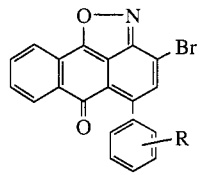
5-Substituent	C–N_3	C=O	C=N	References
H	2136	1665	1645	9/86
–NHPh-Me-*p*	2143	1680	1620	9/86
–NHPh Me_2-*p*	2120	1672	1620	9/86
–NHPh OEt-*p*	2130	1670	1620	9/86
–OCH_2Ph	2115	1672	1636	9/86
–OPh Bu-*tert*-*p*	2110	1657	1630	9/86
–OPh Me-*p*	2110	1658	1630	9/86
–OPh	2115	1657	1636	9/86

TABLE 2.IB. (*continued*)

5-Azido-3-substituted 6H-6-oxo-anthra[1,9-c,d]-isoxazole

3-Substituent	$C-N_3$	C=O	C=N	References
H	2115	1660	1640	9/86

Compound	C=O	C=N	References
5-Aminoanthra[1,9-*c*,*d*]-isoxazol-6-one-5-amylaminoanthra-	1638(s)	1685(s)	8/79
5-Amylaminoanthra-	1631(s)	1686(m)	8/79
5-Cyclohexylaminoanthra-	1637	1670 1691(m)	8/79
5-Benzylaminoanthra-	1628(m)	1680(m)	8/79
5-Phenylaminoanthra-	1630(s)	1656(cp)	8/79
3-Chloro-5-amylanthra-	1632(s)	1681(s)	8/79
3-Bromo-5-phenylaminoanthra-	1622(s)	1677(s)	8/79
3-Amylaminoanthra-	1642(s)	1671(m)	8/79
3-Methylaminoanthra-	1631(m)	1671(m)	8/79
3-Amino-5-chloroanthra-	1632(s)	1670(s)	8/79
6*H*-6-Oxo-5-bromo-4-(4′-methoxy-phenyl)-anthra[1,9-*c*,*d*]-isoxazole	1650	1630	5/88
6H-6-oxo-5-bromo-4-(4′-ethoxy-phenyl)-anthra[1,9-*c*,*d*]-isoxazole	1660	1640	5/88
6*H*-6-Oxo-5-(4′-methoxyphenyl)-3-haloanthra[1,9-*c*,*d*]isoxazole	1660	1640	5/88
6*H*-6-Oxo-5-(4′-ethoxyphenyl)-3-haloanthra[1,9-*c*,*d*]isoxazole	1660	1640	5/88



	R	C=O	N=N	References
a	4-Me	1660	1630	5/88
b	4-Et	1640	1630	5/88
c	3,4-Me_2	1660	1630	5/88
d	3,6-Me_2	1660	1630	5/88
e	4,6-Me_2	1660	1630	5/88
f	2,4,6-Me_3	1660	1630	5/88

2.II. TABLES ON UV SPECTRA OF 2,1-BENZISOXAZOLES AND ANTHRAISOXAZOLONES

TABLE 2.IIA. UV SPECTRA OF 2,1-BENZISOXAZOLES

Compound (solvent)	λ_{max} (nm) (ε_{max})	References
1. 3-Phenyl	345(14,400), 255(24,500), 249(14,400)	1/89
2. 6-Chloro-3-phenyl	346(15,020), 256(19,290), 252(17,500)	1/89
3. 5-Chloro-3-phenyl	351(14,680), 256(15,130), 249(13,450)	1/89
4. 5-Fluoro-3-phenyl	346(14,890), 255(15,200), 248(13,750)	1/89
5. 6-Methyl-3-phenyl	43(15,200), 254(17,290), 250(16,560)	1/89
6 5-Methyl-3-phenyl	348(14,560), 256(16,055), 250(14,970)	1/89
7. 5-Nitro-3-phenyl	387(13,270), 322(5380), 309(5505), 258(24,000), 253(sh)(23,290)	1/89
8. Perfluoro-3-methyl	286(1900), 243(4800), 216(5900)	5/91
9. 7-Methoxy-3,4,5,6-tetramethyl	330(27,600)	1/67
10. 6-Nitro-3-carboxylic acid	262(36,100), 296(9100), 308(6900), 343(6100)	1/70
11. 3-Ylacetic acid -3-(2-nitrophenyl)(EtOH)	323	1/74
12. 3-(2-Benzoyl-1-phenylacylidenemethyl)-6-nitro	360(13.0), 278(21.5)	1/73
13. 6-nitro-3-(1,3-dipivaloylpropen-2-yl)	360(87), 332(9.55), 276(16.7)	1/73
14. 6-Methyl-3a,5-cyclohexadieno[4,5-*d*]-isoxazoline-3,7-dione *N*-oxide	430, 345	6/77
15. *N*-*tert*-Butyl-3-methyl-2,1-benzisoxazolium perchlorate (H_2O)	335 (log ε, 3.72), 268 (3.68), 205(4.43)	6/78
16. 3-(*p*-Dimethylamino-α-methylstyryl)-1-methyl-2,1-benzisoxazolium perchlorate (MeCN)	574(log ε, 4.71), 305(4.01)	6/78
17. 1,3-Dimethyl-2,1-benzisoxazolium perchlorate (H_2O)	335(log ε, 3.54), 201 (4.40)	6/78
18. 3-Formyl-1-methyl-2,1-benzisoxazolium perchlorate-p-nitrophenylhydrazone (MeCN)	485(log ε, 4.48)	6/78

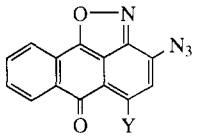
(*continued*)

TABLE 2.IIA. (*continued*)

Compound (solvent)	λ_{max} (nm) (ε_{max})	References
19. 1-Methyl-2,1-benzisoxazolium trimethylcyanine perchlorate (MeCN)	615(log ε, 4.56)	6/78
20 *N*-Acetyl-3-*p*-(*N*,*N*-dimethylaminostyryl) 2,1-benzisoxazolium perchlorate (CH_2Cl_2)	650(log ε, 4.45)	6/78
21. 3-Phenyl-2,1-benzisoxazole solvent		7/79
a. Ethanol	343 255 248 —	
b. Concentrated HCl	367 298 270 258	
c. Concentrated H_2SO_4	366 298 — 257	
d. 48% HBr	367 298 — —	
22. Bispotassium-3,7-bis(2-propanedinitrile-2-ylidine)(3*H*,7*H*)benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-1,5-diamide (MeOH)	422(4.12), 375(4.30), 246(4.04), 206 (4.34)	3/81
23. Bispotassium-3,7-bis(3-oxo-3-phenyl-propanenitrile-2-ylidene)(3*H*,7*H*)benzo-[1,2-*c*: 4,5-*c*′]diisoxazole-1,5-diamide (MeOH)	421(4.62), 300(4.03), 235(4.50), 204(4.72)	3/81
24. Bispotassium-3,7-bis(ethylcyanoacetate-ylidene)(3*H*,7*H*)benzo [1,2-*c*: 4,5-*c*′]-diisoxazole-1,5-diamide (MeOH)	420(4.09), 387(4.20), 252(4.09), 226(4.31), 204(4.51)	12/81
25. Bispotassium-3,7-bis-(phenylsulphonyl-imino)(3*H*,7*H*)benzo[1,2-*c*: 4,5-*c*′]diisoxazole-1,5-diamide (MeOH)	205(4.47)359(4.25), 322(4.53), 218(4.38)	12/81
26. Bissodium-3,7-bis-4-methylphenyl-sulfonylimino)(3*H*,7*H*)benzo [1,2-*c*: 4,5-*c*′]diisoxazole1,5-diamide (MeOH)	359(4.25), 332(4.56), 223(4.44), 204(4.50)	12/81
27. Bisdiisopropylammonium-3,7-dioxo-3*H*,7*H*-benzo[1,2-*c*: 4,5-*c*′]diisoxazole-4,8-diolate (H_2O)	346(4.25), 282(4.17), 234(4.04)	12/81
28. 3,7-Diethoxy-4*H*,8*H*-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-dione (MeCN)	290(4.0), 273(3.9), 213(3.9)	3/78
29. 3,7-Dipiperidino-4*H*,8*H*-benzo-[1,2-*c*: 4,5-*c*′] diisoxazole-4,8-dione (MeCN)	351(4.2), 312(4.4), 217(4.2)	3/78
30. 3,7-Diamino-4*H*,8*H*-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-dione (MeOH)	26(4.0), 284(4.1), 216(3.8)	3/78
31. 3,7-Dimethoxy-4*H*,8*H*-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-4,8-dione (MeCN)	295(3.75), 278(3.98), 218(3.70)	7/80

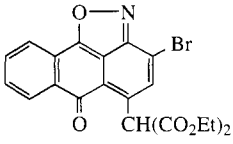
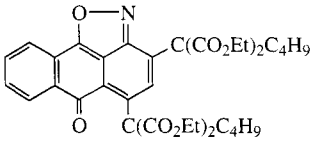
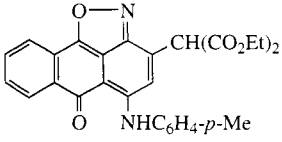
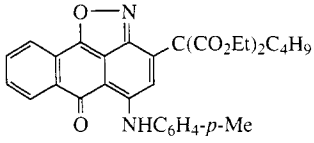
TABLE 2.IIB. UV SPECTRA OF ANTHRAISOXAZOLONES

3-Azido-5-substituted 5H-6-oxo-anthra[1,9-c,d]isoxazole



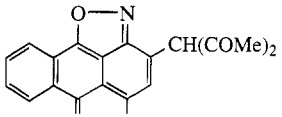
Substituent	λ_{max} (nm) (log ε)	References
H	440(4.13), 463(4.25)	9/86
NHArMe-*p*	498(4.19), 529(4.21)	9/86
NHArCHMe$_2$)-*p*	495(4.22), 527(4.27)	9/86
NHArOEt-*p*	500(3.97), 520(4.02)	9/86
O-CH$_2$Ar	460(4.20), 478(4.18)	9/86
O-Ar-*tert*-Bu-*p*	455(4.20), 472(4.22)	9/86
O-ArMe-*p*	454(4.22), 471(4.21)	9/86
O-Ar	460(4.19)	9/86

Substituted 6H-6-oxo-3(5)-halogenoanthra[1,9-c,d]isoxazoles

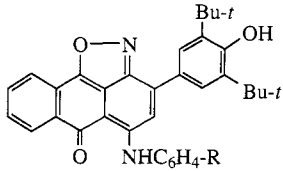
Compound	λ_{max} (nm) (log ε)	References
	434(4.16), 455(4.18)	4/85
	452(4.12), 472(4.15)	4/85
	505(4.18), 527(4.23)	4/85
	520(4.19), 523(4.24)	4/85

(*continued*)

TABLE 2.IIB. (*continued*)

	505(4.14), 528(4.19)	4/85

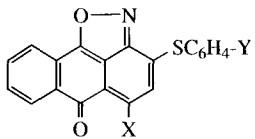
6H-6-Oxo-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-5-aryl-aminoanthra-[1,9-c,d]isoxazole



Compound	λ_{max} (nm) (log ε)	References
p-Me	544(4.33)	10/84
H	542(4.34)	10/84
m-Me	544(4.33)	10/84
o-OMe	534(4.30)	10/84
6*H*-6-Oxo-bromo-[5-(*o*-anisidino)-anthra[1,9-*c*,*d*]isoxazole	536(4.25)	10/84
3-(Phenylaminocarbonyl)anthra-[1,9-*c*,*d*]-6-isoxazolone	459(4.20)	8/84
3-Dimethylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	502(4.23)	9/82
3-Dimethylaminoanthra[1,9-*c*,*d*]-isoazol-6-one	505(4.26)	9/82
3-Piperidinoanthra[1,9-*c*,*d*]-isoxazole-6-one	523(4.23)	9/82
3-Diethylamino-5-chloroanthra-[1,9-*c*,*d*]-isoxazole-6-one	506(4.27)	9/82
3-Amylamino-5-chloroanthra-[1,9-*c*,*d*]-isoxazole-6-one	505(5.39)	9/82
5-Dimethylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	488(4.22), 512(4.23)	9/82
5-*N*-amyl-*N*-benzylaminoanthra-[1,9-*c*,*d*]-isoxazole-6-one	490(4.38), 510(4.36), 524(4.36)	9/82
5-Amylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	495(4.29), 530(4.34)	9/82
5-Aminoanthra[1,9-*c*,*d*]-isoxazole-6-one	468(4.06), 503(4.07)	8/79
5-Cyclohexylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	495(4.17), 533(4.22)	8/79
5-Benzylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	493(4.17), 528(4.20)	8/79
5-Phenylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	488(4.18), 523(4.22)	8/79
5-Chloro-5-amylanthra[1,9-*c*,*d*]- isoxazole-6-one	493(4.16), 522(4.19)	8/79
5-Bromo-5-phenylanthra[1,9-*c*,*d*]-isoxazole-6-one	500(4.20), 538(4.24)	8/79
3-Chloro-5-amylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	502(4.16), 532(4.23)	8/79
3-Amylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	503(5.69)	8/79
3-Methylaminoanthra[1,9-*c*,*d*]-isoxazole-6-one	500(5.07)	8/79

TABLE 2.IIB. (*continued*)

3-Arylthio-6H-6-oxo-anthra[1,9-c,d]isoxazoles



Compound	X	Y	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε)	References
a	H	H	84	155	255(4.44), 449(4.31), 477(4.41)	10/79
b	H	4-CH_2	80	157	255(4.53), 450(4.27), 478(4.42)	10/79
c	H	4-Cl	86	180	230(4.46), 255(4.51), 448(4.22), 477(4.37)	10/79
d	H	4-Br	76	188	235(4.52), 255(4.52), 449(4.22), 477(4.37)	10/79
e	H	2,4-Me_2	79	143	230(4.52), 255(4.55), 449(4.31), 478(4.46)	10/79
f	H	4-OMe	83	51	235(4.52), 255(4.51) 451(4.28), 479(4.43)	10/79
g	H	4-*tert*-Bu	76	158	230(4.48), 255(4.53), 451(4.32), 479(4.46)	10/79
h	H	4-Et	83	122	230(4.44), 255(4.51), 451(4.27), 479(4.37)	10/79
i	H	3,4-Me_2	82	147	230(4.51), 255(4.58), 451(4.32), 480(4.46)	10/79
j	OH	H	88	148	245(4.60),440(4.00), 454(4.00), 490(3.54)	10/79
k	OH	4-Me	88	180	245(4.60), 440(4.00), 454(3.98), 492(3.53)	10/79

(*continued*)

TABLE 2.IIB. (*continued*)

Compound	X	Y	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε)	References
l	OH	4-Cl	86	160	245(4.62), 443(3.96), 457(3.96), 490(3.53)	10/79
m	OH	4-Br	87	179	245(4.62), 443(3.98), 455(3.98), 490(3.54)	10/79
n	OH	4-*tert*-Bu	80	174	245(4.54), 442(3.97), 455(3.96), 490(3.53)	10/79
o	OH	4-OMe	84	185	245(4.61), 436(3.99), 454(3.97), 492(3.51)	10/79
p	OH	4-Et	79	166	245(4.57), 442(3.97), 454(3.96), 491(3.51)	10/79
q	OH	4-*sec*-Bu	71	111	245(4.60), 442(3.98), 454(3.98), 491(3.54)	10/79
r	OH	2,4-Me_2	85	185	245(4.62), 442(3.99), 454(3.98), 492(3.54)	10/79
s	OH	3,4-Me_2	83	190	245(4.54), 441(4.00), 453(3.99), 492(3.54)	10/79

TABLE 2.IIB. (*continued*)

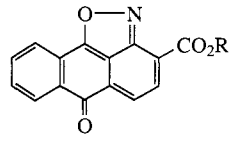
Constants, yields, and UV data of 6-acyloxy-5H-5-oxo-anthra[1,9-c,d]isoxazoles (a–j)

Compound	R_1	R_2	R_3	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε),	References
a	*o*-Ph	H	Ar	87	195	235(4.84), 384(3.81), 402(3.81)	11/90
b	*o*-Ph	H	Me	89	186	235(4.70), 386(3.72), 403(3.72)	11/90
c	*o*-ArMe-*p*	H	Ar	85	204	235(4.84), 384(3.81), 402(3.81)	11/90
d	*o*-ArMe-*p*	H	Me	86	190	235(4.69), 386(3.74), 403(3.74)	11/90
e	*o*-ArCl-*o*	H	Ar	97	225	235(4.82), 386(3.75), 403(3.75)	11/90
f	*o*-Ar-*t*-C_5H_{11}-*p*	H	Ar	89	154	235(4.83), 384(3.77), 402(3.77)	11/90
g	*s*-Ar	H		93	204	240(4.64), 367(4.14)	11/90
h	*s*-ArMe-*p*	H	Me	92	207	240(4.64), 367(4.15)	11/90
i	Br	H	Ar	90	206	235(4.65), 401(3.64)	11/90
j	Br	H	Ar	88	240	235(4.76), 404(3.79)	11/90

(*continued*)

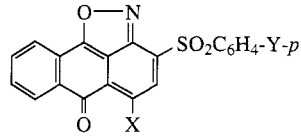
TABLE 2.IIB. (*continued*)

Constants, yields, and UV data of 3-alkoxycarbonyl-anthra[1,9-c,d]-6-isoxazolones



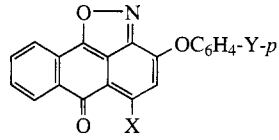
Compound	R	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε)	References
a	Me	95	215–217	460(4.05)	9/84
b	Et	96	186–188	460(4.07)	9/84
c	*n*-Pr	83	158–159	460(4.04)	9/84
d	*n*-Bu	87	167–169	460(4.08)	9/84
e	*iso*-C_5H_{11}	87	154–156	461(4.08)	9/84
f	C_6H_{13}	81	129–130	461(4.09)	9/84

Constants, yields, and UV data of 3-arylsulfonylanthra- [1,9-c,d]-6-isoxazolones a–g)



Compound	X	Y	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε)	References
a	H	H	88	183	300(4.08), 466(3.98)	5/84
b	OH	H	89	167	300(3.97), 480(3.90), 505(3.88)	5/84
c	H	Me	86	221	300(4.08), 466(3.81)	5/84
d	OH	Me	82	187	300(4.01), 480(3.88), 505(3.84)	5/84
e	H	Cl	89	213	305(4.08), 468(4.01)	5/84
f	OH	Cl	91	177	300(4.08), 480(3.93), 508(3.90)	5/84
g	OH	Br	80	197	300(4.05), 480(3.90), 508(3.88)	5/84

3-Aryloxanthra[1,9-cd]isoxazol-6-ones

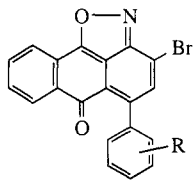


Compound	X	Y	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε)	References
a	OH	H	78	160	240(4.70), 410(3.92)	3/80
b	OH	4-Me	81	146	240(4.70), 419(3.98)	3/80
c	OH	4-Cl	76	148	240(4.70), 419(3.92)	3/80
d	OH	2-Cl	79	136	240(4.78), 410(4.01)	3/80
e	OH	4-Me_3	74	131	240(4.70), 410(3.94)	3/80

TABLE 2.IIB. (*continued*)

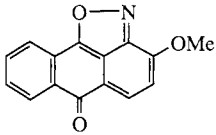
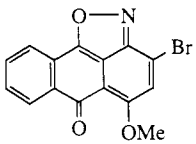
Compound	X	Y	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε)	References
f	OH	4-CMe_2Et	83	148	240(4.78), 410(4.00)	3/80
g	NHPh	4-CMe_3	87	151	252(4.32), 485(4.25) 516(4.29)	3/80
h	NH[2,4-$Me_2C_6H_2$]	4-CMe_3	91	175	252(4.46), 485(4.30), 515(4.36)	3/80
i	NH[2,4-$Me_2C_6H_3$]	4-CMe_2Et	89	158	252(4.39), 485(4.20), 515(4.26)	3/80
j	NH[2,4,6-$Me_3C_6H_2$]	4-Me	83	146	252(4.49), 485(4.30) 551(4.34)	3/80
k	NH[2,4,6-$Me_3C_6H_2$]	4-CMe_3	81	171	252(4.53), 485(4.32), 515(4.35)	3/80
l	NH[2,4,6-$Me_3C_6H_2$	4-C(Me)Et	79	168	252(4.54), 485(4.32), 515(4.38)	3/80

UV data of products from the reaction of alkyl phenyl ethers and alkylbenzenes with halogen-substituted 6H-6-oxo-anthra[1,9-c,d]isoxazoles



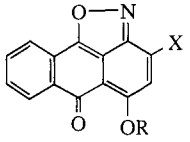
Compound	R	λ_{max} (nm) (log ε)	References
a	4-Me	212(4.55), 247(4.40), 308(3.94) 342(3.87), 451(4.08)	5/88
b	4-Et	212(4.53), 248(4.39), 307(3.94) 342(3.86), 451(4.06)	5/88
c	3,4-Me_2	214(4.49), 248(4.34), 309(3.86) 342(3.83), 450(4.07)	5/88
d	3,6-Me_2	213(4.53), 247(4.38), 309(3.86) 449(3.86)	5/88
e	4,6-Me_2	208(4.61), 247(4.48), 308(3.89) 339(3.76), 379(3.62), 447(4.10)	5/88

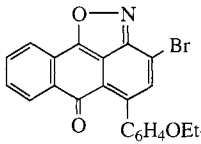
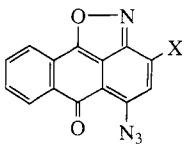
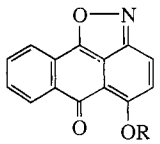
UV data of 3(5)alkoxy-6H-6-oxo-anthra[1,9-c,d]isoxozole

Compound	R	X	λ_{max} (nm) (log ε)	References
			245(4.41), 306(3.37) 422(4.17), 446(4.35)	10/90
			251(4.20), 294(3.73) 321(3.70), 441(4.08) 457(4.166)	10/90

(*continued*)

TABLE 2.IIB. (*continued*)

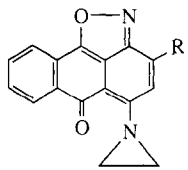
Compound	R	X	λ_{max} (nm) (log ε)	References
	Me	H	248(4.48), 321(3.97) 446(4.18), 468(4.18)	10/90
	n-Pr	Cl	251(4.41), 322(3.83) 449(4.13), 470(4.15)	10/90
	n-Bu	Cl	251(4.39), 322(3.74) 449(4.09), 469(4.10)	10/90
	n-Pr	Br	252(4.28), 320(3.88) 440(4.16), 458(4.22)	10/90
	n-Bu	Br	251(4.30), 295(3.88) 320(3.89), 439(4.15) 458(4.21)	10/90
	n-Pr	H	249(4.40), 320(3.82) 446(4.10), 465(4.10)	10/90
	n-Bu	H	249(4.40), 320(3.86) 448(4.08), 464(4.07)	10/90
	Ph	Br	248(5.07), 443(4.16) 455(4.19)	10/90

Compound	λ_{max} (nm) (log ε)	References
6*H*-6-Oxo-5-fluoroanthra[1,9-*c*,*d*]isoxazole	446(4.07)	9/86
	397(3.97), 423(3.97) 451(3.97)	6/87
	448(3.94), 468(4.03)	9/86
		

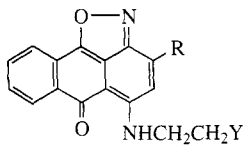
Compound	R	m.p. (°C)	λ_{max} (nm) (log ε)	Yield (%)	References
	Me	227–228	244(4.99), 249(5.1), 445(4.16), 467(4.16)	70.8	9/83
	Et	204–206	244(5.0), 249(5.10), 445(4.12), 466(4.12)	62.5	9/83
	n-Pr	171–172	244(4.99), 249(5.10), 445(4.14), 466(4.13)	77.1	9/83

TABLE 2.IIB. (*continued*)

Compound	R	m.p. (°C)	λ_{max} (nm) (log ε)	Yield (%)	References
	iso-Pr	143–145	244(5.99), 249(5.06), 445(4.12), 466(4.12)	53.0	9/83
	n-Bu	146–148	243(5.99), 249(5.08), 446(4.17), 465(4.17)	50.0	9/83
	iso-Bu	154–155	244(5.98), 249(5.07), 446(4.13), 465(4.13)	56.3	9/83
	Ph	185–186	243(5.03), 248(5.07), 443(4.16), 455(4.19)	56.0	9/83
	p-MeAr	186–187	243(5.03), 249(5.08), 444(4.14), 456(4.14)	85.0	9/83
	p-ClAr	222–223	243(5.06), 248(5.19), 442(4.14), 459(4.14)	68.0	9/83
	p-CMe_3Ar	221–222	243(5.06), 248(5.11), 442(4.74), 459(4.16)	58.0	9/83



R	λ_{max} (nm) (log ε)	References
H	480(4.18), 454(4.16), 259(4.38), 249(4.38)	7/84
Me	480(4.11), 452(4.10), 257(4.40), 250(4.41)	7/84
Cl	485(4.20), 460(4.19), 260(4.42), 253(4.39)	7/84
Br	488(4.20), 460(4.19), 260(4.38), 256(4.48)	7/84



R	Y	λ_{max} (nm) (log ε)	References
H	Cl	520(4.26), 486(4.22), 258(4.50), 252(4.44)	7/84
H	Br	520(4.25), 488(4.20), 260(4.51), 253(4.43)	7/84
H	OCOMe	522(4.35), 490(4.27), 260(4.55), 253(4.48)	7/84
Me	Cl	515(4.29), 485(4.23), 259(4.98), 253(4.47)	7/84

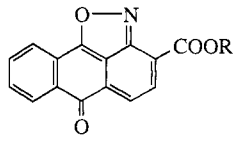
(*continued*)

TABLE 2.IIB. (*continued*)

R	Y	λ_{max} (nm) (log ε)	References
Me	Br	515(4.29), 483(4.23), 260(4.48), 252(4.44)	7/84
Me	OCOMe	538(4.30), 485(4.25), 259(4.52), 252(4.50)	7/84
Cl	Cl	255(4.43), 261(4.53), 533(4.23), 498(4.18)	7/84
Cl	OCOMe	533(4.23), 498(4.19), 261(4.53), 255(4.43)	7/84
Br	OCOMe	532(4.29), 496(4.19), 262(4.54), 255(4.42)	7/84

Anthra[1,9-c,d]-6-isoxazolone-5-(N-pyridinium)chloride

Compound	R	λ_{max} (nm) (log ε)	References
a	C_6H_{11}	555(4.35)	8/83
b	C_4H_9	555(4.17)	8/83



R	Yield (%)	m.p. (°C)	λ_{max} (nm) (log ε)	References
Me	95	215–217	460(4.05)	9/84
Et	96	186–188	460(4.07)	9/84
Pr	83	158–159	460(4.04)	9/84
Bu	87	167–169	460(4.08)	9/84
iso-C_5H_{11}	87	54–156	461(4.08)	9/84
C_6H_{13}	81	129–130	461(4.29)	9/84

2.III. TABLES ON ^{1}H-NMR SPECTRA OF 2,1-BENZISOXAZOLES AND ANTHRAISOXAZOLONES

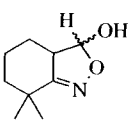
TABLE 2.IIIA. ^{1}H-NMR SPECTRA OF 2,1-BENZISOXAZOLES

Compound (solvent)	Concentration (ppm)	References
1. 6-Methyl-3-phenyl	2.4(s,3*H*,Me), 6.8–8.2(m,8*H*,ArH)	1/89
2. 5-Methyl-3-phenyl	2.4(s,3*H*, Me, 7.1–8.1[m,9*H*(ArH+1/2 H_2O)]	1/89
3. 3-Ethyl ($CDCl_3$)	1.46(t, J = 7.6 Hz), 3.18(q, J = 7.6 Hz,CH_2), 6.80–7.57 (m,4ArH)	8/91
4. 3-(Diethylamino)-5-(phenylamino) ($CDCl_3$)	1.35(t, 6*H*), 3.92(q,4*H*), 6.23(s,1*H*), 7.21–7.50 (m,5*H*), 8.02(bs,1*H*)	7/91
5. 3-Ethoxy-5-[(4-fluorophenyl)amino]-2,1- benzisoxazole-4,7-dione ($CDCl_3$)	1.61(s,3*H*), 4.85(q,2*H*), 6.14(s,1*H*), 7.10–7.29 (m,4*H*), 7.69 (bs,1*H*)	7/91
6. 3-Phenyl-5-(phenylamino)2,1-benzisoxazole-4,7-dione (DMSO-d_6)	6.02(s,1*H*), 7.27–7.45(m,5*H*), 7.63–7.78 (m,3*H*), 8.45(d,2*H*), 9.67 (bs,1*H*)	7/91
7. 4-Methyl ($CDCl_3$)	2.5(s,3*H*), 6.7(dd,1*H*), 7.3(m,2*H*), 9.1(s,1*H*)	4/86
8. 4-Bromomethyl ($CDCl_3$)	4.6(s,2*H*), 7.2(m,3*H*), 9.3(s,1*H*)	4/86
9. 4-Formyl	7.6(m,3*H*), 9.7(s,1*H*), 9.9(s,1*H*)	4/86
10. 4-[4-(2,1-Benzisoxazolyl)]-2,6-dimethyl-1-dihydropyridine-3,5-dicarboxylate	2.3(s,6*H*), 3.6(s,6*H*), 5.3(s,1*H*) 6.3(br,s,1*H*), 6.9(d,1*H*,J = 6 Hz), 7.3(m,2*H*), 9.3(s,1*H*)	4/86
11. 3-(*o*-Carboxyphenyl)-5-phenylanthranil (60 MHz) (DMSO-d_6)	13.3(br,s,1,O*H*), 7.3–8.2(m,12,ArH)	3/87
12. 5-Bromo-3-(*o*-carboxyphenyl)(60 MHz)($CDCl_3$)	12.5(br,s,1,CO_2H), 7.3–8.3(m,7,ArH)	3/87
13. 5-Bromo-3-(*o*-carbomethoxyphenyl) (60 MHz, $CDCl_3$)	7.3–8.3(m,7,ArH), 3.77(s,3,CO_2Me)	3/87
14. 3-[α-(Ethoxycarbonyl)benzoyl]-($CDCl_3$)(90 MHz)	10.4(br,enol,OH), 8.0–8.35, 6.95–7.75(9*H*,m,ArH), 5.15(s,C*H*),4.0–4.35(2*H*,q,CH_2), 0.9–1.25(3*H*,t,Me)	2/86
15. 3-[4-(4-Phenoxyphenyl)]-5-bromo-($CDCl_3$)	8.06–8.07(d,2H), 8.03(s,1*H*), 7.07–7.87(m,13*H*)	9/85
16. 3-[4-(4-Phenylphenoxy)phenyl]-5-bromo	8.00(s,1*H*), 7.95-9.98(d,1*H*), 7.16–7.65(m,13*H*)	9/85
17. 3-[4-(Phenoxyphenoxy)phenyl]-5-bromo ($CDCl_3$)	7.99(s,1*H*),7.93–7.96(d,2*H*),7.02–7.53(m,13*H*)	9/85

(*continued*)

TABLE 2.IIIA. (*continued*)

Compound (solvent)	Concentration (ppm)	References
18. 5-Formyl-3-phenyl-($CDCl_3$; 270 MHz)	10.01(s,1*H*), 7.63–8.41(m,8*H*)	10/85
19. 5-Hydroxymethyl-3-phenyl-($CDCl_3$; 270 MHz)	7.30-8.01(m,8*H*),4.75(s,2*H*),2.95(brs,1*H*)	10/85
20. 5-Chloromethyl-3-phenyl-($CDCl_3$; 270 MHz)	7.36–8.01(m,8*H*), 4.64(s,2*H*)	10/85
21. 5,5′-(1,2-ethenediyl)bis(3-phenyl ($CDCl_3$; 270 MHz)	7.52–7.77(m,16*H*), 6.74(s,2*H*)	10/85
22. 1-*tert*-Butyl-3-phenyl-2,1-benzisoxazoline	7.38(5*H*,s,ArH), 6.8–7.25(4*H*,m,ArH), 6.41 (1*H*,s, C–*H*), 1.32 (9H, s,Me_3C–)	2/70
23. 1-*tert*-Butyl-6-methyl-3-phenyl-2,1-benzisoxazoline	6.8-7.2(4*H*,m,ArH); 5.14(2*H*,s,-CH_2), 1.24 (9*H*,s,Me_3C–)	2/70
24. 1-*tert*-Butyl-5-chloro-6-methyl-3-phenyl-2,1-benzisoxazoline	7.36(5*H*,s,Ar*H*), 6.81–6.90(2*H*,2s,ArH), 6.32(1*H*,s, C*H*), 2.34(3H,s,Ar-Me), 1.32 [9*H*,s,$(Me_3)C$–]	2/70
25. 3-Aryl-C_6H_4Me-4	6.90–8.05(m,Ar*H*), 2.35(s,Me)	4/83
26. 3-Aryl-C_6H_4Br-4	6.90–7.90 (Ar*H*)	4/83
27. 3-Aryl-C_6H_4OMe-4	6.90–8.05(Ar*H*), 3.80(s,Me)	4/83
28. 3-Aryl-$C_6H_3(Me)_2$-2,6	6.65–7.75(m,Ar*H*), 2.10(s,Me)	4/83
29. 3-Aryl-$C_6H_3(Me)_2$-2,4)	6.80–7.65(m,Ar*H*), 2.45(s,Me, 2.35(s,Me)	4/83
30. 3-Aryl-$C_6H_3(OMe)_2$-2,6	6.55–7.70(m,Ar*H*), 3.70(s,Me)	4/83
31. 3-Aryl-$C_6H_2(Me)_3$-2,4,6)	7.57–7.87(d,7*H*),7.20–7.40(t,5*H*,6*H*), 6.85–7.00(m,3′,5′,4*H*), 2.35(s,Me), 2.05(s,2Me)	4/83
32. 5-(2-Methyl-1,3-dioxalan-2-yl)-3-[4-biphenylene-2-yloxy)phenyl] ($CDCl_3$)	7.17–8.02(q,4*H*),7.89–7.90(d,1*H*),7.57–7.60(d,1*H*), 7.41–7.45(dd,1*H*),6.41–6.79(m,7*H*), 3.81–4.11(m,4*H*),1.70(s,3H)	8/86
33. 9-[5-(3-Phenyl-2,1-benzisoxazolyl)]-9-[4′-(2-methyl-1,3-dioxalan-2-yl)phenyl] fluorene ($CDCl_3$, 1% TMS)	6.89–7.87(m,20*H*,Ar*H*), 3.82(A_2B_2,m,4*H*,Me), 1.58 (s,3*H*,Me)	7/81
34. 2,1-Benzisoxazol-3-yl-acetic acid (DMSO)	7.3–7.8(m,3*H*,Ar*H*),6.95–7.15(m,1*H*,ArH),	4/70
35. 3-Nitrobiphenyl-2,1-benzisoxazole	6.8–8.3(complex multiplet)	1/74
36. 3-Ethyl-7-(1-methoxy-3-bromopropyl)	7.83(d,H-4), 7.73(d,H-7), 7.21(dd,H-5), 3.51 (dd,1*H*,CH–OMe), 2.31–2.70(m,2*H*,CH_2,Br), 1.82,(t,3H,Me)	1/78

37. 3-Methoxy-2,1-benzisoxazole-7-carboxylic acid	7.05–8.25(m,3*H*,Ar*H*), 3.99 (s, 3*H*, Me)	1/75
38. 5-Chloro-6-nitro-3-phenyl	7.88(s,H-7), 7.60(s,H-4), 3.21(q,CH_2), 1.52 (t, Me).	5/76
39. 7-Chloro-6-nitro-3-phenyl	7.38(d,*J* = 8.8Hz,H-5), 7.06(d,*J* = 8.8Hz,H-4), 3.16(q,CH_2), 1.48(t,CH_3)	5/76
40. 4-Chloro-6-nitro-3-phenyl	8.46(dd,H-1′), 7.48(d,*J* = 1.8Hz, H-5); 3.39(q,CH_2), 1.4(t,Me)	5/76
41. 3-Ethyl-4-methoxy	7.24(d,H-7), 6.81(dd,H-6), 6.37(d,H-4), 3.57(s,OMe), 2.93(q,CH_2), 1.32(t,Me), [*J* (*ortho*) = 8 Hz; *J* (*meta*) = 2Hz]	5/76
42. 1-*tert*-Butyl-2,1-benzisoxazolium-tetrafluoroborate (D_2O)	10.8(s,1*H*), 7.4–8.3 (m,4*H*), 1.95(s,9*H*)	5/77
43. 1-*tert*-Butyl-2,1-benzisoxazolium-3-ol (DMSO)	6.4–7.5(m,4*H*), 1.24(s,9*H*)	5/77
44. 3,4-Tetramethylene-isoxazole (CCl_4)	8.07(s,1*H*), 2.35–2.85(m,4*H*), 1.5–2.0(m,2*H*)	7/78
45. 5-Phenyl-3,4-tetramethyleneisoxazole	7.2–7.95(m,5*H*), 2.4–3.1(m,4*H*), 1.5–2.1(m,4*H*)	7/78
46. 5-*p*-Methoxyphenyl-3,4-tetramethylene-isoxazole ($CDCl_3$)	7.55(d,2*H*,*J* = 9Hz), 6.85(d,2*H*,*J* = 9Hz), 3.78(s,3*H*) 2.15–3.0 (m,6*H*)	7/78
47. 5-*p*-Chlorophenyl-3,4-(1-methyltetra-methylene)isoxaole ($CDCl_3$)	7.62(d,2*H*,J = 9 Hz), 7.35(d,2*H*,J = 9 Hz), 2.25–3.2 (m,3*H*), 1.40(d,7*H*,*J* = 8 Hz),1.3–2.2(m)	7/78
48. 7-Aza-5,5-Dimethyl-8-oxabicyclo[4.3.0]-6,9-nonadiene (CCl_4)	7.98(t,1*H*,*J* = 1Hz),2.35–2.7(m,2H),1.5–2.0(m,4H) 1.32 (s,6H)	7/78
49. 4,5-Dihydronaphth[1,2-C]isoxazole (CD_3CN)	7.6–8.0(m,*H*), 7.05–7.35(m,3*H*), 5.5–5.9 (m,1*H*,by D_2O wash became d, *J* = 6 Hz), 4.45–4.75(m,1*H*,washed out with D_2O) 2.7–3.5(m,3*H*), 1.65–2.3 (m,2*H*)	7/78
50. Tricyclo[4.3.1.1]undecan[4,5-C]isoxazole ($CDCl_3$)	7.95(d,1*H*,*J* = 1 Hz), 2.85–3.45(m,2*H*), 1.2–2.35 (m,12 *H*)	7/78
51. 	5.83(d,0.5*H*, *J* = 7 Hz), 5.57(d,0.5*H*, *J* = 2.5 Hz, 4.1–4.65(b, 1*H*), 2.85–3.45(m,1*H*), 1.0–2.5 (m, 12*H*, large spikes at δ 1.15,1.23)	
52. *N*-Ethyl-3-methoxy-2,1-benzisoxazoline (CCl_4)	6.6–7.4(m,4*H*), 6.20(s,1*H*), 3.30, 3.28, 3.25(s, q, *J* = 7 Hz), q, *J* = 7 Hz,5*H*), 1.19 (t,3*H*, *J* = 7 Hz)	15/84
53. *N*-Methyl-3-methoxy-2,1-benzisoxazoline (CCl_4)	6.6–7.4 (m,4*H*), 6.23(s,1*H*), 3.32(s,3*H*), 3.03(s,3*H*)	15/84

(*continued*)

TABLE 2.IIIA. (*continued*)

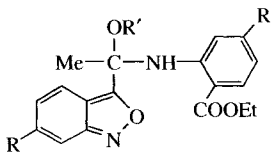
Compound (solvent)	Concentration (ppm)	References
54. *N*-Ethyl-3-ethoxy-2,1-benzisoxazoline (CCl_4)	6.6–7.4(m,4*H*), 6.25(s,1*H*), 3.66, 3.25 (q, J = 7 Hz, q, J = 6.5 Hz, 4*H*), 1.19, 1.16 (t, J = 7 Hz, t, J = 7Hz, 6*H*)	15/84
55. *N*-*tert*-Butyl-3-methoxy-2,1-benzisoxazoline (CCl_4)	6.8–7.3(m,4*H*), 6.10(s,1*H*), 3.32(s,3*H*) 1.25(s,9*H*)	15/84
56. *N*-Ethyl-3-cyano-2,1-benzisoxazoline (CD_3NO_2)	6.8–7.6(m,1*H*), 6.23(s,1*H*), 3.48, 3.43 (2q, 2*H*, J = 7 Hz), 1.25(t,3*H*, J = 7 Hz)	15/84
57. *N*-*tert*-Butyl-3-cyano-2,1-benzisoxazoline	6.8–7.4(m,4*H*), 5.94(s,1*H*), 1.23(s,9*H*)	15/84
58. *N*-Ethyl-3-azido-2,1-benzisoxazoline (CCl_4)	6.4–7.4(m,4*H*), 6.33(s,1*H*), 3.27(q,2*H*,J = 7 Hz), 1.20(t, 3*H*,J = 7 Hz)	15/84
59. N-*tert*-butyl-3-azido-2,1-benzisoxazoline (CCl_4)	6.7–7.4(m,4*H*), 6.39(s,1*H*), 1.29 (s,9*H*)	15/84
60. 3-(*n*-*tert*-Butyl-2,1-benzisoxazolinyl)-tri-*n*-butylphosphonium perchlorate (CD_3CN)	7.0–7.5(m,4*H*), 6.53(d,1*H*,J = 12.5 Hz),1.8–2.5 (m,6*H*),1.28, 1.1–1.8(s, m, 21*H*),0.7–1.1(m,9*H*)	15/84
61. 1,3-dimethyl-2,1-benzisoxazolium perchlorate (CD_3CN)	7.8(m,4*H*), 4.4(s,3*H*), 3.0(s,3*H*)	4/78
62. *N*-*tert*-Butyl-3-methyl-2,1-benzisoxazolium perchlorate (CD_3CN)	8.0(m,3*H*), 7.4(m,1*H*), 3.0(s,3*H*), 1.9(s,9*H*)	4/78
63. 3-(*p*-Dimethylaminostyryl)-1-methyl-2,1-benzisoxazolium perchlorate (CF_3CO_2H)	7.5–8.3(m,10*H*), 4.5(s,3*H*), 3.5(s,6*H*)	4/78
64. 3-(*p*-Dimethylamino-α-methylstyryl)-1-methyl-2,1-benzisoxazolium perchlorate (CF_3CO_2H)	7.0–7.9 (m,9*H*), 4.2(s,3*H*), 3.2(s,6*H*), 2.5(s,3*H*)	4/78
65. 3-Azido-1,3-dimethyl-2,1-benzisoxazoline ($CDCl_3$)	6.8–7.6(m,4*H*), 3.1(s,3*H*), 1.91(s,3*H*)	4/78
66. 1,3-Dimethyl-2,1-benzisoxazoline ($CDCl_3$)	6.4–7.2(m,4*H*), 5.3(q,1*H*,J = 7 Hz), 3.0(s,3*H*), 1.5(d,3*H*,J = 7 Hz).	4/78
67. *N*-Methylanthranilium fluoroborate (CD_3NO_2)	9.91(s,1*H*), 7.5–8.4(m,4*H*), 4.77(s,3*H*)	12/84
68. *N*-Ethylanthranilium fluoroborate (CD_3NO_2)	9.97(s,1*H*), 7.5–8.3(m,4*H*), 5.05(q, 2*H*,J = 7 Hz), 1.72 (t, 3*H*, J = 7 Hz)	12/84

69. *N*-Isopropyl anthranilium fluoroborate (CD_3NO_2)	9.96(s,1*H*), 7.5–8.35(m,4*H*), 5.63(septet,1*H*,*J* = 7 Hz) 1.80(d,6*H*, *J* = 7Hz),	12/84
70. *N-tert*-Butyl anthranilium fluroroborate (CD_3NO_2)	10.00(s,1*H*), 7.5–8.35(m,4*H*), 1.98(s,9*H*)	12/84
71. *N*-1′-Adamantyl anthranilium perchlorate (CD_3NO_2)	10.06(s,1*H*), 8.0–8.3(m,3*H*), 7.5–7.8(m.1*H*) 2.2–2.8(m.9*H*), 1.8–2.1(m,6*H*).	12/84
72. 3-(*N-tert*-Butyl-2,1-benzisoxazolinyl-triphenyl phosphonium perchlorate (CD_3CN)	8.48(br,s,1*H*), 7.15–7.9(m,19*H*), 1.50(s,9*H*)	12/84
73. *N-tert*-Butyl-*N*-methyl-3-(dimethoxy-phosphenyl)-2,1-benzisoxazolium perchlorate (CD_3CN)	7.82 (br,s,4*H*), 6.31(s,1*H*), 3.95, 3.93 3.73 (s, d, *J* = 11 Hz, *J*,*J* = 11 Hz, 9*H*) (~ 3:3:3), 1.60 (s,9*H*)	12/84
74. 1,5-Dimethyl-3,4,7,8-tetrahydro[1,2-*c*: 4,5-*c*′]diisoxazole-3,4,7,8-tetraone (DMSO-d_6)	4.07 (s,Me)	7/80
75. 1,5-Diethyl-3,4,7,8-tetrahydrobenzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-3,4,7,8-tetrone (acetone-d_6)	4.64 (q,*J* = 7.2 Hz,CH_2), 1.47(t, *J* = 7.2 Hz, Me)	7/80
76. 3,7-Diethoxy-(4*H*,8*H*)-benzo-[1,2-*c*: 4,5-*c*′]-diisoxazole-8-hydrazone-4-(DMSO-d_6)	5.07(q,*J* = 7.0 Hz,CH_2), 4.54(q, *J* = 7.0 Hz,CH_2), 3.51(s,NH_2, br), 1.52(t, *J* = 7.0 Hz,3*H*), 1.42(t, *J* = 7.0 Hz, Me)	7/80
77. Bisdiisopropylammonium-3,7-bis(3-oxo-3-phenylpropanenitrile-2-ylidene)(3*H*,7*H*), benzo[1,2-*c*: 4,5-*c*′]diisoxazole-1,5-diamide (60 MHz)	8.05(s,4*H*,NH_2, br), 7.35–7.67 (m,10*H*,Ar*H*), 3.33(septuplet, 4*H*, C–*H*), 1.18(d,Me,24*H*).	3/81
78. Bispotassium-3,7-bis-(4-methoxyphenyl-sulfonylimino)(3H,7H) benzo[1,2-*c*: 4,5-*c*′]diisoxazole-diamide (90 MHz)	7.47–7.94 (m,Ar*H*)	3/81
79. Bissodium-3,7-bis-(4-methoxyphenyl-sulfonylimino)(3*H*,7*H*)benzo[1,2-c: 4,5-*c*′]-diisoxazole-1,5-diamide	7.77(AB system,4H,ArH), 7.30(AB system, 2.35(s,6*H*,2 Me)	3/81
80. Bisdiispropylammonium-3,7-dioxo-(3*H*,7*H*)-benzo[1,2-*c*: 4,5-*c*′]diisoxazole-4,8-diolate (90 MHz, DMSO-d_6)	8.11(s,4*H*,2NH_2^+,br), 3.38(septuplet,4 C*H*, *J* = 7.2Hz), 1.22[d,4CH(Me)$_2$,24*H*, *J* = 7.2 Hz],	8/82

(*continued*)

TABLE 2.IIIA. (*continued*)

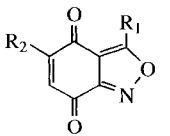
Compound (solvent)	Concentration (ppm)	References
81. Bistetraethylammonium-3,7-dioxo-(3*H*,7*H*)-benzo[1,2-*c*: 4,5-*c'*]diisoxazole-4,8-diolate (90 MHz, D_2O/[D_4]TSPNa)	3.23(q, *J* = 7.3 Hz,16*H*,CH_2), 1.24(t, *J* = 7.3 Hz) J^{14}N.Me = 1.9 Hz,24*H*, Me)	8/82
82. Bistriethylmethylammonium-3,7-dioxo-(3*H*,7*H*)-benzo[1,2-*c*: 4,5-*c'*]diisoxazole-4,8-dione (90 MHz, D_2O/[D_4]TSPNa)	3.30(q, *J* = 7.3 Hz,6*H*,CH_2Me), 2.91(s,3*H*,N–Me), 1.25(t, *J* = 7.3 Hz, ^{14}N-Me = 1.8 Hz, 9*H*, CH–Me)	8/82
83. Bis-(*N*-methylpyridinium)-3,7-dioxo-(3*H*,7*H*)-benzo[1,2-*c*: 4,5-*c'*]-4,8-diolate (90 MHz, D_2O/[D_4]TSPNa)	8.78(d,2*H*,H-2,. H-6), 8.51(t,1*H*,H-4), 8.02 (t, 2*H*, H-3, H-5), 4.41 (s, 3*H*, Me)	8/82
84. *N*-Ethylpyridinium-4,7-dioxo-(4*H*,7*H*)-benzo-[1,2-*c*: 4,5-*c'*]-diisoxazole-3-ethoxy-8-olate (90 MHz, DMSO-d_6)	9.18(d,2*H*,H-2, H-6), 8.62(t,1*H*,H-4), 8.17(t, 2*H*,H-3, H-5), 4.76(q, *J* = 7.2 Hz,2*H*,–OCH_2Me) 4.66(q, *J* = 7.2 Hz,2*H*,–N–CH_2Me),1.56(t, *J* = 7.2 Hz, 3*H*, –N–CH_2-Me), 1.45(t, *J* = 7.2Hz,3H,-*o*-CH_2Me)	8/82
85. Bispyridinium-3,7-dioxo-(3*H*,7*H*)-benzo-[1,2-*c*: 4,5-*c'*]-diisoxazole-4,8-diolate (90 MHz, DMSO-d_6)	8.94(s,3*H*,H-1,H-2,H-6,b), 8.53(t,1*H*,H-4), 8.02 (t, 2*H*,H-3, H-5)	8/82
86. 3,7-Bis(diethylamino)-1-ethyl-4,8-dioxobenzo[1,2-*c*: 4,5-*c'*]-diisoxazole-1-ium tetrafluoroborate (90 MHz, DMSO-d_6)	4.81(q,2H$^+$,N$^+$–CH_2Me,*J* = 7.1 Hz), 3.91 [q,8*H* 2N(CH_2Me)$_2$], 1.27,1.31,1.47(3 t,15H, N(CH_2Me), –N-CH_2Me)	5/80
87. 3,7-Bis-(diethylamino-)1,5-diethyl-4,8-dioxo-(4*H*,8*H*)-benzo[1,2-*c*: 4,5-*c'*]-diisoxzole-1,5-ium-bistetrafluroborate (90 MHz, acetone-d_6)	4.51(3,6*H*,2 N$^+$Me), 4.32(q,4*H*,2CH_2Me), 3.93 (q, 4*H*,2CH_2Me), 1.43(t,12*H*,4CH_2Me)	5/80
88. 3,7-Diethoxy-(4*H*,8*H*)-benzo[1.2-*c*: 4,5-*c'*]-diisoxazole-4,8-dione (90 MHz; CD_3NO_2)	4.8(q, *J* = 7.1 Hz,4*H*,2OMe), 1.59(t, *J* = 7.1 Hz,6*H*, 2 Me)	3/78
89. 3,7-Dipiperidino-(4*H*,8*H*)-benzo[1,2-*c*: 4-5-*c'*]-diisoxazole-4,8-dione (60 MHz, $CDCl_3$)	4.05(m,8*H*,piperidine 2-, 6-H), 1.75(m,12*H*,piperidine-3-,4-,5-H)	3/78
90. 3,7-Dimethoxy-(4*H*,8*H*)-benzo[1,2-*c*: 4,5-*c'*]-diisoxazole-4,8-dione (90 MHz, CD_3CN)	4.4 (s,6*H*,2OMe)	



R	R′	*T*(°C)	R	Me	Et	NH	Ar	References
H	Et	151–153	t,1.28; q,3.3	s,1.33	q,3.01; t,1.14	s,10.30	m,6.62–7.85	4/83
H	Me	114–116	s,3.12	s,1.34	q,2.99; t,1.17	s,10.15	m,6.50–7.83	4/83
t-Bu	Me	142–143	s,3.12	s,1.50	q,3.11; t,1.31	s,10.33	m,6.65–7.86	4/83
Br	Me	159–160	s,3.18	s,1.38	q,3.02; t,1.18	s,10.32	m,6.90–7.80	4/83
NO_2	Me	176–177	s,3.30	s,1.50	q,3.21; t,1.21	s,10.34	m,7.48–8.21	4/83
Cyclopropyl	Me	—	m,0.75–1.51(6*H*) m,3.80(1*H*)	s,1.30	q,3.01; t,1.15	s,10.26	m,6.70–7.84	4/83
H	*i*-Pr	116–117	m,0.65–1.71(7*H*) m,3.21–3.69(2*H*)	s,1.35	q,3.08; t,1.19	s,10.30	m,6.73–8.02	4/83
H	*p*-Bu	85–87	m,0.64–1.51(8*H*)	s,1.32	q,3.08; t,1.19	s,10.31	m,6.68–7.93	4/83

(*continued*)

TABLE 2.IIIA. (*continued*)

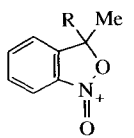


^{1}H-NMR ($CDCl_3$) (a) and ^{1}H-NMR (DMSO-d_6) (b)

R_1	R_2		6*H*	NH	R_1	R_2	References
OMe	OMe	(a)	6.12	—	3.91(s,3*H*)	4.47(s,3*H*)	2/74
Me	NHPh	(a)	6.34	7.66	2.84(s,3*H*),	—	2/74
Me	NHC_6H_4Me-*o*	(a)	6.89	7.45	2.85(s,3*H*)	2.26(s,3*H*, *o*-Me)	2/74
Me	$NNHC_6H_4Me$-*m*	(a)	6.33	7.61	2.84(s,3*H*)	2.38(s,3*H*, *m*-Me)	2/74
Me	NHC_6H_4Cl-*p*	(a)	6.28	7.59	2.84(s,3*H*)		2/74
OMe	NHPh	(a)	6.38	—	4.42(s,3*H*)		2/74
NMe_2	NHPh	(a)	6.38	7.94	3.54(s,3*H*)		2/74
NHMe	OMe	(a)	6.13	9.1	3.02(s,3*H*)	3.84(s,3*H*)	2/74
NHEt	OMe	(a)	6.11	9.18	1.18(t,3*H*, *J* = 3.5 Hz) 3.46(q,3*H*, *J* = 3.5 Hz)	3.84(s,3*H*)	2/74
NMe_2	OMe	(a)	6.17	—	3.41(s,6*H*)	3.83(s,3*H*)	2/74
NH_2	OMe	(b)	6.12	8.93	3.83(s,3*H*)		2/74
1-Piperidinyl	OMe	(b)	6.16	—	1.66(br,6*H*) 3.93(br,4*H*)	3.84(s,3*H*)	2/74
1-Morpholinyl	OMe	(b)	6.19	—	3.6–4.0 (m,8*H*)	3.84(s,3*H*)	2/74
NMe_2	NHEt	(a)	5.61	—	3.50(s,6*H*) 1.32(t,3*H*, *J* = 6 Hz)	3.24(q,2*H*, *J* = 6 Hz),	2/74
NMe_2	1-Piperidinyl	(b)	5.58	—	3.44(s,6*H*)	1.72(m,6*H*) 3.14(m,4*H*)	2/74

^{1}H-NMR ($CDCl_3$) (a) and ^{1}H-NMR (DMSO-d_6) (b)

R_1	R_2		6*H*	NH	R_1	R_2	References
1-Piperidinyl	NMe_2	(b)	5.58	—	1.66(br,6*H*) 3.83(br,4*H*)	3.16(s,6*H*)	
NH_2	NHPh	(b)	5.78	3.31 9.05	—	—	
NMe_2	NMe_2	(a)	5.69	—	3.46(s,6*H*)	3.21(s,6*H*)	
$NHCH(Me)_2$	NHPh	(a)	5.95	7.70 6.7	1.40(d,6*H*,*J* = 3 Hz) 4.2(m,1*H*)		
1-Morpholinyl	NHPh	(a)	6.20	7.4	3.95(m,4*H*) 5.15(m,4*H*)		
NHCH-COOEt	NHPH	(a)	6.20	7.0	3.32(d,2*H*,*J* = 3 Hz)		
CH_2Ph					4.9(m,1*H*,*J* = 3 Hz) 1.28(tr,3*H*,*J* = 3.5 Hz) 4.25(q,2*H*,*J* = 3.5 Hz)		



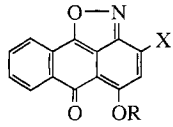
^{1}H-NMR Spectra of N-Oxo-5,5-Dialkyl[3,4]Benzo[1,2]Oxoazoniaolines

Compound	Me	Me	Me	ArH H_1	ArH H_2	ArH H_3	ArH H_4	References
R = Me; X = BF_4	2.17(s,3*H*)	—	—	8.49(d)	8.10(t)	8.55(t)	8.15(d)	4/76
R = Me; X = SbF_6	2.24(s,3*H*)	—	—	8.47(d)	8.11(t)	8.53(t)	8.17(d)	4/76
R = Et; X = BF_4	2.14(s,3*H*)	2.52(q,2H)	0.93(t,3H)	8.47(d)	8.05(t)	8.47(t)	8.09(d)	4/76
R = Et; X = SbF_6	2.21(s,3*H*)	2.59(q,2H)	1.02(t,3H)	8.49(d)	8.19(t)	8.55(t)	8.13(d)	4/76

(*continued*)

Table 2.IIIA. (*continued*)

		3(5)-Alkoxy-6H-6-oxo-6H-anthra[1,9-c,d]isoxazoles	
a	OMe	4.20(s,3*H*,Me), 6.76–8.33(m,6*H*,Ar)	10/90

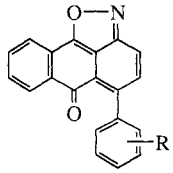


	R	X		Referencces
b	Me	H	4.20(s,3*H*,Me), 6.73–8.45(m,6*H*,Ar)	10/90
c	Me	Br	4.20(s,3*H*,Me), 6.73–8.37(m,5*H*,Ar)	10/90
d	n-Pr	Cl	1.20(t,3*H*,Me), 2.00(m,2*H*,CH_2), 4.37(m,2*H*,CH_{22}) 6.83–8.40(m,5*H*,Ar)	10/90
e	n-Bu	Cl	0.93(t,3*H*,Me), 1.67(m,4*H*,CH_2), 4.40(t,2*H*,CH_2) 6.83–8.40(m,5*H*,Ar)	10/90
f	n-Pr	Br	1.10(t,3*H*,Me), 1.90(m,2*H*,Me), 4.23(t,2*H*,CH_2) 6.90–8.37(m,5*H*,Ar)	10/90
g	n-Bu	Br	0.93(t,3*H*,Me), 1.67(m,4*H*,CH_2), 4.32(t,2*H*,CH_2) 6.80–8.35(m,5*H*,Ar)	10/90
h	n-Bu	H	1.11(t,3*H*,Me), 1.95(m,3*H*,CH_2), 4.37(t,2*H*,CH_2) 6.78–8.40(m,6*H*,Ar)	10/90
i	C_4H_9	H	1.07(t,3*H*,Me), 1.78(m,4*H*,CH_2), 4.43(t,2*H*,CH_2) 6.73–8.50(m,6*H*,Ar)	10/90
j	C_6H_4OEt-*p*	Br	1.40(t,3*H*,CH_3), 4.05(q,2*H*,CH_2), 6.80–8.23(m,9*H*,Ar)($CDCl_3$)	6/87

Anthra[1,9-c,d]-6-isoxazolone-5-(N-pyridinium)chloride

R		References
C_6H_{11}	1.00–2.05(m,11*H*), 5.85–8.50(m,9*H*), 11.58(d,1*H*,NH,*J*=12 Hz)	8/83
t-Bu	1.25(s,9*H*), 5.85–8.50(m,11*H*), 11.75(s,1*H*,NH)	8/83

TABLE 2.IIIB. ^{1}H-NMR SPECTRA OF ANTHRAISOXAZOLONES



R			References
a	Me-4	2.42(s,3*H*,Me), 6.83–8.33(m,9*H*,Ar)	5/88
b	Et-4	1.25(t,3*H*,Me), 2.70(q,2*H*,CH_2), 7.07–8.27(m,9*H*,Ar)	5/88
c	3,4-Me_2	2.28(s,6*H*,Me), 7.00–8.30(m,8*H*,Ar)	5/88
d	3,6-Me_2	2.02(s,3*H*,Me), 2.27(s,3*H*,Me), 6.85–8.50(m,8*H*,Ar)	5/88
e	4,6-Me_2	2.03(s,3*H*,Me), 2.32(s,3*H*,Me), 6.82–8.20(m,8*H*,Ar)	5/88
f	2,4,6-Me_3	1.90(s,6*H*,Me)	5/88
g		3.72(s,3*H*,Me),6.77–8.97(m,9*H*,Ar)	5/88
h		1.30(t,3*H*,Me, 4.00(q,2*H*,CH_2), 6.73–8.62(m,9*H*,Ar)	5/88
i		3.70(s,3*H*,Me), 6.77–8.93(m,10*H*,Ar)	5/88
j		1.30(t,3*H*,Me), 3.97(q,2*H*,CH_2), 6.70–8.62(m,10*H*,Ar)	5/88

2. TABLES ON MASS SPECTRA OF 2,1-BENZISOXAZOLES AND ANTHRAISOXAZOLONES

TABLE 2.IVA. MASS SPECTRA OF 2,1-BENZISOXAZOLES

Compound and Properties	References
1. *3-Methyl-2,1-benzisoxazole* (*HRMS*). 133(C_8H_7NO, M^+, 68.4%), 118(1.8, M–CH_3), 105(C_7H_7N, 10.2), 104(C_7H_6N, 55.8), 103(C_7H_5N, 4.3), 91(C_6H_5N, 13.4), 90(C_6H_4N 11.9), 79(C_5H_5N, 23.6), 78(C_6H_6, 39.3; C_5H_4N, 31.1), 77(C_6H_5, 11.9), 76(C_6H_4, 10.3), 75(C_6H_3, 6.1), 74 (C_6H_2, 8.6), 64(C_5H_4, 20.5), 63(C_5H_3, 21.3), 62(C_5H_2, 9.6), 61(C_5H_1, 4.7), 52(C_4H_4, 6.0;C_3H_2N, 0.8), 51(C_4H_3, 15.1), 50(C_4H_2, 15.2), 43(C_2H_3O, 100), 42(C_2H_2O, 4.1), 39(C_3H_3, 14.3), 38(C_3H_2, 7.9), 37 (C_3H_1, 7.4)	8/91
2. *3,4-Dimethyl-2,1-benzisoxazole* (*HRMS*). 147(C_9H_9NO, 100%), 146 (C_9H_8NO, 9.9), 145(C_9H_7NO, 5.0), 132(C_8H_7NO, 5.0), 132(C_8H_6NO, 5.2), 119(C_8H_9N, 21.5), 118(C_8H_8N, 62.9), 115(C_9H_7, 4.5), 105(C_7H_7N, 7.1), 104 (C_7H_6N, 23.4), 103(C_7H_5N, 3.3), 102(C_7H_4N, 2.1), 93(C_6H_7N, 6.7), 92 (C_7H_8;C_6H_6N, 11.2), 91(C_7H_7, 19.0), 90(C_7H_6, 7.8), 89(C_7H_5, 5.9), 79 (C_5H_5N, 2.9), 78(C_6H_6,11.8), 77(C_6H_5, 16.6), 76(C_6H_4, 5.7), 75(C_6H_3, 5.2), 74(C_6H_2, 3.9), 73.5 (M^{2+}, 5.4), 66(C_4H_4N, 2.5), 65(C_5H_6, 6.4), 64(C_5H_4, 4.2), 63(C_5H_3, 9.8), 62(C_5H_2, 4.9), 61(C_5H_1,2.4), 52(C_4H_4, 7.0), 51(C_4H_3, 28.1), 50(C_4H_2, 9.5), 43 (C_2H_3O, 89.7), 39(C_3H_3, 14.4)	8/91
3. *3,7-Dimethyl-2,1-benzisoxazole* (*HRMS*). 147(C_9H_9NO, 100%), 146(C_9H_8NO, 29.1), 145(C_9H_7NO, 4.7), 132(C_8H_6NO, 18.1), 119 (C_8H_9N, 11.9), 118(C_8H_8N, 35.7), 117(C_8H_7N, 7.0), 115(C_9H_7, 2.3), 105(C_7H_7N, 20.5), 104(C_7H_6N, 42.4), 103 (C_7H_5N, 11.0), 102 (C_7H_4N, 3.6), 93(C_6H_7N, 7.3), 92(C_7H_8, 6.4; C_6H_6N, 58.5), 91(C_7H_7, 11.4), 90(C_7H_6, 5.7), 89(C_7H_5, 4.7), 79(C_5H_5N, 5.4), 78(C_6H_6,9.0), 77(C_6H_5, 15.8), 74(C_6H_2, 4.1), 65(C_5H_5, 4.4), 63(C_5H_3, 7.2), 62(C_5H_2, 3.6), 52(C_4H_4, 4.6; C_3H_2N, 3.3), 51(C_4H_3, 13.4), 50(C_4H_2, 9.3), 43(C_2H_3O, 40.2), 39(C_3H_3, 4.0)	8/91
4. *3-Ethyl-2,1-benzisoxazole* (*HRMS*). 147(C_9H_9NO, 100%), 146 (C_9H_8NO, 12.1), 145(C_9H_7NO, 4.7), 132(C_8H_6NO, 14.7), 119(C_7H_5NO,41.5), 118(C_8H_8N, 84.0), 117 (C_8H_7N, 17.7), 115(C_9H_7, 5.5), 106(C_6H_4NO, 5.3), 105(C_7H_7N, 8.4), 104(C_7H_6N, 43.6), 93(C_6H_7N, 8.9), 92(C_6H_6N, 33.6), 91(C_6H_5N, 47.6), 90(C_6H_4N, 21.3), 89(C_7H_5, 7.4), 79(C_5H_5N, 7.6), 78 (C_6H_6, 29.4), 77(C_6H_5, 19.2), 76(C_6H_4, 9.2), 75(C_6H_3, 5.9), 74(C_6H_2, 5.6), 66(C_4H_4N, 4.8), 64(C_5H_4, 31.0), 63 (C_5H_3, 32.3), 62(C_5H_2, 9.8), 61 (C_5H_1, 5.5), 57(C_3H_5O, 36.3), 55(C_3H_3O, 4.8), 53(C_3H_3N, 5.5), 52 (C_4H_4 or C_3H_2N, 9.7), 51(C_4H_3, 18.0), 50(C_4H_2, 11.6), 43(C_2H_3O, 12.1), 42(28.0), 41(C_3H_5, 8.5), 39(C_3H_3, 29.9), 38(C_3H_2, 11.5), 37(C_3H_1, 9.3), 29 (C_2H_5, 48.9)	8/91
5. *3(1′-Methylethyl)-2,1-benzisoxazole* (*HRMS*). 161($C_{10}H_{11}NO$, 100%), 160 ($C_{10}H_{10}NO$, 8.4), 146(C_9H_8NO, 61.1), 133($C_9H_{11}N$, 16.0), 132 ($C_9H_{10}N$, 83.1), 131(C_8H_5NO, 19.7), 130(C_9H_8N, 6.2), 120(C_7H_6NO, 40.8), 119(C_7H_5NO, 31.9), 118 (C_8H_8N, 24.9), 117(C_8H_7N, 25.4), 116(C_8H_6N, 16.2), 115 (C_9H_7, 7.0), 106(C_7H_8N, 4.9), 105(C_7H_7N, 4.7), 104(C_6H_7N, 7.8), 92 (C_6H_6N, 54.8), 91(C_6H_5N; or C_7H_7, 50.6), 90(C_6H_4N, 19.7), 89(C_6H_3N, 12.1), 79(C_5H_5N, 4.1), 78(C_5H_4N, 10.2), 77(C_6H_5,17.2), 76(C_6H_4 or C_5H_2N, 7.6), 75 (C_6H_3, 4.7), 66(C_5H_6 or C_4H_4N, 6.2), 64(C_5H_4, 23.5), 63(C_5H_3, 26.5), 62(C_5H_2, 11.8), 55(C_3H_5N, 6.8), 53(C_3H_3N, 5.6), 52(C_4H_4, 8.6), 51(C_4H_3, 18.7), 50(C_4H_2,11.6), 43(C_3H_7, 39.7; C_2H_3O, 11.7), 42(C_3H_6, 41.5), 41(C_3H_5, 26.8), 40(C_3H_4, 5.0), 39(C_3H_3, 37.7), 38(C_3H_2, 13.2), 37(C_3H_1, 3.6)	8/91

(*continued*)

TABLE 2.IVA. (*continued*)

Compound and Properties	References
6. *3-(1′,1′-Dimethylethyl)-2,1-benzisoxazole* (*HRMS*). 175($C_{11}H_{13}NO$, 38.6%), 160($C_{10}H_{10}NO$, 100), 159($C_{10}H_9NO$, 2.9), 145(C_9H_7NO, 3.8), 133 ($C_9H_{11}N$, 19.7; or C_9H_9O, 2.3), 132($C_9H_{10}N$, 43.5; C_8H_6NO, 8.1), 131(C_9H_9N, 5.7), 130(C_9H_8N, 10.5), 119(C_7H_5NO, 8.9), 118(C_8H_8N, 10.2), 117(C_8H_7N, 18.8), 116(C_8H_6N, 4.4), 115(C_9H_7, 6.7), 105(C_8H_9, 4.0), 104 (C_7H_6N, 4.6), 92(C_6H_4O, 28.1), 91(C_6H_5N, 22.2), 90(C_6H_4N, 14.6), 77 (C_6H_5, 12.3), 64(C_5H_4, 19.4), 63(C_5H_3, 21.9), 62(C_5H_2, 8.1), 57(C_4H_9, 33.3), 52(C_3H_2N, 7.4), 51(C_4H_3, 13.3), 50(C_4H_2, 8.6), 43(C_2H_3O, 21.6), 41 (C_3H_5, 47.3), 40(C_3H_4, 8.4), 39(C_3H_3, 50.9	8/91
7. *3-Phenyl-2,1-benzisoxazole*. 195(M^+, $C_{13}H_9NO$, 100%), 167(M-CO, 38.0), 166($C_{12}H_8N$, 26.2), 105(C_7H_5NO, 7.7), 77(C_6H_5, 46.9), 51(C_4H_3, 21.1)	1/89
8. *6-Chloro-3-phenyl-2,1-benzisoxazole*. 231,229(M^+, $C_{13}H_8ClNO$, 14.1, 36.9%), 203, 201 (M–CO, both <1%), 194 (M–Cl, 9.7), 105(C_7H_5O, 8.8), 77(C_6H_5, 44.6), 51(CC_4H_3, 100)	1/89
9. *5-Chloro-3-phenyl-2,1-benzisoxazole*. 231, 229(M^+, $C_{13}H_8ClNO$, 31.2, 100%), 203, 201(M–CO, 2.3, 7.9), 194(M–Cl, 35.0), 166 ($C_{12}H_8N$, 39.5), 105(C_7H_5O, 11.2), 77(C_6H_5, 59.2), 51(C_4H_3, 30.9)	1/89
10. *5-Fluoro-3-phenyl-2,1-benzisoxazole*. 213(M^+, $C_{13}H_8FNO$, 100%), 185(M–CO, 22.0), 184($C_{12}H_7FN$, 19.5), 105(C_7H_5O, 9.7), 77 (C_6H_5, 45.7), 51(C_4H_3, 59.3)	1/89
11. *6-Methyl-3-phenyl-2,1-benzisoxazole*. 209(M^+, $C_{14}H_{11}NO$, 100%), 208 (61.7), 51(C_4H_3, 23.3)	1/89
12. *5-Methyl-3-phenyl-2,1-benzisoxazole*. 209(M^+, $C_{14}H_{11}NO$, 100%), 208($C_{14}H_{10}NO$, 29.5), 181(M–CO,11.4), 180($C_{13}H_{10}N$, 51.0), 105 (C_7H_5O, 6.7), 77(C_6H_5, 41.5), 51(C_4H_3, 16.3)	1/89
13. *5-Nitro-3-phenyl-2,1-benzisoxazole*. 240(M^+, $C_{13}H_8N_2O_3$, 100%), 194(M–NO_2, 7.1), 166($C_{12}H_8N$, 39.6), 139($C_{11}H_7$, 25.0), 105(C_7H_5O, 28.3), 77(C_6H_5, 98.3), 51(C_4H_3, 27.4)	2/81
14. *5-Chloro-2,1-benzisoxazole*. 153(M^+, 100%), 155(50), 125(83), 98(25), 63(49)	2/81
15. *4-Nitro-5-chloro-2,1-benzisoxazole*. 198(M^+, 30%), 182(5), 170(8), 168(18), 152(5), 126(50), 124(100), 97(50), 88(55)	2/81
16. *3-(4′-Nitrophenyl)-5-chloro-7-nitro-2,1-benzisoxazole*. 319(M^+, 25%), 303(15), 286(100), 273(25), 150(90)	2/81
17. *3-Carbomethoxy-4,6-dinitro-2,1-benzisoxazole*. 267(M^+, 100%), 250(40), 236(88), 222(70), 209(62), 191(85), 144(95)	2/81
18. *3-Ethyl-7-(1-methoxy-3-bromopropyl)-2,1-benzisoxazole*. 299, 297(M^+, 7%), 190(100%)	1/73
19. *3-(2-Benzoyl-1-phenacylideneethyl)-6-nitro-2,1-benzisoxazole*. 412(M^+, 13%), 383(8), 307(100), 291(7), 290(8), 105(off-scale)	1/73
20. *6-Nitro-3-(1,3-dipivaloylpropen-2-yl)-2,1-benzisoxazole*. 372(M^+, 75%), 352(10), 315(100), 288(25), 287(32), 273(20), 271(25), 260(10), 259(20), 245(30), 231(65), 204(25), 203(18), 85(100), 57(off-scale), 41(100)	1/73
21. *3-(2-Benzoyl-1-phenacylideneethyl)-2,1-benzisoxazole*. 367(M^+, 8%), 339(C), 338(8), 262(50), 246(6), 234(5), 105(100)	1/73

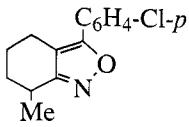
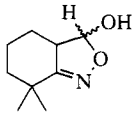


TABLE 2.IVA. (*continued*)

Compound and Properties	References
22. 249.0816(M^+, 2.35%, calcd. 249.0794), 247.0777(M^+, 88, calcd. 247.063), 193(12), 191(41), 141(35), 139(100), 113(15), 111(35)	7/78
23. *7-Aza-5,5-dimethyl-8-oxabicyclo[4.3.0]6,9-nonadiene.* 151.0996(M^+, 10%, calcd.151.0997), 136.0777(M^+, CH_3, 5, calcd. 136.0762), 69(100)	7/78
24. *Tricyclo[4.3.1.1]undecan[4,5-c]isoxazole.* 189.1158(M^+, 53%, calcd. 189.1153), 162(100), 161.1201(M^+-CO, 57, calcd. 161.1204), 79(63), 41(72)	7/78
	
25. 169.1087(M^+, 12%, calcd. 169.1102), 154.0861(M^+-Me, 1; calcd. 154.0867), 153(6),152.1063(M^+-OH, 4; calcd.152.1075), 151.0989 (M^+- H_2O, 2; calcd. 151.0997), 69(31), 55(23), 44(39), 40(100)	7/78
26. *3-Phenyl-5,7-dichloro-2,1-benzisoxazole.* 265(56.7%), 264(17.9), 263(75.4), 228(100), 105(17.7), 77(52.2)	7/79
27. *3,5-Diphenyl-2,1-benzisoxazole.* 271(100%), 270(36.4), 243(8.5), 241(11.2), 139(5), 77(4.1)	7/79
28. *3-Phenyl-5-(4-chlorophenyl)-2,1-benzisoxazole.* 235(30%), 233(100), 203(131), 187(85), 175(10.8), 152(92.3)	7/79
29. *3-Phenyl-5-(4-bromophenyl)-2,1-benzisoxazole.* 350(100%), 270(18.8%), 135(52.5), 121(57.5), 105(19.5), 91(70), 77(75)	6/79
30. *3-Acetyl-4,6-dinitro-2,1-benzisoxazole.* 269(M^+, 100%), 252(27), 235(5), 225(5), 224(8), 222(24), 210(5), 180(3), 130(3), 88(25).	4/90
31. *3-Benzoyl-4,6-dinitro-2,1-benzisoxazole.* 313(M^+, 2%), 213(6), 209(2), 179(2), 167(2), 149(3), 122(12), 120(4), 105(100), 77(91), 51(33)	4/90
32. *3-Propanoyl-4,6-dinitro-2,1-benzisoxazole.* 283(M^+, 10%), 266(100), 249(15), 236(23), 210(12), 169(6), 111(18), 97(7), 95(9), 86(61), 57(88)	4/90
33. *3-Cyclopropylcarbonyl-4,6-dinitro-2,1-benzisoxazole.* 278(M^+,100%), 277(12), 261(11), 250(38), 236(44), 220(16), 190(10), 144(6), 129(4), 116(5), 88(62)	4/90
34. *3-Ethoxycarbonyl-4,6-dinitro-2,1-benzisoxazole.* 281(M^+, 43%), 236(70), 209(100), 179(5), 163(2), 137(7), 116(15), 105(9), 89(50), 80(97), 61(30)	4/90
35. *3-Phenyl-4,6-dinitro-2,1-benzisoxazole.* 285(M^+, 55%), 268(30), 239(25), 181(40), 165(33), 105(24), 103(58), 93(42), 91(97), 77(100), 51(90)	4/90
36. *6-Chloro-4-phenyl-2,1-benzisoxazole.* 229(M^+, 100%), 201(M-28), m^*=178.4, 194(M^+–Cl), m^*=164.3, 166(194-28), m^*=142.0, 105, 77, 51, m^*=137.1(201-Cl)	1/89
37. *6-Methyl-3-phenyl-2,1-benzisoxazole.* 209(M^+, 100%), 208, m^*=207.0(209→208), 194(M^+–CH_3), m^*=108.1(209→194), 180(208-28), m^*=155.8, 105, 77	1/89
38. *1,5-Dimethyl-3,4,7,8-tetrahydrobenzo[1,2-c:4,5-c']diisoxazole-3,4,7,8-tetrone.* 250(M^+, 17%), 126(20), 82(66), 44(100)	6/80
39. *1,5-Diethyl-3,4,7,8-tetrahydrabenzo[1,2-c:4,5-c']diisoxazole-3,4,7,8-tetrone.* 278(M^+, 20%), 112(79), 44(100)	6/80
40. *3,7-Diethoxy-4H,8H-benzo[1,2-c:4,5-c']diisoxazole-8-hydrazone-4-one.* 294(M^+, 2,23%), 292(M^+,100), 248(84), 218(56)	6/80
41. *3,7-Bis-dimethylhydrazino-4H,8H-benzo[1,2-c;4,5-c']-diisoxazole-4,8-dione.* 306(M^+, 8%), 153(62), 59(100)	6/80

(*continued*)

TABLE 2.IVA. (*continued*)

Compound and Properties	References
42. *3,7-Diethoxy-4H,8H-benzo[1,2-c: 4,5-c']diisoxazole-4,8-dione.* 278.05 (M^+, 24%), 250.02(M–C_2H_4, 80), 220.03(M–C_2H_4–CO, 39), 139.03 ($C_6H_5NO_3^+$, 67), 111.03($C_6H_5NO_3^+$-CO, 92), 94.03(C_5H_4NO, 100)	3/78
43. *3,7-Dipiperidino-4H,8H-benzo[1,2-c: 4,5-c']diisoxazole-4,8- dione.* 356 (M^+, 8%), 355(M–H, 9), 328(M–C_2H_4, 2), 300(M–2XC_2H_4, 8), 273 (M–C_5H_9N, 4), 245(M–C_5H_9N-C_2H_4, 22), 84($C_5H_{10}N^+$, 100), 83 ($C_5H_9N^+$, 67)	3/78
44. *3,7-Diamino-4H,8H-benzo[1,2-c: 4,5-c']diisoxazole-4,8-dione.* 220(M^+, 33%), 155(40), 110(M^+, 2,8)	3/78
45. *3-Methyl-7-ethyl-2,1-benzisoxazole.* 161.0866(M^+, 23%), 146(37), 118(35), 91(20), 43(100)	8/87
46. *5-Chloro-3-(2-methylphenyl)-2,1-benzisoxazole.* 243(M^+, $C_{14}H_{10}ClNO$), 242, 214, 208, 200, 180, 91, 65.	2/87
47. *5-Chloro-3-(3-chloro-4-methoxyphenyl)-2,1-benzisoxazole.* 293(M^+, 88%), 278(21), 258(100), 250(79), 187(43)	7/88
48. *4,7-Dimethoxy-2,1-benzisoxazole.* 179(M^+, 100%), 136(48), 108(29), 93(30), 76(31)	5/89
49. *4,8-Dihydroxy-3H,7H-benzo-[1,2-c: 4,5-c']diisoxazole-3,7-dione.* 222 (M^+, 9%), 178(112), 94(32), 68(81), 44(100)	6/81
50. *4,8-Dipiperidino-3H,7H-benzo-[1,2-c: 4,5-c']diisoxazole-3,7-dione* (190°C). 356(M^+, 49%), 293(40), 267(87), 239(95), 184(100), 55(99)	6/81
51. *4,8-Bisdiethylamino-3H,7H-benzo-[1,2-c: 4,5-c']diisoxazole-3,7-dione* (175°C). 323(M^+, 52%), 255(40), 227(73), 201(100).	6/81
52. *4,8-Dianilino-3H,7H-benzo-[1,2-c: 4,5-c']diisoxazole-3,7- dione* (250°C). 372 (M^+, 18%), 284(64), 93(37), 77(100).	6/81
53. *4,8-Bis-(N-methylanilino)-3H,7H-benzo-[1,2-c: 4,5-c']-diisoxazole-3,7-dione.* 400(M^+, 16%), 312(45), 311(68), 77(100).	6/81
54. *4,8-Diethoxy-3H,7H-benzo-[1,2-c: 4,5-c']diisoxazole-3,7-dione.* 278 (M^+, 83%), 250(16), 222(86), 138(25), 112(73), 94(65), 67(100)	3/78
55. *4,8-Dimethoxy-3H,7H-benzo-[1,2-c: 4,5-c']diisoxazole-3,7-dione.* 250 (M^+, 100%), 250(27), 138(38), 80(49)	8/80
56. *3-Carbomethoxy-4,6-dinitro-2,1-benzisoxazole.* 267(M^+, 100%), 250(40), 236(88), 222(70), 209(62), 191(85), 144(95).	2/81
57. *3-(4'-Nitrophenyl)-5-chloro-7-nitro-2,1-benzisoxazole.* 319(M^+, 25%), 303(15), 286(100), 273(25), 150(90)	2/81
58. *3-Substituted 4,6-dinitro-2,1- benzisoxazoles*	4/90

	R	
a	COMe	269(M + NH_4)$^+$, 100%), 252(M+H)$^+$, 27), 235(12), 225(5), 224(8), 222(24), 210(5), 180(3), 130(3), 88(25)
b	CO	313(M^+, 2%), 213(6), 209(2), 179(2), 167(2), 149(3), 122(12), 120(4), 105(100), 77(91), 51(33)
c	COEt	283(M+NH_4)$^+$, 10%), 266(M + H^+), 100%), 249(15), 236(23), 210(12), 169(6), 111(18), 97(7), 95(9), 88(61), 57(88)
d	CO-cyclopropyl	278(M+H)$^+$, 100%), 277(M^+, 12), 261(11), 250(38), 236(44), 220(16), 190(10), 144(6), 129(4), 116(5), 88(62)
e	COOEt	281(M^+, 43%), 236(70), 209(100), 179(5), 163(2), 137(7), 116(15), 105(9), 89(50), 88(97), 61(30)
f	Ph	285(M^+, 55%), 268(30), 239(25), 181(40), 165(33), 105(24), 103(58), 93(42), 91(97), 77(100), 51(90)

TABLE 2.IVB. MASS SPECTRA OF ANTHRAISOXAZOLONES

Compound		References
5-Chloro-3-diethylamino-6H-6-oxo-anthra[1,9-c,d]isoxazole	328(30), 326(80), 313(40), 312(40), 311(100), 299(30), 298(25), 297(50), 291(30)	9/82

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CHAPTER 3

Heterocycles Condensed to the Isoxazole Ring

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3.1. INTRODUCTION

The importance of the isoxazole ring in the chemistry of heterocyclic compounds can be easily illustrated with a simple statistic: more than 3500 references were listed in *Isoxazoles*; Part 1[22/91] published in 1991 as part of this series, and these references concerned only the basic ring and its dihydro and tetrahydro derivatives.

Following the Quilico and Speroni volume on isoxazoles and related compounds, edited in 1962[4/62] which covered the amassed chemistry of this system, only indoxazenes and anthranils (1,2- and 2,1-benzisoxazoles, respectively) have been subsequently reviewed.[11/67,22/81]

Beginning with the first paper published by Friedlaender and Schreiber[1/895] the present review covers, up to 1991, all ring systems containing an isoxazole ring fused to one or more heterocycles.

The synthetic routes that involve the assembly of an isoxazole ring adjacent to a preexisting heterocycle (in either unsaturated or partly saturated form) and those in which a substituted isoxazole is the starting product for further hetero-

cyclizations are reported first, followed by a review of papers dealing with the chemical properties and the manipulations of the condensed ring systems.

When a specific reaction is not mentioned, reference is made to the basic ring system with the maximum number of noncumulative double bonds. The nomenclature is given in accordance to the recommendations of IUPAC (International Union of Pure and Applied Chemistry) and the Chemical Abstract Service. In the hope that this will not diminish the clarity of the schemes, all isoxazole ring systems are oriented in such a way as to emphasize the IUPAC nomenclature.

The physical and spectroscopic properties of compounds discussed in this review are not addressed. The reader is encouraged to consult the original papers, which are replete with such data.

A cross-referenced ring index at the end of the chapter lists fused isoxazoles along with their respective structures.

3.2. METHODS OF PREPARATION

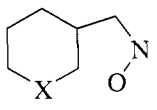
Methods of preparation of fused isoxazoles can be divided into the following two main classes:

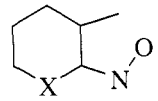
1. The starting product is a heterocycle, and an isoxazole is synthesized with at least one of its bonds condensed to the preexisting heterocycle.
2. The heterocycle is assembled from a functionalized isoxazole ring.

3.2.1. Synthesis of the Isoxazole Ring

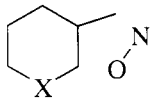
Several synthetic approaches are conceivable, starting from a heterocyclic ring, that involve the following schematic processes:

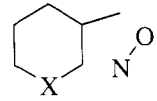
1. [CCCNO] where the bond between O and C5 of the isoxazole ring is formed:



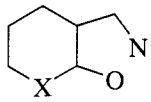
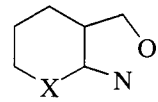


2. [CCC + NO], as above, but both N–C3 and O–C5 bonds are formed, simultaneously or in successive steps:

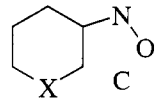




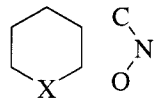
3. [OCCCN] involving the formation of the N–O bond:

4. [CCNO + C] indicates when both bonds O–C5 and C4–C5 are formed:



5. [CNO + CC] represents the classic 1,3-dipolar cycloaddition that may either occur on an acetylenic dipolarophile or via an isoxazolinic intermediate that is then transformed into an isoxazole:



6. the oxidation of a condensed isoxazoline derivative.
7. rearrangements, sometimes involving complex ring transformations.

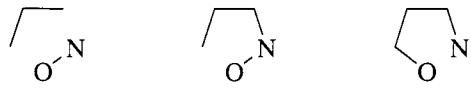
When possible, these approaches will be considered in succession even if a rigid discrimination between the different processes does not appear to be rational, as the next chapter shows.

3.2.1.1. Cyclization Processes [CCCNO] and [CCC + NO]

Cyclization processes represent the oldest and most frequently utilized routes to isoxazoles and condensed isoxazole ring systems. The process involves either the ring closure of a suitably substituted oxime, the reaction of a three-carbon fragment with hydroxylamine (in general to give the oxime shown above), or the ring closure of a nitro group onto a carbon atom in the γ position.

Reactions involving hydroxylamine, which is generally employed as its hydrochloride or acetate salts, may occur with or without the isolation of the initially formed oxime intermediate. In instances where the oxime is isolated prior to cyclization, formation of an *O*-oxime derivative is often relied on to facilitate subsequent ring closures that proceed by attack on the oxime nitrogen atom.

Therefore the reaction of a three-carbon fragment and hydroxylamine to give an isoxazole ring may be formally regarded as three distinct processes involving the formation of bonds: (1) O–C5 and N–C3, (2) O–C, and (3) O–N.



These reactions, which could be discussed in three different sections, will be treated together.

The reaction of a three-carbon fragment with hydroxylamine involves a nucleophilic attack at one of the external carbons, thus the reaction may have different regiochemical outcomes. Furthermore, hydroxylamine is an ambident nucleophile, due to the following pH-dependent equilibrium

$$NH_3^+-OH \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} NH_2-OH \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} NH_2-O^-$$

Several structures, expecially those proposed in older papers, are not supported by suitable chemical or spectroscopic proof and *caution is recommended in trusting these results.*

A minimum structural requirement of the three-carbon component in these cyclizations is the presence of at least one carbonyl group. In addition to β-dicarbonyl compounds, other functional groups positioned in β to the CO are conceivable for a nucleophilic displacement, this being either the first or the last step of the cyclization.

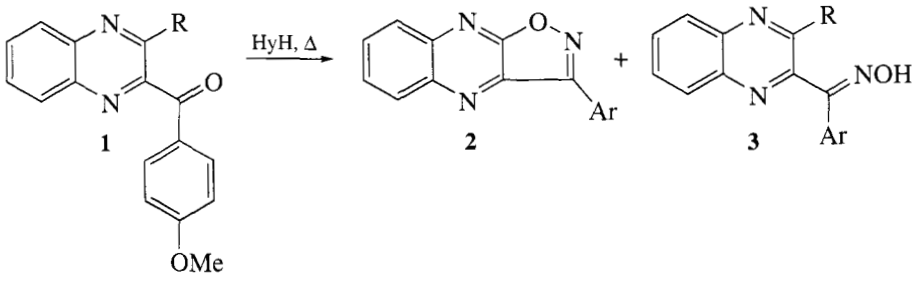
An example of this exists in the reaction of hydroxylamine with different 2-substituted quinoxaline-3-ketones **1**.[4/69] Through the intermediacy of different oximes, some which are isolated (**3**), 3-*p*-methoxyphenyl-isoxazolo[4,5-*b*]quinoxaline **2** may be obtained. The yield of the products in this process depends largely on the nature of the leaving group (Table 3.1) and sometimes no isoxazole is obtained and the oximes become the final products of the reaction.

Surprisingly, the oxime derived from **1** in which R = H can be converted into the isoxazole **2**, in 22% yield, by refluxing it for 4 h in acetic acid. The formal

TABLE 3.1. REACTION CONDITIONS AND YIELDS OF THE PRODUCTS **2** AND **3** FROM **1** AND HYDROXYLAMINE

R	Solvent[a]	Reflux (h)	Isoxazole **2** (%)	Oximes **3** (%)
H	(a)	20	—	50
H	(b)	10	3	66
OH	(a)	3	33	—
Cl	(a)	3	90	—
CN	(a)	3	34	—
COOH	(a)	2	78	—
$CONH_2$	(a)	2	80	—
CH_2Ph	(a)	3	—	70
COPh	(a)	7	—	26

[a] *Key*: (a) ethanol–pyridine; (b) ethanol.



displacement of hydride ion seems rather astonishing, but quinoxaline is an electron-poor heterocycle with the 2 position activated toward nucleophilic attack.

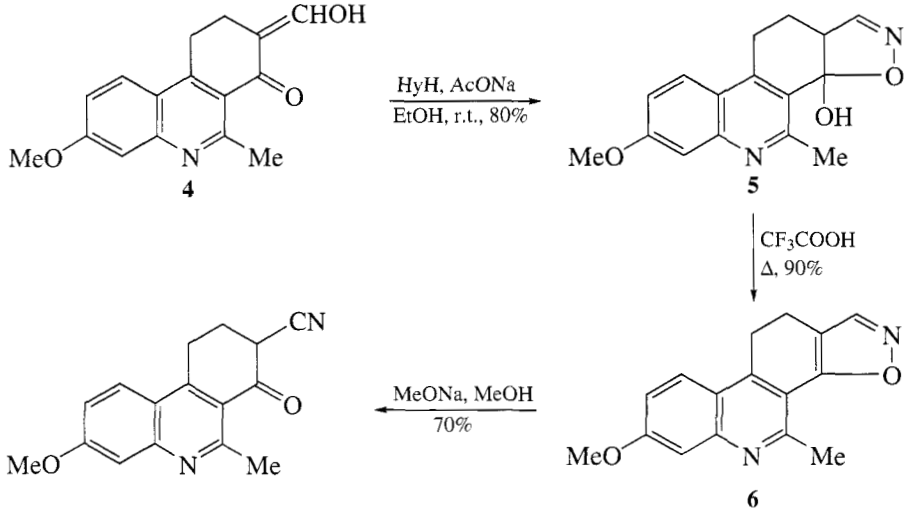
The behavior of different substrates with hydroxylamine will now be briefly reviewed.

3.2.1.1a. Reaction of β-Dicarbonyl Compounds with Hydroxylamine

The oximation of β-dicarbonyl compounds (and related systems) is an old synthetic route to isoxazoles and the most important one for the preparation of condensed isoxazole rings.

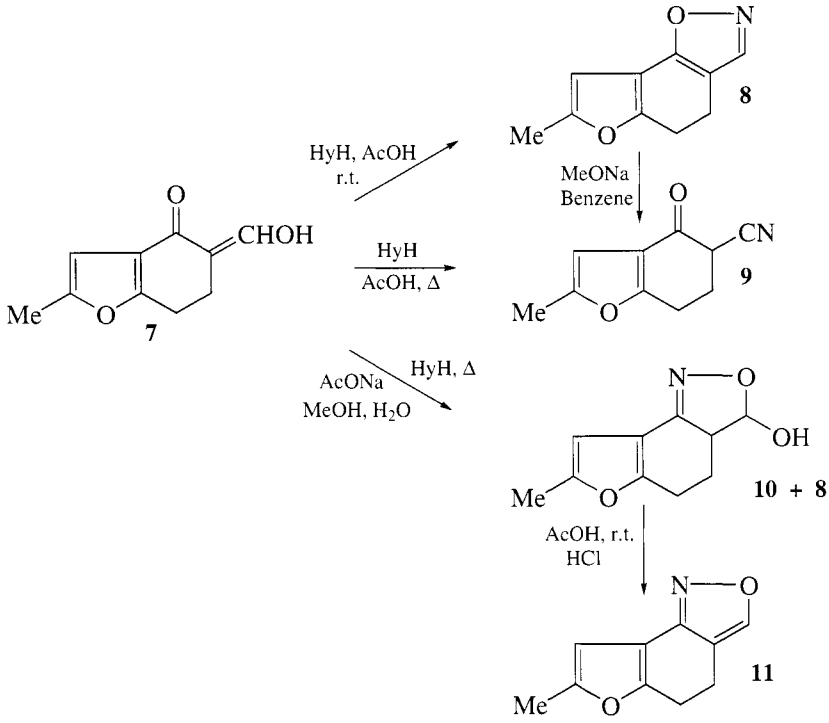
In general, the experimental conditions require a short period at reflux in methanol, ethanol, or acetic acid (or even stirring in water at room temperature) with hydroxylamine hydrochloride. The main variation is the type of base employed (NaOH, AcONa, pyridine, etc.), a factor that strongly influences the nucleophilic species that is involved and occasionally the nature of product.

The results described in two papers allow the mechanism of oximation to be inferred. The reaction of phenanthridine derivative **4** with hydroxylamine hydrochloride and AcONa in ethanol at room temperature (r.t.) gave 80% yield of the hydroxy isoxazoline **5**, a result that offers insight into the identity of the reaction

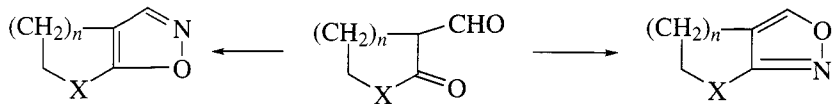


intermediate. This material was readily dehydratated, in 90% yield, to give the isoxazolo[5,4-*i*]phenanthridine derivative **6**.[3/74,9/77] A widely used chemical proof of the isoxazole structure relies on its susceptibility to ring opening in basic media. The formation of an α-cyanocarbonyl compound strongly supports a structure with a 3-unsubstituted isoxazole ring.

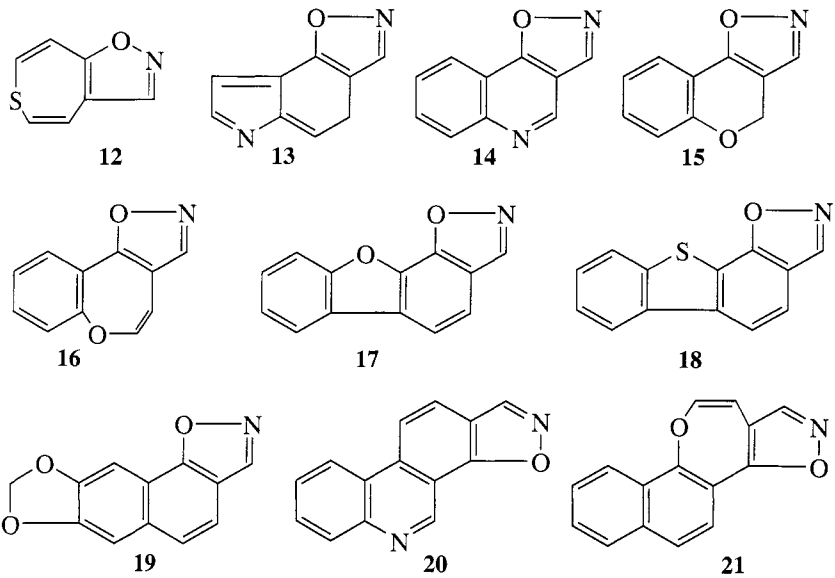
Apart from providing a further example in support of the preceding mechanism, oximation of benzofuran derivative **7** illustrates the point that small changes in the experimental conditions can deeply influence the results.[5/76] If **7** is treated with hydroxylamine hydrochloride in AcOH at r.t. the furo[2,3-*g*]-1,2-benzisoxazole derivative **8** is obtained in a 91% yield. However, when performed under reflux, the same reaction gave α-cyanoketone **9**, a product isolated previously from the ring opening of isoxazole **8** under basic conditions. Alternatively, if **7** is treated with hydroxylamine hydrochloride and AcONa in refluxing methanol, the hydroxy isoxazoline derivative **10** is obtained, in 18% yield, along with the predominant product **8**, formed in 78% yield, and a trace of the dioxime. Under acidic conditions dehydration of **10** affords the furo[2,3-*g*]-2,1-benzisoxazole **11**.



Without considering side products such as dioximes, oximation of compounds that can be regarded as β-ketoaldehydes can give rise to two regioisomeric isoxazoles whose extent of formation largely depends on the experimental conditions.

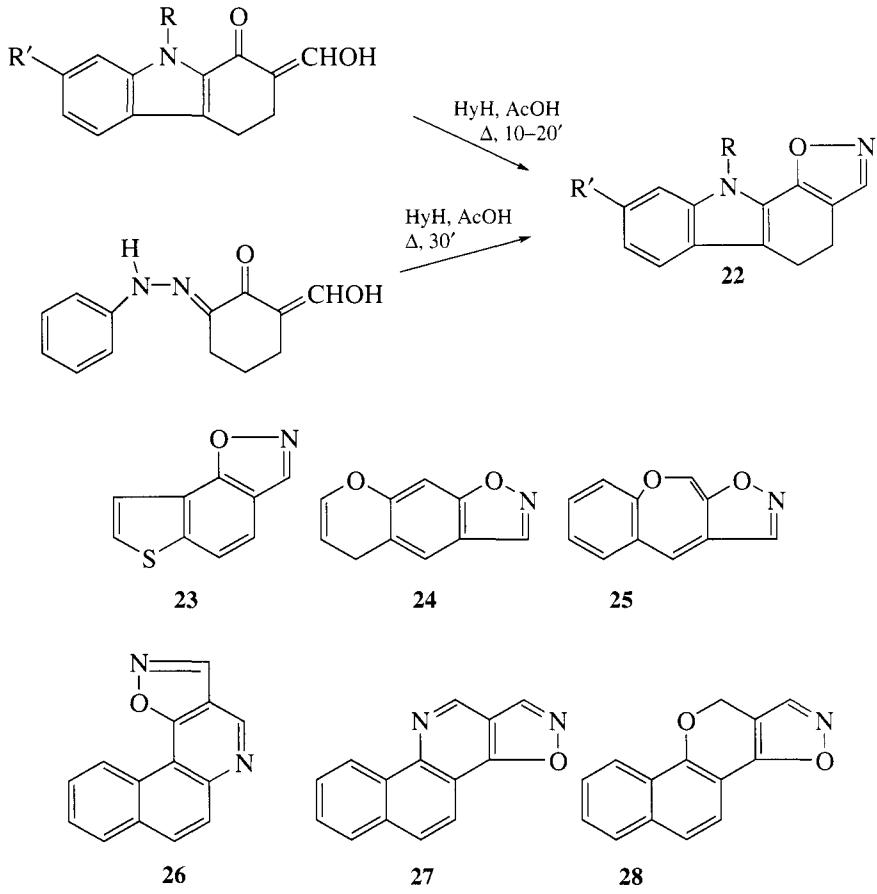


Attack of the nitrogen atom at the aldehyde carbonyl is strongly favored if the reaction is performed with hydroxylamine hydrochloride in the absence of bases, in AcOH, and sometimes in water–ethanol under refluxing conditions. The following fused isoxazoles were synthesized from β-ketoaldehyde-containing substrates and the structure of these products was chemically demonstrated: thiepino [4,5-*d*]isoxazole **12**,[5/68] 4*H*-pyrrolo[2,3-*g*]-1,2-benzisoxazole **13**,[3/71,7/82] isoxazolo [4,5-*c*]quinoline **14**,[6/68] 4*H*-[1]benzopyrano[3,4-*d*]isoxazole **15**,[8/66,7/76,5/79,16/80] [1] benzoxepino[4,5-*d*]isoxazole **16**,[18/84] benzofuro[3,2-*g*]-1,2-benzisoxazole **17**,[4/60] [1]benzothieno[3,2-*g*]-1,2-benzisoxazole **18**,[1/55] 8*H*-[1,3]dioxolo[6,7]naphth[2,1-*d*]isoxazole **19**,[5/69] isoxazolo[5,4-*i*]phenanthridine **20**,[21/84] and naphth[2′,1′: 6,7] oxepino[4,5-*d*]isoxazole **21**.[18/84]



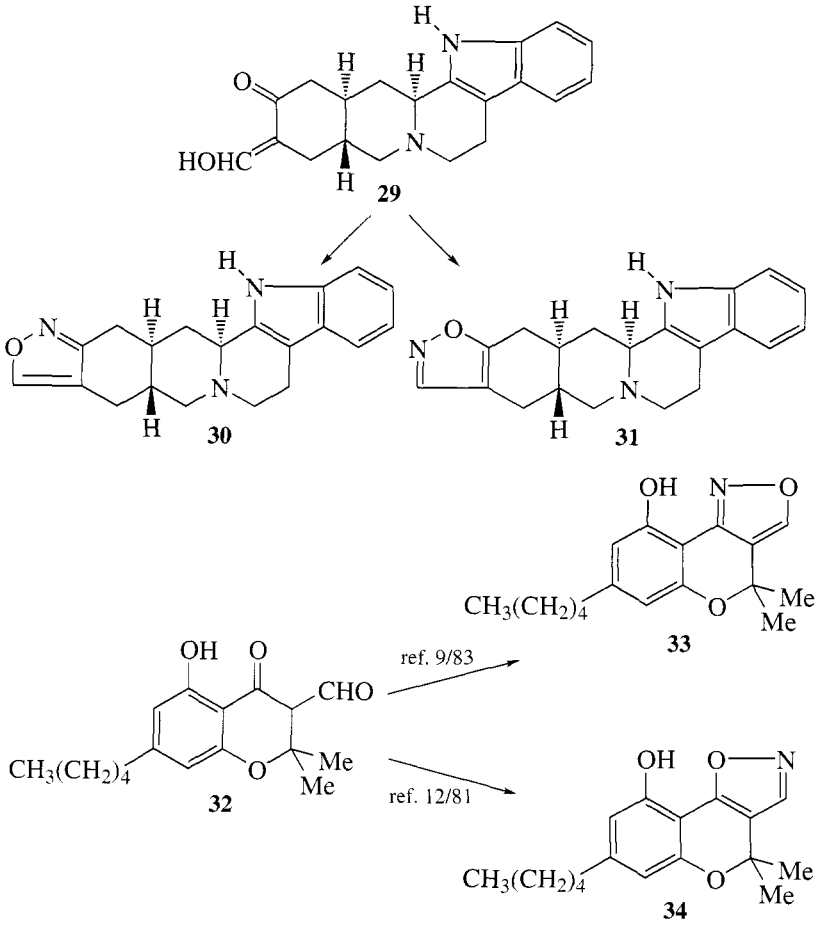
A nice example of this selectivity is the synthesis of 10*H*-isoxazolo[5,4-*a*] carbazole derivatives **22**,[2/60] where both the oximation and a tandem Fisher indole reaction gave the same regioisomer **22**.

Without any chemical support for their assignment, derivatives of the following ring systems were reported to be obtained in accord with the previously demonstrated selectivity: thieno[2,3-*g*]-1,2-benzisoxazole **23**,[12/71,30/84] 5*H*-pyrano[3,2-*f*]-1,2-benzisoxazole **24**,[16/84] [1]benzoxepino[4,3-*d*]isoxazole **25**,[21/77] benz[*f*]isoxazolo[4,5-*c*]quinoline **26**,[16/86,13/87] benz[*h*]isoxazolo[4,5-*c*]quinoline **27**,[13/87] and 11*H*-naphtho[2′,1′:5,6]pyrano[3,4-*d*]isoxazole **28**.[22/84]



Sometimes both regioisomers are formed and these can be isolated as admixtures only, for example, 4*H*-thiopyrano[3,4-*d*]isoxazoles and 4*H*-thiopyrano[4,3-*c*]isoxazoles,[2/77] isoxazolo[4,5-*c*]pyridines and isoxazolo[4,3-*c*]pyridines.[2/77] Analogous behavior is also noted for 18-hydroxymethileneyohimban-17-one **29**, which affords **30** and **31** on treatment with hydroxylamine hydrochloride in refluxing AcOH.[2/63,3/64,2/65,3/65,1/66,11/74] If the mixture of 1*H*,8*H*-2,1-benzoisoxazolo[5,6-*g*]indolo[2,3-*a*]quinolizine and 1,2-benzoisoxazolo[5,6-*g*]indolo[2,3-*a*]quinolizine derivatives (**30** and **31**, respectively) are treated with MeONa or EtONa, the latter undergoes ring opening to a ketonitrile while the former can be isolated unchanged. Alternatively, **30** can be obtained as the sole product from the reaction of **29** with hydroxylamine freebase in AcOH/AcONa.[2/66]

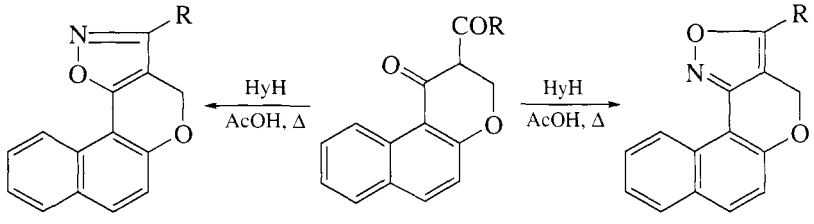
As a further comment on the regiochemical behavior of ketoaldehyde derivatives in some instances, selective attack by nitrogen at the ketone carbonyl group seems to occur. Two such examples involve the formation of a 7*H*-isoxazolo[4,3-*c*]pyrrolo[3,2,1-*i*, *j*]quinoline from the suitable substrate[19/73] and the isolation of 4*H*-[1]benzopyrano[3,4-*d*]isoxazole **33**, in 44% yield, following reaction of



32 and hydroxylamine hydrochloride in AcOH at reflux.[9/83] The same starting material (**32**) had previously been reported to give the "normal" 4*H*-[1]benzopyrano[3,4-*d*]isoxazole **34** in 59% yield under these conditions.[12/81] The latter result was subsequently reconfirmed,[19/85] but melting-point and NMR spectral data are inconsistent.

The preceeding example is not the most intriguing mystery of the section however. In 1984 the reaction of two 1-oxo-1*H*-naphtho[2,1-*b*]pyrones (**35a**, R = H; **35b**, R = COOEt) with hydroxylamine hydrochloride in refluxing acetic acid (3 h) was described.[22/84] The apparent result was the formation of two 4*H*-naphtho[1′,2′:5,6]pyrano[3,4-*d*]isoxazoles: **36a** (R = H), m.p. 111–113°C, IR(KBr) 1600 and 1680 cm^{-1}; **36b** (R = COOEt), m.p. 112–114°C. Two years later, the same group reported the same result using the 8-bromo derivatives of **35a** and **35b**.[21/86] Then, in 1986, **35a** and **35b** were reported to react with hydroxylamine hydrochloride in acetic acid (after 7 minutes at reflux in an oil bath mantained at 170°C).[20/86] Again the result obtained from **35a** was the formation

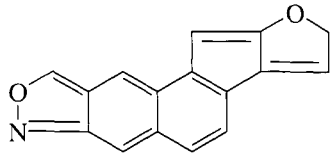
of **36a**, but the melting point was 149°C and the infrared spectrum contained an absorbtion at 1640cm^{-1}. Conversely, **35b** reportedly gave 4*H*-naphtho[1′,2′: 5,6] pyrano[4,3-*c*]isoxazole **37b** (R=COOEt; m.p. 102°C). A careful reexamination of these results is highly recommended.



36a,b **35a** (R = H) **35b** (R = COOEt) **37b**

If the oximation of β-ketoaldehydes with hydroxylamine hydrochloride is performed in the presence of a base such as pyridine, AcONa–water, when Ac OH, ethanol or pyridine are used as solvents or when hydroxylamine acetate is used, nitrogen selectively attacks the keto group.

This preference seems to be operative in the formation of a derivative of the 2*H*-furo[2′,3′:2,3]indeno[7,6-*f*]-2,1-benzisoxazole ring system **38**.[21/82]



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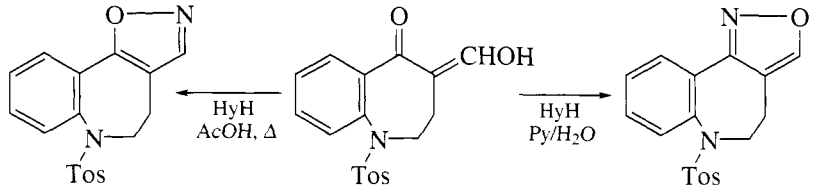
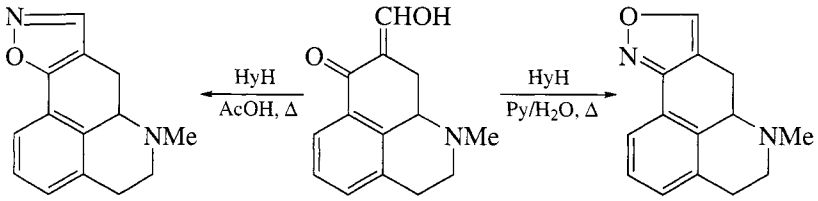
Control over potential regiochemical outcomes is possible in 1,2,3,4-tetrahydro-4-hydroxymethylene-1-tosyl-1-benzazepin-5-one **39**, which reacts with hydroxylamine hydrochloride in refluxing AcOH (10h) to give 6*H*-isoxazolo[4,5-*d*]-1-benzazepine derivative **40**, in 74% yield. When the reaction was conducted in refluxing pyridine–water 8 : 1 (6h), a 79% yield of 6*H*-isoxazolo[4,3-*d*]-1-benzazepine **41** was obtained.[8/78]



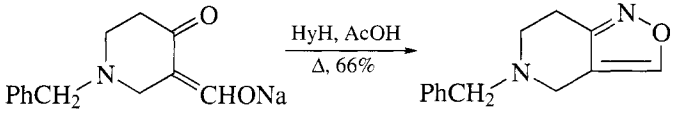
40 **39** **41**

Analogously, 8-hydroxymethylene-1-methyl-2,3,7,8,9,9a-hexahydro-1*H*-benzo[*de*]quinolin-7-one **42**, with hydroxylamine hydrochloride in refluxing AcOH gave, in 83% yield, 4*H*-benz[*d*,*e*]isoxazolo[5,4-*g*]quinoline **43**, while the use of a refluxing pyridine–water (8 : 1) mixture gave the 4*H*-benz[*d*,*e*] isoxazolo[3,4-*g*] quinoline derivative (**44**) in 62% yield.[11/82]



43 **42** **44**

Sometimes the substrate itself may serve as the base. The sodium salt of 1-benzyl-3-hydroxymethylene-4-piperidone **45**, when refluxed with hydroxylamine hydrochloride in AcOH, gave the isoxazolo[4,3-*c*]pyridine derivative **46**, in 66% yield and whose stability toward MeONa serves as proof of structure.[6/71]

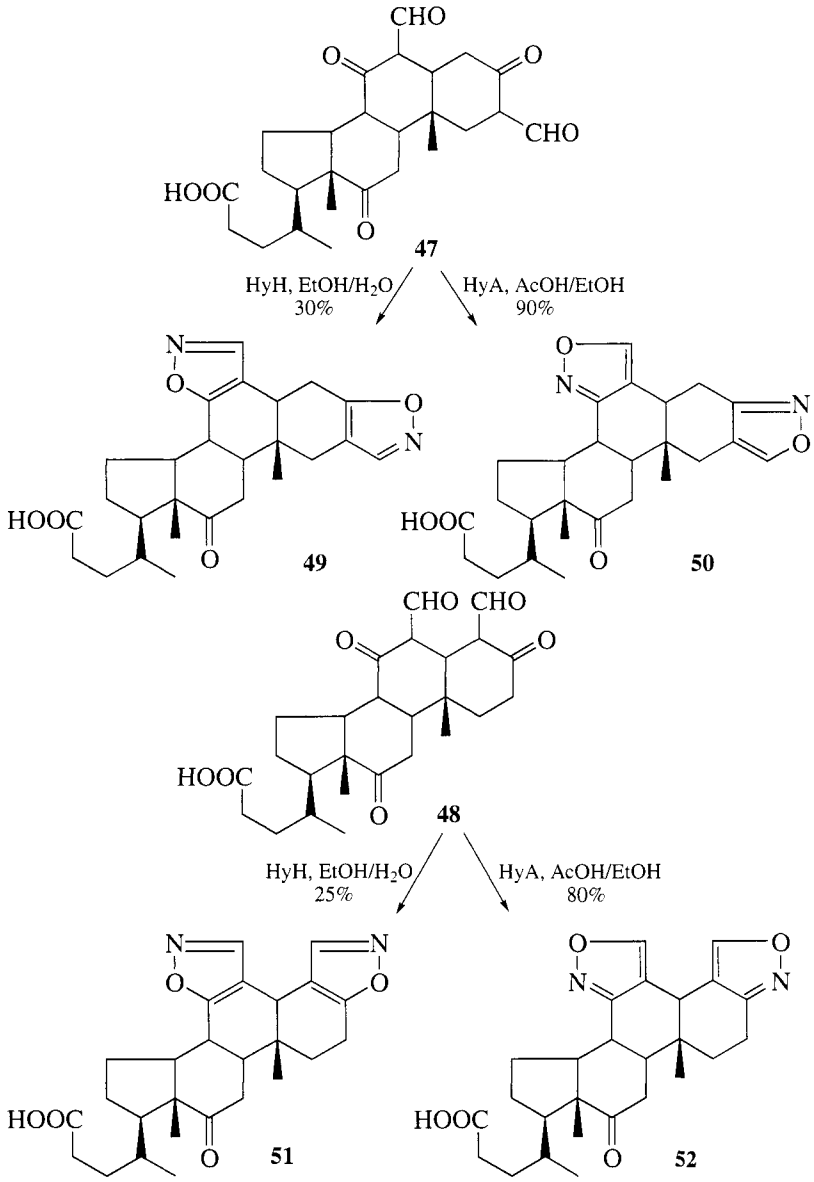


45 **46**

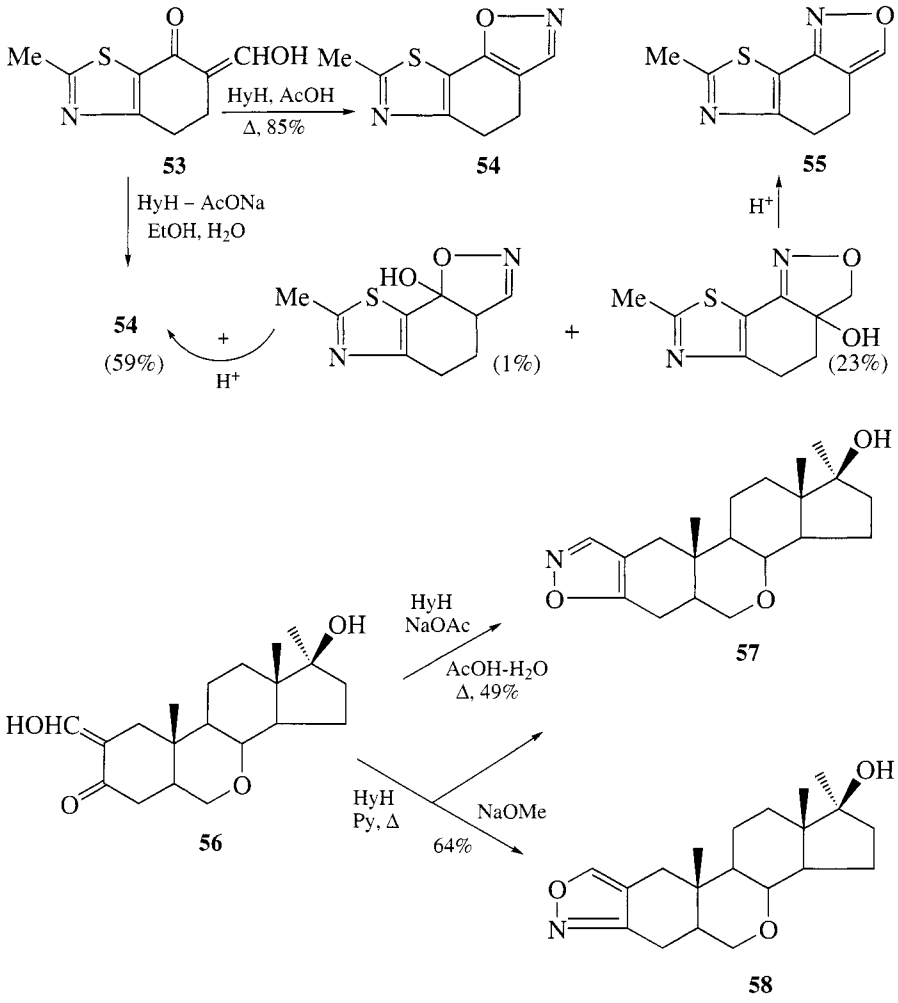
The best example in support of the dichotomy illustrated above is provided by the oximation of the diformyl derivatives of 3,7,12-triketocholanic acids **47** and **48**.[6/69] When the reaction is conducted in refluxing EtOH/H_2O, attack of hydroxylamine hydrochloride onto the formyl groups occurs to give **49** and **51**, which were opened under basic conditions. If the reactions are instead performed with hydroxylamine acetate in refluxing EtOH, two products (**50** and **52**) are obtained which arise from attack on the keto group and are stable under basic conditions. The products are derivatives of the following basic ring systems: 1*H*-cyclopenta[7,8]phenanthro[3,2-*d*:10,9-*d*′]diisoxazole (**49**); 1*H*-cyclopenta[7,8]phenanthro[2,3-*c*:9,10-*c*′]diisoxazole (**50**); 1*H*-cyclopenta[7,8]phenanthro[1,2-*d*:10,9-*d*′]diisoxazole (**51**); 1*H*-cyclopenta[7,8]phenanthro[2,1-*c*:9,10-*c*′]diisoxazole (**52**).

In some respects, oximation of benzothiazole derivative **53**,[7/73] follows the rules described above; **54** is obtained, in 85% yield, from hydroxylamine hydrochloride in refluxing AcOH. With hydroxylamine hydrochloride and AcONa in refluxing EtOH/H_2O both regioisomers are produced, giving thiazolo[4,5-*g*]-1,2- and thiazolo[4,5-*g*]-2,1-benzisoxazole, **54** and **55** respectivley in a ratio of 3 : 1.

In an example that illustrates that both regioisomers are, on occassion, obtained under basic conditions, 7-oxa-2-hydroxymethyleneandrostan-3-one

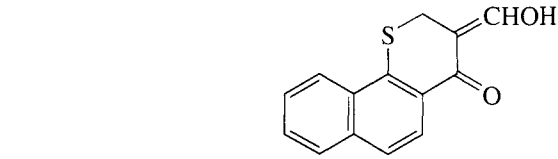


derivative **56** reacted[14/73, 16/75,18/76] with hydroxylamine hydrochloride and AcONa in refluxing AcOH/H_2O to give **57**, which is derived from "*N*-to-formyl" attack. When the reaction was performed in refluxing pyridine, both cyclopenta[7,8]-[1]benzopyrano[4,3-*f*]-1,2-benzisoxazole and 1*H*,5*H*-cyclopenta[7,8][1]benzo-pyrano[4,3-*f*]-2,1-benzisoxazole derivatives (**57** and **58**, respectively) were



obtained, with **58** isolated in 64% yield from the mixture after treatment with MeONa. The naphthothiopyrane derivative **59**[13/73] reacted with hydroxylamine hydrochloride in refluxing AcOH to give "*N*-to-formyl" attack, but the resulting adduct was unstable and the α-cyanoketone **60** was obtained instead. With hydroxylamine hydrochloride and AcONa in refluxing MeOH/H_2O, the 11*H*-naphtho[2′,1′:5,6]thiopyrano[3,4-*d*]isoxazole **61**, which is unstable toward MeONa, was obtained in 85% yield. Alternatively, when the reaction was performed in refluxing pyridine, 1*H*-naphtho[2′,1′:5,6]thiopyrano[4,3-*c*]isoxazole derivative **62** was isolated in 65% yield.

β-Ketopyruvic esters are known to afford isoxazol-3-carboxylic esters by oximation of the activated carbonyl group.[22/91] If a heterocyclic ring that incorporates these features is oximated with hydroxylamine hydrochloride in refluxing ethanol or acetic acid, a single regioisomer is obtained.



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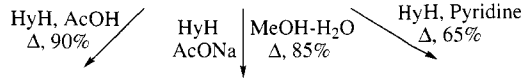

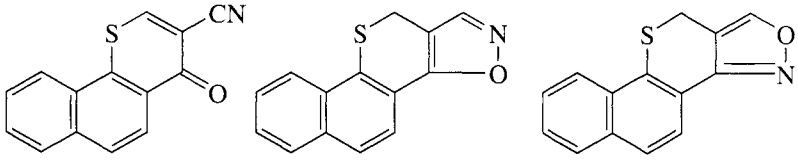

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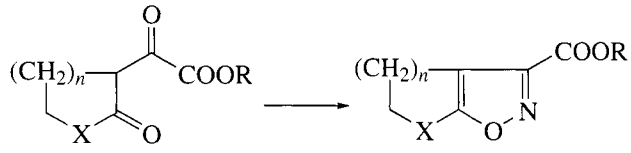
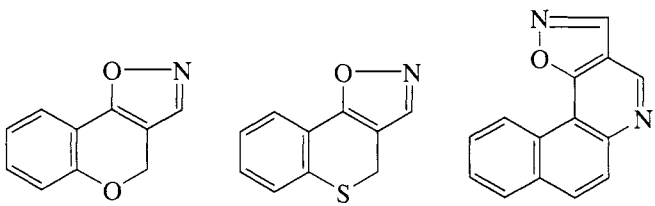


Examples prepared by application of this general rule include derivatives of 4*H*-1-benzopyrano[3,4-*d*]isoxazole (**15**),[8/71,9/71,10/71,5/72,14/72,10/74] 4*H*-1-benzothiopyrano[3,4-*d*]isoxazole (**63**),[14/75] benz[*f*]isoxazolo[4,5-*c*]quinoline (**26**),[16/86,13/87] benz[*h*]isoxazolo[4,5-*c*]quinoline (**27**),[13/87] indeno[2′,1′:5,6]thiopyrano[3,4-*d*]isoxazole (**64**),[22/83] 5*H*-furo[2′,3′:7,8][1]benzothiopyrano[3,4-*d*]isoxazole (**65**),[22/83] 11*H*-naphtho[2′,1′:5,6]thiopyrano[3,4-*d*]isoxazole (**61**),[15/88] 4*H*,11*H*-1-benzothiopyrano[3′,4′:5,6]thiopyrano[3,4-*d*]isoxazole (**66**),[10/80,24/87] 2-benzothiopyrano[3′,4′:5,6]thiopyrano[3,4-*d*]isoxazole (**67**),[19/82] 4*H*,11*H*-isoxazolo[5′,4′:4,5]thiopyrano[3,2-*c*]-1,2-benzothiazine (**68**),[7/79] isoxazolo[5′,4′:4,5]thiopyrano[3,2-*c*]-2,1-benzothiazine (**68a**),[12/82] and thieno[3″,2″:4′,5′]thiopyrano[2′,3′:5,6]thiopyrano[3,4-*d*]isoxazole (**69**)[18/82] were obtained.



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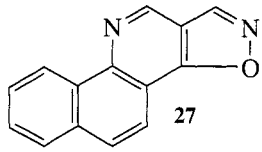
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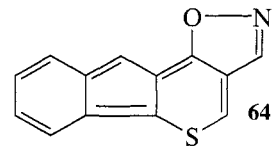
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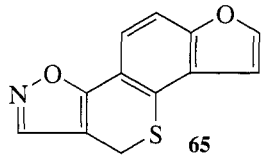
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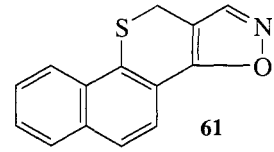
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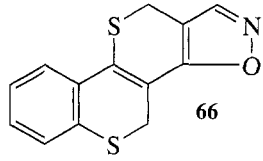
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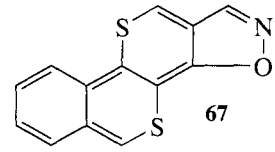
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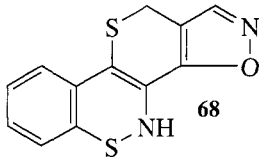
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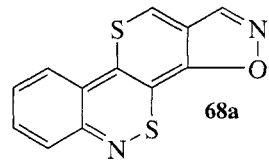
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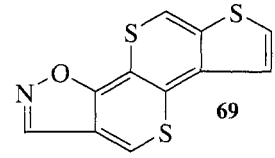
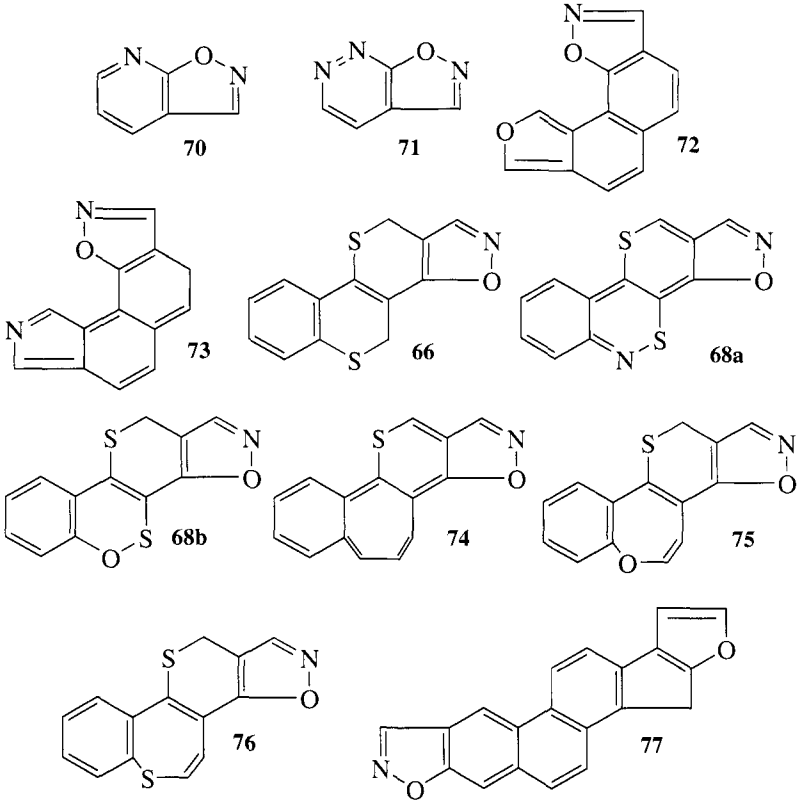

69

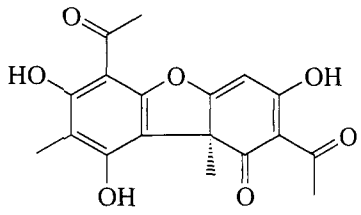
Several examples concerning the oximation of "β-diketone-like" structures, in which one carbonyl group is contained within a heterocyclic ring, have been reported.

The experimental conditions generally employ hydroxylamine hydrochloride, either in the presence of a base (NaOH, AcONa, pyridine) or without any base in refluxing ethanol, AcOH, or pyridine. In a fashion that appears to be independent of the nature of the substituent (R = alkyl or aryl groups), attack of the hydroxylamine nitrogen atom invariably occurs on the side-chain carbonyl group. Thus, derivatives of the following ring systems were obtained: isoxazolo[5,4-*b*]pyridine (**70**),[1/73,2/78,3/83] isoxazolo[5,4-*c*]pyridazine (**71**),[9/90] isobenzofuro[5,4-*g*]-1,2-benzisoxazole (**72**),[11/73] 4*H*-isoindolo[5,4-*g*]-1,2-benzisoxazole (**73**),[11/73] 4*H*,11*H*-[1]benzothiopyrano[3′,4′:5,6]thiopyrano[3,4-*d*]isoxazole (**66**),[10/80] isoxazolo-[5′,4′:4,5]thiopyrano[3,2-*c*]-2,1-benzothiazine (**68a**),[12/82] 11*H*-1,2-benzoxathi-

ino[3′,4′:5,6]thioprano[3,4-*d*]isoxazole (**68b**),[23/84] benzo[3′,4′]cyclohepta[1′,2′:5,6]thiopyrano[3,4-*d*]isoxazole (**74**),[25/87] 12*H*-[1]benzoxepino[4′,5′:5,6]-thiopyrano[3,4-*d*]isoxazole (**75**),[25/87] 12*H*-[1]benzothiepino[4′,5′:5,6]thiopyrano-[3,4-*d*]isoxazole (**76**),[25/87] and 4*H*-furo[2″,3″:4′,5′]cyclopenta[1′,2′-:7,8]phenanthro[3,2-*d*]isoxazole (**77**).[23/73,12/74,19/76,21/80]



The lichen antibiotic (+)-usnic acid (**78**) may be oximated at either the 2- or 6-acetyl group, thereby permitting ring closure at either the 1 or 3 position. Although this material does not react with hydroxylamine hydrochloride in ethanol,[10/76] various degrees of reactivity have been noted:



1. An intermediate oxime was obtained in pyridine at r.t.
2. The oxime isolated from (1) cannot be obtained in pure form because of an inherently facile cyclization process.
3. 1h refluxing in EtOH completed the cyclization of the products from (2).
4. The same result was obtained after 1h at 110°C in pyridine.
5. Heating 1.5 h at 80°C in 1:1 pyridine/EtOH gave the cyclized products directly.

Under these conditions, three products can be obtained, two of them related to the topic of this review, but in yields that depend largely on the experimental conditions (Table 3.2).

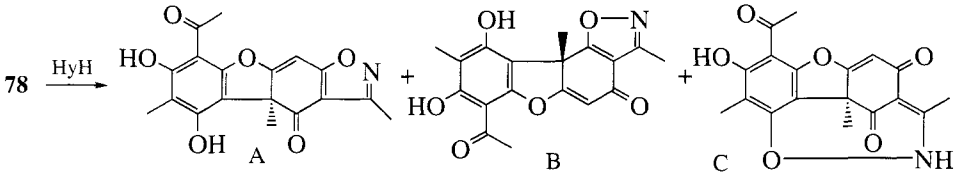


TABLE 3.2. YIELDS OF THE REACTION BETWEEN (+)-USNIC ACID AND HYDROXYLAMINE

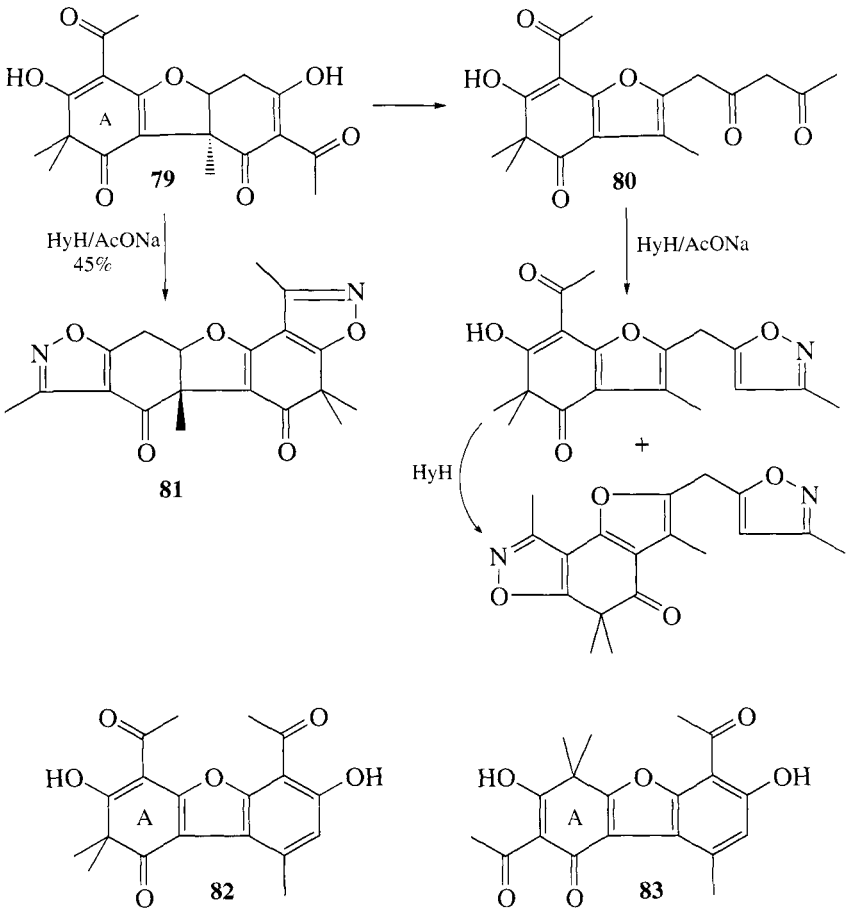
Conditions	A%	B%	C%	Total yield (%)
1,3	21	5.5	60.5	87
1–3	20	57	2	79
1,2,4	16	58	21	5
5	30.5	nd	nd	nd

Thus, attack by nitrogen occurs invariably at the 2-acetyl group while ring closure may proceed at several sites.

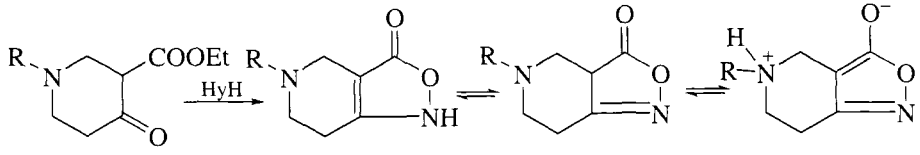
When 8-methyl usnic acid **79** and its hydrolysis product **80** were subjected to oximation,[1/62,2/62] **79** easily gave the furo[2,3-*e*:4,5-*f*']bis-1,2-benzisoxazole derivative **81**, whereas **80** was derivatized at an exocyclic position rather than in the ring.

The same reaction, when performed on the so-called anhydromethyldihydrousnic acid **82** and isoanhydromethyldihydrousnic acid **83**,[3/63,4/63] gave selective oximation of ring A. Preferential attack of nitrogen at the acetyl group was observed, and derivatives of benzofuro[2,3-*e*]-1,2-benzisoxazole and benzofuro[3,2-*f*]-1,2-benzisoxazole, respectively, were obtained.

Oximation of heterocyclic derivatives related to β-ketoesters with hydroxylamine or its hydrochloride salt in the presence of NaOH or AcONa is reported to occur preferentially at the ketonic carbonyl group. Ring closure on the ester



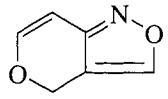
gives an isoxazolone derivative whose tautomeric equilibrium depends not only on pH, but also on the nature of the condensed heterocyclic ring.



The studies in the field were undertaken because the products are rigid structural analogues of GABA (γ-aminobutyric acid) and glycine, the major inhibitory neurotransmitters in the brain and in the spinal cord, respectively. This topic will be discussed in detail in a later section of this review.

Several ring systems were synthesized in a highly selective fashion using this route: 4*H*-pyrano[4,3-*c*]isoxazole (**84**),[7/84] isoxazolo[3,4-*c*]pyridine (**85**),[1/79]

isoxazolo[4,3-*c*]pyridine (**86**),[1/57,1/86] 4*H*-isoxazolo[3,4-*c*]azepine (**87**),[1/86] 4*H*-isoxazolo[4,3-*c*]azepine (**88**),[1/86] and, by a double-oximation process, 4*H*,8*H*-benzo- [1,2-*c*:5,4-*c*']diisoxazole (**89**).[2/15]



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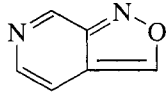

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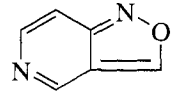

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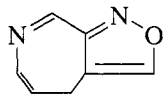

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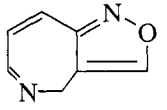

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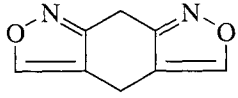
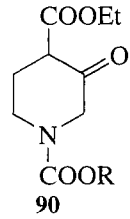


89

Curiously, an example of nonselective oximation concerns 4-ethoxycarbonyl-1-methoxycarbonyl-3-piperidone **90** (R = Me), which is reported to give a mixture of isoxazolo[3,4-*c*]pyridine and isoxazolo[5,4-*c*]pyridine derivatives,[14/82] whereas the 1-tert-butoxycarbonyl analog (**90** $R = C(CH_3)_3$) gives the former ring system only.[1/79]



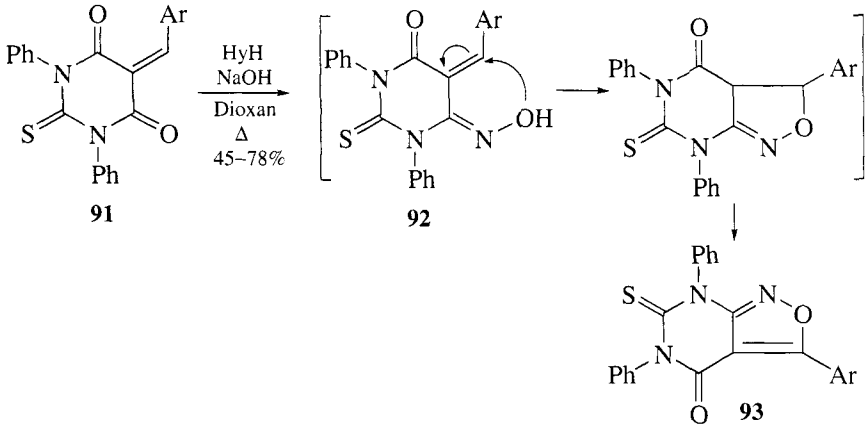
90

3.2.1.1b. Reaction of Hydroxylamine and α,β-Enones

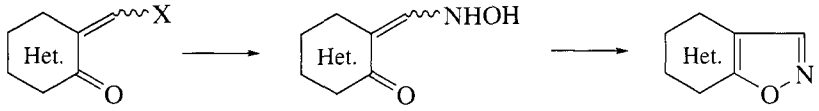
It is known that hydroxylamine reacts with α,β-unsaturated ketones to give different products (isoxazolines, hydroxylamino oximes, and dioximes) depending on the reaction conditions.[22/91] Sometimes isoxazoles have been isolated from oxidation processes. An example of this is provided by the reaction of 5-arylidene derivatives of *N*,*N*'-diphenyl thiobarbituric acid **91** with hydroxylamine. On the basis of UV spectral data, the structure of 5-aryl-5,7-diphenyl-6-thioisoxazolo[3,4-*d*]pyrimidin-4-(5*H*,7*H*)-one (**93**) was assigned to the product derived from the ring closure of the α,β-unsaturated oxime **92**.[18/85]

Obviously, if the unsaturated oxime contains a leaving group, ring closure through intramolecular nucleophilic substitution can occur and the intermediate process involving *in situ* oxidation of the isoxazoline can be circumvented.

If an α,β-unsaturated carbonyl system that belongs to a heterocyclic ring has an electron-releasing group (X) in the β position, initial attack by hydroxylamine at the β position is preferred and results in nucleophilic substitution followed by ring closure on the carbonyl group. This can be rationalized as the attack of a



soft nucleophile under molecular-orbital (MO) control, a concept that can be extended to rationalize the reactivity of various substituted enones.



If the α,β-unsaturated carbonyl system is assumed to undergo the same polarization of the orbital coefficients induced by substituents in butadiene, an electron-donating group (X) in the β position has a destabilizing effect and increases the LUMO coefficient of the adjacent carbon atom.[17/76,22/77] An electron-withdrawing group (Z) in the same position has the opposite effect. This simple MO reasoning, which is illustrated in Figure 3.1, suggests that attack of a soft nucleophile at the β position will be favored in a substrate which bears an electron-releasing substituent. Conversely, substrates bearing electron-withdrawing groups at the β position prefer a mode of attack in which the carbonyl group is targeted.

A good number of examples exist which provide experimental verification of the MO depiction of reaction of β-amino enones with hydroxylamine.

The reaction of 3-(pyrrolidinomethylene)-4-chromanone **94** with hydroxylamine hydrochloride in refluxing ethanol, in the presence of 1 equiv. of HCl, gave 4*H*-benzopyrano[3,4-*d*]isoxazole **15**.[13/86] The nucleophilic replacement of pyrrolidine as an intermediate step in the reaction is supported by the observation that the same reaction, when conducted in the absence of HCl, gave an oxime (**95**) that cyclized under acidic conditions.

The reaction of 4-dimethylaminomethylene-2*H*-thiopyran-3,5(4*H*,6*H*)dione **96** with hydroxylamine hydrochloride, in refluxing methanol, gave a single regioisomer, the 7*H*-thiopyrano[4,3-*d*]isoxazolo derivative **97**, that underwent facile ring opening to the corresponding cyanothiopyrandione.[8/84]

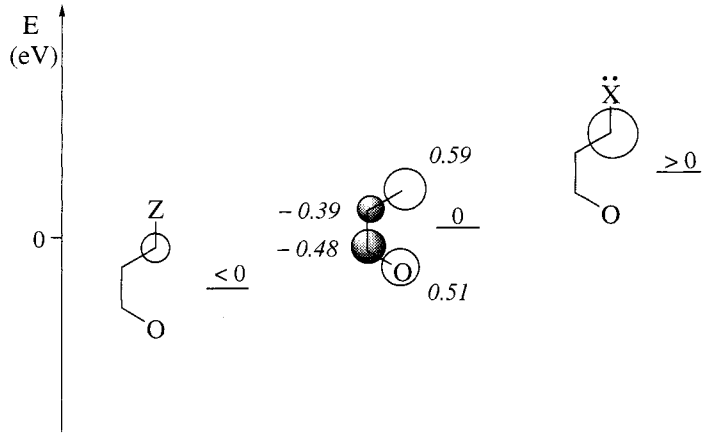
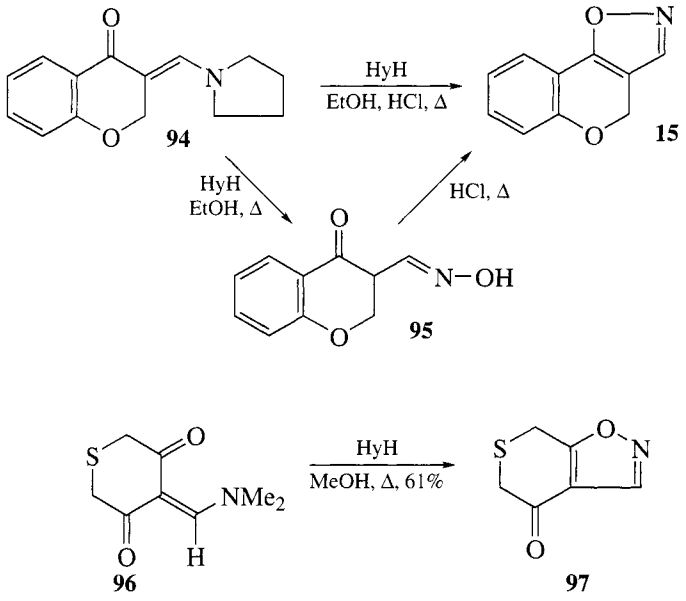
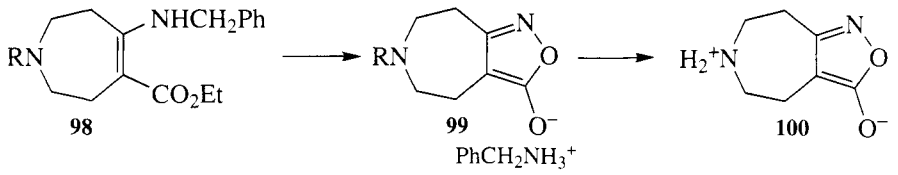


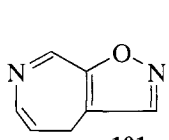
Figure 3.1. Schematic representation of the LUMO energy levels and coefficients of β-substituted α,β-enones.



Reaction of several azepine derivatives (**98**) with hydroxylamine hydrochloride and sodium methoxide in refluxing methanol gave rise to the benzylammonium salts of isoxazolo[3,4-*d*]azepines **99**. The latter are useful precursors to the zwitterionic product **100**, a structural analog of GABA.[15/73]

Derivatives of 4*H*-isoxazolo[5,4-*c*]azepine **101**[13/78] and 5*H*-isoxazolo[5′,4′:4,5]thiopyrano[3,2-*g*]-1,2,3-benzothiadiazole **102** [23/87] have been synthesized in an analogous fashion.

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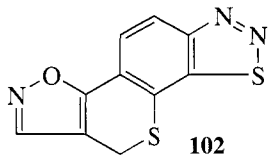
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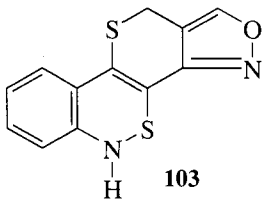
A reversal in the mode of attack by hydroxylamine gives rise to 5*H*,11*H*-isoxazolo[3′,4′:4,5]thiopyrano[3,2-*c*]-2,1-benzothiazine (**103**)[12/82] and 11*H*-1,2-benzoxathiino[3′,4′:5,6]thiopyrano[4,3-*c*]isoxazole (**104**) derivatives.[23/84]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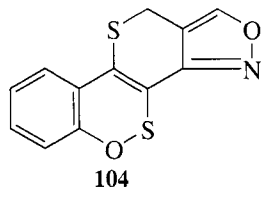
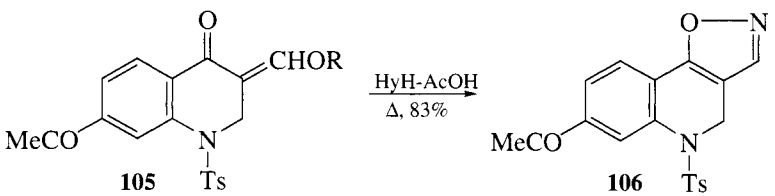
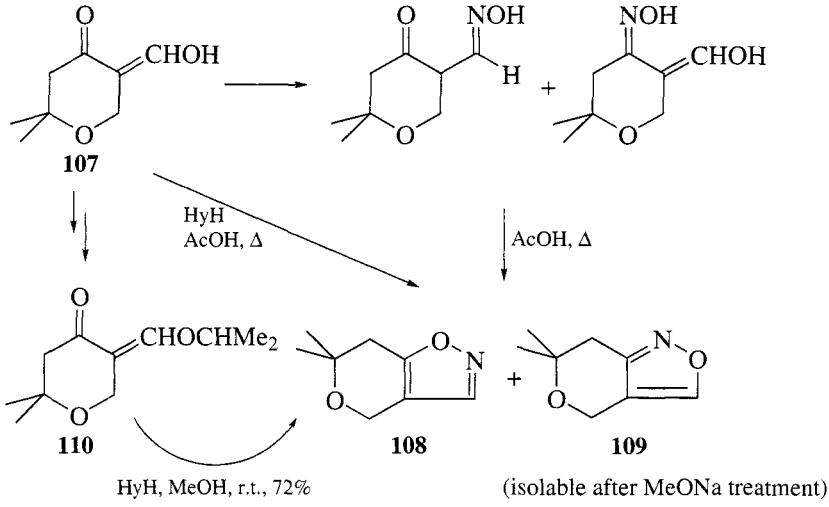

104

The reactivity of β-alkoxyenones is in general accord with the preferred β-attack mode of hydroxylamine. A mixture of 3-alkoxymethylene- and 3-hydroxymethylene-4-quinolone derivatives (**105**) reacted with hydroxylamine in refluxing acetic acid to give the isoxazolo[4,5-*c*]quinoline derivative **106**.[1/63] This 3-unsubstituted isoxazole was opened under basic conditions.

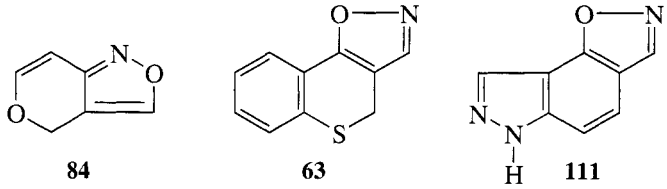


This selectivity can occasionally be applied to achieve the synthesis of both regioisomers of a given isoxazole-containing ring system. Depending on the choice of reaction conditions, 2,2-dimethyl-5-formyltetrahydro-4*H*-pyran-4-one **107** gives either a mixture of regioisomeric oximes, which may subsequently be cyclized to the pyrano[3,4-*d*]- and pyrano[4,3-*c*]isoxazole derivatives (**108** and **109**, respectively), or a mixture of these condensed isoxazoles directly.[15/75] If this mixture is treated with NaOMe, **108** is destroyed and pure **109** is obtained.

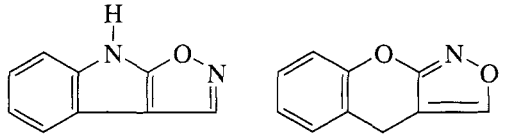
Alternatively, if **107** is converted into its *iso*-propoxymethylene derivative **110** and then treated with hydroxylamine hydrochloride in MeOH at r.t., pure **108** can be obtained in 72% yield.



Further examples of this regioselective attack are provided in the syntheses of 4*H*-pyrano[4,3-*c*]isoxazole **84**[4/70,7/71] and 4*H*-[1]benzothiopyrano[3,4-*d*]isoxazolele **63**[14/68] derivatives. Initial condensation at the carbonyl group, to ultimately give the opposite regioisomer, occurs in the synthesis of the 6*H*-pyrazolo[3,4-*g*]-1,2-benzisoxazole derivative **111**.[6/76] The structures of the products were not verified by subsequent chemical conversion to the corresponding nitriles.

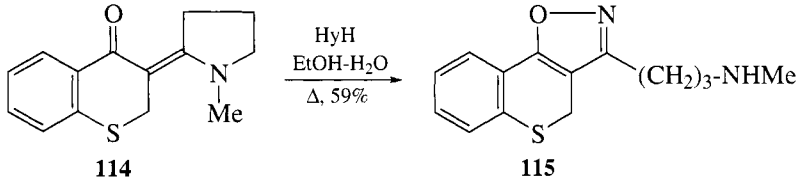


The syntheses of 8*H*-isoxazolo[5,4-*b*]indole **112**[1/23] and 4*H*-[1]benzopyrano [2,3-*c*]isoxazole derivative **113**[19/83] are reported to involve nucleophilic replacement of the β–thioalkoxy group in α,β-enones with hydroxylamine.



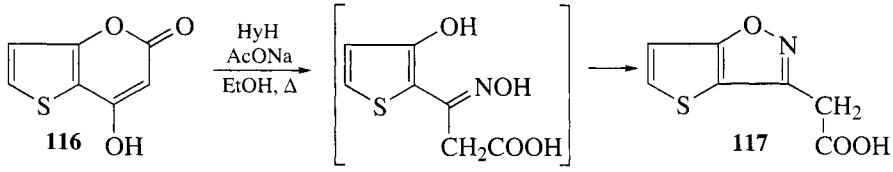
The last examples of this section concern systems that formally contain the types of functional groups that permit isoxazole ring formation but react in ways that involve a rearrangement of the original ring system.

The attack of hydroxylamine at the β position of the 3-pyrrolidinyl derivative of benzothiopyran-4-one (**114**) induces cleavage of the pyrrolidine ring to give 4*H*-[1]benzothiopyrano[3,4-*d*]isoxazole derivative **115**.[10/83]



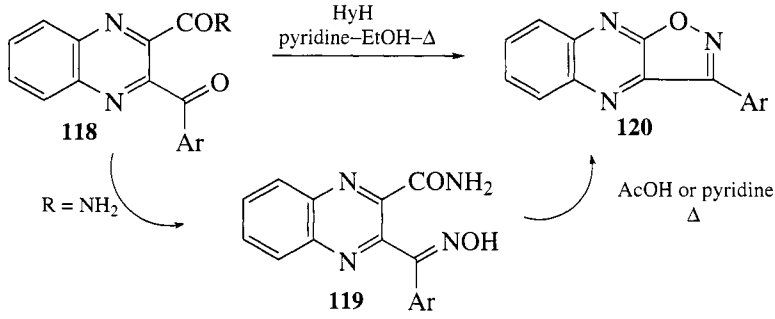
114 **115**

The attack of hydroxylamine on the thienopyran derivative **116** occurs in the β-position too, to give 3-thieno[2,3-*d*]isoxazolyl acetic acid **117**.[5/87]



116 **117**

Reactions of hydroxylamine with α,β-enones bearing electron-withdrawing groups, such as the 2-aroylquinoxalines **118**, have been reported.[10/66] The presumed intermediate oximes **119** (isolated in the presence of the amide group) cyclize to the same isoxazolo[4,5-*b*]quinoxaline **120**. A process in which nucleophilic attack is followed by elimination of HCOR seems reasonable for the cyclization step, although alternative intermediates cannot be excluded.



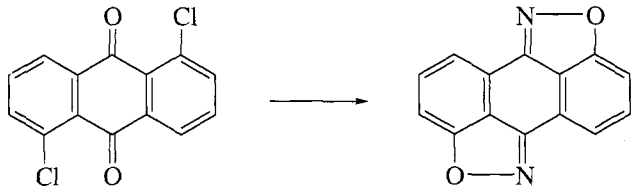
118 **120**

119

A large number of examples concern the reaction of hydroxylamine with heterocyclic rings that contain a β-chloro enone moiety within the ring. In general,

hydroxylamine (used as either its hydrochloride or the free base) reacts mainly with the carbonyl group and the cyclization is completed by nucleophilic replacement of chloride ion. This is the general trend, but several variations have been observed depending on the different substrates.

The reaction of 1,5-dichloroanthraquinone **121** with hydroxylamine hydrochloride in ethanol at 180°C under pressure,[2/10] which gives anthra[9,1-*c*,*d*:10,5-*c*′,*d*′] diisoxazole **122**, likely proceeds via oxime formation followed by nucleophilic aromatic substitution.

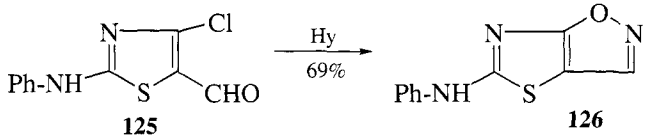


121 **122**

In an analogous fashion, oximation of 5-aroyl-6-chlorobenzofuran derivatives[12/84] gives furo[3,2-*f*]-1,2-benzisoxazolo derivatives **123**; similarly, 6*H*-pyrazolo[3,4-*c*]isoxazoles **124**[1/84] are obtained from the appropriately substituted bromopyrazolones.

123 **124**

Chloro-substituted electron-rich heterocycles, such as thiazole derivative **125**, react with hydroxylamine to give thiazolo[5,4-*d*]isoxazole **126**.[25/89]

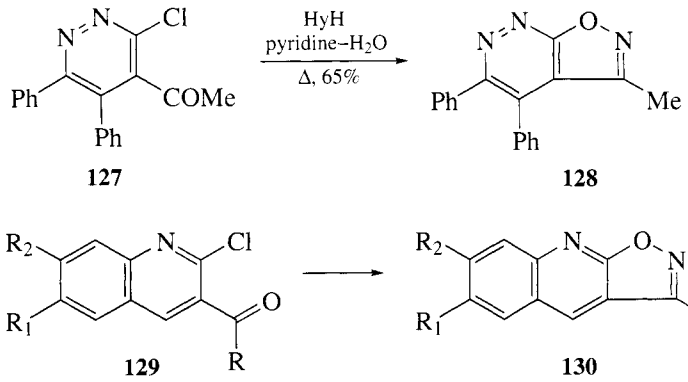


125 **126**

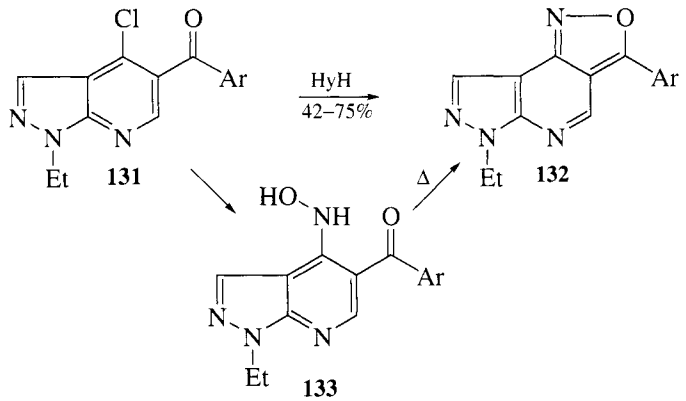
More significant examples concern the reaction of electron-deficient heterocycles whose chloro substituents are activated toward nucleophilic substitution.

4-Acetyl-3-chloropyridazine **127** reacts with hydroxylamine hydrochloride in refluxing pyridine to give the isoxazolo[5,4-*c*]pyridazine **128**.[5/89]

Both 3-acetyl and 3-aroyl-2-chloroquinolines **129** react with hydroxylamine hydrochloride in refluxing methanol, in the presence of AcONa, to give the isoxazolo[5,4-*b*]quinolines **130**.[13/84]

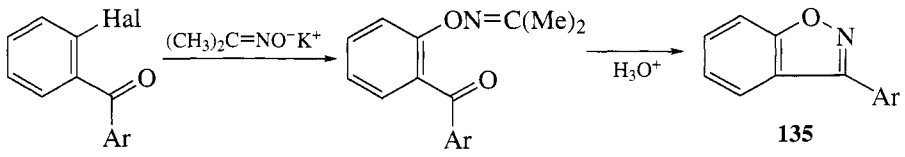


The normal sequence of oxime formation followed by ring closure is reversed in the reaction of 5-aroyl-4-chloro-1-ethyl-1*H*-pyrazolo[3,4-*b*]pyridines **131** with hydroxylamine in MeOH or with hydroxylamine hydrochloride in a mixture of AcOH–HCl at reflux. The unexpected formation of 3-aryl-6-ethyl-6*H*-isoxazolo[3,4-*d*]pyrazolo[3,4-*b*]pyridines **132**, proceeds through the intermediacy of **133**, which was isolated as by-product of the reaction and can be converted to **132** by heating in toluene.[18/86,10/88]

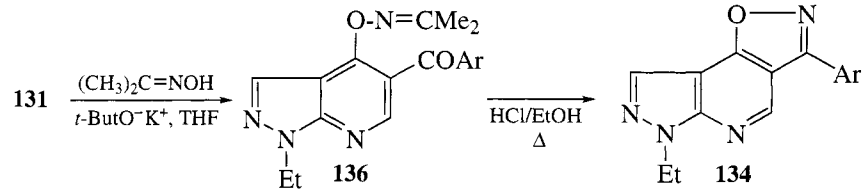


When chloro groups are activated toward nucleophilic substitution, as in **131**, hydroxylamine may either attack at the carbonyl group or at the position that bears the halogen.

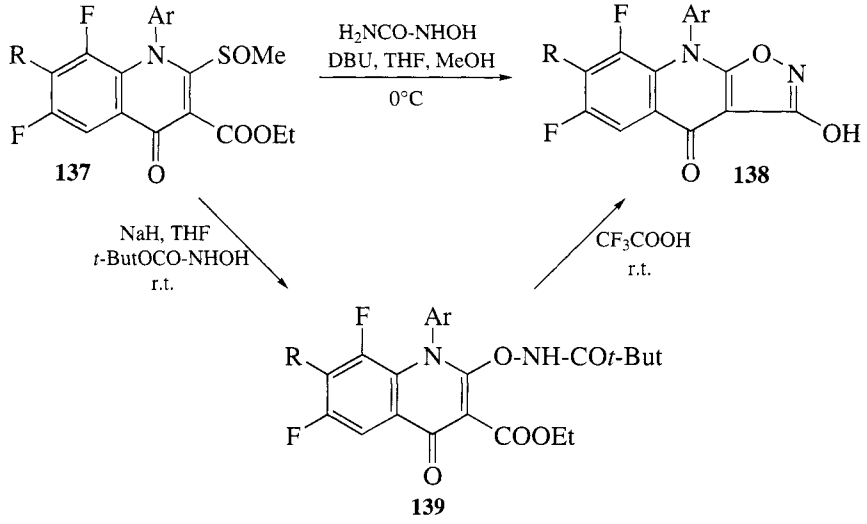
It must be mentioned that isomeric 6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridines **134**, which arise from apparent condensation with the carbonyl group, can be obtained from **131**, but not in the usual fashion. The method that is employed utilizes the potassium salt of acetone oxime followed by deprotection of the NH_2 group under acidic conditions and has also been used to prepare 3-phenyl-1,2-benzisoxazoles **135** from *o*-halobenzophenones.[29/84]



In an extension of this methodology, when 4-chloropyrazolopyridines (**131**) were treated with acetone oxime and potassium *tert*-butoxide in dry THF products of heteroaromatic nucleophilic substitution (**136**) were obtained. Following deprotection of the oxime nitrogen the 6*H*-isoxazolo[5,4-*d*]pyrazolo[3,4-*b*]pyridine derivatives (**134**), which are isomers of **132**, were obtained.[12/86,10/88]



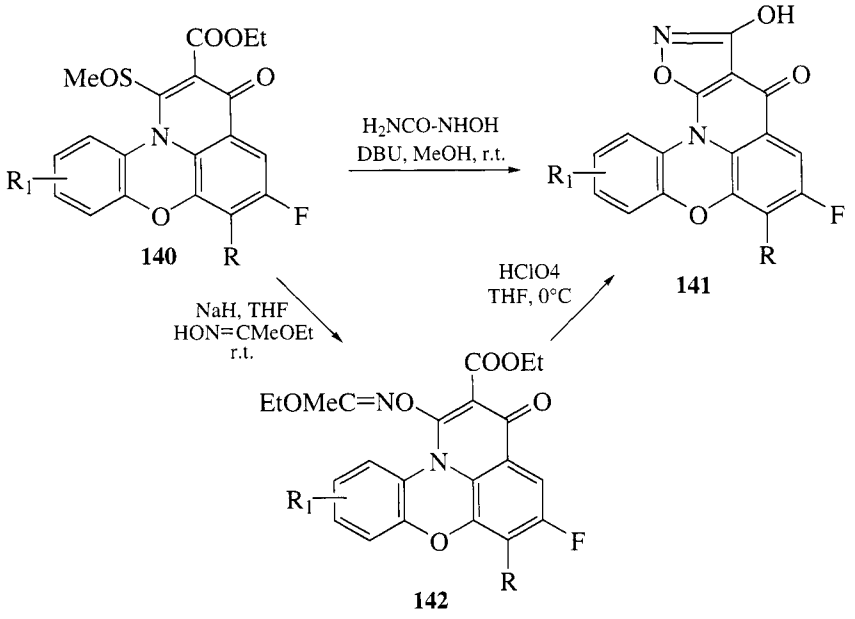
Various *N*-protected hydroxylamines have been used to prepare 3-hydroxyisoxazole derivatives. Thus, quinolone derivatives (**137**), when treated with *N*-hydroxyurea in the presence of various bases [e.g., 1,8-diazabicyclo-[5.4.0] undec-7-ene (DBU)], gave isoxazolo[5,4-*b*]quinoline derivatives (**138**). Treatment of **137** with *tert*-butyl *N*-hydroxycarbamate afforded quinolone-2-carbamate **139**, which cyclized to **138** on exposure to trifluoroacetic acid.[20/87]



A similar approach, involving either *N*-hydroxyurea or ethyl acetohydroxamate (HON=CMeOEt), was taken in order to synthesize 4*H*-isoxazolo[4′,5′:5,6]

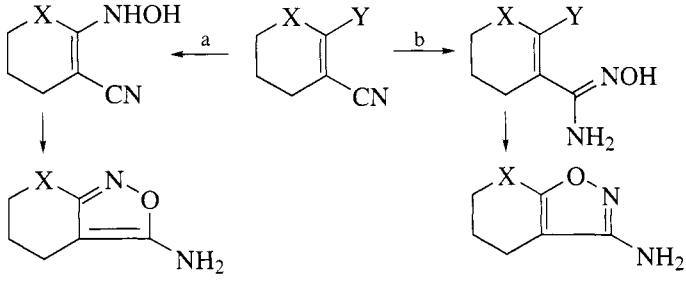
pyrido[3,2,1-*k*,*l*]phenoxazine derivatives **141**. The former reagent gave **141** from **140** in a single step; the latter reagent gave the hydroxamate **142** as an isolable intermediate.[26/87]

The advantage of this approach is that the potential ambident character of hydroxylamine is changed in a way that permits only nucleophilic substitution.



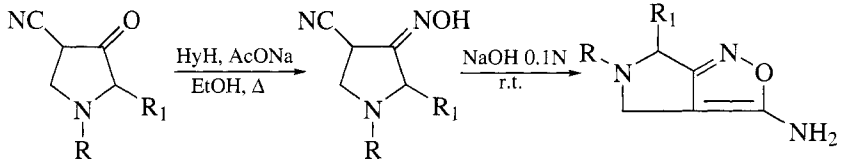
3.2.1.1c. Reaction of Hydroxylamine with β-Substituted Unsaturated Nitriles

α,β-Unsaturated nitriles contained within a heterocyclic ring may react with hydroxylamine either by displacement of the substituent in the β position or by addition to the cyano group. Pathway (a), which proceeds by formation of a hydroxylamino nitrile intermediate, gives 5-amino-substituted isoxazoles. Pathway (b) gives the regioisomeric 3-aminoisoxazoles through the intermedacy of an amide oxime.



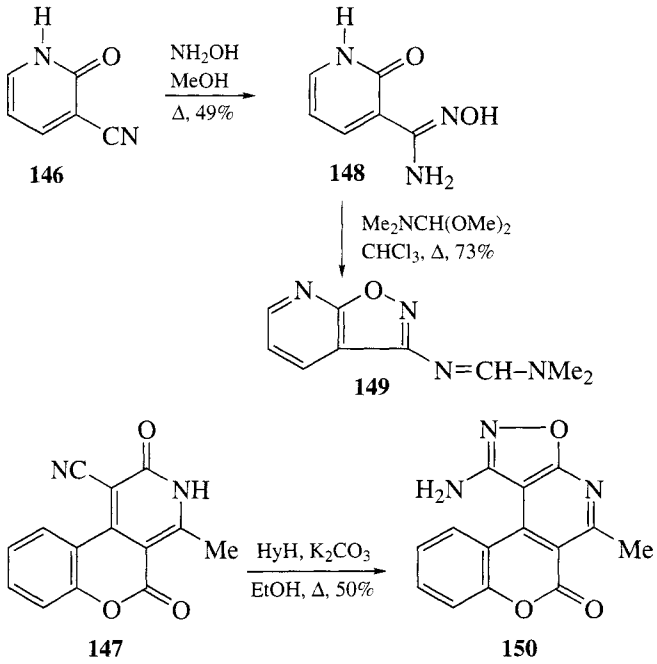
Progression along one of the two reaction pathways depends mainly on the nature of the substituent Y and the degree of aromaticity of the preexisting heterocycle.

When Y is a hydroxyl group in tautomeric equilibrium with a carbonyl group, as in 4-oxa-3-pyrrolidinonitriles **143**, pathway (a) is followed.[5/67,1/68,5/71] In this instance, the use of hydroxylamine hydrochloride gave the cyano oxime **144**, which under basic conditions, cyclized to 4*H*-pyrrolo[3,4-*c*]isoxazolo derivatives **145**, useful as diuretic and hypertensive agents.



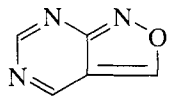
143 **144** **145**

When the carbonyl group has pyridone character, attack at the cyano group results. Compounds **146** and **147** react with hydroxylamine hydrochloride at the CN group to give 3-aminoisoxazolo[5,4-*b*]pyridine **149**[4/84] and 1-amino-6*H*-[1]benzopyrano[4,3-*d*]isoxazolo[5,4-*b*]pyridine derivative **150**,[13/91] respectively. The intermediate in the former case, acetamide oxime **148**, can be isolated.



146 **148** **149** **147** **150**

Thiomethylnitriles, belonging either to uracil[8/87] or to benzothiopyran[13/81] rings, react with substitution of thiomethyl group to afford derivatives of isoxazolo[3,4-*d*]pyrimidine (**151**) and 4*H*-[1]benzothiopyrano[2,3-*c*]isoxazole (**152**).



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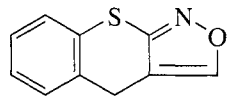
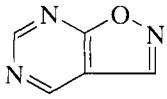


152

One example is known of addition to CN, followed by elimination of a CCl_3 group to give a derivative of isoxazolo[5,4-*d*]pyrimidine **153**.[4/79]

Three chlorocyanopyridines,[19/87] even if a typing error in the starting products has to be corrected, give the three amino derivatives of isoxazolo[4,5-*b*]-, [4,5-*c*]-, and [5,4-*b*]pyridines (**154**, **155**, and **70**, respectively). Conversely, chloropyrimidinediones[16/83] give initially the products of nucleophilic replacement of chloride followed by cyclization to derivatives of isoxazolo[3,4-*d*]pyrimidine **151**.



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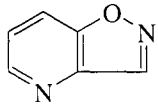

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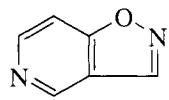

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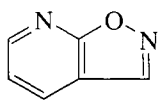

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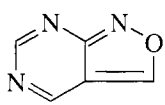
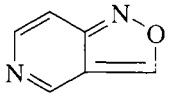


151

β-Enaminonitriles exhibit various types of behavior on exposure to hydroxylamine. In one instance, a tetrahydropyridine[14/76] afforded a derivative of isoxazolo[4,3-*c*]pyridine **86**, while pyridazine[10/90] and pyrazolo[5,1-*c*]-1,2,4-triazine[11/83] derivatives underwent addition to the CN group. In both cases amidooxime intermediates were isolated and converted, under basic or acid conditions, into derivatives of isoxazolo[4,5-*d*]pyridazine and isoxazolo[5,4-*e*]pyrazolo[5,1-*c*]-1,2,4-triazine (**156** and **157**, respectively).



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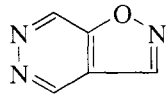

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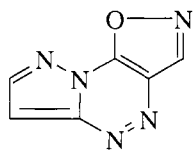
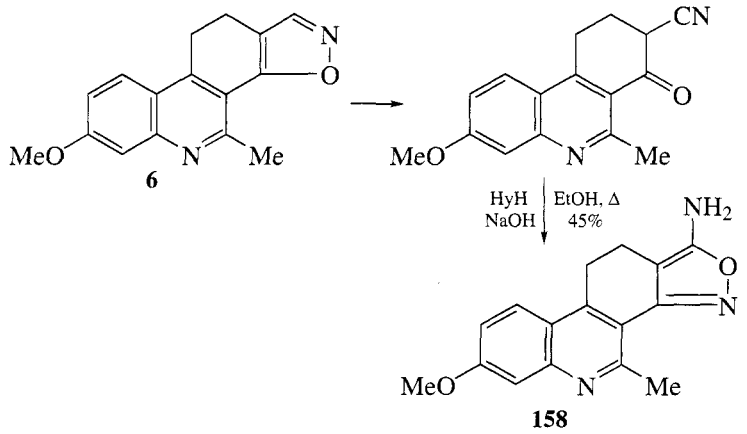


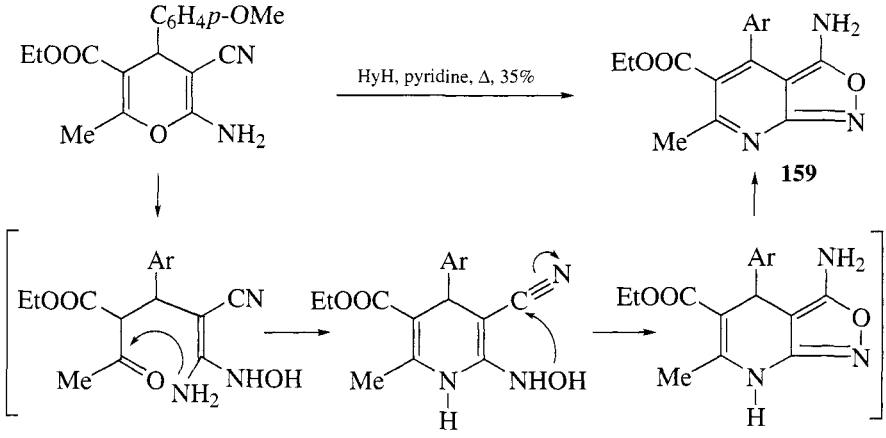
157

The reaction of hydroxylamine with heterocyclic α-ketonitriles can be a good method for inverting the regiochemistry of a condensed isoxazole. It has already

been mentioned that isoxazolo[5,4-*i*]phenanthridine derivative **6** is opened under basic conditions to give an α-cyanocarbonyl compound (§ 3.2.1.1a.). If this product is oximated in basic media, the isomeric isoxazolo[3,4-*i*]phenanthridine **158** is obtained in a reasonable yield.[9/77]



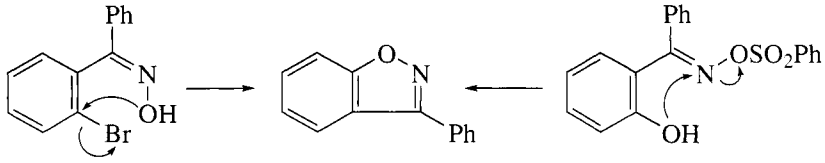
To close this section, the reaction of ethyl 6-amino-4-aryl-5-cyano-4*H*-pyran-3-carboxylate with hydroxylamine hydrochloride in refluxing pyridine, reported to give the isoxazolo[3,4-*b*]pyridine derivative **159**,[22/89] is reviewed. This can be rationalized to result from attack at C2, which enables the pyran oxygen to act as a leaving group. Subsequent double ring closure, followed by aromatization of the dihydropyridine is then proposed to account for the formation of **159**



3.2.1.1d. Ring Closure of Oximes

This section is similar to the previous one since it concerns the ring closure of an oxime, this being (in most cases) the obvious second step of the sequence involving the reaction of hydroxylamine with suitably substituted enones.

Two differing pathways, involving either the formation of the N–O bond or the formation of the C–O bond, can be followed for ring closure to an isoxazole ring, events whose occurrence largely depends on the nature of the substituents. Two examples, in which the oxime of *o*-bromobenzophenone or the oxime sulfonate derived from *o*-hydroxybenzophenone, give the same product illustrate the difference.[11/67,22/81]

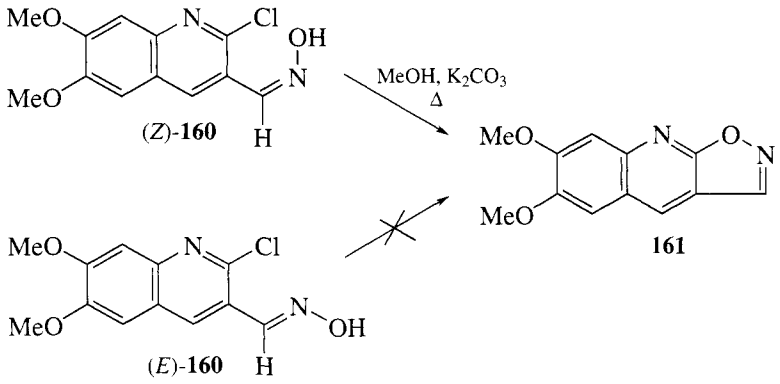


The former cyclization proceeds via intramolecular displacement of bromide by the oxime anion while the latter proceeds via nucleophilic attack of the phenolic hydroxyl on the electron-deficient nitrogen atom.

For the sake of simplicity and to give a certain order to a complicated field, these two processes will be considered, as far as possible, successively.

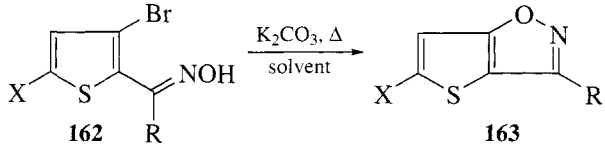
As is evident from the previous example, the configuration of the oxime is important for the course of the reaction. While the (*Z*)-oxime undergoes ring closure to an isoxazole derivative, the (*E*)-oxime is not suitably oriented for attack and is either recovered unchanged or undergoes a Beckmann rearrangement.

The (*Z*)- and (*E*)-isomers of 2-chloro-6,7-dimethoxy-quinoline-3-aldoxime (**160**) can be separated. The former, when refluxed in MeOH in the presence of K_2CO_3, yielded the isoxazolo[5,4-*b*]quinoline **161**, while the latter failed to cyclize.[14/84]



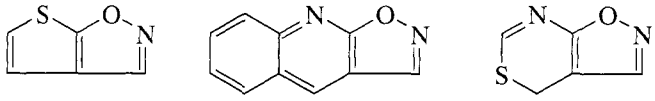
Different behavior might be expected for halogens in electron-rich and electron-poor heterocycles, but too few examples are known to make a generalization.

Several 2-acyl-3-bromothiophenoximes **162** cyclize in good yields to thieno[2,3-*d*]isoxazoles **163** when heated in the range 80–150°C (DMF or $EtOCH_2$-CH_2OH in the presence of K_2CO_3 and sometimes with CuCl).[18/87,3/88]



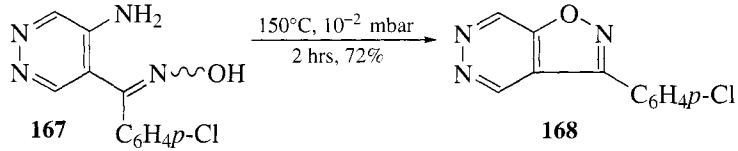
162 **163**

The same result was obtained when suitably substituted 2-chlorothiophenes were converted to thieno[3,2-*d*]isoxazole derivatives **164**.[3/88] Since low yields were obtained when a 2-chloroquinoline derivative was converted into isoxazolo[5,4-*b*] quinoline **165**[4/87] and 4-chloro-1,3-thiazine into 4*H*-isoxazolo[5,4-*d*]-1,3-thiazine **166**,[25/84] the previously mentioned influence of oxime configuration on the reactivity of these compounds may be operative.



164 **165** **166**

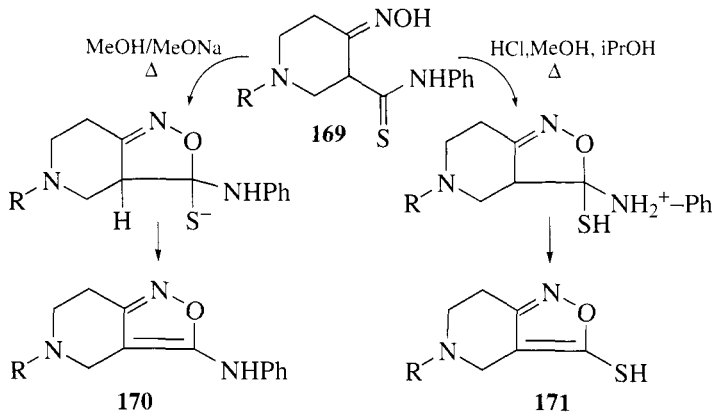
This type of heteroaromatic nucleophilic substitution may involve leaving groups other than halogens. An example is the thermal cyclization of 5-aminopyrazin-4-yl *p*-chlorophenyl ketone oxime **167** which, even as a likely mixture of (*E*)- and (*Z*)-isomers, gave a 72% yield of 3-*p*-chlorophenylisoxazolo[4,5-*d*] pyridazine **168** when heated *in vacuo*.[9/86]



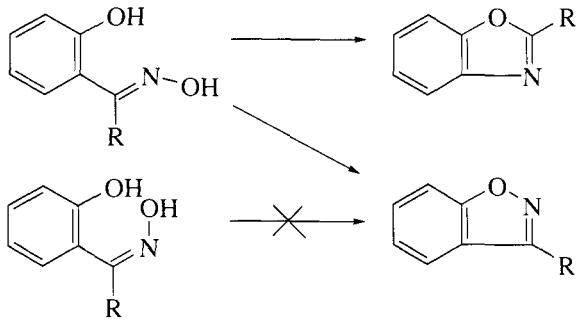
167 **168**

On occasion, formation of the O–C bond may not involve a heteroaromatic nucleophilic substitution. Ring closure to isoxazolo[4,3-*c*]pyridines from 4-oximino-3-thiocarbonylamidopiperidines **169**[2/70] occurs either under basic conditions (the SH group is preferentially lost to give **170** as main product) or by heating it in MeOH/iPrOH/HCl, which affords **171** as the main product by loss of aniline.

As mentioned in the introduction, formation of the N–O bond involves the attack of a hydroxyl group onto the nitrogen atom of the oxime. Again the configuration of the oxime is important and, even if there is some confusion in the literature, it seems established (at least in the field of 1,2-benzisoxazoles[24/73]) that



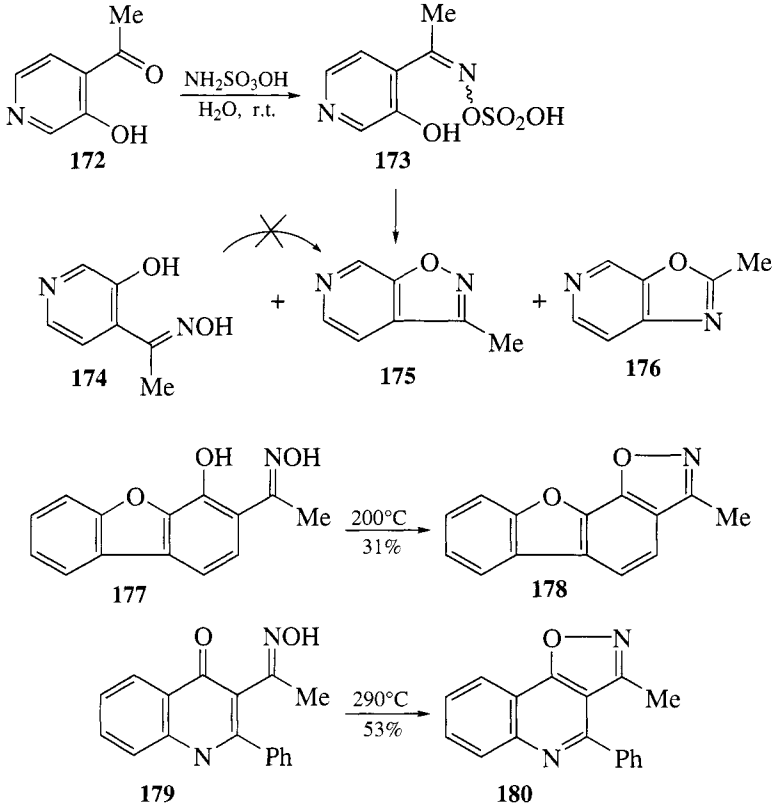
(*E*)-oximes, in the presence of a base strong enough to generate the phenolate anion, give either benzisoxazoles through the substitution reaction or benzoxazoles through a Beckmann rearrangement. Conversely, (*Z*)-oximes do not give benzisoxazoles.



Reaction of 4-acetyl-3-hydroxypyridine **172** with hydroxylammonium *O*-sulfonate in water gave the oxime *O*-sulfonate **173**,[4/82] which, when treated with $NaHCO_3$ at r.t., gave a mixture of oxime **174**, 3-methylisoxazolo[5,4-*c*]pyridine **175**, and 2-methyloxazolo[5,4-*c*]pyridine **176** in 33%, 27%, and 8% yields, respectively. The formation of 3-methylisoxazolo[5,4-*c*]pyridine **175** can be rationalized by an intramolecular nucleophilic displacement of the (*E*)-oxime ester, which proceeds in competition with the Beckmann rearrangement that leads to **176**. The (*Z*)-oxime ester fraction, if formed, may have been converted to the oxime **174**, known to be inert to every attempt at cyclization. A somewhat similar result was observed with 2-acetyl-3-hydroxypyridine.[6/87]

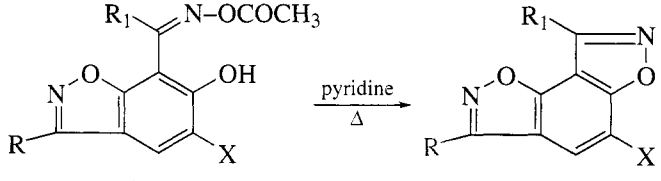
The ease of cyclization of a heterocyclic hydroxy oxime to a condensed isoxazole ring is enhanced by conversion of the oxime to a good leaving group, and by the configuration of such derivatives.

The difficulty of effecting ring closure in the absence of a good leaving group is demonstrated by the conversion of **177** to 3-methylbenzofuro[3,2-*g*]-1,2-

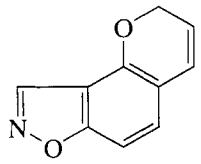


benzisoxazole **178**[1/54] and of **179** to the isoxazolo[4,5-*c*]quinoline derivative **180**,[9/66] transformations that both require very high temperatures.

Conversely, several 6-hydroxy-7(1,2-benzisoxazolyl) alkyl or aryl (*O*-acetyloximes) **181** have been cyclized to benzo[1,2-*d*:3,4-*d'*]diisoxazole derivatives **182** in good yields following brief periods of heating in pyridine.[5/77,20/80]



Derivatives of 2*H*-pyrano[2,3-*e*]-1,2-benzisoxazoles,[20/77,6/79] 7*H*-pyrano[3,2-*f*]-1,2-benzisoxazoles,[20/77,6/79] 7*H*-pyrano[2,3-*g*]-1,2-benzisoxazoles[6/79] and 4*H*-benzopyrano[3,4-*d*]isoxazole[16/78] (**183**, **184**, **185**, and **15**, respectively) were obtained from similar reactions.



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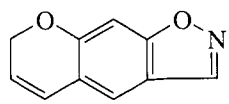

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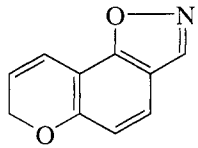

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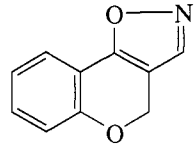
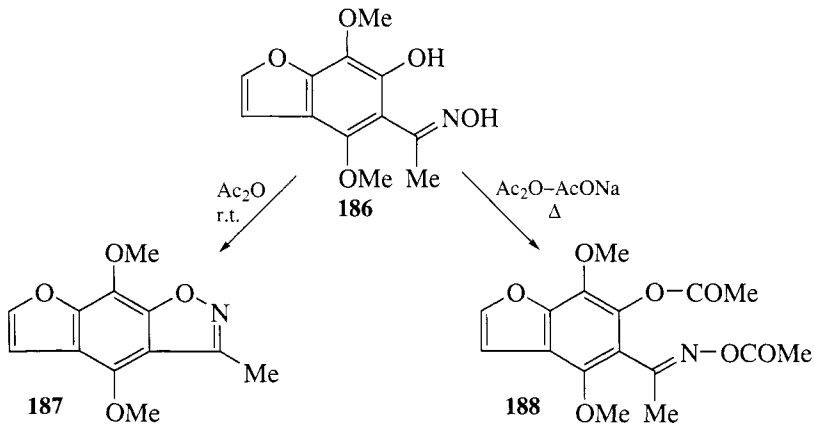


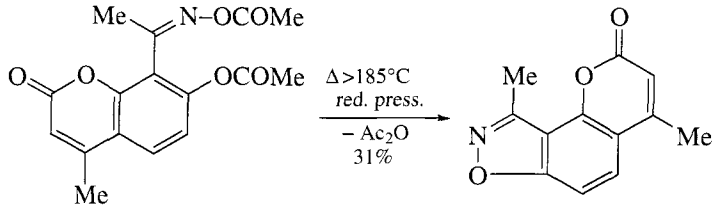
15

In general, the acetyl derivatives of oximes are prepared in situ, and cyclization to the corresponding isoxazole derivative occurs under the experimental conditions. The choice of conditions may be crucial since the acidities of the oxime and phenolic hydroxyl are very similar. Sometimes the synthesis of *O*-acetyl oximes requires the use of a stoichiometric amount of acetic anhydride. For instance, the already mentioned starting products of pyrano-1,2-benzisoxazoles[6/79] that show significant chemoselectivity to acylation. Sometimes the *O*-acetyl oximes may be obtained under controlled conditions as in the cyclization of the so-called khellinon oxime **186** with acetic anhydride at r.t. In the former case the cyclized product **187** is obtained, whereas heating **186** with Ac_2O/AcONa gives the diacetyl derivative **188**.[1/58]



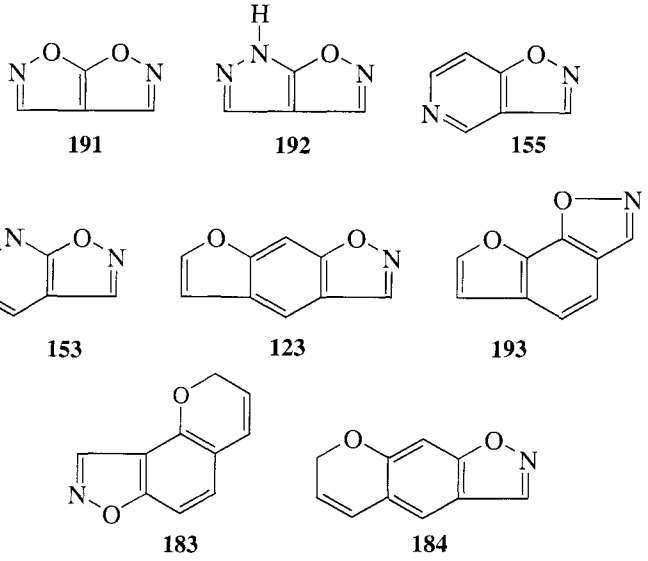
The formation of these diacetyl derivatives must be avoided since high temperatures are then required for their cyclization as illustrated in the synthesis of a 2*H*-pyrano[2,3-*e*]-1,2-benzisoxazole derivative (**190**) from **189**.[8/77]

Through the in situ acetylation of hydroxyoximes, several condensed isoxazoles were obtained: isoxazolo[4,5-*d*]isoxazole **191**,[1/59] 6*H*-pyrazolo[4,3-*d*]isox-



189 **190**

azole **192**,[5/65] isoxazolo[4,5-*c*]pyridine **155**,[3/84] isoxazolo[5,4-*d*]pyrimidine **153**,[5/73] furo[3,2-*f*]-1,2-benzisoxazole **123**,[14/78,1/56] furo[3,2-*g*]-1,2-benzisoxazole **193**,[1/52] 2*H*-pyrano[2,3-*e*]-1,2-benzisoxazole, and 7*H*-pyrano[3,2-*f*]-1,2-benzisoxazole derivatives (**183** and **184**, respectively).[18/89]

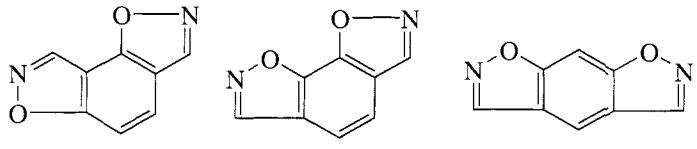


191 **192** **155**

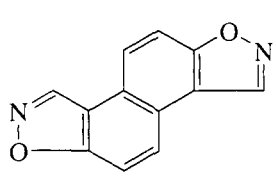
153 **123** **193**

183 **184**

This approach is also useful for the synthesis of two or even three condensed isoxazole rings starting from the suitable di- or trioxime. Thus derivatives of the following ring systems were obtained: benzo[1,2-*d*:3,4-*d'*],[1/64] benzo[1,2-*d*:4,3-*d'*],[1/52] and benzo[1,2-*d*:5,4-*d'*]diisoxazoles[1/56] (**194**, **195**, and **196**, respectively), naphtho[1,2-*d*:5,6-*d'*]diisoxazole **197**,[1/51] and benzo[1,2-*d*:3,4-*d'*:5,6-*d''*]triisoxazole **198**.[1/64]



194 **195** **196**



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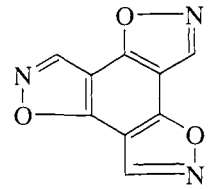
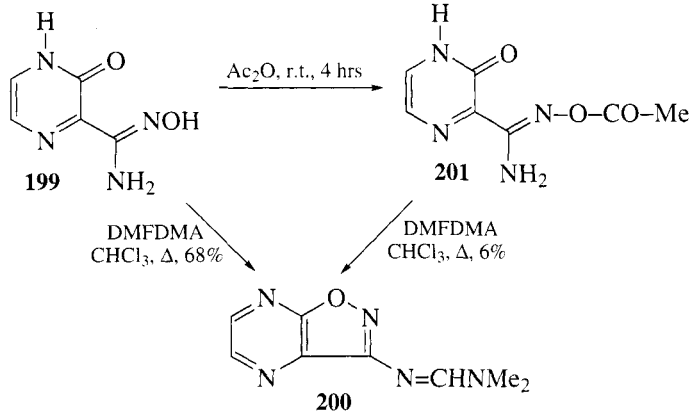


198

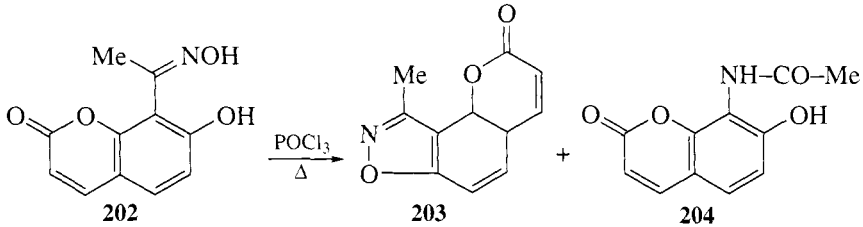
An exception is known in which an oxime cyclized more readily than its *O*-acetyl derivative. 2-Oxo-1,2-dihydropyrazin-3-carboxamide oxime **199** reacts with dimethyl formamide–dimethylacetal [Me_2N–CH$(OMe)_2$–DMFDMA] in refluxing $CHCl_3$ to give the isoxazolo[4,5-*b*]pyrazine **200** in 68% yield. Its *O*-acetyloxime **201**, under the same experimental conditions, gave **200** in only 6% yield. The reason for this may originate in a side reaction involving cyclization of the side-chain residue of **201** to oxazole.[5/82,6/82]



199 201 200

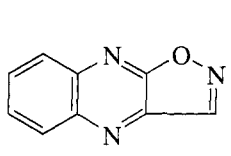
Cyclization of hydroxyoximes may be accomplished via the *in situ* formation of other labile intermediates.

Phosphoric esters can be generated from $POCl_3$ but, under the experimental conditions, a substrate such as **202** suffers from competition between a ring-closure pathway, to afford 2*H*-pyrano[2,3-*e*]-1,2-benzisoxazole derivative **203** and the Beckmann rearrangement, which affords **204**.[1/35]



202 203 204

The synthesis of isoxazolo[4,5-*b*]quinoxaline derivatives (**205**) has been accomplished by treatment of an oxime precursor either with $POCl_3$ in refluxing dioxane[9/85,10/85,11/85] or with polyphosphoric acid (PPA).[6/72,26/84] A 3*H*-isoxazolo-[3,4,5-*k*,*l*]acridine (**206**) has been similarly prepared.[12/91]



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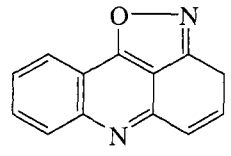
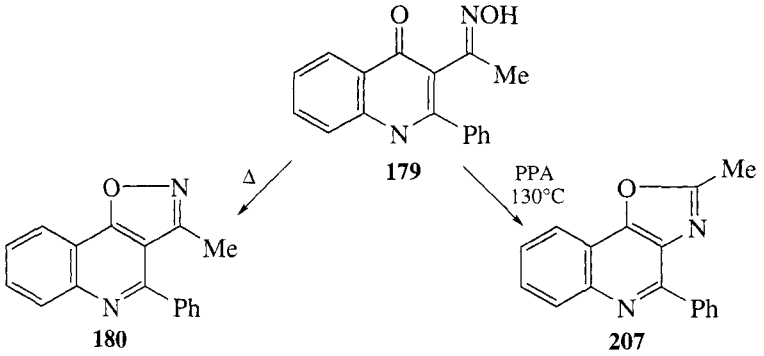
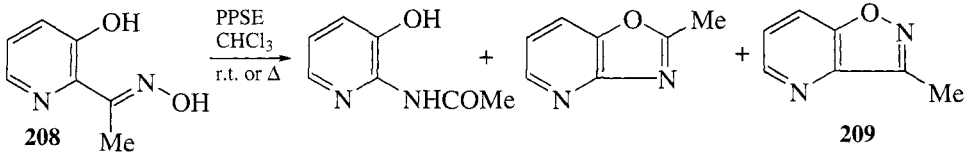


206

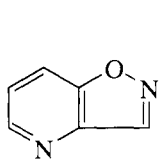
In some instances, substrates such as **179**, which are converted to an isoxazole product (**180**) under thermal conditions, undergo Beckmann rearrangement to give the oxazole derivative **207** when treated with PPA.[9/66]



Similar results are obtained when (*E*)-2(3-hydroxypyridinyl) methyl ketone oxime **208** is treated in $CHCl_3$ with trimethylsilyl polyphosphate (PPSE), either at r.t. or under reflux. Two of the three products arise from a Beckmann rearrangement, while the other, an isoxazolo[4,5-*b*]pyridine (**209**), is formed only in trace (7%) amounts.[6/87]



Various sulfur reagents have also been used to effect cyclization of oximes: $SOCl_2$ under mild conditions (−70°C) gave derivatives of isoxazolo[4,5-*b*]pyridine **154**,[1/89] tosyl chloride (0°C) gave 1,2-benzisoxazolo[5,4,3a,3-*d*,*e*,*f*]quinoline **210**,[12/73] and even concentrated H_2SO_4, which was employed in the synthesis of 4*H*-pyrano[2,3-*e*]-1,2-benzisoxazole derivatives **211**.[8/76]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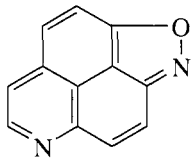
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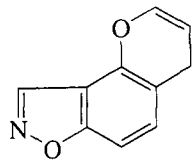
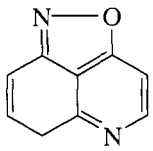

211

Less common reagents used for this purpose include ethyl chloroformate ($CHCl_3$, pyridine, r.t., 2 days, 90% yield), to give 6*H*-isoxazolo[5,4,3-*d*,*e*]-quinoline **212**,[10/82] trichloroacetyl isocyanate ($Cl_3CCONCO$), and chlorosulfonyl isocyanate (ether or THF, r.t., or reflux, yields varying from 1% to 78%) which afford isoxazolo[4,5-*b*]pyridine **154**.[6/87] This last paper[6/87] presents a large number of options for the synthesis of *N*-oxides of the above ring systems. (*E*)-Oxime **208**, when treated with sodium hypoclorite or lead(IV) acetate, gave excellent yields of 3-methylisoxazolo[4,5-*b*]pyridine 2-oxide **213**. Both (*E*)- and (*Z*)-1-oxido-2-pyridyl ketone oxime (*E*-**214**; *Z*-**214**) (inert toward $SOCl_2$) under the same experimental conditions gave 2,4-dioxide **215**. The latter can be converted into **213** with PCl_3 (standard conditions for the reductions of pyridine *N*-oxides).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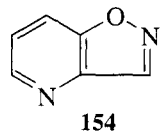
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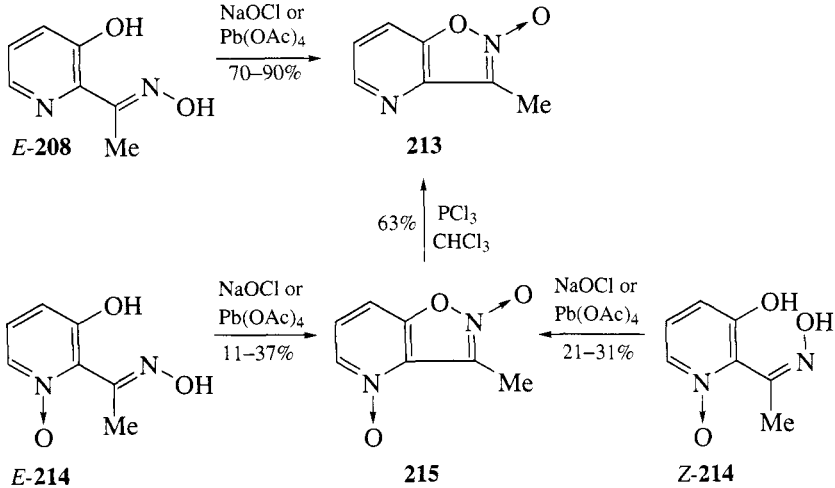
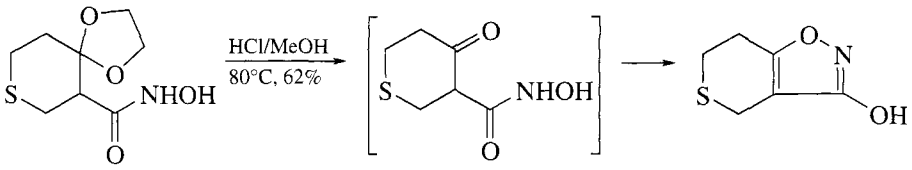
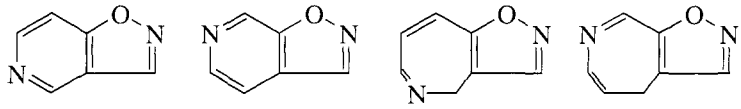


Finally, the results of an investigation that focused on the synthesis of conformationally restricted analogues of muscarinic agonists are reported. When tetrahydrothiopyran-3-hydroxamic acid bearing a protected 4-oxo group (**216**) was heated for 10 min. in methanolic HCl, the 4*H*-thiopyrano[3,4-*d*]isoxazole derivative **217** was obtained in good yield.[5/88] Under acidic conditions, deprotection occurs, and it is presumed that the protonated hydroxamic acid moiety is attacked by the deprotected carbonyl group. Hence this ring closure should fall among those involving the formation of 1–5 bond in the isoxazole ring.



216 **217**

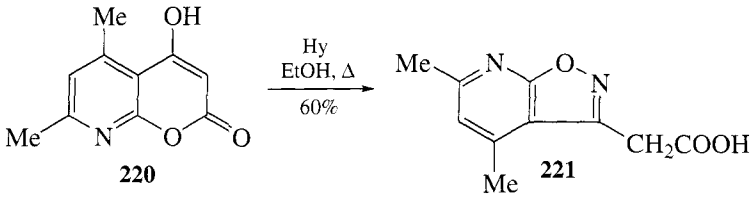
In analogy to the preceding approach, the following ring systems have been obtained: isoxazolo[4,5-*c*] and [5,4-*c*]pyridines[5/74,4/77] (**155** and **218**, respetively), 4*H*-isoxazolo[4,5-*c*], and [5,4-*c*]azepines[4/77] (**219** and **101**, respectively).



155 **218** **219** **101**

To close this section, some reactions of hydroxylamine with chromanone derivatives are reported.

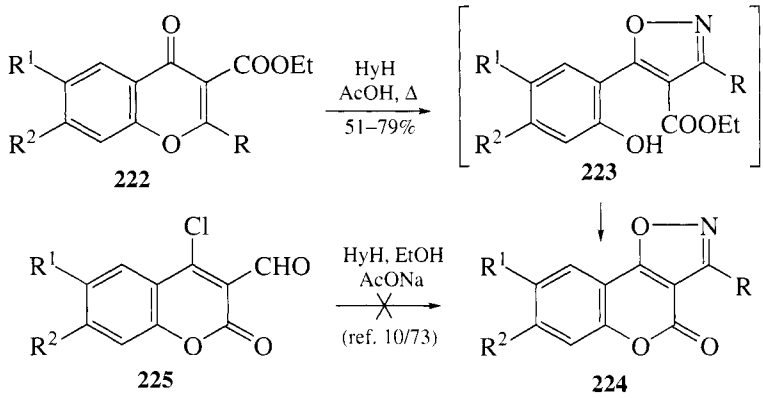
Upon treatment with hydroxylamine, the 4-hydroxy-2*H*-pyrano[2,3-*b*]pyridin-2-one derivative **220**,[4/75] undergoes attack at the masked carbonyl group in position 4, followed by ring opening of the pyran ring to give the isoxazolo[5,4-*b*]pyridine derivative **221**.



220 **221**

Great care is required in the analysis of the results of reactions between hydroxylamine and chromanone substrates. To support this,[17/84] a paper is reviewed that is an excellent "hatchet job" of a series of previously published results on 4-oxo-4*H*-[1]benzopyran-3-carboxylates (**222**) and 3-acetyl-4-hydroxycoumarin (**226**).

When chromones **222** were treated with hydroxylamine hydrochloride in refluxing AcOH a series of 4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-one **224** were obtained, presumably through the intermediacy of **223**. Subsequently, compound **224a** (with R = Me, $R_1 = R_2 = H$, m.p. = 175–176°C) was prepared by an unambiguous independent synthesis from the acid of **223**.



222 **223** **225** **224**

These compounds (**224**, R = H) were erroneously reported to be obtained from hydroxylamine hydrochloride and 4-chloro-3-formylcoumarins **225**;[10/73] since the claimed starting products were, in fact, not prepared.[23/83]

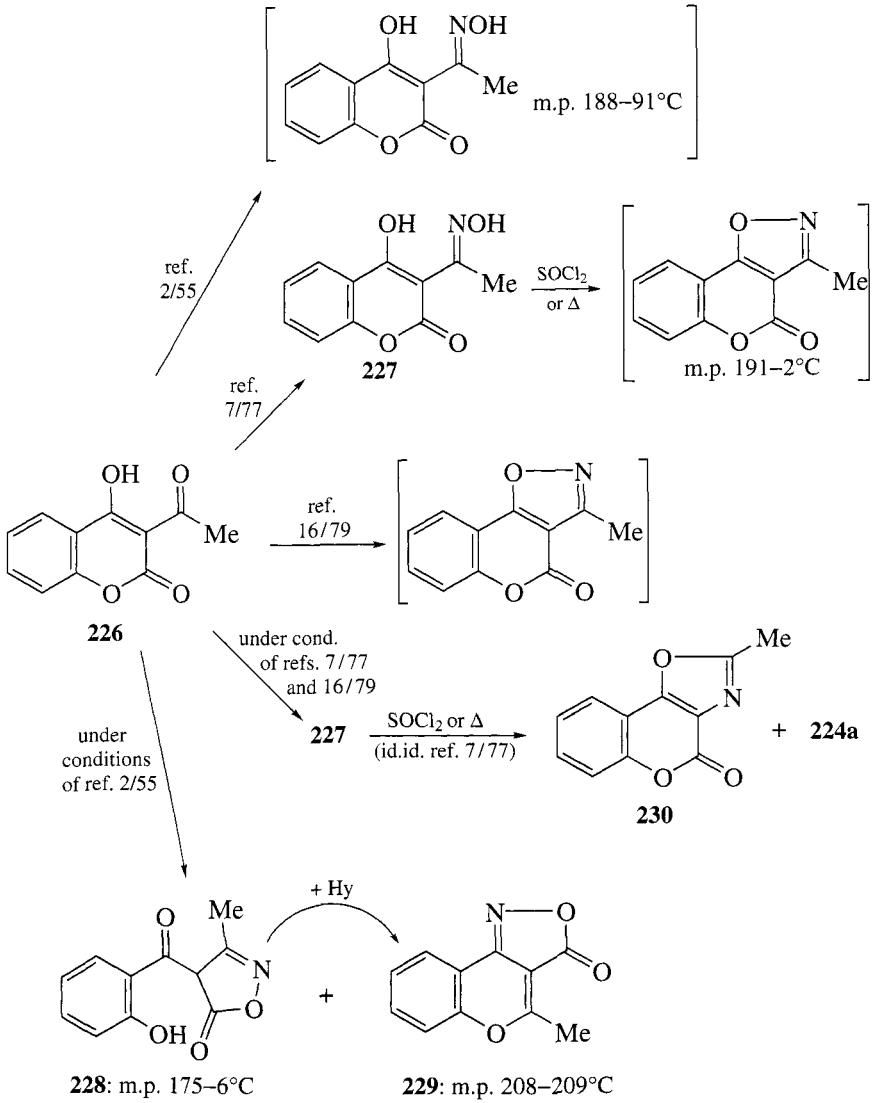
Even more curious are the results of the reaction between 3-acetyl-4-hydroxycoumarin **226** and hydroxylamine. The state of the art, before the previously mentioned paper of the French authors,[17/84] was as follows:

1. In 1955, Klosa[2/55] reported that **226** and HyH/AcOK, in refluxing ethanol, gave an "oxime" m.p. 188–91°C.
2. In 1977, Desai and Usgaonkar[7/77] reported that the true oxime (**227**—obtained at r.t.) had m.p. 211–2°C and Klosa's product was "3-methyl-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-one," since this was obtained from the same oxime under heating or when treated with $SOCl_2$. Unfortunately this product had m.p. 191–2°C, different from that of **224a** (m.p. 175–176°C) reported in the previous scheme.
3. In 1979, Makkay and Makkay[16/79] reported the formation, at r.t., of the same condensed isoxazole, but its m.p. was again different from that of **224a**.

The French authors[17/84] repeated the reaction under the conditions of ref. 2/55 and obtained a mixture of 4-(2-hydroxybenzoyl-3-methylisoxazol-5-one **228** (the main product) and 4-methyl-3*H*-[1]benzopyrano[4,3-*c*]isoxazol-3-one **229**. The former product was converted into the latter one with further hydroxylamine. Also, under the conditions of both refs. 7/77 and 16/79, the French authors obtained the oxime **227**, but this, when treated with $SOCl_2$ or even in refluxing

AcOH, gave 2-methyl-4*H*-[1]benzopyrano[3,4-*d*]oxazol-4-one **230** (the product of the Beckmann rearrangement) in 50% yield and authentic **224a** in 12% yield.

In conclusion, of all products reported in the four questioned papers, only the oxime **227** described in the Desai–Usgaonkar paper [7/77] had the structure correctly assigned. Sic transit gloria mundi.

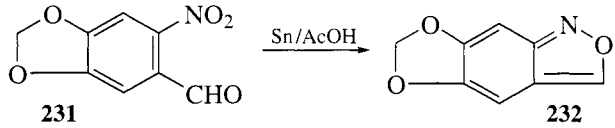


3.2.1.1e. Synthesis from *o*-Nitro Heterocyclic Compounds

Ring closures effected between a nitro (or nitroso) group and either a carbonyl (via reductive cyclization) or an alkyl group (under dehydrating condi-

tions) are useful approaches to the synthesis of indoxazenes and anthranils. Although they are not widely used, these strategies have been successfully applied to the synthesis of isoxazoles condensed with various heterocyclic rings.

Cyclization between nitro and carbonyl groups requires reductive conditions of the type employed by Friedlaender in 1895[1/895] in the synthesis of the first isoxazole fused to a heterocyclic ring. Using the methodology developed in this early work on the synthesis of anthranils,[1/882] 6-nitropiperonal **231** was reduced with tin and acetic acid to give 6*H*-1,3-dioxolo[4,5-*f*]-2,1-benzisoxazole **232**.

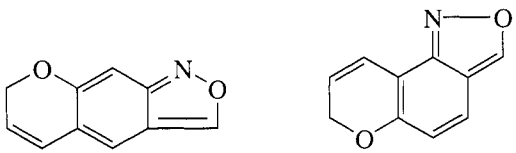


231 **232**

Through the same approach, but with $SnCl_2$ in HCl, isoxazolo[4,3-*h*] and [4,3-*b*]quinolines (**233** and **234**, respectively)[2/59,3/58] were obtained, the latter as the 3-hydroxy derivative since the ring closure occurred between NO_2 and an ester group.

233 **234**

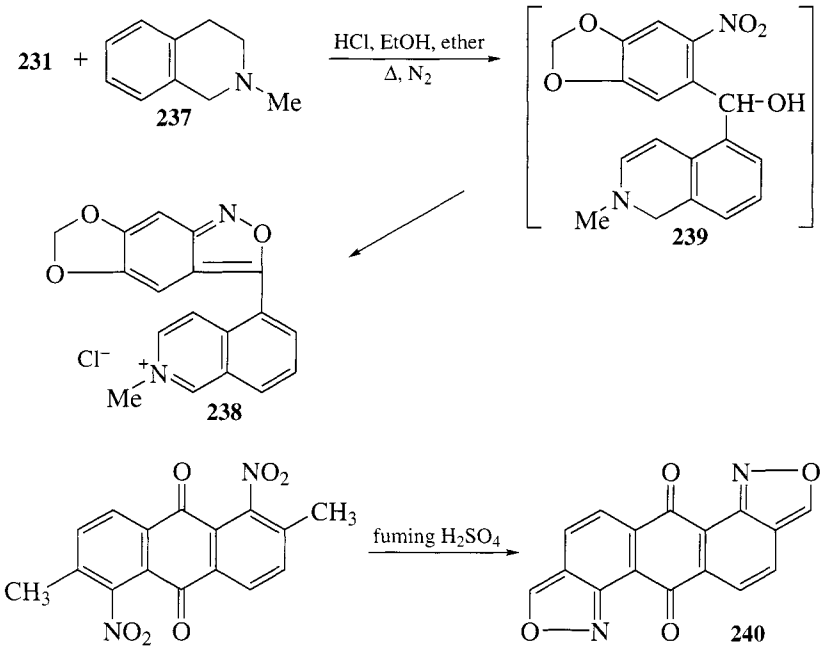
Catalytic hydrogenation with Pd 1% on $BaSO_4$ was used to prepare 7*H*-pyrano[3,2-*f*] and [2,3-*g*]-2,1-benzisoxazolo derivatives (**235** and **236**, respetively).[1/36]



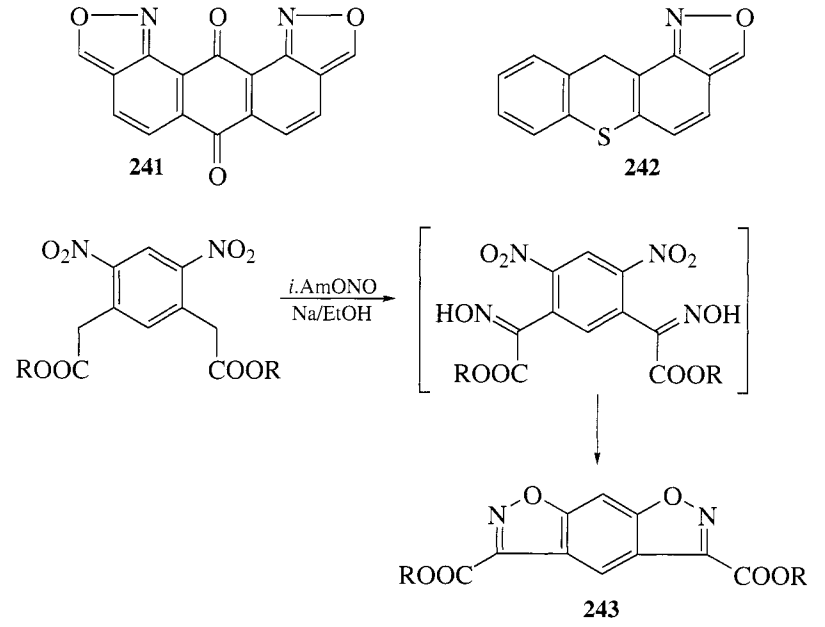
235 **236**

In an unusual case, 2-methyl-1,2-dihydroisoquinoline (**237**) acted as a reducing agent toward 6-nitropiperonal **231** to give the 3(2-methylisoquinolinium chloride)-substituted 1,3-dioxolo[4,5-*f*]-2,1-benzisoxazole **238**.[3/69] The prposed mechanism involves the condensation of **231** and **237** to give the nitro alcohol **239**, which is then presumably reduced by the dihydroisoquinoline **237**.

The conversion of *ortho*-nitroalkyl-heteroaromatic compounds to condensed isoxazoles can be performed under strongly acidic conditions, as in the case of 1,5-dinitro-2,6-dimethyl and 1,8-dinitro-2,7-dimethylanthraquinones, whic when heated with fuming H_2SO_4, gave anthra[1,2-*c*:5,6-*c*′]-and [1,2-*c*:8,7-*c*′]diisoxazole quinones (**240** and **241**, respectively).[1/26]



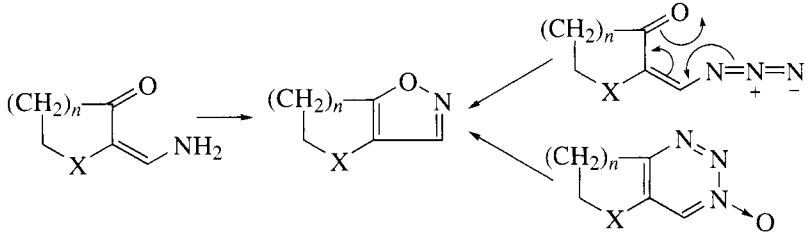
Similarly, derivatives of 11*H*-[1]benzothiopyrano[2,3-*g*]-2,1-benzisoxazole **242** were obtained from the corresponding nitroalkyl derivatives when the latter were stirred in oleum at 0–10°C under a CO_2 atmosphere.[2/57,2/58]



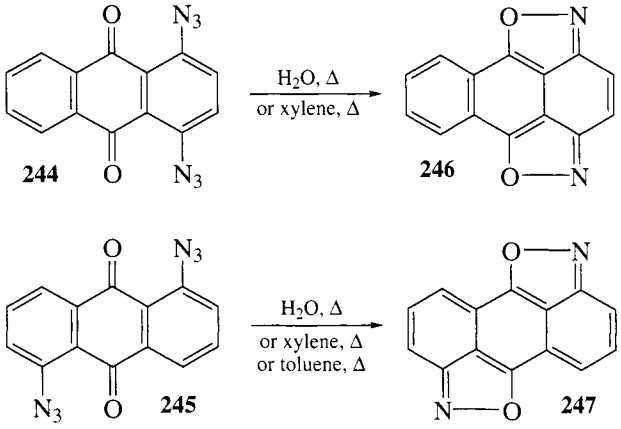
A method that combines the above strategies can be used in compounds having NO_2 and CH_2–COOR groups in the *ortho* position. Following nitrosation, an intermediate oxime is obtained that then cyclizes in the presence of strong bases. Without isolating the dioxime, in 1914 Borsche and Bahr[1/14] obtained 3,5-dialcoxycarbonylbenzo[1,2-*d*:5,4-*d'*]diisoxazoles **243** following this route.

3.2.1.2. Cyclization Process [OCCCN]

Cyclization processes involving the formation of the N–O bond have already been described in the section reporting the ring closure of oximes to isoxazoles. Nevertheless, the typical pathway starts from α,β-enones (belonging to heterocyclic rings) that have a suitable nitrogen-containing group, such as an amine, an azide, or a polyaza-heterocyclic ring, in the β position. The mechanism may involve either the attack of a β-acyl vinylnitrene or a concerted π-bond reorganization.



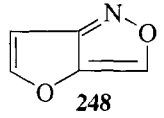
In one of the earlier routes to condensed isoxazoles to be described, Schaarschmidt, in 1916,[1/16] synthesized 1,4- and 1,5-diazidoanthraquinones (**244**, **245**) by double diazotization of a diamine. Decomposition of an aqueous suspension of the respective diazide by heating, gave anthra[1,9-*c*,*d*:4,10-*c'*,*d'*]



and [1,9-*c*,*d*:5,10-*c*′,*d*′]diisoxazoles, christened isobisanthranil (**246**) and bisanthranil (**247**), respectively.

More useful conditions, such as short heating or recrystallization of both diazides with xylene, were later found.[1/28] Heating **245** in toluene at 90°C until the evolution of nitrogen ceased gave excellent yields of both products.[13/82]

Through the same route furo-, thieno-, and selenolo[3,2-*c*]isoxazoles (**248**, **249**, and **250**, respectively)[2/76] (whose physical and spectral data were not in accord with those previously reported for a claimed identical preparation[2/75]) were obtained. The same approach was used in the synthesis of 4*H*-[1]benzopyrano[4,3-*c*]isoxazole[25/90] and 4*H*-naphtho[1′,2′:5,6]pyrano[4,3-*c*]isoxazole[11/91] (**251** and **252**, respectively) as well as 4*H*,8*H*-benzo[1,2-*c*:4,5-*c*′]diisoxazole (**253a**),[6/78] isoxazolo[4,3-*c*]quinoline[5/90] and isoxazolo[3,4-*c*]quinoline[1/53] (**253** and **254**) derivatives.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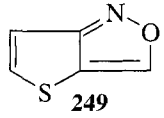
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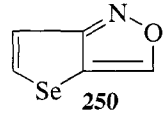
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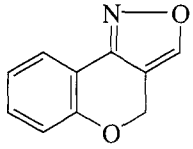
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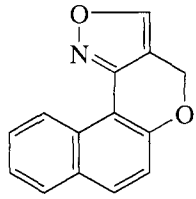
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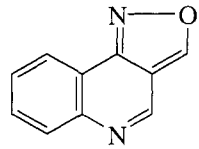
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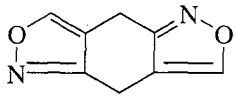
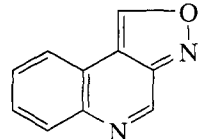
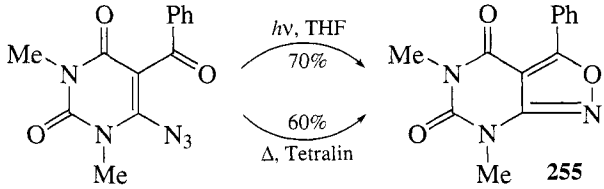

253a


254

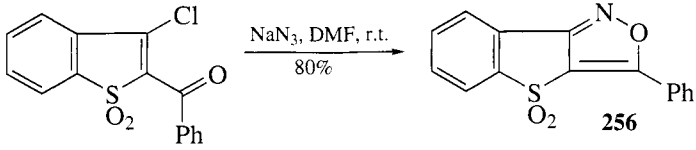
The temperature required to effect decomposition of the various azides ranged from 40 to 156°C, in general a lower temperature is required if the carbonyl-containing group is an aldehyde.

Azides can also be decomposed under photochemical conditions and yields are somewhat better as the synthesis of the following isoxazolo[3,4-*d*]pyrimidine derivative (**255**) shows:[5/83]

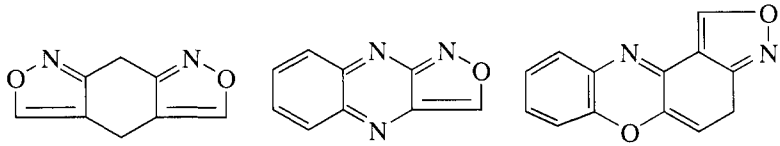


255

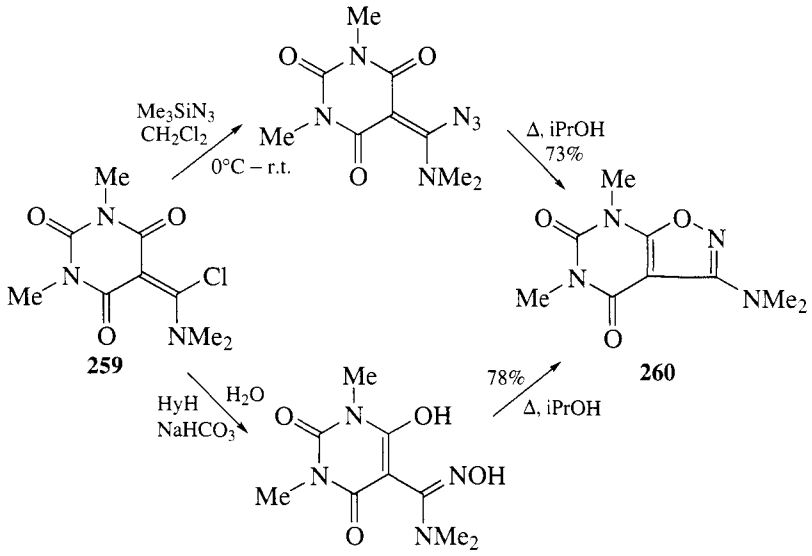
A useful protocol avoids the isolation of occasionally dangerous azido compounds, by mixing the heterocyclic chloro derivative with NaN_3 in DMF or methanol. Through this one-pot route, 3-phenyl-1-benzothieno[3,2-*c*]isoxazolo-4,4-dioxide (**256**) was obtained.[5/78]



With chloride as the leaving group in the nucleophilic substitution reaction, 4*H*,8*H*-benzo[1,2-*c*: 5,4-*c'*]diisoxazole (**89**),[6/80] isoxazolo[3,4-*b*]quinoxaline **257**,[14/81] and 4*H*-isoxazolo[4,3-*a*]phenoxazine **258**[9/67] derivatives were prepared. These results could be duplicated in instances where –OCOOEt was the leaving group.[9/67]



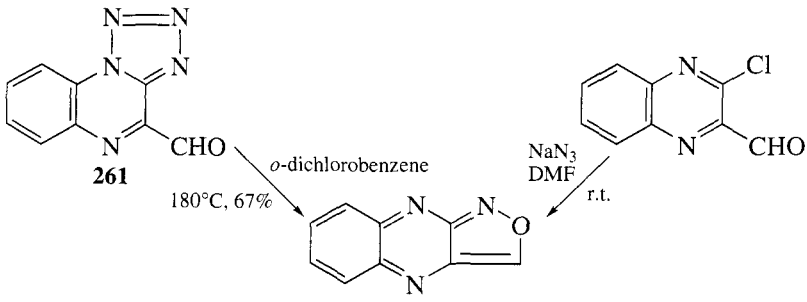
From dimethylaminochloromethylene barbituric acid derivative **259** and azidotrimethylsilane, an intermediate amido azide is obtained that can be decomposed under mild conditions to give a 3-dimethylaminoisoxazolo[5,4-*d*]



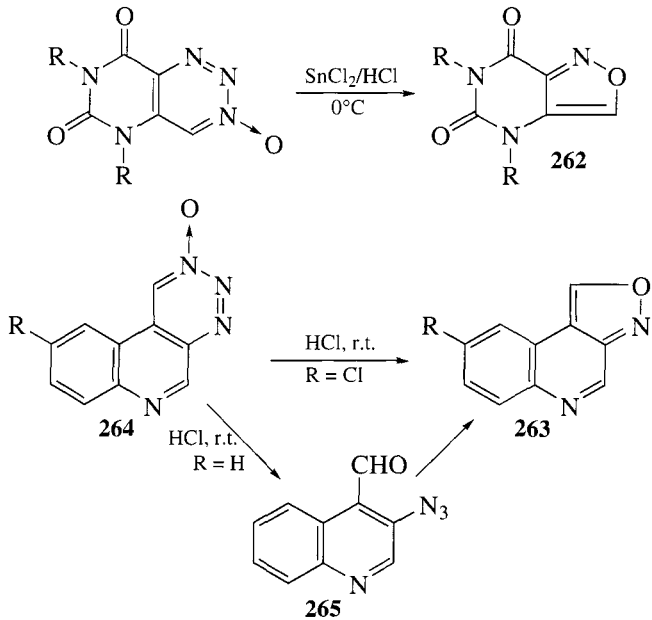
pyrimidine (**260**).[5/80] The same product can be obtained in a comparable yield from **259** with hydroxylamine hydrochloride through the intermediacy of an amidoxime.

Some polyaza heterocycles may serve as useful azido-group equivalents.

The thermolysis of tetrazolo[1,5-*a*]quinoxalin-4-aldehyde **261**, for which an isomeric azide structure can be invoked, gives, under forcing conditions, the same isoxazolo[3,4-*b*]quinoxaline **257** obtained from the azide generated *in situ* by another route.[14/81] In both reactions, as with many of this type, a nitrene is a potential intermediate.



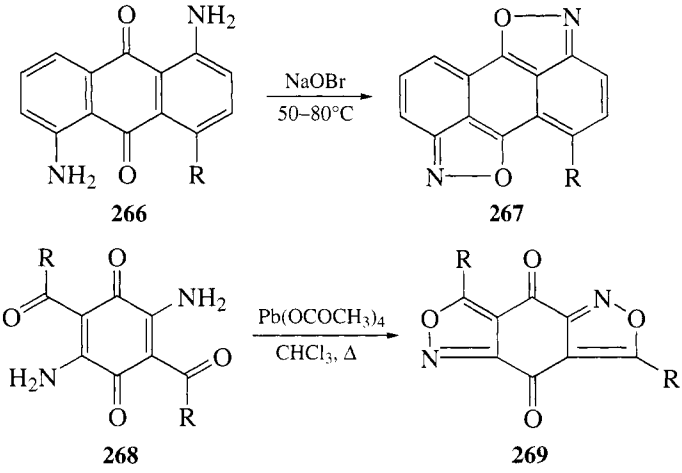
Condensed 1,2,3-triazine-*N*-oxides are good starting materials for the synthesis of condensed isoxazoles. Their conversion occurs under mildly acidic conditions such as those obtained with $SnCl_2$/HCl at 0°C, in the synthesis of



isoxazolo[4,3-*d*]pyrimidine derivatives **262**,[3/62] and HCl at r.t. for that of isoxazolo[3,4-*c*]quinoline (**263**, R = Cl).[1/53] The isolation of azide **265** from **264** (R = H) is taken as evidence of this as the intermediate of the reaction.

Under oxidizing conditions, formation of the N–O bond can occur between a carbonyl and a suitably placed amino group.

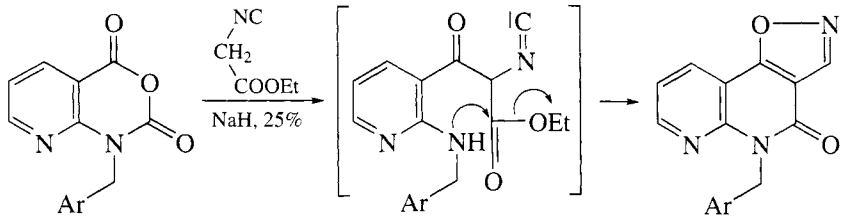
Anthra[1,9-*c*,*d*: 5,10-*c*′,*d*′]diisoxazoles **267** were obtained by hypobromide oxidation of 1,5-diaminoanthraquinones **266**.[1/21] More recently 4*H*,8*H*-benzo[1,2-*c*:4,5-*c*′]diisoxazoles **269** were prepared by $Pb(OAc)_4$ oxidation of 2,5-diamino-3,6-dicarbonylbenzoquinones **270**.[6/90] A nitrene intermediate is presumed to be involved in both reactions.



266 **267**

268 **269**

As the last example of this section, the intriguing reaction between the so-called 3-azaisatoic anhydride **270** and ethyl isocyanoacetate[12/85] is proposed. The formation of isoxazolo[4,5-*c*]-1,8-naphthyridine derivative **271** could involve a "carbene to nitrene" rearrangement of the intermediate formed when azaisatoic anhydride is opened by the ethyl isocyanoacetato carbanion with loss of CO_2.

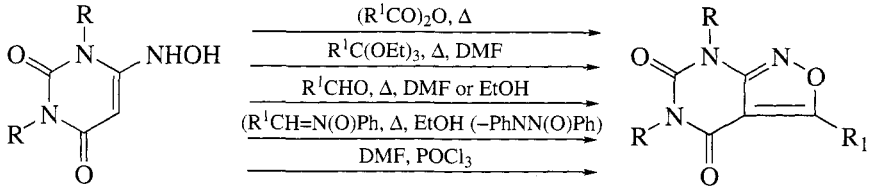


270 **271**

3.2.1.3. *Cyclization Process [CCNO + C]*

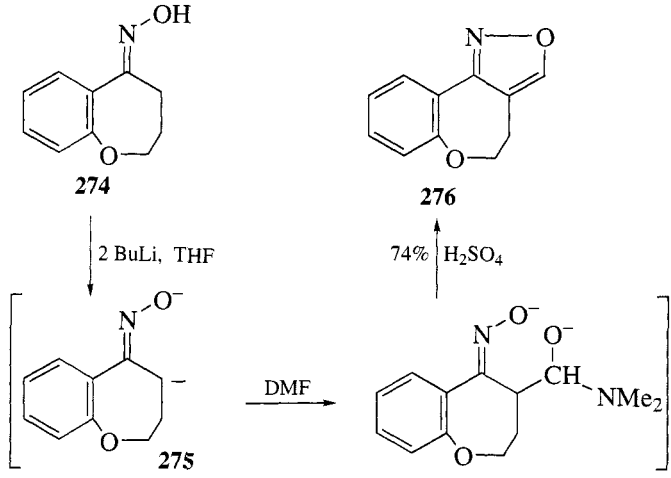
The formation of bonds C4–C5 and C5–O in condensed isoxazoles is a widely used method for preparation of isoxazolo[3,4-*d*]pyrimidine-4,6-diones since it takes advantage of the enaminic character of the double bond at the C5–C6 position of 1,3-dialkylpyrimidin-2,4-diones when C6 has an *N*-hydroxylamino group.

Thus **272** reacts with anhydrides,[3/77,17/77,18/77] orthoesters,[17/77,18/77] aldehydes,[3/78,14/79] nitrones,[11/84] and dimethylformamide/$POCl_3$[3/78,21/81] (under Vilsmeier reaction conditions) to give **273** (R = H, alkyl or aryl groups), which are useful as analgesics. The electron-rich C5 position of **272** attacks the electrophilic carbon atom of each respective reagent, a step that is followed by the cyclization–elimination step. The reaction with *N*-phenylnitrones is interesting in as much as azoxybenzene is isolated from the mother liquors, providing a potential clue to the mechanism of the reaction.

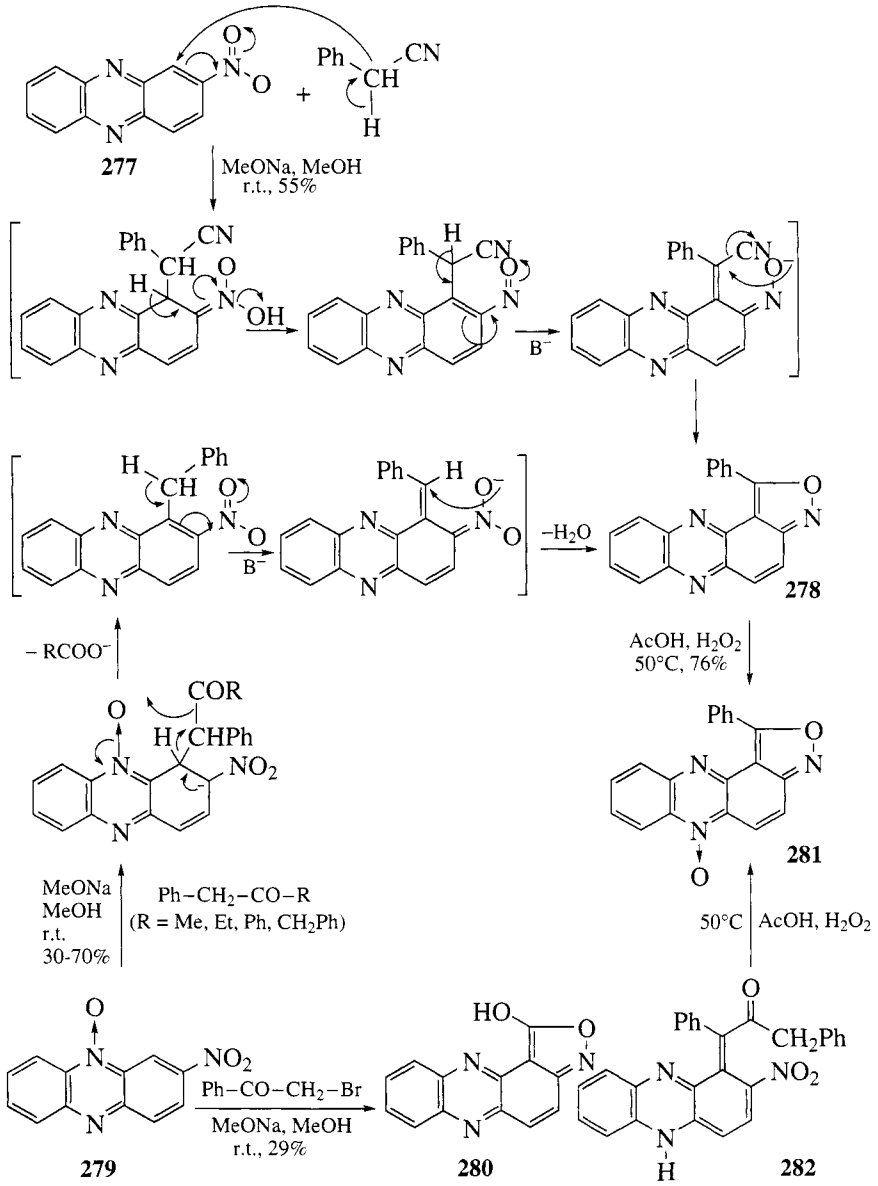


272 **273**

A vastly different approach was used by Olofson and co-workers[19/84] for the synthesis of [1]benzoxepino[5,4-*c*]isoxazole derivative **276**. Following a method developed by the same group,[17/78] the 1,4-dilithiooxime **275** was obtained with BuLi in THF from **274**; this was acylated with DMF, and H_2SO_4 treatment induced cyclization to **276**.



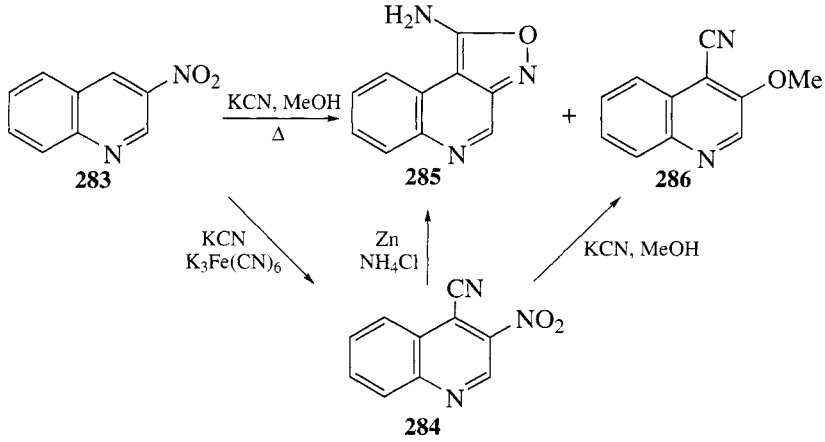
The last approach recalls, to a certain extent, the synthesis of anthranils from nitrobenzenes and benzylcyanides.[3/60] Similarly, 2-nitrophenazine **277** reacted with benzylcyanide in the presence of MeONa to give 1-phenylisoxazolo[4,3-*a*]-phenazine **278** in good yield.[10/68] The same product was obtained from 2-nitro-phenazine-10-oxide **279** with several benzylketones, but not with ω-bromo-acetophenone since 1-hydroxyisoxazolo[4,3-*a*]phenazine **280** was obtained. The mechanism of these reductive cyclizations is outlined below in a schematic form.



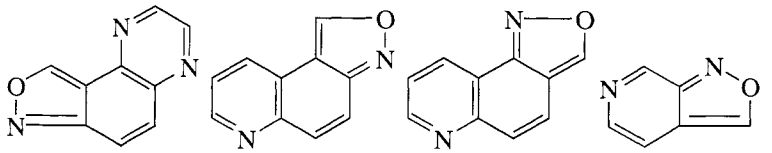
Finally **278**, on treatment with peracetic acid, gave 1-phenyl isoxazolo[4,3-*a*]phenazine-6-oxide **281**, the same product that was obtained, under identical conditions, from 1(α-phenylacetylbenzyliden)2-nitro-5*H*-phenazine **282**. The reasoning advanced to explain the reactivity shown above is that the electron-poor heterocycle, activated by a nitro group, easily undergoes the attack of carbanions.

The same logic can be invoked to explain several reactions involving nitroderivatives of electron-poor heterocycles that undergo the attack of the weak CN nucleophile.

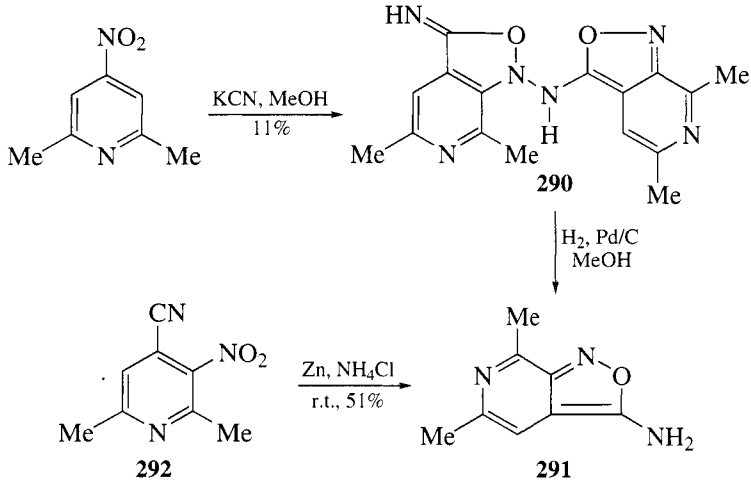
Thus 3-nitroquinoline **283** reacts with KCN in the presence of potassium ferricyanide to give 4-cyano-3-nitroquinoline **284**.[13/68] Subsequent reduction with Zn dust and NH_4Cl gave 1-aminoisoxazolo[3,4-*c*]quinoline **285**. The nucleophilic substitution–reduction–cyclization can be performed in "one pot" by refluxing **283** with KCN in MeOH. The nitrocyanide **284** intermediate can react under two competitive pathways: by ipso substitution, to give 4-cyano-3-methoxyquinoline **286** (the viability of this pathway was demonstrated starting from **284**) versus an intramolecular cyclization following reduction of the nitro group, to afford condensed isoxazole **285**.



The same result, complicated by differing degrees of competition from the *ipso*-substitution pathway, was obtained using 7-nitroquinoxalines,[6/70] 6-nitroquinoline,[20/83] 5-nitroquinoline-*N*-oxide,[4/71] and 2,6-dimethyl-4-nitropyridine,[28/84] respectively, to give the corresponding isoxazolo[4,3-*f*] quinoxaline **287**, isoxazolo[4,3-*f*]quinoline **288**, isoxazolo[3,4-*f*]quinoline **289**, and isoxazolo[3,4-*c*] pyridine **85** derivatives.



The last example reviews the reaction of 2,6-dimethyl-4-nitropyridine with KCN in methanol.[28/84] Four products, arising from ipso substitution, hydrolysis, and other mechanisms, were obtained, one of which was the dimer (**290**) of 3-amino-5,7-dimethylisoxazolo[3,4-*c*]pyridine **291**. The monomer was obtained either by catalytic reduction of **290** or by reduction of 4-cyano-2,6-dimethyl-3-nitropyridine **292**.



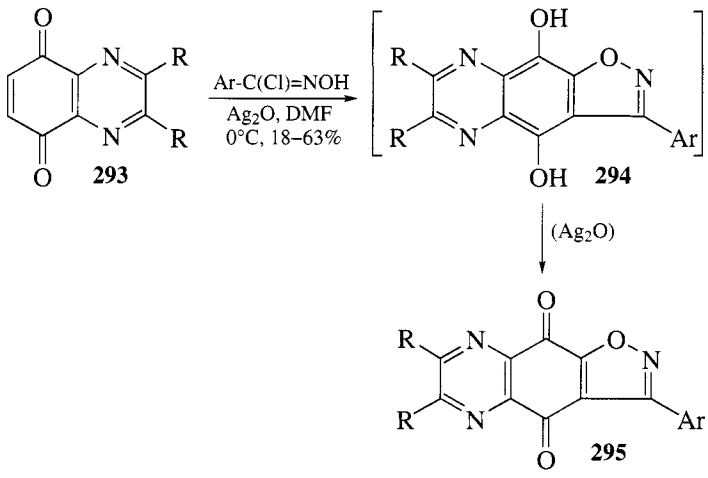
3.2.1.4. Cyclization Process [CNO + CC]

1,3-Dipolar cycloaddition, the leading process in the assembly of isoxazoles from acetylenes (and isoxazolines from olefins) is of only marginal importance in the synthesis of condensed isoxazoles.

Since endocyclic triple bonds are not commonly present among heterocycles, this approach can be essentially used under three conditions:

1. When addition of nitrile oxide (NO) to a heterocyclic double bond is followed by a more or less spontaneus process of oxidation
2. When addition of a NO occurs at a double bond carrying a group that is subsequently eliminated, thus converting the condensed isoxazoline into a condensed isoxazole
3. When an intramolecular NO cycloaddition (the well-known INOC) with a triple bond as dipolarophile

A typical example of *type*-1 methodology is the reaction of 5,8-quinoxalinequinone **293** with an aryl oximinoyl halide in the presence of Ag_2O to give 4,9-isoxazolo[4,5-*g*]quinoxalinequinone **295**[11/87] through the intermediacy of **294**. In the absence of the oxidant, Ag_2O, **294** is formed in lower yield, in a 1:1



293 294 295

ratio with 5,8-dihydroxyquinoxaline. Under these conditions, the quinone starting material behaves as the oxidant.

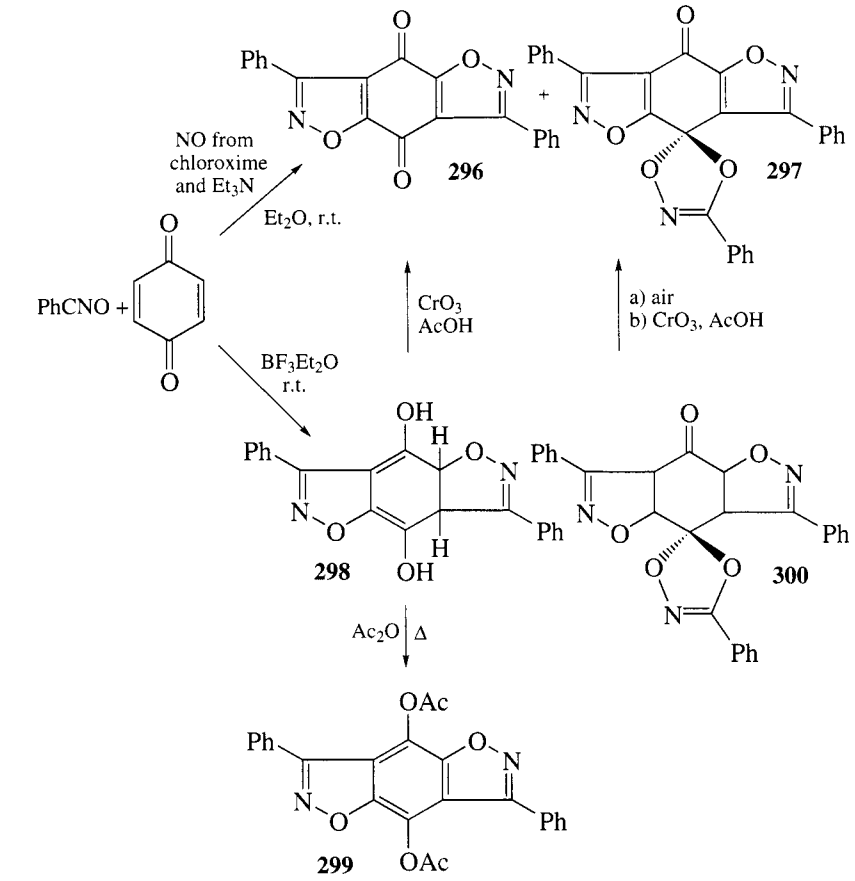
5,8-Quinolinequinone and the nitrile oxide derived from chloro-benzaldoxime reacted in the absence of any specific oxidant,[13/72] with chloranil,[12/72] or with H_2O_2,[9/74] to give products reported to be active as bactericides and herbicides but whose structures were ambiguously reported as isoxazolo[4,5-*g*]- or isoxazolo[5,4-*g*]quinolines.

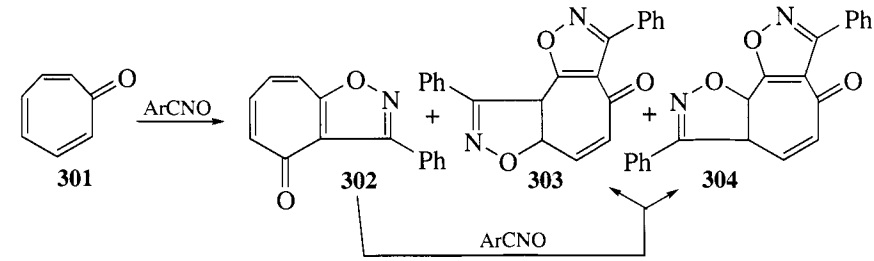
Air is presumably the oxidant in the reaction of benzonitrile oxide and *p*-benzoquinone.[9/68,2/69] In partial correction of a previous paper,[1/50] 2 mol of nitrile oxide were found to add head to tail and a third, eventually, onto a C=O group to give two derivatives of benzo[1,2-*d* : 4,5-*d'*]diisoxazoles (**296** and **297**). If the reaction is performed using BF_3 as a catalyst, 4,8-dihydroxy-3a*H*, 8a*H*-benzo[1,2-*d* : 4,5-*d'*]diisoxazole **298** is obtained in good yield. The latter can be stabilized either as the 4,8-diacetoxy aromatic derivative **299**, or oxidized to quinone **296**. Similarly, **297** can be obtained by oxidation of its tetrahydro derivative **300** via a stable dihydro species.

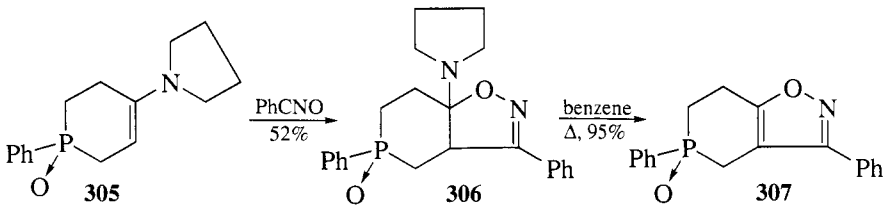
The benzo[1,2-*d* : 4,5-*d'*]diisoxazole derivative is the only product reported to be obtained, in 45% yield, from the reaction of benzonitrile oxide, generated in Et_2O at 0°C, and the benzensulfonyl derivative of *p*-benzoquinone monoimine.[18/73]

Arylnitrileoxides react with other systems as well. Tropone **301** yields a mixture of at least eight products,[2/74] two of which are of interest to this review as derivatives of 4*H*-cyclohepta[1,2-*d* : 3,4-*d'*]- and 4*H*-cyclohepta[1,2-*d* : 4,3-*d'*] diisoxazoles (**303** and **304**, respectively). The latter are presumed to arise from cycloaddition of the nitrile oxide with the monoadduct **302** and have been obtained independently by this route.

An example of *type*-2 approach exists in the reaction of benzonitrile oxide with 1(1,2,3,6-tetrahydro-1-phenyl-4-phosphorinyl)-pyrrolidine *P*-oxide **305**.[2/72]

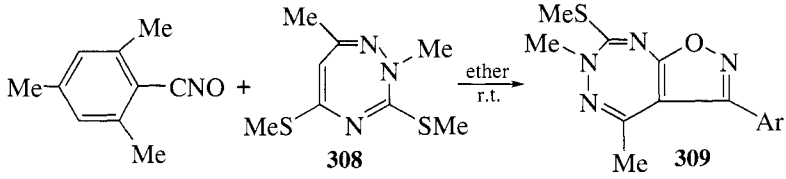

PhCNO +
NO from chloroxime and Et_3N
Et_2O, r.t.
296
297
CrO_3 AcOH
a) air
b) CrO_3, AcOH
BF_3Et_2O r.t.
298
300
Ac_2O Δ
299


ArCNO
301
302
303
304
ArCNO


PhCNO
52%
benzene
Δ, 95%
305
306
307

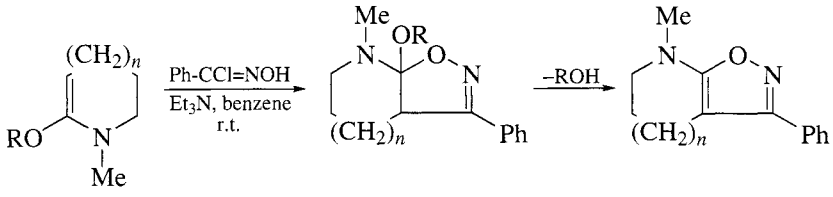
When refluxed in benzene, the adduct **306** loses pyrrolidine to afford the phosphorino[3,4-*d*]isoxazole derivative **307**.

The spontaneous loss of MeSH occurs during the reaction of mesitylnitrile oxide and triazepine **308**,[8/85] to give, in 80% yield, the 6*H*-isoxazolo[5,4-*e*]-1,2,4-triazepine derivative **309**.



308 **309**

As the last example of the *type*-2 approach, the reaction of benzonitrile oxide with cyclic ketene N,O-acetals **310**[4/86] is reported. Since the reaction is $HOMO_{acetal}$–$LUMO_{nitrile\ oxide}$-controlled, the regiochemistry is easily predicted from simple MO considerations (Fig. 3.2). The isoxazolo[5,4-*b*]pyridine and 4*H*-isoxazolo[5,4-*b*]azepine derivatives (**312b**, $n = 1$, and **312c**, $n = 2$, respetively) were isolated in 85% and 87% yields following spontaneous loss of ROH. The pyrrolo[3,2-*d*]isoxazole derivative **311a**, $n = 0$, is stable because of the unfavorable *syn* elimination that would be required for elimination of ROH. The products in this instance were isolated in 90% and 65% yield for R = Me and Et, respectively.



310 **311a-c** **312b,c**

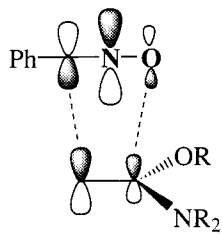
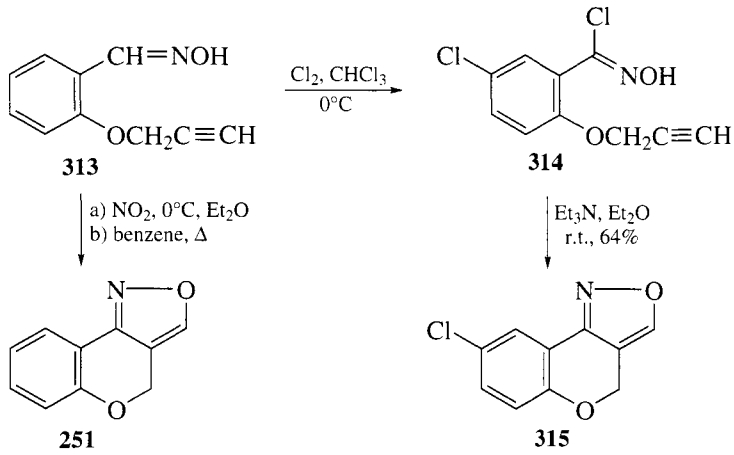
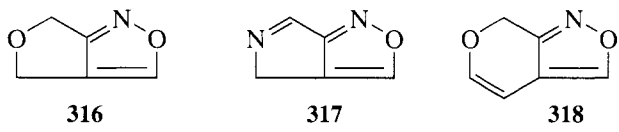


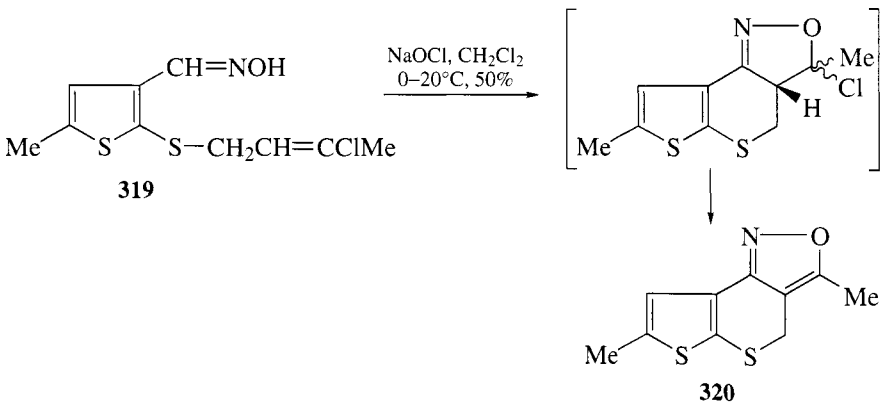
Figure 3.2. MO interactions between $HOMO_{N,O\ acetal}$ and $LUMO_{NO}$ (schematic representation).

The INOC *type*-3 approach was used by an Italian group in the synthesis of some condensed isoxazoles. An example of this reaction involves chlorination of acetylenic oxime **313** at the oximic hydrogen and at the activated aromatic proton to give **314**. Nitrile oxides generated from **313** via oxidation with NO_2, and from **314**, by treatment with Et_3N, gave the 4*H*-chromene[4,3-*c*]isoxazole derivatives, **251** and **315**, respectively.[8/75]

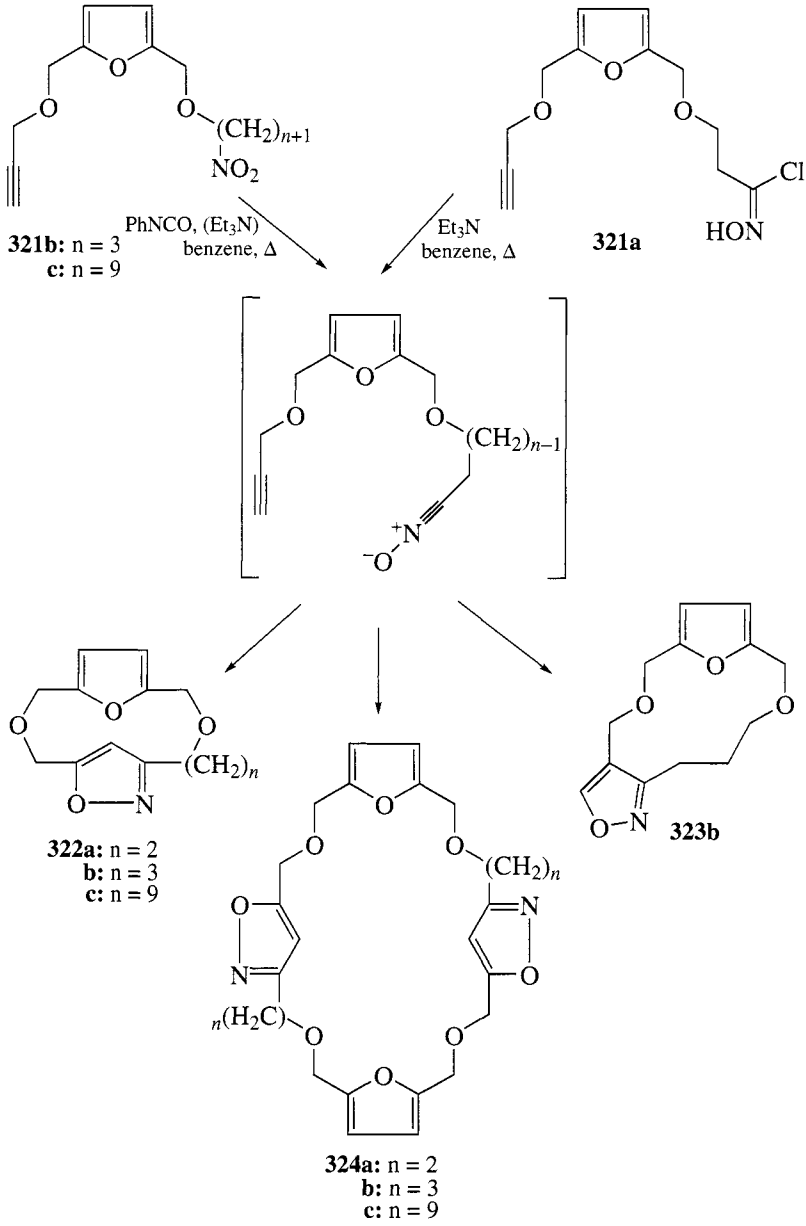


Acetylenic chloroximes react, in the presence of Et_3N, to afford 4*H*,6*H*-furo[3,4-*c*]isoxazole **316**,[1/75] 4*H*-pyrrolo[3,4-*c*]isoxazole **317**[9/79] and 7*H*-pyrano [3,4-*c*]isoxazole **318**[3/80] derivatives. Alternatively, aliphatic nitroacetylenes, on dehydration following the Mukaiyama protocol (PhNCO, benzene, Me_3N, r.t.), can be made to furnish **316**.[16/91]





One example is known in which a masked acetylene underwent an INOC. On treatment with NaOCl, thiophene derivative **319**, containing a felicitously placed vinylic halide, afforded 4*H*-thieno[3′,2′:5,6]thiopyrano[4,3-*c*]isoxazole derivative **320** following spontaneous loss of HCl from the initally formed cycloadduct.[18/91]



To close this section, an example is reported that links INOC and supramolecular chemistry. Furans having both an acetylenic chain and a nitroaliphatic or a chloroximic chain (**321a–c**) were subjected to conditions (Mukayama protocol or Et_3N treatment, respectively) suitable for generation of nitrile oxides.[20/89] The resulting INOC was in no way selective, and mixtures of both regioisomers (e.g., **322b** and **323b**) or mixtures of monomers and dimer (e.g., **322b**, **323b**, and **324b**) were obtained. Even if the yields were poor (except **322b** obtained in 36%; all other yields are in the range 0.1–6%), all these products were isolated, were characterized, and offer a view into the fascinating world of supramolecular devices. The following ring systems were obtained.

322a: 3,6,11,16-tetraoxa-7-azatricyclo[11.2.1.$1^{5,8}$]heptadeca-5(17),7,13,15 tetraene

322b: 3,6,12,17-tetraoxa-7-azatricyclo[12.2.1.$1^{5,8}$]octadeca-5(18),7,14,16-tetraene

322c: 3,6,18,23-tetraoxa-7-azatricyclo[18.2.1.$1^{5,8}$]tetracosa-5(24),7,20,22-tetraene

323b: 6,11,14,15-tetrahydro-7,10-epoxy-4*H*,13*H*-[1,8]dioxacyclotetradecino[4,3-*c*]ixoazole

324a: 3,6,11,18,21,26,31,33-octaoxa-7,22-diazapentacyclo-[26.2.1.$1^{5,8}$.$1^{13,16}$.$1^{20,23}$]tetratriaconta-5(34),7,13,15,20(32),22,28,30-octaene

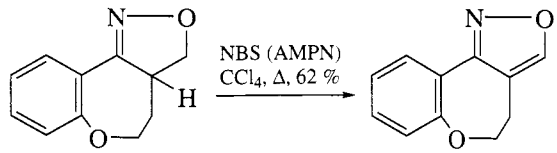
324b: 3,6,12,19,22,28,33,35-octaoxa-7,23-diazapentacyclo-[28.2.1.$1^{5,8}$.$1^{14,17}$.$1^{21,24}$]hexatriaconta-5(36),7,14,16,21(34),23,30,32-octaene

324c: 3,6,18,25,28,40,45,47-octaoxa-7,29-diazapentacyclo-[40.2.1.$1^{5,8}$.$1^{20,23}$.$1^{27,30}$]octatetraconta-5(48),7,20,22,27(46),29,42,44-octaene.

3.2.1.5. Oxidation of Condensed Isoxazolines

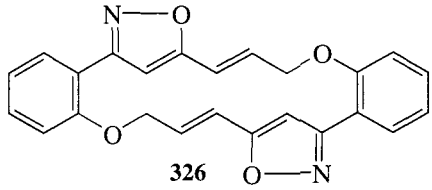
Condensed isoxazolines, which are generally derived from cycloadditions involving an ethylenic dipolarophile, can be transformed into condensed isoxazoles by the action of a variety of oxidants.

An example involves conversion of **325** into a derivative of 1-benzoxepino[5,4-*c*]isoxazole **276** with *N*-bromosuccinimide (NBS) and a trace of 2,2′-azobis(2-methylpropionitrile) (AMPN) in refluxing CCl_4.[9/75]



325 **276**

NBS was employed as the oxidant in the synthesis of 6*H*,18*H*-12,9:24,21-dimethenodibenzo[*d*,*n*][1,6,11,16,2,12]tetraoxadiazacycloeicosine and the 13,10:26,23-dimetheno-10*H*,23*H*-dibenzo[*d*,*o*][1,6,12,17,2,13]tetraoxadiazacyclodocosine derivatives, **326** and **327**.[9/75] NiO_2 was used to synthesize isothiazolo[5,4-*d*]isoxazole **328**[2/89] and nitrobenzene gave several 5*H*-pyrrolo[3,4-*d*]-isoxazolo derivatives **329**.[14/87]



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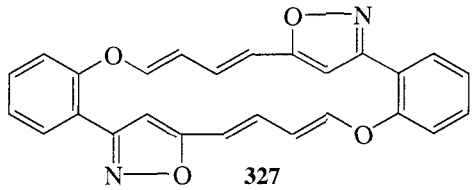

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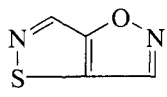

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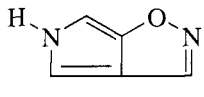

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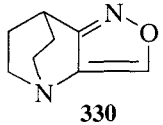
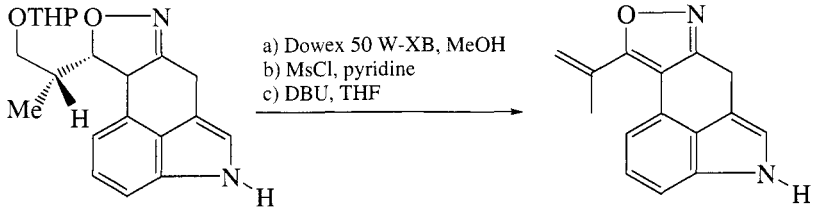


330

An intermediate isoxazoline is probably oxidized during the reported conversion of *p*-nitrobenzylidenequinuclidinone oxime into 3-*p*-nitrophenyl-6,7-dihydro derivative of 5*H*-4,7-ethanoisoxazolo[4,3-*b*]pyridine **330**.[15/80]

Sometimes the oxidation can be an undesired process, as in the synthesis of the ergot alkaloid (+)-paliclavine.[15/81,20/84] During dehydration of the hydroxyl-containing side chain of the isoxazoline **331**, deprotection and dehydration occurred with concomitant aromatization, and the undesired 6,9-dihydro achiral derivative of indolo[4,3-*e*,*f*]-2,1-benzisoxazole **332** was obtained.

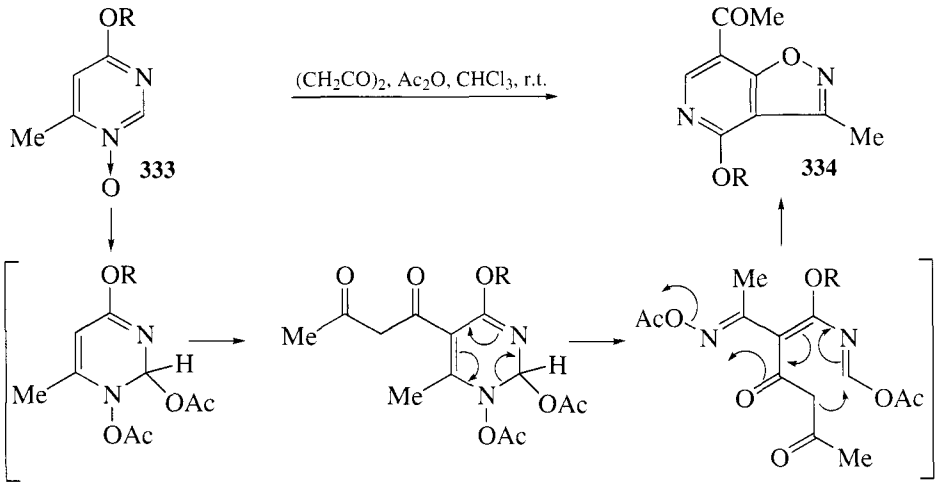


331 **332**

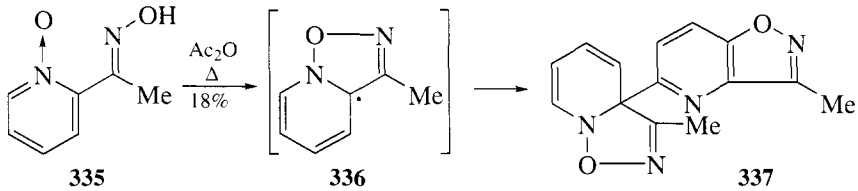
3.2.1.6. Rearrangements

This section collects a variety of papers whose common feature is the generation of the condensed isoxazole ring system through a complicated transformation that generally involves one or more bond migrations.

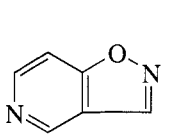
An example is found in the reaction of pyrimidin-*N*-oxide **333** with diketene and Ac_2O[12/88] that gives rise to isoxazolo[4,5-*c*]pyridine derivatives **334** in poor yields. Acylation, to afford an acetoxypyrimidinium salt, is likely followed by nucleophilic attack of the 2-acetoxy group and further acylation by diketene. Subsequent [4π + 2σ] electrocyclic ring opening and final ring closure ultimately provide **334**.



Conversion of the oxime (**335**) derived from 2-acetylpyridine *N*-oxide into the isoxazolo[4,5-*b*]pyridine derivative **337** may involve dimerization of radical intermediate **336**, followed by 1,3-sigmatropic shift and oxidation.[19/86]



The following reactions are presumed to proceed by complicated mechanisms that are difficult to rationalize: that of dehydrobenzoylacetic acid and hydroxylamine, which gives isoxazolo[4,5-*c*]pyridine **155**,[1/12] 3-acetylpyran-4-one oxime, and diketene, to produce 6*H*-pyrano[3,4-*d*]isoxazole **338**,[6/67] and cyan-



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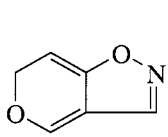

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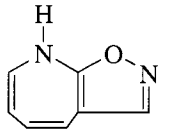
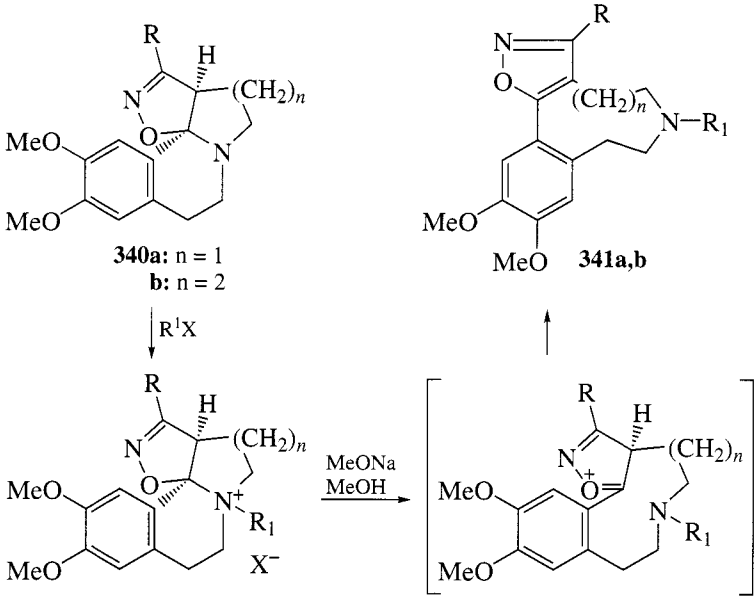


339

odihydrocarvone and amyl nitrite, to give 8*H*-isoxazolo[5,4-*b*]azepine **339** derivatives.[7/67]

This section concludes with a discussion of the synthesis of azamacrocycles **341a,b** from polycyclic isoxazoline precursors **340a,b**,[19/89,14/91] by nitrile oxide cycloaddition of readily available tricyclic enamines. Quaternization with various alkyl bromides or iodides, followed by either solvolysis in polar solvents or base-induced elimination, gave the desired 4*H*-isoxazolo[4,5-*f*]-3-benzazonine and isoxazolo[4,5-*g*]-3-benzazecine derivatives (**341a,b** respectively) in good yields.



3.2.2. Synthesis of the Heterocyclic Ring

By introduction and manipulation of the appropriate substituents, a new heterocyclic ring can be assembled from an existing isoxazole ring.

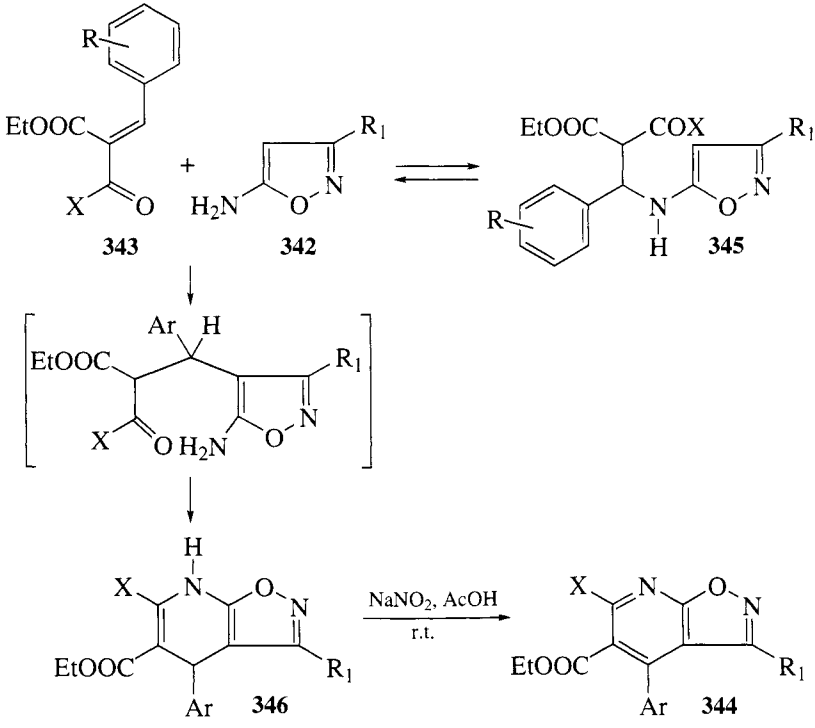
In this section the appending of individual ring systems onto isoxazole precursors will be discussed.

3.2.2.1. Syntheses of the Pyridine Ring

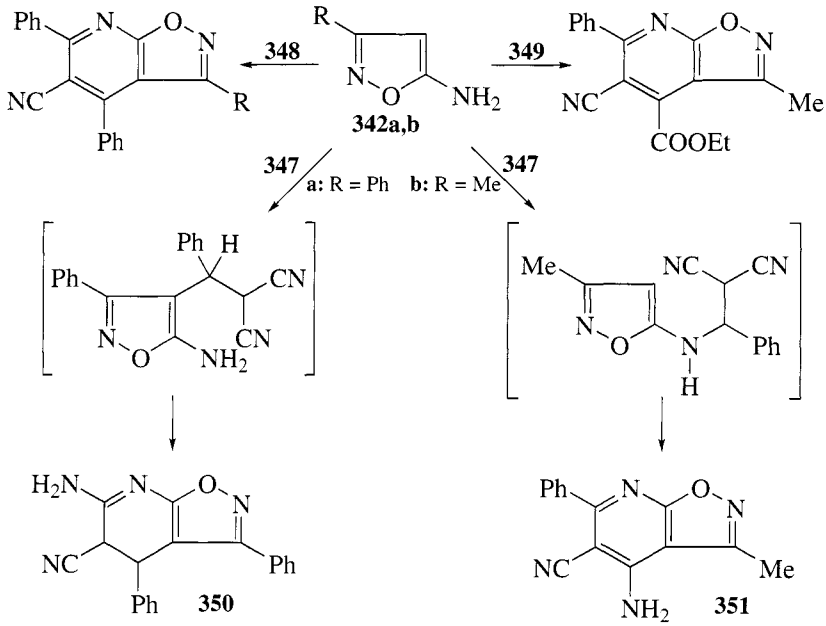
3.2.2.1a. Cyclization Process [CCC + CCN]

The classic Hantzsch reaction of 5-aminoisoxazoles **342** and α,β-unsaturated carbonyl compounds **343** can be usefully applied to the synthesis of isoxazolo[5,4-*b*]pyridine derivatives **344**. A detailled investigation[6/85] of the mechanism was undertaken since 5-aminoisoxazoles have the properties of an ambident nucleophile. Under kinetic conditions, Michael addition involves the NH_2 group and adducts **345** are formed that may be isolated when ethylene glycol or acetic acid is used as the solvent. If monohydroxylic alcohols are used under reflux, a retro-Michael reaction proceeds to give the starting materials, which ultimately form the thermodynamically stable products **346** via Michael addition of the 4 position of the isoxazole ring to the β position of **343**. The most useful solvent for obtaining **346** directly and with better yields is *tert*-butanol, which was used with a series of benzylidene–acetoacetates.[5/84,17/86,2/90,21/90] The 4,7-dihydroisoxazolo[5,4-*b*]pyridines **346** are stable as such and can be oxidized under the conditions of the Hantzsch synthesis (e.g. $NaNO_2$ and AcOH).

Owing to the well-known biological activity of 1,4-dihydropyridines (e.g., nifedipine, nicardipine), the above-mentioned adducts were tested as cholesterol biosynthesis inhibitors, antihypertensive, and calcium antagonists, but in general their activity was found to be lower than the uncondensed parent compounds.



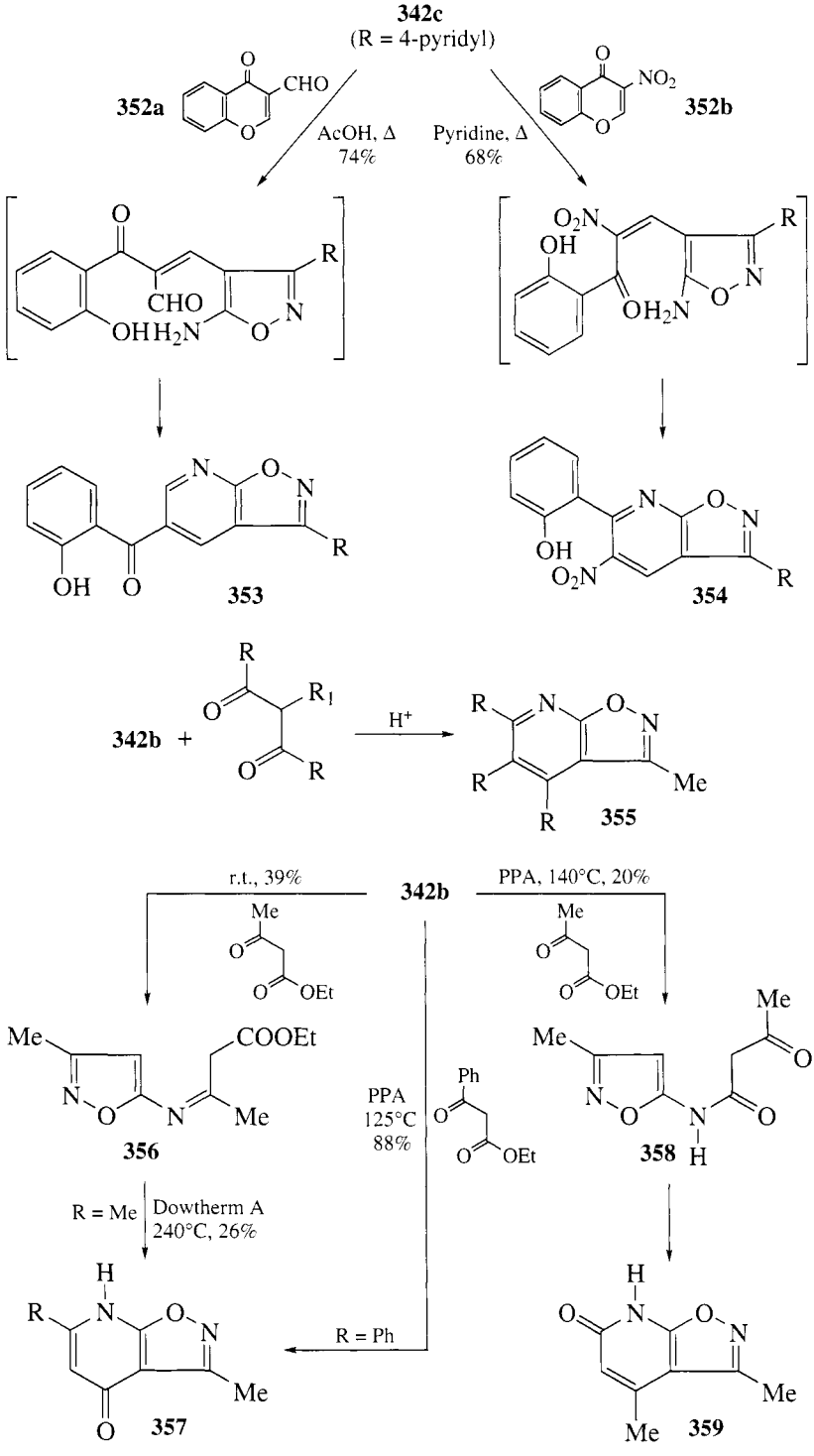
The Hantzsch reactions of benzylidenemalononitrile [PhCH=C(CN)$_2$ **347**],[2/83,13/88] benzylidenecyanoacetophenone [PhCH=C(CN)COPh **348**],[2/83,13/88] and benzylidene-cyanoacetate [PhCH=C(CN)COOEt **349**][13/88] with 3-phenyl-[2/83] or 3-methyl-[13/88] 5-aminoisoxazoles (**342a,b**) have been investigated. Surprisingly, **342a** and **342b** reacted with **347** in opposite regiochemical fashions. The product of initial attack by C4 of the isoxazole ring, the 6-aminoisoxazolo[5,4-*b*]pyridine **350**, is formed from **342a**, while the 4-amino derivative (**351**) results from **342b**.



Michael attack by the C4 position of **342c** (R = 4-pyridil) on 3-electron-withdrawing substituted chromones **352a,b** is followed by ring opening to give a material that can then recyclize to give fused pyridines. When a formyl group (**352a**)[2/81] is suitably placed to undergo ring closure, 5-(*o*-hydroxybenzoyl)-isoxazolo[5,4-*b*]pyridine **353** is obtained. The nitro-substituted chromone (**352b**)[3/81] undergoes a different ring closure that involves the benzoyl group, ultimately giving a 4-(*o*-hydroxy-phenyl)isoxazolo[5,4-*b*]pyridine (**354**).

By analogy with a classic approach to the synthesis of pyridines, the reaction of β-dicarbonyl compounds with 5-aminoisoxazole gives isoxazolo[5,4-*b*]pyridines. The preceding reaction is known to give **355** with symmetrical β-diketones,[13/88,11/68] or masked β-dialdehyde.[4/75]

The reaction of ethylacetoacetate with 5-amino-3-methylisoxazole **342b**[12/68] seems to parallel the synthesis of quinolones from the former and aniline. At room temperature, the kinetic product, Schiff base **356**, can be isolated and then cyclized at 240°C to give isoxazolo[5,4-*b*]pyrid-4-one **357** (R = Me). At 140°C, in the presence of PPA, the thermodynamically stable amide **358** cyclized to isoxazolo[5,4-*b*]pyrid-6-one **359**.

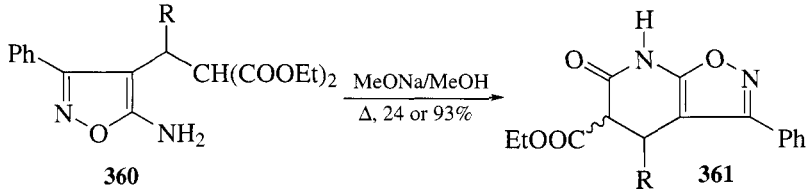

342c
(R = 4-pyridyl)
352a
352b
AcOH, Δ
74%
Pyridine, Δ
68%
353
354
342b +
H+
355
r.t., 39%
342b
PPA, 140°C, 20%
356
PPA
125°C
88%
358
R = Me
Dowtherm A
240°C, 26%
R = Ph
357
359

In constrast with this behavior, the reaction of **342b** with ethyl benzoylacetate gives the isoxazolo[5,4-*b*]pyrid-4-one **357** (R = Ph) when heated with PPA at 125°C.[13/76]

3.2.2.1b. Cyclization Process [CCCCCN]

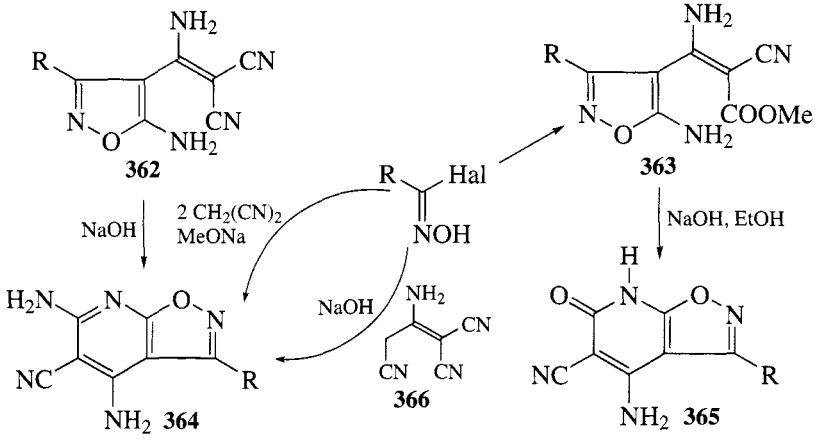
An obvious route to pyridines involves ring closure between nitrogen and a carbon atom in the ε position.

A useful approach for the synthesis of isoxazolo[5,4-*b*]pyridines involves condensation of a suitably substituted 5-aminoisoxazole, such as **360**, with a methylene–diethylmalonate group to give **361**.[15/87]

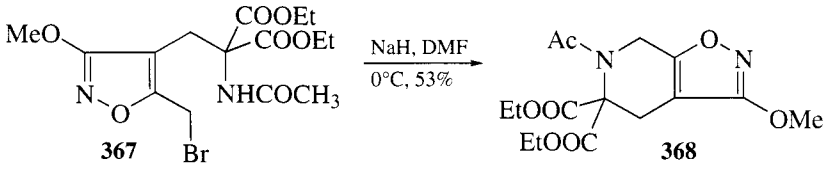


360 361

A further variation makes use of isoxazoles that are substituted at the 4 position with either a 2-aminoethylen-1,1-dicarbonitrile (**362**) or a 2-aminoethylen-1-cyano-1-methyl-carboxylate (**363**). Under basic conditions, the former[1/80,19/81] gives 4,6-diamino-5-cyano-isoxazolo[5,4-*b*]pyridine (**364**), while the latter[1/80,18/81] affords the 4-amino-5-cyano-6-hydroxy isomer (**365**). The 3-trifluoromethyl derivative (**364**, R = CF_3) is obtained in low yield from the respective halogenated oxime and excess malonitrile.[7/87] The dimeric malononitrile **366**, which is a postulated intermediate, gave **364** on reaction with the same aromatic halooximes,[1/80] while the trifluoroacetohydroximoyl bromide (R = CF_3, Hal = Br) did not give any of the fused isoxazole.[7/87]



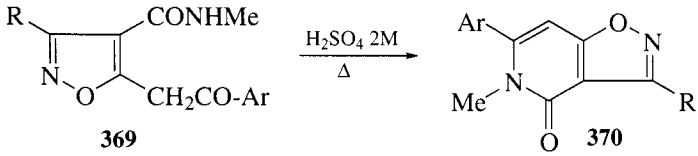
The isoxazolo[5,4-*c*]pyridine derivative **368** is obtained by intramolecular cyclization, under basic conditions, of bromomethyl isoxazole **367**.[3/85]



367 **368**

A similar reaction, which afforded an isoxazolo[4,5-*c*]pyridine derivative in 65% yield, has been performed on a 4–bromomethyl isomer whose activated ethylamino group occupies the 5 position.[2/86]

Isoxazolo[4,5-*c*]pyridine derivatives **370** were conveniently prepared by ring closure, under acidic conditions, of isoxazoles having general structure **369**.[11/76,10/77,11/77,13/77,14/77,15/77,9/78,10/78,11/78,12/80,13/80]



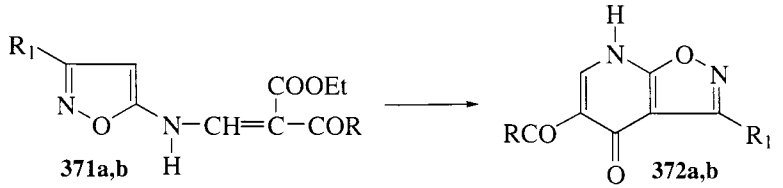
369 **370**

Variants involving the migration of the *N*-methyl group in 2-methylisoxazolium salts to the N5 position of the condensed ring,[12/77] or PPA-induced ring closure on the 5-(*β*-hydroxyphenethyl) group to give 6,7-dihydroderivatives of **370**,[12/78] are known.

3.2.2.1c. Cyclization Process [CCCNCC]

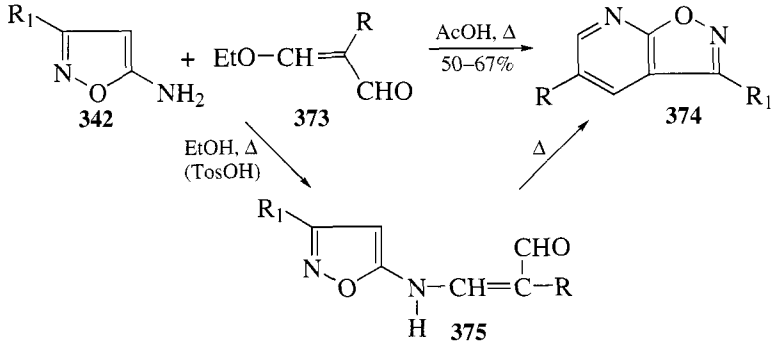
The synthesis of fused pyridines by formation of the C–C bond between the 3 and 4 positions involves condensation of a 4- or 5-amino isoxazole with a three-carbon fragment. The resulting adduct then cyclizes by nucleophilic attack of a carbon atom, which has enamine character, on a carbonyl function in the newly installed sidechain.

Thus, isoxazoles having either 5-aminomethylenemalonate (**371a**: R = OEt) or 5-aminomethylenacetacetate (**371b**: R = Me) groups, when heated at about 120°C, are cyclized to isoxazolo[5,4-*b*]pyridine derivatives **372a,b**;[1/72,9/72,10/72,16/73,20/73,4/74,10/75,11/75,2/88] the cyclization in **371b** proceeds only on the ester group.[1/72,8/72,12/76]

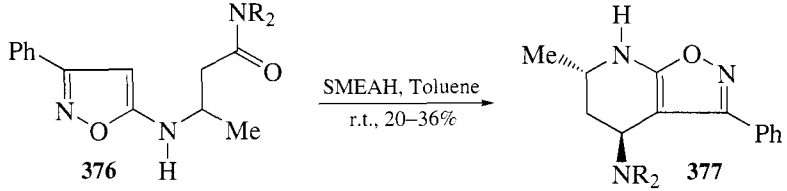


371a,b **372a,b**

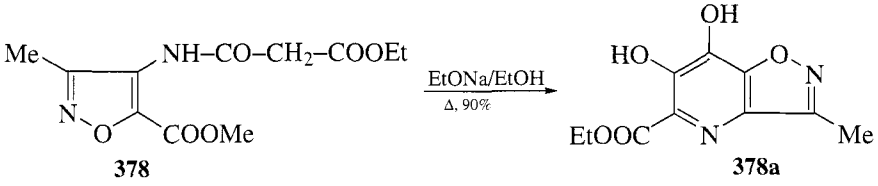
Condensation of 2-alkyl-3-ethoxyacroleins **373** with 5-aminoisoxazoles **342** in AcOH gave 5-alkyl-isoxazolo[5,4-*b*]pyridines **374**.[13/79] In one instance, the intermediate 5(2-alkyl-2-formylethenylamino)isoxazole **375** (R = Me) has been isolated.



If the intramolecular cyclization of 3-(5-isoxazolylamino)butanamides **376** is performed under reducing conditions,[15/87] using sodium bis(2-methoxyethoxy) aluminum hydride (SMEAH) in toluene, tetrahydroisoxazolo[5,4-*b*]pyridines **377** are produced.

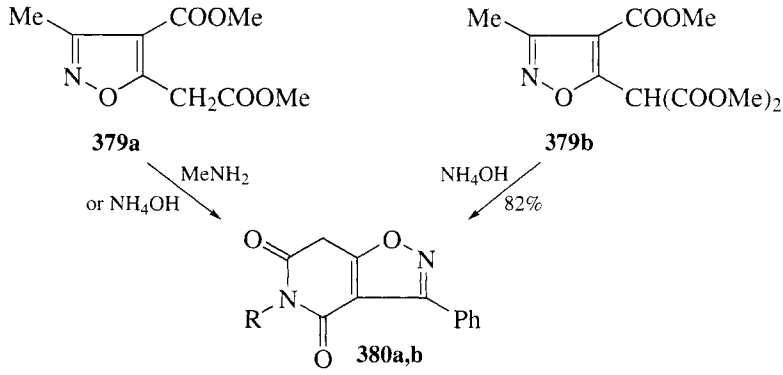


The effect of the electron-rich character of the isoxazole ring on the electrophilic nature of the carbomethoxy group in **378** required the formation of a stabilized carbanion to effect cyclization to isoxazolo[4,5-*b*]pyridine **378a**.[1/82]



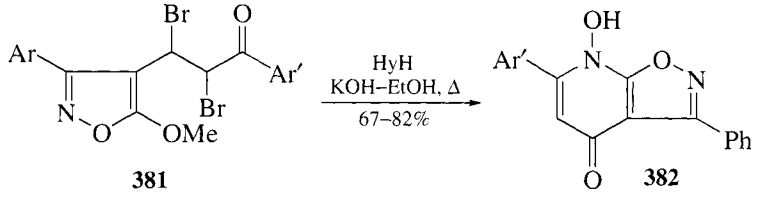
3.2.2.1d. Cyclization Process [CCCCC + N]

Ring closures based on the condensation of a 1,5-biselectrophile with an amino group are frequently employed in the synthesis of azines. This methodology has found application in the synthesis of isoxazolo[4,5-*c*]pyridine deriva-



tives **380a,b** from isoxazole-4-carboxylates having 5-acetic acid or 5-malonic acid sidechains (**379a,b**, respectively).[3/75]

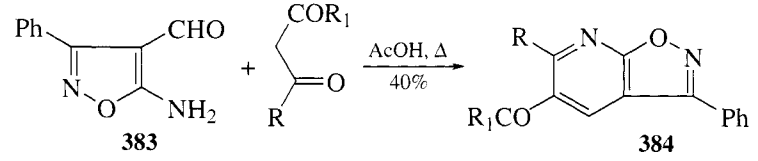
A similar strategy was used in the reaction between 4-dibromopropanoyl-5-methoxyisoxazoles (**381**) and hydroxylamine hydrochloride, to give 7-hydroxyisoxazolo[5,4-*b*]pyridin-4-one **382**.[26/89]



3.2.2.1e. Cyclization Process [CCCN + CC]

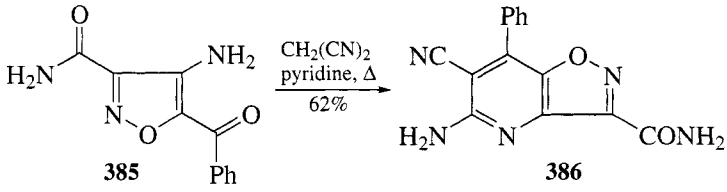
The condensation of α,β-enamino aldehydes with methyleneketones is a well-known route to pyridines that falls in the class of cyclizations involving a 1,4-nucleophile-electrophile that reacts with a 1,2-electrophile–nucleophile.

Some variants of the classic approach are known in the field of condensed isoxazolopyridines. These are represented by the reaction of **383** with β-dicarbonyl compounds to give isoxazolo[5,4-*b*]pyridine derivatives **384**.[16/77]

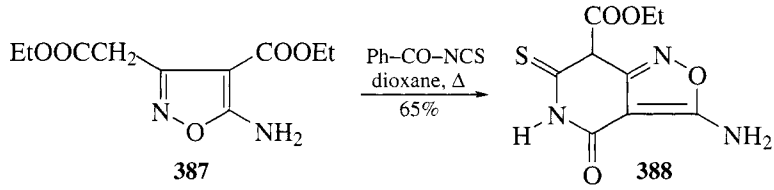


Ethyl 5-amino-3-methylisoxazole-4-carboxylate reacts with sodium diethylmalonate to give ethyl 4,5-dihydroxy-3-methylisoxazolo[5,4-*b*]pyridino-5-carboxylate.[1/77]

Ring closure can also be made to occur onto a cyano group. Ethyl cyanoacetate[16/77] and malononitrile[16/77,2/80] are suitable partners; the latter allows the synthesis of 5-amino-6-cyanoisoxazolo[4,5-*b*]pyridine derivative **386**[2/80] since the ring closure on the 5-benzoyl group of **385** is obviously preferred to that on the 3-amido group.



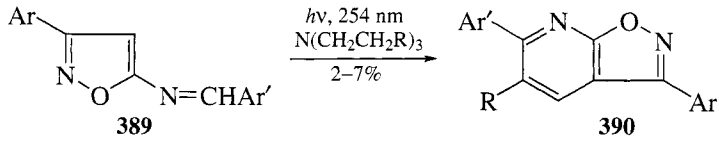
Unexpectedly, the amino group may sometimes remain uninvolved in the cyclization process. An example is the reaction of ethyl 5-amino-3-ethoxycarbonyl-4-isoxazole acetate **387** whose 3- and 4-substituents cyclize with benzoylisothiocyanate (behaving as a C–N fragment) to give the isoxazolo[4,3-*c*]pyridine derivative **388**.[2/84]



3.2.2.1f. Further Ring Closures

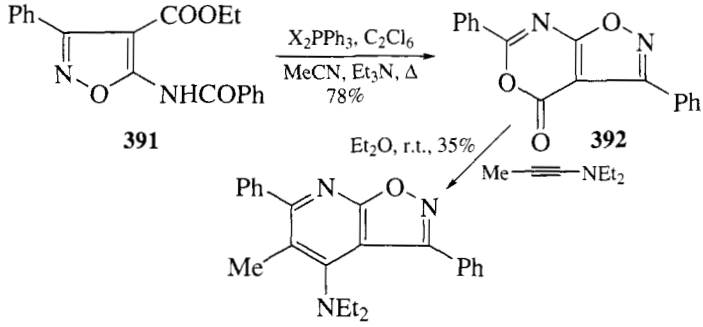
This section reports some interesting cyclizations involving the Schiff bases of aminoisoxazoles.

The irradiation of 5-arylideneaminoisoxazoles **389** at 254 nm, in a mixture of trialkylamine and aceto- or benzonitrile, gave (besides several oxidation and reduction products) very low (but nevertheless significant) yields of isoxazolo[5,4-*b*]pyridines **390**, which are the results of a regioselective cyclization process with the alkylamine as the second partner.[3/76]

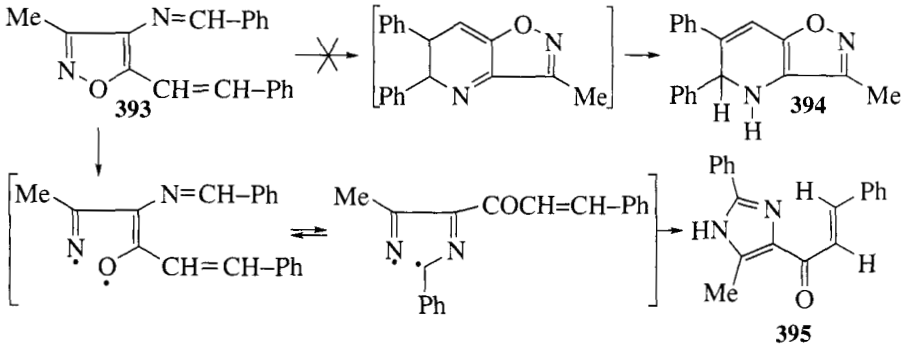


A nice sequence of reactions, which may be regarded to involve a Schiff base, commences with the reaction of **391**, behaving as *N*-acylated-*β*-enaminoester, with dihalotriphenylphosphorane to give 3,6-diphenyl-4*H*-isoxazolo[5,4-*d*]-1,3-oxazin-4-one **392**.[1/87] This cyclic Schiff base behaves as an azadiene and reacts

with diethylaminopropyne in an inverse electron demand hetero-Diels–Alder (DA) reaction. The primary adduct undergoes a retro-DA with extrusion of CO_2 to give the isoxazolo[5,4-*b*]pyridine.



Not only may the Schiff bases undergo the DA reaction, as illustrated above, but 4-aminobenzylidene-3-methyl-4-styrilisoxazole **393** may, as reported, undergo 6π-electrocyclic ring closure followed by 1,5-sigmatropic shift, to give the isoxazolo[4,5-*b*]pyridine derivative **394**.[1/83,2/85] Unfortunately, this is not the correct structure since the proposed electrocyclic rearrangement is in fact a thermal cleavage of the isoxazole N–O bond that gives 4-cinnamoyl-5-methyl-2-phenylimidazole **395**.[15/85]

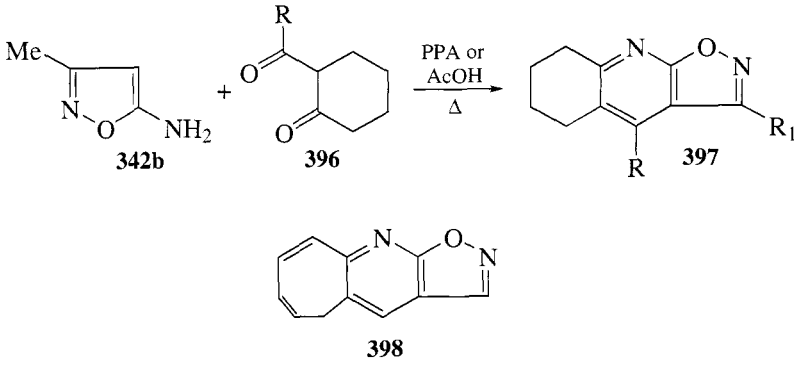


3.2.2.2. Syntheses of Quinoline, Isoquinoline, and Related Rings

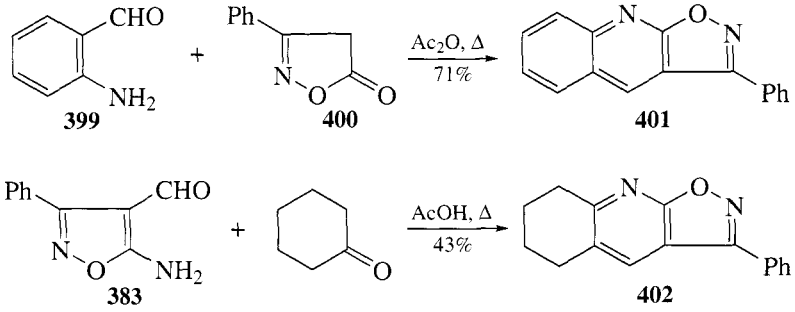
Isoxazolo quinolines can be prepared using strategies applied in some of the classic approaches to quinoline and its derivatives.

Condensation of 5-amino-3-methylisoxazole **342b** and a suitable 2-acylcyclohexanone **396** under acidic conditions, as in the Combes synthesis, gives the isoxazolo[5,4-*b*]quinoline derivatives **397** (R_1 = Me).[11/68,13/79]

With 2-formylcycloheptanone as a substrate for the previous condensation, a derivative of 5*H*-cyclohept[*b*]isoxazolo[4,5-*e*]pyridine **398** was obtained.[13/79]

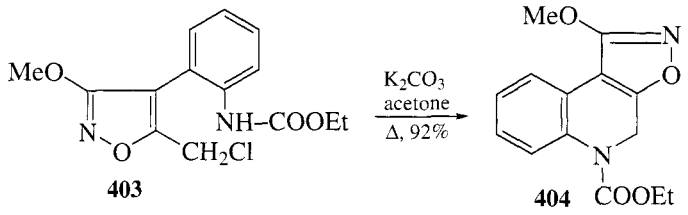


Friedlander cyclocondensations, such as those of *ortho*-aminobenzaldehyde **399** with 3-phenyl-5-isoxazolone[7/78] **400** and 5-amino-3-phenyl-4-isoxazolecarbaldehyde **383** with cyclohexanone,[15/79] afford derivatives of isoxazolo[5,4*b*]-quinoline (**401** and **402**, respectively).

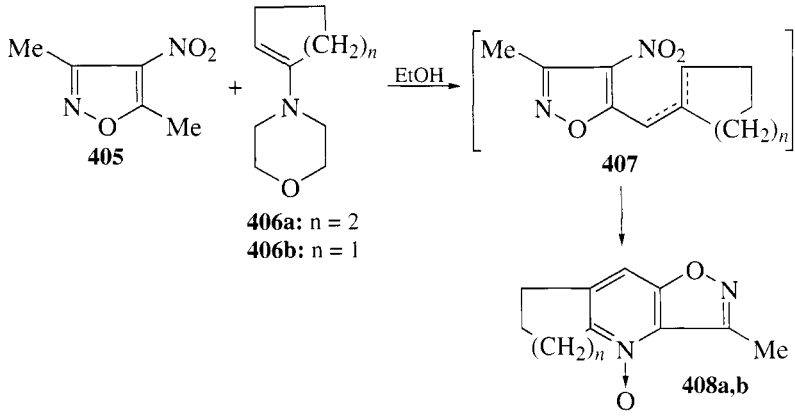


The latter variation has successfully employed methyl 5-amino-3-trifluoromethylisoxazole-4-carboxylate, cyclohexanone, and aniline as condensation partners.[10/86] In the presence of phosphorous pentoxide and triethylamine hydrochloride, the initial cyclization product, 4-hydroxyisoxazolo[5,4-*b*]quinoline **397** ($R_1 = CF_3$), is converted *in situ* to the 4-anilino derivative.

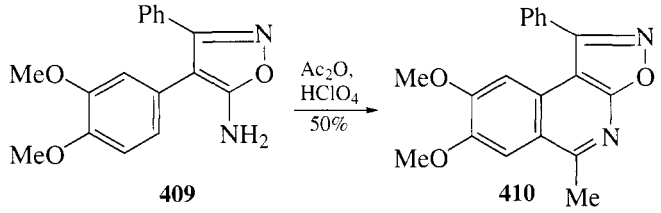
Facile intramolecular nucleophilic attack of the activated NH group in 5-chloromethylisoxazole **403** leads to the isoxazolo[5,4-*c*]quinoline derivative **404** in excellent yield.[21/89]



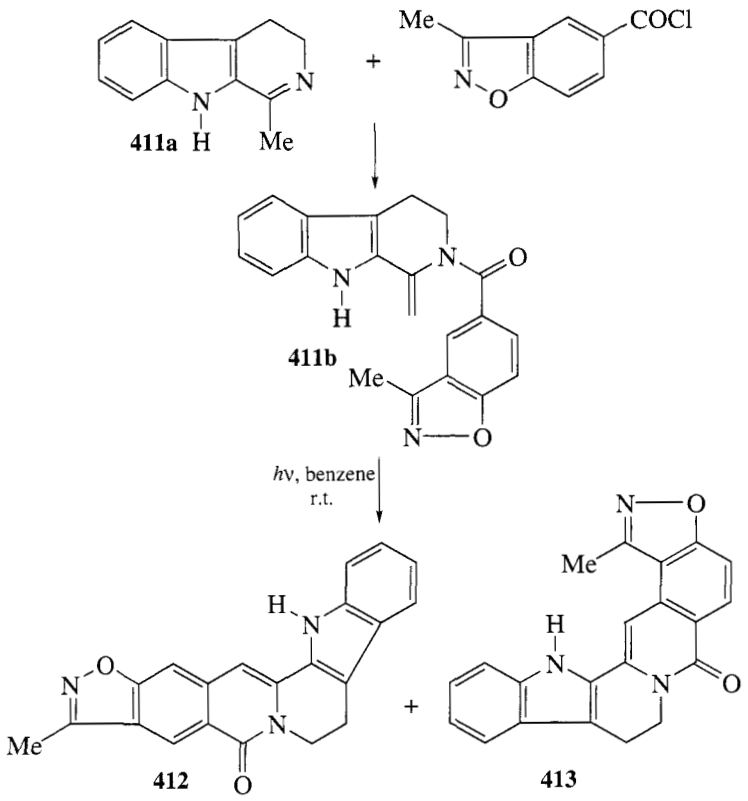
An original approach takes advantage of the acidity of the 5-methyl group in 3,5-dimethyl-4-nitroisoxazole **405**. Condensation of **405** with cyclohexenyl– or cyclopentenyl–morpholine (**406a,b**) to give intermediate **407** (which could be isolated under controlled conditions), was followed by cyclization to 3-methyl-5,6,7,8-tetrahydroisoxazolo[4,5-*b*]quinoline-4-oxide (**408a**) or to the corresponding cyclopent[*b*]isoxazolo[5,4-*e*]pyridine-4-oxide (**408b**).[9/91]



The Bischler–Napieralski isoquinoline synthesis can be applied to the 5-amino-4-arylisoxazole derivative **409**, which cyclizes in the presence of acetic anhydride to give the isoxazolo[5,4-*c*]isoquinoline **410**.[24/90]

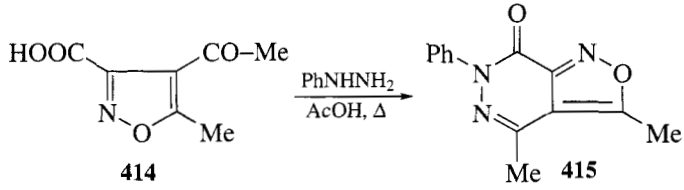


As the last example of this section, a synthesis developed during an original approach to alkaloid yohimbine is reported. This applies a process widely used by the Ninomya group to the synthesis of several alkaloids and consists of a 6π-electrocyclic ring closure of a dienamide under photochemical conditions. When **411b** (prepared from harmalane **411a** and 3-methyl-1,2-benzisoxazole-5-carbonyl chloride) was irradiated with a high-pressure mercury lamp through a Pyrex filter, photoinduced ring closure gave 1,2-benzisoxazolo[5,6-*g*]indolo[2,3-*a*]quinolizine derivative **412** and 6*H*,8*H*-1,2-benzisoxazolo[5,4-*g*]indolo[2,3-*a*]quinolizine derivative **413** in 3% and 19% yields, respectively.[17/80]

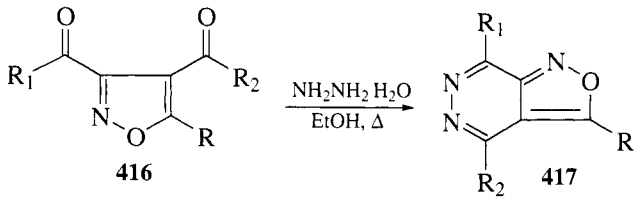


3.2.2.3. *Synthesis of the Pyridazine Ring*

As part of a detailed study of the reaction between 4-acetyl-5-methylisoxazole-3-carboxylic acid **414** and phenylhydrazine in 1939,[1/39] Musante reported the reaction between a dicarbonylisoxazole and hydrazine to give derivatives of isoxazolo[3,4-*d*]pyridazine (**415**). This basic approach was later extended to the reaction of a variety of dicarbonylisoxazoles and hydrazines.

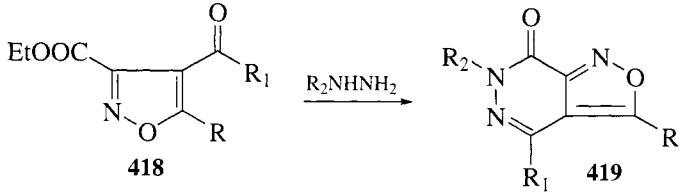


Symmetrically[2/56,3/68] or asymmetrically substituted 3,4-diketones (**416**),[3/68,2/91] when heated with hydrazine hydrate in ethanol, gave 4,7-disubstituted isoxazolo[3,4-*d*]pyridazines **417**.



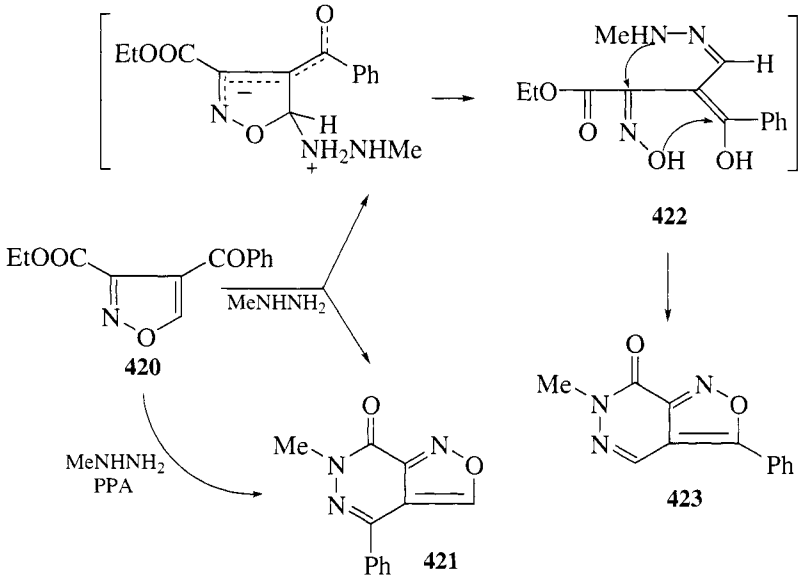
416 **417**

Owing to their reactivity toward hydrazine, 5-substituted ethyl 4-acylisoxazole-3-carboxylates (**418** R = alkyl, aryl) are widely used starting materials for the synthesis of 3-substituted isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones (**419** R_2 = H).[4/65,6/66,10/67,1/69,4/91] Reaction with monosubstituted hydrazines proceeds through attack of the NH_2 group on the ketonic carbonyl group, followed by the ring closure of RNH on the ester group, thus giving 6-substituted isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones (**419** $R_2 \neq$ H).[4/65,5/66,1/69,3/73,6/89,4/91,6/91]



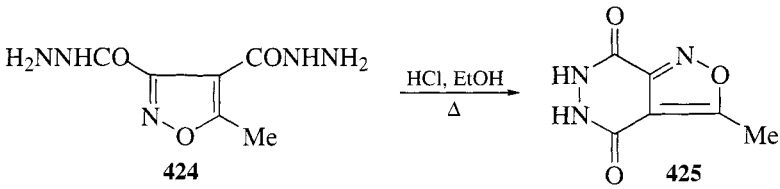
418 **419**

The reaction is somewhat more complicated if the 5 position has a hydrogen atom[1/69,3/73,5/91] (e.g., ethyl 4-benzoylisoxazole-3-carboxylate **420**). The latter reacts with methylhydrazine, in the presence of polyphosphoric acid (PPA),[5/91]



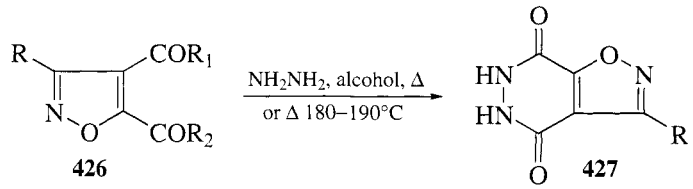
through the pathway mentioned above, to give 6-methyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one **421**. If the reaction is conducted in refluxing ethanol,[5/91] **421** becomes the by-product (15% yield) and the main pathway involves nucleophilic attack of NH_2NHMe at the 5 position. This mechanism is favored by the presence of an electron-withdrawing substituent at the 4 position and leads to ring opening, to give **422**, followed by cyclization to the isomeric 6-methyl-3-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one **423** (80% yield).

Ring closure to 3-methylisoxazolo[3,4-*d*]pyridazine-4,7-(5*H*,6*H*)-dione **425** can also be effected by heating 5-methylisoxazole-3,4-dicarbohydrazide **424**.[10/67]



424 **425**

The reaction between a dicarbonylisoxazole and hydrazine can be used to synthesize the isoxazolo[4,5-*d*]pyridazine ring system. Diethyl 3-phenylisoxazole-4,5-dicarboxylate (**426**, $R_1 = R_2 = OEt$),[3/66,3/67] the analogous dimethyl ester (**426**, $R_1 = R_2 = OMe$)[11/66] (when heated with excess hydrazine hydrate), 5(4)-carbomethoxy-3-phenylisoxazole-4(5)-carbohydrazide (**426**, R_1 or R_2 = OMe or $NHNH_2$),[11/66] 5-carbamoyl-3-methylisoxazole-4-carbohydrazide (**426**, R_1 = $NHNH_2$, $R_2 = NH_2$),[1/85] or 3-methylisoxazolo-4,5-dicarbohydrazide (**426**, $R_1 = R_2 = NHNH_2$)[1/85] (when heated at 180–190°C) all gave 3-phenyl (respectively 3-methyl) isoxazolo[4,5-*d*]pyridazine-4,7(5*H*,6*H*)-diones (**427**, R = Me or Ph).

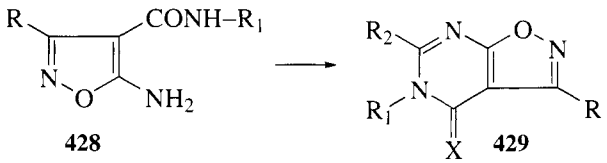


426 **427**

The same approach, previously described for 3,4-ketoesters, has been applied to ethyl 5-ketoisoxazole-4-carboxylates (**426**, R_1 = OEt, R_2 = alkyl or aryl) to give isoxazolo[4,5-*d*]pyridazin-4(5*H*)-ones.[1/90]

3.2.2.4. Synthesis of the Pyrimidine Ring

The most important starting products for the syntheses of isoxazolopyrimidine ring systems are 5-aminoisoxazole-4-carboxamides **428**. In 1964 Taylor and Garcia[2/64] described the reaction of **428** (R_1 = H) with triethyl orthoformate



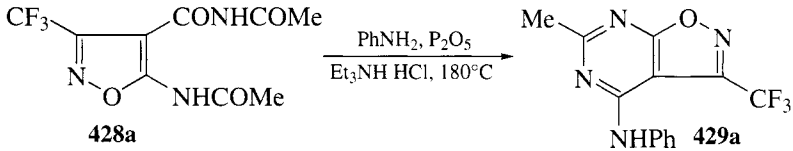
428 **429**

(TEOF) and Ac_2O to give 3-substituted isoxazolo[5,4-*d*]pyrimidine-4(5*H*)-ones **429** ($R_1 = R_2 = H$, X = O).

The same basic approach has been followed by several groups to prepare a large number of compounds. These endeavors have employed the following:

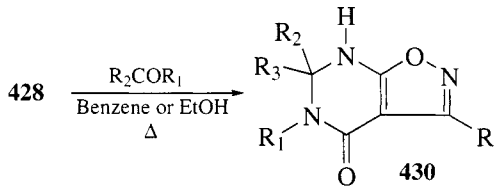
1. Unsubstituted aminoamides **428** (R_1 = H) and TEOF/Ac_2O, to synthesize 5,6-unsubstituted products **429** ($R_1 = R_2 = H$, X = O)[8/67,7/69]
2. *N*-Substitued amides **428** (R_1 = aryl) and TEOF/Ac_2O, to synthesize 5-substituted products **429** (R_1 = aryl, R_2 = H, X = O)[27/84,8/89]
3. Unsubstituted aminoamides **428** (R_1 = H) and acyl chlorides or anhydrides, to synthesize 6-substituted products **429** (R_1 = H, R_2 = alkyl or aryl, X = O)[3/66,4/67,7/69,11/71]
4. Aminothioamides, to synthesize 4-thione derivatives **429** (R_1 = H, R_2 = H or alkyl, X = S)[16/90]
5. 5-(2-Furoylamino)-4-cyanoisoxazoles with H_2O_2/NaOH, to synthesize **429** (R_1 = H, R_2 = 2-furyl, X = O)[17/73,6/74]
6. Methyl 5-acetylaminoisoxazole-4-carboxylate with $PhNH_2/P_2O_5/Et_3N$ HCl, to synthesize **429** (R_1 = Ph, R_2 = Me, X = O)[10/86]

Under the conditions described in the final category, 5-acetylamino-3-trifluoromethyl-isoxazole-4-*N*-acetylcarboxamide **428a** gave the isoxazolo[5,4-*d*]pyrimidine **429a**.[10/86]



428a **429a**

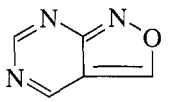
Amides of general structure **428** reacted with aldehydes or ketones to give 6,7-dihydroisoxazolo[5,4-*d*]pyrimidine-4(5*H*)-ones **430**[22/73,14/88,7/89,28/89,29/89,30/89,22/90]



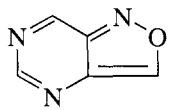
430

The same products (**430**) can be obtained from 5-aminoisoxazole-4-carboxylic acid, aromatic amines, and aldehydes,[17/90] or methyl 4-aminoisoxazole-5-carboxylates and isocyanates.[11/86]

A variation of these reactions makes use of both 3-aminoisoxazole-4-carboxamide and the analogous 4-cyano compound. With aldehydes[22/73] (or with TEOF/H_2SO_4[21/73]) derivatives of isoxazolo[3,4-*d*]pyrimidines **151** are obtained. The isomeric 4-aminoisoxazole-3-carboxamide gives derivatives of isoxazolo[4,3-*d*]pyrimidine **431** with TEOF and Ac_2O.[2/80]

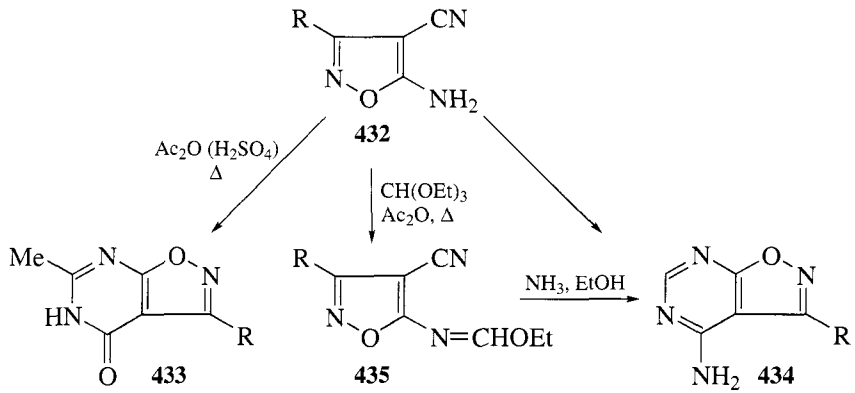


151



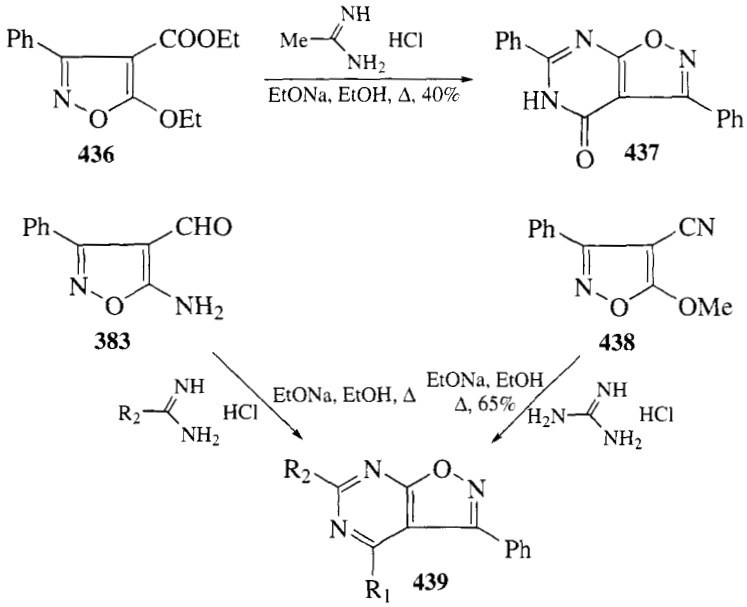
431

5-Amino-4-cyanoisoxazoles **432** are excellent starting materials for the synthesis of the ring system discussed in this section. With Ac_2O and a catalytic quantity of H_2SO_4, isoxazolo[5,4-*d*]pyrimidines (**433**) are obtained.[4/73] On exposure to TEOF and Ac_2O followed by ethanolic NH_3, 4-aminoisoxazolo[5,4-*d*]pyrimidines **434** are obtained via intermediate 4-cyano-5-ethoxymethyleneaminoisoxazoles **435**.[2/64]

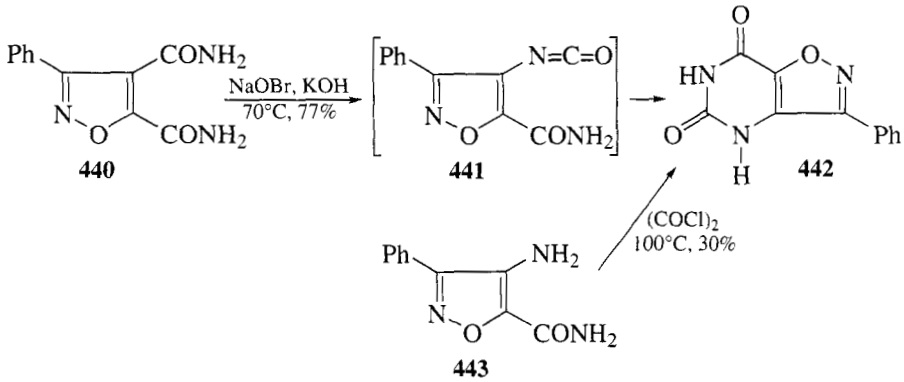


It is well known that the most fruitful method for the construction of a pyrimidine ring is the reaction of a three-carbon fragment with a diamino component that later becomes the N1C2N3 part of the ring. This approach was used in the reaction of ethyl 3-phenyl-4-methoxyisoxazole-5-carboxylate **436** and acetamidine to synthesize 3,6-diphenylisoxazolo[5,4-*d*]pyrimidine-4(5*H*)-one **437**.[4/73]

Modifications of this traditional approach include the reactions of 5-amino-3-phenylisoxazole-4-aldehyde **383** with amidines,[16/77,4/80] and 5-methoxy-3-phenyl-4-cyanoisoxazole **438** with guanidine hydrochloride[1/60] to give the isoxazolo[5,4-*d*]pyrimidines **439** with R_1 = H and R_1 = R_2 = NH_2, respectively.

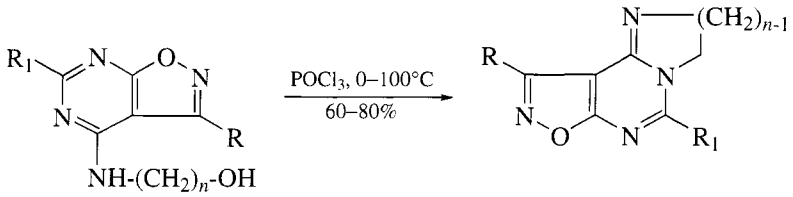


The different rates of reactivity of isoxazole-4- and 5-dicarboxamides have been used advantageously under conditions of the Hoffmann rearrangement. When 3-phenylisoxazolo-4,5-dicarboxamide **440** was gently heated with NaBrO,[3/66,2/67] the group in the 4 position underwent the rearrangement first, to give the intermediate 4-isocyanato-5-carboxamide **441**. Subsequent intramolecular cyclization gave 3-phenylisoxazolo[4,5-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione **442**. The same product **442** was also obtained from 4-amino-3-phenylisoxazolo-5-carboxamide **443** and oxalyl chloride.[1/67]

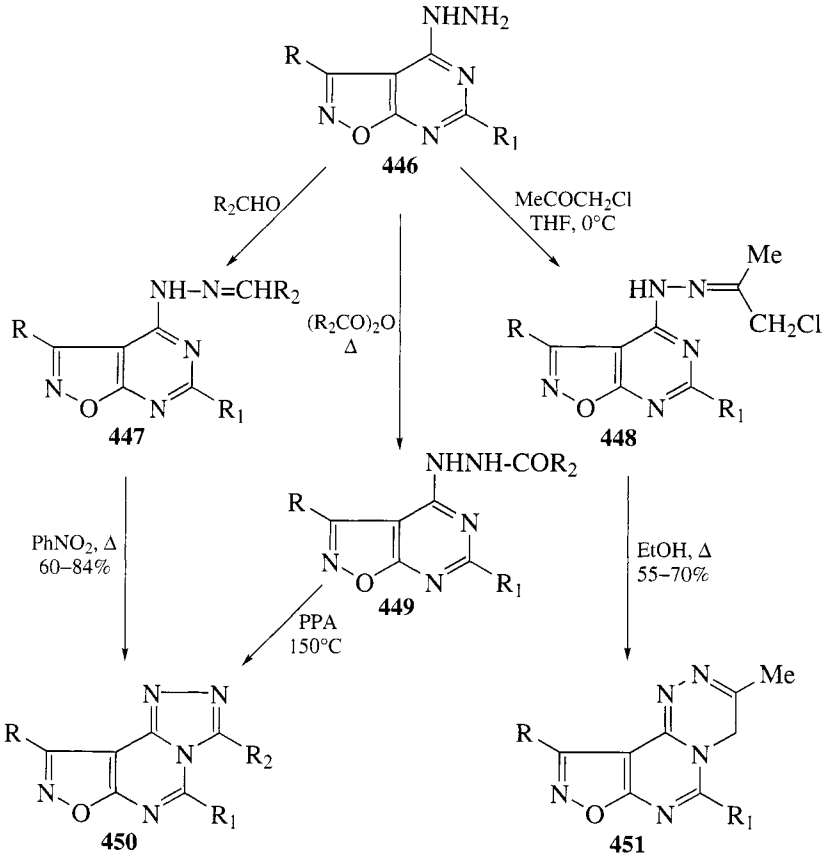


To close this section, use of isoxazolo[5,4-*d*]pyrimidines as starting products for the syntheses of more complicated condensed systems will be discussed.

4(2-hydroxyethylamino) or (3-hydroxypropylamino)isoxazolo[5,4-*d*]pyrimidines (**444a** and **444b**) cyclized in the presence of $POCl_3$ to give good yields of imidazo[1,2-*c*]isoxazolo[4,5-*e*]pyrimidine and 2*H*-isoxazolo[4,5-*e*]pyrimido[1,2-*c*]pyrimidine derivatives (**445a** and **445b**, respectively).[23/90,21/91]



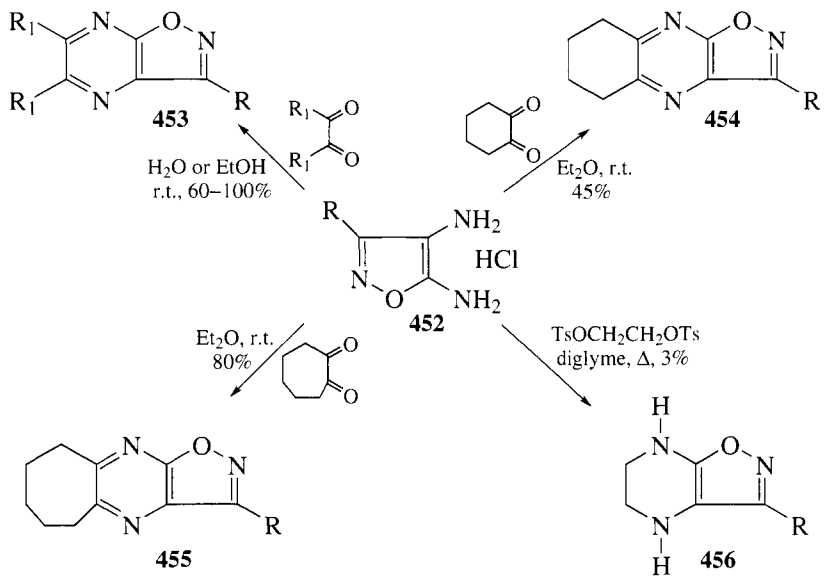
4-Hydrazinoisoxazolo[5,4-*d*]pyrimidines **446** gave, with aldehydes or chloroacetone, their respective hydrazono derivatives **447** and **448**, and, with anhydrides, the acylhydrazines **449**. The oxidative cyclization of **447** with



nitrobenzene gave the isoxazolo[4,5-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidines **450**,[6/81] also obtained by heating **449** with polyphosphoric acid. The intramolecular nucleophilic substitution of chlorine from **448** gave good yields of 4*H*-isoxazolo[5′,4′: 4,5]pyrimido[6,1-*c*]-1,2,4-triazines **451**.[6/88]

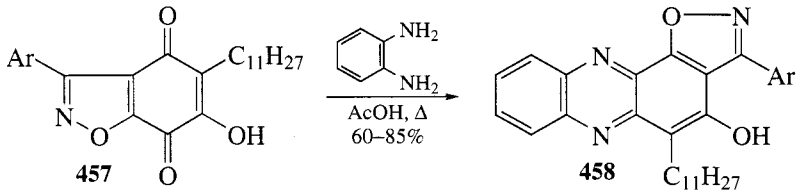
3.2.2.5. Synthesis of Pyrazine and Related Rings

The isoxazolopyrazine ring system was the last condensed diazine to be synthesized by this route. This was due to the intrinsic difficulty of preparing either isoxazolo-4,5-diones (which remain unknown!) or 4,5-diaminoisoxazoles, which could be the natural precursor to this ring system. When the latter compounds (**452**) became available (by reduction of 5-amino-4-nitroisoxazoles with $NaBH_4$ in the presence of Pd/C),[4/68] they were easily condensed with α-diketones to give isoxazolo[4,5-*b*]pyrazines **453**,[4/68,6/73,19/91] isoxazolo[4,5-*b*]quinoxalines **454**,[4/68] and 5*H*-cyclohepta[*b*]isoxazolo[4,5-*e*]pyrazines **455**,[4/68] whereas diethylene glycol di-*p*-tosylate gave 4,5,6,7-tetrahydroisoxazole[5,4-*b*]pyrazines **456**.[19/91]

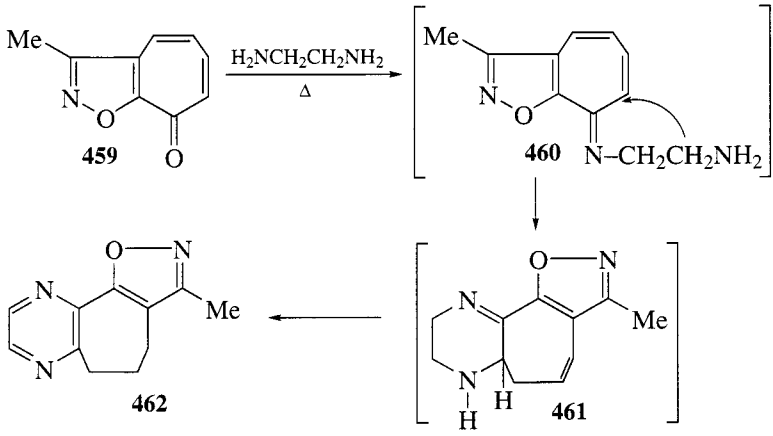


Although 4,5-isoxazolediones are as yet unknown, some benzisoxazoles behaving as 6,7-diones (**457**) were prepared that react with *o*-phenylendiamine to give the isoxazolo[5,4-*a*]phenazine derivatives **458**.[20/91]

The reaction between 3-methyl-8*H*-cyclohepta[*d*]isoxazol-8-one **459** and 1,2-ethanediamine, under reflux, gave a very low yield (2.4%) of the 4*H*-isoxazolo[5′,4′:3,4]cyclohepta[1,2-*b*]pyrazine derivative **462**.[12/83] The mechanism can be assumed to involve formation of the Schiff base **460**, followed by



the ring closure to **461**. Migration of the double bond from the seven-membered ring into the heterocyclic ring results in aromatization. Precedent for this type of migration exists in the reaction between 4,5-benzotropolone and 1,2-ethanediamine. The reaction of **459** with 1,2-propanediamine behaved analogously but was not regioselective.

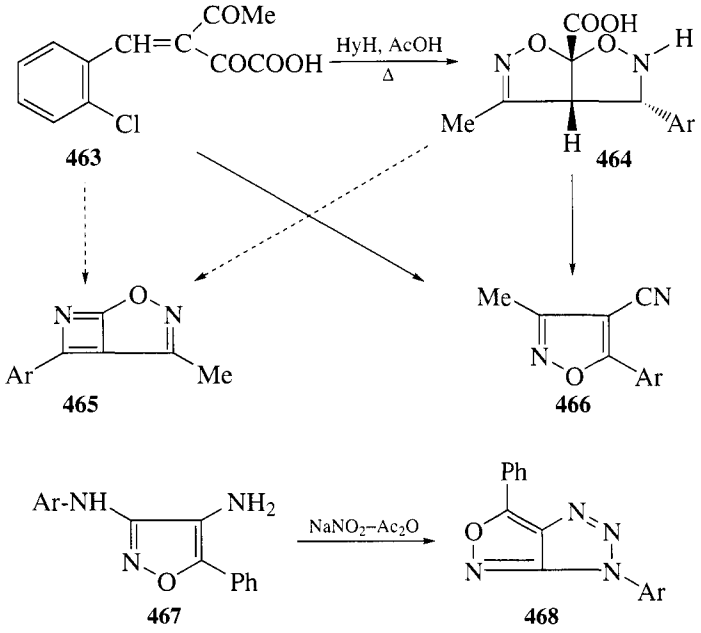


3.2.2.6. Syntheses of Other Nitrogen-Containing Heterocycles

A variety of miscellaneous nitrogen-containing heterocycles that contain a fused isoxazole ring have been synthesized.

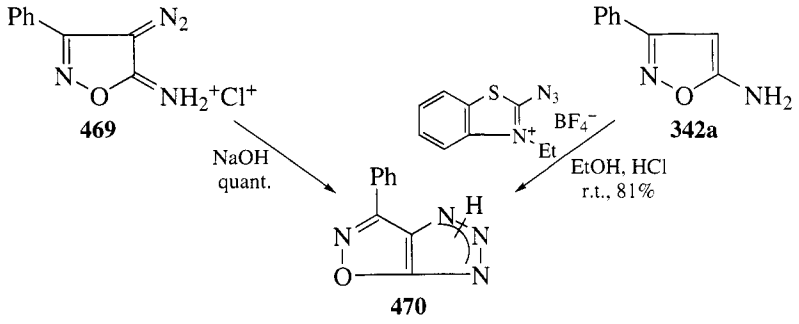
No examples of a four-membered ring with an appended isoxazole are known. However, it was erroneously reported that oximation of 3-arylidene acyl piruvic acid **463** or the thermal rearrangement of the isoxazolidinoisoxazoline **464** afforded 3-methyl-4-(*o*-chlorophenyl)azeto[3,2-*d*]isoxazole **465**.[1/76] Unfortunately this assignment was shown to be in error and the structure subsequently assigned that of the less exotic 5-(*o*-chlorophenyl)-3-methylisoxazole-4-carbonitrile **466**.[20/76,23/77]

In 1910 Erwin Gmelin and the Nobel laureate Heinrich Wieland reported the products of the reaction between 4-amino-3-anilino- (or *p*-anisidino)-5-phenylisoxazole **467** and sodium nitrite in acetic anhydride.[1/10] Their correct assignment of the structure of the resulting 3-aryl-6-phenylisoxazolo[3,4-*d*]-

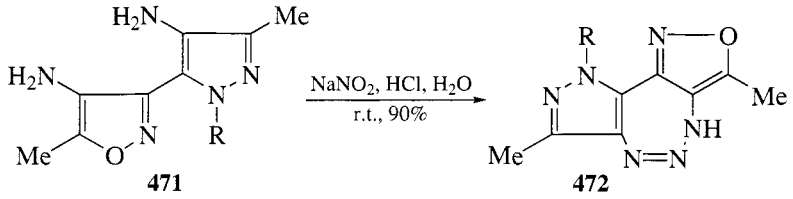


1,2,3-triazoles **468** is evidence of the powers of ratiocination possessed by the Chemists of that day.

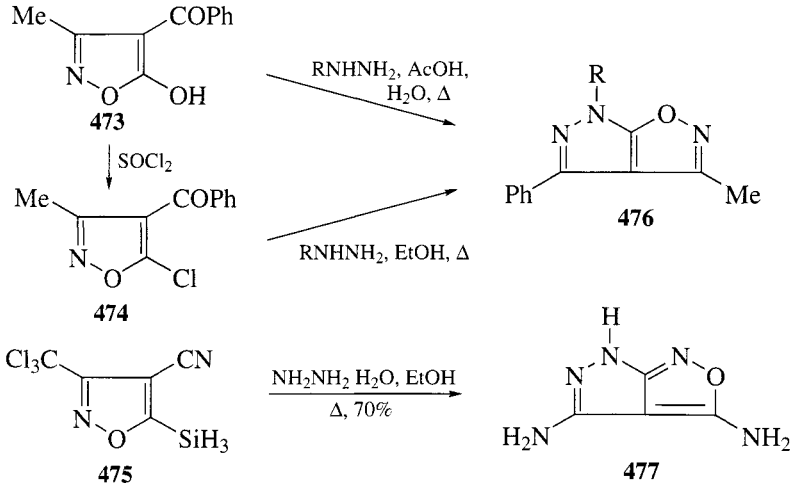
Diazotation of 3-phenyl-4,5-diaminoisoxazole with isoamyl nitrite gave 4-diazo-5-iminoisoxazole hydrochloride **469**, which, when dissolved in aqueous NaOH and then acidified (or after standing few hours in EtOH-H_2O), gave a quantitative yield of 6-phenylisoxazolo[4,5-*d*]-1,2,3-triazole **470**.[1/70] The same product was obtained from 5-amino-3-phenylisoxazole **342a** by diazo-group transfer from 2-azido-3-ethylbenzothiazoliumtetrafluoborate.[1/78]



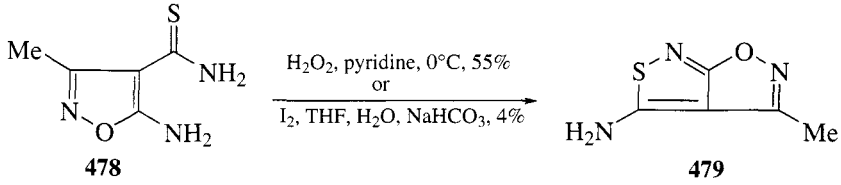
When diazotized, compounds having two amino groups frequently give rise to new condensed heterocycles, even if the groups do not belong to the same ring. The synthesis of the 4*H*,9*H*-isoxazolo[4,3-*d*]pyrazolo[3,4-*f*]-1,2,3-triazepine derivatives **472** from **471**[12/87] is a good example of this strategy.



Many of the substrates that, on treatment with hydroxylamine, give isoxazoles also react with hydrazine to give pyrazoles. Examples include β-chloro or β-hydroxyenones and, cyano derivatives β-substituted with a good leaving group. Examples of these strategies applied to the topic of this review are the reactions of 4-benzoyl-5-chloro (or 5-hydroxy)-3-methylisoxazoles (**473** and **474**, respectively) with hydrazines,[3/59] as well as the reaction of 5-amino-3-trichloromethylisoxazole-4-carbonitrile **475**.[2/84] The former reaction gave the 6*H*-pyrazolo[4,3-*d*]isoxazolo derivative **476**; the latter, 3,4-diamino-6*H*-pyrazolo[3,4-*c*]isoxazole **477**.

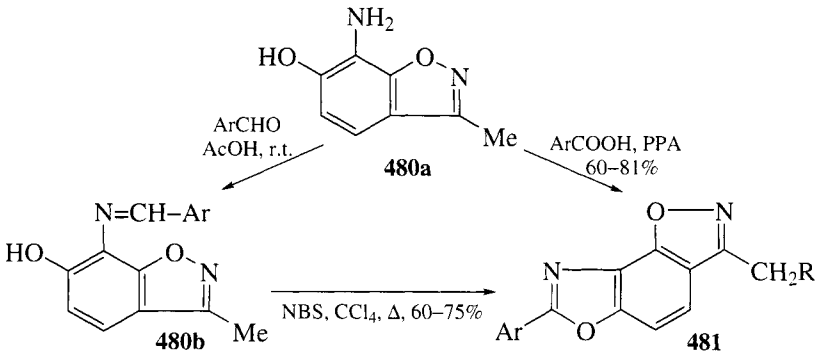


Oxidation of 5-amino-3-methylisoxazolo-4-thiocarboxamide **478** with H_2O_2 or, less effectively, I_2[16/90] has been used as a means of obtaining the isothiazolo[4,3-*d*]isoxazole ring **479**.



The synthesis of 3-methyl-4*H*-pyrrolo[3,4-*d*]isoxazolo-4,6(5*H*)-dione should be mentioned as an example of a pyrroloisoxazole. The latter is prepared by heating 4-carbamoyl-3-methyl-5-isoxazolcarboxylic acid in refluxing thionyl chloride.[1/82]

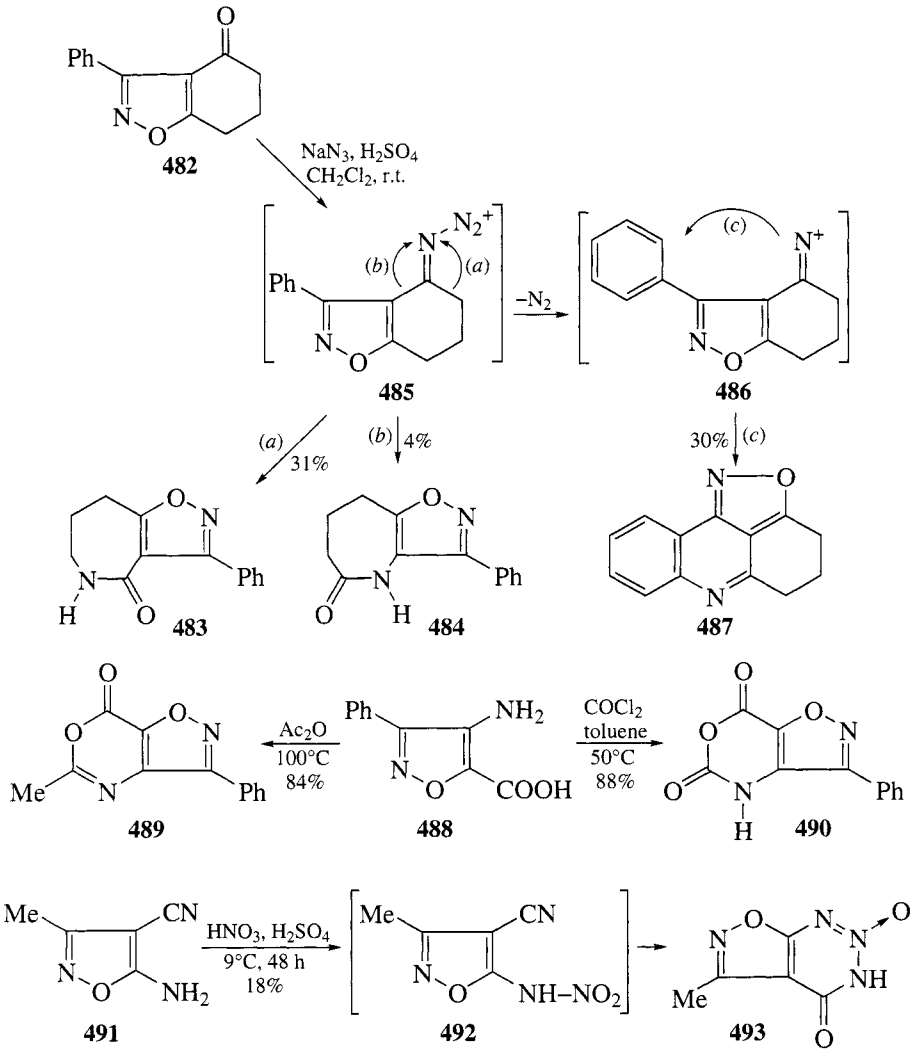
Turning to oxazole-containing ring systems, 7-amino-6-hydroxy-3-methyl-1,2-benzisoxazole **480a** is a good starting product, as are all 1,2-amino alcohols, for the synthesis of this heterocycle. Compound **480a** reacts with either aromatic acids in the presence of PPA to give 7-aryl-3-methyloxazolo[5,4-*g*]-1,2-benzisoxazoles **481** (R = H), or with aldehydes and their Schiff's bases **480b**, which are converted to **481** (R = Br) when submitted to oxidative cyclization with *N*-bromosuccinimide (NBS).[10/87]



Turning to condensed seven-membered rings, when 6,7-dihydro-3-phenyl-1,2-benzisoxazol-4(5*H*)-one **482** was exposed to the conditions of the Schmidt reaction (NaN_3, H_2SO_4, CH_2Cl_2, r.t.),[14/90,20/90] two lactams were obtained (**483** and **484**), derivatives of the 4*H*-isoxazolo[4,5-*c*] and [4,5-*b*]azepine ring systems, respectively. Their formation can be rationalized by pathways (a) and (b), as both are alkyl migrations from the intermediate **485**. A further product was isolated that falls within the topic of this review. Following loss of nitrogen a nitrenium ion (**486**) is formed and its intramolecular attack [path (*c*)] on the aromatic substituent gives 5,4-dihydro-3*H*-isoxazolo[5,4,3-*k*,*l*]acridine **487**.

In addition to the previously mentioned synthesis of 3,6-diphenyl-4*H*-isoxazolo[5,4-*d*]-1,3-oxazin-4-one **392a**,[1/87] the 1,3-oxazine ring can be easily assembled starting from 4-amino-3-phenylisoxazole-5-carboxylic acid **488**. When this is heated with acetic anhydride, 5-methyl-3-phenylisoxazolo[4,5-*d*]-1,3-oxazin-7-one **489** is obtained;[1/67] the reaction with phosgene in toluene gives 3-phenyl-5*H*-isoxazolo[4,5-*d*]-1,3-oxazin-5,7(4*H*)-dione **490**.[11/90]

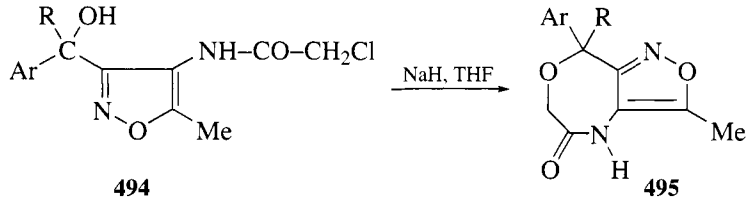
The presence of an amino group in the 5 position of the isoxazole ring enables the assembly of a condensed triazine. Thus, nitration of 5-amino-3-methylisoxazole-4-carbonitrile **491** with fuming nitric acid and H_2SO_4 gives 3,4-dihydro-5-methyl-4-oxoisoxazolo[5,4-*d*]-1,2,3-triazine 2-oxide **493**, probably through an intermediate nitroamine **492**.[8/88]



3.2.2.6a. Syntheses of Nitrogen Heterocycles by Closure of a Chain

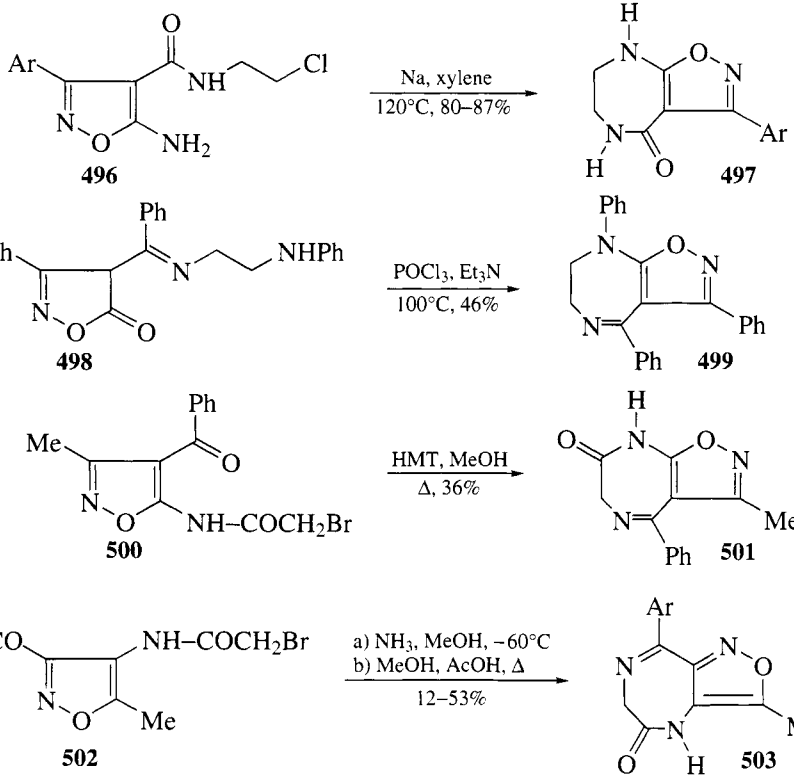
Several strategies are available for transformation of an isoxazole side chain into a condensed heterocycle and generally involve nucleophilic substitution, formation of an amide bond, or condensation to give a Schiff base.

Intramolecular nucleophilic substitution has a wide range of applications; for example, the nucleophile can be either oxygen or nitrogen, and the leaving group is frequently a halogen atom. Typical starting products are 4-chloroacetamido-3-hydroxybenzylisoxazoles **494**, which, in the presence of a strong base, cyclize to 4,8-dihydro-8-arylisoxazolo[4,3-*e*]-1,4-oxazepin-5(6*H*)-ones **495**. The latter are useful as antihypertensives.[10/89]



494 **495**

As above, the starting product carries both the nucleophile and the leaving group; sometimes it lacks the halogen atom (inserted at the level of nonisolated intermediate), and sometimes the nucleophile is introduced during a one-pot process. Four examples are reported showing the above strategies. The first starting product (**496**) has substituents suitably placed to give rise to an intramolecular alkylation but, to enhance the nucleophilicity of NH_2, the conversion to its sodium salt is preferred. In the second example, the experimental conditions suggest the formation of a 5-chloroisoxazole intermediate from **498**. In the last two examples the nucleophiles are the imino derivatives developed in situ from the ketonic groups of **500** and **502** with NH_3 or hexamethyltetramine (HMT). The first three reactions gave 4*H*- or 6*H*-isoxazolo[5,4-*e*]-1,4-diazepine derivatives **497**, **499**, and **501**, respectively;[1/74,19/91] the last reaction gave the 4*H*-isoxazolo[4,3-*e*]-1,4-diazepine derivatives **503**.[14/85]



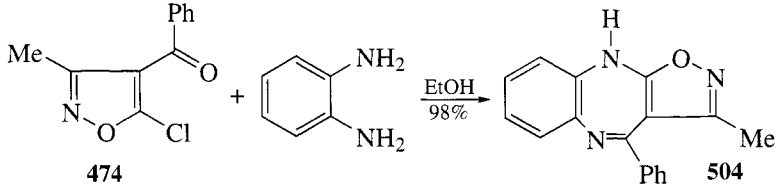
496 **497**

498 **499**

500 **501**

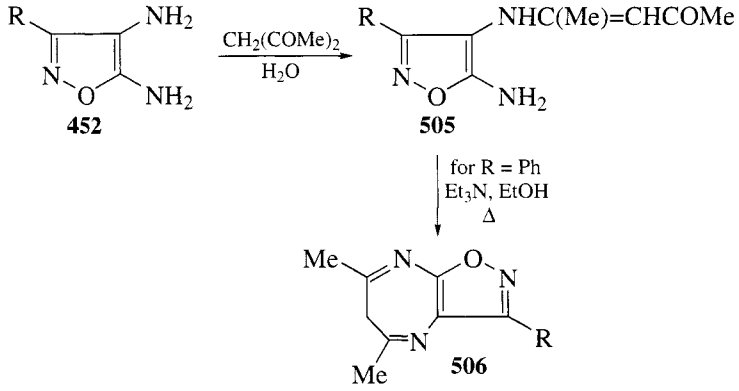
502 **503**

An example on the borderline between ring closure by formation of a Schiff base or by nucleophilic substitution is the reaction of 4-benzoyl-5-chloro-3-methylisoxazole **474** with 1,2-phenylendiamine[3/59] to give 3-methyl-4-phenyl-10*H*-isoxazolo[5,4-*b*]-1,5-benzodiazepine **504**.



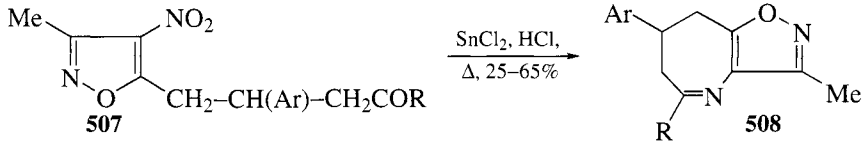
474 504

The reaction between 4,5-diaminoisoxazoles **452** and 2,4-pentanedione offers a good example of intramolecular cyclization through the formation of a Schiff base. When R = Ph[1/70] at room temperature, an open-chain intermediate (**505**), which can be isolated, cyclizes to 6*H*-isoxazolo[4,5-*b*]-1,4-diazepine derivative **506** on heating. When R = Me,[6/73] the reaction occurs in a single step.



452 505 506

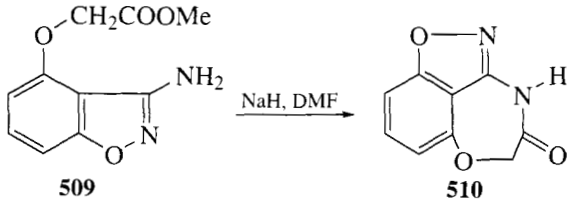
The amino group required for formation of a Schiff base is sometimes installed *in situ*. Reduction of 4-nitroisoxazoles **507** to the corresponding amino compounds with $SnCl_2$ and HCl, enables cyclization to the 7,8-dihydro-6*H*-isoxazolo[4,5-*b*]azepine derivatives **508** to occur.[4/78,7/81,8/81,2/87]

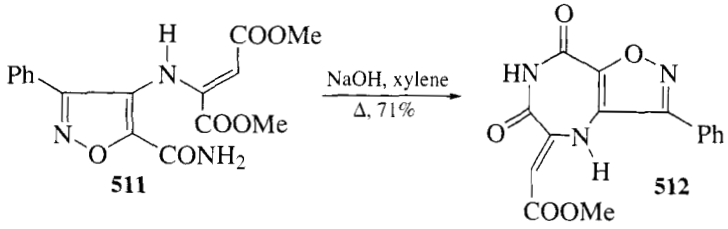


507 508

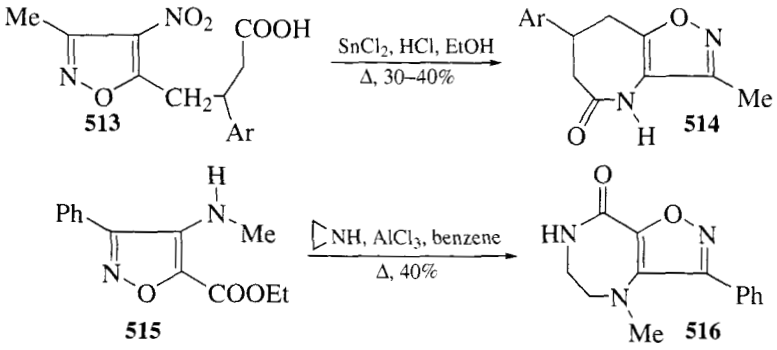
Formation of an amide bond is often relied on to effect ring closure as in the synthesis of 3*H*-isoxazolo[3,4,5-*e*, *f*]-1,4-benzoxazepin-4(5*H*)-one (**510**) from

509.[31/89,12/90] In a similar fashion, **511** has been converted to a rather unusual derivative (**512**) of the 4*H*-isoxazolo[4,5-*e*]-1,4-diazepine ring system.[3/87]





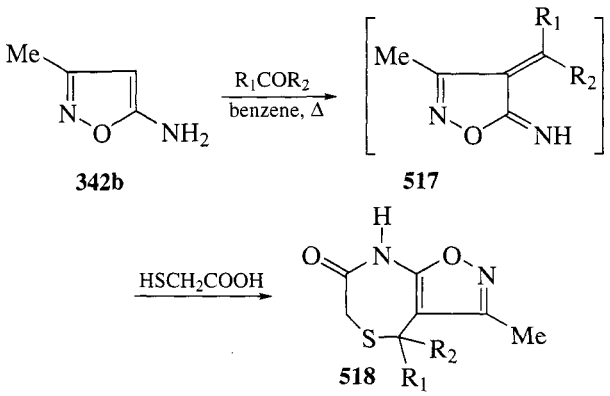
Occasionally the groups required for intramolecular amide bond formation are introduced *in situ* from obvious precursors. 4-Nitroisoxazole carboxylic acids **513** are converted into 4*H*-isoxazolo[4,5-*b*]azepine derivatives **514** under conditions that initiate a reduction–esterification–cyclization sequence.[4/90] Ethyl 4-methylamino-3-phenylisoxazole-5-carboxylate **515** can be converted into 4-methyl-3-phenyl-4,5,6,7-tetrahydro-8*H*-isoxazolo[4,5-*e*]-1,4-diazepin-8-one **516** by heating with aziridine and $AlCl_3$.[11/90] The nucleophilic opening of aziridine catalyzed by the Lewis acid seems to be an obvious intermediate step.



This section concludes with two examples that, in a wide sense, are encompassed by the last strategy of ring closure.

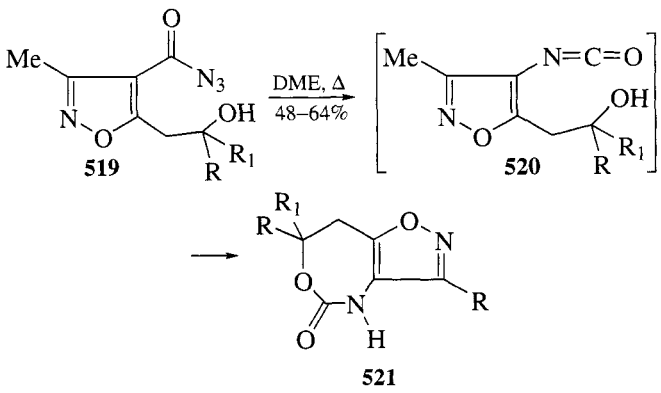
In benzene, the condensation products of 5-amino-3-methylisoxazole **342b** and aldehydes or ketones undergo further reaction on addition of thioglycolic acid to the reaction medium. The products, initially described as derivatives of

the isoxazolo[5,4-*d*]-1,3-thiazepine in a patent,[5/70] were later reported to be isoxazolo[5,4-*e*]-1,4-thiazepine derivatives **518**.[13/75] The presumed intermediate, an 4-ylidene-5-iminoisoxazole (**517**), then undergoes Michael addition followed by ring closure to complete the sequence.



342b 517 518

When crude 5-(2-hydroxyalkyl)isoxazole-4-carboxazides **519** were subjected to the conditions of a Curtius rearrangement in refluxing 1,2-dimethoxyethane, the resulting isocyanate **520** underwent intramolecular cyclization to give the cyclic derivatives of isoxazolo[4,5-*d*]-1,3-oxazepine (**521**).[4/81]

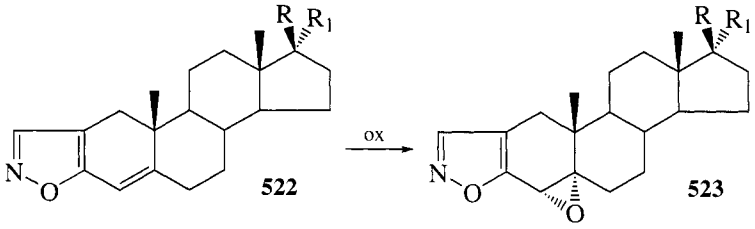


519 520 521

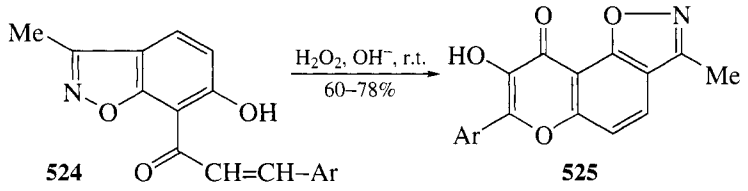
3.2.2.7. Syntheses of Heterocycles with Oxygen and Sulfur Atoms

When androst-4-eno[2,3-*d*]isoxazoles **512** are treated with either peracetic acid (under buffered conditions)[16/68] or *m*-chloroperbenzoic acid,[24/89] the 4α,5α-epoxyandrostano[2,3-d]isoxazole **523** is readily obtained. The latter is considered to be a derivative of the 1*H*,5a*H*,6a*H*-cyclopenta[5′,6′]naphtho[1′,2′-*f*]oxirano [2,3-*g*]-1,2-benzisoxazole ring system. Incredibly, the same result has been obtained with buffered (AcONa/AcOH) perchloric acid.[15/68] Some strong

analogies with ref. 16/68 (both patents come from the same group and the concentration of both peracetic and perchloric acid is 42.2%), however, suggest a print error.



Oxiran derivatives are also involved in the reaction of 7-cinnamoyl-6-hydroxy-1,2-benzisoxazole **524** and H_2O_2, under basic conditions, to give the 9*H*-pyrano[2,3-*g*]-1,2-benzisoxazole derivatives **525**.[9/73] Epoxidation by hydroperoxide ion, followed by intramolecular opening of the oxirane ring, seems to be a rational sequence to account for the observed products.

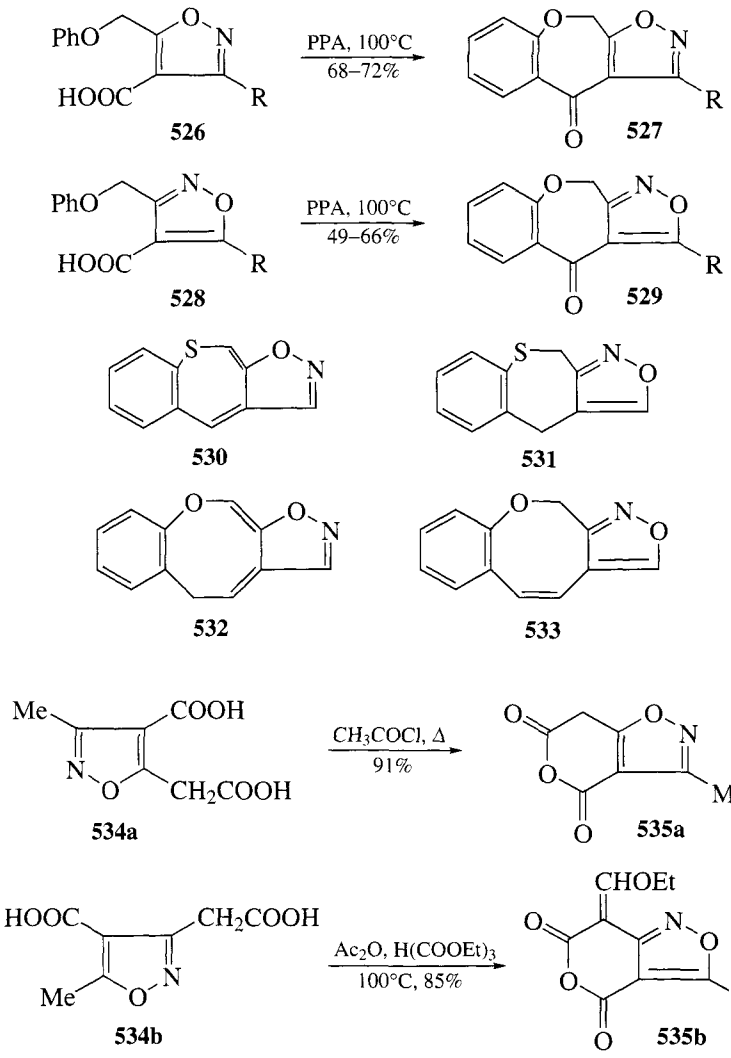


Seven- and eight-membered rings can be constructed by intramolecular electrophilic acylation. Thus 5- or 3-phenoxymethylisoxazole-4-carboxylic acids (**526** and **528**), when heated at 100°C with PPA, gave [1]benzoxepino[4,3-*d*]- and 4*H*,10*H*-[1]benzoxepino[3,4-*c*]isoxazole derivatives **527** and **529**, respectively.[17/85]

Through the same route, derivatives of [1]benzothiepino[4,3-d]isoxazole (**530**),[17/85] 4*H*,10*H*-[1]benzothiepino[3,4-*c*]isoxazole (**531**),[17/85] 5*H*-[1] benzoxoci no[4,3-*d*]isoxazole (**532**),[14/86] and 11*H*-[1]benzoxocino[3,4-*c*]isoxazole (**533**)[14/86] were also obtained.

An obvious approach to the 4*H*-pyrano[3,4-*d*]isoxazole ring was the cyclization of the isoxazole bicarboxylic acid **534a** into its anhydride **535a**.[4/89] With some slight modifications, the same route was used to synthesize the 4*H*-pyrano[4,3-*c*]isoxazole derivative **535b** from **534b**.[6/86]

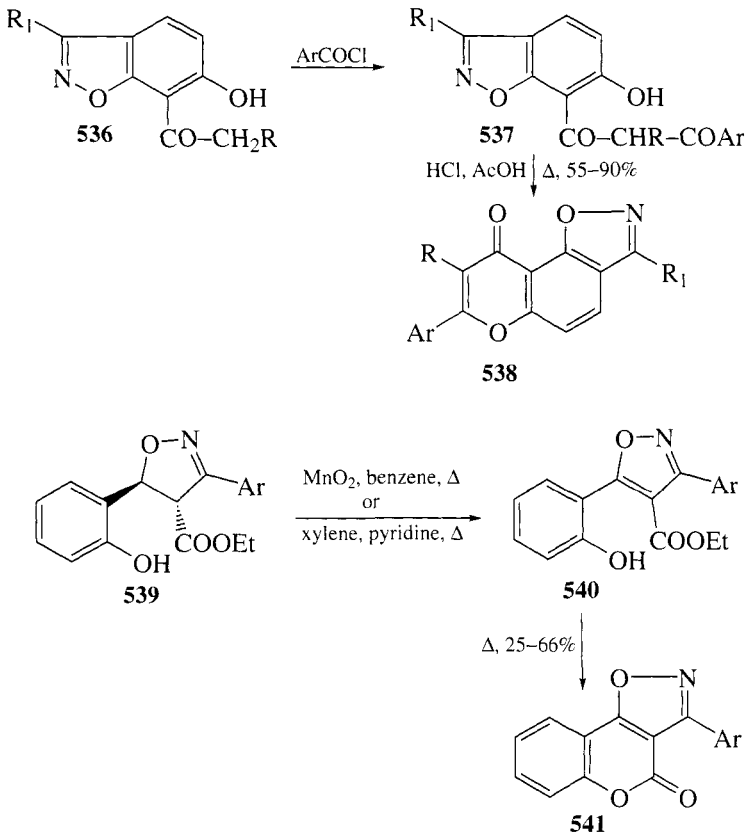
A derivative of the 4*H*-pyrano[4,3-*c*]isoxazole ring system has also been obtained by intramolecular acylation of both 3-isobutenylisoxazole-4-carboxylic acid and 4-acetyl-3-isobutenyl-isoxazol-5-one,[7/84] whereas a derivative of 6*H*-pyrano[3,2-*d*]isoxazole was reported to be obtained from 5-amino-3-phenylisoxazole and acrylonitrile or ethyl acrylate.[2/83]



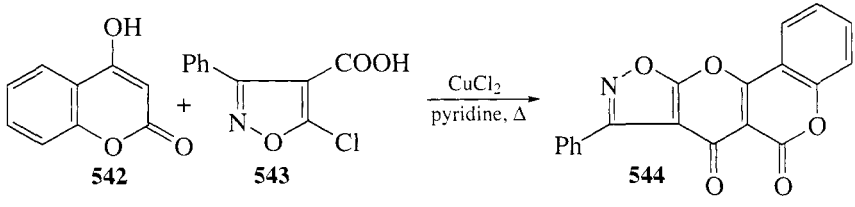
The synthesis of 7*H*- or 9*H*-pyrano[2,3-*g*]-1,2-benzisoxazole derivatives has been approached from 7-acyl-6-hydroxy-1,2-benzisoxazoles **536**, which were transformed into the acetoacyl derivatives **537** and finally cyclized to **538** under acidic conditions.[8/73,19/77] The same ring system was synthesized from the corresponding aldehyde under the conditions of the Perkin condensation.[6/77]

The isoxazolinic cycloadducts **539** (obtained from an aryl nitrile oxide and ethyl *o*-hydroxycinnamate) are good starting materials for the synthesis of 4*H*-[1]benzopyrano[3,4-*d*]isoxazole derivatives (**541**), via oxidation to isoxazoles **540** and cyclization.[15/90]

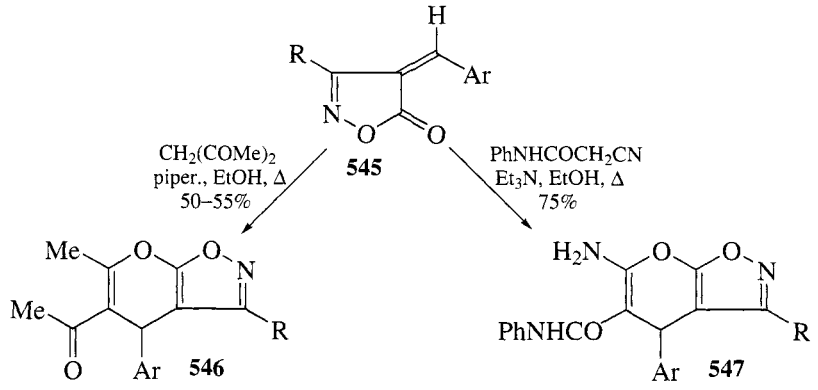
4-Hydroxycoumarin **542** and 3-phenyl-5-chloroisoxazole-4-carboxylic acid **543** underwent cyclocondensation in refluxing pyridine in the presence of



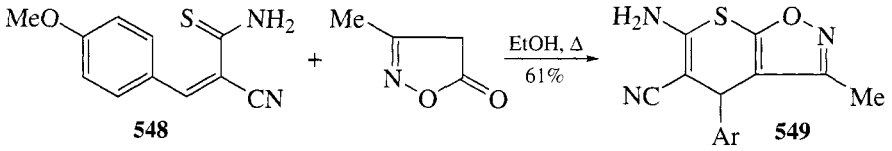
copper(II) chloride. On the basis of its spectral data, the product was identified as the 6*H*,7*H*-[1]benzopyrano[3′,4′:5,6]pyrano[3,2-*d*]isoxazole derivative **544**.[17/75]



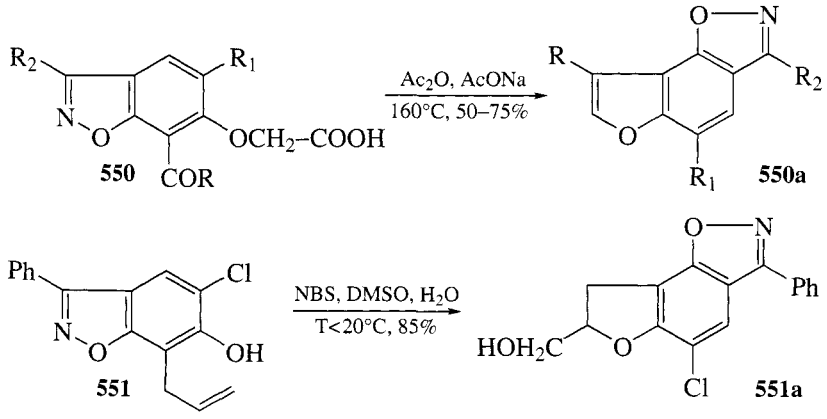
A useful approach to 4*H*-pyrano[3,2-*d*]isoxazoles involves the cyclocondensation of 4-arylidene-5-isoxazolones **545** with active methylene compounds, such as acetylacetone[12/75] and *N*-phenylcyanacetamide,[17/83] under basic conditions. A Michael-type addition of the anion, followed by the ring closure on COMe or CN, gave **546** and **547**, respectively.

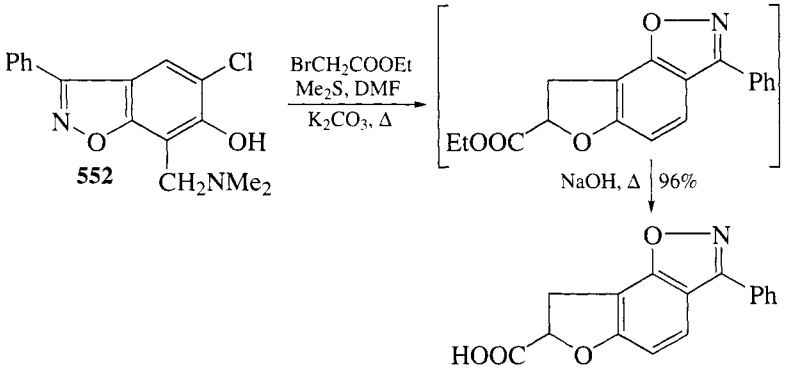


A similar mechanism could be involved in the reaction of 3-methylisoxazol-5-one with 2-thiocarbamoyl cinnamonitrile **548**.[22/87] Michael-type addition of the isoxazolone onto the β position of the α,β-unsaturated thiocarbonyl system, followed by ring closure, can give rise to the 4*H*-thiopyrano[3,2-*d*]isoxazole derivative **549**, one of the few sulfur heterocycles built fused to the isoxazole ring.



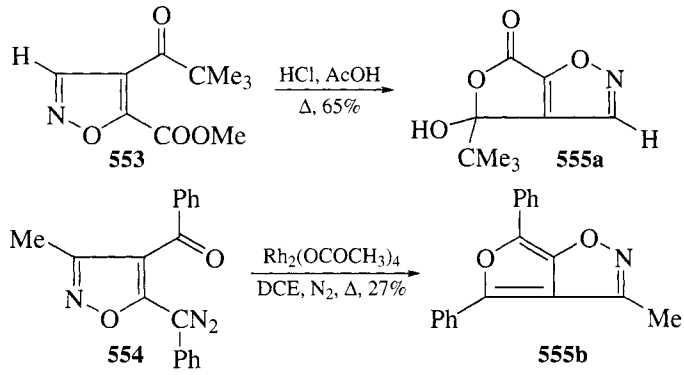
Furo[2,3-*g*]-1,2-benzisoxazole derivatives (**550a**) are frequently synthesized by cyclization of 7-acyl-1,2-benzisoxazole-6-oxyethanoic acids (**550**) in refluxing acetic anhydride (Kostanecki–Tamber method).[5/77,19/80] Similarly, 7-allyl-6-hydroxy-1,2-benzisoxazole **551** has been cyclized to **551a** with the aid of





NBS[12/89,13/89] while 7-dimethylaminomethyl-6-hydroxy-1,2-benzisoxazole **552** reacts with ethylbromoacetate to give the desired product **552a**.[14/89]

Furan ring formation is the key step in the synthesis of furo[3,4-*d*]isoxazole derivatives **555** under standard conditions from **553**,[17/91] using a metal-catalyzed nitrogen extrusion from diazo compound **554**.[1/91] Quantum-mechanical calculations were performed on the ground and excited states of both **555b** and the unsubstituted parent compound.



3.2.2.8. Synthesis of the Condensed Heterocycles by Pericyclic Reactions

The bond lengths (in angstroms) of **555b** have been determined by ab initio quantum-chemical calculations on the parent compound in the ground state[1/91] (Fig. 3.3).

The π-electrons in the furan ring are highly localized; hence they are expected to behave as a diene and to undergo facile Diels–Alder reactions. On treatment with $Rh_2(OAc)_4$, the diazo compound **556** reacts with dipolarophiles, such as *N*-benzylmaleimide (NBMI) or dimethyl acetylenedicarboxylate (DMAD), to

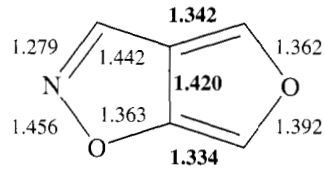
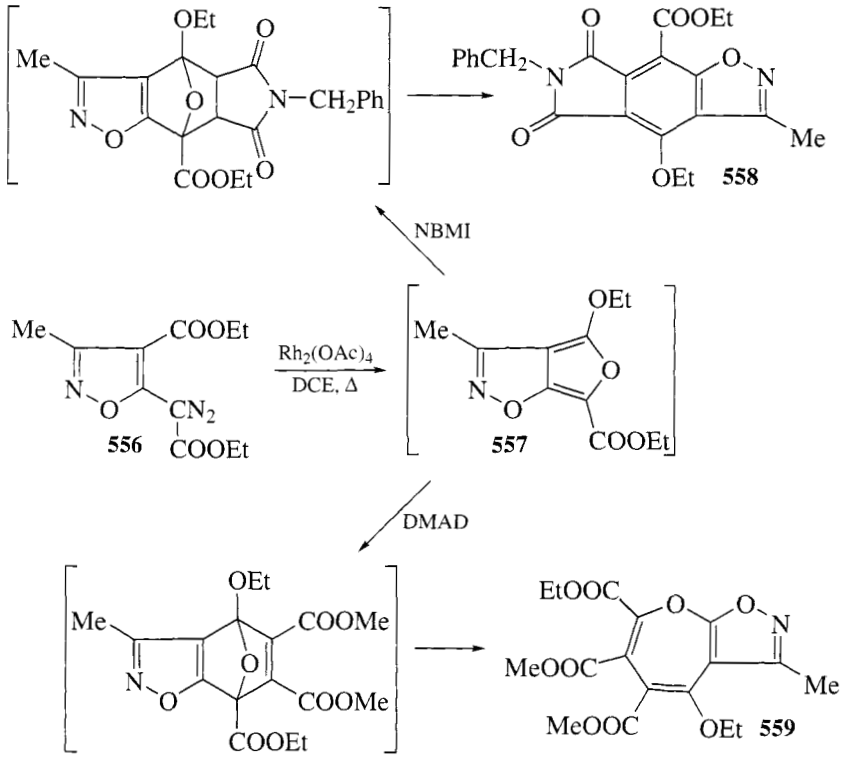


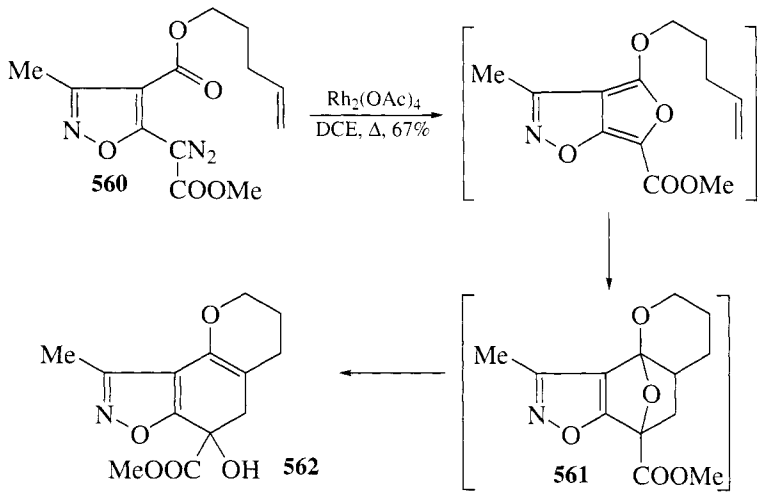
Figure 3.3. Bond lengths in the ground state off furo[3,4-*d*]isoxazole, calculated by ab initio quantum-chemical calculations.

give a derivative of 5*H*-pyrrolo[3,4-*f*]-1,2-benzisoxazole (**558**) and **559**, a derivative of oxepino[3,2-*d*]isoxazole.[15/91] The reaction is believed to proceed via reaction of the transient furo[3,4-*d*]isoxazole **557**, formed *in situ*, to give highly strained cycloadducts that undergo bridge opening to afford the final products.

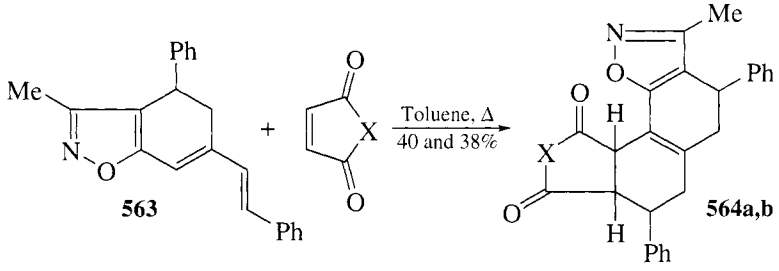


When decomposed under the standard conditions,[4/89] diazo compound **560** is presumed to give rise to cycloadduct **561**, which suffers bridge opening to ultimately afford a derivative of 2*H*-pyrano[2,3-*e*]-1,2-benzisoxazole (**562**).

It is well known that electron-rich dienes prefer electron-poor dienophiles since the reaction, which is under FMO control, involves the $HOMO_{diene}$–

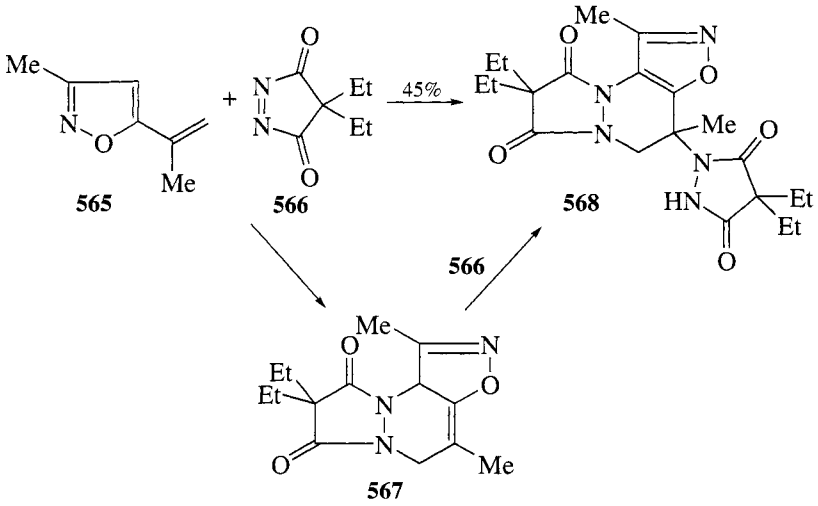


$LUMO_{dienophile}$ interaction. These are the so-called DA reactions with direct electron demand; examples include the reaction of 6-styryl-4,5-dihydro-1,2-benzisoxazole **563** with maleic anhydride (X=O) and *N*-phenyl maleimide (X=N Ph). The products thus obtained[11/73] are derivatives of isobenzofuro[5,4-*g*]-1,2-benzisoxazole and 4*H*-isoindolo[5,4-*g*]-1,2-benzisoxazole ring systems—**564a** (X = O) and **564b** (X = NPh), respectively—with the configurations unknown.

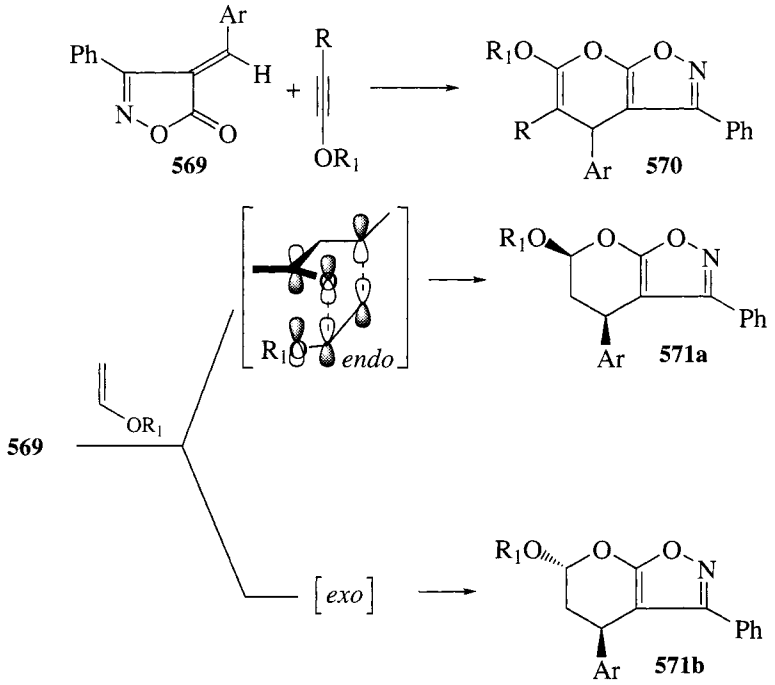


In an interesting sequence of reactions, 5-isopropenyl-3-methylisoxazole **565** and 4,4-diethyl-pyrazolin-3,5-dione **566** give rise to adduct **568**.[11/88] It is presumed that the product of a direct electron-demand Diels–Alder reaction affords an intermediate cycloadduct (**567**) that undergoes an ene reaction with a second equivalent of the dipolarophile to give the product **568**, a derivative of 7*H*-isoxazolo[4,5-*c*]pyrazolo[1,2-*a*]pyridazine.

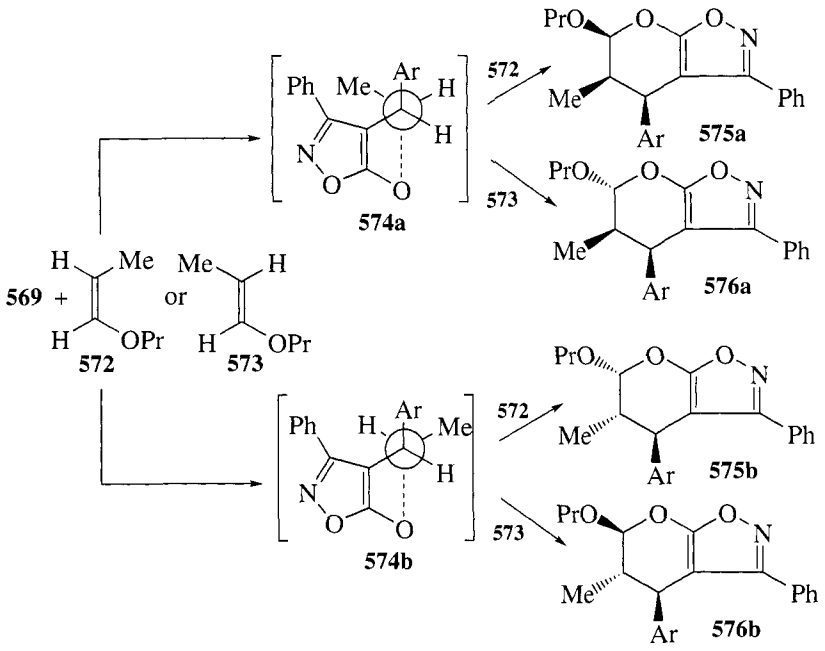
If the diene component is electron-poor, it reacts easily with an electron-rich dienophile and the DA reaction is controlled by the interaction: $HOMO_{dienophile}$–$LUMO_{diene}$. Reactions of this type are said to be governed by inverse electron demand.[6/75]



Examples of this class are the reactions between 4-arylidene-5-isoxazolones, which react in the *E* configuration (**569**), and alkenyl or alkynyl ethers. With the latter as dienophiles, a single 4*H*-pyrano[3,2-*d*]isoxazole derivative **570** is obtained,[2/71] but with ethenyl ethers two adducts, **571a** and **571b**, are obtained. The main product, the *cis* isomer **571a**,[3/70,1/71] arises as result of the favorable MO "nonbonding" interaction in the *endo* transition state.[7/66,2/68,6/75]



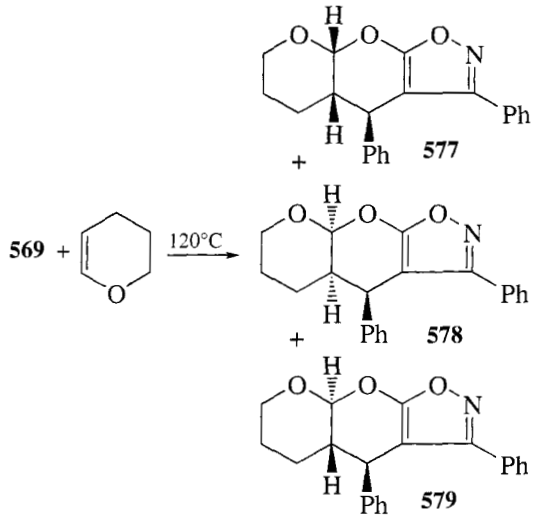
With *cis*- and *trans*-propenylpropyl ethers (**572** and **573**, respectively), the direction of nucleophilic attack dictates the relative configuration at the 4 and 5 positions. The most congested transition state **574a** always gives the minor isomers **575a** and **576a**; thus the main products **575b** and **576b**, with a 4,5-*trans* relationship, are those that derive from the less crowded transition state **574b**.[2/71]

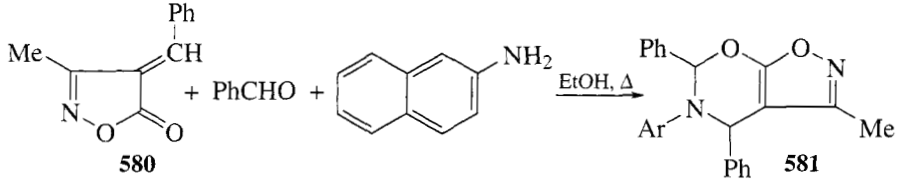


All the vinyl ethers shown above retain the initial configuration of their substituents in the adducts. This behavior, which corresponds to the so-called *cis* principle in the DA reaction, is in part violated when the vinyl ether is dihydropyran. From **569** three products are obtained, all of which are derivatives of the 4*H*,5*H*-pyrano[3′,2′:5,6]pyrano[3,2-*d*]isoxazole ring system.[7/72] Of these, **577** and **578** retain the *cis* configuration, while **579** has a [4a,8a-*trans*] configuration that suggests a transition state with a strong dipolar character.

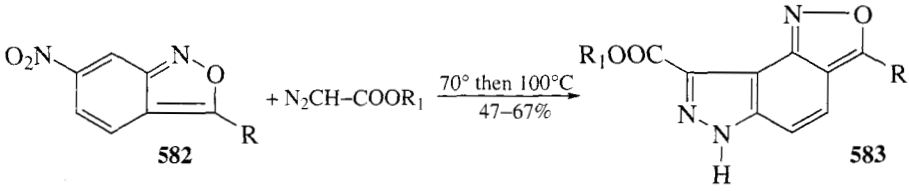
A forerunner in the field of hetero-DA reactions was probably Betti,[1/15] who, in 1915, performed the reaction between 3-methyl-4-benzylidene-5-isoxazolone **580**, benzaldehyde, and 2-naphthylamine. The 4*H*-isoxazolo[4,5-*e*]-1,3-oxazine derivative **581** can be regarded as the product of a hetero-DA reaction between **580** and the Schiff base formed *in situ* from benzaldehyde and 2-naphthylamine.

1,3-Dipolar cycloadditions with heterocyclic double bonds behaving as dipolarophiles could be useful routes to condensed ring systems, although there is a limitation imposed by the lower reactivity that accompanies the increasing aromatic character of the heterocycle.





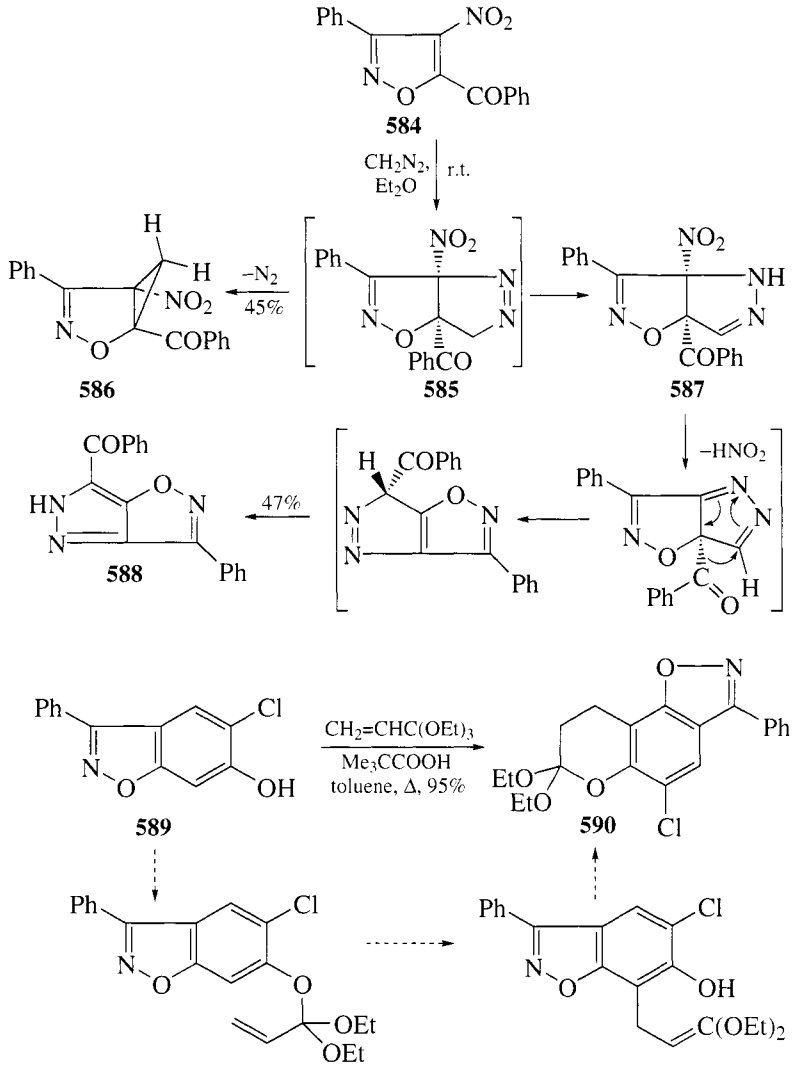
6-Nitro-2,1-benzisoxazoles **582** react with diazo acetates regioselectively at the C6–C7 bond. The loss of nitrous acid from the resulting adducts gives the 6*H*-pyrazolo[3,4-*g*]-2,1-benzisoxazole derivatives **583** in good yields.[8/82]



The C4–C5 double bond of 5-benzoyl-4-nitro-3-phenylisoxazole **584** reacts regioselectively with diazomethane.[1/88] The intermediate, **585**, can undergo either nitrogen extrusion to give **586** or a Dimroth rearrangement, affording the unstable but spectroscopically identified isoxazolinic adduct (**587**). The subsequent loss of nitrous acid, followed by a [1,5]-sigmatropic shift and a second Dimroth rearrangement, ultimately affords the 6-benzoyl-3-phenyl-5*H*-pyrazolo[3,4-*d*]isoxazole **588**.

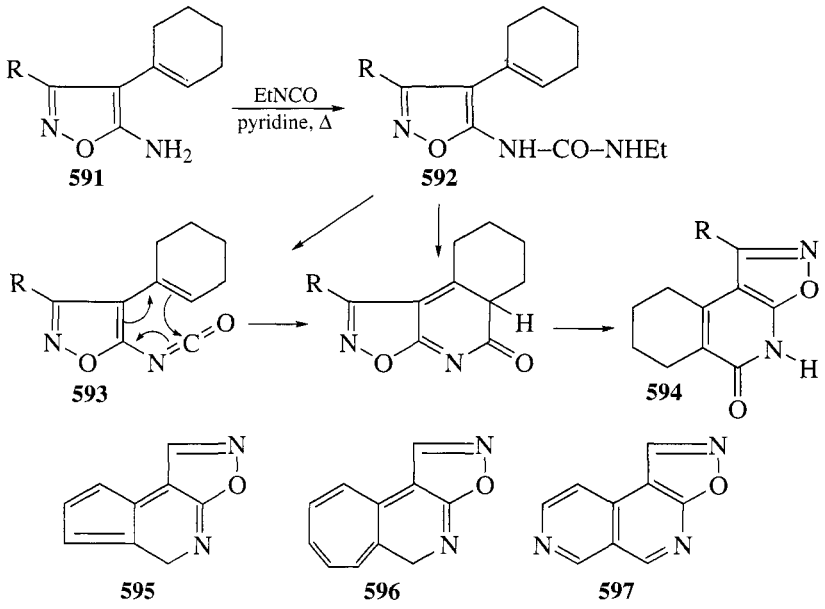
An example of a sigmatropic rearrangement is provided by the reaction of 5-chloro-6-hydroxy-3-phenyl-1,2-benzisoxazole **589** and triethyl orthopropeno-

ate. These reagents, in the presence of pivalic acid, gave 7*H*-pyrano[2,3*g*]-1,2-benzisoxazole derivative **590**, probably through the Claisen rearrangement illustrated below.[13/89]



This section concludes with an example that can be regarded as a 6π-electrocyclic reaction. A series of ring systems, related to condensed isoquinoline, were synthesized from 5-amino-4-cycloalkenylisoxazoles (**591** is the cyclohexenyl derivative) and ethyl isocyanate.[21/83,15/84] The intermediate urea **592**, which can be isolated when pyrazole is the starting product, can give the isoxazolo[5,4-*c*]isoquinoline derivative **594** either by direct ring closure or by loss of amine and

6π-electrocyclic reaction of the isocyanate **593**. This route would seem to represent a flexible methodology in as much as, in addition to the preceding ring system, derivatives of 5*H*-cyclopent[*d*]isoxazolo[5,4-*b*]pyridine **595**, 5*H*-cyclohept[*d*]isoxazolo[5,4-*b*]pyridine **596**, and isoxazolo[5,4-*c*]-2,7-naphthyridine **597** were obtained.[21/83,15/84]

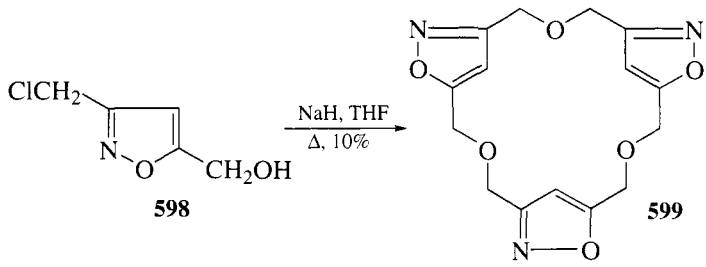


3.2.2.9. Syntheses of Supramolecular Devices

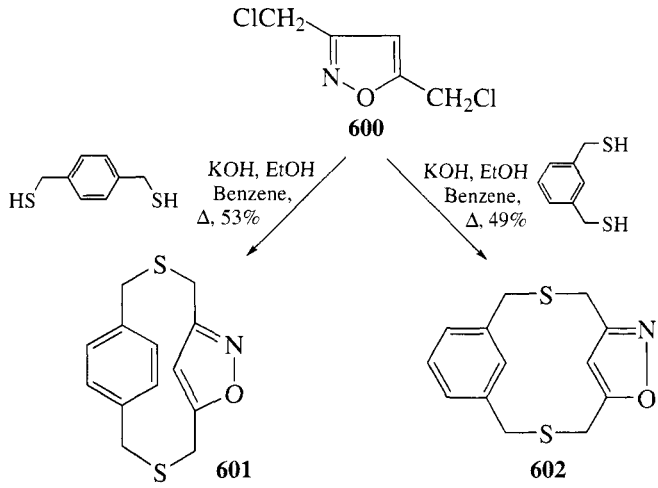
This topic is becoming increasingly popular for the fascinating character of borderline research between the traditional chemical fields. Some syntheses, characterized by the construction of the isoxazole ring, have been reviewed in § 3.2.1.4. The opposite approach starts from simple isoxazolic units, and the supramolecular device is then assembled by formation of bonds incorporating the suitable heteroatoms.

The first synthesis was developed by Alberts and Cram,[8/79] and the cyclotrimerization of 3-chloromethyl-5-hydroxymethylisoxazole **598** gave 3,6,10,13,17,20-hexaoxa-7,14,21-triazatetracyclo[17.2.1.1^{5,8}.1^{12,15}]tetracosa-5(24),7,12(23),14,19(22),21-hexaene **599**. This route was abandoned as a result of the unpleasant dermatological properties of both the starting material (1,2-dichloroacetaldehyde oxime) of isoxazole **598** and the isoxazole itself.

A somewhat similar starting product, 3,5-bis(chloromethyl) isoxazole **600** (dermatogically less dangerous since reagents were 1,5-dichloropentane-2,4-dione and hydroxylamine), cyclized with *m*- or *p*-xylenedithiols to give very

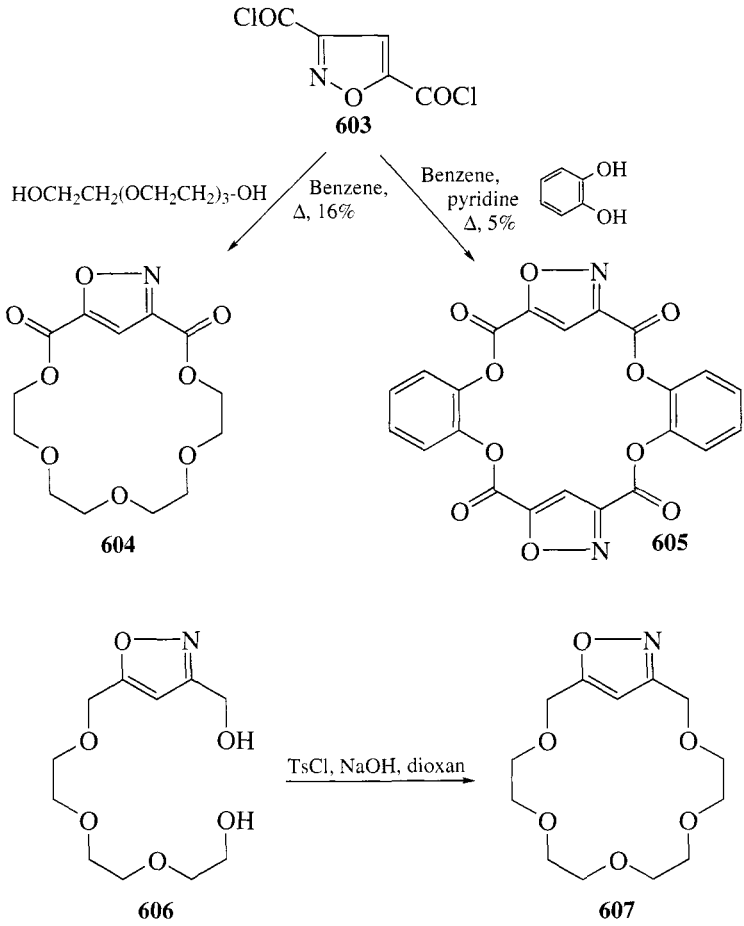


good yields, for this field, of 6-oxa-3,10-dithia-7-azatricyclo[10.2.2.1^{5,8}] heptadeca-5(17),7,12,14,15-pentaene **601** and 6-oxa-7,10-dithia-7-azatricyclo [10.3.1.1^{5,8}]heptadeca-1(6),5(17),7,12,14-pentaene **602**.[14/83] Some by-products were obtained in both this and the previous reaction, but these were not fully characterized.



The reactions of isoxazole-3,5-dicarbonylchloride **603** with dihydroxy derivatives[17/81] are examples of ester bond formation as a tool in supramolecular chemistry. For strain reasons, whereas tetraethylene glycol gave 3,6,9,12,15,18-hexaoxa-19-azabicyclo[15.2.1]eicosa-17(20),19-diene-2,16-dione **604** (with reagents ratio 1:1), pyrocatecol gave 6*H*,18*H*-10,7:22,19-dimetheno-11*H*,23*H*-dibenzo[*f*,*p*][1.5.8.11.15.18.2.12]hexaoxadiazacycloeicosine-6,11,18,23-tetrone **605**, with reagents in the ratio 2:2 as determined by mass spectroscopy.[17/82]

The last approach involves a ring closure of the macrocycle by nucleophilic displacement of a tosyl group introduced *in situ* on **606**. Thus 3,6,9,12,15,18-hexaoxa-1-azabicyclo[15.2.1]eicosa-17(20),19-diene **607** was obtained and its crystal structure determined by X-ray analysis.[13/83] The conformation in the solid state has the C4 position of the isoxazole inside and the N–O linkage outside, presumably in order to minimize the energy strain of the macrocycle.



3.3. CHEMICAL PROPERTIES

Heterocyclic rings exhibit specific types of chemical reactivity that may be ascribed to the general behavior of electron-rich or electron-poor heterocycles, although some modes of reactivity are specific for each ring.

In this context, isoxazole is an electron-rich heterocycle with some specific characteristics, such as a weak N–O bond that can be easily cleaved, which confer on it wide utility in synthesis.

For condensed heterocyclic systems that contain an isoxazole ring, the overall reactivity can be summarized by classifying the reactions as involving either the isoxazole or the second ring. Some reactions are trivial and follow the principles of basic organic chemistry or adhere to the generally accepted behavior of the single, isolated heterocycle.

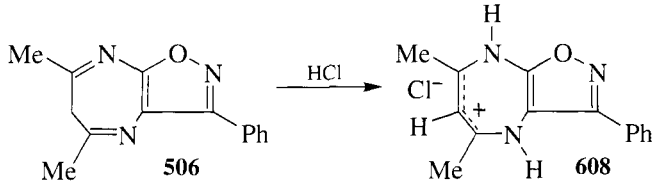
In some instances a synergistic interaction is produced by both components of the condensed ring system, and unique chemical behaviors may then result.

The effort to achieve a comprehensive review requires the acknowledgment of trivial reactions as well as original examples of specific reactivity. As far as possible, we will focus on these latter examples.

3.3.1. Properties of the Heterocycle Condensed to Isoxazole

3.3.1.1. Protonation and Quaternization

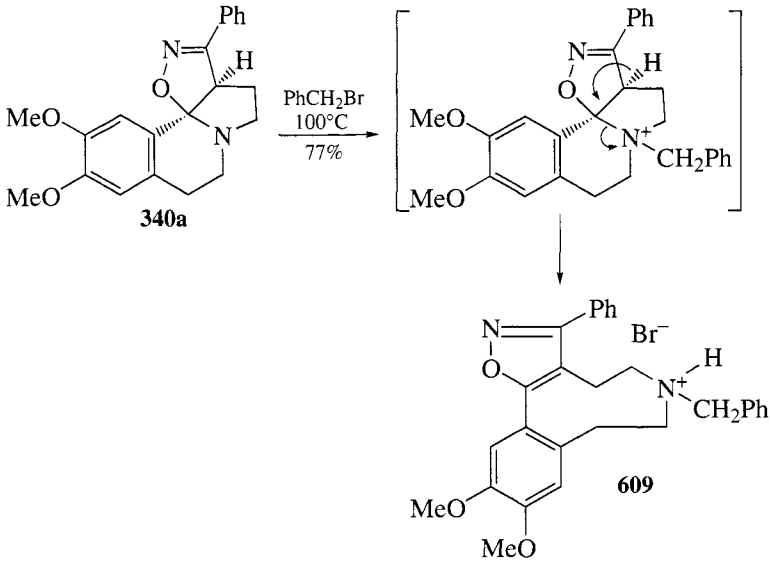
Isoxazoles are weak bases that do not readily undergo protonation. If isoxazole is condensed to a heterocycle with a basic nitrogen atom, protonation can involve this center. When 6*H*-isoxazolo[4,5-*b*]-1,4-diazepine **506** is dissolved in methanolic HCl, a deep violet-blue color develops, due to the formation of the isoxazolodiazepine cation **608**.[1/70] Its λ_{max} at 548 nm is not far from the reported absorbance of the analogous benzodiazepinium cation[4/59] and supports this assignment.

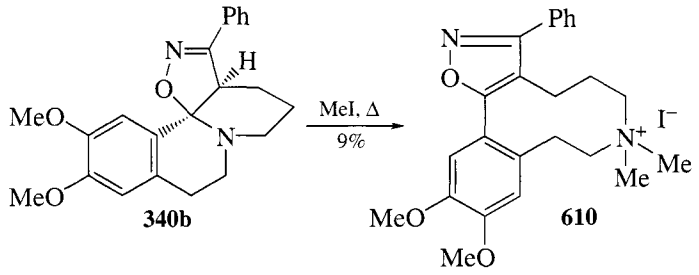


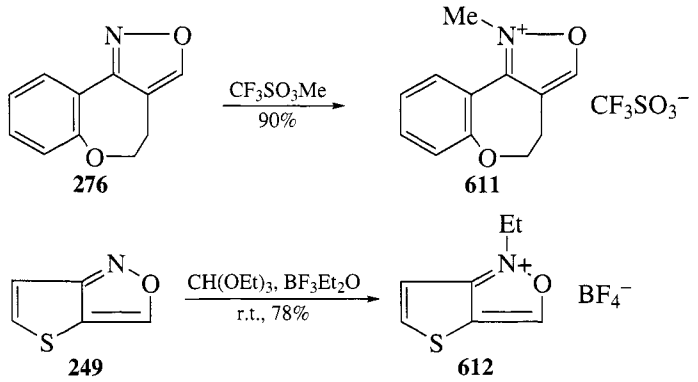
A similar result was obtained by heating **340a** with benzyl bromide. Under conditions that cause rearrangement to condensed azamacrocycles (see § 3.2.1.6), alkylation of the more nucleophilic nitrogen atom ultimately gives 6-benzyl-10,11-dimethoxy-3-phenyl-5,6,7,8-tetrahydro-6*H*-isoxazolo[4,5-*f*]-3-benzazonine hydrobromide **609**, in good yield.[14/91]

Although the formation of isoxazolium salts from isoxazoles on treatment with alkylating agents is a well-known reaction, when a basic nitrogen center exists in the adjacent heterocycle, this is quaternized instead. An example of this is the reaction of **340b** in refluxing MeI.[14/91] Even the efficiency of the overall conversion is disappointing; 4*H*-isoxazolo[4,5-*g*]-3-benzocinium iodide **610** is the only product isolated.

In the absence of any basic nitrogen atoms, alkylation occurs at the isoxazole ring, as in the case of 1-benzoxepino[5,4-*c*]isoxazole derivative **276**, which reacted with CF_3SO_3Me to give 1-methyl isoxazolium salt **611** in excellent yield.[19/84] Similarly, thieno[3,2-*c*]isoxazole **249** gives 1-ethyl isoxazolium fluoborate **612**[2/76] with $CH(OEt)_3/BF_3$; this topic will be reviewed more extensively in the next section.


Ph
N
O
H
MeO
MeO
N
340a
PhCH2Br
100°C
77%
Ph
N
O
H
MeO
MeO
N+
CH2Ph
Ph
N
O
Br−
H
N+
CH2Ph
MeO
MeO
609

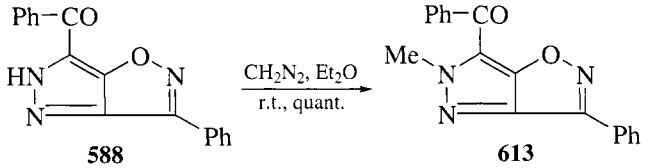

Ph
N
O
H
MeO
MeO
N
340b
MeI, Δ
9%
Ph
N
O
I−
N+
Me
Me
MeO
MeO
610


N
O
O
276
CF3SO3Me
90%
Me
N+
O
O
CF3SO3−
611
N
O
S
249
CH(OEt)3, BF3Et2O
r.t., 78%
Et
N+
O
S
BF4−
612

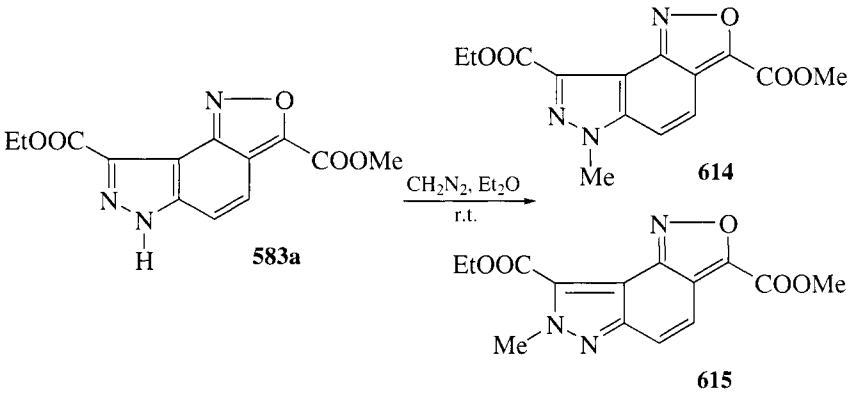
3.3.1.2. Alkylations and Acylations

These reactions, closely related to those reviewed in the previous section, deal with the reactions of condensed heterocycles and alkylating (or acylating) agents. Again the formation of isoxazolinium salts could conceivably occur with similar reagents, but if more nucleophilic heteroatoms are present in the condensed ring, alkylation or acylation takes place at these sites.

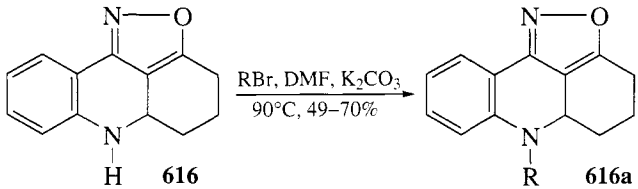
When 6-benzoyl-3-phenyl-5*H*-pyrazolo[3,4-*d*]isoxazole **588** is allowed to react with diazomethane, the 5-methyl derivative **613** is obtained in quantitative yield.[1/88]



Occasionally with condensed pyrazoles, regioisomeric monomethyl derivatives are obtained. Thus **583a** gave 6-methyl and 7-methylpyrazolo[3,4-*g*]-2,1-benzisoxazoles (**614** and **615**); the former was the main reaction product.[8/82]



Several alkylations that involve allyl or benzyl halides have been reported.[14/87] In one such example 3*H*-isoxazolo[5,4,3-*k*,*l*]acridine derivative **616** was converted to **616a** (R = $CH_2CH=CH_2$, CH_2Ar).[14/90,20/90]

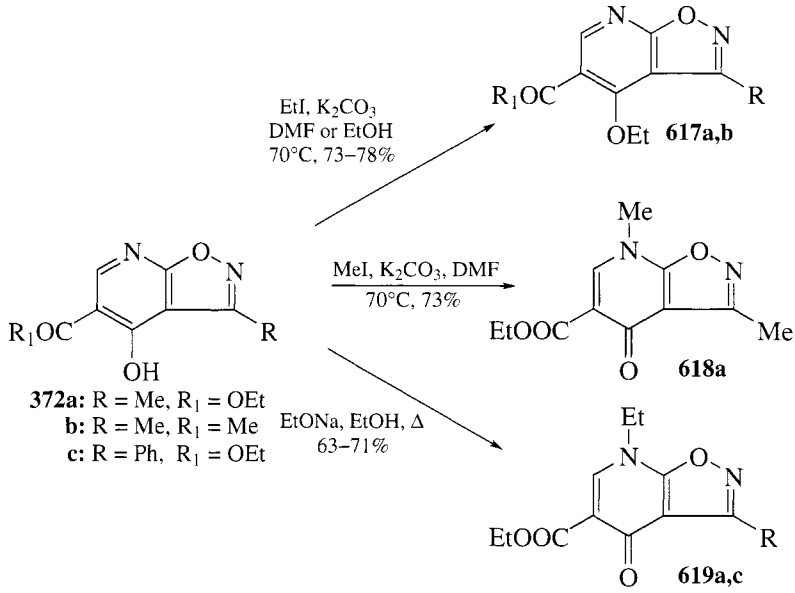


Among the ring systems that may be condensed to isoxazole, heterocycles for which a tautomeric equilibrium exists have frequently been used as substrates for reactions with alkylating agents.

The regiochemical outcome of reactions of pyridone with electrophiles is dictated by the nature of the alkylating or acylating reagent and the conditions under which the corresponding anion is generated. Sodium and potassium salts predominantly undergo *N*-alkylation, diazomethane gives mainly *O*-alkylation, and acylation prefers the *O*-center.[15/85]

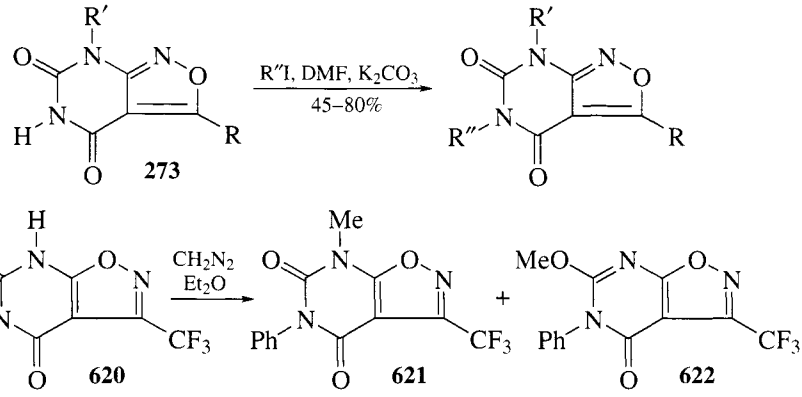
In the 1970s, Denzel and co-workers[1/72,9/72,10/72,16/73,20/73,4/74,10/75,11/75] reported that alkylation of ethyl 4-hydroxyisoxazolo[5,4-*b*]pyridine-5-carboxylates (**372a**: $R_1 = OEt$) and the analogous 5-acetyl derivatives (**372b**: $R_1 = Me$) with ethyl iodide in DMF or EtOH and K_2CO_3 gave good yields of the *O*-alkylated products (**617a,b**). Under the same experimental conditions, however, methyl iodide gave the *N*-methyl derivative **618a**.

In 1988, Chiarino and co-workers,[2/88] in order to synthesize potential antimicrobical agents, sought to obtain the *N*-ethyl derivatives of both **372a** and its phenyl analog **372c**. To avoid the tendency toward *O*-ethylation in aprotic media, they conducted the reaction in a solvent that would permit hydrogen bonding with the β-ketoester fragment. Their choice of ethyl iodide in EtOH, in the presence of sodium ethoxide, proved effective and led to formation of the *N*-ethyl products **619a,c** in good yields.

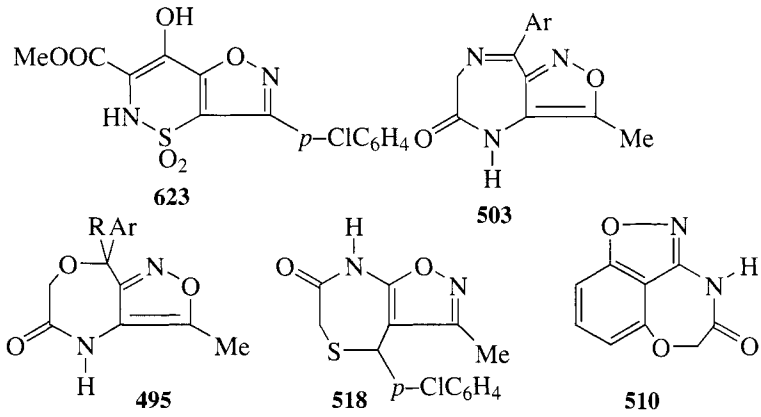


This example shows the paramount importance of the solvent in governing the choice between *O*- and *N*-alkylation, but again it is hard to rationalize *O*-ethylation versus *N*-methylation of **372a**, observed by the German group under identical experimental conditions.

Further examples from the literature include the exclusive *N*-alkylation of 7-alkylisoxazolo[3,4-*d*]pyrimidin-4,6-dione **273** with methyl or ethyl iodide[18/77] and the behavior of 3-trifluoromethyl-5-phenylisoxazolo[5,4-*d*]pyrimidine-4,6-dione **620**, which gave both *N*-methyl and *O*-methyl derivatives (**621** and **622** in 42% and 21% yields, respectively) with diazomethane.[11/86]

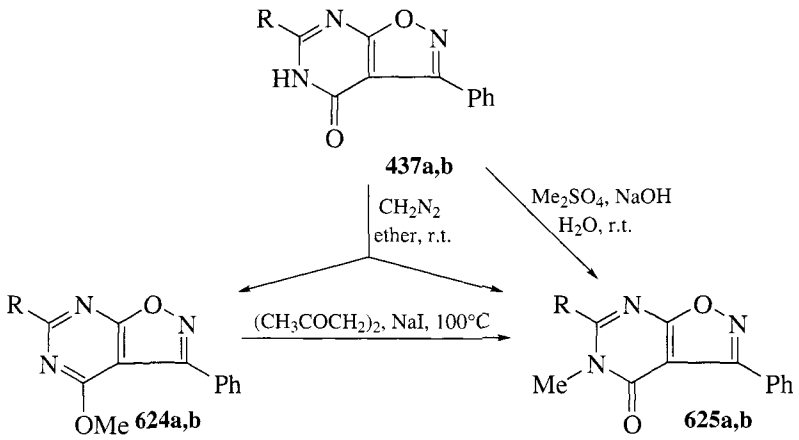


Exclusive *N*-alkylation was observed on 5*H*-isoxazolo[5,4-*e*]-1,2-thiazine (**623**),[2/89] 4*H*-isoxazolo[4,3-*e*]diazepine (**503**),[14/85] 4*H*,8*H*-isoxazolo[4,3-*e*]-1,4-oxazepine (**495**),[10/89] isoxazolo[5,4-*e*]-1,4-thiazepine (**518**),[13/75] and 3*H*-isoxazolo[3,4,5-*e*,*f*]-1,4-benzoxazepine (**510**)[31/89,12/90] derivatives on treatment with alkyl halides or methyl sulfate, a reaction frequently conducted in the presence of a base (NaH or NaOH), with DMF or H_2O as the solvent.

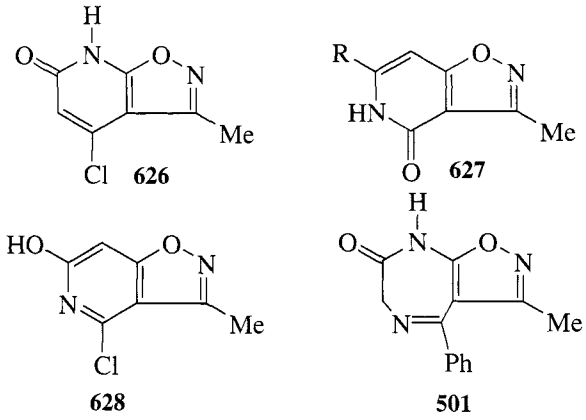


6-Substituted 3-phenyl-isoxazolo[5,4-*d*]pyrimidine-4(5*H*)-ones (**437a**: R = Ph; **437b**: R = Me) were subjected to methylation either with ethereal diazomethane or with dimethyl sulfate in aqueous NaOH.[4/67] Under the former conditions a mixture of *O*-Me (**642a,b**) and *N*-Me (**625a,b**) derivatives was obtained. Methylation with Me_2SO_4 gave *N*-methyl derivatives only. The struc-

tures were subsequently established by chemical conversion in which the *O*-methyl derivatives were obtained by nucleophilic replacement of the corresponding chlorocompounds (see § 3.3.1.6). The *N*-methyl derivatives were then prepared by rearrangement of the *O*-methyl isomers in boiling acetonylacetone and NaI (a well-known protocol in pyrimidine chemistry).[4/67]



A mixture of *N*- and *O*-methyl derivatives was obtained with diazomethane, as an either ethereal or methanolic solution, from isoxazolo[5,4-*b*]pyridine (**626**),[1/77] isoxazolo[4,5-*c*]pyridine (**627** and **628**),[3/75] and 6*H*-isoxazolo[5,4-*e*]-1,4-diazepine (**501**)[1/74] derivatives.

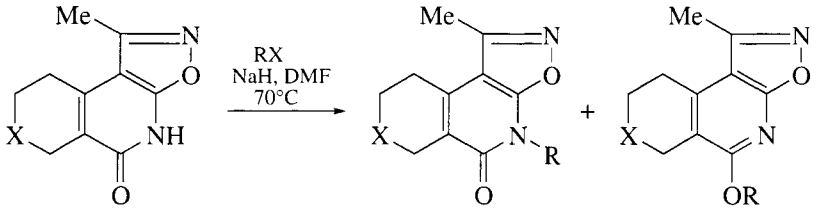


The research of Barone, Winters and co-workers[21/83,17/87] dispels the notion that *N*-alkylation is the sole reaction mode when inorganic salts of the substrate are employed and a mixture of isomers results from treatment with diazomethane. Alkylation of 5*H*-cyclopenta[*d*]isoxazolo[5,4-*b*]pyridine (**629a**: X = –), isoxazolo[5,4-*c*]isoquinoline (**629b**: X = CH_2), 5*H*-cyclohepta[*d*]isoxa-

TABLE 3.3. *N*- VERSUS *O*-ALKYLATION OF **629a–c**

Starting product	X	R	**630** (*N*)%	**631** (*O*)%
629a	—	Et	39	61
629a	—	*i*-Pr	9	91
629b	CH_2	Me	78	22
629b	CH_2	Et	48	52
629b	CH_2	*i*-Pr	11	89
629c	$(CH_2)_2$	Et	38	62
629c	$CH_2)_2$	*i*-Pr	7	93

zolo[5,4-*b*]pyridine [**629c**: X=$(CH_2)_2$], and isoxazolo[5,4-*c*]-2,7-naphthyridine (**629d**: X = N–R) derivatives with alkyl halides and NaH in DMF, gave mixtures of *N*-substituted and *O*-substituted compounds (**630** and **631**). Some significant examples of the *N*/*O* ratio for various substrates are reported in Table 3.3.

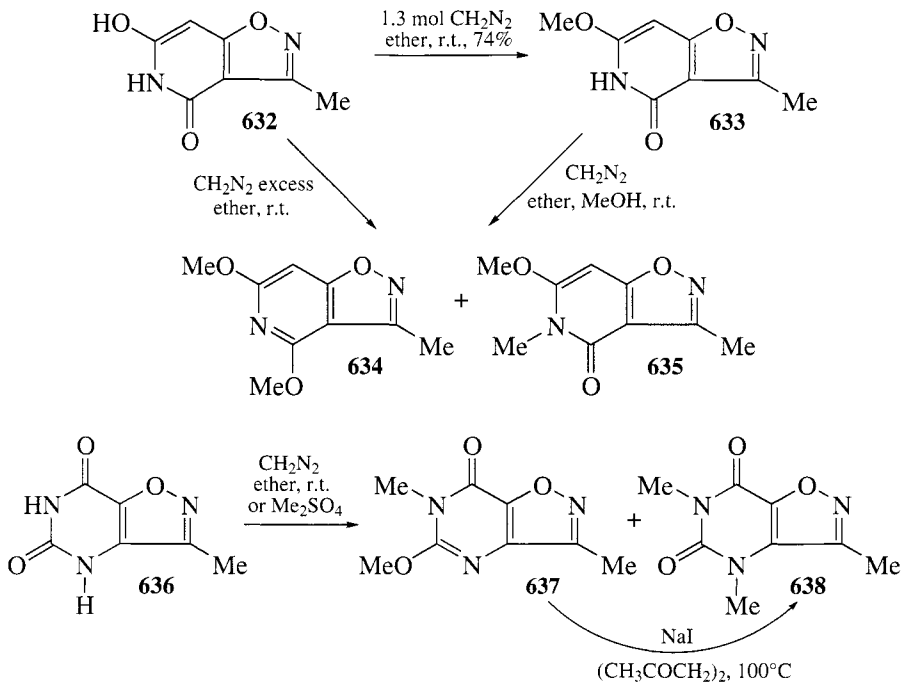


629a-d **630a-d** **631a-d**

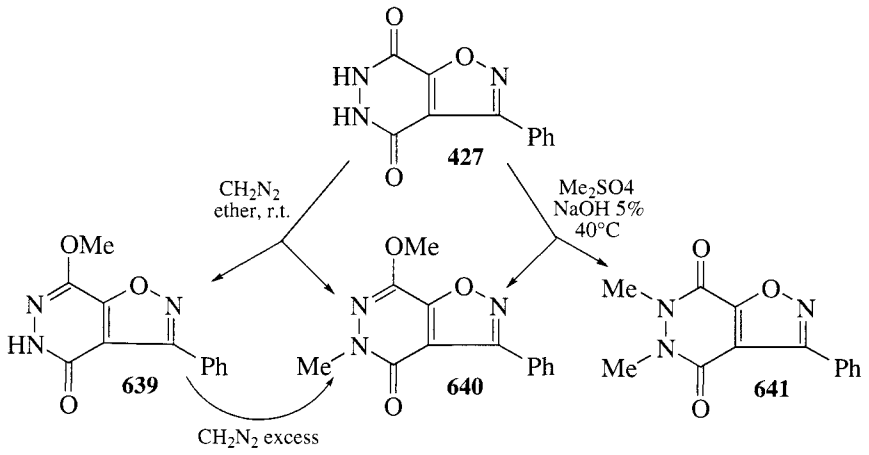
The highest yields of *N*-substituted products were obtained with methyl iodide, whereas a preference for *O*-alkylation increases with the degree of steric hindrance in the alkylating group, and this is a further factor to be taken into account when attempting to rationalize results in this field.

This field would not have been adequately illustrated if two additional topics were not briefly discussed. For isoxazolo-fused heterocycles in which more tautomeric NH- and OH-containing structures exist, the outcome of methylation can be reasonably foreseen. In the solid state 6-hydroxy-3-methylisoxazolo[4,5-*c*]pyridin-4(5*H*)-one (**632**) exists in the hydroxyoxo form, but in solution has significant contribution from the dioxo form, reacts with an excess of diazomethane to afford a mixture of *O*,*O*- and *N*,*O*-dimethylderivatives (**634** and **635**).[3/75] As expected, the initially formed product is the 6-methoxy derivative **633**.

When-phenylisoxazolo[4,5-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione (**636**) was methylated with diazomethane or dimethyl sulfate, a mixture of 5-methoxy-6-methyl- (**637**) and 4,6-dimethyl (**638**) derivatives was obtained.[2/67] The former product (**637**) can be converted into the latter one (**638**) by heating with NaI in acetonylacetone, conditions that also allow conversion of 5,7-dimethoxy-3-methylisoxazolo[4,5-*d*]pyrimidine into **638**.

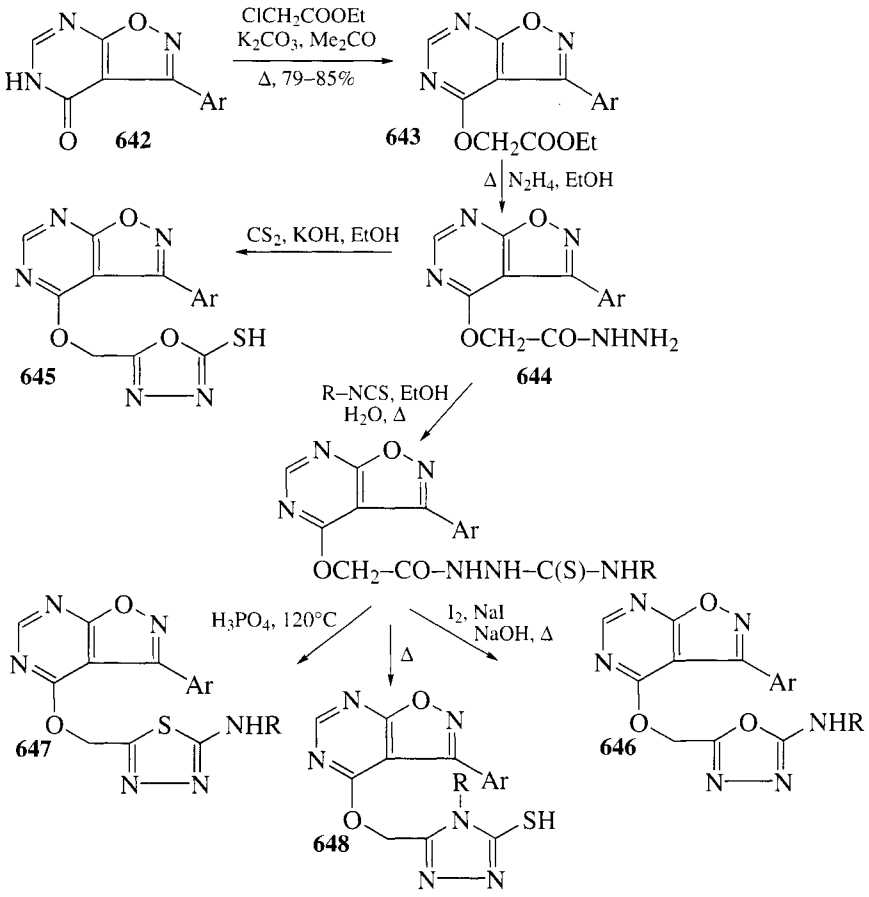


Methylations with diazomethane and with dimethyl sulfate rarely give the same products. When 3-phenylisoxazolo[4,5-*d*]pyridazin-4,7(5*H*,6*H*)-dione (**427**) was treated with diazomethane, the main product, the 7-methoxy derivative **639**, was accompanied by the 7-methoxy-5-methyl derivative **640**. The latter was slowly obtained from **639** with excess of diazomethane.[3/67] The behavior of **427** with dimethyl sulfate was significantly different; the *O*,*N*-dimethyl derivative **640** was obtained together with the *N*,*N*-dimethyl derivative **641** in a 1:1 ratio.



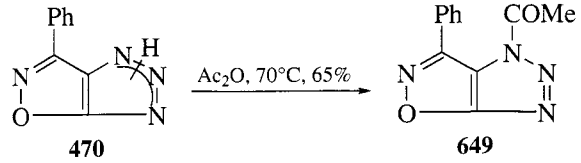
Alkylation may be a useful tool for further elaborations of the condensed isoxazole system, as concisely illustrated by the following example.

3-Arylisoxazolo[5,4-*d*]pyrimidin-4(5*H*)-ones (**642**), with ethyl chloroacetate and K_2CO_3 in refluxing acetone, give excellent yields of the *O*-alkylated products **643** exclusively.[16/88] The newly introduced ester group reacts with hydrazine to give acyl hydrazides **644**, which can serve as the starting products for construction of the following pendant heterocycles: oxadiazoles **645** and **646**, thiadiazoles **647**, and triazoles **648**.



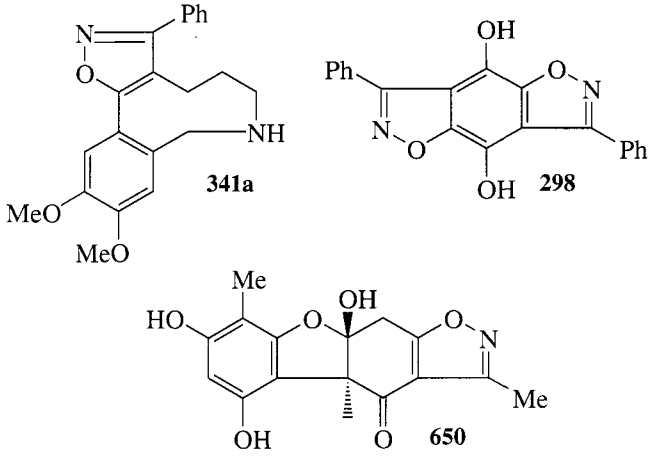
The acylation may be highly regioselective. Among the different possible products that can result from the existence of three NH tautomers, the 1-acetylderivative **649** is the only reaction product of 6-phenylisoxazolo[4,5-*d*]-1,2,3-triazole **470** with acetic anhydride.[1/70]

If the heterocycle condensed to the isoxazole ring has either NH or OH groups, these are easily acylated.[15/87] This has been observed on the NH group of 4*H*-isoxazolo[4,5-*f*]-3-benzazonine derivative **340a**,[14/91] on both OH groups of



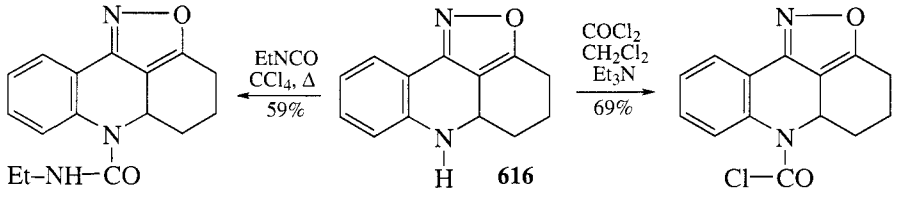
470 **649**

4,8-dihydroxy-3,7-diphenylbenzo[1,2-*d*:4,5-*d'*]diisoxazole **298**,[9/68] and on both phenolic groups of benzofuro[3,2-*f*]-1,2-benzoisoxazole derivative **650** (the third OH group is eliminated as part of a water molecule under the experimental conditions).[9/76]



341a **298** **650**

Acylations have been performed with various reagents and the reactions of 3*H*-isoxazolo[5,4,3-*k*,*l*]acridine derivative **616** with ethyl isocyanate and with phosgene are two good examples.[20/90]



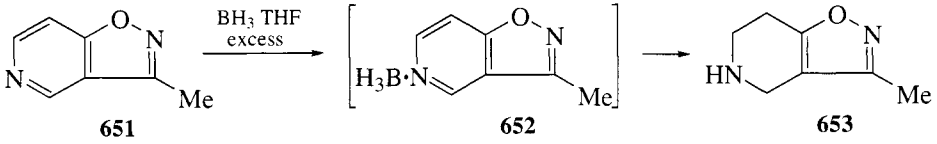
616

3.3.1.3. Oxidation and Reduction

In the synthesis of isoxazolo-fused heterocycles, a subsequent reduction or an oxidation step may be required.

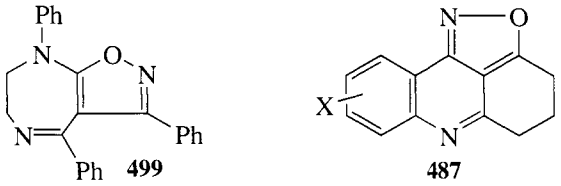
A fully aromatic ring can be reduced, as in the case of 3-methylisoxazolo-[4,5-*c*]pyridine **651**, which reacts with borane–THF complex to give the 4,5,6,7-

tetrahydro derivative **653**.[2/82] Formation of an intermediate complex **652** is prevented by various substituents and causes a different reaction pathway to be followed. This topic will be discussed in § 3.3.2.2c.



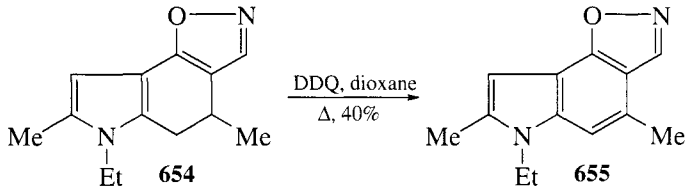
651 **652** **653**

If the heterocycle is partly reduced but retains a C=N double bond, the ring can be fully reduced with $NaBH_4$ or $NaBH_3CN$ as in the case of 6,7,8-trihydroisoxazolo[5,4-*e*]-1,4-diazepine (**499**)[19/91] and 3,4.5-trihydroisoxazolo [5,4,3-*k*,*l*]acridine (**487**)[14/90] derivatives.



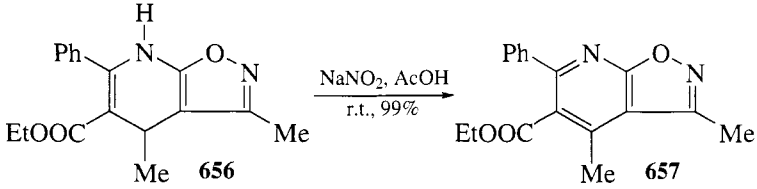
499 **487**

Conversely, a partly reduced heterocyclic ring can be aromatized. Oxidation of 4,5,6-trihydropyrrolo[2,3-*g*]-1,2-benzisoxazole derivative **654** by 5,6-dichloro-2,3-dicyanobenzoquinone (DDQ) affords the 6*H*-aromatic system **655**.[3/71]



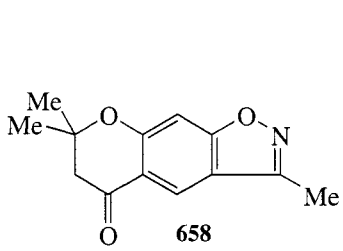
654 **655**

It is well known that dihydroquinolines obtained from the Skraup synthesis can be easily aromatized with oxidating agents. 4,7-Dihydroisoxazolo[5,4-*b*]pyridine **656** was oxidized with $NaNO_2$ in acetic acid, to give the aromatic derivative **657**[6/85] and a similar result was obtained with $KMnO_4$ in acetone.[21/90]

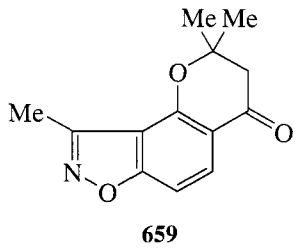


656 **657**

Sites of unsaturation may be introduced in unconventional ways as well. The 7*H*-pyrano[3,2-*f*] and 2*H*-pyrano[2,3-*e*]-1,2-benzisoxazole derivatives were obtained from **658** and **659**, respectively, by reducing the carbonyl groups with $NaBH_4$. Dehydration was then effected using *p*-toluenesulfonic acid in refluxing benzene to give the conjugated double bond.[18/89]

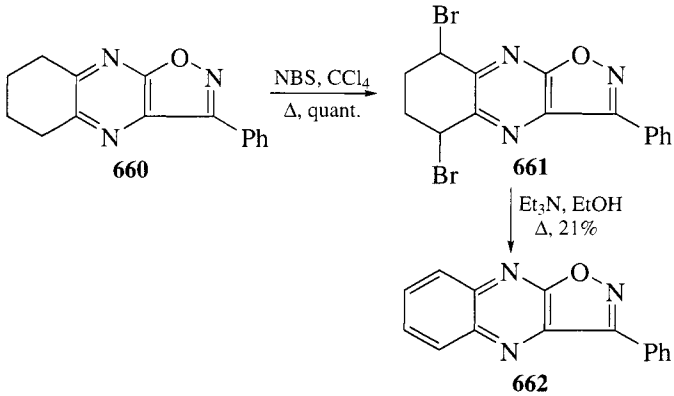


658



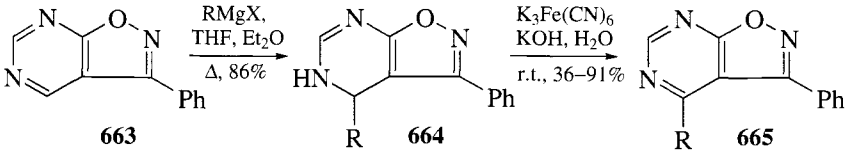
659

The 5,6,7,8-tetrahydroisoxazolo[4,5-*b*]quinoxaline **660** was aromatized by bromination with NBS and dehydrobromination with Et_3N to give **662** through the isolable 5,8-dibromo derivative **661**.[4/68]



660 **661** **662**

A formal sequence of reduction–oxidation of the pyrimidine ring in 3-phenylisoxazolo[5,4-*d*]pyrimidine **663** suggests an elegant way to functionalize the 4 position. Grignard reagents added to the C4–N5 double bond of **663** to give excellent yields of **664**, which, in turn, were oxidized with potassium ferricyanide in basic media, to yield the aromatic products **665**.[4/80]

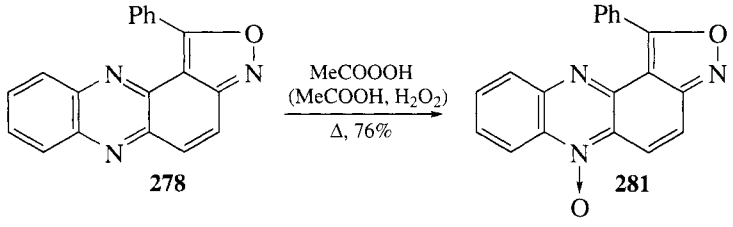


663 **664** **665**

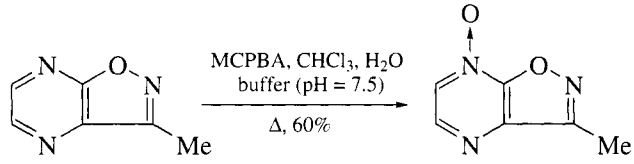
Oxidation or reduction may be confined to individual heteroatoms within the structure. Nitrogen atoms can be oxidized to the corresponding *N*-oxides

or these reduced, while oxidation on sulfur can give sulfoxide or sulfone derivatives.

1-Phenylisoxazolo[4,3-*a*]phenazine **278** and 3-methylisoxazolo[4,5-*b*]pyrazine **666** are oxidized selectively by peracids to give the 6-*N*-oxide **281** (also synthesized by an independent route)[10/68] and the 7-*N*-oxide **667**.[6/73] The observed selectivity is presumed to result from the steric impediment to oxidation at N11 and N4 exerted by the phenyl and methyl groups, respectively.

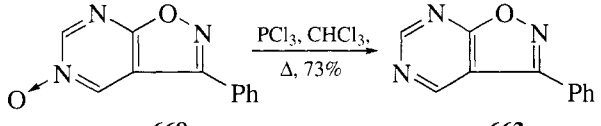


278 **281**

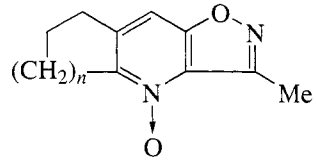


666 **667**

As *N*-oxides usually do, 3-phenylisoxazolo[5,4-*d*]pyrimidine-5-oxide **668**, when heated with phosphorous trichloride in chloroform, is reduced to **663** in a good yield[4/80] similar results were obtained on 4*H*-cyclopent[*b*]isoxazolo-[5,4-*e*]pyrimidine and isoxazolo[4,5-*b*]quinoline-4-oxide derivatives (**408b**: $n = 1$ and **408a**: $n = 2$).[9/91]



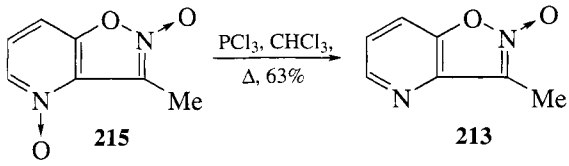
668 **663**



408a,b

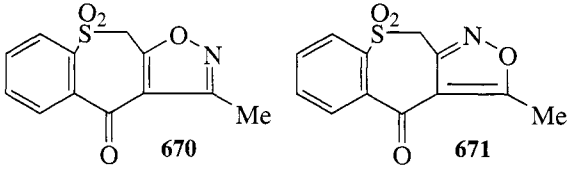
An interesting example of selective deoxygenation of an *N*-oxide with PCl_3 was described for 3-methylisoxazolo[4,5-*b*]pyridine-2,4-dioxides **215**.[6/87] The

pyridine *N*-oxide was selectively reduced, thus providing the 2-oxide derivative **213** in a good yield.



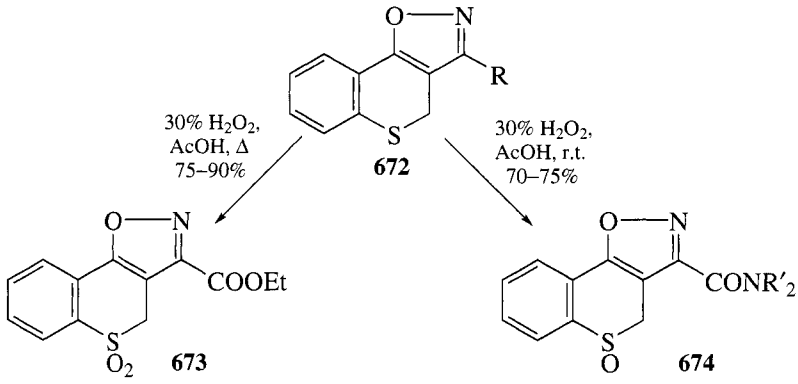
215 **213**

Very little is known about oxidation of condensed thiaheterocycles. 3-Methyl-1-benzothiepino[4,3-*d*] and [3,4-*c*]isoxazol-4(10*H*)-ones were easily oxidized by *m*.chloroperbenzoic acid to the corresponding 9,9-dioxide derivatives **670** and **671**.[17/85]



670 **671**

An interesting example of selectivity concerns the sulfur atom of 4*H*-1-benzothiopyrano[3,4-*d*]isoxazoles **672**. This is oxidized with 30% H_2O_2 and acetic acid under refluxing conditions to 5,5-dioxide **673** if R is an ester group, but, when R is an amido group, at room temperature the 5-monoxide **674** is obtained.[14/75]



673 **672** **674**

3.3.1.4. Basic Reactions on Substituents

This section is devoted to those reactions, reported for reasons of completeness, that mainly concern some simple modifications of substituents, which are

in general easily predicted by basic organic chemistry. For this reason some results are reported in a telegraphic style and the references allow the reader to find which heterocyclic ring is involved in each reaction.

A CH_2OH group can be oxidized to an aldehyde[21/90] or an acid.[12/89] An acid can be esterified,[5/79,16/80,27/84] and an ester can be hydrolyzed[9/72,27/84,14/89,15/89] or hydrolized and decarboxylated.[1/77,1/82,15/87] Esters may also be reduced[15/87,21/90] or transformed into an amide.[27/84]

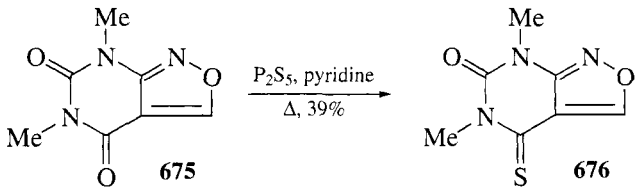
Bromine adds to an unsaturated diene,[19/86] whereas a benzylic methyl group is tranformed by NBS to CH_2Br.[10/77]

Either CH_2Br or CH_2OTs groups easily undergo nucleophilic substitution to give CH_2NR_2,[10/77,15/87] or the former may be transformed into a sulfonamide group.[5/87]

A carbonyl group belonging to an heterocyclic ring can be reduced to CHOH[31/89,12/90] or transformed into hemiacetals,[14/88,30/89,17/90,22/90] acetals,[14/88,8/89,29/89,30/89,22/89] or, by formal addition of an amine, into α-amino-α-hydroxy derivatives.[14/88,30/89,22/90]

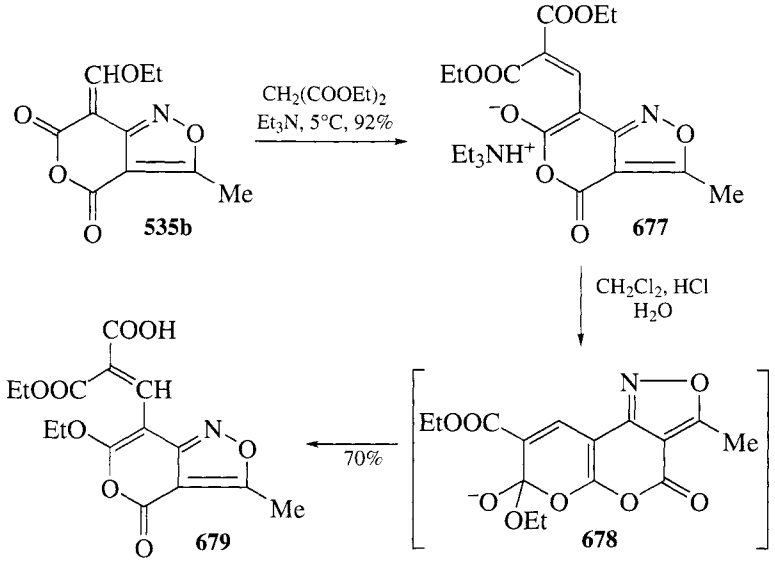
The carbonyl portion of a heterocycle can react with hydrazine to give hydrazones.[16/78,11/81] Heterocyclic hydrazines can react with simple aldehydes or ketones to give hydrazones[10/72,6/81,6/88] or with β-diketones to afford pyrazoles.[16/87]

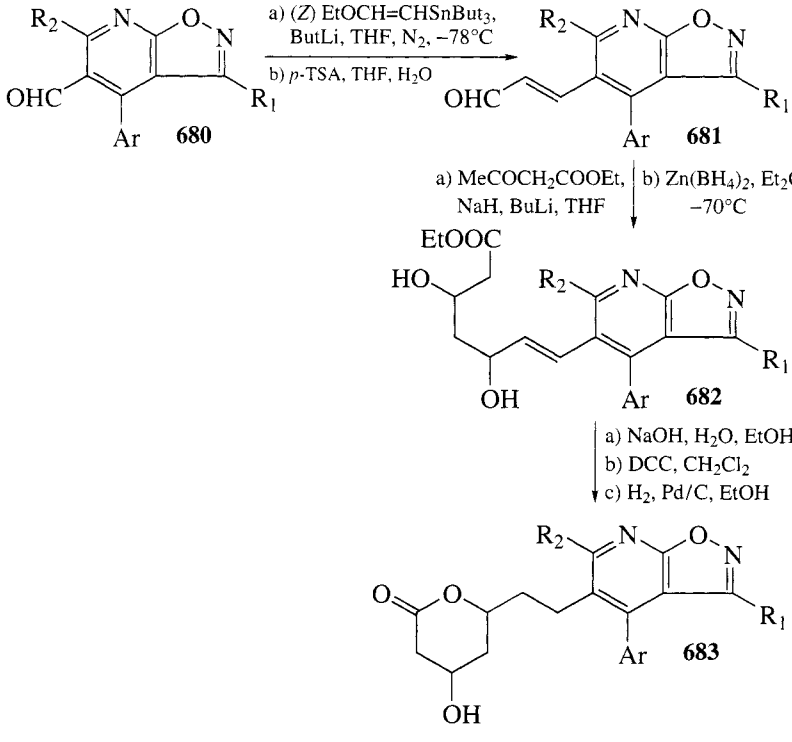
An example of selectivity occurs in the reaction of 5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione **675** with P_2S_5, such that only one isomer, the 6-one-4-thione (**676**), is produced,[3/78] probably due to the flanking of the 6 position by two methyl groups.



When 7-ethoxymethylene-3-methylpyrano[4,3-*c*]isoxazole-4,6(7*H*)-dione **535b** was condensed with diethyl malonate, an ethoxy-group migration was observed.[6/86] The initially formed triethylammonium salt **677** can conceivably give rise to a 4*H*,7*H*-pyrano[2′,3′-6,5]pyrano[4,3-*c*]isoxazole intermediate (**678**) followed by malonate **679** in which the ethoxy group has migrated into the 6 position.

This section concludes with a patented synthetic route toward isoxazolo[5,4-*b*]pyridine derivatives **683**,[21/90] which are inhibitors of cholesterol biosynthesis. Homologation of aldehyde **680** via condensation with (*Z*)-ethoxystannylethylene was followed by isomerization with *p*-toluenesulfonic acid to the β-substituted acrylaldehyde **681**. Subsequent condensation with ethyl acetoacetate and reduction with $Zn(BH_4)_2$ afforded the dihydroxy carboxylic ester **682**. Hydrolysis, lactonization with dicyclohexylcarbodiimide (DCC), and catalytic reduction of the residual double bond gave the target molecules.


CHOEt
535b
CH2(COOEt)2
Et3N, 5°C, 92%
COOEt
EtOOC
Et3NH+
677
CH2Cl2, HCl
H2O
COOH
EtOOC
CH
EtO
679
70%
EtOOC
OEt
678

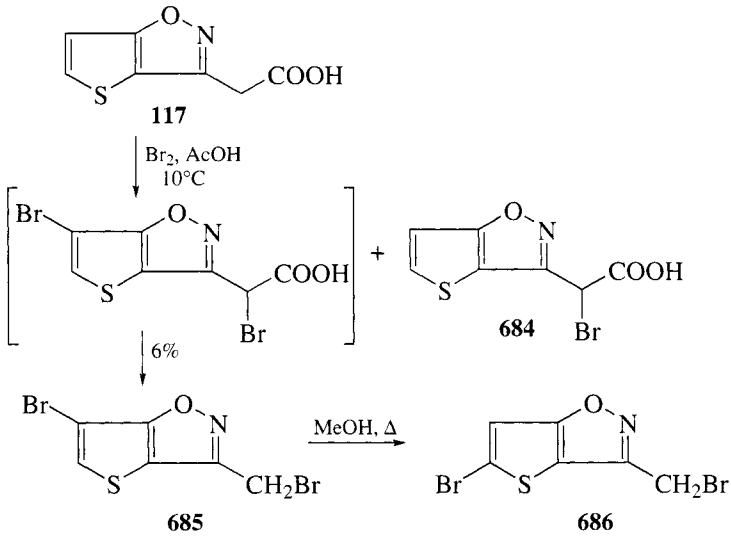

680
a) (Z) EtOCH=CHSnBut3,
ButLi, THF, N2, −78°C
b) p-TSA, THF, H2O
OHC
681
a) MeCOCH2COOEt,
NaH, BuLi, THF
b) Zn(BH4)2, Et2O,
−70°C
EtOOC
HO
OH
682
a) NaOH, H2O, EtOH
b) DCC, CH2Cl2
c) H2, Pd/C, EtOH
683

3.3.1.5. Electrophilic Substitution

If the ring condensed to an isoxazole is an electron-rich heterocycle, it may undergo an electrophilic substitution. This could conceivably occur in competition with reaction of the isoxazole itself, but it never does for two reasons. Toward electrophiles, isoxazole is one of the least reactive five-membered heterocycles, and when it does react in this way, substitution at the 4 position, which is *never* free in a condensed system, occurs.

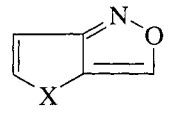
Few examples of electrophilic substitution have been reported in the literature, but some of them allow one to infer reactivity and regiochemistry.

Bromination of thieno[2,3-*d*]isoxazole acetic acid **117**[5/87] resulted in attack at the exocyclic methylene group and gave, in addition to **684**, a by-product, in 6% yield after decarboxylation, whose structure was determined to be 6-bromo-3-bromomethylthieno[2,3-*d*]isoxazole **685**. When this material was crystallized from methanol, rearrangement to the thermodynamically stable 5-bromo derivative **686** occurred.



With respect to electrophilic bromination, thieno[2,3-*d*]isoxazole does not mimic thiophene, which reacts at the so-called α position, but rather benzo[*b*]-thiophene, which gives predominantly 3-substituted products.[20/85] Migration of bromine is not new in the thiophene field, but the conversion of 2-bromo (the kinetically formed isomer) into 3-bromothiophene was found to occur under decidedly more severe conditions.[13/71]

A paper of Gronowitz and co-workers[2/76] provided some important details on the electrophilic substitution of condensed isoxazoles. Three basic fused systems were synthesized: furo, thieno, and selenolo[3,2-*c*]isoxazoles (**248**: X = O; **249**: X = S; **250**: X = Se).



248–250

Three carbon atoms are now available for the electrophilic substitution: C3, C5, and C6 which, in uncondensed rings, correspond to the C5 of isoxazole and to Cα and Cβ of the second heterocycle, respectively. The ^{13}C-NMR spectra were obtained, and Figure 3.4 plots the chemical shifts of the above-mentioned carbon atoms, as well as δCα and δCβ of the uncondensed heterocycles,[20/85] against E_X, the electronegativity of the heteroatom X (O = 3.5, S = 2.5, Se = 2.4). The chemcal shifts always show linear relationships with the heteroatom electronegativity, but have different slopes. Correlation of δC3 clearly indicates a significant transmission of the electronic effect of X to the adjacent isoxazole ring. Furthermore, the differences between δC5 and δC6 are larger than those for δCα and δCβ. Hence, while the electron density at C5 is reduced by an isoxazole, that of C6 is increased. Therefore, the result of the fusion with an isoxazole on ^{13}C-NMR chemical shifts is the same as expected for furan, thiophene, and selenophene if an electron-withdrawing substituent and an electron-donating substituent are placed in the α and β positions, respectively.

When electron donating (ED) subtituents in the β position strengthen the 4-directing power of an electron-withdrawing group (EW) in the α position, both

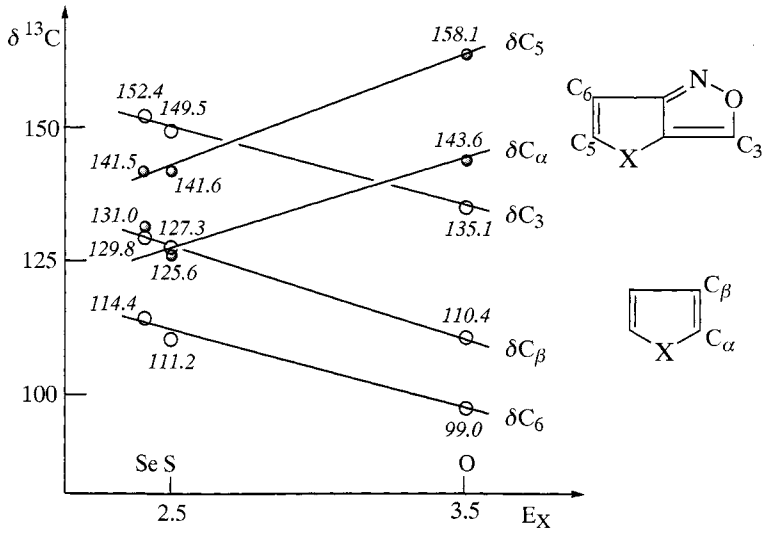
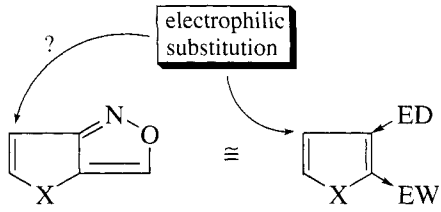


Figure 3.4. Correlations between the electronegativities of the heteroatom (E_X) and the ^{13}C chemical shifts of C3, C5, and C6 of **248–250** and Cα, Cβ of uncondensed furan, thiophene, and selenophene.

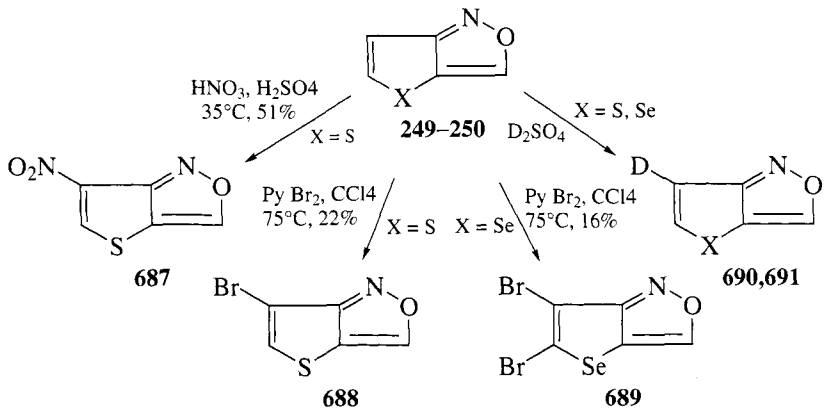
bromination and nitration occur on thiophene exclusively in the 4 position.[5/63] To determine whether this model of reactivity describes the reactivity of condensed systems, electrophilic substitutions, such as bromination, nitration, and hydrogen/deuterium (H/D) exchange, were conducted on thieno and selenolo isoxazoles **249–250**. The analogous furo derivative **248** was obtained in insufficient quantity for use in these experiments.



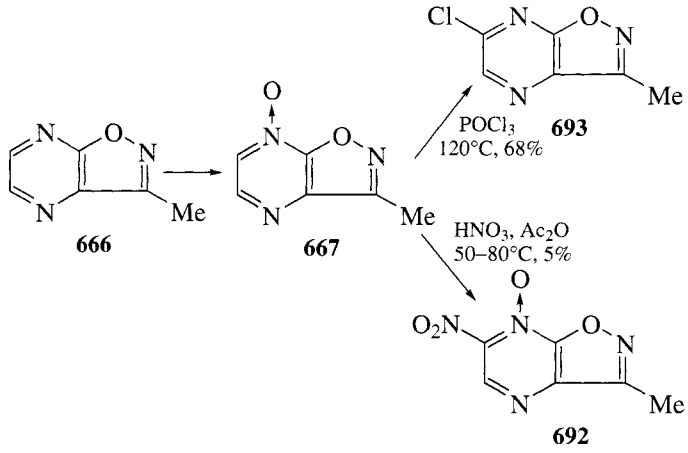
248–250

Nitration of **249** (X = S) was performed with fuming HNO_3 and H_2SO_4 and gave a 51% yield of 6-nitro derivative **687**. Bromination was performed with the complex pyridine–bromine in CCl_4 at 75°C. The thieno derivative **249** gave a 22% yield of 6-bromo (**688**); the selenolo derivative **250** gave a 16% yield of 5,6-dibromo derivative **689**. The H/D exchange, performed with D_2SO_4 and followed by NMR, resulted in the formation, within 2 weeks at room temperature, of about 50% of the 6-D derivatives (**690** and **691**: X = S and Se, respectively) all other signals of the spectra remained unaltered. Thus, as expected, electrophiles preferentially attack the 6 position of these condensed isoxazole systems.

If the ring condensed to isoxazole is an electron-poor heterocycle, electrophilic substitutions are expected to be very difficult reactions. In one of the only known examples, isoxazolo[4,5-*b*]pyridazine **666** must first be converted into its 7-*N*-oxide **667**. Nitration of the latter gave 6-nitro-7-oxide derivative **692**, albeit in a very poor yield.[6/73]



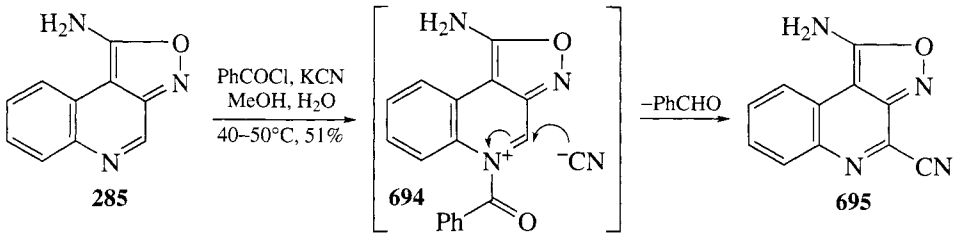
Of greater preparative value is the chlorination of the pyridazine ring in **667**,[6/73] to give 6-chloro-3-methylisoxazolo[4,5-*b*]pyridazine **693**. This reaction proceeds through the formation of an oxypyridazinium cation and a chloride ion. Its subsequent nucleophilic attack is a reaction that will be reviewed in greater detail in the next section.



3.3.1.6. Nucleophilic Substitution

A large number of isoxazoles that are condensed with several types of azines have been described. All these rings are electron-poor heterocycles, and hence are activated for a nucleophilic substitution. It is therefore obvious that this is the topic of a large number of papers and, by far, one of the most studied from either the preparative or the mechanistic point of view.

The behavior of an azine condensed to isoxazole is not very different from that of the azine itself. For instance, 1-aminoisoxazolo[3,4-*c*]quinoline **285**, when subjected to cyanation under the conditions of the Reissert reaction, provided 1-aminoisoxazolo[3,4-*c*]quinoline-4-carbonitrile **695**, presumably via the intermediacy of **694**.[4/71]



Nucleophilic replacement of a hydrogen atom requires either hard nucleophiles (Tschitschibabin reaction) or, as illustrated above, activation of the ring by quaternization of nitrogen. Substitution of halogen atoms or other good leaving groups requires mild conditions.

Preparation of chloro derivatives of isoxazoloazines from the corresponding hydroxy derivatives can be effected with $POCl_3$. Sometimes phenylphosphonic dichloride ($PhPOCl_2$) is used if the reaction requires more severe conditions. Bromo derivatives are prepared from the corresponding chloro derivatives with PBr_3. Other leaving groups are introduced by nucleophilic replacement of halogen precursors.

It is worth noting that no reactions of hetarynes, analogous to those derived from 3-halopyridines, have been observed in azines condensed with isoxazoles. Nucleophiles replace halogen at its specific position in the ring, and migrations have not been observed. Hence, there is no evidence to the contrary for a classic S_{AE} mechanism of nucleophilic displacement via a Meisenheimer intermediate.

The following reactions of 3,6-disubstituted 4-chloroisoxazolo[5,4-*d*]pyrimidines (**696**) are provided as examples of the methods available to effect nucleophilic replacement of a chlorine atom:

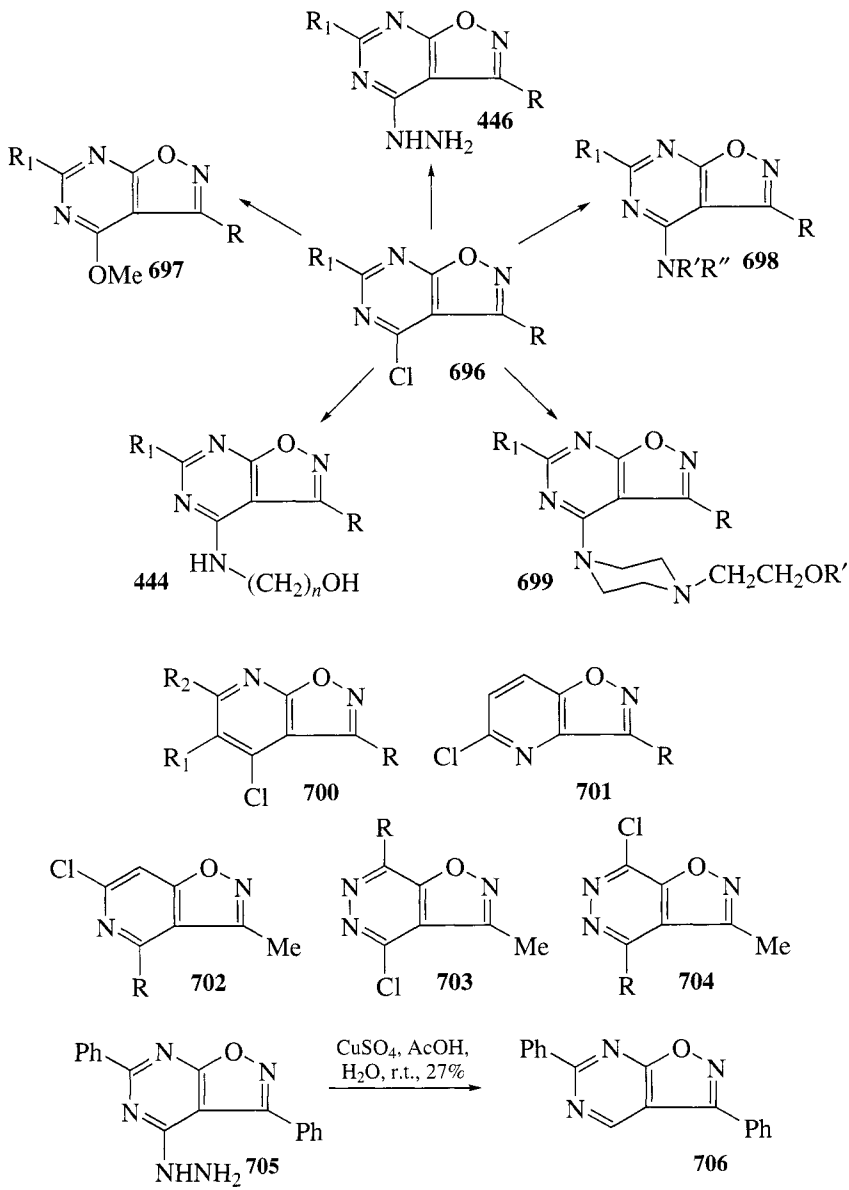
- Methoxy (**697**): MeONa, MeOH, reflux[4/67]
- Hydrazino (**446**): NH_2NH_2 hydrate, dioxan, r.t.[4/67,6/81,16/87,6/88]
- Amino (**698**: R′ = R″ = H): NH_4OH, H_2O, EtOH, reflux[8/67,15/78]
- Substituted amino (**698**): amine, eventually solvent, r.t.[8/67,15/78]
- Hydroxyalkylamino (**444** and **699**): aminoalcohol, EtOH, reflux[11/72,17/73,6/74,7/74,23/90]

Some of these compounds exhibit biological activity as antibacterial agents[17/73,6/74,23/90] or fungicides[15/78,23/90] or are useful in the treatment of angina and myocardial shock.[11/72,7/74]

Similar protocols were applied to 4-chloroisoxazolo[5,4-*b*]pyridines (**700**)[1/72,8/72,9/72,10/72,11/75,12/76,13/76] in the preparation of ethoxy, amino, and hydrazino derivatives. Similarly, 5-chloroisoxazolo[4,5-*b*]pyridines (**701**)[1/82] can be manipulated to afford methoxy and hydrazino derivatives, while 6-chloroisoxazolo-[4,5-*c*]pyridines (**702**)[3/75,2/90] are used to obtain sulfides and methoxy derivatives. Finally, 4-chloro and 7-chloroisoxazolo[4,5-*d*]pyridazines (**703** and **704**, respectively)[1/85] afford the corresponding methoxy and hydrazino derivatives.

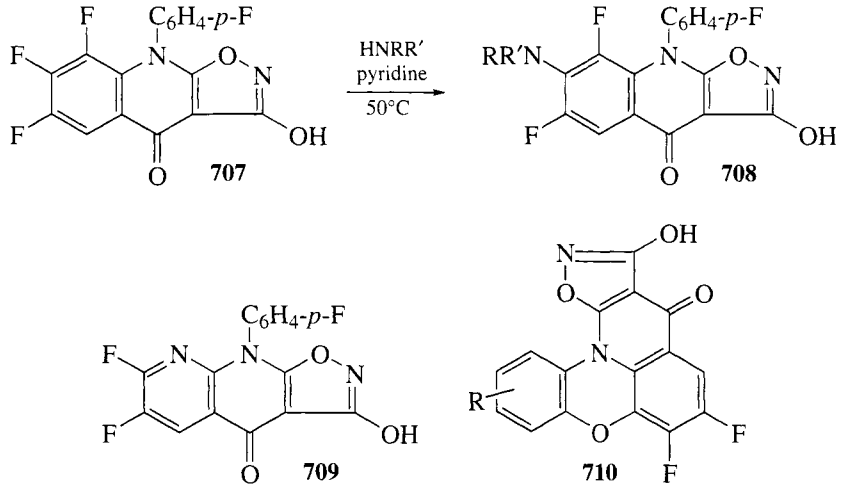
Hydrazino derivatives are of interest as precursors to pyrazoloazines (this topic will be considered in a future section) or, following oxidation and subsequent decomposition, to the unsubstituted ring system. For example, 4-hydrazino-3,6-diphenylisoxazolo[5,4-*d*]pyrimidine **705** was converted into diphenyl derivative **706** with cupric sulfate in acetic acid.[4/67]

Similar oxidations have been effected using air bubbled through a solution of benzene–NaOH aq 2*N*[1/82,1/85] or by conversion to tosylhydrazino derivatives followed by heating in ethylene glycol with Na_2CO_3.[3/75]

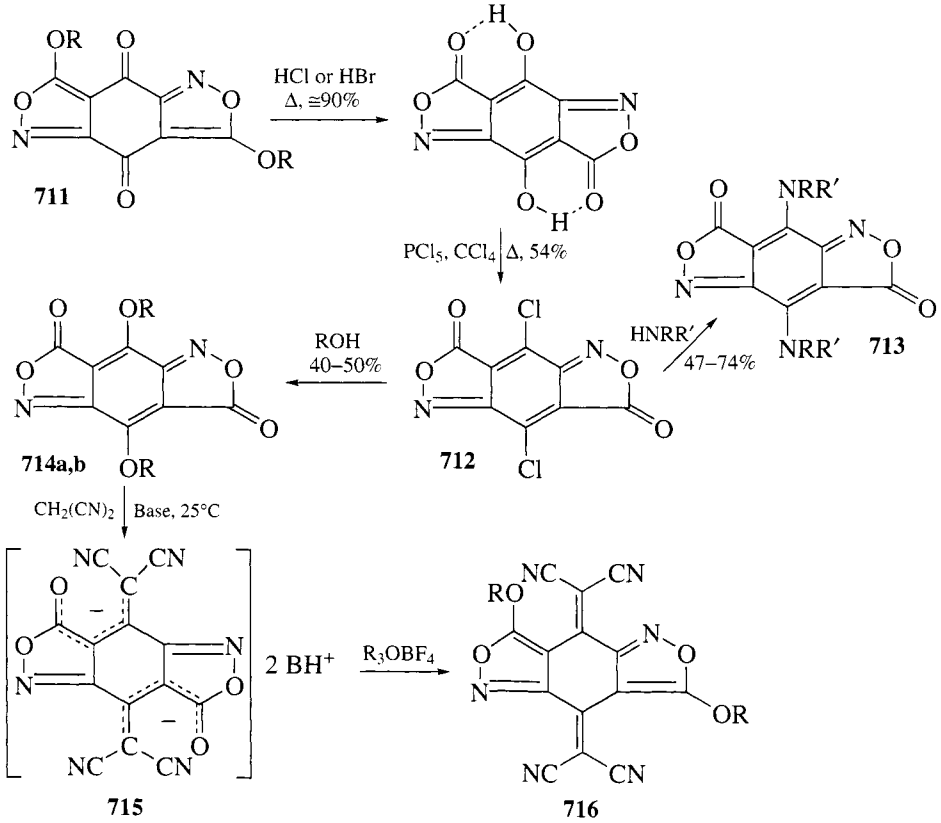


In behavior reminiscent of that of 7-bromoquinoline, selective replacement of fluorine in the 7 position in 9-aryl-6,7,8-trifluoro-3-hydroxyisoxazolo-[5,4-*b*]quinoline-4(9*H*)-one (**707**), to give **708**, could be achieved on treatment with several amines in pyridine at 50°C.[20/87]

When the reactivity of the uncondensed heterocycles is taken into account, the nucleophilic substitutions of fluorine atoms in position 7 of both isoxazolo[5,4-*b*]-1,8-naphthyridine and 4*H*-isoxazolo[4′,5′:5,6]pyrido[3,2,1-*k*,*l*]phenoxazine derivatives **709** and **710**, appear less unusual.[20/87,26/87]



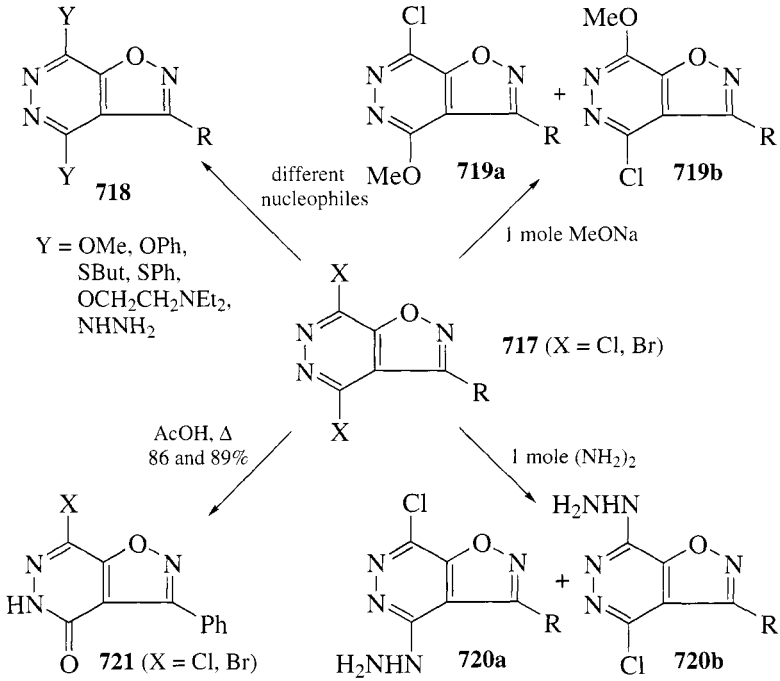
Some reactions in this section concern the benzo[1,2-*c*:4,5-c]diisoxazole ring system (§ 3.3.2.1). The 4,8-dichloro-3*H*,7*H*-derivative **712** (obtained in good yields from 3,7-dialkoxy-4*H*,8*H*-derivatives **711**[10/81]) readily underwent nucle-



ophilic substitution with amines, to give **713**, or with simple alchols to give **714a,b** (a: R = Me; b: R = Et).[10/81] Treatment of the latter compound with malononitrile or β-oxobenzenepropanenitrile brought about replacement of the ethoxy group (only the former reaction is reported in the scheme) to give the colored salts **715**, which, on alkylation, afforded **716**. A 1 : 1 charge-transfer complex of the latter with 2-(1,3-dithiol-2-ylidene)-1,3-dithiole has been prepared.[3/90]

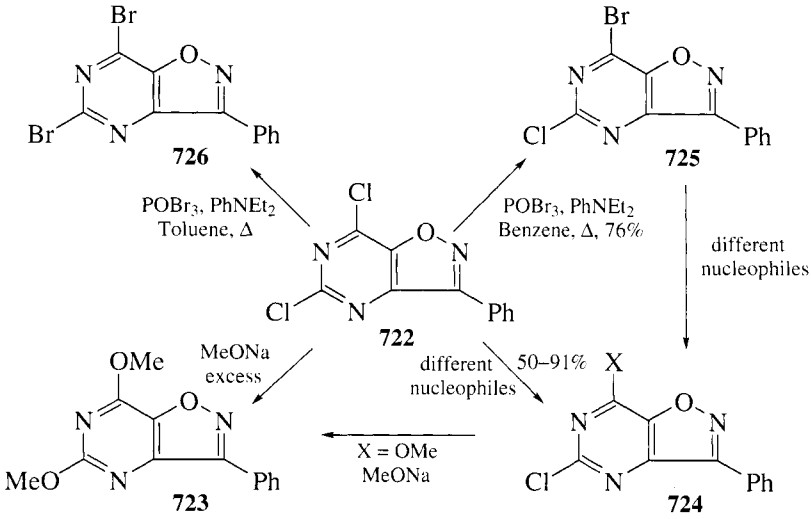
Since it is known that the reactivity of halogens largely depends on their position in the azine ring (for a quantitative evaluation of the reactivity, the review by Illuminati[4/64] is still very useful), the presence of two halogen atoms on isoxazolo-azines permits an investigation of their relative reactivity and the influence of the condensed isoxazole ring on selectivity toward reagents.

Some ring systems show poor selectivity; 4,7-dichloro (or dibromo) isoxazolo[4,5-*d*]pyridazines (**717**) react with various nucleophiles to give disubstituted hydrazino, alkoxy, alkyl- and arylthio derivatives (**718**).[3/66,11/66,3/67,1/85] In the presence of one mole of nucleophile, a mixture of 4- and 7-substituted derivatives (**719,720a,b**) was obtained in a ratio that varies between 2 : 1 and 1 : 2 depending on substituents.[3/67,1/85]



Hydrolysis of the halogen atoms is often very selective. When the dihalo-derivatives **717** were refluxed for 1 h in acetic acid,[3/67] the halogen in the 4-position was displaced and 7-bromo (or chloro)-3-phenylisoxazolo[4,5-*d*]pyridazin-4(5*H*)-one **721** was obtained whose structure was also confirmed by X-ray analysis.[3/72]

Different results were obtained with 5,7-dichloro-3-phenylisoxazolo-[4,5-*d*]pyrimidine **722**.[2/67] On treatment with excess sodium methoxyde, **723** was obtained, but one equivalent of reagent led to replacement of the chlorine in the 7- position to afford **724**. The selectivity is even more pronounced with phenoxide, thiourea, ammonia, and various amines that, when used in excess, gave replacement of the 7-chloro group exclusively. The structure of these products was unequivocally assigned by synthesis from 7-bromo-5-chloro-3-phenylisoxazolo[4,5-*d*]pyrimidine (**725**) (obtained from **722** in refluxing benzene, whereas in refluxing toluene dibromide **726** was obtained), and the position of the halogen atoms was determined by X-ray analysis.[4/72]

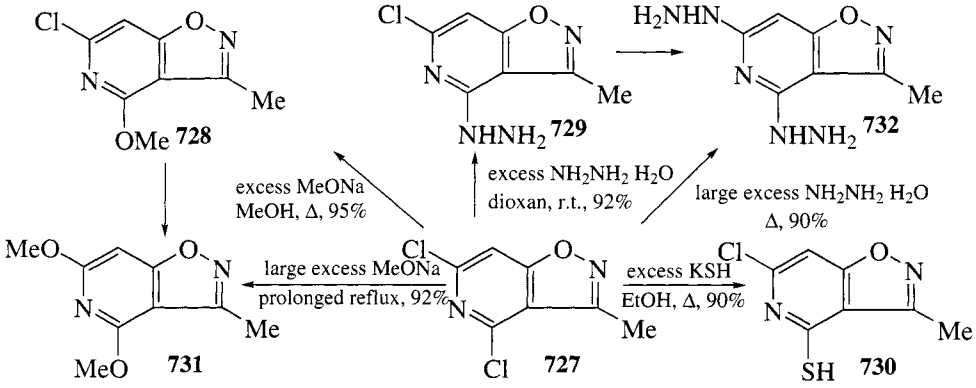


This is not an unexpected result; chlorine atoms in the 2 and 4 positions of pyrimidines and quinazolines show significantly different reactivity such that the 4 position is more reactive toward nucleophiles. The relative rates of nucleophilic substitution of chlorine with piperidine[4/64] in ethanol as solvent are sufficiently different to allow one to determine a clear selectivity.

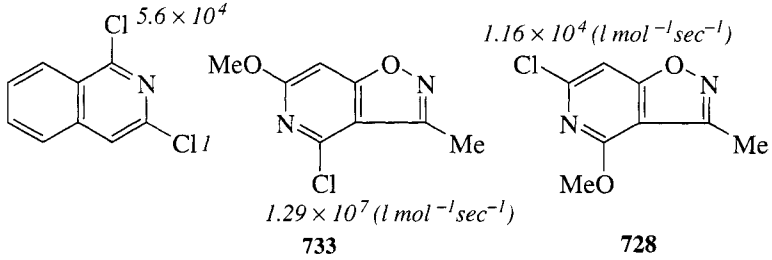
The reactivity of different isoxazolopyridine ring systems toward nucleophilic substitution was studied in detail by NMR.[5/75,15/82]

Treatment of 4,6-dichloro-3-methylisoxazolo[4,5-*c*]pyridine **727** with sodium methoxide, hydrazine, or potassium hydrogensulfide[3/75,2/90] gave the product of selective replacement of the 4-chloro group. Thus **728**, **729**, and **730**

were obtained in high yields even with an excess of the nucleophilic species, and only under forcing conditions were the dimethoxy **731** and dihydrazino **732** derivatives produced.

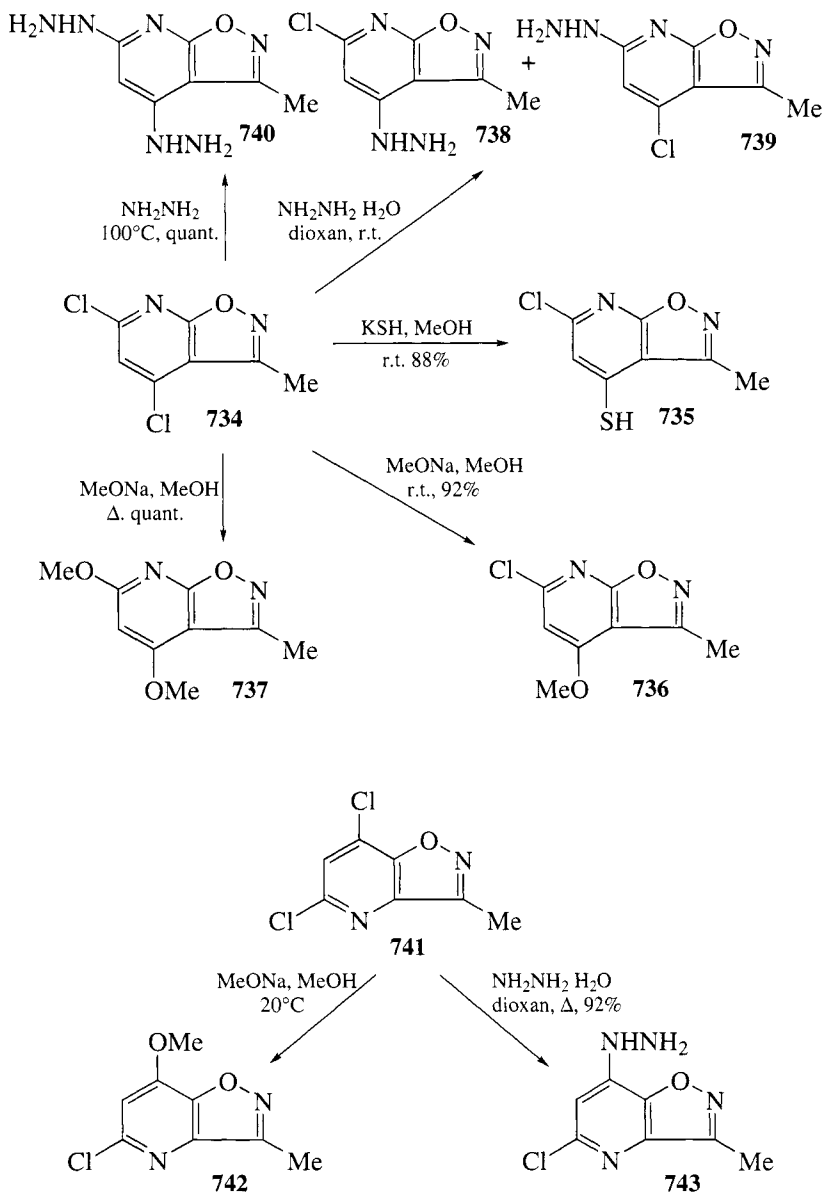


The symmetry of 2,6-dichloropyridine does not permit comparison with **727**; rather, the reactivity of the latter can be related to that of 1- versus 3-chloroisoquinoline whose relative rates for ethoxydechlorination at 20°C are 5.6×10^4 and 1, respectively.[4/64] This ratio is not far from that of the methoxy-dechlorination at 50°C for 4-chloro-6-methoxy- and 6-chloro-4-methoxy-3-methyl-isoxazolo-[4,5-*c*]pyridines (**733** and **728**, respectively).[2/79]



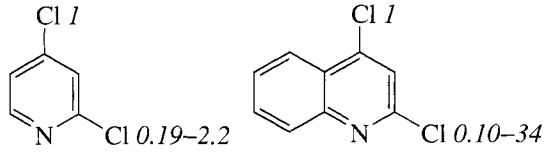
Lower selectivity is exhibited by 4,6-dichloro-3-methylisoxazolo[5,4-*b*]pyridine (**734**) in its reactions with potassium hydrosulfide and sodium methoxide, to give 6-chloro-3-methylisoxazolo[5,4-*b*]pyridine-4-thiol (**735**) and 6-chloro-4-methoxy-3-methylisoxazolo[5,4-*b*]pyridine (**736**), respectively.[1/77,2/79,2/90] When the latter reaction is conducted under reflux, the dimethoxy derivative **737** is obtained. Reaction of **734** with hydrazine hydrate at room temperature gave 6-chloro-4-hydrazino- and 4-chloro-6-hydrazino-3-methylisoxazolo[5,4-*b*]pyridines (**738** and **739**, respectively) in a ratio of about 3:1. The dihydrazino derivative **740** was obtained from anhydrous hydrazine at 100°C.

Exposure of 5,7-dichloro-3-methylisoxazolo[4,5-*b*]pyridine (**741**) to sodium methoxide or hydrazine hydrate gave exclusively the products of 7-substitution,



namely, the 5-chloro-7-methoxy- and 5-chloro-7-hydrazino-3-methylisoxazolo[4,5-*b*]pyridines (**742** and **743**) respectively.[1/82]

The different reactivities exhibited by 2- and 4-chloropyridine and 2- and 4-chloroquinoline can be considered as models for the selectivity exhibited by **734** and **741**.

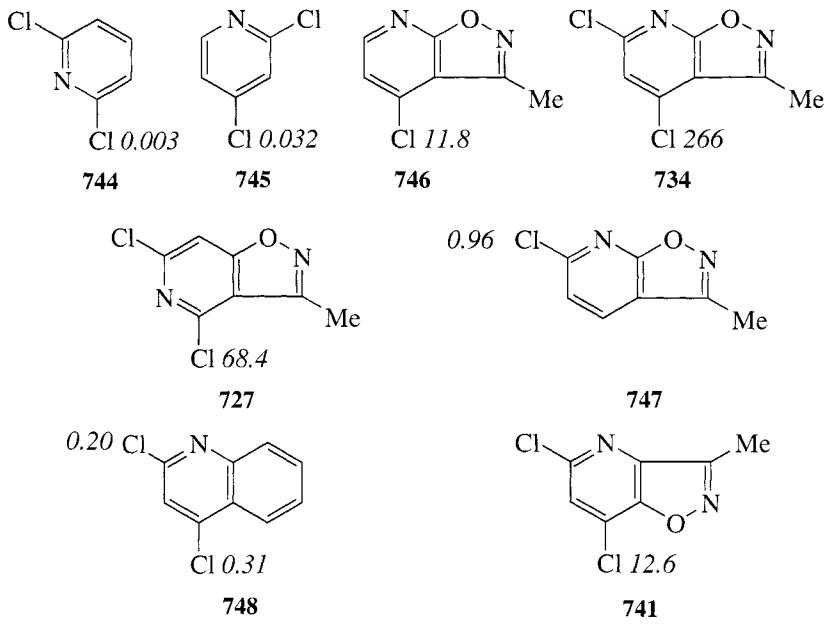


A wealth of kinetic data on the reactivity of 2- and 4-chloro substituents in these systems is available.[4/64] Depending on the nature of the nucleophile and choice of experimental conditions, the relative rates for substitution in the 2-chloro derivatives may be slower by a factor of 10 or faster by a factor of 34 relative to the rate of the same reaction performed on 4-chloro derivatives. Selectivity in these systems may be reversed depending on reaction conditions, and generalizations cannot be made.

If only displacement of chloride by methoxide is considered, some useful comparisons can be made on the reactivity and selectivity of dichloroisoxazolopyridines relative to those of dichloropyridines and dichloroquinolines. The second-order rate constants at 20°C of various model systems and product distributions are reported in Table 3.4 near the atom that suffers replacement.

Displacement of chloride by methoxide in 2,4-dichloropyridine and 2,4-dichloroquinoline occurs at the 4 position but with lower selectivity in the quino-

TABLE 3.4 RATE CONSTANTS ($10^4 \times k_2$ l mol^{-1} s^{-1}) FOR THE METHOXY-DECHLORINATION REACTION[a]

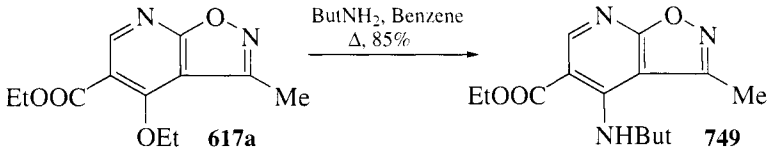


[a] Data taken from refs. 4/64, 3/79, and 1/81 and homogeneously referred at 20°C.

line system. The reaction in **734** and **741** prefers the same chlorine atom (4 and 7, respectively), but selectivity is certainly much greater since the ratio between k_2 values of 6-chloro and those of 4-chloro-3-methylisoxazolo[5,4-*b*]pyridines **747** and **746** is about 12.[2/79]

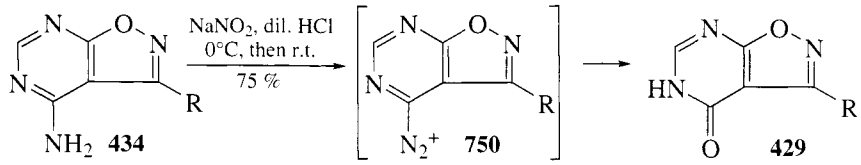
The most impressive result in Table 3.4 is the enhancement of the rate of halide replacement attainable by the fusion of an isoxazole ring. The potential for delocalization of the negative charge on the nitrogen atom of the isoxazole ring[1/82] in a Meisenheimer intermediate may in part account for the observed rate increase in **727** and **734**.

Although chloride is the most common leaving group in these systems, the presence of other substituents may confer enhanced levels of reactivity on groups that do not normally participate as leaving groups. One such example, the conversion of ethyl 4-ethoxy-3-methylisoxazolo[5,4-*b*]pyridino-5-carboxylate (**617a**) into the 4-butylamino derivative (**749**),[9/72,16/73,20/73,4/74,10/75] illustrates how a relatively unreactive ethoxy group can be induced to depart when it is incorporated within a vinylogous ester.



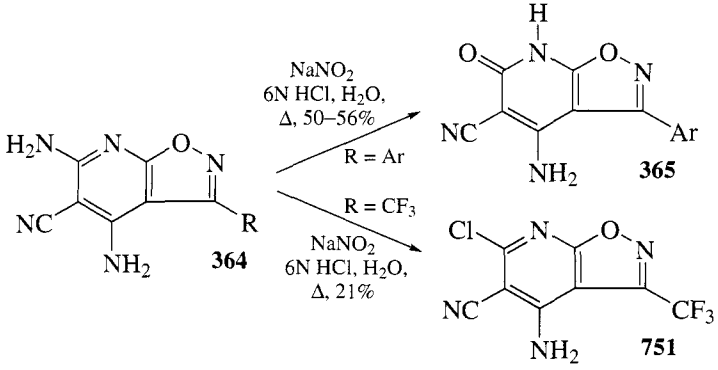
This section concludes with a discussion of the diazotization of some amino derivatives of isoxazolo-azines and the facile nucleophilic substitutions of the resulting diazonium species.

It is known that the stability of pyridine-2-diazonium and pyridine-4-diazonium cations resembles that of aliphatic rather than aromatic parent compounds. Thus, 4-aminoisoxazolo[5,4-*d*]pyrimidines **434**, when diazotated with sodium nitrite in dilute hydrochloric acid at 0°C, gave isoxazolo[5,4-*d*]pyrimidin-4-(5*H*)-ones **429**.[2/64] Benzenediazonium ions are stabilized by mesomerism through electron donation from the ring. This stabilization is not offered, either by the electron-poor pyrimidine or by the adjacent electron-rich isoxazole, to intermediate **750**, which reacts with the aqueous solvent to give the product of nucleophilic substitution.



Diazotization of 4,6-diaminoisoxazolo[5,4-*b*]pyridine-5-carbonitriles **364** is very selective, and even with the use of excess sodium nitrite, in boiling HCl,

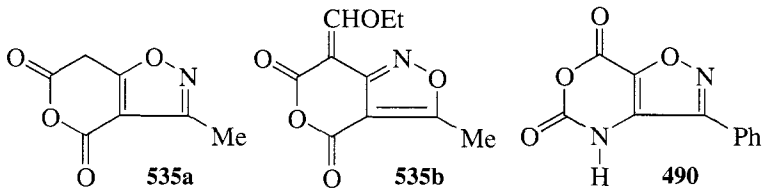
only the amino group in the 6 position is diazotized. When R is an aryl group the products obtained are 4-amino-6(7*H*)-oxoisoxazolo[5,4-*b*]pyridin-5-carbonitriles (**365**),[1/80,19/81] but when R is a trifluoromethyl group, 4-amino-5-cyano-3-trifluoromethyl-6-chloroisoxazolo[5,4-*b*]pyridine **751** is isolated.[7/87]



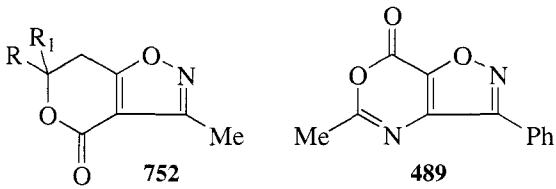
3.3.1.7. Ring Opening

Ring-opening of heterocycles condensed to isoxazole can be governed by the intrinsic character of the ring or by the presence of the isoxazole.

Some 4H-pyrano[3,4-*d*]isoxazole (**535a**),[4/89] 4*H*-pyrano[4,3-*c*]isoxazole (**535b**),[6/86] and 5*H*-isoxazolo[4,5-*d*]-1,3-oxazine (**490**)[11/90] derivatives, which behave like cyclic anhydrides, have been opened with different nucleophiles, such as methanol, amines, and diethylmalonate, to give the products expected from such reactions.

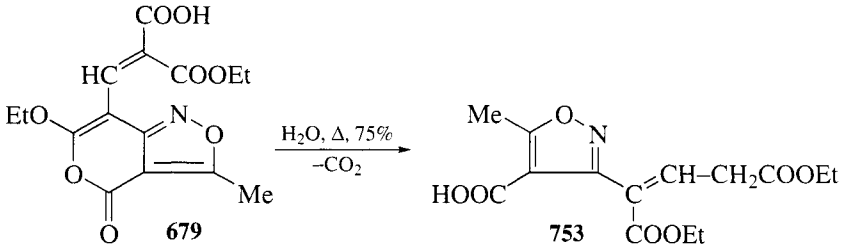


Analogously, some 4*H*-pyrano[3,4-*d*]isoxazole (**752**),[4/81] and 7*H*-isoxazolo[4,5-*d*]-1,3-oxazine (**489**)[1/67] derivatives have been opened with aqueous

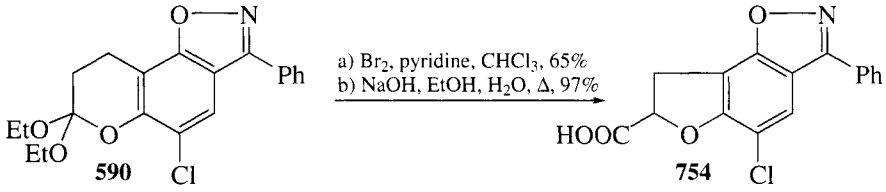


$NaHCO_3$ or hydrazine hydrate to give products that arise from the lactone character of the systems.

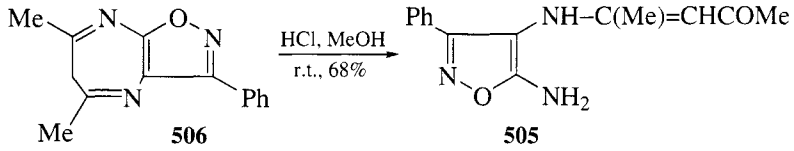
Under aqueous conditions, hydrolysis of the lactone-like ring in 4*H*-pyrano[4,3-*c*]isoxazole **679** gave the acid ester **753** following loss of carbon dioxide.[6/86]



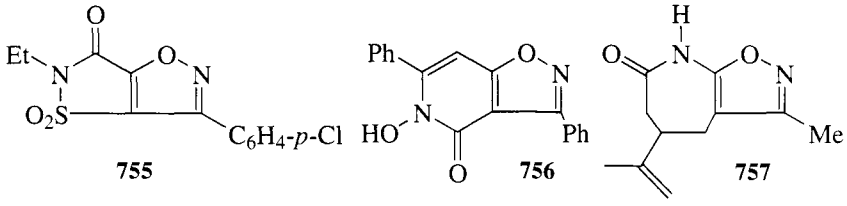
The cyclic *ortho*-ester derivative of 7*H*-pyrano[2,3-*g*]-1,2-benzoisoxazole (**590**) underwent ring-contraction on treatment with bromine and pyridine, to afford 5-chloro-3-phenyl-7,8-dihydrofuro[2,3-*g*]-1,2-benzoisoxazole-7-caboxylic acid **754**.[13/89]



As might be expected, under acidic conditions, 5,7-dimethyl-3-phenyl-6*H*-isoxazolo[4,5-*b*]-1,4-diazepine **506** is protonated and then hydrolyzed to **505**.[1/70]

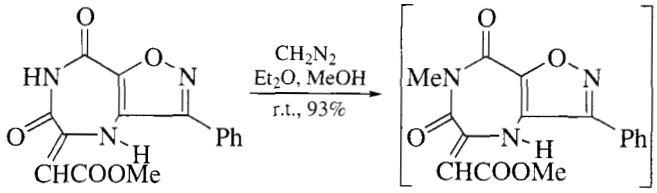


More severe conditions are required to open a heterocyclic ring with the properties of a cyclic amide. A system of this type, isothiazolo[5,4-*d*]isoxazolo derivative **755**, required EtONa to effect the desired cleavage.[2/89] Boiling

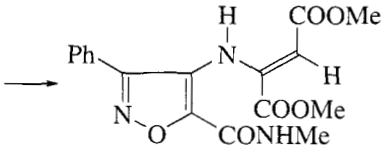


hydrochloric acid was needed for 5-hydroxy-3,6-diphenylisoxazolo[4,5-*c*]-pyridin-4-one **756**[1/12] and 8*H*-isoxazolo [5,4-*b*] azepin-7-one derivative **757**.[7/67]

Conversely, unusually mild conditions effect the ring opening of 5-carbomethoxymethylene-3-phenyl-5*H*-isoxazolo[4,5-*e*]-1,4-diazepine-6,8(4*H*,7*H*)-dione **512**.[3/87] On treatment with diazomethane in ether–methanol, the amino amide **759** was obtained, presumably through the intermediacy of the unstable *N*-methyl derivative **758**.

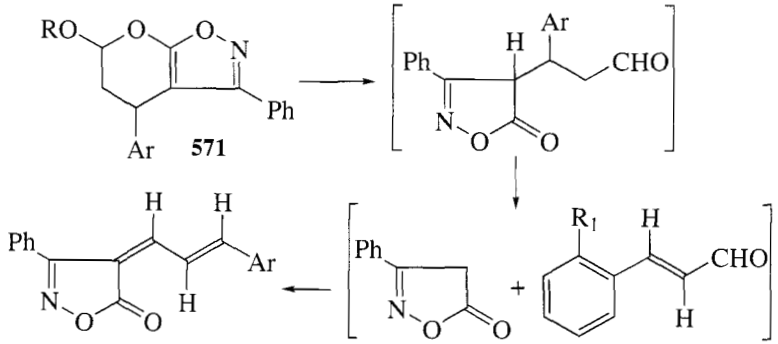


512 **758**



759

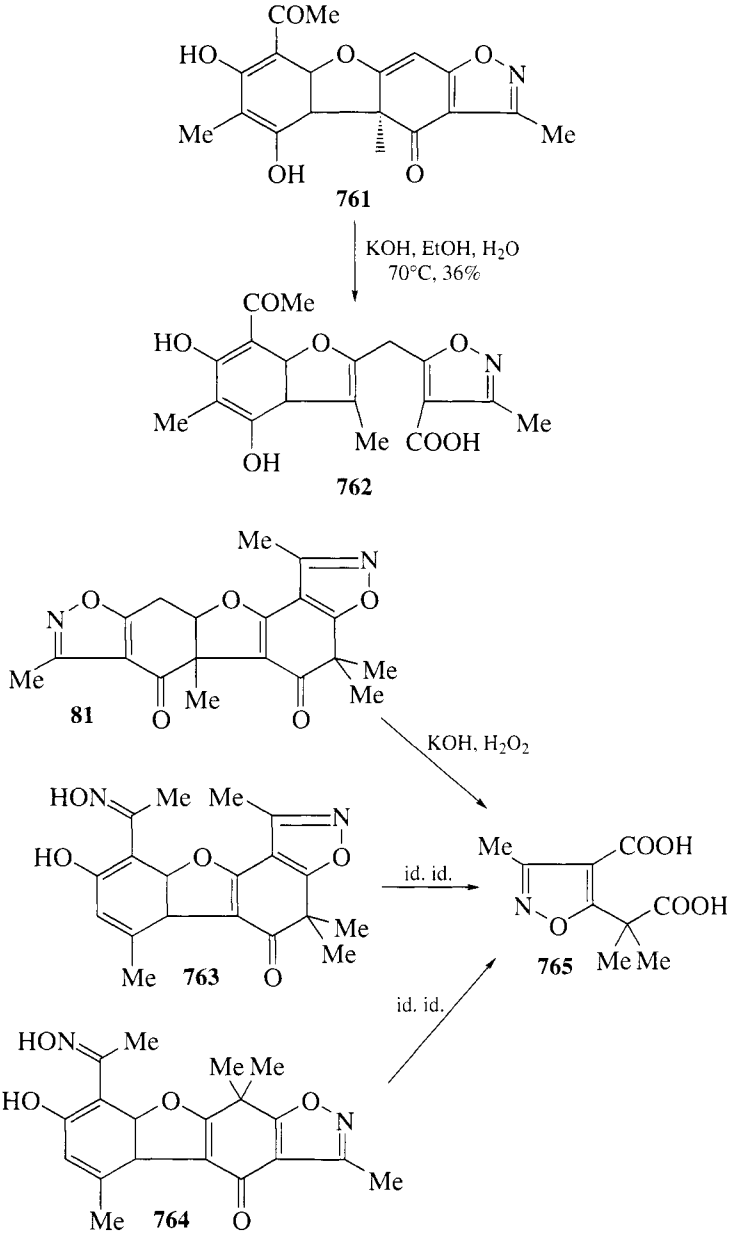
The hydrolytic cleavage of 6-alkoxy-3,4-diaryl-5,6-dihydro-4*H*-pyrano[3,2-*d*]isoxazoles **571** was used to determine their structure by chemical degradation in addition to spectroscopic methods. Under acidic conditions, cleavage of the acetal is followed by a retro-Michael reaction and recondensation of the intermediates 3-phenylisoxazol-5-one and cinnamaldehydes to give 4-cinnamylidene-3-phenyl-isoxazol-5-ones **760**.[7/66,2/68,2/71]



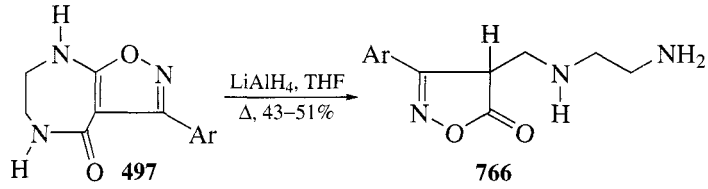
571 **760**

The benzofuro[3,2-*f*]-1,2-benzisoxazole derivative **761** was hydrolyzed under basic conditions to give **762**.[10/76] Under oxidative conditions, the somewhat similar compounds; furo[2,3-*e*:4,5-*f*′]bis-, benzofuro[2,3-*e*]-, and benzofuro[3,2-*f*]-

1,2-benzisoxazole derivatives (**81**, **763**, and **764**) were cleaved to the isoxazole dicarboxylic acid **765**.[1/62,3/63,4/63]

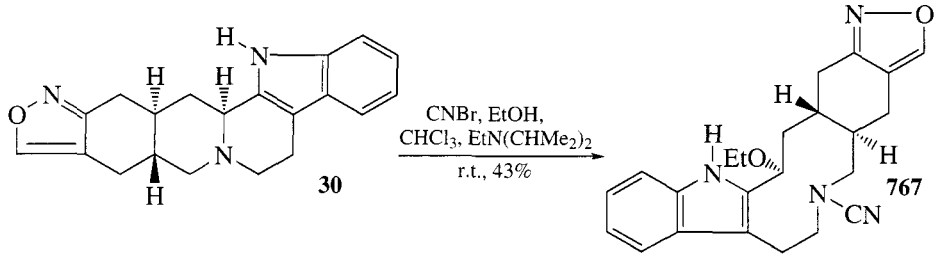


The 5,6,7,8-tetrahydroisoxazolo[5,4-*e*]-1,4-diazepin-4-one **497** can be cleaved under reductive conditions to give 4-[(2-aminoethyl)aminomethyl]-3-phenyl-5(4*H*)-isoxazolone **766**.[19/91]



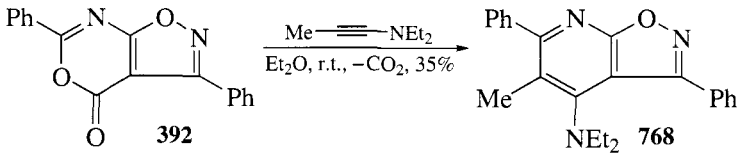
497 766

The inner quinolizine ring of the 1*H*,8*H*-2,1-benzisoxazolo[5,6-*g*]indolo[2,3-*a*]quinolizine derivative **30**, ordinarily called "yohimbano[17,18-*c*]isoxazole," suffered C–N bond cleavage on treatment with cyanogen bromide and ethanol to give **767**, a derivative of 4*H*-indolo[2′,3′:7,8] azecino[3,4-*f*]-2,1-benzisoxazole.[15/72]



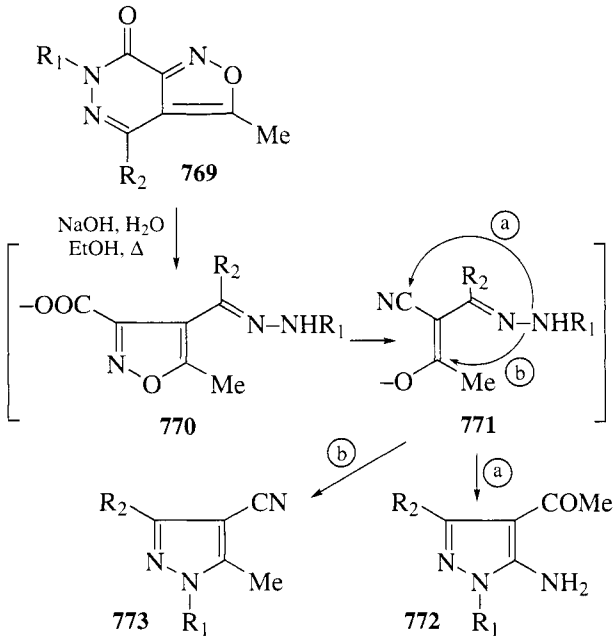
30 767

Cleavage of the oxazine ring in 3,6-diphenyl-4*H*-isoxazolo[5,4-*d*]-1,3-oxazin-4-one **392**, occurred during Diels–Alder reaction with *N*,*N*-diethyl-1-propynylamine. Loss of CO_2 by a retro-DA process from the intermediate cycloadduct gave 4-diethylamino-5-methyl-3,6-diphenylisoxazolo[5,4-*b*]pyridine **768**.[1/87]

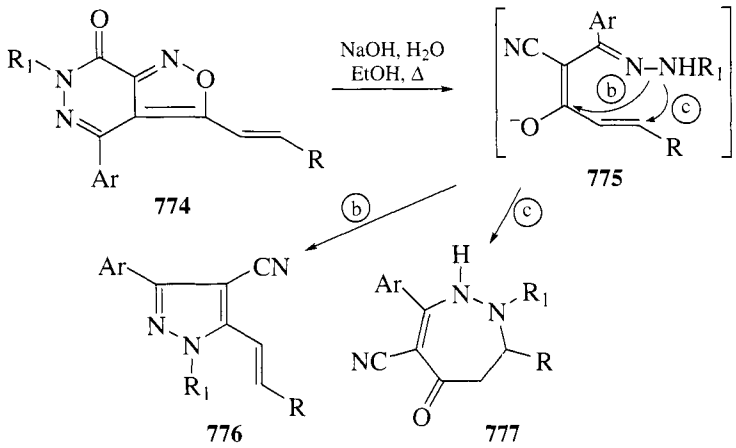


392 768

To close this section, cleavage of isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones is reviewed. Under basic conditions, **769** was hydrolyzed to an unstable isoxazole-3-carboxylate (**770**) that then underwent CO_2 extrusion and the ring opening typical of 3-unsubstituted isoxazoles in alkaline medium (see §3.3.2.2a). The resulting *cis*-cyanoenolate (**771**) underwent ring closure along two competitive pathways. If cyclization occurred on the cyano group [route (a)], 4-acetyl-5-aminopyrazoles **772** were obtained; if the carbonyl group underwent attack by the NH group [route (b)], 5-methylpyrazole-4-carbonitriles **773** were obtained.[7/85] When R_1 = Ph, the former route was preferred; the latter was prevalent when R_1 was H or Me.



When the 3 position in **774** bears a styryl or a thienoethenyl group, the *cis*-cyanoenolate ion **775** can cyclize in two ways. Ring closure to pyrazole-4-carbonitrile **776** [pathway (b)] or attack on the C=C double bond [pathway (c)] to give 6-cyano-2,3-disubstituted-1,2,3,4-tetrahydro-5*H*-1,2-diazepin-5-ones **777**, produced the main products.[9/84,7/88,6/91]



3.3.2. Properties of the Condensed Isoxazole Ring

3.3.2.1. Basic Reactions on Substituents

The substituent in the 3 position of the isoxazole ring (that does not necessarily correspond to the position 3 of the condensed ring system) can undergo modifications easily predicted by basic organic chemistry. Most of these modifications correspond to the reactions of the substituents of the condensed heterocyclic partner described in the § 3.3.1.4, and will be reported with the same telegraphic style.

Esters can be hydrolyzed,[8/71,9/71,10/74,14/75,7/79] reduced with $LiAlH_4$[10/71,5/72,3/88] (or with DIBAL[3/88]), or converted into amides,[8/71,9/71,10/74,14/75] hydrazides,[8/71,9/71,10/74] and nitriles.[8/71,9/71,10/74] Nitriles react with nucleophiles to give derivatives of carboxamidines[8/71,10/74] (subsequently converted into imidazolines), amide oximes,[8/71] carboximidates[8/71] or can be reduced to an amino group.[9/71]

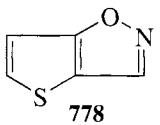
A hydroxymethylene group can be converted to a carbamate[10/71,5/72] with phosgene and an amine or phenylisocyanate or NaCNO/trifluoroacetic acid or carbamoyl chloride. The same group gives *p*-toluenesulfonates[9/71] with tosyl chloride and sulfites with thionyl chloride.[3/88]

A bromomethylene group can be obtained via NBS bromination of a methyl group,[4/75] by bromination/decarboxylation of an acetic acid residue,[5/87] or from a hydroxymethylene group with phosphorousoxybromide.[3/88] In each case $-CH_2Br$ is the starting product for nucleophilic substitutions with NaCN[4/75] or Na_2SO_3;[5/87,3/88] the sulfites are later converted into sulfamido derivatives.

Amino derivatives can be prepared either by basic cleavage of a formamidine[4/84] or by nucleophilic substitution of a *p*-toluenesulfonate.[9/71] Carbamates can be obtained by the Curtius rearrangement of carbohydrazides.[9/71]

A substituted phenyl group may undergo simple modifications of its substituents.[8/74,18/87]

All the above mentioned reactions involve the following ring systems: thieno[2,3-*d*]isoxazole (**778**),[5/87,18/87,3/88] thieno[3,2-*d*]isoxazole (**164**),[3/88] isoxazolo[5,4-*b*]pyridine (**70**),[4/75,4/88] 4*H*-1-benzopyrano[3,4-*d*]isoxazole (**15**),[8/71,9/71,10/71,5/72,10/74] 4*H*-1-benzothiopyrano[3,4-*d*]isoxazole (**63**),[14/75] isoxazolo[5,4-g]quinoline (**779**),[8/74] and 4*H*,11*H*-isoxazolo [5′,4′:4,5]thiopyrano[3,2-*c*]-1,2-benzothiazine (**68**).[7/79]



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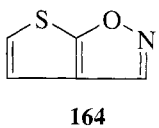

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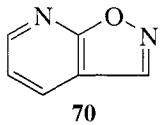

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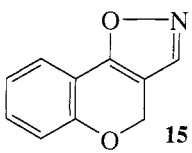

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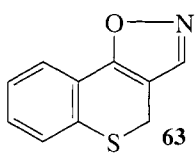

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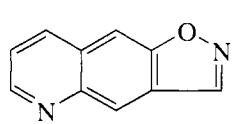

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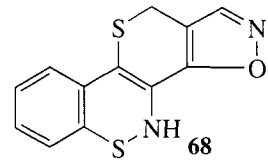
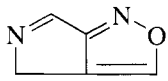


68

Substituents in the 5 position also undergo ordinary reactions. Amino groups undergo hydrogen/deuterium exchange,[8/87] alkylation,[16/83] and acylation.[1/68,16/83] Treatment with orthoesters gives carboximidoesters[1/68,5/71] that can be converted into carboxamidines.[1/68,5/71] Catalytic hydrogenation has been reported to cleave 5-hydrazino derivatives to afford the 5-amino compound.[28/84] The preceding reactions involve the 4*H*-pyrrolo[3,4-*c*]isoxazole (**317**),[1/68,5/71] isoxazolo-[3,4-*c*]pyridine (**85**),[28/84] and isoxazolo[3,4-*d*]pyrimidine (**151**)[16/83,8/87] ring systems.



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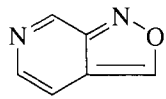

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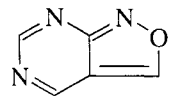
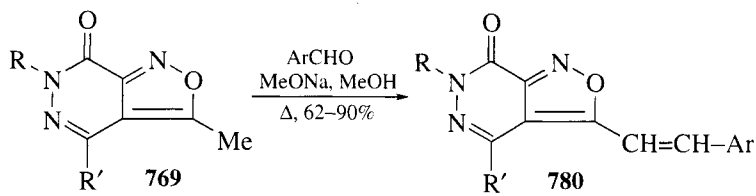


151

It is known that the protons in the α position of 5-alkylisoxazoles are acidic and enable condensation with electrophilic reagents. The methyl group of isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones **769** reacts with aromatic and heteroaromatic aldehydes in the presence of bases to give a variety of condensation products **780**.[4/76,9/84,8/86,4/91,7/91]



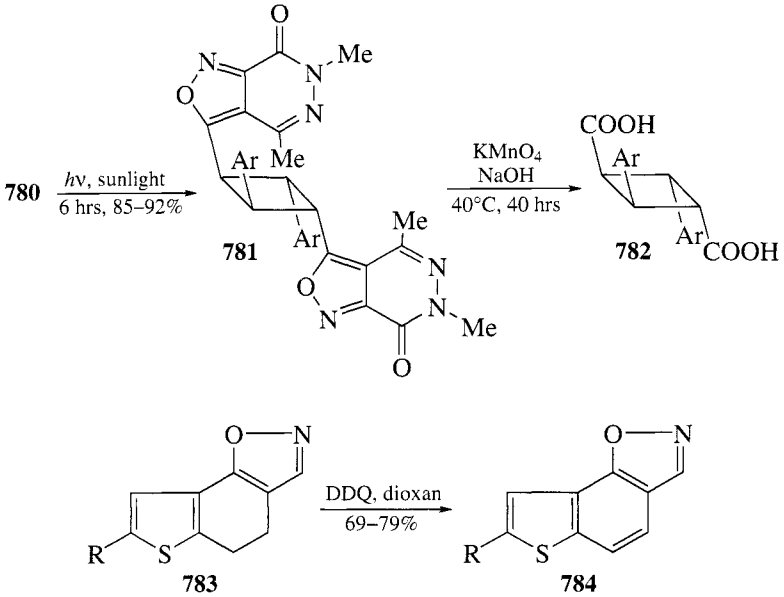
769 780

Styryl derivatives, such as **780**, photodimerize in the solid state on irradiation with sunlight to give excellent yields of head-to-tail cyclobutanes **781**. The configurations of the latter were demonstrated by oxidative cleavage to α-truxilic acid **782**.[8/86]

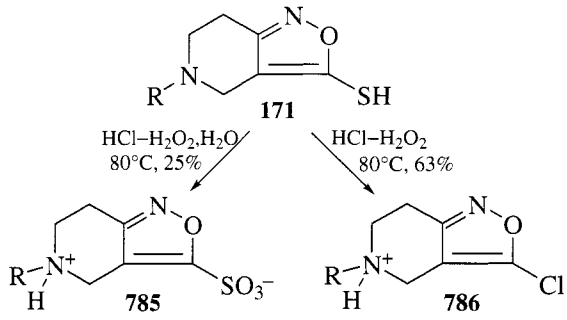
In an example of oxidation involving the benzisoxazole ring, 4,5-dihydrothieno[2,3-*g*]-1,2-benzisoxazoles **783** react with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give **784**.[12/71,30/84]

Nucleophiles effect displacement of suitable groups in the 5 position of the isoxazole ring. In condensed systems there can be competition between nucleophilic substitution and base-catalyzed ring opening, a reaction that will be reviewed in detail in the next section.

When quaternized by treatment with methyl iodide, 5-substituted 3-mercapto-4,5,6,7-tetrahydroisoxazolo[4,3-*c*]pyridines **171** give the 3-sulfonic acids

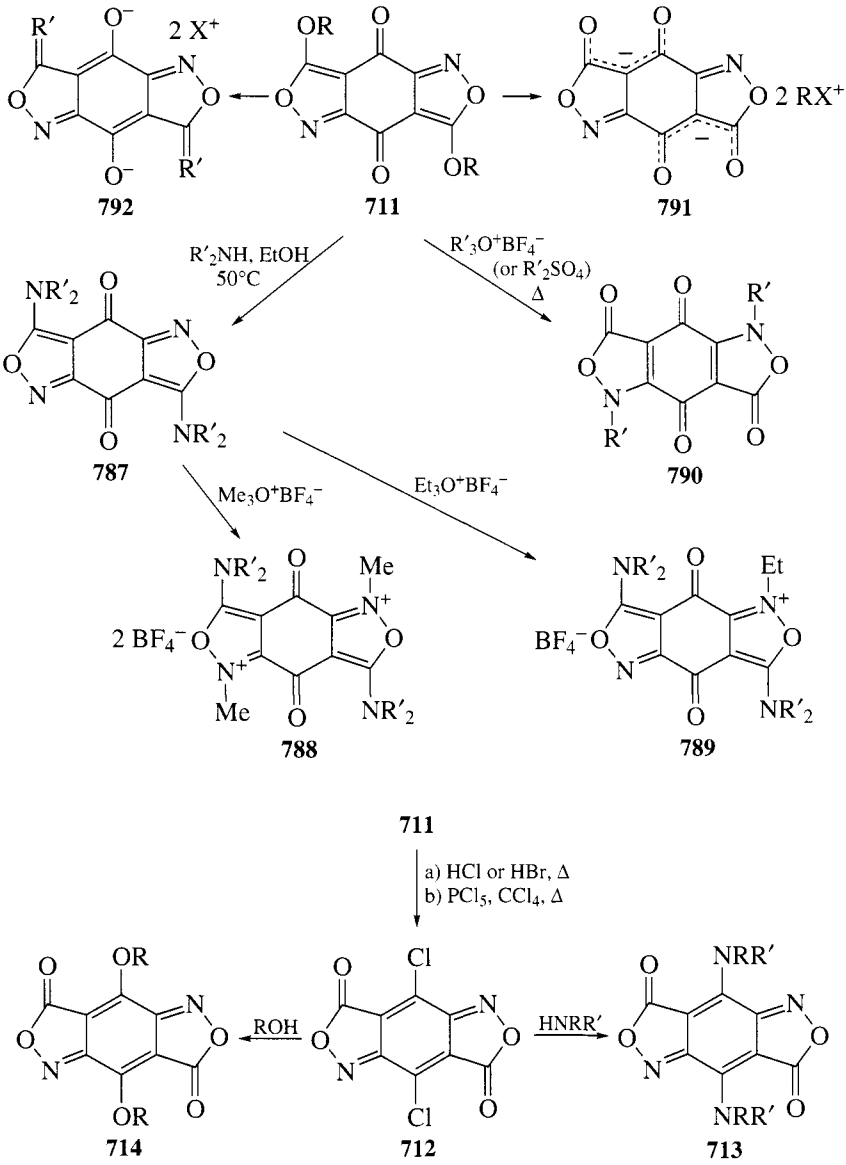


785 when heated with H_2O_2 and HCl/H_2O, and the 3-chloro derivatives **786** when treated with H_2O_2 and concentrated hydrochloric acid.[2/70]



The alkoxy derivatives **711**, under mild conditions, react with various amines to give excellent yields of the 3,7-diamino derivatives **787**.[6/78,8/80] Although hydrazine gave 4-hydrazino derivatives, *N,N*-dimethylhydrazine afforded the displacement product **787** (R′ = H, NMe_2).[9/80] These diaminodiisoxazoles (**787**), in the presence of trialkyloxonium fluoroborates, gave either mono- or bis alkylation at the isoxazole nitrogen atom (**788** or **789**),[8/80] whereas **711** gave 1,5-dialkyl-3,4,7,8-tetrones **790**.[9/80,8/91] Treatment of derivatives **711** with diisopropylammonium thiophenolate, triethylamine, or pyridine afforded the corresponding salts (**791**).[9/82] Nucleophiles such as malononitrile, cyanoacetophenone, ethyl cyanoacetate, and sulfonamides gave salts of type **792** [R′ = $C(CN)_2$, C(CN)Ph, C(CN)COOEt, NSO_2Ar, respectively].

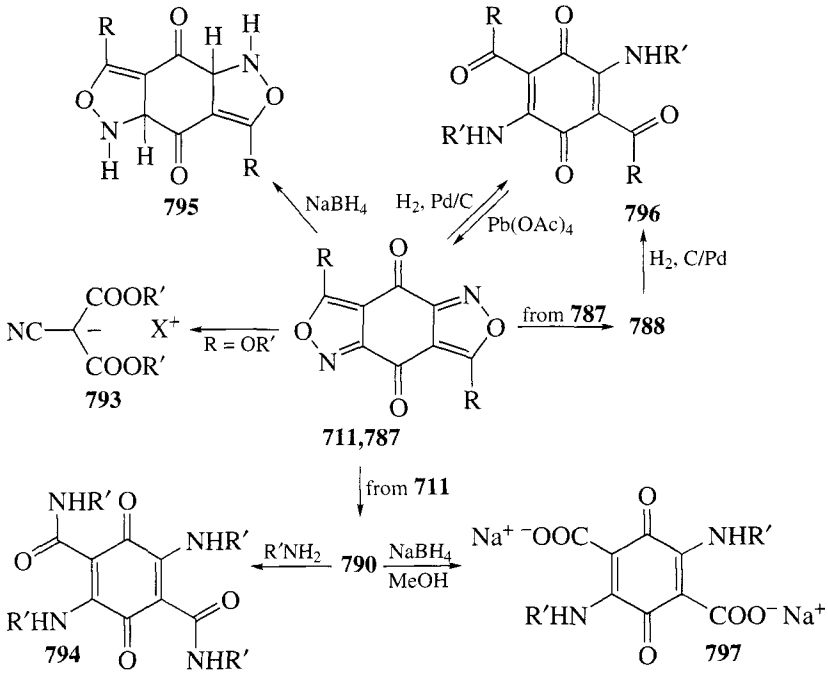
The previously-mentioned 3,7-dialkoxydiisoxazolediones **711** were hydrolyz ed and converted, by treatment with PCl_5 to 4,8-dichloro derivatives **712**. These underwent nucleophilic substitution with amines and alcohols to give the 4,8-disubstituted derivatives **713** and **714**, respectively.[10/81]



Ring cleavage of the benzodiisoxazole ring system may occur either under basic conditions or by reduction.

Dialkoxy compounds (**711**) gave malonate salts **793** on treatment with KOH and with sterically hindered amines,[7/80] whereas tetrones **790**, even at room temperature, were opened to quinones **794** by amines.[8/91] Treatment with morpholine effected opening of only one isoxazole ring.

Both the 3,7-dialkoxy and the 3,7-diamino derivatives (**711** and **787**) could be reduced with $NaBH_4$ to the tetrahydro derivatives (**795**) or opened to quinones (**796**) by H_2 and Pd/C. The latter could be reconverted to the starting products by oxidation with $Pb(OAc)_4$.[6/90] Treatment of tetrones **790** with $NaBH_4$ led to ring opening to the quinone carboxylates **797**,[9/80] whereas benzodiisoxazole-1,5-diium salts **788** were opened to amidoquinones **796** by catalytic hydrogenation.[8/91]

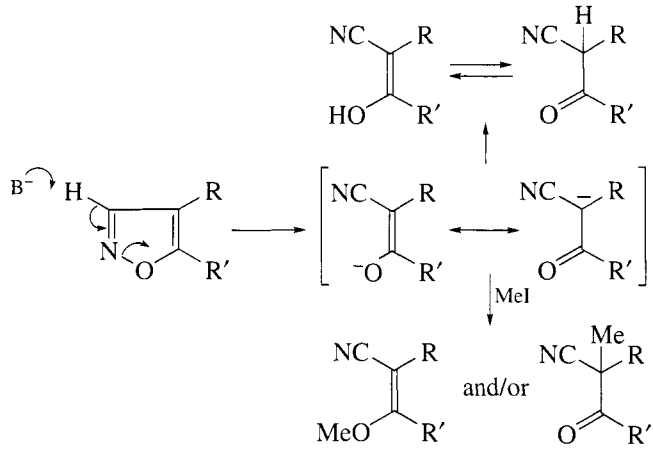


3.3.2.2. Isoxazole Ring Cleavage

It is well known that the isoxazole ring can be cleaved, generally by fission of the labile N–O bond, under a variety of conditions and that the stability of the ring is strongly affected by substituents.

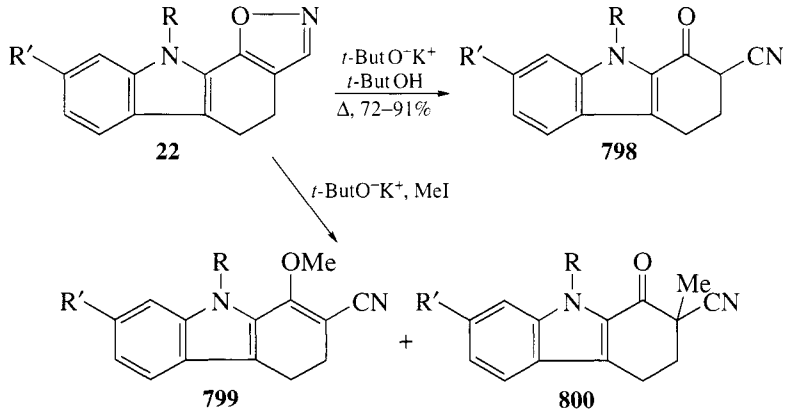
3.3.2.2a. Cleavage under Basic Conditions

3-Unsubstituted isoxazoles are cleaved by bases, and this behavior has been applied to solve structural problems related to the regioisomeric products obtained in isoxazole syntheses, problems now more conveniently solved by spectroscopic methods.



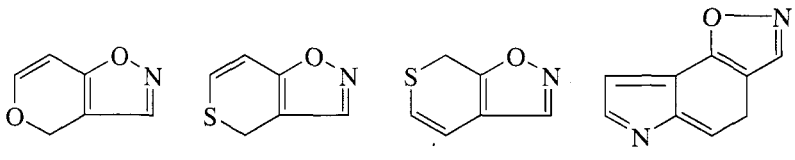
Kinetic studies on simple isoxazoles have established that the reaction is second-order (first-order in base and substrate)[22/91] and that deprotonation is concerted with the ring opening. The resulting α-cyano enolate can tautomerize after protonation to an α-cyanoketone or, as a bidentate anion, can give either *C*- or *O*-methylation with methyl iodide.

One of the earliest reported examples is the ring opening of 4,5-dihydro-10*H*-isoxazolo[5,4-a]carbazoles **22**.[2/60] With potassium *tert*-butoxide, 1-oxo-2-cyano-1,2,3,4-tetrahydrocarbazoles **798** were obtained. When R is a methyl group and R′ is a hydrogen, the 1-methoxy-2-cyano-3,4-dihydrocarbazole derivative **799** and its 2-methyl-1-oxo-2-cyano isomer **800** were obtained.

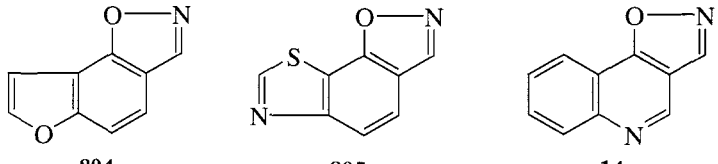


Ring cleavage with NaOH/MeOH has been accomplished in the 4*H*-pyrano[3,4-*d*]isoxazole **801**[15/75] and 4*H*-thiopyrano[3,4-*d*]isoxazole **802**[2/77] systems. Derivatives of the following ring systems were cleaved with sodium methoxide or ethoxide: 7*H*-thiopyrano[4,3-*d*]isoxazole **803**,[8/84] 4*H*-pyrrolo[2,3-g]-1,2-benzisoxazole **13**,[3/71,7/82] furo[2,3-*g*]-1,2-benzisoxazole **804**,[5/76] thiazolo

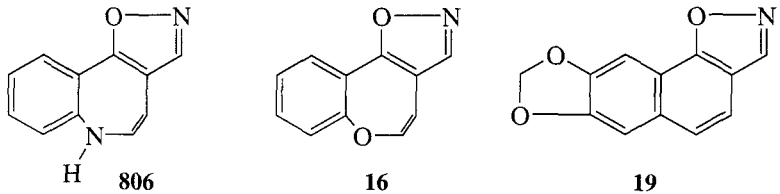
[4,5-g]-1,2-benzisoxazole **805**,[7/73] isoxazolo[4,5-c]quinoline **14**,[6/68] 6*H*-isoxazolo [4,5-*d*]-1-benzazepine **806**,[8/78] 1-benzoxepino[4,5-d]isoxazole **16**,[18/84] 8*H*-1,3-dioxolo[6,7]naphth[2,1-*d*]isoxazole **19**,[5/69] isoxazolo[5,4-*i*]phenanthridine **20**,[9/77] and naphth[2′,1′:6,7]oxepino[4,5-d]isoxazole **21**.[18/84]



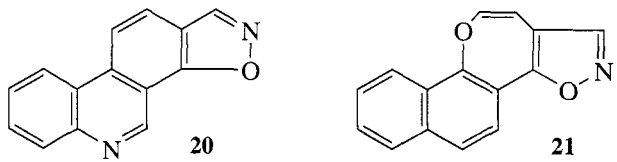
801 **802** **803** **13**



804 **805** **14**



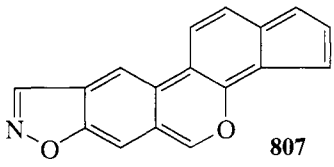
806 **16** **19**



20 **21**

A series of complex isoxazole derivatives, derived from steroid or alkaloid structures, was cleaved in the hope of exploiting the different behavior of various regioisomers. Thus unknown structures were identified, or regioisomers stable in alkaline media were purified from minor amounts of the unstable ones, or β-oxo-cyano-functionalized ring systems were synthesized. Derivatives of the following systems were studied: cyclopenta[7,8]-1-benzopyrano[4,3-*f*]-1,2-benzisoxazole (**807**),[14/73] 1*H*,5a*H*,6*H*-cyclopenta[5′,6′]naphtho[1′,2′-*f*]oxirano[2,3-g]-1,2-benzisoxazole (**808**),[15/68,16/68,24/89] 4*H*-cyclopenta[7,8]phenanthro[1,2-*d*:10,9-*d*′] diisoxazole(**809**),[6/69] 1*H*-cyclopenta[7,8]phenanthro[3,2-*d*:10,9-*d*′]diisoxazole (**810**),[6/69] and 1,2-benzisoxazole[5,6-*g*]indolo[2,3-*a*]quinolizine (**811**).[2/63,3/64,3/65]

Ring cleavage under basic conditions, in the presence of methyl iodide, was performed on derivatives of isoxazolo[4,5-*c*]quinoline (**14**),[1/63] benzofuro[3,2-*g*]-



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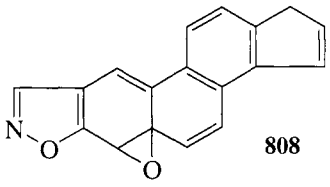

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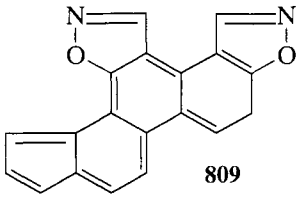

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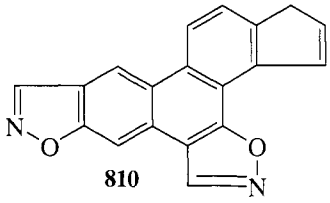

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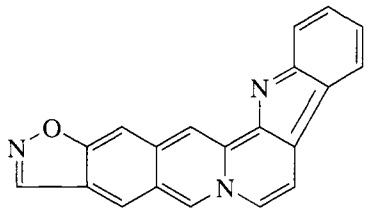
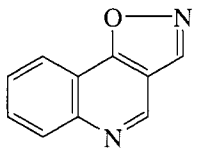


811

1,2-benzisoxazole (**17**),[4/60] 1-benzothieno[3,2-*g*]-1,2-benzisoxazole (**18**),[1/55] and 11*H*-naphtho[2′,1′:5,6]thiopyrano[3,4-*d*]isoxazole (**61**).[13/73] The first example gave *C*- and *O*-methylation in a ratio of about 7:1; the last three examples gave *C*-methylation only.



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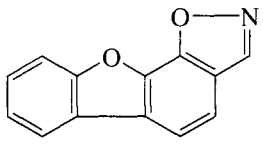

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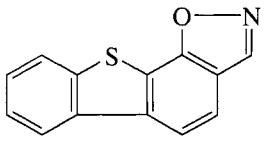

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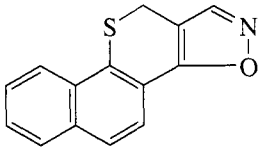
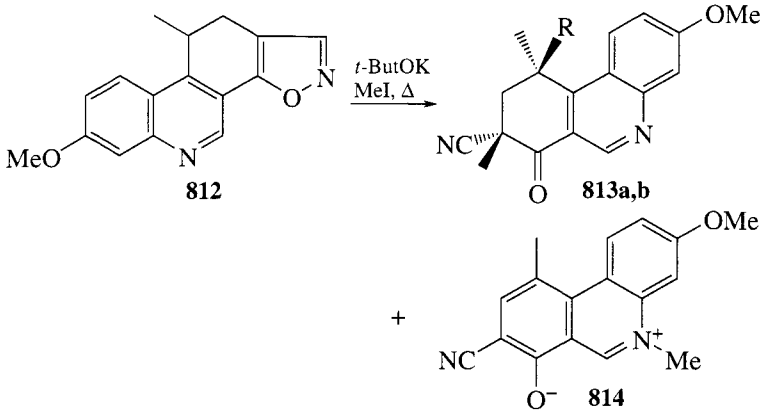


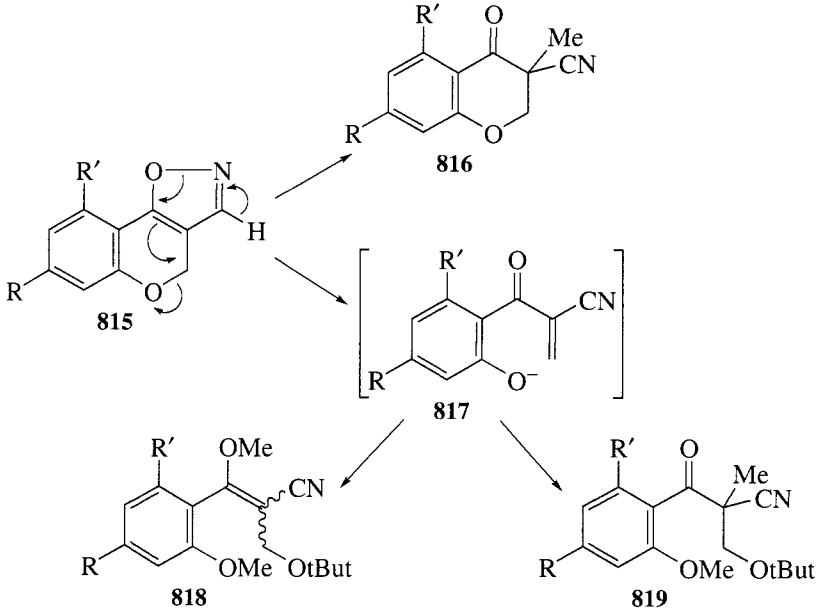
61

An interesting ring opening was achieved with potassium *tert*-butoxide and methyl iodide and 7-methoxy-10-methyl-10,11-dihydroisoxazolo[5,4-*i*]phenanthridine **812** as a substrate. In addition to 8-methylated 8-cyano-7-phenanthridone **813a** (R = H, 20% yield) and its 10-methyl derivative (**813b**, R = Me, 4%), the zwitterionic phenanthridinium ion **814** was obtained in 40% yield.[21/84]

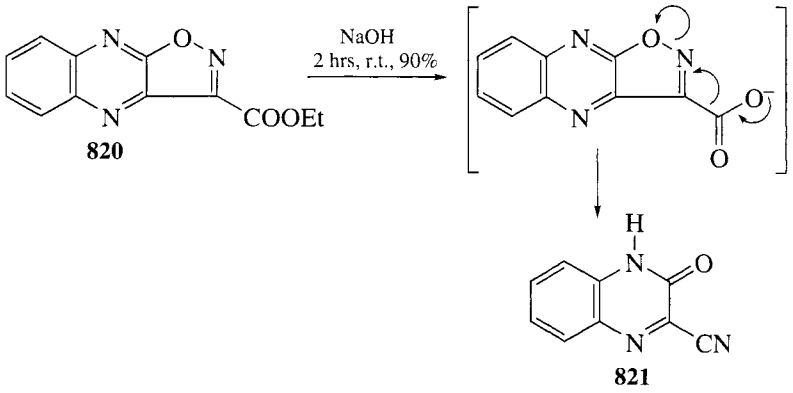


The following results were obtained when 3-unsubstituted 4*H*-benzopyrano[3,4-*d*]isoxazoles **815** were treated with methyl iodide in basic media:

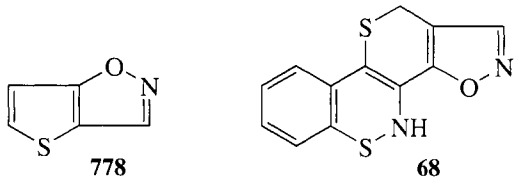
1. MeONa, EtONa, and *i*-PrOK gave 2-cyano-2-methylchroman-4-ones (**816**) in 45–60% yields[8/66,8/68]
2. *tert*-ButOK caused mainly ring opening of both the isoxazole and chromane rings to give several products (e.g., **818** and **819**) derived from anion **817**.[8/66,8/68,7/75,7/76] A similar cleavage (obviously without methylation) occurred with KOH/EtOH/H_2O.[5/79]



As is the case with many isoxazoles that bear an ester at the 3 position, ethyl isoxazolo[4,5-*b*]quinoxaline-3-carboxylate **820** gave 3-cyano-1,2-dihydroquinoxalin-2-one **821** presumably through a sequence of hydrolysis, decarboxylation, and ring opening.[6/72]



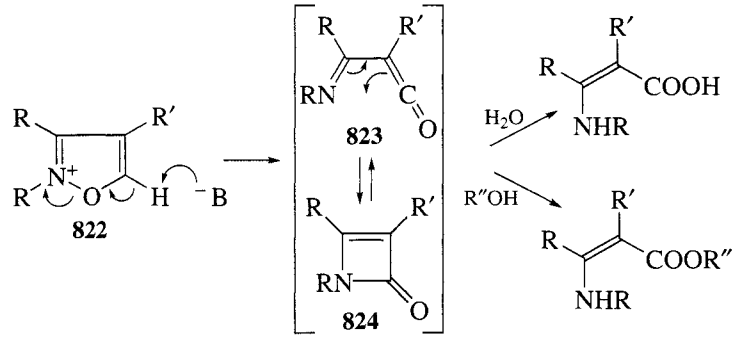
Analogous behavior was observed from esters of both thieno[2,3-*d*]isoxazole (**778**)[3/88] and 4*H*,11*H*-isoxazolo[5′,4′:4,5]thiopyrano[3,2-*c*]-1,2-benzothiazine (**68**).[7/79]

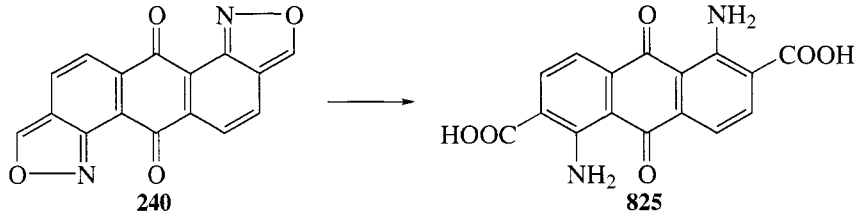


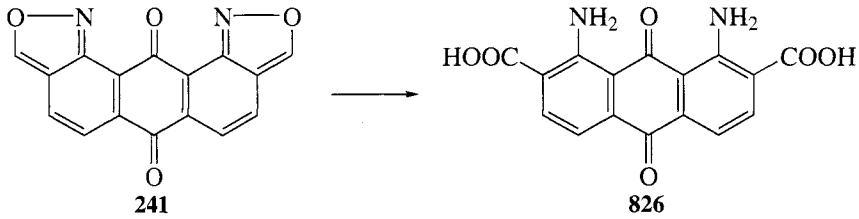
A condensed isoxazole invariably has the 4 position contained in the ring junction; hence further examples of ring cleavage under basic conditions involve isoxazoles with the 5 position free from substituents. These isoxazoles may be deprotonated by bases even if the reaction on non condensed isoxazoles requires more severe conditions that does the attack on 3-unsubstituted derivatives.[22/91] A model for this reaction exists in the base-catalyzed cleavage of 5-unsubstituted isoxazolium salts **822**, which gives rise to an intermediate that is usually described as ketene **823** in equilibrium with azetinone **824**.[14/84]

Obviously neither ketene or azetidone can be isolated when isoxazoles are cleaved and β-enaminoacids or -esters are obtained, depending on the experimental conditions.

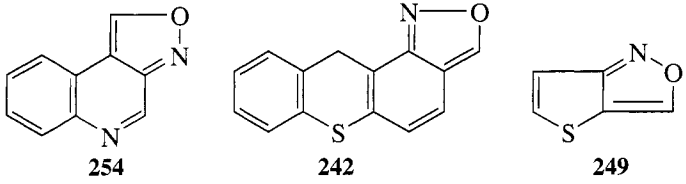
An example of this ring cleavage can be found in a patented synthesis of *o*-amino acids of anthraquinones **825** and **826**, by alkaline hydrolysis of anthra[1,2-*c*:5,6-*c*′] and [1,2-*c*:8,7-*c*′]diisoxazole-6,12-diones (**240** and **241**, respectively).[2/26]





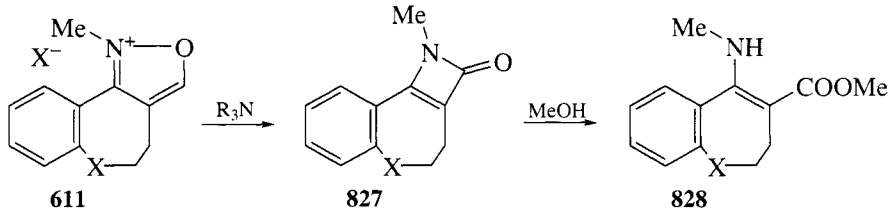


Similarly, derivatives of isoxazolo[3,4-*c*]quinoline (**254**)[1/53] and 11*H*-1-benzothiopyrano[2,3-*g*]-2,1-benzisoxazole (**242**)[2/57] gave, with aqueous NaOH, the corresponding aminoacids. Thieno[3,2-*c*]isoxazole **249**,[2/76] with aqueous methanolic solution of NaOH, gave, albeit in low yield, methyl 3-aminothiophen-2-carboxylate.



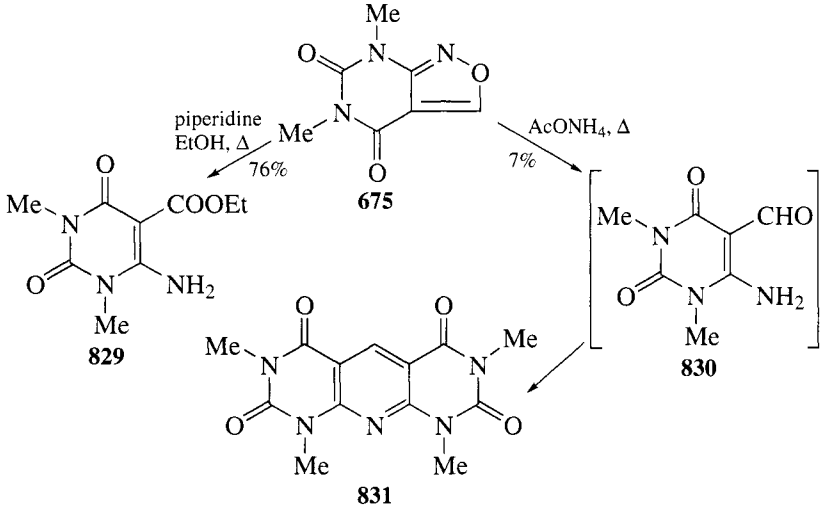
The ring opening of 5-unsubstituted isoxazoles is facilitated by initial conversion into isoxazolium salts. When a tertiary amine was added to 1-benzoxepino[5,4-*c*]isoxazolium salt (**611**), the intermediate azetinone (**827**, X = O) was observed by ^{13}C-NMR[19/84] even if it was much less stable than its analog with

X = CH_2. When the reaction was carried out in the presence of methanol, the aminoester **828**, expected from the addition of the nucleophile to azetidone (or its assumed imino ketene precursor), was obtained.



611 **827** **828**

Organic bases can also cleave 5-unsubtituted isoxazoles under mild conditions. Thus 5,7-dimethylisoxazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione **675**,[3/78] when refluxed in piperidine and ethanol, gave ethyl 6-amino-1,3-dimethyluracil-5-carboxylate (**829**) in a good yield, and when heated at 170°C with ammonium acetate, gave pyrido[2,3-*d*:6,5-*d'*]dipyrimidine derivative **831**. The presumed initial product in the latter conversion, 6-amino-5-formyl-1,3-dimethyluracil **830**, has been prepared independently and was found to dimerize to **831** when heated in refluxing acetic acid.

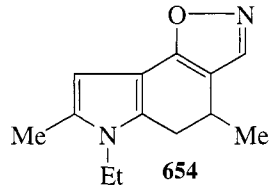


829 **675** **830** **831**

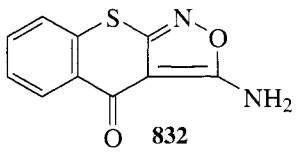
The behavior of amine bases may be less straightforward.

Under mild conditions, hydroxylamine afforded 4*H*-pyrrolo[2,3-*g*]-1,2-benzisoxazole derivative **654** from the suitable formyl oxo derivative. Since prolonged heating of the reaction mixture resulted in the formation of the related cyanooxo derivative,[3/71] the behavior of hydrazine as a base that opens the 3-unsubstituted isoxazole ring seems reasonable. Hydroxylamine was reported to react with 3-amino-4*H*-1-benzothiopyrano[2,3-*c*]isoxazol-4-one **832**[13/81] (this

product is supposed to be the intermediate of the reaction between 2-methylthio-4-oxo-4*H*-1-benzothiopyran-3-carbonitrite and hydroxylamine hydrochloride in pyridine) to give 2-amino-4-oxo-4*H*-1-benzothiopyran-3-carboxamide, but its mechanism must be deeply different.

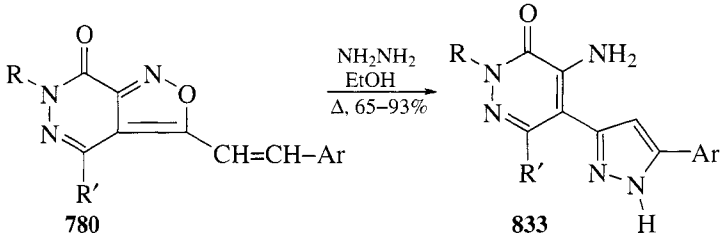


654



832

Amine bases may behave as nucleophiles, and the hydrazine-promoted cleavage of the N–O bond in 3-styrylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones **780** to give 4-amino-5-(5′-aryl-1*H*-pyrazol-3-yl)pyrazin-3(2*H*)-ones **833**[7/86,4/91] can be rationalized by assuming attacks at the "soft" styryl center (the "hard" center is the lactam CO involved in the attack of the hydroxy ion, § 3.3.1.7).



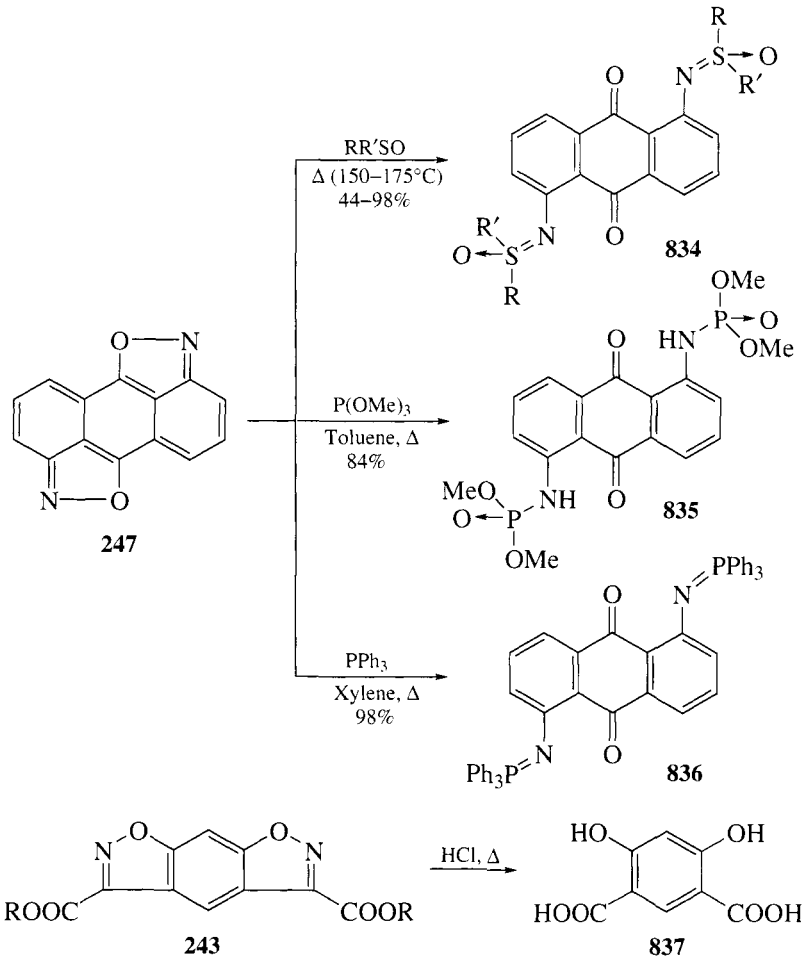
780 **833**

The ideal bridge between this section and the next one is the ring cleavage of anthra[1,9-*c*,*d*:5,10-*c*′,*d*′]diisoxazole **247**, which can be effected by several nucleophiles. Alkyl- and aryl-sulfoxides, trimethylphosphite, and triphenylphosphine[13/82] give *N*,*N*-(anthraquinon-1,5-diyl)-bis(*S*,*S*-dialkyl or diaryl)disulfonimides, or *N*,*N*-(anthraquinon-1,5-diyl)-bis(*N*-dimethoxyphosphoramidate), or *N*,*N*-(anthraquinon-1,5-diyl)-bis (triphenylphospharene) (**834**, **835**, and **836**, respectively).

The mechanism could involve, as suggested,[13/82] nucleophilic attack at the nitrogen of the heterocyclic ring with oxygen behaving as the leaving group. An alternative mechanism could involve a coordination of the "nucleophiles" to the nitrogen lone pair, using empty *d* orbitals, a topic for the forthcoming section.

3.3.2.2b. Acidic Cleavage

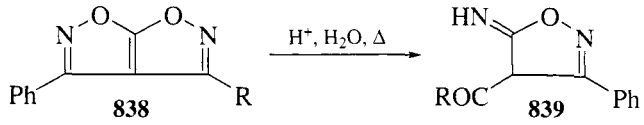
A very early example of condensed isoxazole cleavage was reported by Borsche and Bahr[1/14] in which dimethyl and diethyl benzo[1,2-*d*:5,4-*d*′]diisoxazole-3,5-dicarboxylates (**243**), when heated with HCl, gave 4,6-dihydroxyisophthalic acid **837**.



Cleavage of the isoxazole ring with acids very rarely occurs,[22/91] but when the ring is condensed with other heterocycles, several examples are known; this is evidently a result of the influence of the neighboring system.

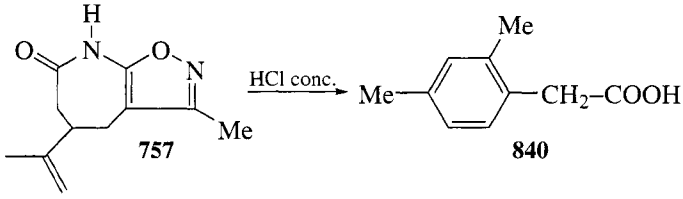
The ease of cleavage of isoxazolo[4,5-*d*]isoxazoles **838** under acidic conditions is not surprising if the system is regarded to contain an acetalic carbon.[1/59]

Certainly this reaction must involve several steps if nitrogen migrates at the isoxazole 5 position of **839**, but yields lower than 50% and by-products such as CO_2, NH_3, and benzoic acid can in part explain this. When R is a methyl group,



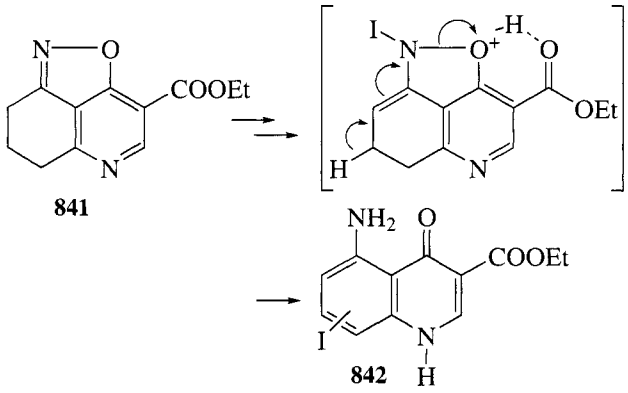
the ring cleavage is very selective and involves the isoxazole with the aliphatic substituent

Sometimes a complex rearrangement is involved as in the HCl-promoted transformation of 4,5,6,8-tetrahydro-5-isopropylidene-3-methyl-7*H*-isoxazolo [5,4-*b*]azepin-7-one derivative **757** into 2,4-dimethylphenylacetic acid **840**.[7/67]



757 **840**

Occasionally, ring opening requires several steps (including an acid-catalyzed N–O bond fission), as illustrated in the oxidative cleavage of the 6*H*-isoxazolo[5,4,3-*d*,*e*]quinoline derivative **841** with iodine, KI, and a catalytic amount of *p*-toluenesulfonic acid. The amino quinolone derivative **842** contains iodine in the 6 or 8 position since the aromatic protons appear as doublets in the ^{1}H-NMR spectrum with a coupling constant of 9 Hz.[10/82]



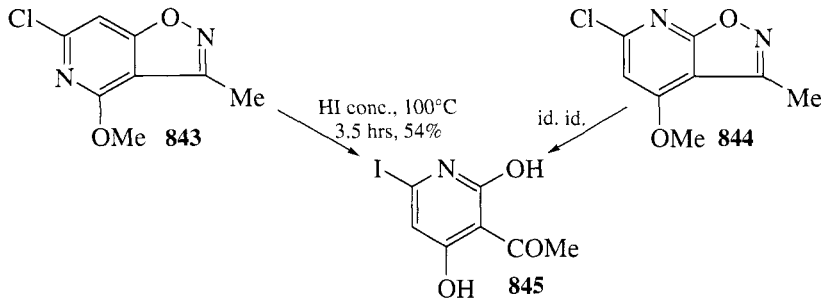
841 **842**

Incorporation of chlorine into the residual heterocycle occurs when derivatives of isoxazolo[5,4-*b*]pyridine **70**[20/73] and thieno[3,2-*c*]isoxazole **249**[2/76] are cleaved with HCl.

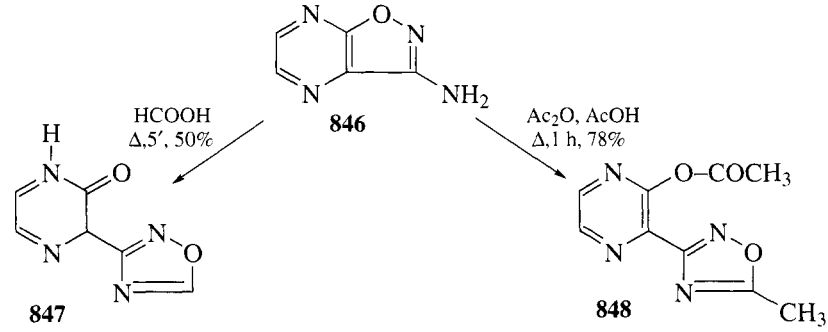
70 **249**

An example of iodination was reported during the cleavage of condensed isoxazoles with HI, but this was found to involve the substitution of a preexisting

chlorine atom since both 6-chloro-4-methoxy-3-methylisoxazolo[4,5-*c*] and [5,4-*b*]pyridines **843** and **844** gave the same 3-acetyl-2,4-dihydroxy-6-iodopyridine **845**.[1/77]



From these results it can be assumed that the acidic cleavage of isoxazole involves an intermediate hydroxyoxime that is subsequently hydrolyzed to give a hydroxyketone. The hydroxyoxyme was trapped when 3-aminoisoxazolo-[4,5-*b*]pyrazine **846** was hydrolyzed by either a short period of heating with formic acid or boiling with Ac_2O/AcOH. Oxadiazoles **847** and **848** were the respective products.[5/82,6/82]



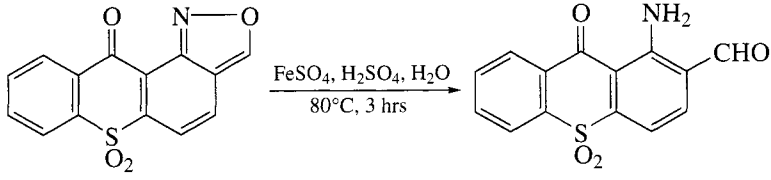
3.3.2.2c. Hydrogenolytic Ring Cleavage

Cleavage of the isoxazole N–O bond commonly involves treatment with reducing agents to afford β-enaminoaldehydes or ketones.

Some early reactions were performed with reagents that have since been supplanted, including Fe_2SO_4 in H_2SO_4 for 11*H*-1-benzothiopyrano[2,3-*g*]-2,1-benzisoxazole derivative **849**,[2/58] Fe and acetic acid for 3-methylisoxazolo[4,3-*h*] quinoline **850**,[2/59] and $SnCl_2$ and HCl for 6*H*-pyrazolo[4,3-*d*]isoxazole derivative **851**.[5/65]

More recently, the standard protocol for conversion of isoxazoles into β-enaminocarbonyl compounds has become catalytic hydrogenation. The reaction has a wide applicability with several catalysts and in general occurs with excellent yields.

The most widely-used catalyst is palladium-on-charcoal and the conversion of **851** into **852**, described above with $SnCl_2$, was performed with H_2–Pd/C, in acetic acid/H_2O under 1 atm pressure,[5/65] and this is one of the early example of catalytic hydrogenolysis of a condensed isoxazole.



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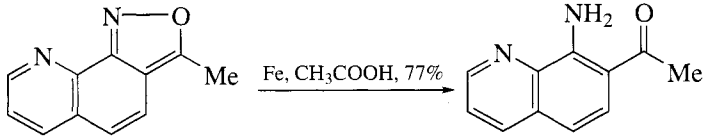

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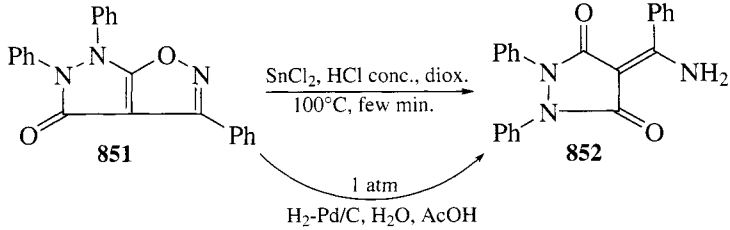
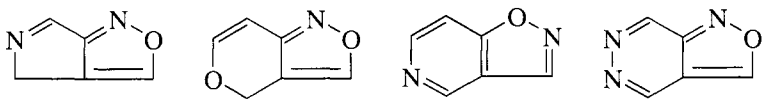


851 **852**

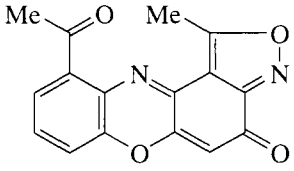
Hydrogenation with palladium/charcoal is usually conducted in ethanol, but acetic acid,[2/73] acetone,[13/79] dimethylformamide,[2/64] and methyl cellosolve[1/68] have also been employed. Reactions may be run at atmospheric pressure, although higher-pressure (2–4-atm) reactions have been conducted in a Parr bomb. Derivatives of the following ring systems have been cleaved to afford β-enamino carbonyl compounds: 4*H*-pyrrolo[3,4-*c*]isoxazole **317**,[1/68] 4*H*-pyrano[4,3-*c*]isoxazole **84**,[6/86] isoxazolo[4,5-*c*]pyridine **155**,[11/76,11/77,12/77,13/77,14/77,15/77,9/78,10/78,11/78,12/78,11/80,12/80,13/80,2/90] and isoxazolo[3,4-*d*]pyridazine **853**.[7/86,3/91,5/91]



317 **84** **155** **853**

Sometimes, under the experimental conditions used for cleavage of the isoxazole ring, the condensed heterocycle is partly or even fully reduced. The 4*H*-isoxazolo[4,3-*a*]phenoxazine derivative **854**[9/67] gave a product that was reoxidized with air to 3-amino-4,5-diacetyl-2*H*-phenoxazin-2-one. 3,5-Dimethy-

lisoxazolo[5,4-*b*]pyridine **855**[13/79] and the 5*H*-cyclohept[*b*]isoxazolo[4,5-*e*] pyridine derivative **856**,[13/79] when reduced at 4 atm pressure, gave the fully hydrogenated heterocycles.



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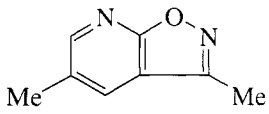

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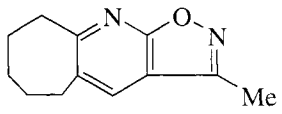
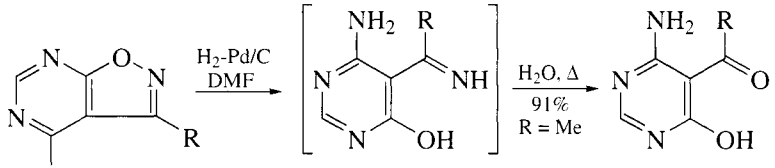


856

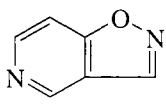
The intermediate imines, initial products of the reductive cleavage, are often too unstable for characterization, and attempts to isolate these as pure compounds generally fail. Hence, the hydrogenation product is hydrolyzed under basic conditions (usually a short period of boiling in water is enough) to give a *β*-dicarbonyl compound in its more stable tautomeric form.

Thus 4-amino-3-methyl and 4-amino-3-phenylisoxazolo[5,4-*d*]pyrimidines **434**, when hydrogenated with 10% palladium on charcoal, gave hydroxy imine intermediates (**857**) that gave 5-acyl-4-amino-6-hydroxypyrimidines **858** on hydrolysis.[2/64]



434 **857** **858**

Similar behavior was observed with derivatives of isoxazolo[4,5-*c*]pyridine **155**,[2/82] isoxazolo[5,4-*b*]pyridine **70**,[2/73,16/73,4/74,10/75] isoxazolo[4,5-*d*]pyridazine



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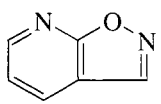
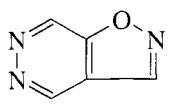


70



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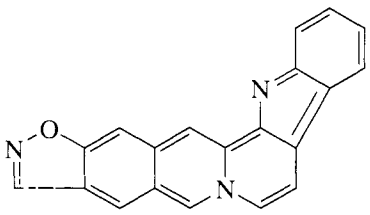

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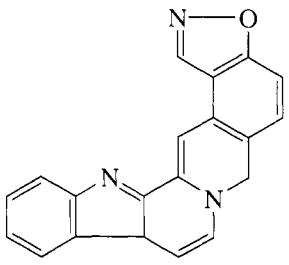
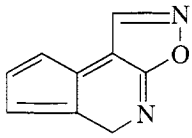


859

156,[1/85,1/90] 1,2-benzisoxazolo[5,6-*g*]indolo[2,3-*a*]quinolizine **811**,[17/80] and 6*H*, 8*H*-1,2-benzisoxazolo[5,4-*g*]indolo[2,3-*a*]quinolizine **859**[17/80] ring systems.

An alternative catalyst suitable for cleaving an isoxazole to an enaminoketone is Pt (or PtO_2) used in MeOH, EtOH, AcOH, or HCOOH. This catalyst has been used in the reductive cleavage of derivatives of 5*H*-cyclopent[*d*]isoxazolo[5,4-*b*]pyridine **595**,[15/83,17/87] isoxazolo[5,4-*c*] isoquinoline **860**,[15/83,17/87] isoxazolo[5,4-*c*]-2,7-naphthyridine **597**,[15/83] 5*H*-cyclohept[*d*]isoxazolo[5,4-*b*]pyridine **596**,[15/83,17/87] and benzofuro[3,2-*f*]-1,2-benzisoxazole **861** ring systems.[9/76,10/76] The isoxazolo[5,4-*b*]pyridine derivative **657**,[6/85] when hydrogenated with Pt in EtOH/AcOH and chromatographed on silicagel, gave ethyl 3-acetyl-4-methyl-2-oxo-6-phenylpyridine-5-carboxylate.



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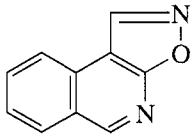

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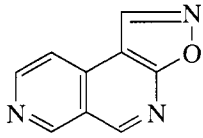

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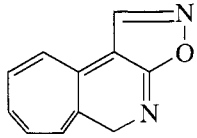

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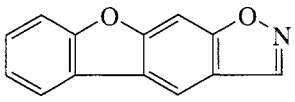

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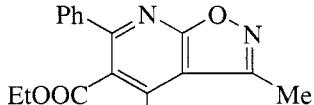
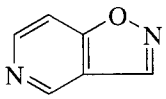


657

Raney nickel has also been employed to cleave the isoxazole ring. By this method the expected β-enaminoketones were obtained from isoxazolo[4,5-*c*]pyridine **155**[12/88] and isoxazolo[3,4-*d*]pyridazine **853**[1/65,4/66,10/67,3/68] derivatives.



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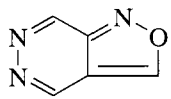
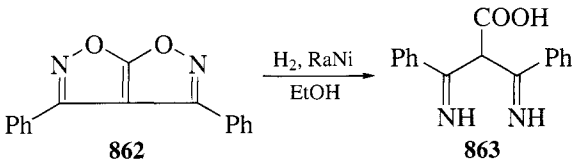


853

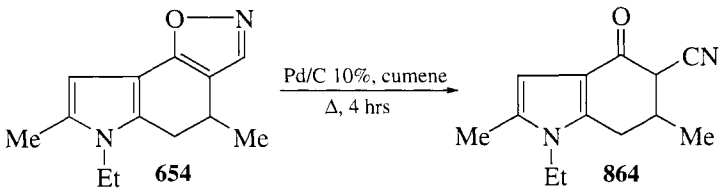
A similar cleavage was carried out on 3,4-diphenylisoxazolo[4,5-*d*]isoxazole **862**,[1/59] to give what, at a first glance, may seem an unusual reaction product (**863**).



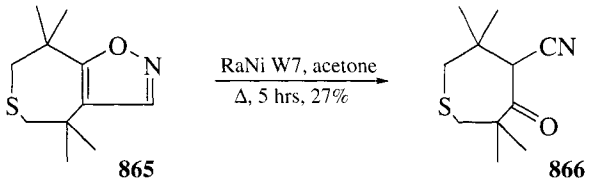
862 **863**

In some instances, in the absence of hydrogen, catalysts may behave as bases and give α-oxocarbonitrile products. The 4*H*-pyrrolo[2,3-*g*]-1,2-benzisoxazole

derivative **654**[3/71] and thiepino[4,5-*d*]isoxazole derivative **865**[5/68] gave **864** and **866**, respectively with Pd/C in refluxing cumene and RaNi W7 in refluxing acetone. These unusual reactions are reviewed in this section even if the W7 procedure, which gives a quite alkaline RaNi,[6/65] suggests that the latter reaction may be a true base-catalyzed ring opening.

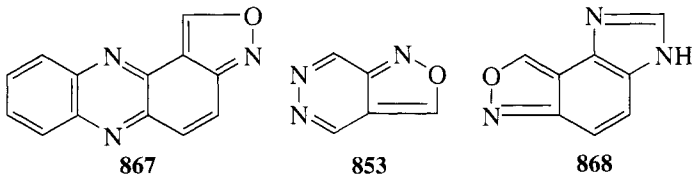


654 **864**

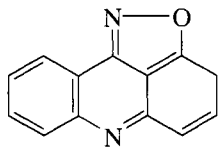


865 **866**

Catalytic hydrogenolysis may occur in the presence of nonstandard sources of hydrogen, such as hydrazine or phenylhydrazine and palladium–charcoal[10/68,3/91] or Raney nickel.[18/83] In addition, cleavage may be effected under conditions of transfer hydrogenation with Pd/C and 1-octene.[20/90] The corresponding *β*-enaminoketones were obtained from derivatives of isoxazolo[4,3-*a*]phenazine **867**,[10/68] isoxazolo[3,4-*d*]pyridazine **853**,[3/91] 3*H*-imidazo[4,5-*e*]-2,1-benzisoxazole **868**,[18/83] and 3*H*-isoxazolo[5,4,3-*k*,*l*] acridine **869**[20/90] ring systems.

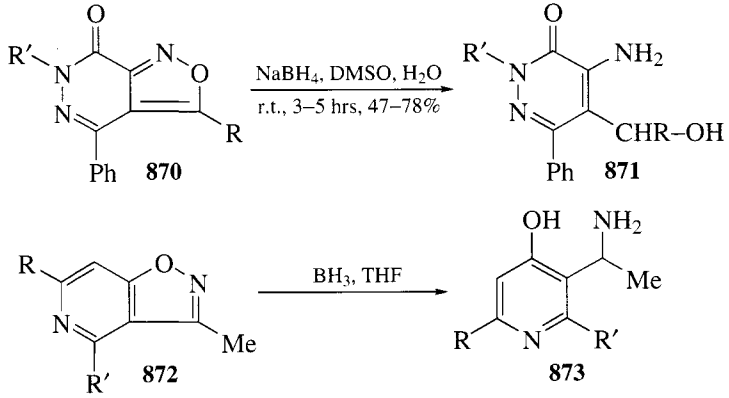


867 **853** **868**



869

Further reagents for hydrogenolysis include $NaBH_4$[3/91] and BH_3,[2/82] the former effected ring opening of isoxazolo[3,4-*d*]pyridazine derivatives **870**, to give **871**, while the latter cleaved isoxazolo[4,5-*c*]pyridines **872** to amino-alcohol **873**. In this conversion, substituents (R and R′) retard coordination of borane to the pyri-

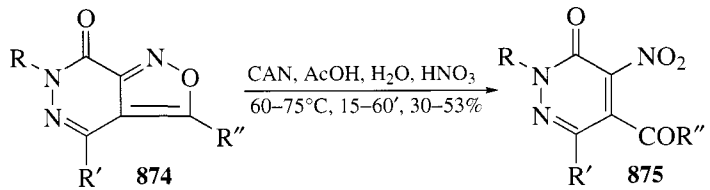


dine nitrogen atom (see also § 3.3.1.3) and force the reagent to attack the isoxazole ring.

3.3.2.2d. Oxidative Ring Opening

Cleavage of the isoxazole ring under oxidizing conditions cannot be considered a rare event,[22/91] but it is of no synthetic relevance since it promotes degradation of the substrate to benzoic acid by-products.

It is for this reason that a recently disclosed method for controlled oxidative ring opening has received attention. When 7-oxo-6,7-dihydroisoxazolo[3,4-*d*]pyridazines **874** are treated with ceric ammonium nitrate (CAN) at 60–75°C in acetic acid/water in the presence of nitric acid, selective ring opening of the isoxazole takes place and 5-acyl-4-nitro-3-oxo-2,3-dihydropyridazines **875** are obtained in fair yields.[6/89,4/91,7/91]



At the moment there are an insufficient number of examples to predict whether this reaction is a curiosity or a potentially valuable tool for the introduction of a nitro group in electron-poor heterocycles. Certainly further research is warranted to define the limits of the reaction.

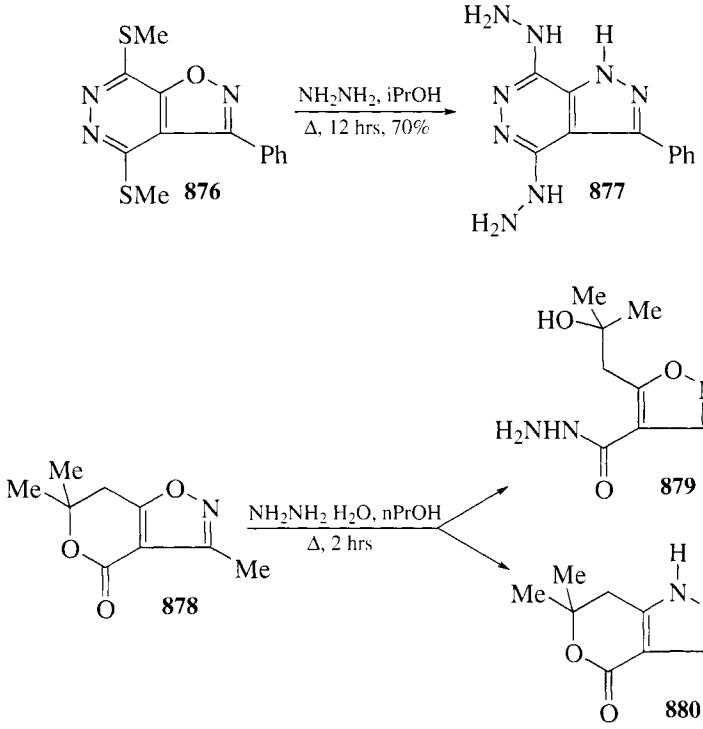
3.3.2.3. Ring Transformations into Other Heterocyclic Systems

Ring transformation of isoxazole derivatives is a well-known method for synthesis of other heterocycles even if this may sometimes be an undesired side

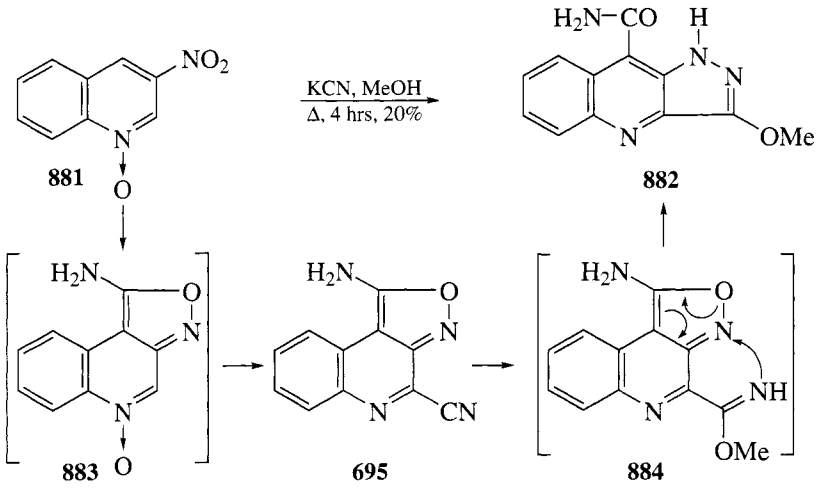
reaction promoted by the ring cleavage of isoxazole under the experimental conditions.

3.3.2.3a. Transformations under Chemical Conditions

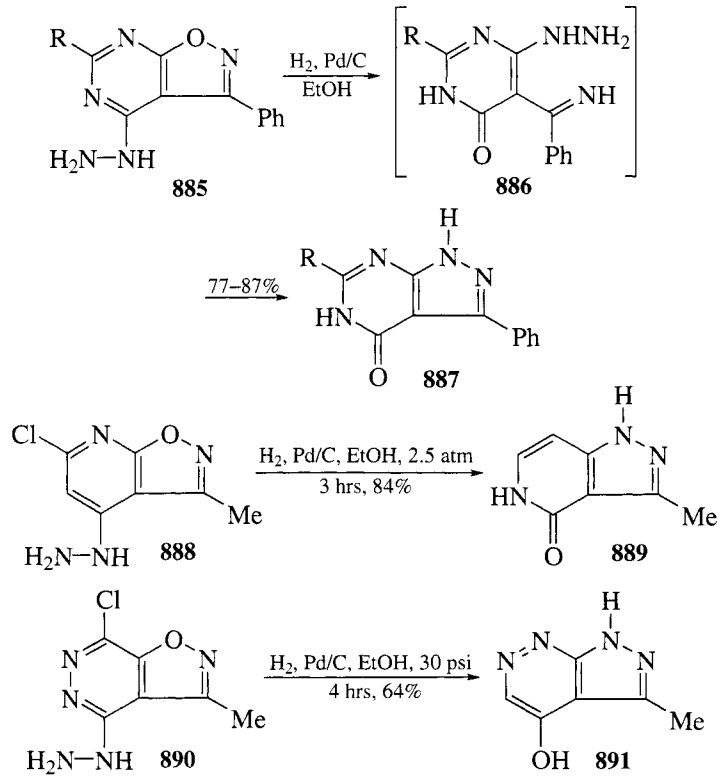
A reaction often observed when condensed isoxazoles are treated with hydrazine is the conversion of the isoxazole nucleus into a pyrazole. For example, 4,7-dimethylthio-3-phenylisoxazolo[4,5-*d*]pyridazine **876**, when treated with hydrazine, gave 4,7-dihydrazino-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyridazine **877**.[11/66] Similarly, 3,6,6-trimethyl-4-oxo-6,7-dihydro-4*H*-pyrano[3,4-*d*]isoxazole **878** underwent the desired cleavage of the lactone ring, to afford **879**, as well as competing hydrazinolysis of the isoxazole ring, which produced **880**.[4/81]



During a study directed toward the synthesis of methoxycyano heterocyclic *N*-oxides and condensed aminoisoxazoles, 3-nitroquinoline-1-oxide **881** was treated with methanolic potassium cyanide.[4/71] In addition to the expected 3-methoxy-4-cyanoquinoline-1-oxide, 3-methoxy-1*H*-pyrazolo[4,3-*b*]quinoline-9-carboxamide **882** was obtained. Formation of the latter is envisioned to result from reductive cyanation of 1-aminoisoxazolo[3,4-*c*]quinoline-5-oxide **883**, to give **695**, a product previously prepared by an independent route. When **695** was subjected to treatment with methanol, intramolecular cyclization to **882** through the intermediacy of **884** occurred.

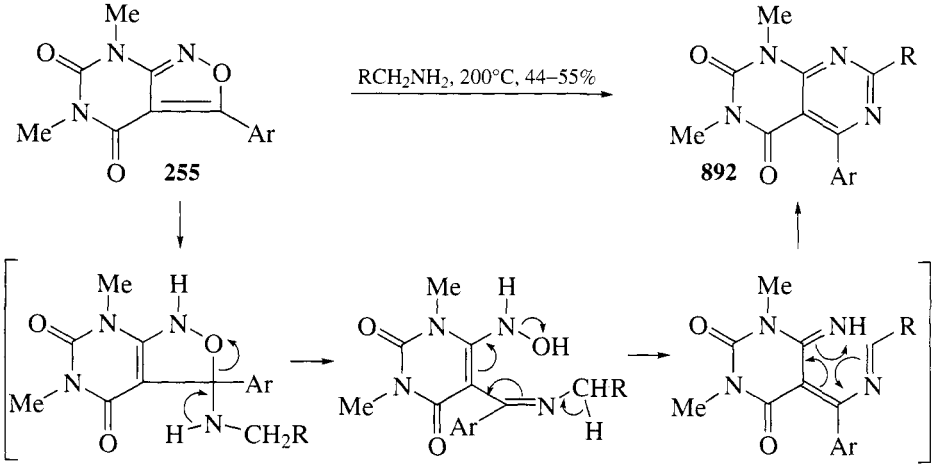


The hydrogenation of hydrazino-substituted condensed isoxazoles is the best route available for their conversion into condensed pyrazoles. Hydrogenation of 4-hydrazino-3-phenylisoxazolo[5,4-*d*]pyrimidines **885** with palladium–charcoal gave pyrazolopyrimidinones **887**, in excellent yields, through the intermediacy

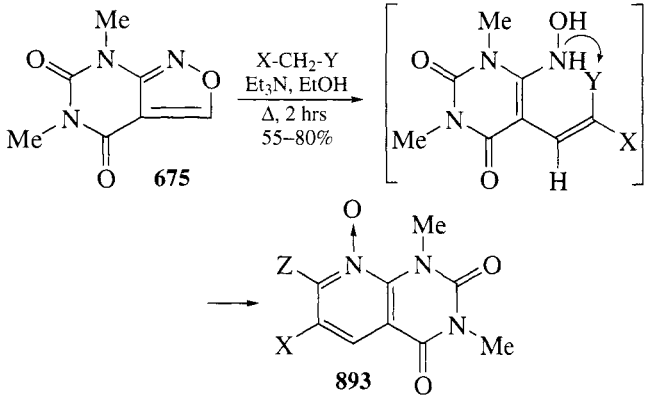


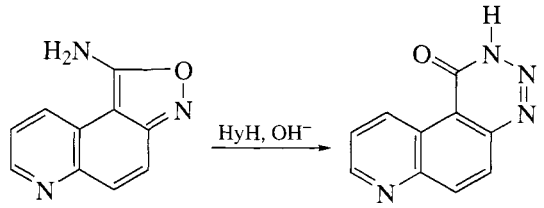
of pyrimidones **886**.[4/67] Similarly, 6-chloro-4-hydrazino-3-methylisoxazolo[5,4-*b*]pyridine **888** was efficiently converted to pyrazolopyridone **889**,[4/88] while 7-chloro-4-hydrazino-3-methylisoxazolo[4,5-*d*]pyridazine **890** gave the pyrazolo [3,4-*c*]pyridazine **891**.[1/85] In both reactions, cleavage of the isoxazole ring was coupled with reductive dechlorination.

Cleavage of condensed isoxazoles may be used for their conversion into six-membered ring heterocycles. Isoxazolo[3,4-*d*]pyrimidine-4,6-diones **255**, when heated with benzylamine (or its 3-pyridyl analog), gave pyrimido[4,5-*d*]pyrimidines **892**[14/79, 5/81] through a proposed nucleophilic ring opening followed by a 6π-electrocyclic ring closure and an oxidation.



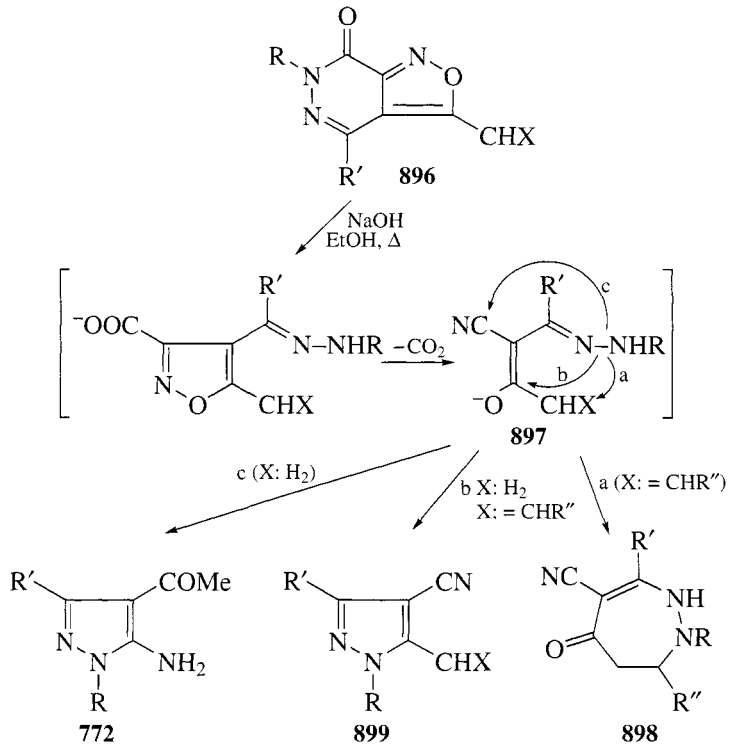
Isoxazoles may also be converted into pyridines or triazines. Isoxazolo[3,4-*d*]pyrimidine-4,6-dione **675**, when condensed with active methylene compounds (X = CN, COOEt, $CONH_2$; Y = CN, COOEt), led to ring opening and cyclization to pyridopyrimidine-8-oxides **893**,[6/83] whereas 1-aminoisoxazolo[4,3-*f*]quinoline **894** gave the triazinoquinoline derivative **895** with hydroxylamine.[20/83]





894 **895**

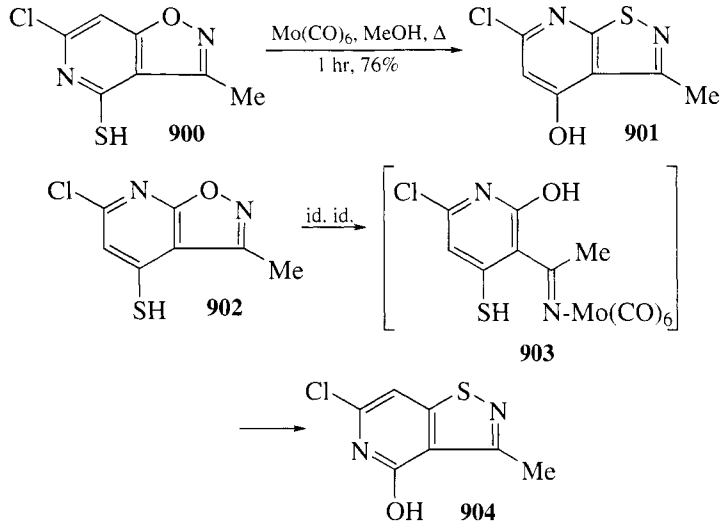
Suitably substituted derivatives allow complex transformations that involve ring opening of both the isoxazole and adjacent heterocyclic ring. Under basic conditions, isoxazolo[3,4-*d*]pyridazin-7-ones **896** may give 1,2-diazepin-5-ones **898**[9/84,7/88,6/91] or pyrazoles **772** and **899**[7/85,7/88,6/91] depending on the nature of the substituents. In these transformations, opening of the pyridazine ring by nucleophilic attack at the heterocyclic lactam group is followed by ring opening of the isoxazole with loss of CO_2. At this stage, intramolecular cyclization may occur at various positions in the intermediate **897** and three products may be obtained, in ratios that depend largely on the nature of the substituents.



772 **899** **898**

The reaction of 6-chloro-3-methylisoxazolo[4,5-*c*]pyridine-4-thiol and its isomer, 6-chloro-3-methylisoxazolo[5,4-*b*]pyridine-4-thiol (**900** and **902**, respec-

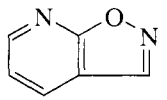
tively), with molybdenum hexacarbonyl has been reported. The products, isothiazolo[5,4-*b*]pyridine **901** and isothiazolo[4,5-*c*]pyridine **904**,[2/90] are presumed to arise from a nitrene such as **903** (represented as its molybdenum hexacarbonyl complex), which can be also produced from the photochemical ring opening of the isoxazole ring. This topic will be further addressed in the next section.



3.3.2.3b. Tranformations under Photochemical Conditions

Several studies have been devoted to the ring opening of isoxazoles by irradiation with UV light.[22/91] The photochemical pathway is usually considered to involve the cleavage of the weak N–O bond with concomitant formation of a nitrene intermediate that evolves further to an aziridine and/or keteneimine, followed by a final isomerization to oxazole.

Early studies on the photochemical behavior of condensed isoxazole systems were mainly concerned with the synthesis of oxazoles. The photochemical conversion of derivatives of isoxazolo[5,4-*b*]pyridine **70**,[3/79] isoxazolo[5,4-*c*]pyridine **218**,[4/82] isoxazolo[3,4-*d*]pyrimidin-4,6-dione **255**,[3/78] and 5*H*-cyclo-



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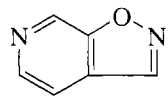

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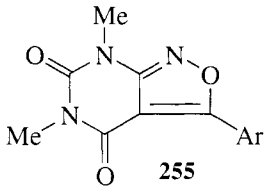

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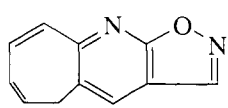
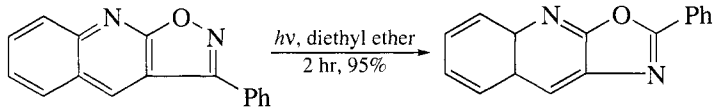


398

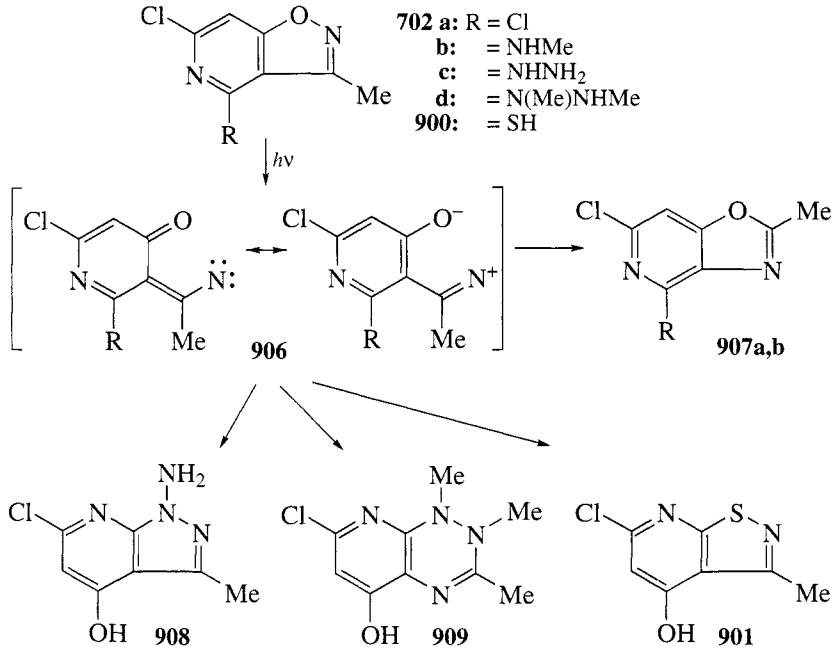
hept[*b*]isoxazolo[4,5-*e*]pyridine **398**[3/79] into the corresponding oxazoles has been studied.

Conversion of 3-phenylisoxazolo[5,4-*b*]quinoline (**401**) to 2-phenyloxazolo[5,4-*b*]quinoline **905** proceeded in nearly quantitative yield,[3/79] although other substrates were less efficient participants and the yields for these processes ranged within 10–50%.

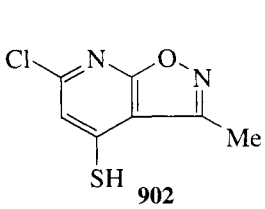


401 **905**

In an effort to detect the intermediate of the photochemical process, an in-depth study was undertaken on 6-chloro-3-methylisoxazolo[4,5-*c*]pyridines (**702a-d**,**900**), carrying different substituents in the 4 position.[1/81,2/90] Irradiation of 4-chloro- and 4-methylamino derivatives (**702a**,**b**) gave the expected oxazoles **907a**,**b**, but the 4-hydrazino derivative **702c** gave 1-aminopyrazolo[3,4-*b*]pyridine **908**. The 4-(*N*,*N*′-dimethylhydrazino) derivative **702d** gave pyrido[3,2-*e*]-1,2,4-triazine **909**, and the 4-thiol derivative **900** gave isothiazolo[5,4-*b*]pyridine **901**. All these results are consistent with a nitrene intermediate (**906**) that is trapped intramolecularly by substituent atoms.



Similar results were obtained with 6-chloro-3-methylisoxazolo[5,4-*b*]pyridine-4-thiol **902**,[2/90] 6-chloro-3-methyl-4-hydrazinoisoxazolo[5,4-*b*]pyridine **888**,[4/88] and 7-chloro-3-methyl-4-hydrazinoisoxazolo[4,5-*d*]pyridazine **910**.[1/85]



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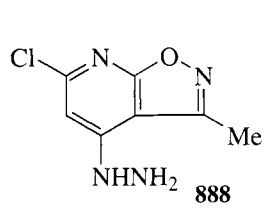

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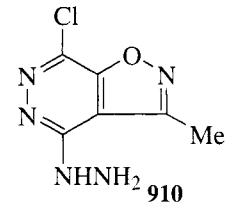
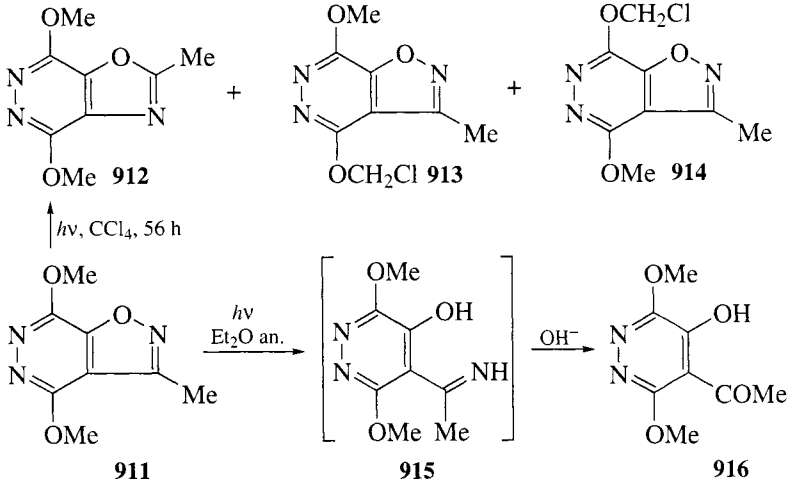


910

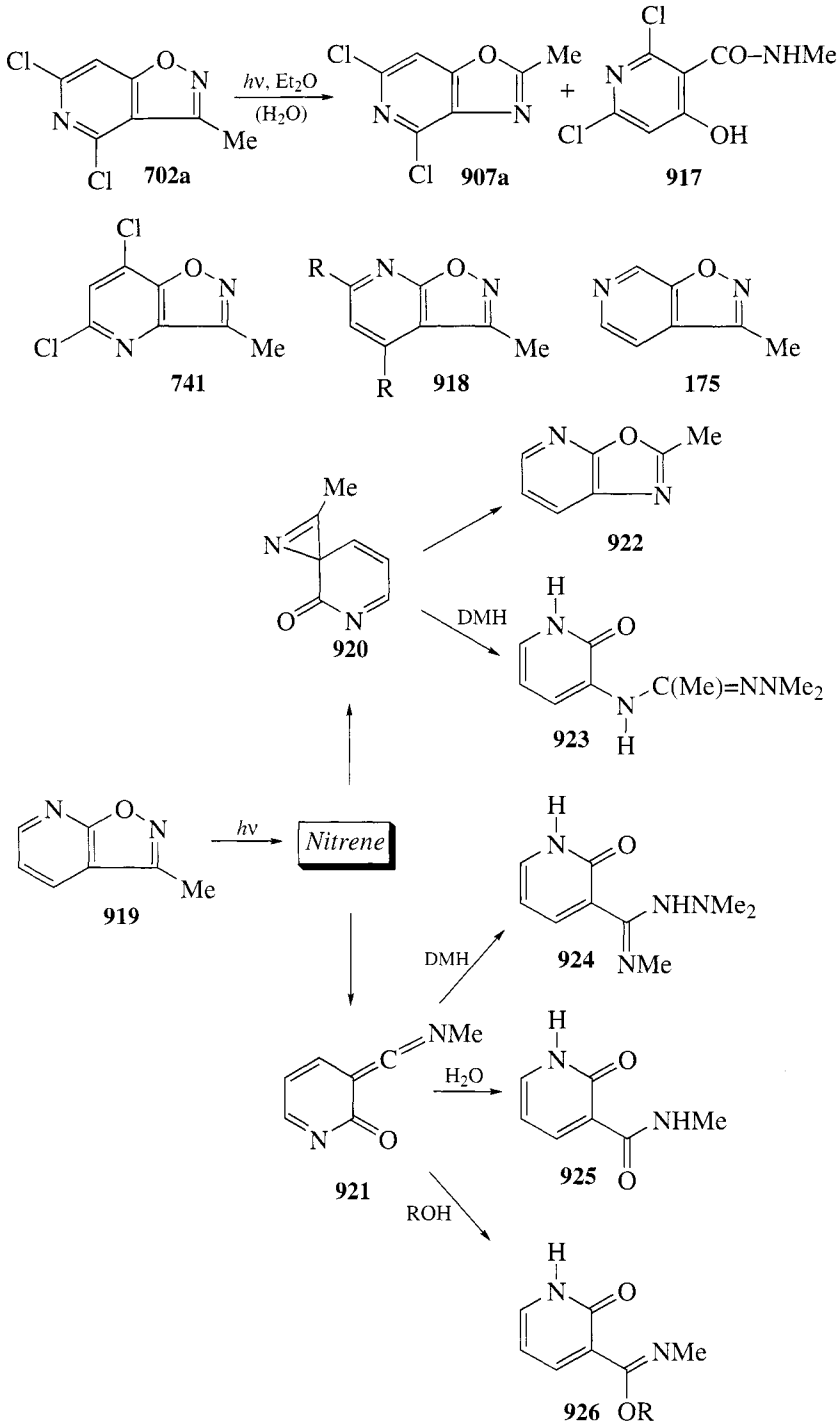
Further work was needed to address questions that remained open such as:

1. Which intermediate was involved in the conversion of the nitrene to the oxazole?
2. If 4,7-dimethoxy-3-methylisoxazolo[4,5-*d*]pyridazine **911**[1/85] in carbon tetrachloride gave oxazole **912** (in addition to chloromethoxyisoxazoles **913** and **914**), but in diethylether gave hydrogen abstraction to **915** (eventually hydrolyzed to **916**), what was the role of the solvent?



The solvent was found to be important in the irradiation of 4,6-dichloro-3-methylisoxazolo[4,5-*c*]pyridine **702a**. In anhydrous ether only the oxazole **907a** was obtained,[1/81] while in wet ether, in addition to **907a** (obtained in 55% yield), the product of a 1–2 methyl group shift, *N*-methylcarboxamide **917** was isolated in 9% yield.[4/88]

Derivatives of isoxazolo[4,5-*b*]-, isoxazolo[5,4-*b*]-, and isoxazolo[5,4-*c*]pyridines (**741**, **918**, and **175**)[4/88] behaved similarly; the corresponding oxazoles and carboxamides were obtained in ratios ranging from 6:1 to 18:1.


hν, Et2O
(H2O)
702a
907a
917
741
918
175
920
922
DMH
923
C(Me)=NNMe2
919
hν
Nitrene
DMH
924
NHNMe2
NMe
921
H2O
925
NHMe
ROH
926
OR

A careful flash photolysis study on 3-methylisoxazolo[5,4-*b*]pyridine **919**[7/90] in various solvents gave some answers to the questions listed above. Independent of the solvent, an intermediate nitrene gives rise to both spiroazirine **920** and keteneimine **921**. These transient species exhibit absorption spectra in *i*-PrOH with λ_{max} at 335 and 370 nm, respectively. Spiroazirine **920** decayed, following first-order kinetics, to oxazole **922** (or to hydrazoamide **923** if the reaction is performed in the presence of *N*,*N*-dimethylhydrazine–DMH). Kinetic data indicate that the rate is affected by the solvents, such that k at 20°C was determined to be 75, 390, and 0.6 s^{-1} in *i*-PrOH, MeOH, and MeCN, respectively. The behavior of keteneimine **921** followed a double exponential decay and gave (with DMH, H_2O, or ROH) hydrazidoimine **924**, amide **925**, and iminoether **926**.

With these results in hand, the photochemistry of condensed isoxazoles may become a predictable reaction of synthetic value.

3.4. BIOLOGICALLY ACTIVE CONDENSED ISOXAZOLES

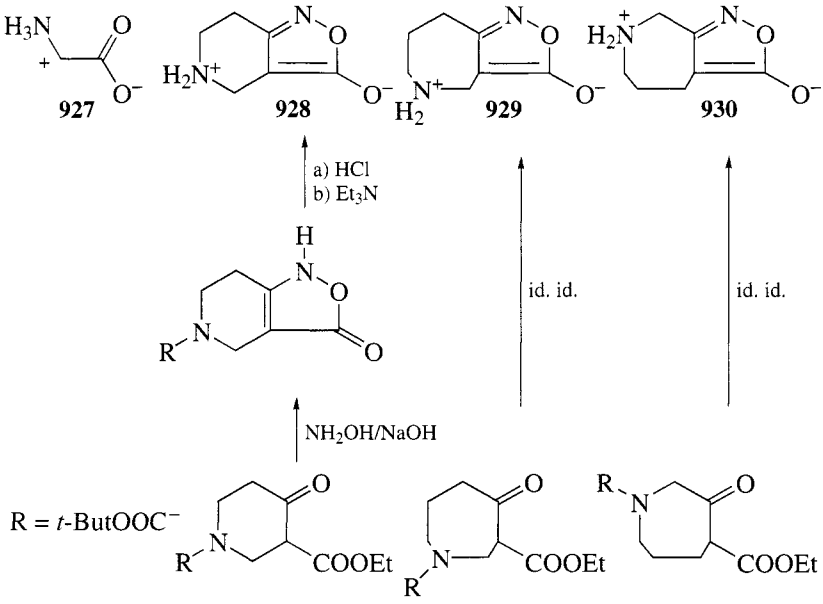
Given the structural and functional diversity of many of the previously-described biologically active isoxazole derivatives, it is difficult to present a concise structure–activity correlation. Nevertheless, one class of compounds is amenable to such a discussion.

It is known that a number of aminoacids and aminoacid derivatives play an important role in the function of the mammalian central nervous system. While glycine is the major inhibitory neurotransmitter in the spinal cord, 4-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain, and (*S*)-glutamic and (*S*)-aspartic acids are putative central excitatory neurotransmitters. Furthermore, a cholinergic deficit has been identified as a characteristic of Alzheimer's disease.

In an effort to design therapeutically useful agonists and antagonists, semi-rigid and rigid analogs of the aminoacid-derived neurotransmitters have been synthesized. Among the semirigid structures, several isoxazoles have proved to be useful agents. Obviously the next step was to test rigid models derived from condensed isoxazole ring systems, and this section contains a short review of these efforts. Each structure will be reviewed on the basis of the reported biological activity, and sometimes the same ring system will fall, properly, in two different sections.

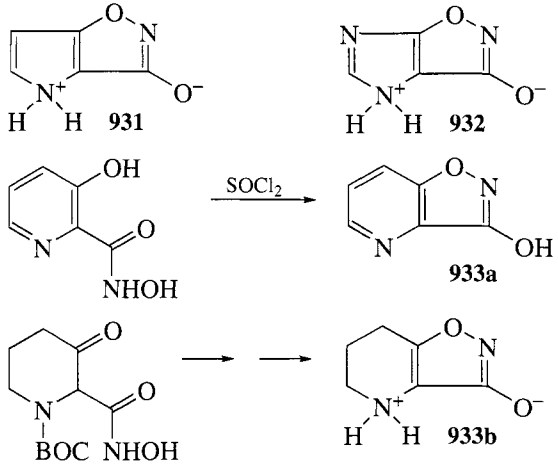
3.4.1. Glycine Analogs

To probe the neurochemical role of glycine (**927**), three bicyclic zwitterionic isoxazoles derived from 3-hydroxyisoxazolo[4,3-*c*]pyridine (**928**), 4*H*-isoxazolo[4,3-*c*]azepine (**929**), and the 4*H*-isoxazolo[3,4-*c*]azepine (**930**) ring sytems were synthesized.[1/86]



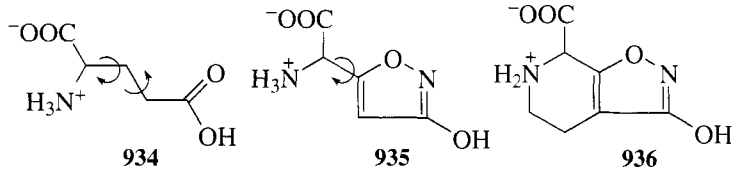
All the zwitterionic compounds prepared above are glycine antagonists, but the isoxazolo[4,3-*c*]pyridine derivative (**928**) is also a moderately potent inhibitor of GABA uptake and will be discussed in more detail.

Evaluation of the structural complementarity between glycine and the proposed agonists, as either the neutral or the zwitterionic species, by molecular modeling techniques has revealed significant differences in calculated parameters. For instance, the separation between nitrogen and oxygen in 3-hydroxy-4*H*-pyrrolo[2,3-*d*]isoxazole (**931**), 3-hydroxy-4*H*-imidazo[4,5-*d*]isoxazole (**932**), and 3-hydroxy-isoxazolo[4,5-*b*]pyridine (**933a,b**) derivatives compared with that observed in glycine was found to be greater by at least 0.53 Å.[1/89]



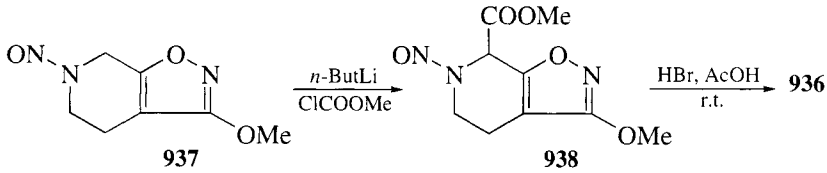
3.4.2. Glutamic Acid Agonists

Naturally occurring aminoacids, such as ibotenic acid (**935**), that are semi-rigid heterocyclic analogs of glutamic acid (**934**), have been found to stimulate neurons in the mammalian central nervous system. An obvious extension was to test 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-7-carboxylic acid (**936**) as a conformationally constrained analog of **935**.



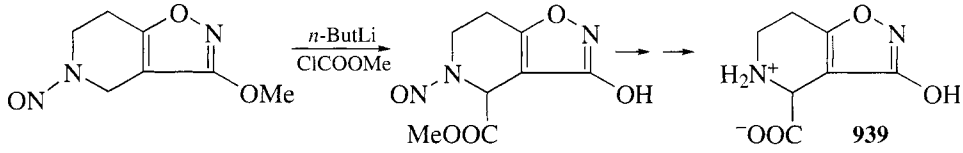
934 **935** **936**

Acylation of 3-methoxy-6-nitroso-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine (**937**) gave the *N*-nitrosamine **938**, which was subsequently converted into the target **936** on treatment with hydrogen bromide in acetic acid at room temperature.[24/84,3/85]



937 **938**

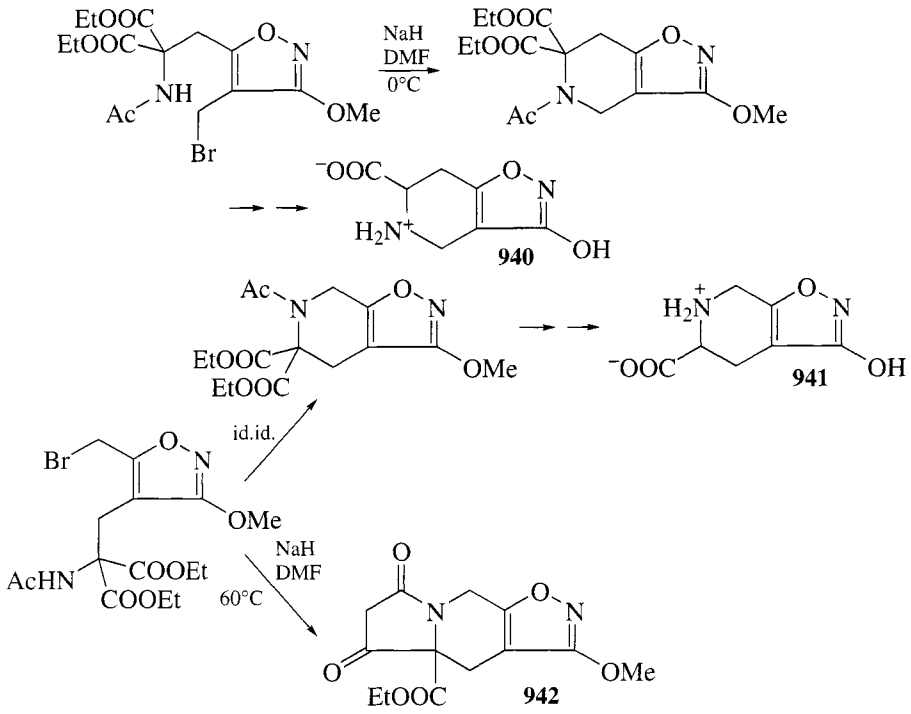
The same synthetic approach was employed to give 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-4-carboxylic acid **939**.[2/86]



939

Two related analogs, 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridine-6-carboxylic acid (**940**) and 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine-5-carboxylic acid (**941**), were synthesized by intramolecular cyclization.[3/85, 2/86] If the reaction is conducted at 60°C, a derivative (**942**) of isoxazolo[5,4-*f*] indolizine, is obtained as the major product.[16/85]

With the aid of X-ray crystallographic[3/85] and ^{1}H-NMR[2/86] analysis, acids **936** and **940** were shown to adopt conformations in which the carboxylate group occupies an equatorial position. The newly synthesized compounds were evaluated as agonists and antagonists of the excitatory aminoacid receptors on spinal



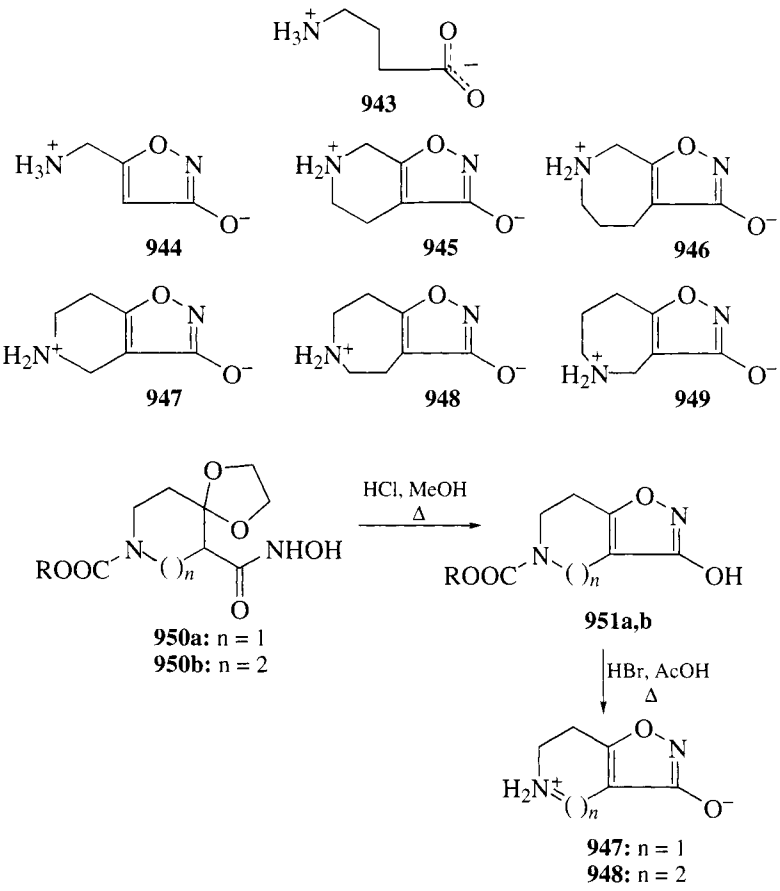
neurons. However, neither **939** or **940** showed any significant effects at these receptors, although **941** and **936** proved to be potent agonists of glutaric acid receptors.

3.4.3. GABA Agonists and Antagonists

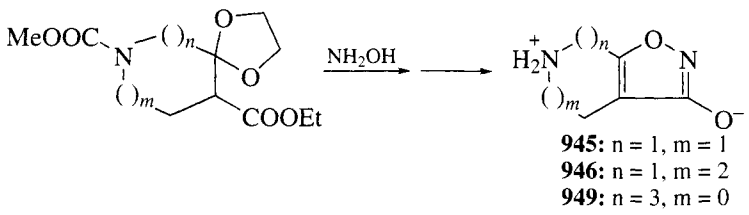
4-Aminobutyric acid (GABA, **943**) is reported to be the major inhibitory neurotransmitter in the brain. Since the semirigid analog muscimol **944** was found to be a weak inhibitor of GABA uptake, reasearch on bicyclic derivatives was initiated. From this effort were produced the 3-hydroxytetrahydro- derivatives of isoxazolo[5,4-c]pyridine (**945**) and 4*H*-isoxazolo[5,4-*c*]azepine (**946**), as well as derivatives of isoxazolo[4,5-*c*]pyridine (**947**), 4*H*-isoxazolo[4,5-*d*]azepine(**948**), and 4*H*-isoxazolo[4,5-*c*]azepine (**949**).

Compounds **947** and **948** were prepared by the acid-catalyzed hydrolysis and subsequent cyclization of the ketal derivatives of the appropriate β-oxo-hydroxamic acids **950a,b**.[5/74] Cleavage of the amine protecting group of **951a,b** provided the desired materials.

Surprisingly, **947** was a more potent inhibitor of GABA uptake than muscimol,[18/75] whereas **948**, although shown by X-ray analysis to have the expected zwitterionic structure, was inactive.[16/76]



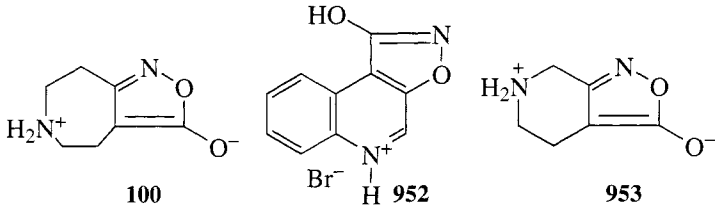
In analogy with the previously described route, ethylene ketals derived from 3-hydroxy-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*c*]azepines (**949**), 3-hydroxy 5,6,7,8-tetrahydro-4*H*-isoxazolo[5,4-*c*]azepines (**946**), and 3-hydroxy-4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridine (**945**) were prepared.[4/77,14/82]



The clinical candidate[20/81] 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol **945** (THIP) is a potent GABA receptor agonist *in vivo* and *in vitro*.[17/79,5/85] As a consequence of its therapeutic promise and the need for detailed pharmacokinetic

studies, THIP has become the topic of extended research involving deuterium-labelled[20/82] and various *N* and *O* derivatives.[3/82,4/83,27/89]

Included among the derivatives of THIP that have been prepared are 4*H*-isoxazolo[3,4-*d*]azepine derivative **100**,[15/73] isoxazolo[5,4-*c*]quinoline derivative **952**,[21/89] and isoxazolo[3,4-*c*]pyridine derivative **953**,[1/79] also referred to as "*iso*-THIP", all of which have proved to be less active than THIP itself.

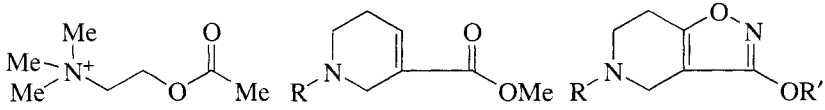


100 **952** **953**

Molecular comparison of the GABA structure with some agonist and antagonist derivatives, offers some insight into the structural basis of their mechanism of action.[4/85,21/87]

3.4.4. Muscarinic Agonists

The neurotransmitter acetylcoline **954** and the isosteric analogs norarecoline (**955a**) and arecoline (**955b**) have been used as leads in the search for therapeutically useful muscarinic agonists.

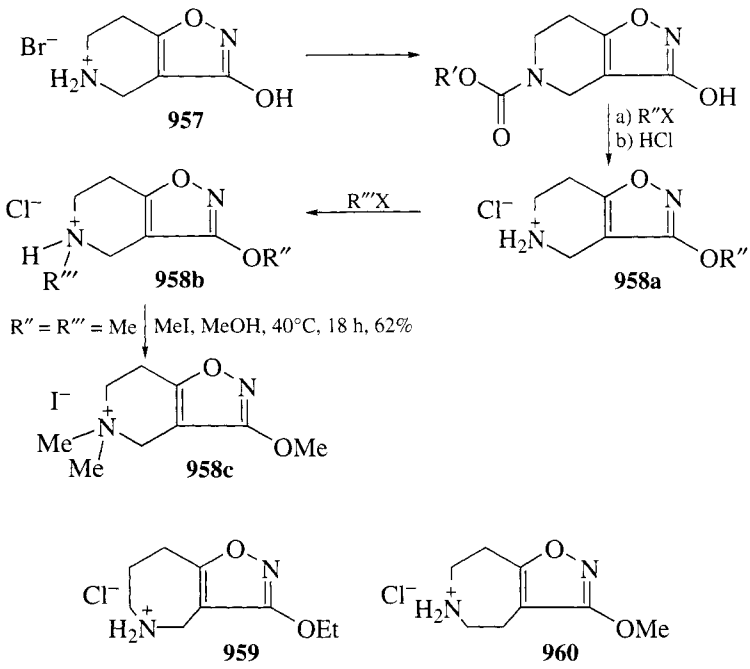


954 **955a:** R = H **955b:** R = Me **956**

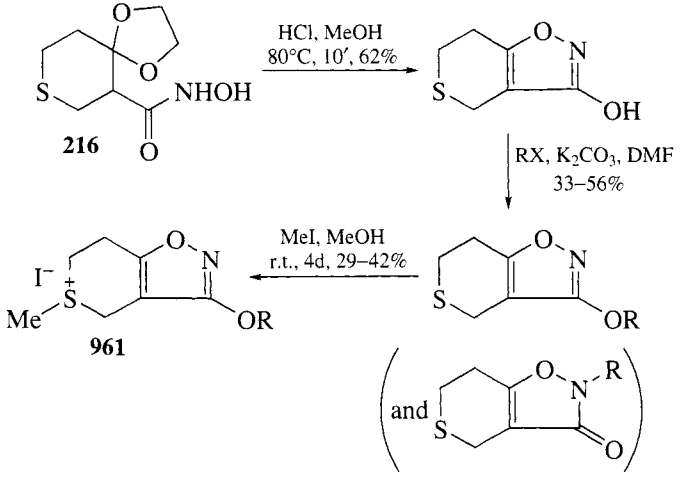
The first conformationally restricted analog to be tested contained the 4,5,6,7-tetrahydroisoxazolo[4,5-*c*]pyridin-3-ol skeleton (**956**), a compound whose synthesis has already been reported.[5/74,3/84]

Protection of the 5-amino group in **957** allowed the preparation of several 3-alkoxy-5-unsubstituted and 3-alkoxy-5-substituted derivatives (**958a–c**),[3/86,5/88] whose low pK_a values are likely to facilitate passage of the compounds through the blood–brain barrier.

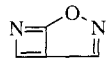
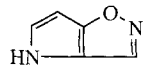
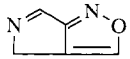
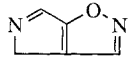
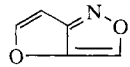
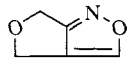
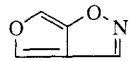
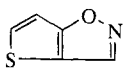
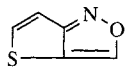
Some interesting clinical results were obtained with 3-ethoxy-5,6,7,8-tetrahydro-4*H*-isoxazolo[4,5-*c*]azepine **959**[11/89] and 3-methoxy-4,5,6,7-tetrahydro-4*H*-isoxazolo[4,5-*d*]azepine **960**.[9/89] The former was found to be an effective enhancer of cognitive function when tested in patients suffering from Alzheimer's disease. The latter has been demonstrated to reverse electroconvulsive shock–induced amnesia.

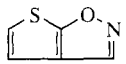
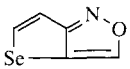
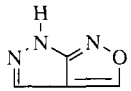
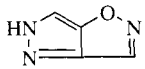
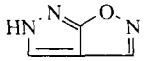
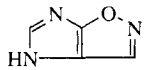
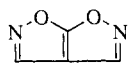
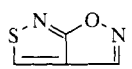
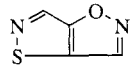


This section concludes with the synthesis of the first isoxazole condensed with sulfur heterocycle, behaving as muscarinic agonist. In a manner similar to that described for **947** and **948**, 3-alkoxy-5-methyl-6,7-dihydro-4*H*-thiopyrano[3,4-*d*]isoxazol-5-ium derivatives (**961**) were synthesized from hydroxamic acid **216**.[5/88] Depending on the nature of the substituents, these compounds were found to behave as muscarinic agonists or antagonists.

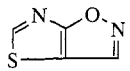
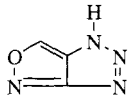
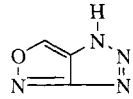
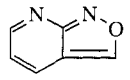
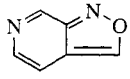
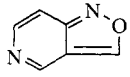
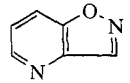
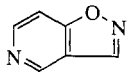


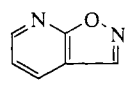
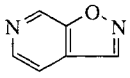
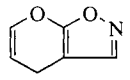
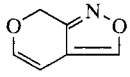
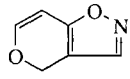
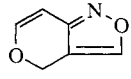
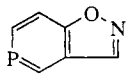
3.5. RING INDEX

Basic heterocylic systems[a]	Formula numbers	References
C_3N-C_3NO		
 Azeto[3,2-*d*]isoxazole	**465**	1/76, 20/76, 23/77
C_4N-C_3NO		
 4*H*-Pyrrolo[2,3-*d*]isoxazole	**931**	1/89
 4*H*-Pyrrolo[3,4-*c*]isoxazole	**145, 317**	5/67, 1/68, 5/71, 9/79
 4*H*-Pyrrolo[3,4-*d*]isoxazole	**329**	1/82,14/87
C_4O-C_3NO		
 Furo[3,2-*c*]isoxazole	**248**	2/76
 4*H*,6*H*-Furo[3,4-*c*]isoxazole	**316**	1/75, 16/91
 Furo[3,4-*d*]isoxazole	**555, 557**	4/89, 1/91, 15/91, 17/91
C_4S-C_3NO		
 Thieno[2,3-*d*]isoxazole	**117, 163, 684, 685, 686, 778**	5/87, 18/87, 3/88
 Thieno[3,2-*c*]isoxazole	**249, 612, 687, 688, 690**	2/75, 2/76

Basic heterocylic systems[a]	Formula numbers	References
	**164**	3/88
Thieno[3,2-*d*]isoxazole		
$C_4Se–C_3NO$		
	**250, 689, 691**	2/75, 2/76
Selenolo[3,2-*c*]isoxazole		
$C_3N_2–C_3NO$		
	**124, 477**	1/84, 2/84
6*H*-Pyrazolo[3,4-*c*]isoxazole		
	**588, 613**	1/88
5*H*-Pyrazolo[3,4-*d*]isoxazole		
	**192, 476, 851**	3/59, 5/65
5*H*-Pyrazolo[4,3-*d*]isoxazole		
	**932**	1/89
4*H*-Imidazo[4,5-*d*]isoxazole		
$C_3NO–C_3NO$		
	**191, 838, 862**	1/59
Isoxazolo[4,5-*d*]isoxazole		
$C_3NO–C_3NS$		
	**479**	16/90
Isothiazolo[4,3-*d*]isoxazole		
	**328, 755**	2/89
Isothiazolo[5,4-*d*]isoxazole		

(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
 Thiazolo[5,4-*d*]isoxazole	**126**	25/89
$C_3NO-C_2N_3$		
 1*H*-Isoxazolo[3,4-*d*]-1,2,3-triazole	**468**	1/10
 1*H*-Isoxazolo[4,5-*d*]-1,2,3-triazole	**470, 649**	1/70, 1/78
C_3NO-C_5N		
 Isoxazolo[3,4-*b*]pyridine	**159**	22/89
 Isoxazolo[3,4-*c*]pyridine	**85, 290, 291, 953**	1/79, 14/82, 28/84, 21/87
 Isoxazolo[4,3-*c*]pyridine	**46, 86, 170, 171, 388, 785, 786, 928**	1/57, 2/70, 6/71, 14/76, 2/77, 2/84, 1/86
 Isoxazolo[4,5-*b*]pyridine	**154, 209, 213, 215, 337, 378a, 386, 701, 741, 742, 743, 933**	2/80, 1/82, 15/82, 1/83, 2/85, 15/85, 19/86, 6/87, 19/87, 4/88, 1/89
 Isoxazolo[4,5-*c*]pyridine	**155, 334, 370, 380, 627, 628, 632, 633, 634, 635, 651, 652, 653, 702, 727, 728, 729, 730, 731, 732, 733, 756, 843, 872, 900, 939, 940, 947, 951, 956, 957, 958**	1/12, 5/74, 3/75, 18/75, 11/76, 1/77, 2/77, 10/77, 11/77, 12/77, 13/77, 14/77, 15/77, 9/78, 10/78, 11/78, 12/78, 2/79, 11/80, 12/80, 13/80, 1/81, 2/82, 15/82, 20/82, 3/84, 3/85, 2/86, 3/86, 19/87, 21/87, 4/88, 5/88, 12/88, 2/90

Basic heterocylic systems[a]	Formula numbers	References
 Isoxazolo[5,4-*b*]pyridine	**70, 149, 221, 312b, 344, 346, 350, 351, 353, 354, 355, 357, 359, 361, 364, 365, 372, 374, 377, 382, 384, 390, 394, 617, 618, 619, 626, 656, 657, 680, 681, 682, 683, 700, 734, 735, 736, 737, 738, 739, 740, 746, 747, 749, 751, 768, 844, 855, 888, 902, 918, 919**	11/68, 12/68, 1/72, 8/72, 9/72, 10/72, 1/73, 2/73, 16/73, 20/73, 4/74, 4/75, 5/75, 10/75, 11/75, 376, 12/76, 13/76, 1/77, 16/77, 2/78, 2/79, 3/79, 13/79, 1/80, 2/81, 3/81, 18/81, 19/81, 15/82, 2/83, 3/83, 15/83, 4/84, 5/84, 6/85, 4/86, 17/86, 1/87, 7/87, 15/87, 19/87, 2/88, 4/88, 13/88, 26/89,2/90,7/90,7/90, 8/90, 21/90
 Isoxazolo[5,4-*c*]pyridine	**175, 218, 368, 936, 937, 938, 941, 945**	4/77, 1/79, 17/79, 18/79, 20/81, 3/82, 4/82, 14/82, 15/82, 20/82, 4/83, 24/84, 3/85, 4/85, 5/85, 21/87, 4/88, 27/89
C_3NO-C_5O		
 4*H*-Pyrano[3,2-*d*]isoxazole	**546, 547, 570, 571, 575, 576**	7/66, 2/68, 3/70, 1/71, 2/71, 6/75, 12/75, 2/83, 17/83, 26/89
 7*H*-Pyrano[3,4-*c*]isoxazole	**318**	3/80
 4*H*-Pyrano[3,4-*d*]isoxazole	**108, 338, 535a, 752, 801, 878**	6/67, 15/75, 4/81, 4/89
 4*H*-Pyrano[4,3-*c*]isoxazole	**84, 109, 535b, 677, 679**	4/70, 7/71, 15/75, 7/84, 6/86
C_3NO-C_5P		
 Phosphorino[3,4-*d*]isoxazole	**307**	2/72

(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
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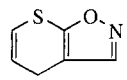
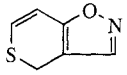
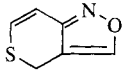
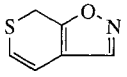
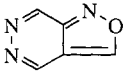
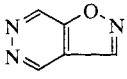
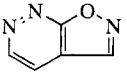
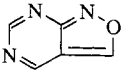
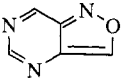
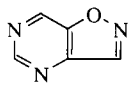
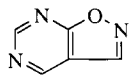
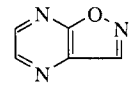
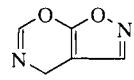
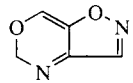
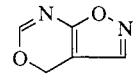
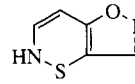
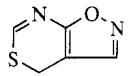
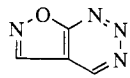
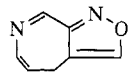
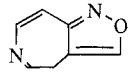
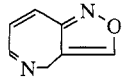
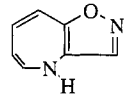
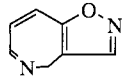
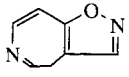
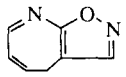
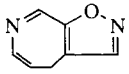
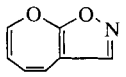
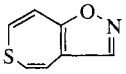
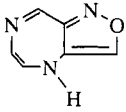
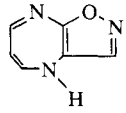
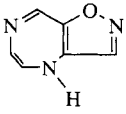
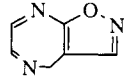
 4*H*-Thiopyrano[3,2-*d*] isoxazole	**549**	22/87
 4*H*-Thiopyrano[3,4-*d*] isoxazole	**217, 802, 961**	2/77, 5/88
 4*H*-Thiopyrano[4,3-*c*] isoxazole		2/77
 5*H*-Thiopyrano[4,3-*d*] isoxazole	**97, 803**	8/84
$C_3NO-C_4N_2$		
 Isoxazolo[3,4-*d*]pyridazine	**415, 417, 419, 421, 423, 425, 769, 774, 780, 781, 853, 870, 874, 896**	1/39, 2/56, 1/65, 4/65, 4/66, 5/66, 6/66, 10/67, 368, 1/69, 3/73, 4/76, 9/84, 7/85, 7/86 8/86, 7/88, 6/89, 2/91, 3/91, 4/91, 5/91, 6/91, 7/91
 Isoxazolo[4,5-*d*]pyridazine	**156, 168, 427, 639, 640, 641, 703, 704, 717, 718, 719, 720, 721, 876, 890, 910, 911, 913, 914**	3/66, 11/66, 3/67, 3/72, 1/85, 9/86, 1/90, 10/90
 Isoxazolo[5,4-*c*]pyridazine	**71, 128**	5/89, 9/90
 Isoxazolo[3,4-*d*]pyrimidine	**93, 151, 255, 273, 675, 676**	21/73, 22/73, 3/77, 17/77, 18/77, 3/78, 14/79, 5/81, 21/81, 5/83, 6/83, 16/83, 11/84, 18/85, 8/87
 Isoxazolo[4,3-*d*]pyrimidine	**262, 431**	3/62, 2/80

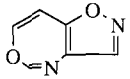
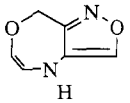
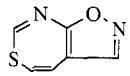
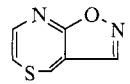
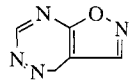
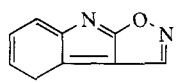
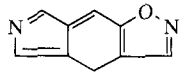
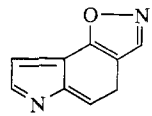
Basic heterocylic systems[a]	Formula numbers	References
 Isoxazolo[4,5-*d*]pyrimidine	**442, 636, 637, 638, 722, 723, 724, 725, 726**	3/66, 1/67, 2/67, 472
 Isoxazolo[5,4-*d*]pyrimidine	**153, 260, 429, 430, 433, 434, 437, 439, 444, 446, 447, 448, 449, 620, 621, 622, 624, 625, 642, 643, 644, 645, 646, 647, 648, 663, 664, 665, 668, 696, 697, 698, 699, 705, 706, 750, 885**	1/60, 2/64, 3/66, 4/67, 8/67, 7/69, 11/71, 11/72, 4/73, 5/73, 17/73, 22/73, 6/74, 7/74, 16/77, 15/78, 4/79, 4/80, 5/80, 6/81, 27/84, 10/86, 11/86, 16/87, 6/88, 14/88, 16/88, 7/89, 8/89, 28/89, 29/89, 30/89, 16/90, 17/90, 22/90, 23/90, 21/91
 Isoxazolo[4,5-*b*]pyrazine	**200, 453, 456, 666, 667, 692, 693, 846**	4/68, 6/73, 5/82, 6/82, 19/91
C_3NO-C_4NO		
 4*H*-Isoxazolo[4,5-*e*]-1,3-oxazine	**581**	1/15
 5*H*-Isoxazolo[4,5-*d*]-1,3-oxazine	**489, 490**	1/67, 11/90
 4*H*-Isoxazolo[5,4-*d*]-1,3-oxazine	**392**	1/87
C_3NO-C_4NS		
 5*H*-Isoxazolo[5,4-*e*]-1,2-thiazine	**623**	2/89

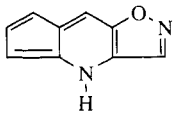
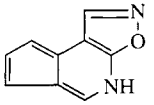
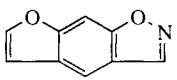
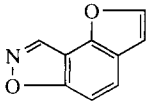
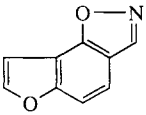
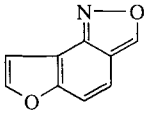
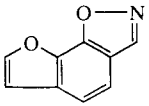
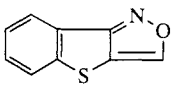
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
	**166**	25/84
4*H*-Isoxazolo[5,4-*d*]-1,3-thiazine		
$C_3NO-C_3N_3$		
	**493**	8/88
Isoxazolo[5,4-*d*]-1,2,3-triazine		
C_3NO-C_6N		
	**87, 930**	1/86
4*H*-Isoxazolo[3,4-*c*]azepine		
	**99, 100**	15/73, 21/87
4*H*-Isoxazolo[3,4-*d*]azepine		
	**88, 929**	1/86
4*H*-Isoxazolo[4,3-*c*]azepine		
	**484, 508, 514**	4/78, 7/81, 8/81, 2/87, 4/90, 20/90
4*H*-Isoxazolo[4,5-*b*]azepine		
	**219, 483, 949, 959**	4/77, 11/89, 20/90
4*H*-Isoxazolo[4,5-*c*]azepine		
	**948, 951b, 960**	5/74, 16/76, 9/89
4*H*-Isoxazolo[4,5-*d*]azepine		

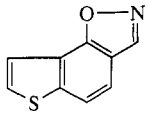
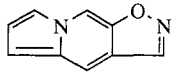
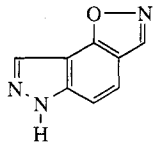
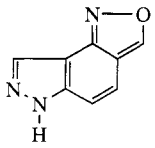
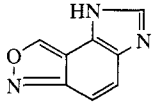
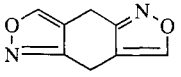
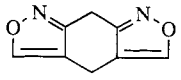
Basic heterocyclic systems[a]	Formula numbers	References
	**312c, 339, 757**	7/67, 4/86
4*H*-Isoxazolo[5,4-*b*]azepine		
	**101, 946**	4/77, 13/78
4*H*-Isoxazolo[5,4-*c*]azepine		
C_3NO-C_6O		
	**559**	15/91
Oxepino[3,2-*d*]isoxazole		
C_3NO-C_6S		
	**12, 865**	5/68
Thiaepino[4,5-*d*]isoxazolo		
$C_3NO-C_5N_2$		
	**503**	14/85
4*H*-Isoxazolo[4,3-*e*]-1,4-diazepine		
	**506, 608**	1/70, 6/73
4*H*-Isoxazolo[4,5-*b*]-1,4-diazepine		
	**512, 516, 758**	3/87, 11/90
4*H*-Isoxazolo[4,5-*e*]-1,4-diazepine		
	**497, 499, 501**	1/74, 19/91
4*H*-Isoxazolo[5,4-*e*]-1,4-diazepine		

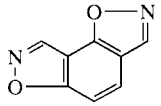
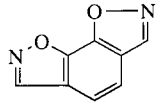
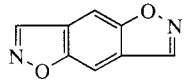
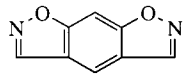
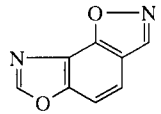
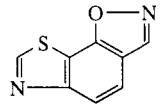
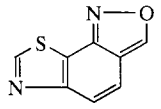
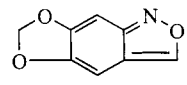
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
C_3NO-C_5NO		
 Isoxazolo[4,5-*d*]-1,3-oxazepine	**521**	4/81
 4*H*,8*H*-Isoxazolo[4,3-*e*]-1,4-oxazepine	**495**	10/89
C_3NO-C_5NS		
 Isoxazolo[5,4-*d*]-1,3-thiazepine		5/70
 Isoxazolo[5,4-*e*]-1,4-thiazepine	**518**	5/70, 13/75
$C_3NO-C_4N_3$		
 4*H*-Isoxazolo[5,4-*e*]-1,2,4-triazepine	**309**	8/85
$C_3NO-C_4N-C_6$		
 4*H*-Isoxazolo[5,4-*b*]indole	**112**	1/23
 4*H*-Pyrrolo[3,4-*f*]-1,2-benzisoxazole	**558**	15/91
 4*H*-Pyrrolo[2,3-*g*]-1,2-benzisoxazole	**13, 654, 655**	3/71, 7/82

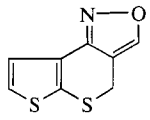
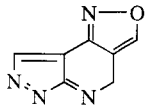
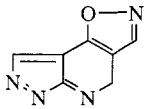
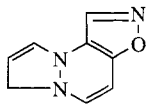
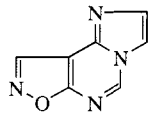
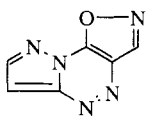
Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_5-C_5N$		
	**408b**	9/91
4*H*-Cyclopent[*b*]isoxazolo [5,4-*e*]pyridine		
	**595, 629a, 630a, 631a**	15/83, 21/83, 15/84, 17/87
4*H*-Cyclopent[*d*]isoxazolo [5,4-*b*]pyridine		
$C_3NO-C_4O-C_6$		
	**123, 187**	1/56, 1/58, 14/78, 12/84
Furo[3,2-*f*]-1,2-benzisoxazole		
		2/62
Furo[2,3-*e*]-1,2-benzisoxazole		
	**8, 754, 550a, 551a, 552a, 804**	5/76, 5/77, 19/80, 12/89, 13/89, 14/89
Furo[2,3-*g*]-2,1-benzisoxazole		
	**11**	5/76
Furo[2,3-*g*]-2,1-benzisoxazole		
	**193**	1/52
Furo[3,2-*g*]-1,2-benzisoxazole		
$C_3NO-C_4S-C_6$		
	**256**	5/78
1-Benzothieno[3,2-*c*]isoxazole		

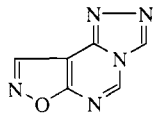
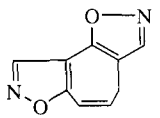
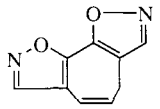
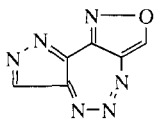
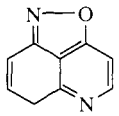
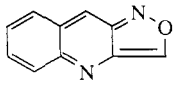
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
	**23, 783, 784**	12/71,30/84
Thieno[2,3-*g*]-1,2-benzisoxazole		
$C_3NO-C_4N-C_5N$		
	**942**	16/85
Isoxazolo[5,4-*f*]indolizine		
$C_3NO-C_3N_2-C_6$		
	**111**	6/76
4*H*-Pyrazolo[3,4-*g*]-1,2-benzisoxazole		
	**583, 614, 615**	8/82
4*H*-Pyrazolo[3,4-*g*]-2,1-benzisoxazole		
	**868**	18/83
1*H*-Imidazo[4,5-*e*]-2,1-benzisoxazole		
$C_3NO-C_3NO-C_6$		
	**253a, 269, 711, 716, 787, 788, 789**	6/78, 8/80, 9/80, 10/81, 9/82 3/90, 6/90, 8/91
4*H*,8*H*-Benzo[1,2-*c*:4,5-*c*′] diisoxazole		
	**89**	2/15, 1/53, 6/80
4*H*,8*H*-Benzo[1,2-*c*:5,4-c′]diisoxazole		

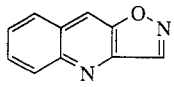
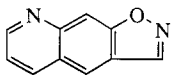
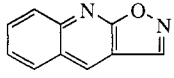
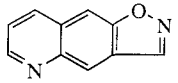
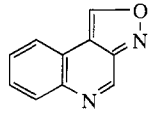
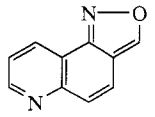
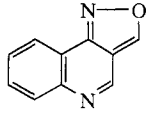
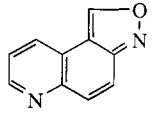
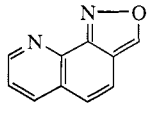
Basic heterocylic systems[a]	Formula numbers	References
 Benzo[1,2-*d*: 3,4-*d'*]diisoxazole	**182, 194**	1/64, 5/77, 20/80
 Benzo[1,2-*d*: 4,3-*d'*]diisoxazole	**195**	1/52
 Benzo[1,2-*d*: 4,5-*d'*]diisoxazole	**296, 297, 298, 299**	1/50, 9/68, 2/69, 18/73
 Benzo[1,2-*d*: 5,4-*d'*]diisoxazole	**196, 243**	1/14, 1/56
 Oxazolo[5,4-*g*]-1,2-benzisoxazole	**481**	10/87
$C_3NO-C_3NS-C_6$		
 Thiazolo[4,5-*g*]-1,2-benzisoxazole	**54, 805**	7/73
 Thiazolo[4,5-*g*]-2,1-benzisoxazole	**55**	7/73
$C_3NO-C_3O_2-C_6$		
 6*H*-1,3-Dioxolo[4,5-*f*]-2,1-benzisoxazole	**232, 238**	1/882, 1/895, 3/69

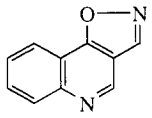
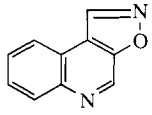
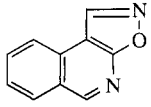
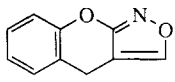
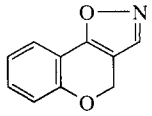
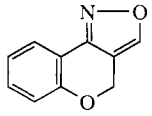
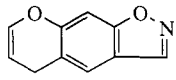
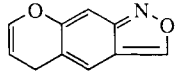
(*continued*)

Basic heterocyclic systems[a]	Formula numbers	References
$C_3NO-C_4S-C_5S$		
 4*H*-Thieno[3′,2′:5,6] thiopyrano[4,3-*c*]isoxazole	**320**	18/91
$C_3NO-C_3N_2-C_5N$		
 4*H*-Isoxazolo[3,4-*d*]pyrazolo [3,4-*b*]pyridine	**132**	18/86, 10/88
 4*H*-Isoxazolo[5,4-*d*]pyrazolo [3,4-*b*]pyridine	**134**	12/86, 10/88
$C_3NO-C_3N_2-C_4N_2$		
 7*H*-Isoxazolo[4,5-*c*]pyrazolo [1,2-*a*]pyridazine	**567, 568**	11/88
 Imidazo[1,2-*c*]isoxazolo [4,5-*e*]pyrimidine	**445a**	23/90
$C_3NO-C_3N_2-C_3N_3$		
 Isoxazolo[5,4-*e*]pyrazolo [5,1-*c*]-1,2,4-triazine	**157**	11/83

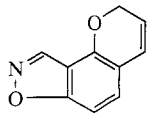
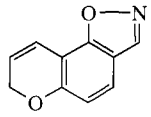
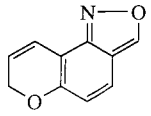
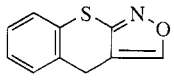
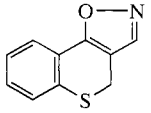
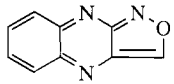
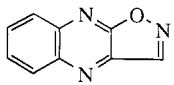
Basic heterocyclic systems[a]	Formula numbers	References
$C_3NO-C_2N_3-C_4N_2$		
 Isoxazolo[4,5-*e*]-1,2,4-triazolo [4,3-*c*]pyrimidine	**450**	6/81
$C_3NO-C_3NO-C_7$		
 4*H*-Cyclohepta[1,2-*d*: 3,4-*d'*] diisoxazole	**303**	2/74
 4*H*-Cyclohepta[1,2-*d*: 4,3-*d'*] diisoxazole	**304**	2/74
$C_3NO-C_3N_2-C_4N_3$		
 Isoxazolo[4,3-*d*]pyrazolo [3,4-*f*]-1,2,3-triazepine	**472**	12/87
$C_3NO-C_5N_3-C_6$		
 3*H*-Isoxazolo[5,4,3-*d,e*] quinoline	**212, 814**	10/82
 Isoxazolo[4,3-*b*]quinoline	**234**	3/58

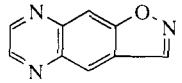
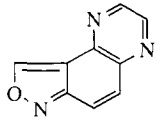
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
 Isoxazolo[4,5-*b*]quinoline	**408a**	9/91
 Isoxazolo[4,5-*g*]quinoline	**779**	12/72, 13/72, 8/74, 9/74
 Isoxazolo[5,4-*b*]quinoline	**130, 138, 161, 165, 397, 401, 402, 707, 708**	11/68, 7/78, 3/79, 13/79, 15/79, 13/84, 14/84, 10/86, 4/87, 20/87
 Isoxazolo[5,4-*g*]quinoline	**779**	12/72, 13/72, 8/74, 9/74
 Isoxazolo[3,4-*c*]quinoline	**254, 263, 285, 694, 695, 883, 884**	1/53, 13/68, 4/71
 Isoxazolo[3,4-*f*]quinoline	**289**	4/71
 Isoxazolo[4,3-*c*]quinoline	**253**	5/90
 Isoxazolo[4,3-*f*]quinoline	**288, 894**	20/83
 Isoxazolo[4,3-*h*]quinoline	**233, 850**	2/59

Basic heterocylic systems[a]	Formula numbers	References
 Isoxazolo[4,5-*c*]quinoline	**14, 106, 180**	1/63, 9/66, 6/68
 Isoxazolo[5,4-*c*]quinoline	**404, 952**	21/89
 Isoxazolo[5,4-*c*]isoquinoline	**410, 594, 629b, 630b, 631b, 860**	15/83, 21/83, 15/84, 17/87, 24/90
$C_3NO-C_5O-C_6$		
 4*H*-1-Benzopyrano[2,3-*c*] isoxazole	**113**	19/83
 4*H*-1-Benzopyrano[3,4-*d*] isoxazole	**15, 34, 224, 541, 815**	8/66, 8/68, 8/71, 9/71, 10/71, 5/72, 14/72, 10/73, 10/74, 7/75, 7/76, 7/77, 16/78, 5/79, 16/79, 16/80, 11/81, 12/81, 17/84, 19/85, 13/86, 15/90
 4*H*-1-Benzopyrano[4,3-*c*] isoxazole	**33, 229, 251, 315**	8/75, 9/83, 17/84, 25/90
 5*H*-Pyrano[3,2-*f*]-1,2-benzisoxazole	**24, 184, 658**	20/77, 6/79, 16/84, 18/89
 5*H*-Pyrano[3,2-*f*]-2,1-benzisoxazole	**235**	1/36

(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
 2*H*-Pyrano[2,3-*e*]-1,2-benzisoxazole	**183, 190, 203, 211, 562, 659**	1/35, 8/76, 8/77, 20/77, 6/79, 4/89, 18/89
 4*H*-Pyrano[2,3-*g*]-1,2-benzisoxazole	**185, 525, 538, 590**	8/73, 9/73, 6/77, 19/77, 6/79, 13/89
 4*H*-Pyrano[2,3-*g*]-2,1-benzisoxazole	**236**	1/36
$C_3NO-C_5S-C_6$		
 4*H*-1-Benzothiopyrano[2,3-*c*]isoxazole	**152, 832**	13/81
 4*H*-1-Benzothiopyrano[3,4-*d*]isoxazole	**63, 115, 672, 673, 674**	14/68, 14/75, 10/83
$C_3NO-C_4N_4-C_6$		
 Isoxazolo[3,4-*b*]quinoxaline	**257**	14/81
 Isoxazolo[4,5-*b*]quinoxaline	**2, 120, 205, 454, 660, 661, 662, 820**	10/66, 4/68, 4/69, 6/72, 26/84, 9/85, 10/85, 11/85

Basic heterocyclic systems[a]	Formula numbers	References
 Isoxazolo[4,5-*g*]quinoxaline	**294, 295**	11/87
 Isoxazolo[4,3-*f*]quinoxaline	**287**	6/70
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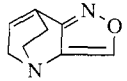
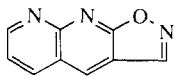
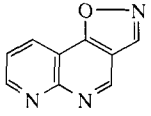
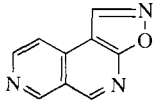
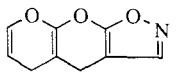
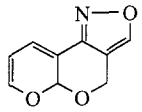
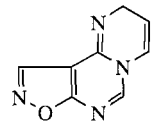
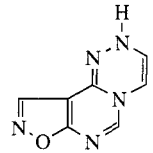
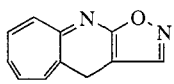
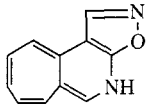
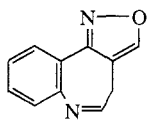
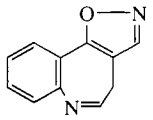
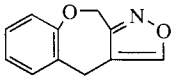
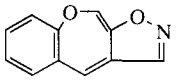
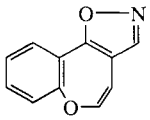
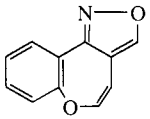
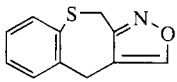
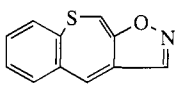
 5*H*-4,7-Ethanoisoxazolo [4,3-*b*]pyridine	**330**	15/80
 Isoxazolo[5,4-*b*]-1,8-naphthyridine	**709**	20/87
 Isoxazolo[4,5-*c*]-1,8-naphthyridine	**271**	12/85
 Isoxazolo[5,4-*c*]-2,7-naphthyridine	**597, 629d, 630d, 631d**	15/83, 21/83, 15/84
$C_3NO-C_5O-C_5O$		
 4*H*,5*H*-Pyrano[3′,2′:5,6] pyrano[3,2-*d*]isoxazole	**577, 578, 579**	7/72

(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
	**678**	6/86
4*H*,5a*H*-Pyrano[2′,3′:6,5]pyrano[4,3-*c*]isoxazole		
$C_3NO-C_4N_2-C_4N_2$		
	**445b**	23/90, 21/91
2*H*-Isoxazolo[4,5-*e*]pyrimido[1,2-*c*]Pyrimidine		
$C_3NO-C_3N_3-C_4N_2$		
	**451**	6/88
2*H*-Isoxazolo[5′,4′:4,5]pyrimido[6,1-*c*]-1,2,4-triazine		
$C_3NO-C_5N-C_7$		
	**398, 856**	3/79, 13/79
4*H*-Cyclohept[*b*]isoxazolo[4,5-*e*]pyridine		
	**596, 629*c*, 630c, 631c**	15/83, 21/83, 15/84, 17/87
4*H*-Cyclohept[*d*]isoxazolo[5,4-*b*]pyridine		
$C_3NO-C_6-C_6N$		
	**41**	8/78
4*H*-Isoxazolo[4,3-*d*]-1-benzazepine		

Basic heterocyclic systems[a]	Formula numbers	References
 4*H*-Isoxazolo[4,5-*d*]-1-benzazepine	**40, 806**	8/78
$C_3NO-C_6-C_6O$		
 4*H*,10*H*-1-Benzoxepino[3,4-*c*]isoxazole	**529**	17/85
 1-Benzoxepino[4,3-*d*]isoxazole	**25, 527**	21/77, 17/85
 1-Benzoxepino[4,5-*d*]isoxazole	**16**	18/84
 1-Benzoxepino[5,4-*c*]isoxazole	**276, 611**	9/75, 19/84
$C_3NO-C_6-C_6S$		
 4*H*,10*H*-1-Benzothiepino[3,4-*c*]isoxazole	**531, 671**	17/85
 1-Benzothiepino[4,3-*d*]isoxazole	**530, 670**	17/85

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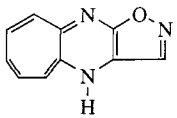
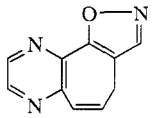
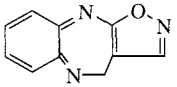
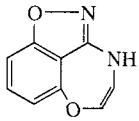
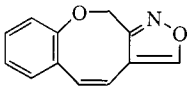
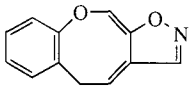
Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_4N_2-C_7$		
 4*H*-Cyclohept[*b*]isoxazolo [4,5-*e*]pyrazine	**455**	4/68
 4*H*-Isoxazolo[5′,4′:3,4] cyclohepta[1,2-*b*]pyrazine	**461, 462**	12/83
$C_3NO-C_6-C_5N_2$		
 4*H*-Isoxazolo[5,4-*b*]-1,5-benzodiazepine	**504**	3/59
$C_3NO-C_6-C_5NO$		
 3*H*-Isoxazolo[3,4,5-*e*,*f*]-1,4-benzoxazepine	**510**	31/89, 12/90
$C_3NO-C_6-C_7O$		
 11*H*-1-Benzoxocino[3,4-*c*] isoxazole	**533**	14/86
 5*H*-1-Benzoxocino[4,3-*d*] isoxazole	**532**	14/86

Basic heterocyclic systems[a]	Formula numbers	References
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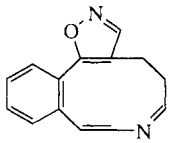
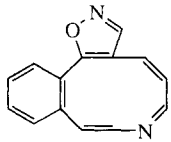
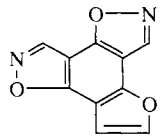
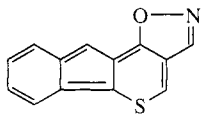
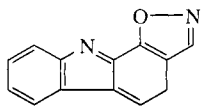
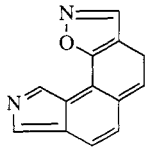
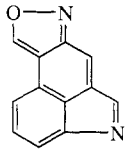
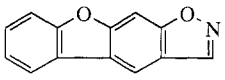
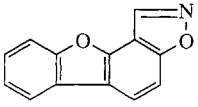
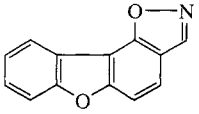
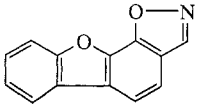
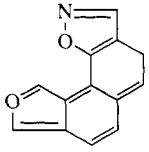
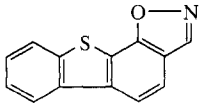
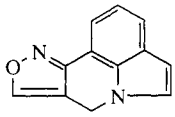
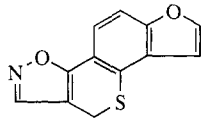
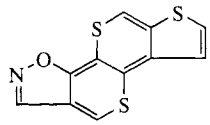
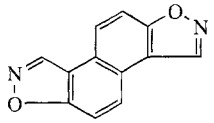
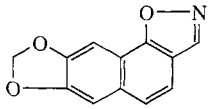
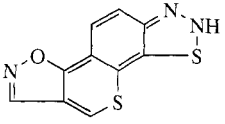
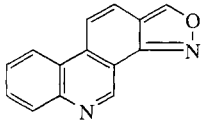
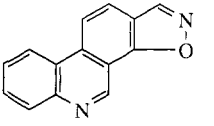
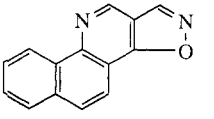
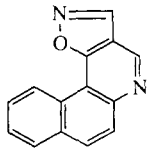
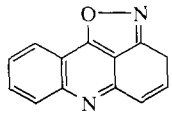
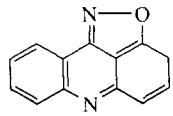
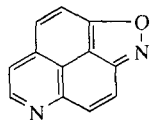
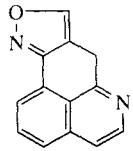
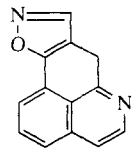
 4*H*-Isoxazolo[4,5-*f*]-3-benzazonine	**341a, 609**	19/89, 14/91
$C_3NO-C_6-C_9N$		
 Isoxazolo[4,5-*g*]-3-benzazecine	**341b, 610**	14/91
$C_3NO-C_3NO-C_3NO-C_6$		
 Benzo[1,2-*d*:3,4-*d'*:5,6-*d''*]triisoxazole	**198**	1/64
$C_3NO-C_5-C_5S-C_6$		
 Indeno[2′,1′:5,6]thiopyrano[3,4-*d*]isoxazole	**64**	22/83
$C_3NO-C_4N-C_6-C_6$		
 4*H*-Isoxazolo[5,4-*a*]carbazole	**22**	2/60

Basic heterocylic systems[a]	Formula numbers	References
 4*H*-Isoindolo[5,4-*g*]-1,2-benzisoxazole	**73, 564b**	11/73
 Indolo[4,3-*e*,*f*]-2,1-benzisoxazole	**332**	15/81, 20/84
$C_3NO-C_4O-C_6-C_6$		
 Benzofuro[3,2-*f*]-1,2-benzisoxazole	**650, 761, 764, 861**	4/63, 9/76, 10/76
 Benzofuro[2,3-*e*]-1,2-benzisoxazole	**763**	3/63
 Benzofuro[2,3-*g*]-1,2-benzisoxazole		10/76
 Benzofuro[3,2-*g*]-1,2-benzisoxazole	**17, 178**	1/54, 4/60

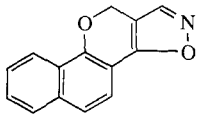
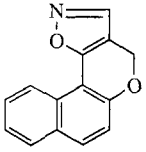
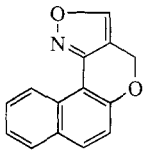
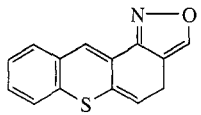
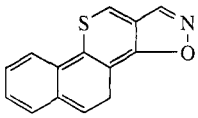
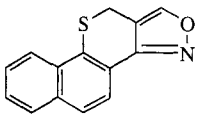
Basic heterocylic systems[a]	Formula numbers	References
	**72, 564a**	11/73
Isobenzofuro[5,4-*g*]-1,2-benzisoxazole		
$C_3NO-C_4S-C_6-C_6$		
	**18**	1/55
1-Benzothieno[3,2-*g*]-1,2-benzisoxazole		
$C_3NO-C_4N-C_5N-C_6$		
		19/73
7*H*-Isoxazolo[4,3-*c*]pyrrolo[3,2,1-*i*,*j*]quinoline		
$C_3NO-C_4O-C_5S-C_6$		
	**65**	22/83
5*H*-Furo[2′,3′:7,8]-1-benzothiopyrano[3,4-*d*]isoxazole		
$C_3NO-C_4S-C_5S-C_5S$		
	**69**	18/82
Thieno[3″,2″:4′,5′]thiopyrano[2′,3′:5,6]thiopyrano[3,4-*d*]isoxazole		

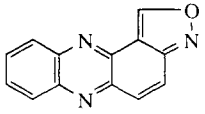
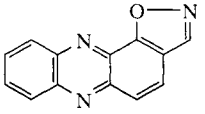
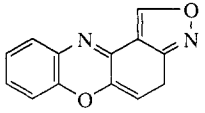
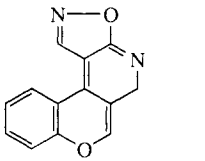
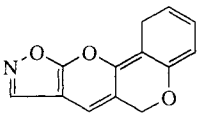
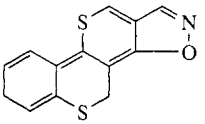
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_3NO-C_6-C_6$		
	**197**	1/51
Naphtho[1,2-*d*:5,6-*d'*]diisoxazole		
$C_3NO-C_3O_2-C_6-C_6$		
	**19**	5/69
8*H*-1,3-Dioxolo[6,7]naphth [2,1-*d*]isoxazole		
$C_3NO-C_2N_2S-C_5S-C_6$		
	**102**	23/87
2*H*-Isoxazolo[5',4':4,5] thiopyrano[3,2-*g*]-1,2,3-benzothiadiazolo		
$C_3NO-C_5N-C_6-C_6$		
	**158**	9/77
Isoxazolo[3,4-*i*]phenanthridine		
	**6, 20, 812**	3/74, 9/77, 21/84
Isoxazolo[5,4-*i*]phenanthridine		
	**27**	13/87
Benz[*h*]isoxazolo[4,5-*c*] quinoline		

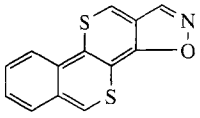
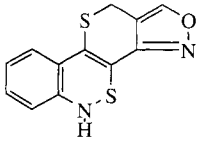
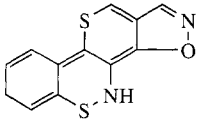
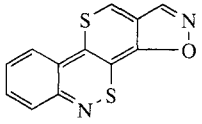
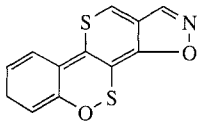
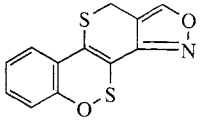
Basic heterocylic systems[a]	Formula numbers	References
 Benz[*f*]isoxazolo[4,5-*c*]quinoline	**26**	16/86, 13/87
 3*H*-Isoxazolo[3,4,5-*k*,*l*] acridine	**206**	12/91
 3*H*-Isoxazolo[5,4,3-*k*,*l*] acridine	**487, 616, 869**	14/90, 20/90
 1,2-Benzisoxazolo[5,4,3a,3-*d*,*e*,*f*] quinoline	**210**	12/73
 4*H*-Benz[*d*,*e*]isoxazolo[3,4-*g*] quinoline	**44**	11/82
 4*H*-Benz[*d*,*e*]isoxazolo[5,4-*g*] quinoline	**43**	11/82

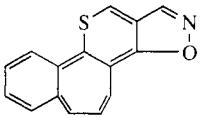
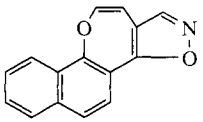
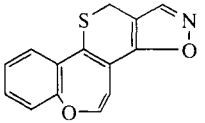
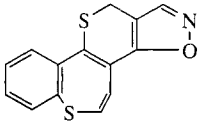
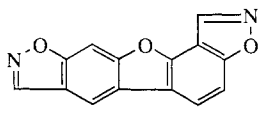
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_5O-C_6-C_6$		
 4*H*-Naphtho[2′,1′:5,6]pyrano [3,4-*d*]isoxazole	**28**	22/84
 4*H*-Naphtho[1′,2′:5,6]pyrano [3,4-*d*]isoxazole	**36**	22/84, 20/86, 21/86
 4*H*-Naphtho[1′,2′:5,6]pyrano [4,3-*c*]isoxazole	**37b, 252**	20/86, 11/91
$C_3NO-C_5S-C_6-C_6$		
 4*H*-1-Benzothiopyrano[2,3-*g*]-2,1-benzisoxazole	**242, 849**	2/57, 2/58
 4*H*-Naphtho[2′,1′:5,6] thiopyrano[3,4-*d*]isoxazole	**61**	13/73, 15/88
 11*H*-Naphtho[2′,1′:5,6] thiopyrano[4,3-*c*]isoxazole	**62**	13/73

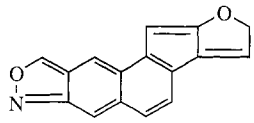
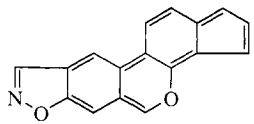
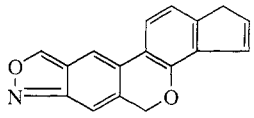
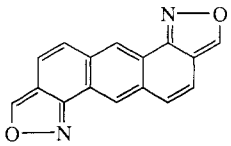
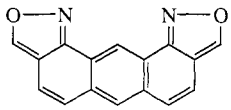
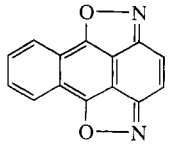
Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_4N_2-C_6-C_6$		
 Isoxazolo[4,3-*a*]phenazine	**278, 280, 281, 867**	10/68
 Isoxazolo[5,4-*a*]phenazine	**458**	20/91
$C_3NO-C_4NO-C_6-C_6$		
 4*H*-Isoxazolo[4,3-*a*]phenoxazine	**258, 854**	9/67
$C_3NO-C_5S-C_5O-C_6$		
 5*H*-1-Benzopyrano[4,3-*d*] isoxazolo[5,4-*b*]pyridine	**150**	13/91
$C_3NO-C_5O-C_5O-C_6$		
 1*H*,6*H*-1-Benzopyrano[3′,4′:5,6] pyrano[3,2-*d*]isoxazole	**544**	17/75
$C_3NO-C_5S-C_5S-C_6$		
 4*H*,7*H*-1-Benzothiopyrano[3′,4′:5,6] thiopyrano[3,4-*d*]isoxazole	**66**	10/80, 24/87

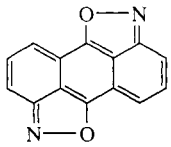
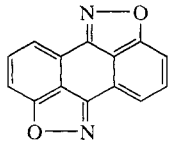
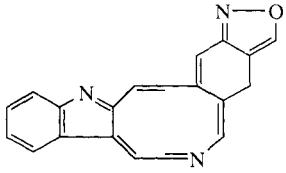
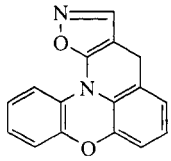
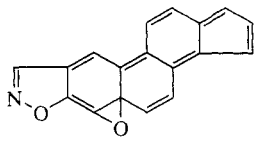
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
	**67**	19/82
2-Benzothiopyrano[3′,4′:5,6] thiopyrano[3,4-*d*]isoxazole		
$C_3NO-C_4NS-C_5S-C_6$		
	**103**	12/82
5*H*,11*H*-Isoxazolo[3′,4′:4,5] thiopyrano[3,2-*c*]2,1-benzothiazine		
	**68**	7/79
4*H*,7*H*-Isoxazolo[5′,4′:4,5] thiopyrano[3,2-*c*]-1,2-benzothiazine		
	**68a**	12/82
Isoxazolo[5′,4′:4,5]thiopyrano [3,2-*c*]-2,1-benzothiazine		
$C_3NO-C_4SO-C_5S-C_6$		
	**68b**	23/84
7*H*-1,2-Benzoxathiino[3′,4′:5,6] thiopyrano[3,4-*d*]isoxazole		
	**104**	23/84
11*H*-1,2-Benzoxathiino[3′,4′:5,6] thiopyrano[4,3-*c*]isoxazole		

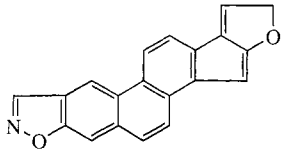
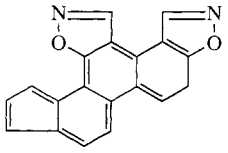
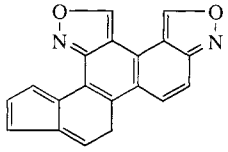
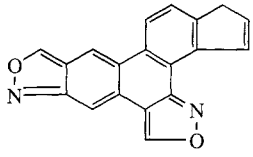
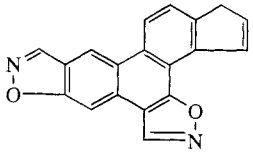
Basic heterocyclic systems[a]	Formula numbers	References
$C_3NO-C_5S-C_6-C_7$		
 Benzo[3′,4′]cyclohepta [1′,2′:5,6]thiopyrano[3,4-*d*] isoxazole	**74**	25/87
$C_3NO-C_6-C_6-C_6O$		
 Naphth[2′,1′:6,7]oxepino[4,5-*d*] isoxazole	**21**	18/84
$C_3NO-C_5S-C_6-C_6O$		
 8*H*-1-Benzoxepino[4′,5′:5,6] thiopyrano[3,4-*d*]isoxazole	**75**	25/87
$C_3NO-C_5S-C_6-C_6S$		
 8*H*-1-Benzothiepino[4′,5′:5,6] thiopyrano[3,4-*d*]isoxazole	**76**	25/87
$C_3NO-C_3NO-C_4O-C_6-C_6$		
 Furo[2,3-*e*:4,5-*f*]bis-1,2-benzisoxazole	**81**	1/62

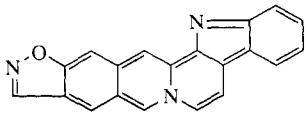
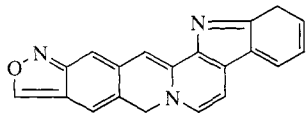
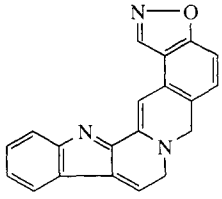
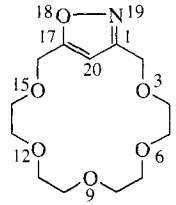
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_4O-C_5-C_6-C_6$		
	**38**	21/82
2*H*-Furo[2′,3′:2,3]indeno [7,6-*f*]-2,1-benzisoxazole		
$C_3NO-C_5-C_5O-C_6-C_6$		
	**57, 807**	14/73, 16/75, 18/76
Cyclopenta[7,8]-1-benzopyrano [4,3-*f*]-1,2-benzisoxazole		
	**58**	14/74, 16/75
1*H*,5*H*-Cyclopenta[7,8]-1-benzopyrano[4,3-*f*]-2,1-benzisoxazole		
$C_3NO-C_3NO-C_6-C_6-C_6$		
	**240**	1/26, 2/26
Anthra[1,2-*c*:5,6-*c*′]diisoxazole		
	**241**	1/26, 2/26
Anthra[1,2-*c*:8,7-*c*′]diisoxazole		
	**246**	1/16, 1/28
Anthra[1,9-*c*,*d*:4,10-*c*′,*d*′] diisoxazole		

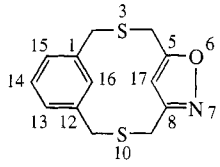
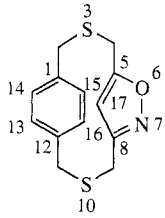
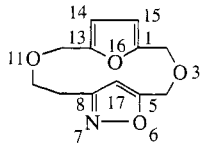
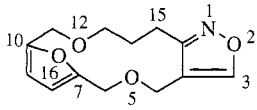
Basic heterocylic systems[a]	Formula numbers	References
 Anthra[1,9-*c*,*d*:5,10-*c*′,*d*′] diisoxazole	**247, 267**	1/16, 1/21, 1/28, 13/82
 Anthra[9,1-*c*,*d*:10,5-*c*′,*d*′] diisoxazole	**122**	2/10
$C_3NO-C_4N-C_6-C_6-C_9N$		
 4*H*-Indolo[2′,3′:7,8]azecino [3,4-*f*]-2,1-benzisoxazole	**767**	15/72
$C_3NO-C_4NO-C_5N-C_6-C_6$		
 4*H*-Isoxazolo[4′,5′:5,6]pyrido [3,2,1-*k*,*l*]phenoxazine	**141, 710**	26/87
$C_2O-C_3NO-C_5-C_6-C_6-C_6$		
 Cyclopenta[5,6]naphtho [1,2-*f*]oxirano[2,3-*g*]-1,2-benzisoxazole	**523, 808**	15/68, 16/68, 24/89

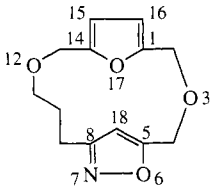
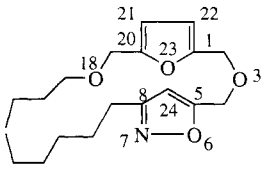
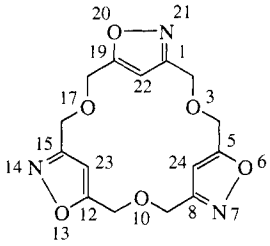
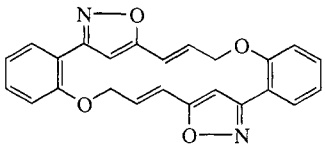
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_4O-C_5-C_6-C_6-C_6$		
 2*H*-Furo[2″,3″: 4′,5′]cyclopenta [1′,2′:7,8]phenanthro[3,2-*d*] isoxazole	**77**	23/73, 12/74, 19/76, 21/80
$C_3NO-C_3NO-C_5-C_6-C_6-C_6$		
 4*H*-Cyclopenta[7,8]phenanthro [1,2-*d*:10,9-*d*′]diisoxazole	**51, 809**	6/69
 6*H*-Cyclopenta[7,8]phenanthro [2,1-*c*:9,10-*c*′]diisoxazole	**52**	6/69
 1*H*-Cyclopenta[7,8]phenanthro [2,3-*c*:9,10-*c*′]diisoxazole	**50**	6/69
 1*H*-Cyclopenta[7,8]phenanthro [3,2-*d*:10,9-*d*′]diisoxazole	**49, 810**	6/69

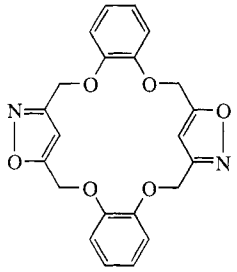
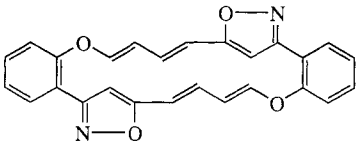
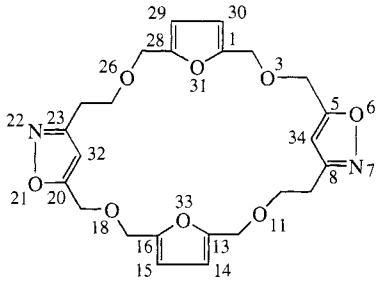
Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_4N-C_5N-C_5N-C_6-C_6$		
 1,2-Benzisoxazolo[5,6-*g*] indolo[2,3-*a*]quinolizine	**31, 412, 811**	2/63, 3/64, 2/65, 3/65, 1/66, 11/74, 17/80
 1*H*,8*H*-2,1-Benzisoxazolo [5,6-g]indolo[2,3-*a*] quinolizine	**30**	2/63, 3/64, 2/65, 3/65, 1/66, 2/66, 15/72, 11/74
 6*H*,8*H*-1,2-Benzisoxazolo [5,4-*g*]indolo[2,3-*a*] quinolizine	**413, 859**	17/80
$C_3NO-C_{13}O_5$		
 3,6,9,12,15,18-Hexaoxa-19-azabicyclo[15.2.1]eicosa-17(20),19-diene	**604, 607**	17/81, 17/82, 13/83

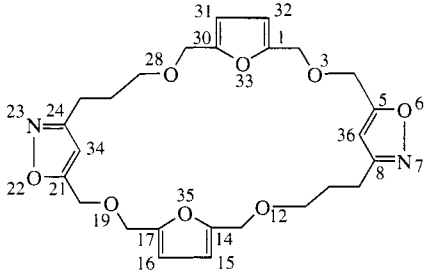
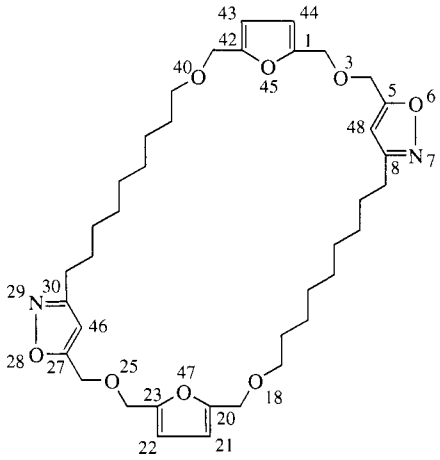
(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_6-C_{10}S_2$		
	**602**	14/83
6-Oxa-3,10-dithia-7-azathicyclo [10.3.1.1^{5,8}]heptadeca-1(16), 5(17),7,12,14-pentaene		
$C_3NO-C_6-C_{11}S_2$		
	**601**	14/83
6-Oxa-3,10-dithia-7-azatricyclo [11.2.1.1^{5,8}]heptadeca-5(17), 7,12,14,15-pentaene		
$C_3NO-C_4O-C_{10}O_3$		
	**322a**	20/89
3,6,11,16-Tetraoxa-7-azatricyclo [11.2.1^{5,8}]heptadeca–5(17), 7,13,15-tetraene		
	**323b**	20/89
6,11,14,15-Tetrahydro-7,10-epoxy-4*H*,13*H*-[1,8]dioxacyclotetradecino [4,3-*c*]isoxazole		

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO–C_4O–C_{11}O_3$		
	**322b**	20/89
3,6,12,17-Tetraoxa-7-azatricyclo[12.2.1.1^{5,8}]octadeca-5(18),7,14,16-tetraene		
$C_3NO–C_4O–C_{17}O_3$		
	**322c**	20/89
3,6,18,23-Tetraoxa-7-azatricyclo[18.2.1.1^{5,8}]tetracosa-5(24),7,20,22-tetraene		
$C_3NO–C_3NO–C_3NO–C_{15}O_3$		
	**599**	8/79
3,6,10,13,17,20-Hexaoxa-7,14,21-triazatetracyclo[17.2.1.1.^{5,8}1^{12,15}]-tetracosa-5(24),7,12(23),14,19(22),21-hexaene		
$C_3NO–C_3NO–C_6–C_6C_{16}O_2$		
	**326**	9/75
6*H*,18*H*-12,9:24,21-Dimethenodibenzo[*d*,*n*][1.6.11.16.2.12]tetraoxadiazacycloeicosine		

(*continued*)

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_3NO-C_6-C_6-C_{14}O_4$		
	**605**	17/81, 17/82
6*H*,18*H*-10,7:22,19-Dimetheno-11*H*,23*H*-dibenzo[*f*,*p*] [1.5.8.11.15.18.2.12] hexaoxadiazacycloeicosine		
$C_3NO-C_3NO-C_6-C_6-C_{18}O_2$		
	**327**	9/75
13,10:26,23-Dimetheno-10*H*,23*H*-dibenzo[*d*,*o*] [1.6.12.17.2.13] tetraoxadiazacyclodocosine		
$C_3NO-C_3NO-C_6-C_6-C_{14}O_4$		
	**324a**	20/89
3,6,11,18,21,26,31,33-Octaoxa-7,22-diazapentacyclo[26.2.1.1^{5,8}.1^{13,16}.1^{20,23}]tetratriaconta-5(34),7,13,15,20(32),22,28,30-octaene		

Basic heterocylic systems[a]	Formula numbers	References
$C_3NO-C_3NO-C_6-C_6-C_{14}O_4$		
	**324b**	20/89
3,6,12,19,22,28,33,35-Octaoxa-7,23-diazapentacyclo[28.2.1.1.^{5,8}1^{14,17}.1^{21,24}]hexatriaconta-5(36),7,14,16,21(34),23,30,32-octaene		
$C_3NO-C_3NO-C_4O-C_4O-C_{34}O_6$		
	**324c**	20/89
3.6,18,25,28,40,45,47-Octaoxa-7,29-diazapentacyclo[40.2.1.1.^{5,8}1.^{20,23}1^{27,30}]octatetraconta-5(48),7,20,22,27(46),29,42,44-octaene		

[a]The term *basic heterocycles systems* refers to those having the maximum number of noncumulated double bonds. The additional hydrogen atoms are taken at the positions with the lowest number, but the formula numbers may be related to a different tautomer. This except all macrocycles that are listed at the end of the ring index.

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CHAPTER 4

Partially Saturated Polynuclear Isoxazoles

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4.1. INTRODUCTION

This chapter is devoted to condensed isoxazole systems not covered by the preceding chapters: (1) Isoxazoles (and their dihydro or tetrahydro derivatives) fused with nonaromatic homocyclic moieties, (2) Isoxazoles fused with partially saturated heterocyclic moieties, and (3) Partially saturated isoxazoles fused with heteroaromatic moieties.

The synthetic approaches to these partially saturated polynuclear isoxazoles do not differ notably from the methods already described for mononuclear isoxazoles and illustrated in Part 1 of this monograph, and reference to the relevant treatment in other portions of the text is provided. Special emphasis has been put on methods of preparation or reactions specifically limited to polynuclear systems. Within the single paragraphs, treatment of the subject follows the increase of size and complexity of the ring fused with the isoxazole, as well as the increase of saturation in the isoxazole ring.

Illustration of the physical properties is postponed until the discussion of synthetic and chemical properties, and concerns only remarkable differences between polynuclear and mononuclear systems.

No previous review of the restricted subject of this chapter is known, but several recent reviews [i.e., published after *Chemical Abstracts*, Vol. 101 (1984), deadline of Part 1] cover more or less extensive parts of isoxazole chemistry, and are listed here:

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4.2. METHODS OF PREPARATION

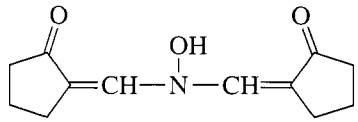
4.2.1. [CCC + NO] Processes

4.2.1.1. Oximation of 1,3-Dicarbonyl (and Related) Compounds

The oximation of open-chain β-dicarbonyl compounds has been dealt with in Part I, § 1.3.1.1, and the influence of reaction medium, pH, and substituents has been thoroughly discussed. The reactions of 2-acylated cycloalkanones conform to the same general rules, although with some peculiarities.

Oximation of aliphatic α-ketoaldehydes has long been known to give rise to 3-unsubstituted isoxazoles as the sole or prevalent products, but other compounds, such as isomeric 5-unsubstituted isoxazoles, monoximes, or disubstituted hydroxylamines, have often been isolated from the reaction mixture.

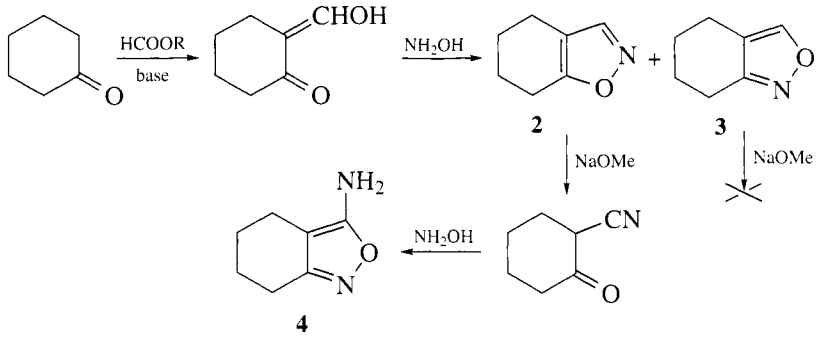
Extension of the reaction to the cyclic analogs shows completely different behavior between the five- and the six-membered rings. Both cyclopentanone and cyclohexanone are easily α-formylated by condensation with ethyl formate. However, oximation of 2-hydroxymethylenecyclopentanone gives the red bis (1-keto-2-cyclopentanylidenemethyl)hydroxylamine (**1**), without detectable formation of isoxazole derivatives.[1/45] Similar results have been obtained starting from hydrindones[1/44,1/45] and from camphor.[1/45]



1

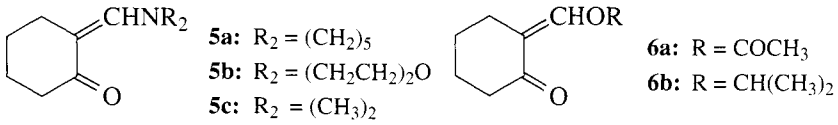
Alternatively, starting from cyclohexanone, a mixture of the two possible regioisomers (**2** and **3**) is often obtained, which resist separation either by chromatographic methods or by distillation.[1/71] The isomer ratio can roughly be evaluated by resorting to chemical means. For example, it is well-known that 3-unsubstituted isoxazoles suffer ring opening on exposure to bases, whereas the 5-unsubstituted isomer is unaffected under the same conditions (see Part 1, § 1.4.6.1). Thus, treatment with alkoxides promptly cleaves isomer **2**, leaving isomer **3** unaffected.[1/25] As a matter of fact, in some cases[1/61,1/62,1/74] the mixture of products has been submitted directly to base-promoted isomerization, with isolation of 2-cyanocyclohexanone as the sole product in about 33% overall yield.

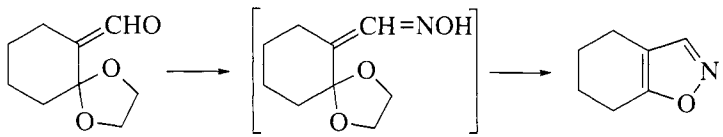
Oximation of this material gives the 3-aminotetrahydroanthranil **4**, which may be accomplished with or without isolation of the intermediate oxime.[2/25,1/70]



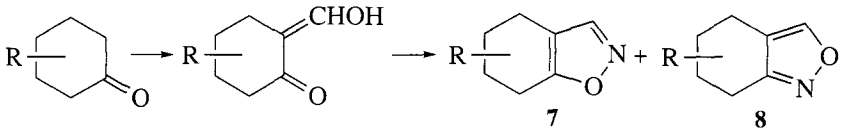
Of course, the isomer ratio can be more precisely evaluated by NMR spectroscopy, a method that relies on integration of the signals corresponding to H5 (compound **3**), which is more strongly deshielded, and H3 (compound **2**). With hydroxylamine hydrochloride in ethanolic solution, a product ratio of 85 : 15 in favor of the isomer **2** has been reported,[2/70,1/76] thus corroborating the original result.[1/25] Conversely, an opposite ratio (20 : 80) has been asserted[3/70] in pyridine/ethanol solution; as partial confirmation of this, a 60% yield of isolated compound **3** has been reported following alkaline treatment.

The controversy has been extended to the enaminoderivatives as well. The *N*-piperidino derivative **5a** reacts with hydroxylamine hydrochloride, in hot aqueous solution, to give pure **2** in 87% yield,[2/70] thus following the general pattern observed in acyclic compounds (see Part I, § 1.3.1.4, p. 165). The same result has been achieved starting from the ketalized aldehyde **6**; neutral hydroxylamine produces the nonisolated oxime, which promptly cyclizes to **2** on treatment with acid.[1/76] Oximation in pyridine/ethanol is reported to yield **3** as the predominant product when starting from the morpholino compound **5b**, and **2** when starting from the dimethylamino derivative **5c**.[3/70] This last compound is claimed to afford only **3** in acidic media.[1/65] Enol ester **6a** or enol ether **6b** afford a regioisomeric mixture.[3/70]

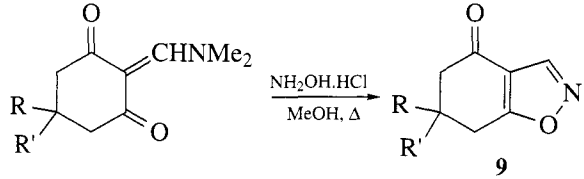




Substituted cyclohexanones have been found to yield the 3-unsubstituted condensed isoxazole in most cases reported.[1/59,1/60,2/61,1/62,2/62,1/67,4/70,1/74,1/75] The experimental conditions generally employ hydroxylamine hydrochloride in glacial acetic acid with the aid of moderate heating. Caution should be exercised in evaluating these results, since often the goal is the preparation of the α-cyanoketone, and the possible presence of minor amounts of the isomeric isoxazole might well have been overlooked. However, in some cases the formation of a mixture of isomers has been observed and quantified. Thus, starting from 2-methylcyclohexanone,[1/25] 3-anisyl-2-methylcyclohexanone,[3/61] and *l*-menthone,[1/45] isomer ratios of 7 : 1, 2.6 : 1, 3.6 : 1, respectively, in favor of isomer **7** have been measured. The amount of the minor isomer has been reported to increase by increasing pH (however, with lower overall yields) or by decreasing reaction temperature. Oximation and cyclization of 2-hydroxymethylene-6,6-dimethylcyclohexanone exhibit marginal selectivity, giving rise to a 1 : 1.3 mixture, where isomer **8** is slightly prevalent. Here too, the pure 3-unsubstituted compound **7** can be obtained in excellent yields by employing the corresponding isopropyl enol ether.[1/68]



The presence of a second keto group in the cyclohexanone ring allows the assembly of, in moderate yields, 6,7-dihydro-1,2-benzisoxazol-4(5*H*)-ones **9**.[1/83]

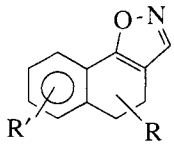


Notably, the use of the anilino-methylenederivatives rather than the corresponding dimethylamino species in this oximation reaction is reported to afford the corresponding hydroxylamino compound, which does not cyclize even in acidic medium, and directly provides 2-cyanocyclohexane-1,3-diones.[1/73]

Derivatives of 2-hydroxymethylene-1-tetralone,[2/70] which bear substituents on the saturated[1/63,2/67] or the aromatic ring[1/56,2/68,5/70,2/76] or on both rings,[1/69,2/69,3/76] are oximated under various conditions. The only reported product is the 3-unsubstituted derivative **10**, an intermediate for the production of the corresponding 2-cyano-1-tetralone or, in a particular case,[2/70] of the *N*-alkylisoxazolium tetrafluoroborate useful for peptide synthesis.

Nevertheless, in the case of oximation of the 6,7-dimethoxyderivative, the usual isomer **11** is formed almost exclusively in buffered solution, whereas a

remarkable amount (38%) of the other regioisomer (**10**) is isolated after alkaline treatment when the reaction is carried out in pyridine.[4/76]



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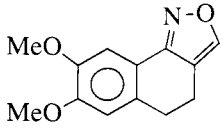

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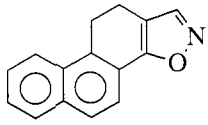

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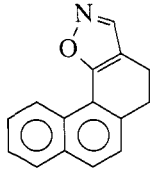
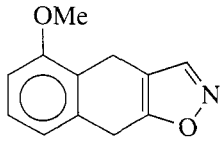


13

When applied to 5-methoxy-2-tetralone, the formylation–oximation sequence leads to a mixture of three of the four possible condensed isoxazole regioisomers **14–16**.[1/64,2/64,2/65,1/66]



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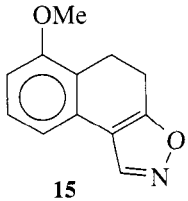

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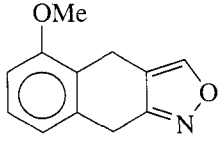
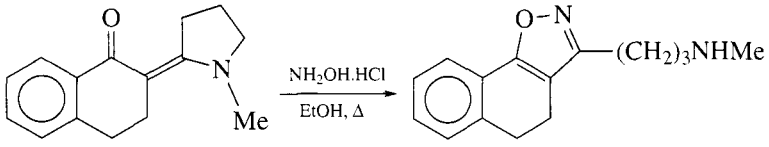


16

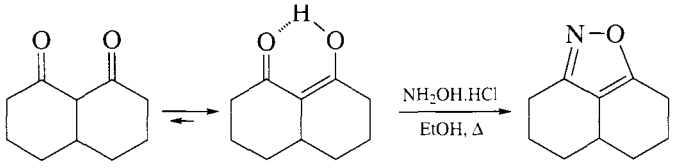
It is worthwhile to note that the enaminoderivative of 1-tetralone (**17**) undergoes attack by hydroxylamine hydrochloride at the exocyclic unsaturated carbon atom to give, after ring opening of the pyrrolidine moiety, the 3-substituted naphth[2,1-*d*]isoxazole **18**.[2/83]



17 **18**

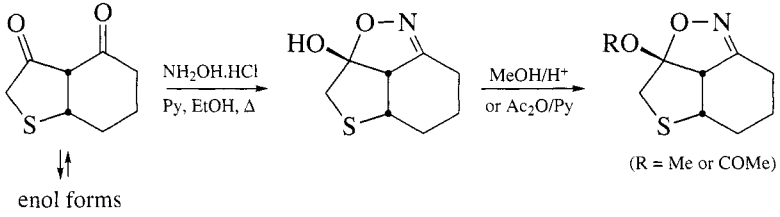
Tetracyclic isoxazoles, such as dihydrophenanthroisoxazole **12**[1/45,1/47,2/76,4/76,1/81,2/81] and **13**,[1/45,1/82] as well as 4,5,10,11-tetrahydro-acenaphthryleno[8,7-*d*]isoxazole,[1/80] have been prepared by the same route.

The tricyclic isoxazole **19** has been prepared with good yields by oximation, under acidic conditions, of decalin-1,8-dione.[1/58]

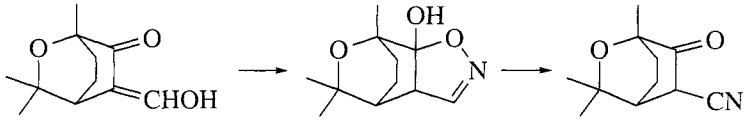


19

When two carbonyl groups are located on adjacent rings in systems containing both a six-membered ring and a five-membered ring, the reaction stops at the 5-hydroxyisoxazoline stage, as illustrated in the following case:[3/81]

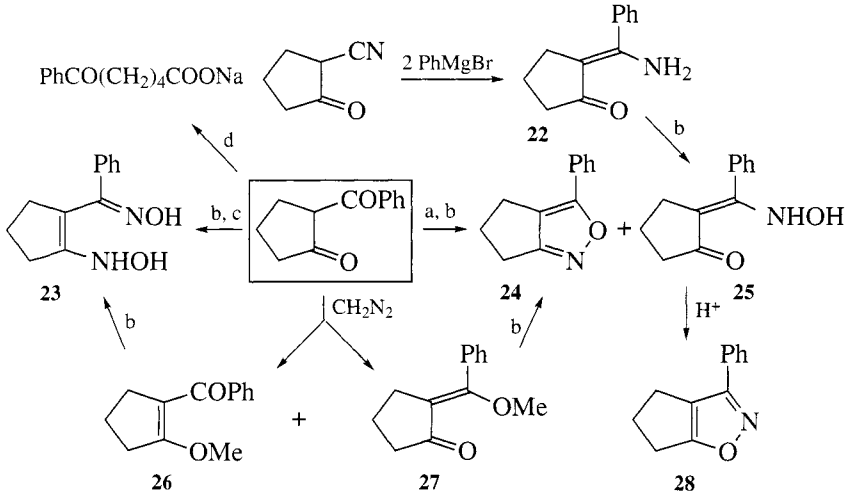


Similarly, the hemiacetal structure **21** is the only product obtainable from the strained system of 3-hydroxymethylene-2-ketocineole (**20**). When conducted under basic conditions, the reaction directly furnishes the corresponding α-cyanoketone,[3/67] without isolation of the intermediate isoxazole.



20 **21**

As illustrated in Scheme 4.1, oximation of 2-benzoylcyclopentanone strongly depends on the pH of the reaction medium. Owing to the reduced reactivity of



22 **23** **24** **25** **26** **27** **28**

[a] $NH_2OH.HCl$ / aq.EtOH, Δ; [b] $NH_2OH.HCl$ / AcONa, ROH, Δ; [c] $NH_2OH.HCl$ / Na_2CO_3 (excess); [d] NH_2OH / aq.NaOH, Δ

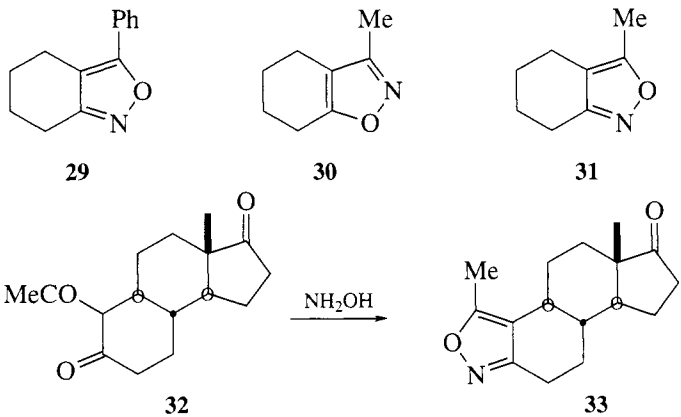
Scheme 4.1

the phenyl-bound carbonyl, in acidified alcoholic solution the condensed 5-phenylisoxazole **24** is formed either alone[2/63] or accompanied by small amounts of the monoxime **25**,[3/64] which easily cyclizes to the isomeric isoxazole **28** by treatment with formic or sulfuric acid.[4/61,3/64] Better yields of the latter isomer are obtained by utilizing either the nitrile oxide–enamine cycloaddition (see § 4.2.2.1) or by preparing the monoxime **25** by oxymation of the enaminoketone **22**, in turn derived from 2-cyanocyclopentanone and phenylmagnesium bromide.[4/61] In buffered solution the dioxime **23** is the only product observed,[5/61] whereas in alkaline solution base-induced ring opening to 5-benzoylpentanoic acid largely prevails.[3/64] Methylation of benzoylcyclopentanone with diazomethane led to isolation of the two methyl enol ethers (**26** and **27**), whose free carbonyl group is attacked by hydroxylamine, giving rise either to the isoxazole **24** or to the dioxime **23**, respectively.[5/61]

Other 2-aroylcyclopentanones behave similarly, yielding 5-aryl-3,4-trimethyleneisoxazoles alone or as the predominant products.[3/64]

2-Acylcyclopentanones are reported to give a chelated monoxime, which however, does not cyclize further.[2/63]

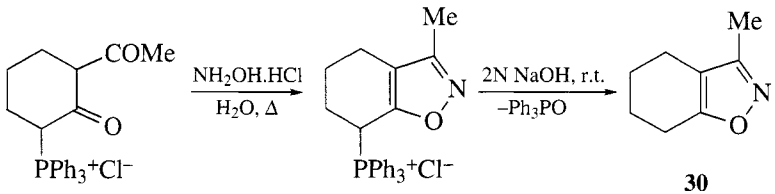
The oxymation of 2-benzoylcyclohexanones is more straightforward. In spite of a previous erroneous statement,[1/14] 3-phenyl-4,5,6,7-tetrahydroanthranil (**29**) is formed as regiospecific product in excellent yields both in acidic and in buffered medium.[2/63,3/64,4/64,3/70] At low temperature, evidence of the intermediate monoxime could be detected.[3/70] Substitution in the phenyl group does not alter the regioselectivity;[3/64] and analogous behaviour is shown by 2-benzoyl-6-methylcyclohexanone.[6/70] Contrary to a different claim,[2/63] 2-acetylcyclohexanone is oximated, although with lower yields, to give a mixture of the two isomeric isoxazoles **30** and **31**, having a 3 : 1 balance in favor of the latter isomer.[3/70,1/76] 2-Cycloalkylcarbonylderivatives are reported to yield almost exclusively the **31**-like product.[7/70] Only the isomer **33** is claimed to be formed by oxymation of the three-membered cyclic triketone **32**.[1/85]



29 **30** **31**

32 **33**

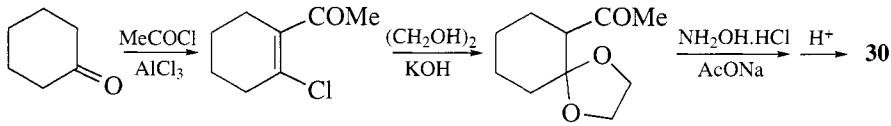
Insertion of a phosphonium group in the position near to the endocyclic carbonyl provokes an inversion of regioselectivity, leading to the tetrahydroindoxazene **34**, which may then be easily dephosphinated to **30**.[2/80]



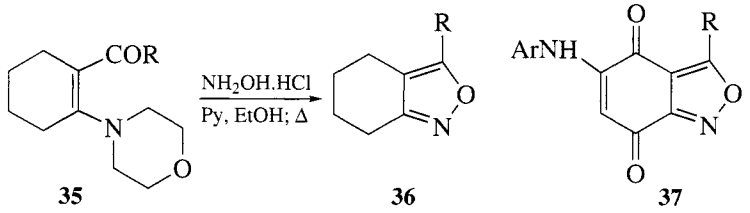
34 **30**

Controversial claims have been made regarding oximation of 2-acetylcyclohexanone in which the endocyclic carbonyl has been monoketalized. In pyridine/ethanol solution a 4 : 1 mixture of the two isomers is reported in which tetrahydroanthranil **31** predominates.[3/70] In AcONa-buffered solution, the product ratio of 85 : 15 favors tetrahydroindoxazene **30**.[1/76]

Pure **30** was conveniently obtained directly from cyclohexanone via monoketalization of 1-acetyl-2-chloro-1-cyclohexene and subsequent oximation.[1/76]

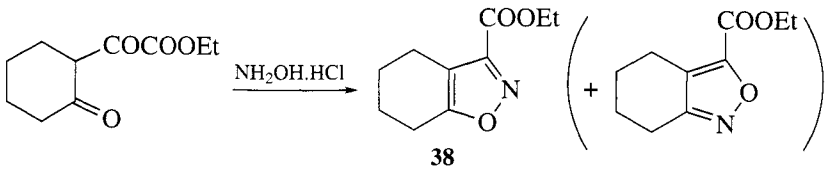


As expected, the enaminoketones **35** are oximated to the pure isomers **36**;[3/70,7/70] moreover, the 2,1-benzisoxazolequinones **37** are obtained by oximation of 2-acyl-3,6-di(arylamino)-1,4-benzoquinones.[3/71,5/76]



35 **36** **37**

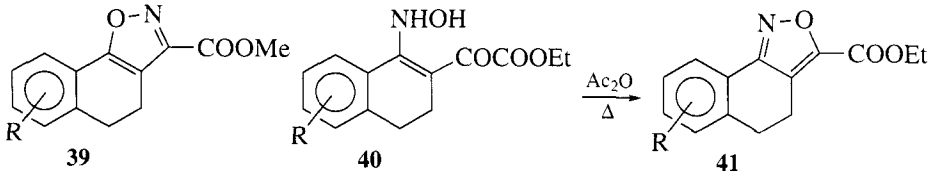
The presence of a vicinal ethoxycarbonyl group enhances the reactivity of the exocyclic carbonyl. Thus, the tetrahydro-1,2-benzisoxazole derivative **38** was



38

exclusively formed by oximation in acidic medium,[3/63,5/64] whereas in neutral medium a mixture of the two isomers was reported, although in unstated ratio.[1/46]

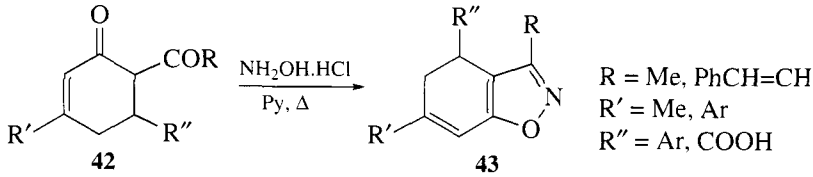
Owing to the structural relationship of the corresponding hydrazides with the important antidepressive drug isocarboxazid, several other substituted[3/63,5/64] or polycyclic[4/67,8/70,2/75,1/81,2/81,1/82] derivatives, such as **39**, have been produced.



39 **40** **41**

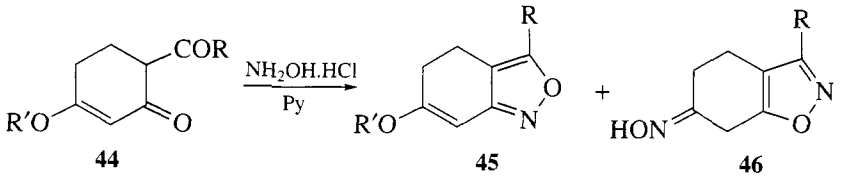
The isomeric methyl 4,5-dihydronaphth[1,2-*c*]isoxazole-3-carboxylate (**41**) could be prepared by treatment of the diketocarboxylate with a buffered solution of hydroxylamine, which permits isolation of monoxime **40**. The cyclization is most conveniently effected by heating with acetic anhydride.[2/71,1/72,2/72]

Modifications in the cyclohexanone ring can modify the regioselectivity of the oximation. Thus, conjugation with a double bond reduces the reactivity of the endocyclic carbonyl and favors attack at the exocyclic carbonyl group. For instance, 6-acetylcyclohexenones **42**, readily prepared by Michael addition of chalcones with acetylacetone, react with hydroxylamine in pyridine solution to give 3-methyl-4,5-dihydro-1,2-benzisoxazoles **43** exclusively.[3/72,3/73,1/77,2/77,30/79,3/80,4/80, 5/80,68/85, 61/87]



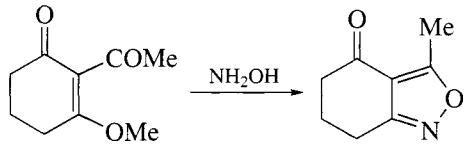
42 **43**

On treatment with hydroxylamine, enol ethers **44** are reported to yield a mixture of the corresponding alkoxydihydroanthranil **45** and the monoximated tetrahydroindoxazene **46**. In these systems R can be an aliphatic,[3/65] an aromatic[2/66] or a heteroaromatic[3/66] residue.



44 **45** **46**

As expected, the isomeric enol ether **47** yields the tetrahydro-2,1-benzisoxazol-4-one **48**.[3/69,4/69]

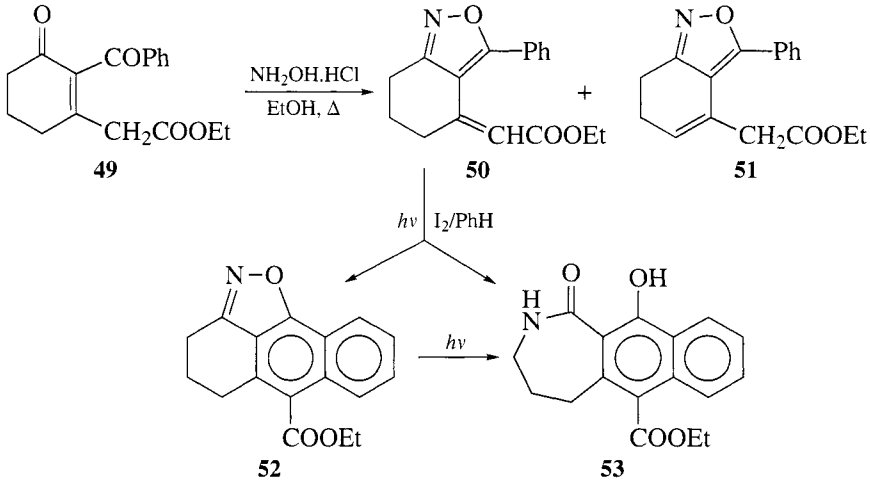


47 48

Other 3-substituted naphthisoxazoles are also known.[2/73,2/74]

The oximation of 2-benzoyl-3-methyl-2-cyclohexenone is highly pH-dependent; whereas in buffered or alkaline medium the reaction affords a mixture of monoxime and dioxime or furnishes many compounds, under acidic conditions good yields of 4-methyl-3-phenyl-6,7-dihydro-2,1-benzisoxazole are obtained. Other substituted analogs give similar results.[4/81]

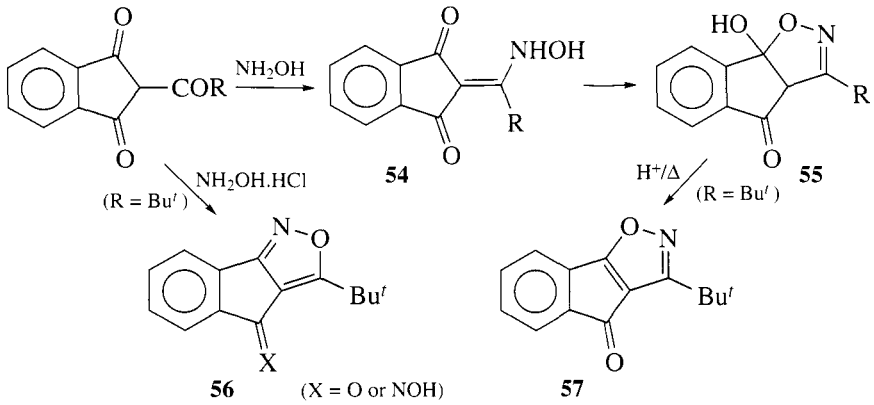
2-Benzoyl-2-cyclohexenone **49** reacts with hydroxylamine hydrochloride to give a mixture of the two isomers (**50** and **51**); photocyclization of the former compound in the presence of an oxidant furnishes the cyclized isoxazole derivative **52** together with the ultimate photo-Beckmann product **53**:[5/81]



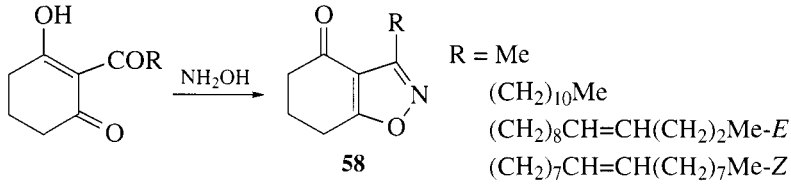
49 50 51 52 53

Triketones have been studied both in the cyclopentane and cyclohexane series. 2-Acetylcyclopentan-1,3-dione, when treated with hydroxylamine under neutral conditions, is attacked on its exocyclic carbonyl, giving rise to the oxime, which resists all attempts of cyclization; under severe treatment with phosphoric anhydride, only Beckmann rearrangement takes place.[11/76] Oximation of 2-acyl-1,3-indandiones gives rise either to the open-chain hydroxylamino derivative **54**, when R is a small group such as Me, or to the hemiacetal form **55**, when R is a bulky group such as aryl or *t*-butyl.[3/83] In the latter case, dehydration to **57** is effected by acidic treatment; if, however, the oximation reaction is carried out

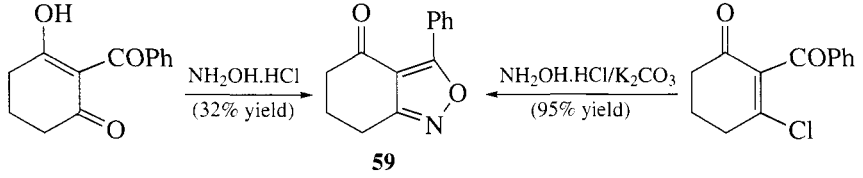
with hydroxylamine hydrochloride in glacial acetic acid, a mixture of products is obtained, in which the isomeric [1,2-*c*]isoxazole **56** (together with its oxime) is predominant.[2/82,3/82.48/84]



In the cyclohexane series, 2-acylcyclohexane-1,3-diones are known to cyclize in neutral conditions to the dihydro-1,2-benzisoxazol-4(5*H*)-ones **58** only.[1/53,44/82,1/88] The isomer having the 5(4*H*)-one structure is also known.[12/98]

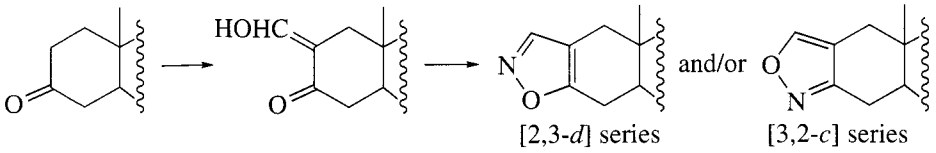


As expected, the use of the benzoyl derivative results in the formation of the isomeric dihydro-2,1-benzisoxazolone **59**, which can, however, be more conveniently prepared from the chloroderivative:[4/81]



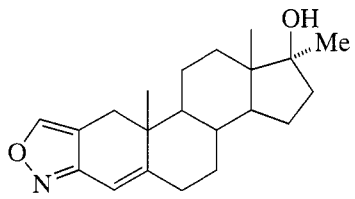
Oximation of α-formyl or α-acyl steroidal ketones is a popular method for synthesizing several steroidoisoxazole compounds that possess interesting biological properties and may be ring-opened to the corresponding α-cyanoketones. Most researchers have focused on the A ring and precisely on the 2-hydroxymethylene-3-keto derivatives as starting materials. Depending on the

experimental conditions, either a mixture of the two possible regioisomers (steroidal [2,3-*d*]isoxazole or [3,2-*c*]isoxazole series, respectively) or the [2,3-*d*]isoxazole alone is formed by treatment with hydroxylamine:

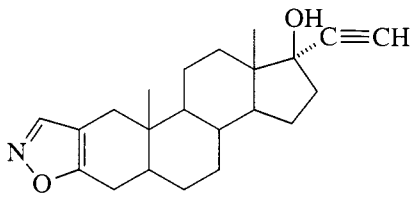


Under acidic conditions (hydroxylamine hydrochloride in hot ethanol or methanol) the [2,3-*d*]isoxazole is obtained as a virtually pure compound. The use of buffered or neutral conditions (hydroxylamine hydrochloride in refluxing pyridine or in alcoholic sodium acetate solution) results in a mixture of the two isomers which is difficult to separate by chromatographic procedures. The pure [3,2-*c*]isoxazole was eventually isolated by treating the mixture with sodium methoxide, which opens the [2,3-*d*] isomer to the 2-cyanoketone sodium salt.[2/60,3/60,6/61,4/63] This last sequence is important for the introduction of the cyano group into the 2 position of the steroid molecule. Under special conditions dioximes can be isolated.[3/62,5/69] Sometimes, under mild conditions, the intermediate 5′-hydroxy-2-isoxazoline of the [3,2-*c*] series could be separated,[5/63,6/63,5/69,6/69] which is readily dehydrated to the isoxazole on heating with acetic anhydride. This latter reagent in pyridine provokes acetylation to the stable 5′-acetoxyderivative.[5/69] Moreover, it has been demonstrated that the 5′-hydroxyisoxazoline derivative is a non-separable mixture of the two epimers.[5/69]

Research on steroidal isoxazoles was especially fruitful in the 1960s following the discovery of the interesting biological activity of some derivatives. Some short reviews[4/66,5/67,6/67] have summarized the results at that stage. In particular, two compounds, 17β-hydroxy-17α-methylandrostano[3,2-*c*]isoxazole (androisoxazole, **60**)[3/60,6/61,3/62] and 17α-ethynyl-17β-hydroxyandrost-4-eno[2,3-*d*]isoxazole (danazol, **61**),[4/62,5/63] have been utilized as anabolic agents with low androgenic activity.



60

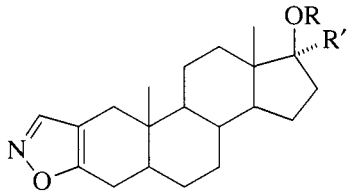


61

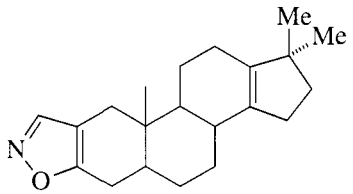
The extensive work of the Sterling–Winthrop research group on steroidal isoxazoles derived by oximation of 2-hydroxymethylene-3-ketosteroids is

included in some crucial patents[4/62,6/64,7/67] and in a thorough paper.[5/63] Several other research groups have prepared identical or analogous compounds starting from the following ketosteroids through formylation and subsequent oximation.

Androstan-17β-ol-3-one or its 17α-methyl homologue yield, depending on experimental conditions, either the [2,3-*d*]isoxazoles **62** (R = H, R′ = H or Me) alone [7/61,3/62,9/70] or a mixture of the two isomers, whose composition is function of the pH of the reaction medium.[3/60,6/61,3/62] Similar isomer mixtures have been obtained starting from the 1α-methylderivative of both steroids[5/66,8/67] or from the 7-ethylthioderivative of **62** (R = H, R′ = Me).[5/69,6/69] It is interesting to note that, if a tertiary 17β-hydroxy group is present in the molecule, highly acidic conditions can lead to the 18-nor derivative like **63**, owing to a retropinacol rearrangement.[5/63,8/64]



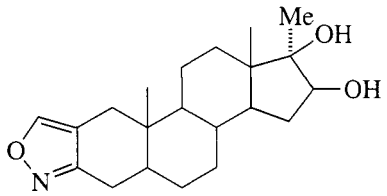
62



63

The 17α-esters or ethers usually lead exclusively to the [2,3-*d*] isomer;[7/63,8/63,7/69,6/76] only a different claim, concerning a 17α-enol ether, is known.[5/62] The same results are obtained starting from a 3-enol ether.[7/64]

The exclusive formation of 16β,17β-dihydroxy-17α-methylandrostano[3,2-*c*]isoxazole (**64**) by oximation in refluxing pyridine has been reported.[4/73]

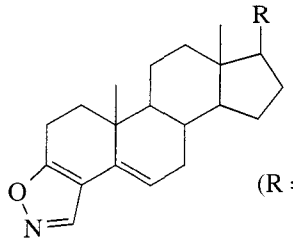


64

Conjugation with a double bond lowers the reactivity of the 3-keto group such that testosterone,[3/60,6/62,34/90] its methylated derivatives,[7/61, 1/79,1/84,2/84,2/87,35/90] and the ethers,[6/76] afford only the corresponding androst-4-eno[2,3-*d*]isoxazole. Some danazol derivatives[1/79,6/85,2/88,35/90] and related 4,6-diene[7/61,61/88] or 4,9-diene[3/74] analogs, as well as compounds derived from norgestrel[36/90] are also known. A retropinacol rearrangement on the tertiary 17α-hydroxy group to give a product derived from **64** has likewise been reported.[6/62,7/63] The same product has been prepared by a formylation–oximation sequence from 17,17-dimethylgona-

4,13-dien-3-one.[4/82] 4,4-Dialkyl substitution provokes the same regioselective effect, which likely originates from steric hindrance.[5/63,4/72,2/87] Conversely, oximation of a 2-isopropoxymethylene derivative has been claimed to form the [3,2-*c*] isomer exclusively.[8/64]

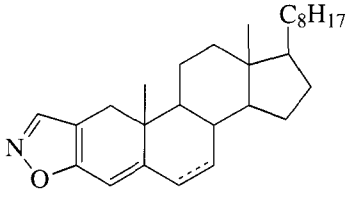
The presence of a formyl group in the 4 position of 3-keto-4-ene steroids enables the preparation of a 3-hydroxy- or 3-morpholino-4-formyl-3,5-dienes. Oximation of the latter offers a route to [4,3-*d*]isoxazoles of type **65**, derived from 17β-hydroxyandrosta-3,5-dieno-, 20-keto-pregna-3,5-dieno- and cholesta-3,5-dieno- systems.[8/69,4/71,5/71,5/72] Oximation under different conditions, specifically, in refluxing pyridine, is reported to afford the isomeric 17α-ethynyl-17β-hydroxyandrost-5-en[3,4-*c*]isoxazole.[5/72] The dependence on the reaction medium (hydroxylamine hydrochloride or acetate in ethanol solution) seems to be particularly high. When oximation of 2- or 4-hydroxymethylene-3,12-diketo-cholanic acid is conducted using hydroxylamine hydrochloride, the [2,3-*d*] and [4,3-*d*] isomers are obtained as minor products along with the corresponding oximes. When hydroxylamine acetate is employed, only the [3,2-*c*] and [3,4-*c*] isomers result.[5/65]



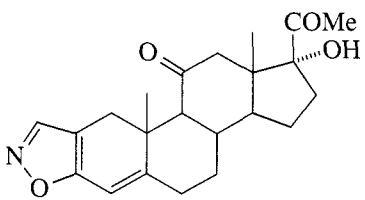
(R = C_8H_{17}, OBu^t, COMe)

65

Cholestan-3-one affords a mixture of the two possible condensed isoxazoles,[2/60] whereas only the [2,3-*d*] isomer (**66**) results from cholest-4-en-3-one[6/65,4/71] and cholest-4,6-dien-3-one.[6/65]



66



67

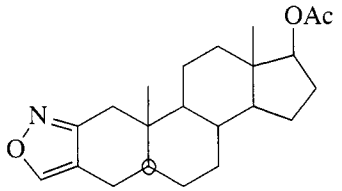
Although a mixture of the two isomeric condensed isoxazoles is reported to be formed from lanost-8-en-3-one,[6/71] the cortisone-condensed [2,3-*d*]isoxazole **67** has been obtained as the only product starting from cortisone BMD (bismethylenedioxy).[3/60]

19-Nor-steroidal derivatives behave normally and give [2,3-*d*]isoxazole derivatives;[7/61,3/62,6/62,7/63,7/65,3/74] but in one case, under appropriate conditions, the oximation leads to the isomeric [3,2-*c*] compound, in admixture with the dioxime.[3/62]

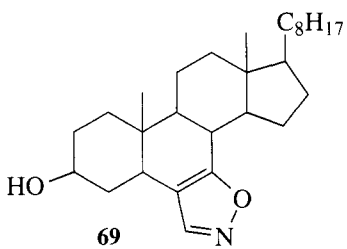
D-Homosteroidal [2,3-*d*]isoxazoles are also known.[74/84]

Choice of a 2-ketosteroid as starting material leads to the 3-hydroxymethylene-2-keto compound. Its oximation in acidic medium furnishes a mixture of two isomeric isoxazoles, which, after treatment with sodium methoxide leaves the [2,3-*c*] isomer. Thus 5α-androstano[2,3-*c*]isoxazol-17β-ol acetate (**68**) was isolated in 59% yield.[8/65,3/68]

Oximation of steroidal β-diketones is a poorly studied area; the reaction product obtained from 17β-acetoxy-2-acetylandrostan-3-one seems to be homogenous and the proposed structure has a 3′-methyl-[2,3-*d*]isoxazole pattern.[9/64]

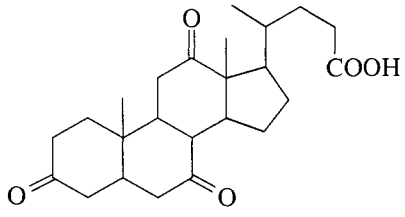


68

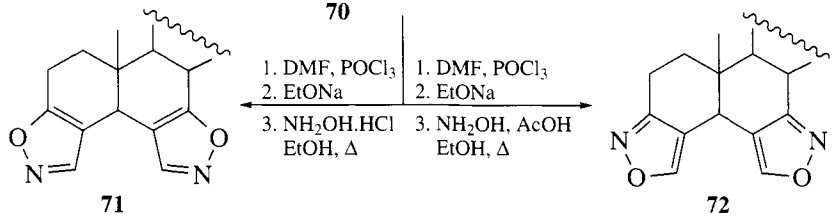


69

Steroidal isoxazoles involving ring B are also known. A cholestan[6,7-*d*]isoxazole (**69**) has been produced from 7-ketocholestanol,[6/62] and both isomeric isoxazoles have been obtained by formylation–oximation of 7,12-diketocholanic acid. The [6,7-*d*] isomer, together with preponderant dioxime, results if the oximation is carried out with hydroxylamine hydrochloride while the [7,6-*c*] isomer is obtained when hydroxylamine acetate is employed.[25/65] Moreover, starting from 3,7,12-triketocholanic acid **70**, selective bisformylation can occur at posi-



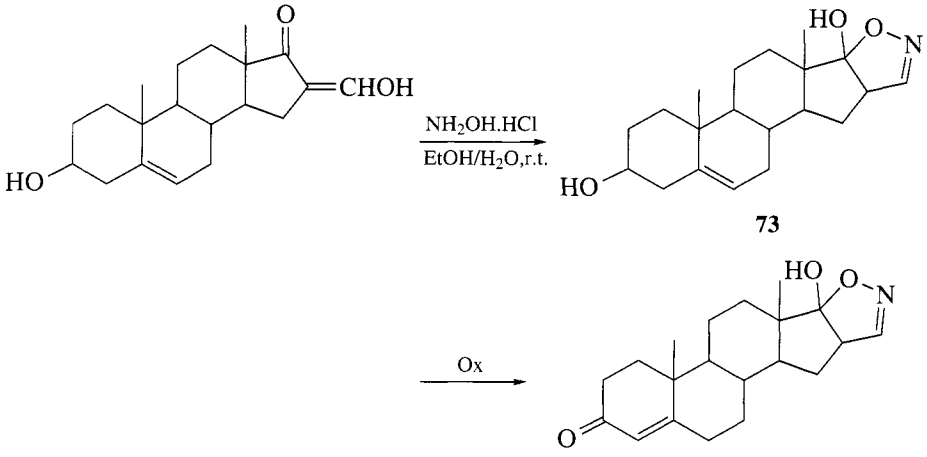
70



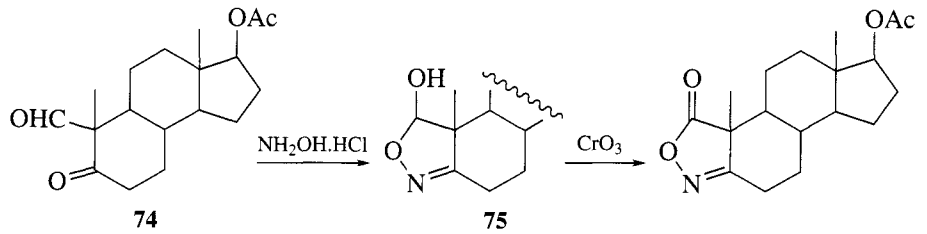
71 **72**

tions 2,6 or 4,6 and the product having the former arrangement affords either the [2,3-*d*][6,7-*d*]diisoxazole or the [3,2-*c*][7,6-*c*]diisoxazole. The [4,3-*d*][6,7-*d*] diisoxazole **71** (with the corresponding tetraoxime) or the [3,4-*c*][7,6-*c*] compound **72** result when the precursor has the 4,6 disubstitution.[9/69] This latter process is exemplified here.

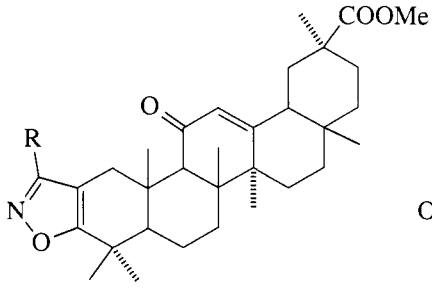
In contrast to the behavior of simple 2-methylenecyclopentanones, the five-membered ring D can be condensed with a 5-hydroxyisoxazoline ring. A stable hemiacetal (**73**) is obtained by oximation of 16-hydroxymethyleneandrost-5-en-3β-ol-17-one;[8/61,9/65,10/69] other analogous structures are known in the estrone field.[10/65,11/65, 6/66,7/71]



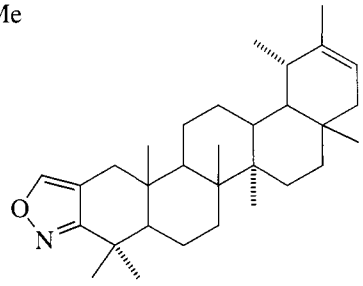
A stable hydroxyisoxazoline **75** also results from oximation of the tricyclic compound **74**.[9/63]



Extension of the formylation-oximation sequence to 3-oxoterpenoids enabled the preparation of some triterpene-fused [2,3-*d*] and/or [3,2-*c*] isoxazoles related to glycyrrhetic acids[7/66,10/70,5/73] (e.g., **76**), ursolic acid,[4/68] and taraxastenone[4/74] (e.g., **77**).

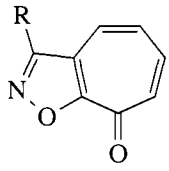


76

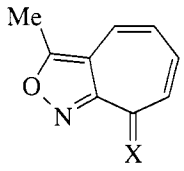


77

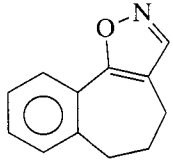
Isoxazoles condensed with a seven-membered ring can be prepared by the method of Johnson using both 3-acetyl-[5/82,1/87] and 3-cinnamyl-[1/89] tropolones. The corresponding 3-substituted 8*H*-cyclohept[*d*]isoxazol-8-ones **78** are produced by oximation under acidic conditions although the oxime precursor is sometimes present as by-product. The same material (**78**, R = Me) is the predominant product when 3-acetyl- or 7-acetyl-2-methoxytropone are the starting materials. Conversely, a complex mixture of products is produced under neutral conditions, in which the isomeric cyclohept[*c*]isoxazolone **79a** and oxime **79b** predominate.[5/82]



78
(R = Me, PhCH=CH)



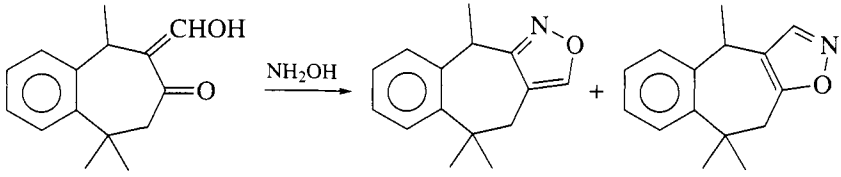
79a: X = O
b: X = NOH



80

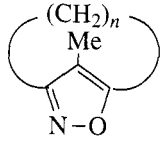
6,7,8,9-Tetrahydro-5*H*-benzocyclo hepten-5-one and its derivatives behave normally, and the usual formylation–oximation procedure yields condensed derivatives such as **80**.[5/68,2/79,6/86]

Oximation of the trimethylated hydroxymethyleneketone **81** may give either isomer; when conducted in acetic acid, isoxazole **82** is the sole product, whereas the use of pyridine as solvent leads to a 1 : 4 mixture in favor of **83**.[3/84]



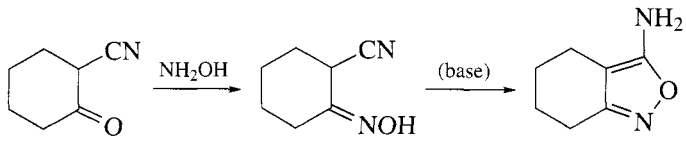
81 **82** **83**

Condensation with larger homocyclic rings is also known and 14-methyl-(3,5)[9]isoxazolophane (**84a**)[6/80] and 16-methyl-(3,5)[11]isoxazolophane (**84b**)[3/79] have been prepared by oximation of the appropriate 2-methylcycloalkane-1,3-dione following acid-catalyzed ring closure of the intermediate monoxime.



84a: $n = 9$
b: $n = 11$

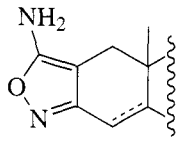
In addition to β-diketones, and their enol ethers and enamines, other derivatives can react with hydroxylamine to give isoxazoles. As mentioned briefly above, α-cyanocyclohexanones are well known to undergo attack at the carbonyl carbon, to give an oxime intermediate, which readily cyclizes in basic medium to **85**:[2/25]



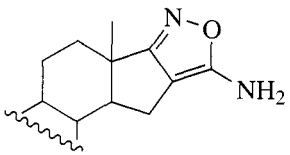
85

Analogous results, without the need for isolation of oxime intermediates, have been obtained from substituted cyanocyclohexanones.[9/72,6/73]

Keeping in mind that 2-cyanocyclohexanones are usually obtained by base-promoted ring opening of the tetrahydrobenzisoxazoles, the complete sequence allows transformation of these compounds into tetrahydroanthranil derivatives.[1/70] The sequence has often been used in the steroidal field for the synthesis of **86**-type[3/62,8/64,6/65,12/65,8/66,9/67] and **87**-type[37/69] derivatives; a naphth[1,2-*c*]isoxazole **88** has also been prepared by the same route.[10/67]



86



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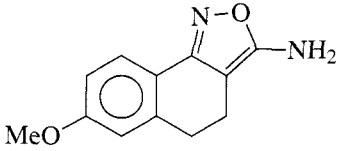
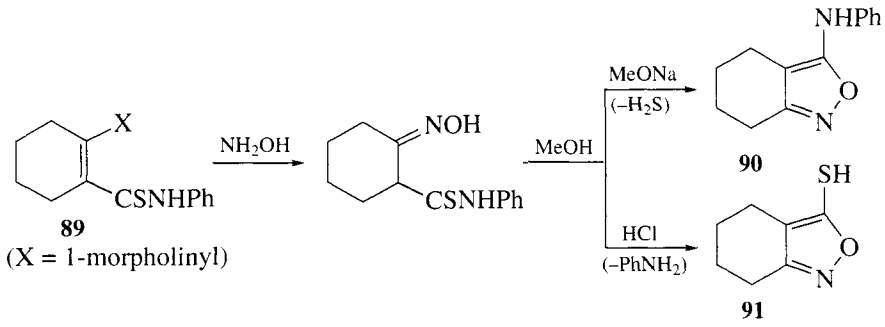
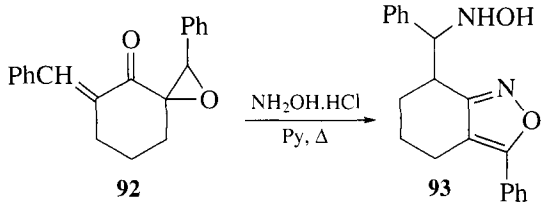


88

A somewhat different approach to tetrahydroanthranils starts from thioanilides such as **89**. The corresponding oxime cyclizes in basic medium to 3-anilinotetrahydroanthranil **90**, and in acidic medium to the thiolderivative **91**, for which an isomeric structure had been claimed previously.[11/70,13/65]

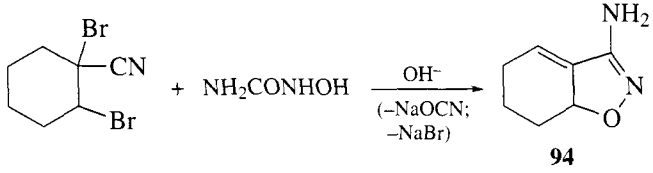


Another procedure relies on oxination of α,β-epoxycyclohexanones, such as **92**, to give the bisoximated product **93**.[6/81]

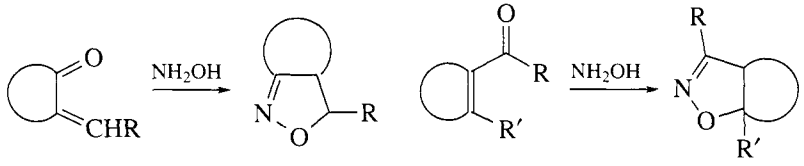


Some steroido[16,17-*d*]isoxazoles have been prepared from 16α, 17α-epoxypregnenolones through the intermediacy of the *anti*-oximes.[34/66] The formation of steroido[17,16-*d*]isoxazolines by direct treatment of 16,17-epoxypregnenolones with ammonia has been claimed.[69/66]

Finally, the peculiar formation of **94** from 1-cyano-1,2-dibromocyclohexane and hydroxyurea in alkaline solution should be mentioned; only traces of the isomeric and more stable 3-amino-4,5,6,7-tetrahydroindoxazene were isolated.[1/70]

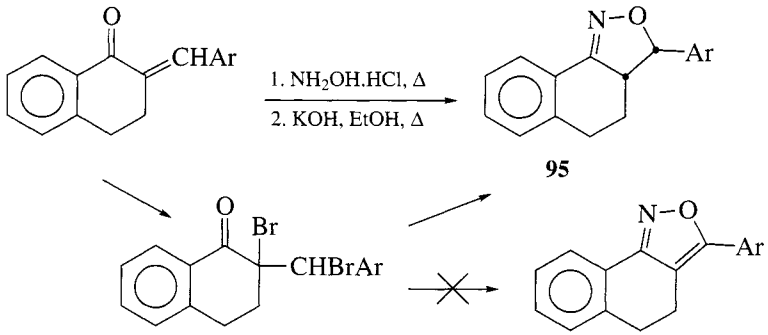


Although it is not as simple as it would appear, one of the oldest methods for preparing 2-isoxazolines is the oximation of α,β-enones (see Part 1, § 2.2.2.1a).



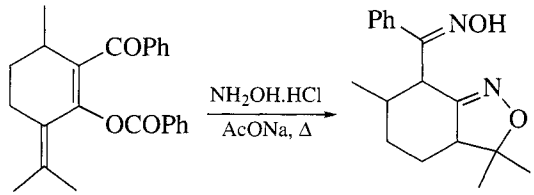
When either the carbonyl group or the double bond is endocyclic, 2-isoxazolines condensed in the 3,4 or in 4,5 position, respectively, can be achieved.

Oximation reactions of the former type usually involve an aryl group linked to the ethylenic double bond. In one example, reaction of 2-arylidene-1-tetralones with hydroxylamine hydrochloride, followed by treatment with potassium hydroxide, gives tetrahydro-3-arylnaphth[1,2-*c*]isoxazoles (**95**) in moderate yields (28–40%). It is worthwhile to note that the dibromo derivative **96**, under the same conditions, does not furnish the expected isoxazoles, but gives instead the same condensed 2-isoxazoline derivatives. This anomalous result has been attributed to a base-promoted debromination instead of the usual dehydrobromination, which is conformationally disfavored in this case.[7/81]



Similar results have been obtained with a substituted arylidenecyclohexanone[6/82] and with some 3-(2-oxocycloalkylidene)indol-2-ones.[37/90]

The unusual cyclization to the bicyclic isoxazoline **98** has been observed when the α-diketone enolester **97** was treated with hydroxylamine acetate.[6/72,7/73]

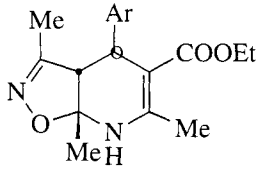


97 98

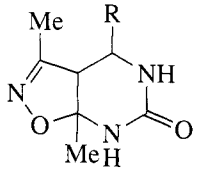
When the α,β-unsaturated carbonyl moiety belongs to a heterocyclic ring, bicyclic heterocyclic systems, such as pyrazoloisoxazoles,[7/80] oxazoloisoxazoles,[7/82] benzochromanoisoxazoles,[7/72] isoxazolopyridazinones,[7/86] isoxazolo-*as*-triazines,[8/82] and bisisoxazolopyridoquinolinediones[52/89] can be produced.

The oximation of some acylheterocycles, possessing an isolated double bond in α,β position, can open a route to partially saturated bicyclic heterocyclic

systems, such as isoxazolino[3,4-*d*]imidazoline,[2/85,3/85] tetrahydroisoxazolino[5,4-*b*]pyridines (**99**),[4/86,2/89] isoxazolino[5,4-*d*]pyrimidines (**100**),[9/66] isoxazolino [4,5-*b*][1.4]benzothiazines,[49/84] and benzopyrano[4,3-*d*]isoxazolines.[3/88] The facile base-promoted C-ring opening of rotenone and isorotenone explains the different behavior of these compounds toward hydroxylamine; in buffered medium the normal oximes are isolated, whereas in alkaline medium the corresponding benzopyrano[4,3-*d*]isoxazoline derivatives are reported to be formed.[1/32,1/33,9/61,2/86]

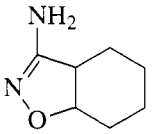


99



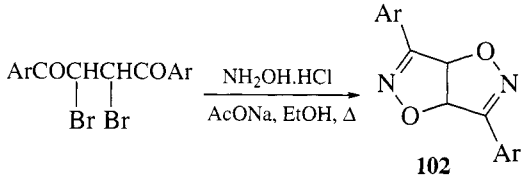
100

(R = Me, Ph)



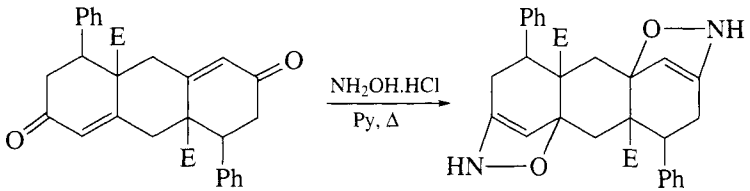
101

Oximation of α,β-ethylenic nitriles with hydroxyurea in basic media is known to yield 3-amino-2-isoxazolines; the extension to the cyclic derivative, 3-aminohexahydro-1,2-benzisoxazole (**101**), is reported to suffer from very low yields.[8/73] An example of the conversion of β–haloketones to 2-isoxazolines from the steroidal field involves preparation of a 3′-methylisoxazolino[17,16-*d*] androst-5-en-3β-ol from the corresponding 16α-chloropregnenolone in excellent yields.[14/65] More interesting still is the formation of 3a,6a-dihydro-3,6-diarylisoxazolo[5,4-*d*]isoxazoles (**102**) from the diaryl 2,3-dibromo-1,4-diketones:[3/77]



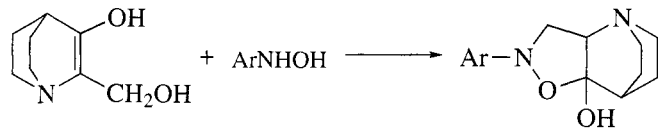
102

Even more peculiar is the possibility of cyclization onto an endocyclic −C=C−C=O system by action of hydroxylamine, as claimed in the following example:[38/90]



(E = COOEt)

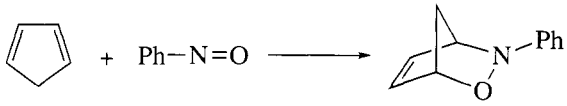
The hemiacetal structure **104** has been attributed to the condensation product between the quinuclidine derivatives **103** and 3-chlorophenylhydroxylamine:[8/81]



103 (Ar = 3-ClC_6H_4) **104**

4.2.1.2. Cycloaddition of Dienes to Nitroso Compounds

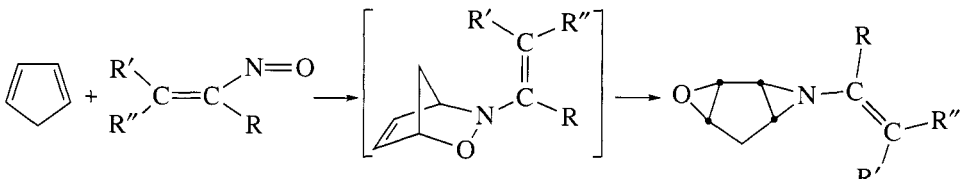
The most convenient method of preparing the 2,3-oxazabicyclo[2.2.1]heptene system takes advantage of the hetero-Diels–Alder cycloaddition of nitroso derivatives to pentacyclic 1,3-dienes. Thus, for example, nitrosobenzene and cyclopentadiene react at room temperature to give adduct **105** in 78% yield:[10/61]



105

Compound **105** is reported to be unstable even at room temperature, decomposing slowly to the starting materials. A stable cycloadduct can be obtained using a nitrosoarene bearing an electron-withdrawing group, such as 2,4-dinitronitrosobenzene.[7/76] Also some electron-poor aliphatic nitroso compounds, such as CF_3NO and RCl_2CNO, have been successfully employed.[11/67,4/77,4/79]

Nitrosoalkenes **106**, generally obtained *in situ* by dehydrohalogenation of α-halooximes, give rise to unstable cycloadducts, which rearrange at room temperature to tricyclic compounds having the epoxyenamine structure **108**:[4/77,4/79,9/81]

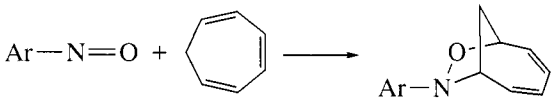


106 **107** **108**

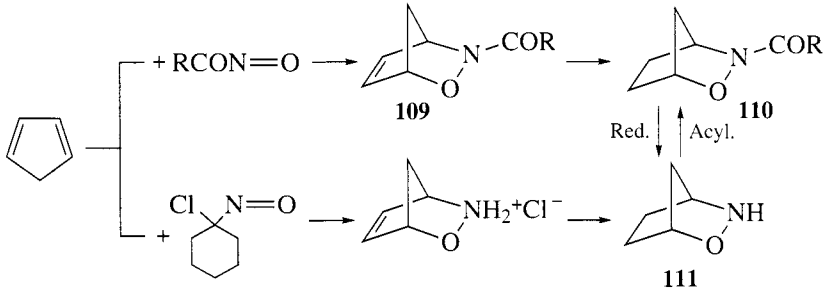
Evidence for the intermediate adduct **107** has been obtained at low temperature by NMR spectroscopy.[4/79] Even 2,5-dimethylfuran and dipheny-

lisobenzofuran can be used as dienes, but in these cases the cycloadduct is not detectable, and decomposes to open-chain unsaturated diketones.[9/81] It should be also added that α-unsubstituted nitrosoalkenes (**106**, R′ = R″ = H) react as dienes, giving rise to condensed 1,2-oxazines.[9/81]

Despite suggestions to the contrary,[10/61] the use of 1,3,5-cycloheptatriene as a cycloaddition partner favors the 1,6-cycloaddition (although with low yields) rather than the 1,4-cycloaddition:[10/66,11/69]



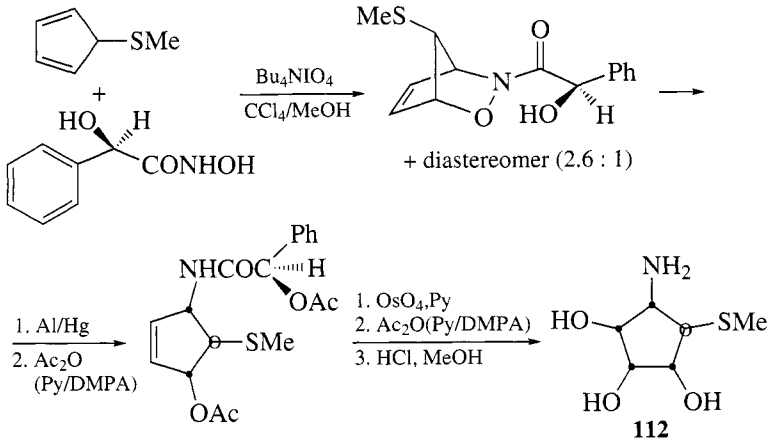
The best studied dienophiles are the acylnitroso compounds, easily generated *in situ* by oxidation of acylhydroxylamines with periodate. Cycloadducts such as **109**, which are useful as key intermediates in synthetic design, have thus been prepared.[7/76,5/79,10/81,4/85] For example, the benzoyl derivative has been involved in an approach to carbapenem synthesis,[32/90] where hydrogenation to **110**, followed by deacylation, leads to the *N*-unsubstituted bicycloheptane system **111**, an aza analog of prostaglandins PGG and PGH frameworks.[7/76] A more direct route to the same system utilizes a large excess of 1-chloro-1-nitrosocyclohexane, as illustrated in Scheme 4.2.[10/81] Excellent yields of cycloadducts **109** (R = OR′ or NR'_2) are also obtained from transient *C*-nitrosoformate esters[5/85,7/85] or *C*-nitrosoformamides.[8/85]



Scheme 4.2

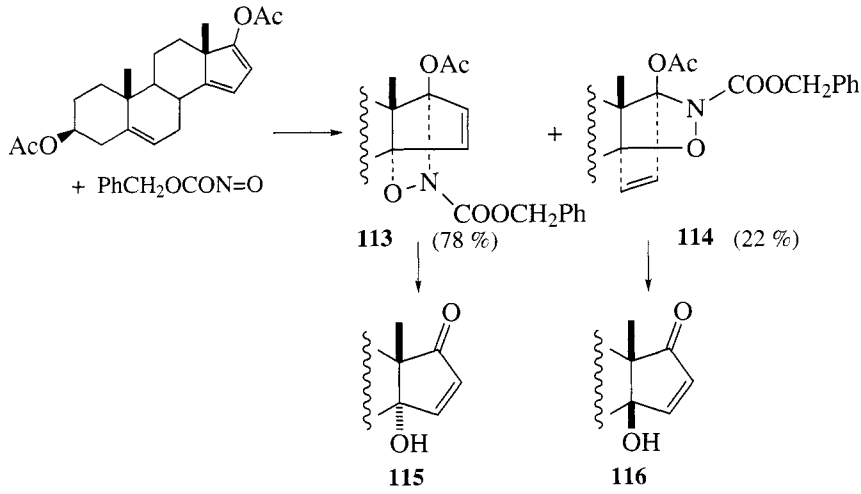
Chiral nitroso compounds impart a remarkable degree of diastereoselection on these cycloadditions.[4/88,3/89,39/90] Using 5-methylthio-1,3-cyclopentadiene as diene partner, an enantioselective six-step synthesis of mannostatin A (**112**) has thus been achieved[1/91] (Scheme 4.3).

An interesting synthesis of either 14β- or 14α-androstane is based on the π-facial diastereoselectivity controlling the cycloaddition of the dienol acetate to

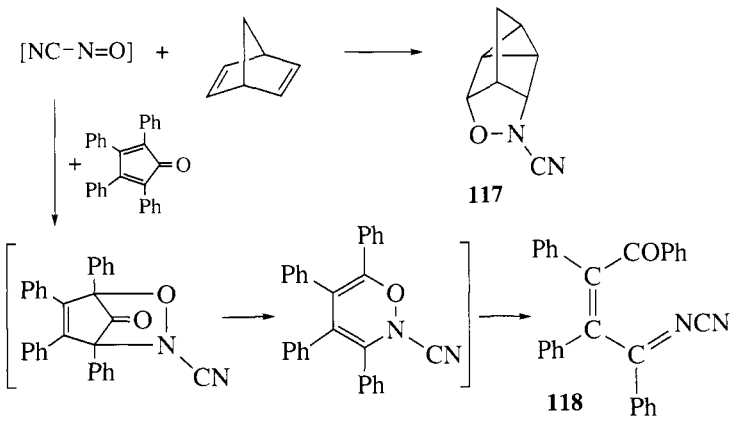


Scheme 4.3

benzyl nitrosoformate to give a mixture of the two diastereomeric cycloadducts **113** and **114**, which can be further elaborated to give either **115** or **116** with good yields.[53/89]

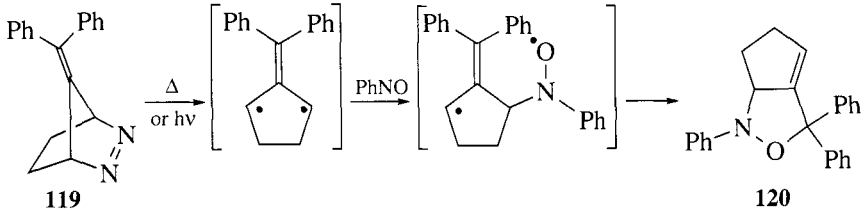


In a variation of the hetero-Diels–Alder reaction, the $[\pi^2 + \pi^2 + \pi^2]$ cycloaddition of norbornadiene with nitrosylcyanide, generated *in situ* by thermal cleavage of its cycloadduct with 9,10-dimethylanthracene, affords cycloadduct **117**. Reaction of the same nitroso compound with tetraphenylcyclopentadienone leads instead to the open-chain product **118**, owing to the high instability of the primary cycloadduct:[11/81]

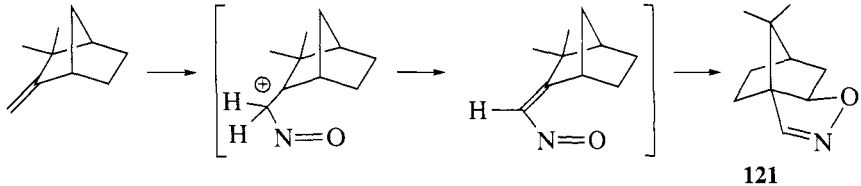


4.2.1.3. Other [CCC + NO] Processes

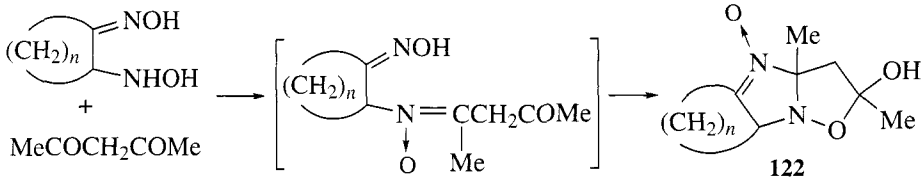
The relative stability of nitroxides is well known, and can be utilized to synthesize condensed isoxazolidine systems. For example, the reactive intermediate 2-diphenylmethylene-1,3-cyclopentadiyl, generated by photolysis or thermolysis of diazabicycloheptene derivative **119**, has been trapped by nitrosobenzene to yield the heterobicyclic adduct **120**:[2/91]



A special example of a [CCC + NO] process is the acid-promoted nitrosation of camphene at low temperature, which produces the highly strained tricyclic isoxazoline **121**; further derivatives have been prepared starting from substituted camphenes:[12/69,5/74,5/77]

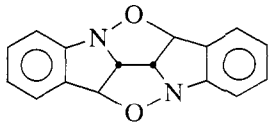


Condensation of acetylacetone with 2-hydroxylaminocyclohexanone oxime (or the corresponding cycloheptanone derivative) furnishes bicyclic tetrahydroimidazo[1,2-*b*]isoxazole **122**. The same reaction, when carried out on the cyclopentanone derivative, does not result in cyclization.[40/90]



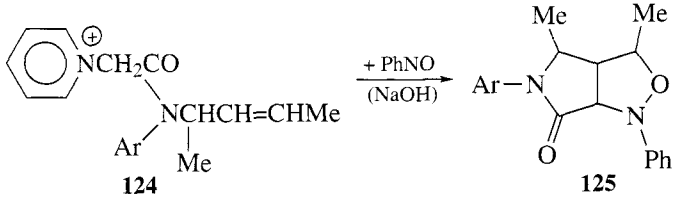
122

A polycyclic diisoxazolidine compound **123** is formed in very low yield (8%) by treatment of phenylacetylene with nitrosobenzene.[6/68]



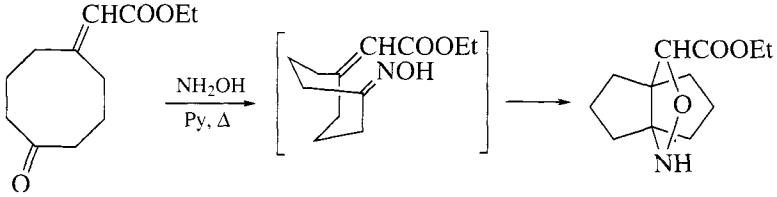
123

A particular case of cyclization process involves the *N*-pyridinioacetyl unsaturated amine **124**, which reacts with nitrosobenzene in basic mediam to give the 3-oxa-2,7-diazabicyclo[3.3.0]octan-8-one system **125** in fairly good yields:[6/79,70/85]



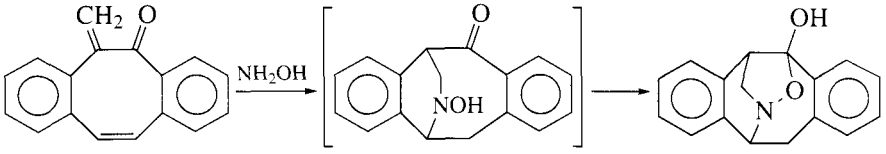
124 **125**

Oximation of 5-ethoxycarbonylmethylenecyclooctanone has been reported to furnish 4-ethoxycarbonyl-3-oxa-2-aza[3.3.3]propellane in 85% yield:[5/86]



The pyridine-promoted cyclization can also be regarded as an intramolecular 1,3-dipolar cycloaddition process.

Finally, the reaction of α-methylenedibenzocyclooctenone with excess hydroxylamine leads to the isolation of annulated cycloadduct **126**, possibly arising from an initial addition of hydroxylamine to the two double bonds, with subsequent cyclization of the γ-ketohydroxylamine (see § 4.2.7.5).[5/88]



126

4.2.2. [CNO + CC] Processes

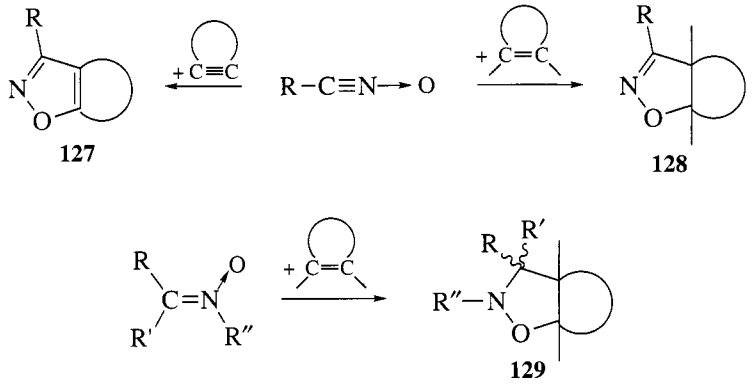
The 1,3-dipolar cycloaddition of nitrile oxides and nitrones to unsaturated (CC double or triple bond) compounds has grown within the last three decades into the most important synthetic method for preparing isoxazole, dihydro- and tetrahydro-isoxazole derivatives. The mechanistic and synthetic implications of this reaction type have been thoroughly illustrated in Part 1, §§ 1.3.2 (pp. 183–208), 2.2.2.2 (pp. 475–523), 2.5.2.1 (pp. 630–637), and 3.3.1 (pp. 686–725). For a discussion on the general mechanism of this reaction and its utility in the synthesis of monocyclic isoxazoles and reduced isoxazoles, reference is made to these chapters.

In the following paragraphs the use of 1,3-dipolar cycloadditions for the synthesis of polycyclic condensed isoxazole derivatives will be illustrated according to the starting material employed. As shown in Scheme 4.4, nitrile oxides can react with cyclic triple- or double-bond-containing compounds to give 4,5-condensed isoxazoles **127** or 2-isoxazolines **128**, respectively. When the unsaturated bond is connected to the nitrile oxide moiety, an intramolecular reaction, the so-called INOC (intramolecular nitrile oxide cycloaddition), can occur to yield either a 3,4-condensed (**132**) or a 3,5-condensed 2-isoxazoline derivative (**133**); similarly, isoxazoles **134** or **135** are obtained when a triple bond is involved.

Condensed isoxazolidines **129** or **131** can be obtained either from the cycloaddition of acyclic nitrones to olefins or from the cycloaddition of cyclic nitrones to acyclic (or cyclic) olefins. The corresponding condensed 4-isoxazolines **130** are formed when the nitrones are reacted with alkynes. The intramolecular versions of these reactions can afford the isoxazolidines (or 4-isoxazolines) **136/137** or **138/139**.

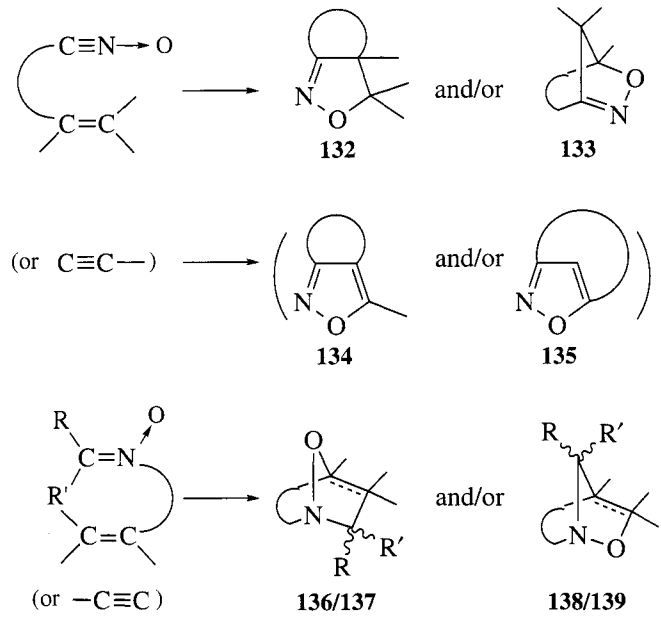
As discussed in Part 1 (see §1.3.2.3), β-diketones and related compounds can act as dipolarophiles in these cycloadditions, and their cyclic counterparts are also examined separately here.

Intermolecular 1,3-dipolar Cycloadditions



127 128 129 130 131

Intramolecular 1,3-dipolar Cycloadditions



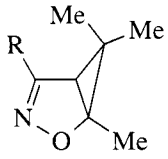
132 133 134 135 136/137 138/139

Scheme 4.4

The use of the same reaction pattern as a key step in the synthesis of complex molecules has also been exemplified in Part 1: § 1.4.12 (pp. 391–416) for isoxazole intermediates, § 2.2.3.3 (pp. 572–602) for 2-isoxazoline intermediates, and § 3.4.10 (pp. 753–777) for isoxazolidine intermediates. In these paragraphs, both monocyclic *and* polycyclic derivatives had been taken into account. Therefore, in the following treatment only examples of multistage syntheses contained within 1985–1991 *Chemical Abstracts* literature will be reported.

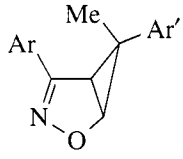
4.2.2.1. Cycloaddition of Nitrile Oxides to Unsaturated Cyclic Compounds

The cycloaddition of nitrile oxides to the simpliest cycloalkene, (i.e., cyclopropene) proceeds without difficulty, leading to 4-substituted 2-oxa-3-azabicyclo[3.1.0]hex-3-enes in good yields.[9/73] Analogous results have been obtained with substituted cyclopropenes. As expected, 1,3,3-trimethyl cyclopropene gives **140**, in which the methyl group occupies the isoxazoline 5-position,[6/74] although in one case the presence of a small amount (2% yield) of the regioisomer has been reported.[8/72]

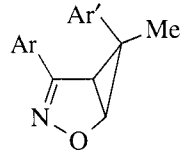


140

(R = Me, Ar)



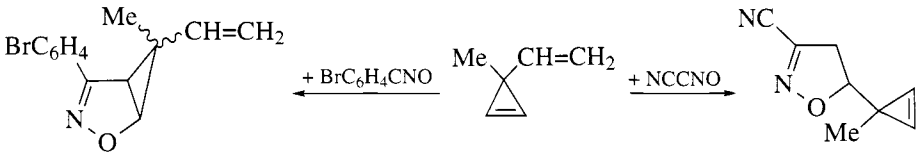
141



142

(Ar = Ph, 4-$NO_2C_6H_4$; Ar′ = Ph, 4-$MeOC_6H_4$)

A thorough study on the cycloaddition of aromatic nitrile oxides to 3,3-disubstituted cyclopropenes[2/90] revealed that a mixture of both predictable stereoisomeric oxazabicyclohexenes is usually obtained when the two 3-substituents are different. Thus, starting from 3-aryl-3-methylcyclopropenes, the formation of derivatives of **142**, in yields of 7–21%, in addition to the sterically favored isomer **141**, in yields of 59–86%, are reported. Moreover, in the case of 3-methyl-3-vinylcyclopropene the strained endocyclic double bond is far more reactive than the vinyl group, so that isolation of the monoadduct **143** (as a mixture of



(82% yield)

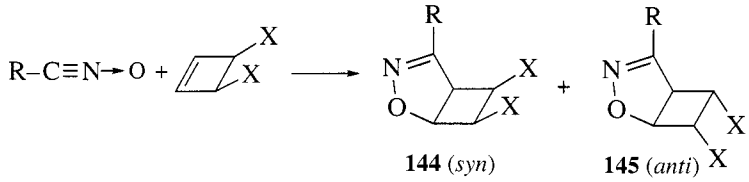
143

(39% yield)

stereoisomers) has been achieved with aromatic nitrile oxides. However, the more electrophilic cyanonitrile oxide reacts, although in lower yields, with the vinyl group.

A spirocyclopropene derivative of indene has also been reported to react with acetonitrile oxide on the double bond of the three-membered ring to give, after isomerization on silica gel, the thermodynamically more stable isomer.[50/84]

An interesting example of facial selectivity exists in the 1,3-dipolar cycloaddition of 3,4-*cis*-disubstituted cyclobutenes, which can react with nitrile oxides, nitrones (see § 4.2.2.5) and other 1,3-dipoles, such as diazoalkanes, nitrile imines, and azomethine imines to give *syn–anti* cycloadducts:



The most striking features of this reaction are the following: (1) a distinct preference for *syn* addition in the case of electron-withdrawing substituents (Cl, OMe, OAc, OSO_2Me, OH); (2) the decrease in *syn* selectivity when the two substituents are embedded in a ring (compare diacetoxy and carbonyldioxy derivatives); (3) the complete *anti* selectivity when the cyclobutene ring is condensed with a small (≤ five-membered) ring. Table 4.1 collects some selected examples of this cycloaddition reaction.

TABLE 4.1. CYCLOADDITION OF NITRILE OXIDES TO 3,4-*cis*-DISUBSTITUTED CYCLOBUTENES

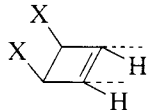
R	X	X	Total yield %	**144:145** ratio (*syn:anti*)	References
Me	Cl	Cl	69	69:31	6b/74
COOEt	Cl	Cl	29	74:26	6b/74
COMe	Cl	Cl	49.5	73:27	6b/74
Ph (Et_2O)	Cl	Cl	82	48:52	6b/74
(MeCN)	Cl	Cl	79	71:29	6b/74
	OH	OH	65		8/76
	OMe	OMe	n.d.	80:20	71/90
	OAc	OAc	88	90:10	40/88
	CH_2–CH_2–CH_2		71	0:100	40/88
	CH_2		65	0:100	4/83
	CO–O–CO		58	0:100	3/91
	COOMe	COOMe	95	9:95	71/90
4-$NO_2C_6H_4$	Cl	Cl	84	61:31	6b/74
4-MeC_6H_4	Cl	Cl	95	42:58	6b/74

(*continued*)

TABLE 4.1. (*continued*)

R	X	X	Total yield %	**144:145** ratio (*syn:anti*)	References
4.2.6-$(MeO)_3C_6H_2$					
(Et_2O)	Cl	Cl	90	7:93	6b/74
(MeCN)	Cl	Cl	60	24:76	6b/74
2,4,6-$Me_3C_6H_2$	Cl	Cl	80	27:73	6b/74
(PhH)	OH	OH	88	90:10	8/76
(MeOH)	OH	OH	65	50:50	8/76
	SMe	SMe	76	10:90	6/88
PhCO	Cl	Cl	53	78:22	71/90
	OH	OH	59	86:14	7/88
	OAc	OAc	66	95:5	40/88
	$O-CH_2-O$		58	0:100	7/88
	$O-CMe_2-O$		68	14:86	7/88
	O–CO–O		51	33:67	7/88
	$CH_2-CO-CH_2$		33	12:88	7/88
	$CH_2-CH_2-CH_2$		68	0:100	7/88

The experimental results can be explained by the following factors: (1) steric effects clearly hinder the *syn* attack, as evidenced by the decrease of *syn/anti* ratio along the series MeCNO > PhCNO > MesCNO, and by the exclusive *anti* addition for bicyclo[3.2.0]heptene derivatives; (2) electrostatic factors, such as the repulsive interaction between the charged oxygen atom of the 1,3-dipole and the heteroatom on the dipolarophile, as evidenced by the increase of *syn* addition on going from 4-methyl to 4-nitro-benzonitrile oxide, and on changing the solvent from the less polar ether to the more polar acetonitrile; (3) the nonplanarity of the cyclobutene double bond, which depends on the tendency to maximize hyperconjugative interactions between the π bond and the allylic σ bonds. In fact, ab initio MO calculations show that cyclobutenes with open-chain electron-withdrawing substituents exhibit a small but not negligible out-of-plane bending of the olefinic hydrogens in *anti* direction as in **146** (thus favoring the *syn* attack of the dipole), cyclobutenes with the heteroatoms embedded in a ring have the double bond almost planar, as in **147**, and cyclobutenes with a carbocyclic disubstitution show a *syn* bending of the olefinic hydrogens as in **148** (thus favoring an *anti* attack).[71/90]



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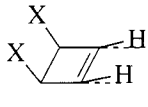

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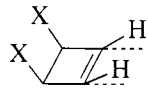
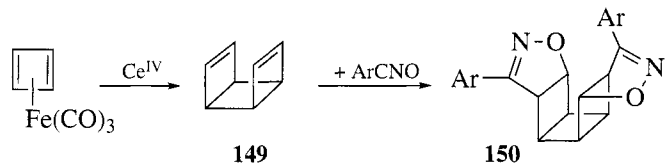


148

The manifestation of hydrogen bonding, which strongly favors the *syn* mode of attack, has been invoked in the case of the dihydroxy compound.[8/76]

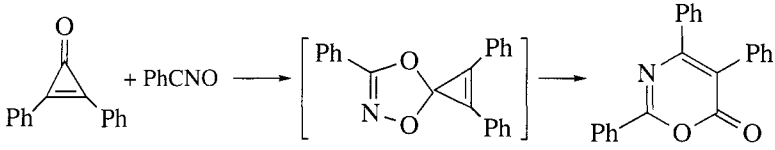
In the presence of tolunitrile oxide, cyclobutadiene, which is liberated from its stable complex with irontricarbonyl by treatment with cerium(IV) ammonium nitrate, gives, in addition to several cyclobutadiene dimers, the bis-2-isoxazoline **150**, derived from the *syn*-dimer **149**, which is formed in 15% yield.[7/74]



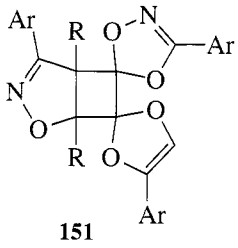
149 **150** (Ar = 4-MeC$_6$H$_4$)

Better yields of the condensed isoxazoline are obtained from the cycloadditions of nitrile oxides to benzocyclobutene. Noteworthily other 1,3-dipoles (nitrones included) are unreactive with the same dipolarophiles.[7/74]

Both carbon–carbon and carbon–oxygen double bonds can form cycloadducts with nitrile oxides; the former are usually more reactive than the latter ones, at least in acyclic compounds or in cyclic compounds containing a five-membered or larger ring. By contrast, diphenylcyclopropenone has been reported to react with benzonitrile oxide exclusively at the C=O bond. The product obtained in this instance, a triphenyl-1,3-oxazin-6-one, likely arises from a non-isolated spiro-1,3,4-dioxazole intermediate.[8/74]



Similarly, in the case of substituted cyclobutenediones the strained C=O bonds react to give mono- and/or bisadducts, having spirodioxazole structures. Occasionally a trisadduct, such as **151**, has been isolated as by-product.[9/76,8/86]



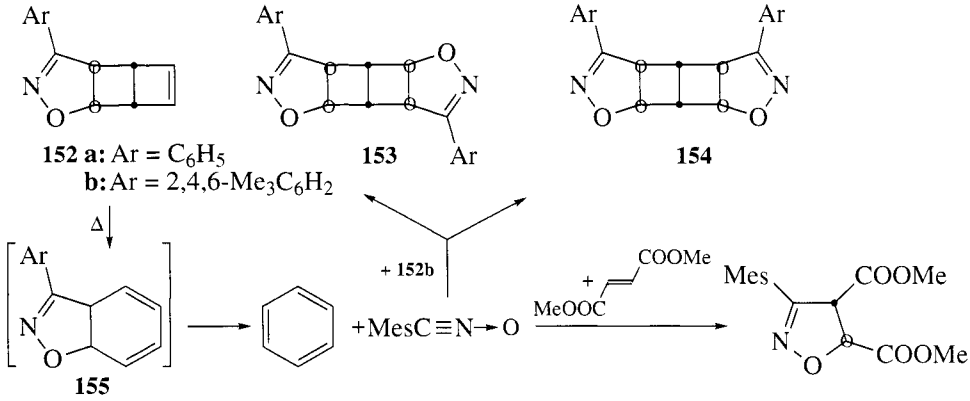
151

(Ar = 2,4,6-Me$_3$C$_6$H$_2$; R = Me or Ph)

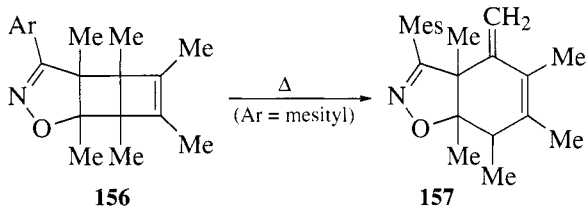
(3–8% yields)

A classic example of strained cyclobutene rings is Dewar benzene, which undergoes cycloaddition with aromatic nitrile oxides to furnish a mixture of the monoadduct **152** and of the regioisomeric bisadducts **153** and **154**.

Decomposition of **152b** at 120° promotes isomerization to the intermediate **155**, which immediately cycloreverts to benzene and mesitonitrile oxide. The latter may react with the monoadduct to yield a 2:1 mixture of the bisadducts **153b/154b** or can be trapped by cycloaddition to dimethyl fumarate.[9/85]



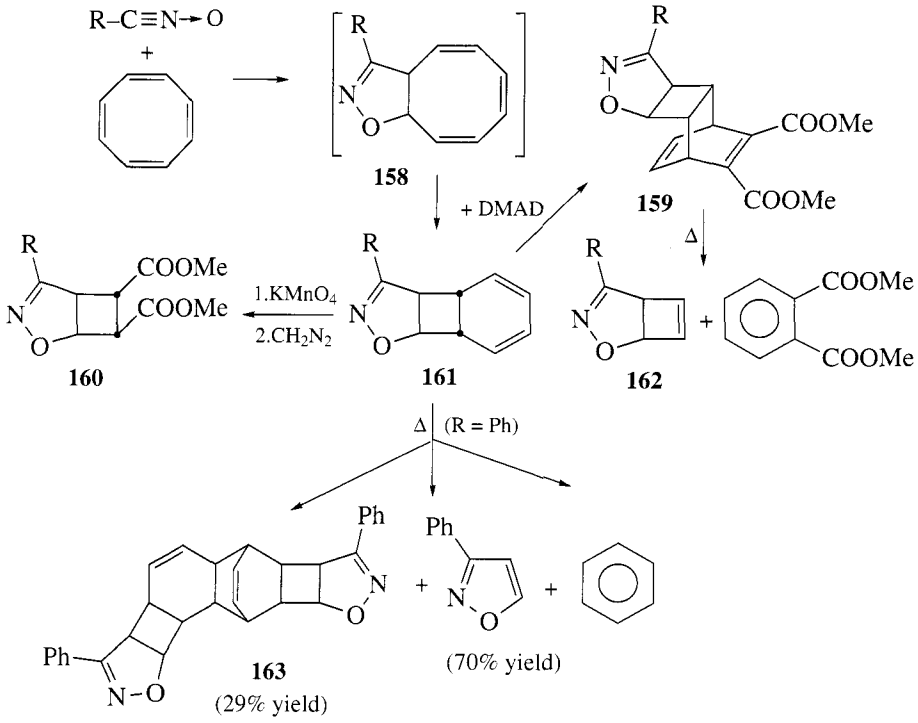
Hexamethyl–Dewar benzene reacts analogously to afford monoadduct **156**, which isomerizes on heating at 130°C to the bicyclic isoxazoline **157**, accompanied by very small amounts of the isomeric monocyclic oxazacyclononatriene derivative.[32/73]



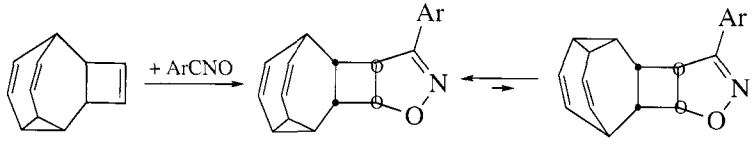
Better yields of the isoxazoline monoadduct, contaminated with small amounts of the bisadducts, have been reported for the cycloaddition of mesitonitrile oxide to hexafluoro–Dewar benzene.[10/73]

Cycloaddition of cyclooctatetraene with nitrile oxides leads to isolation of an oxazatricyclo[4.3.0.0]undecatriene structure **161**;[12/67,7/68] evidence for the intermediacy of the bicyclic intermediate **158** has been obtained by NMR spectroscopy.[7/68,11/73] Yields for this reaction are good with aromatic nitrile oxides,[12/67,11/73] but low with acetonitrile oxide[12/70] and very low with formonitrile oxide.[13/67,12/73] Structure **161** has been characterized by NMR spectroscopy, and has been further confirmed by chemical transformations. Oxidation of **161** affords dimethyl 4-aryl-2,3-oxazabicyclo[3.2.0]hept-2-ene-6,7-dicarboxylate (**160**), thermolytic cycloreversion yields benzene and 3-arylisoxazole,[12/67,12/70,11/73] with minor amounts of the Diels–Alder dimer **163**,[11/73] Diels–Alder cycloaddition to dimethyl acetylenedicarboxylate gives the adduct **159**, which, in turn, can be pyrolyzed to 4-substituted 2,3-

oxazabicyclo[3.2.0]hepta-3,6-dienes **162**,[12/70] the formal monoadducts from nitrile oxides and cyclobutadiene.

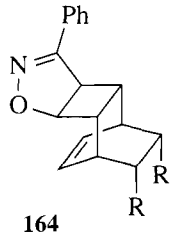


When the cyclobutene ring is condensed with carbocyclic rings containing additional double bonds, both regio- and facial selectivity can arise in cycloadditions. Usually the strained cyclobutene double bond is more reactive toward nitrile oxides than those present in larger rings. This is true for tetracyclo[5.3.2.0.^{2,10}0^{3,6}]dodeca-4,8,11-triene, which is attacked by aromatic nitrile oxides in a 100% stereoselective fashion, *anti* to the homotropilidene moiety, at the cyclobutene double bond. The valence tautomerism and anisodynamicity of the monoadducts have been correlated with conformational and angle strain effects.[11/86]



Another example is the tricyclo[4.2.2.0^{2,5}]undeca-3,7-diene system, which originates from the addition of cyclooctatetraene and maleic acid ester or anhydride, and reacts with benzonitrile oxide on the cyclobutene moiety to give

exclusively the adduct **164**. By contrast, reaction of nitrile oxides with the cycloadduct of cyclooctatetraene and dimethyl acetylenedicarboxylate gives a mixture of **165** and **166**, a result that reveals both disubstituted double bonds to be dipolarophilic, although the cyclohexadiene bond is more reactive.[12/70]



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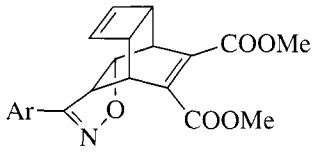
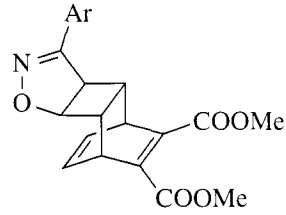
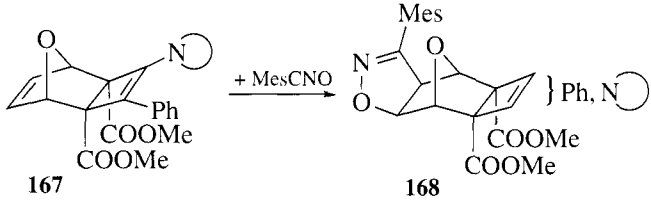


165 (57–70%)



166 (17–18%)

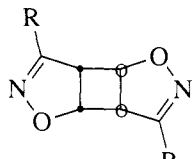
An example of regiospecificity that is perhaps dictated by electronic effects is provided by the tricyclic compound **167**, in which the cyclobutene double bond, an enamine, is unreactive and only the unsubstituted double bond reacts with mesitonitrile oxide. A mixture of the two regioisomers **168** results.[10/76]



167 **168**

When other bicyclic systems that contain a cyclobutene ring, such as bicyclo[2.1.0]pentene,[4/83] bicyclo[3.2.0] heptene,[40/88] dimethyl 5,6-diazabicyclo[2.2.0]hex-2-ene-5,6-dicarboxylate,[62/89] and 3-thiabicyclo[3.2.0]hept-6-ene 3,3-dioxide,[9/82] have been tested for reactivity toward nitrile oxides, only the *anti*-cycloadducts have been observed.

The unsymmetrical 2,3-oxazabicyclo[3.2.0]hepta-3,6-dienes **162** exhibit regio- and stereoselectivity in cycloadditions with nitrile oxides. Among the three isomeric monoadducts formed, the dominant *trans/anti* products (**169**) are accompanied by substantial amounts of the *cis/anti* (**170**) and *trans/syn* (**171**) isomers.[6/77]



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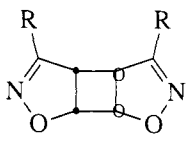

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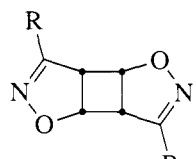
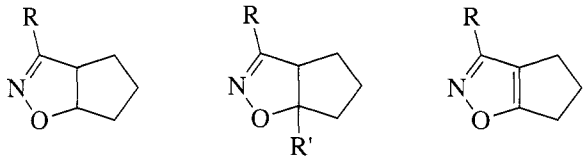


171

Although the reactivity of cyclopentene with benzonitrile oxide is about 5 times slower than that of ethylene, it is a good dipolarophile.[13/73] Cycloaddition with a variety of nitrile oxides, to give 2,3-oxazabicyclo[3.3.0]oct-3-enes **172** has been studied. Examples include aliphatic (**172**, R = H,[13/67,12/73] methyl,[8/68,13/70,14/73,8/80,12/86] ethyl,[8/80,12/86] *t*-butyl,[4/84] 1-propenyl[69/90]), aromatic (**172**, R = phenyl[11/61,7/62,8/71,11/73,8/80]), sulfonyl (**172**, R = $PhSO_2$,[7/79,5/84,6/84] 4-$MeC_6H_4SO_2$ [9/74]), or functionalized nitrile oxides [**172**, R = $Me_2C(OSiMe_3)$,[4/84] $MeC(OCH_2CH_2O)CH_2$,[12/86] NC,[5/83] EtOOC,[10/74,5/83] THP-OCH_2,[5/83] HON=CH[10/74]]. With the exception of formonitrile oxide, the yields are usually good, and their variability in some cases chiefly depends on the method of generating the involved nitrile oxide. Thus the 4-methyl derivative (**172**, R = Me) was obtained in 63% yield when acetonitrile oxide was generated by dehydration of nitroethane in the presence of toluenesulfonyl chloride and potassium carbonate.[12/86] Only a 23% yield of the adduct was obtained with the nitrile oxide generated by photolysis of 3,4-dimethyl-1,2,5-oxadiazole.[8/68]

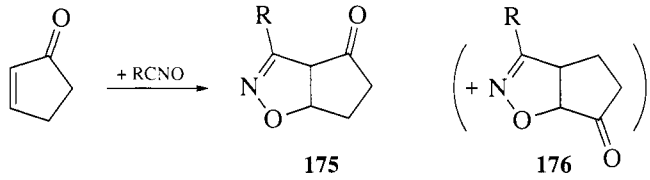


172 **173** **174**

The presence of a substituent on the cyclopentene double bond retards the rate of cycloaddition and influences the regiospecificity of the reaction. The 1,4-disubstituted oxazabicyclo[3.3.0]oct-2-ene **173** is usually obtained as dominant or exclusive isomer.[11/61,12/61,13/61,7/62,10/64,11/66,8/71,10/74, 3/75,8/79,64/88] In the cycloaddition of benzonitrile oxide with 1-ethynylcyclopentene, the ethynyl group is the more dipolarophilic site, and good yields of 5-(1-cyclopentenyl)-3-phenylisoxazole are obtained. Some addition to the endocyclic double bond occurs, as evidenced by the isolation of low amounts of the bis-adduct.[10/64]

A tertiary amino group (R′=1-morpholino, 1-pyrrolidino, 1-piperidino, dimethylamino) enhances the reactivity of the double bond and allows the synthesis of the corresponding 4,5-condensed isoxazole derivatives **174** through Hofmann or Cope elimination reaction[10/63,3/64,4/64, 9/68,13/69,9/71,1/78,9/80,10/85]

Conjugation of a dipolarophile with a carbonyl group has a strong regiodirecting effect that causes the major product to be the cycloadduct in which the position α to the carbonyl group becomes the 4 position in the isoxazoline ring.[11/61,7/62,16/68,8/71,11/76,10/80,8/88] Benzonitrile oxide gives a 92 : 8 ratio of **175 : 176** (R = Ph),[15/73,12/81] and 4-methoxybenzonitrile oxide gives a 90 : 10 ratio; only regioisomer **175** has been obtained from reactions involving 4-nitrobenzo- or mesitonitrile oxide.[15/73] Cyclopentenone ethylene acetal furnishes analogous results.[15/73] Cycloaddition with electron-poor nitrile oxides, such as EtOOC–CNO, proceeds at a slower rate and without regioselectivity.[11/76]



The double bond in the D ring of several steroidal derivatives reacts readily with nitrile oxides, giving rise to steroidal condensed 2-isoxazolines, such as **177**. Although the stereochemical outcome is assured, since the 1,3-dipole always attacks the α side of the steroid, the regiochemistry of the products is not always clear. Sometimes, as can be deduced from Table 4.2, opposite regioisomeric structures have been attributed to the same product, although structure **177** seems more justified by chemical transformations.[11/64] Isoxazolino steroids of different structure have also been prepared (same references of Table 4.2).

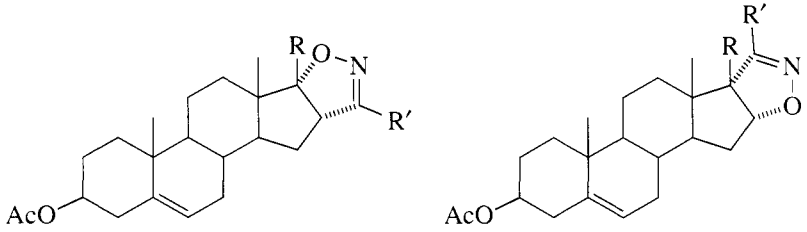


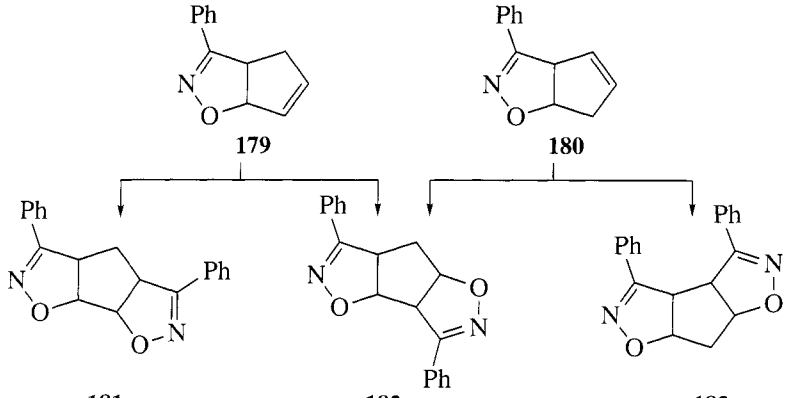
TABLE 4.2. CYCLOADDITION OF NITRILE OXIDES TO UNSATURATED STEROIDAL COMPOUNDS

R	R′	Isomer or isomer ratio	Total yield %	References
H	Me	75:25	65	10/82
COMe	H	**177**	68[a]	10/74
COMe	Me	90:10; **177**; **178**	n.i.; 20; 94.5	10/71, 11/64, 12/64,12/66
OAc	Me	**177**	17	11/64
COMe	COOEt	**177**; **178**	80; 63	11/64, 15/65, 16/65
OAc	COOEt	**177**	80; 31	11/64, 14/69
H	Ph	**177**		11/64
CHO	Ph	**177**	30	11/64
CN	Ph	**177**	43	11/64
COMe	Ph	**177**; **178**	80; 82.5	11/64, 12/64, 12/66
OAc	Ph	**177**	94	11/64
NHAc	Ph	**177**	88	11/64

[a] Included 1 : 2 and 1 : 3 cycloadducts

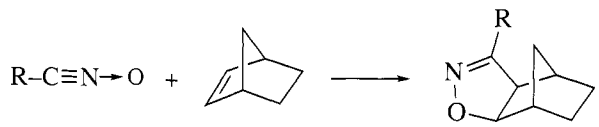
The isoxazoline route led to an easy conversion of dehydroepiandrosterone into 16β-hydroxypregnenolone.[10/82]

Cyclopentadiene reacts with benzonitrile oxide twice as fast as cyclopentene[13/73] and can lead, depending on experimental conditions, to either monoadducts and/or bisadducts.[11/61,7/62,17/65,18/65,10/68,9/79] Regioselectivity in these reactions is generally high. Treatment with excess benzonitrile oxide and careful workup of the reaction mixture allowed an estimation that the monoadduct is a 99 : 1 mixture of the two regioisomers **179** and **180** to be made. Further reaction of these monoadducts with benzonitrile oxide produced up to five regio- and stereoisomeric bisadducts **181–183**, with obvious preponderance of the *anti* isomers. The high regioselectivity corresponds to what expected by the frontier orbital treatment (the LUMO(dipole)–HOMO(diene) interaction is largely predominant here).[16/73]



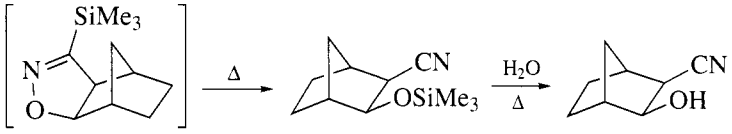
Some evidence of diastereofacial selectivity was observed when a chiral nitrile oxide was added to cyclopentene.[6/83,7/84] A 70 : 30 mixture of the two stereoisomers was reported in the case of 4-cyano-2,2,5,5-tetramethyl-1,3-dioxolane oxide.

Norbornene, which can be viewed as a strained cyclopentene derivative, reacts with benzonitrile oxide 73 times more rapidly than cyclopentene.[13/73] Owing to its high reactivity, norbornene can be used to trap nitrile oxides.[14/70] The cycloaddition is 100% diastereoselective, the *exo*-3,4-oxazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene **184** being isolated as the only one product, usually in excellent yields.



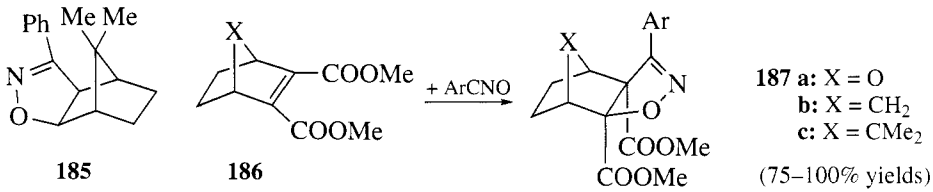
184

The yield of product obtained mainly depends on the method used for generating the 1,3-dipole and yields as high as 99% have been reported when benzonitrile oxide is prepared *in situ* from the appropriate benzohydroximic acid chloride and triethylamine in the presence of excess norbornene.[17/73] Conversely, a 13% yield has been reported for the same reaction when the source of nitrile oxide is the benzaldoxime dehydrodimer.[18/73] Intermediate values (70–83%) have been reported for different experimental conditions.[36/76,19/82,13/86,72/90] Formonitrile oxide,[13/67,12/73,11/85] aliphatic,[7/83,13/86,15/86] aromatic,[8/79] and functionalized[12/73, 7/79,13/81, 11/85,3/86,13/86,14/86] nitrile oxides have been also utilized in this cycloaddition. The adduct from norbornene and trimethylsilanecarbonitrile oxide can be detected spectroscopically but not isolated, although its evolution products are stable.[8/83]



A route to a carbocyclic analogue of PGH_1 has been proposed, which utilizes the cycloaddition of norbornene to 6-methoxycarbonylhexanonitrile oxide as starting step.[4/89]

Monosubstitution on the norbornene double bond with an alkyl group is expected to weaken its dipolarophilicity; only the 2-methyl isomer has been reported to be formed from 2-methylnorborn-2-ene.[8/79] A neat decrease in reaction rate has been observed with apobornene (7,7-dimethylbicyclo[2.2.1]hept-2-ene), which, however, reacts with benzonitrile oxide to furnish only 34% yield of the *exo* monoadduct **185** along with 45% diphenylfuroxan (the nitrile oxide dimer).[17/73] The exclusive attack on the sterically highly congested *exo* face strongly emphasizes that the 100% diastereoselectivity in the parent norbornene cannot be ascribed only to steric effects. Other effects, in particular stereoelectronic effects, should be at work.



185 **186**

187 a: X = O
b: X = CH_2
c: X = CMe_2

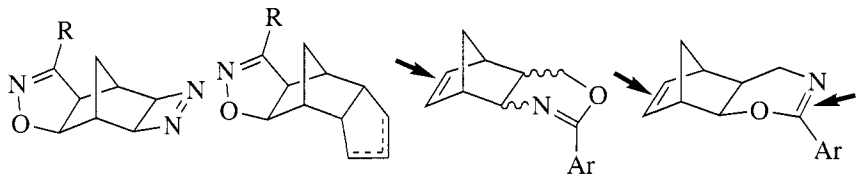
(75–100% yields)

Disubstitution with electron-withdrawing substituents, such as a methoxycarbonyl group, enhances the dipolarophilicity of norbornene double bond, and the effect is particularly strong if the methylene bridge is replaced by an oxygen atom. Indeed, the relative rates of the reaction of mesitonitrile oxide with com-

pounds **186a–c** to give the *exo*-adducts **187a–c** are 53 : 1.1 : 1 for X = O, CH_2, CMe_2, respectively.[14/81]

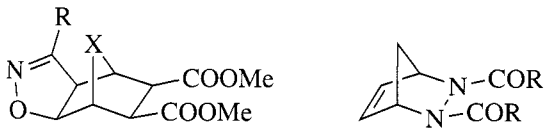
Substitutions or condensation with another ring in positions 5,6 of norbornene and its 7-oxa or 7-aza analogs do not change the cycloaddition patterns. Only products having the *exo* configuration have been reported.

Thus, tetracyclic isoxazolines such as **188** and derivatives have been obtained from a large number of nitrile oxides.[56/81] Dicyclopentadiene reacts at the double bond in the strained bicycloheptene moiety, giving the monoadduct **189**,[1/50,1/52,1/57,12/63,14/67] whose regiochemistry (mixture of two isomers) and stereochemistry have been studied in only one instance (R = CF_3).[15/86] *trans*-5,6-Dicyanonorbornene gives solely, and in moderate yields, the *exo*-monoadduct in which the configuration of the cyano groups is however ambiguous.[15/86] The dipolarophilicity of dihydro-1,3-oxazino-condensed norbornenes of type **190** or **191** (and analogs) has been thoroughly studied. Here, the olefinic double bond is more reactive than the CN double bond of the 1,3-oxazine ring, and the formation of one or two regioisomeric monoadducts or of the bisadducts depends on both the stereo- and regiochemistry (*endo/exo* or 4,5/5,6 fusion) of the dihydrooxazine ring and the nature of the nitrile oxide (aceto- or benzo-).[3/87,4/87,9/88,5/89,4/91] Bond strain and steric effects help to explain the site selectivity.



188 **189** **190** **191**

The Diels–Alder adducts dimethyl 7-oxabicyclo[2.2.1]hept-2-ene-5,6-dicarboxylates (or the corresponding anhydride) are known to react with a large variety of nitrile oxides to give moderate to good yields of *exo*-cycloadducts **192a**.[7/62,51/84,72/84,18/85,9/86,16/86,5/87,6/87,10/88,3/90,5/91] Analogous results have been obtained starting from the Diels–Alder adduct of diphenylfulvene and dimethyl maleate, which furnishes **192b**.[4/90,5/91] Likewise, only the *exo* cycloadduct has been reported as product of the cycloaddition of the diazabicyclo[2.2.1]heptene derivatives **193** with nitrile oxides.[7/79,11/82]



192 a: X = O
b: X = C=CPh$_2$

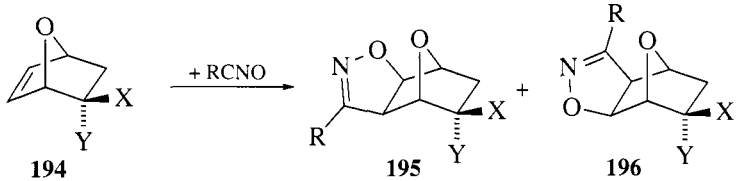
193

TABLE 4.3. CYCLOADDITION OF **194** TO NITRILE OXIDES

X	Y	R	Ratio **195:196**	Total yield %	References
CN	OAc	Me	75:25	75	41/90
=O		Me	52:48	80	41/90
OCH_2CH_2O		Me	60:40	75	41/90
CN	OAc	EtOOC	50:50		6/89
$CH_2CH_2CH_2$		Ph	50 : 50	77	37/87
CN	OAc	Ph	60:40	96	17/86, 6/89
			85:15[a]	96	17/86
=O		Ph	50 : 50	62	37/87
			65:35	96	17/86, 6/89, 5/90
OCH_2CH_2O		Ph	53:47	98	17/86, 6/89
CN	OAc	Mes	50:50	96	6/89
=O		Mes	55:45	97	6/89
OCH_2CH_2O		Mes	55:45	97	6/89

[a] In the presence of ZnI_2.

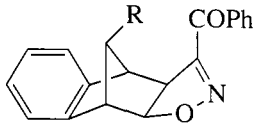
An asymmetrical mono- or disubstitution, as in 7-oxanorbornenes **194**, does not induce considerable regioselectivity, as can be seen from the results in Table 4.3. As expected, further substitution at the double bond usually (but not always) gives rise to complete regioselectivity, and the substituent (Cl, Br, SO_2Ph) occupies the isoxazoline 5 position.[6/89,41/90] Also here, the presence of the oxygen atom in the 7 position increases the reaction rate (about 10 times) in comparison with the norbornene analog.[6/89] In some cases the bisadduct, arising from a subsequent cycloaddition of excess nitrile oxide to the isoxazoline C=N double bond, has also been isolated.



194 **195** **196**

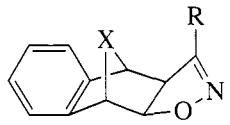
When the asymmetrical functionality is positioned further away from the strained double bond, virtually no regioselectivity is observed.[6/90]

The attack of the nitrile oxides on the *exo* face is also favored in the case of benzonorbornadienes and their 7-aza or 7-oxa analogs. Thus, phenylglyoxylonitrile oxide reacts with *anti*-7-benzoyloxy- or *anti*-7-*t*-butoxy-benzonorbornadiene to give selectively the *exo–syn* adducts **197**, along with minor amounts



197

(R = PhCOO, *t*-Bu)



198

(X = O, $NCOOBu^t$, $C{=}CMe_2$)

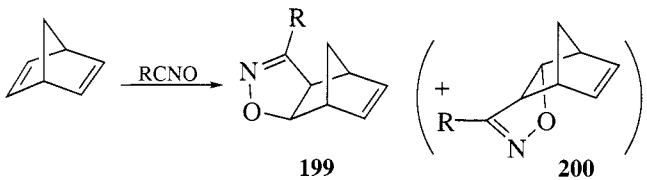
TABLE 4.4. CYCLOADDITION OF MESITONITRILE OXIDE TO STRAINED CYCLOALKENES

Rate constants in CCl_4 at 25°C (l/mol.s × 10^6)	1.2	5.7	22.80	2300	3150
Strain (cycloalkene–cycloalkane) (kcal/mol)	0.15	0.51	9.96	8.91	4.75

(< 5% yield) of the isomeric *endo-syn* adducts.[15/81] 100% stereoselectivity has been always verified in the formation of adducts **198** with a variety of nitrile oxides.[10/72,7/77,11/80,57/81,51/84,6/87,57/84,10/88,5/91]

The reactivity of the bicyclo[2.2.1]hept-2-ene system by far surpasses that of cyclohexene, bicyclo[2.2.2]oct-2-ene, or other similar systems; a kinetic study, summarized in Table 4.4, showed that the rates do not quite parallel strain release.[12/80] The high reactivity of norbornene, as well as its facial selectivity, has been attributed to (1) the higher orbital extension on the *syn*-methano bridge side,[45/76] (2) the almost ideal staggering between forming bonds and allylic σ bonds in the *syn*-methano bridge attack,[16/81,67/82, 61/83,62/83] and (3) pyramidalization of the double bond with distortion of the olefinic hydrogens in *anti*-methano bridge direction.[63/83]

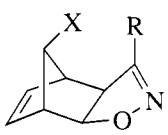
Norbornadiene and its derivatives have been the subject of many important studies concerning stereo-, regio- and site selectivity in 1,3-dipolar cycloadditions. The unsubstituted compound, if employed in large excess (≥ 10 : 1), reacts with nitrile oxides to give monoadducts only, where the *exo*-isomer represents the dominant (or exclusive) product, as shown below. The ratios reported here result from kinetically controlled cycloadditions.



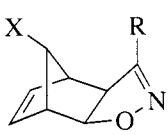
199 **200**

R	**199 : 200**	Total yield %	Ref.
H	100 : 0	41	13/67, 28/73
CF_3	79 : 21	77	15/86
Ph	88 : 12	60	13/66, 11/68, 15/69
	100 : 0	85	72/90
Mes	99 : 1		7/89
PhCO	81 : 19	76	12/76, 8/77

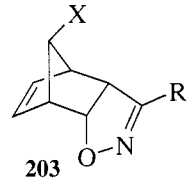
Cycloaddition of norbornadiene to excess benzonitrile oxide (in molar ratio ≤ 1 : 6) led to the isolation of four (out of six possible) bisadducts in the following proportions: *diexo/anti* : *diexo/syn* : *exo–endo/anti* : *exo–endo/syn* = 67 : 23 : 6 : 4 (total yield nearly quantitative; *syn/anti* terminology here relates to regiochemistry).[15/69] More interesting are the results obtained with 7-monosubstituted norbornadienes; in this case four stereoisomeric monoadducts **201–204** are predictable, if the cycloaddition is carried out with excess dipolarophile. The results obtained with phenylglyoxylo-[15/81] and mesitonitrile oxide[7/89] are reported here:



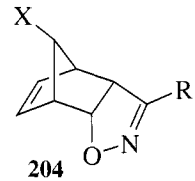
201
exo-syn



202
exo-anti



203
endo-syn



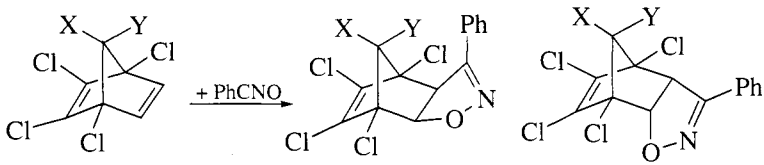
204
endo-anti

R	X	*Exo/endo* ratio	**201:202:203:204**	Total yield %[a]	References
PhCO	PhCOO	0.23	13:6:41:40	76	15/81
PhCO	*t*-BuO	0.30	23:0:37:40	75	15/81
PhCO	HO	0.14	12:0:29:59	66	15/81
PhCO	Ph			85	15/81
PhCO	4-ClC_6H_4			89	15/81
Mes	Me	21.2	0:95.5:2.5:2	>80	7/89
Mes	Ph	27.6	0:96.5:3.4:0.1	>80	7/89
Mes	*t*-BuO	1.78	9:55:22:14	87	7/89
Mes	MeO	2.22	11:58:18:13	90.5	7/89
Mes	AcO	3.0	13:62:14:11	88	7/89
Mes	MeOOCO	2.12	3:65:16:16	>80	7/89
Mes	F_3CCOO	2.28	7:62.5:13:17.5	>80	7/89
Mes	HO	6.14	49.5:36.5:5:9	95	7/89
Mes	Cl	2.57	0:72:12:16	86	7/89

[a] Calculated on nitrile oxide

Interaction[15/81] and electron withdrawal by a 7-substituent have been indicated as factors favoring *endo* attack, especially by an electrophilic nitrile oxide, such as PhCOCNO, whereas electron-rich σ bonds (at position 7) and electron-rich nitrile oxides, such as MesCNO, facilitate the *exo* attack.[7/89]

Another example of dominant *endo*- (or *anti*-methano bridge) addition has been found in the reaction of benzonitrile oxide with electron-poor poly-

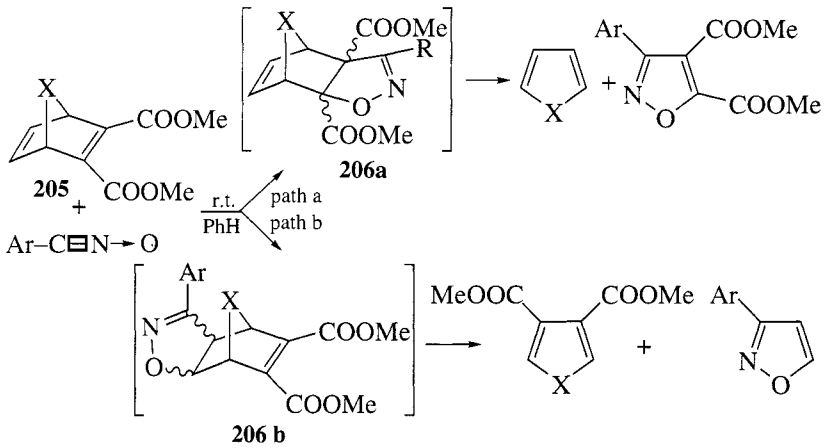


X	Y	*exo/endo* ratio
Cl	Cl	0 : 100
H	Cl	0 : 100
Cl	H	40.5 : 59.5
H	H	83 : 17

chloronorbornadienes, where the influence of the 7-chlorine atom is well documented.[14/80]

Steric and electronic ($\sigma^* - \pi$ interaction) effects have been invoked here in favor of the tendency to *endo* attack. The higher reactivity of the disubstituted double bond in comparison with the tetrasubstituted one has also been verified in the cycloaddition of benzonitrile oxide to aldrin.[13/66]

Site selectivity has been observed in 2,3-disubstituted norbornadienes having both an electron-rich and an electron-poor double bond, such as **205**. The mode of attack on the disubstituted or tetrasubstituted double bond can be influenced by the nature of the nitrile oxide or of the bridge in the 7 position or by the experimental conditions. Since the monoadducts **206** are usually rather unstable, the isomer ratios have been evaluated by analyzing the products arising from Diels–Alder cycloreversion, according to the following scheme:



The site selectivity, illustrated by the results reported in Table 4.5, was nicely rationalized on the basis of FO (HOMO–LUMO) interaction approach.[14/81] Taking into account that in norbornadiene and analogs the highest coefficients in the HOMO and LUMO are on the disubstituted and on the tetrasubstituted double bonds, respectively, and that the latter bond is the more hindered, path (a) is favored by HOMO(dipole)–LUMO(dipolarophile) interaction and path (b), by LUMO(dipole)–HOMO(dipolarophile). Therefore, since an oxygen(or a nitrogen) atom replacing the methylene bridge gives rise to a stabilization of all the orbitals, the path (a)/path (b) ratio increases by

TABLE 4.5. CYCLOADDITION OF NORBORNADIENE DERIVATIVES **205** TO NITRILE OXIDES

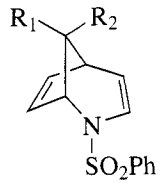
X	Ar		Path (a) : Path (b)	References
CH_2	4-$NO_2C_6H_4$		4 : 96	14/81
CH_2	Ph		13.5 : 86.5	14/81
CH_2	4-$MeOC_6H_4$		11 : 89	14/81
CH_2	MeCO		0 : 100[a]	2/78
CH_2	PhCO		0 : 100[b]	8/77, 24/77, 2/78
CH_2	CF_3		0 : 100[c]	15/86
O	4-$NO_2C_6H_4$		56 : 44	14/81
O	Ph		75 : 25	14/81
O	4-$MeOC_6H_4$		87 : 13	14/81
O	Mes	(PhH)	46 : 54	14/81
O		($MeNO_2$)	36 : 64	14/81
O		(EtO_2)	55 : 45	14/81
O	CF_3		31 : 69	6/87
O	2,5-Me_2-3-furyl		100 : 0	5/91
O	PhCO		55 : 45	9/83
NCOOEt	Mes		45 : 55	11/74, 10/76
$NSiMe_2Bu^t$	Ph		0 : 100	11/88
$NSO_2C_6H_4Me$	CF_3		30 : 70	6/87

[a] *Exo/endo* ratios 1.5–1.7.
[b] *Exo/endo* ratio 1.8–2.0 (3.0 in THF).
[c] *Exo/endo* ratio 7.3 (in toluene or THF).

both changing from electron-poor to electron-rich nitrile oxides and passing from a CH_2 to an O bridge.

In some cases the site selectivity has been found to depend on solvent polarity.[14/81] Moreover, when electrophilic nitrile oxides and norbornadiene–dicarboxylates are involved, a mixture of stereoisomers (**206b**) is produced in which the *exo* isomer is largely predominant, and the ratio *exo/endo* is both solvent- and temperature-dependent. [2/78] Similar results have been obtained with 7-(dimethylmethylene)norbornadiene[14/81] and with norbornadienes having different 2,3-substituents.[12/76,8/77,14/80, 15/86]

Systems such as 2-phenylsulfonyl-2-azabicyclo[3.2.1]octa-3,6-diene (**207a**) and its 8-monosubstituted analogs **207b,c**, are good candidates for the study of factors that influence regio- and stereoselectivity. The 6,7 double bond exhibits a much higher reactivity than the 3,4 double bond, and cycloaddition of **207a** to nitrile oxides (R = PhCO, MeCO, Ph) led to a mixture of regioisomers **208a** and **209a**, in excellent yields, in which the former predominates (65–76 : 35–24).[3/78] Cycloaddition of PhCOCNO to **207b** is more sluggish, but only **208b** and **209b** are obtained, in a 2.1 : 1 ratio.[12/82] Only when **207c** is employed are the two regioisomers **208c** and **209c** accompanied by a small amount of **210**.[15/81] All products showed *exo* stereochemistry. The enamine-like 3,4 double bond shows some, albeit far weaker, dipolarophilic activity, since 2-phenylsulfonyl-2-azabicyclo[3.2.1]oct-3-ene cycloadds nitrile oxides to give **211** in moderate yields and under more severe conditions.[3/78]



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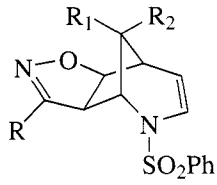

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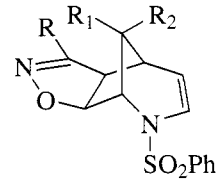
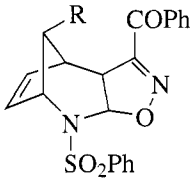


209

for **207–209:** **a:** $R_1 = R_2 = H$
b: R_1 = PhCOO; $R_2 = H$
c: $R_1 = H$; R_2 = PhCOO



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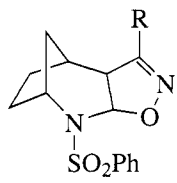

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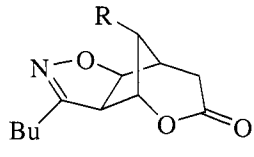
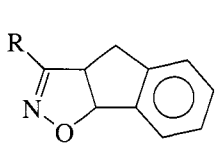


212

The regiospecific and 100% diastereoselective formation of **212** from 8-dimethoxymethyl-2-oxabicyclo[3.2.1]oct-6-en-3-one has been reported.[25/88]

Conjugation with benzene rings also enhances the dipolarophilicity of the cyclopentene double bond. Thus, indene readily reacts with nitrile oxides to yield the adduct **213** exclusively[1/50,2/50,1/57,16/69,15/70,5/91] or in admixture with very small amounts of regioisomer **214**.[15/67,16/73,13/76] Aminoindenes, as expected, react regiospecifically.[10/63, 15/67]

Acenaphthylene is also an active dipolarophile, and alkyl,[12/63] aromatic,[11/61,7/62,13/64,16/69,8/71,11/71,18/73,12/74] heteroaromatic,[16/69,5/91] and functionalized[11/71,14/86] nitrile oxides have been used to furnish the cycloadducts **215** in good to excellent yields.



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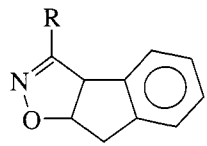
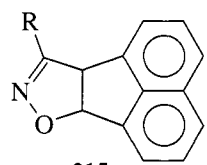


214

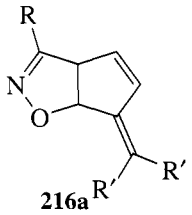


215

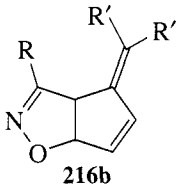
R = Me: 95 : 5 (49% total yield)
R = Ph: 98 : 2 (93% total yield)

In somewhat of an exception, phenanthrene does not usually react with nitrile oxides, although a very low reactivity with benzonitrile oxide has been reported under special conditions (ref. 9/84, p. 334).

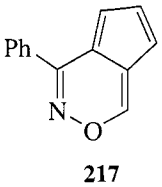
Periselectivity has been discovered in the cycloaddition of nitriles oxides to fulvenes. 6,6-Disubstituted (alkyl or aryl) fulvenes have long been known[1/52] to react with benzonitrile oxide on their endocyclic double bonds to yield mono- and bisadducts. A reinvestigation of the reaction has clarified the regiochemistry and helped establish that a mixture of the two monoadducts **216a,b** are obtained; the former isomers are prevalent.[12/71] Minor amounts of bisadducts are also isolated. Analogous results have been obtained with other nitrile oxides.[14/86, 15/80] With 6-dimethylaminofulvene, however, only the [6 + 4] pathway is followed.



216a



216b

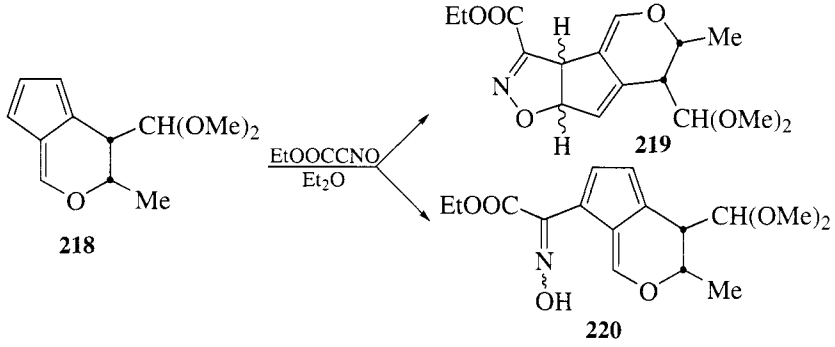


217

R	R′	a : b ratio	Ref.
Ph	Me	65 : 35	12/71
Ph	Ph	86 : 16	12/71
EtOOC	Ph	85 : 15	14/86

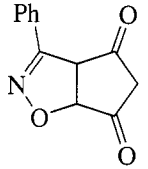
The product **217** is isolated in 60% yield, in addition to *N*,*N*-dimethylbenzamide oxime, which presumably arises from addition of benzonitrile oxide to dimethylamine.[12/71]

Competition between [4 + 2] and [6 + 4] cycloaddition has been invoked in order to explain the formation of a mixture of stereoisomeric cycloadducts **219** (50% yield) besides a minor amount (30% yield) of stereoisomeric oximes **220** in the reaction of ethoxycarbonylformonitrile oxide with the 6-oxafulvene **218**:[18/86]



In the cyclopentenone series, the olefinic double bond is clearly more reactive than the carbonyl group. Cycloaddition of cyclopent-4-en-1,3-dione with

benzonitrile oxide affords 4-phenyl-2,3-oxazabicyclo[3.3.0]oct-3-en-6,8-dione (**221**).[11/61] Tetrasubstituted cyclopentadienones react with aromatic nitrile oxides to give monoadducts **222**, accompanied in some cases by bisadducts.[10/79] Even the strained double bond of bicyclo[4.3.0]dec-1(7)-en-2-one is reactive toward nitrile oxides and yields, in regioselective fashion, the oxazapropellenone **223** in moderate yields.[12/85,19/86] The corresponding unactivated $\Delta^{9,10}$-octaline is unreactive.[12/85]



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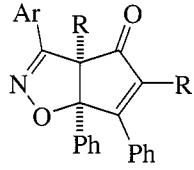

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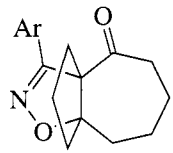
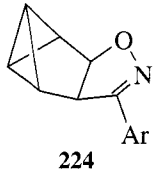
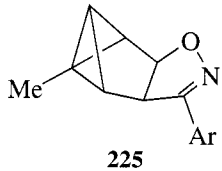


223

Benzvalene reacts with nitrile oxides with a rate comparable to that of norbornene, furnishing the adduct **224** in high yields.[35/73,59/86] Analogous cycloaddition is known for 1-methylbenzvalene, which yields instead a 1 : 1 mixture of the two possible stereoisomers **225** and **226**.[20/86]



224



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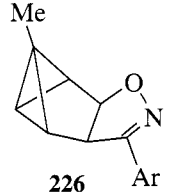
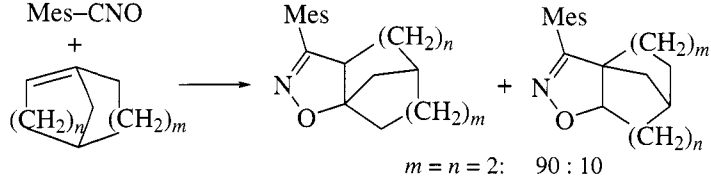


226

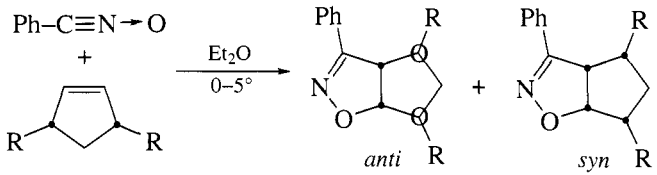
An interesting study has been devoted to 1,3-dipolar cycloadditions of bicyclic olefins having the double bond at the bridgehead position (anti-Bredt olefins). The reaction with mesitonitrile oxide is very fast, and a mixture the two regioisomers is formed quantitatively: [8/79]



$m = n = 2$: 90 : 10
$m = 3, n = 1$: 77 : 23
$m = 1, n = 3$: 64 : 36

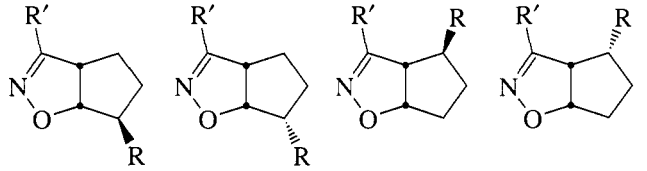
Several studies have been devoted to the regio- and stereoselectivity of the cycloaddition of 3-substituted and 3,5-disubstituted cyclopentenes. Contrary to

the results illustrated above for *cis*-3,4-disubstituted cyclobutenes, where the *syn* monoadducts compete with the *anti* isomers if halogen or oxygen atoms are present in the allylic position, the *cis*-3,5-disubstituted cyclopentenes show a high π-facial diastereoselectivity in favor of the *anti* isomer.[8/84] This latter isomer is the sole product obtained when aliphatic nitrile oxides are employed,[12/86] as well as when the dipolarophiles are the related *cis*-3,5-disubstituted 2,5-dihydrofurans.[8/84]



The high tendency to give *anti* attack has been attributed to conformational flexibility combined with the well-known "outside" repulsive interaction.[8/84]

3-Monosubstituted cyclopentenes show problems both of stereo- and of regioselectivity. Their cycloaddition to benzonitrile oxide furnishes a mixture of products, often containig all four possible isomeric 6- or 8-substituted 3-phenyl-2,3-oxazabicyclo[3.3.0]oct-3-enes.[13/74,4/78]



227 (8-*anti*) **228** (8-*syn*) **229** (6-*anti*) **230** (6-*syn*)

TABLE 4.6. ISOMER RATIOS OF 8- AND/OR 6-SUBSTITUTED 4-PHENYL-2, 3-OXAZA-BICYCLO[3.3.0]OCT-3-ENES.

a) *R′ = Ph*[a]

R	**227:228:229:230**	**227:228** ratio	*anti*/*syn* ratio	References
Me	63:3:33:1	0.83	24.00	13/74, 4/78
Et	43:20:36:1	1.19	3.76	13/74
i-Pr	68:13:18:1	3.79	6.14	13/74
Ph	29:4:66:1	0.44	19.00	13/74
NMe	23:7:70:0	0.33	13.29	13/74
OH	12:30:53:5	0.23	1.86	13/74
OMe	22:3:71:4	0.31	13.29	13/74
OAc	15:5:77:3	0.19	11.50	13/74

(*continued*)

TABLE 4.6. (*continued*)

R	**227:228:229:230**	**227:228** ratio	*anti/syn* ratio	References
Cl	55:nd:45:nd[c]	1.22	—[e]	5/75
Br	67:nd:33:nd	2.03	—[e]	5/75
NHCOPh[b]	nd:90:10:nd		0.11	7/90
$NHCOCF_3$[b]	nd:94:6:nd		0.06	7/90
$NHCOC_6H_4NO_2$[b]	nd:95:5:nd		0.05	7/90

b) $R' = Bu^t$

R	**227:228:229**	Solvent	Total yield %	References
NHCOPh	1:85:14	PhH	90	7/90
	8:57:35	DME	91	7/90
	14:8:78	HMPA	83	7/90
N(Me)COPh[d]	19:5:76	PhH	47	7/90
	24:3:73	DME	30	7/90
	27:4:69	HMPA	63	7/90

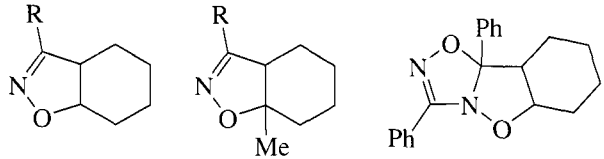
[a] Overall yield >90%; solvent Et_2O and temperature 0–25°C, if not otherwise indicated.
[b] Reaction carried out in benzene.
[c] nd = not detected.
[d] Reaction carried out at 80°C.
[e] *Syn* adducts not detectable.

As shown in Table 4.6, the two regioisomers produced by attack of the 1,3-dipole on the face *anti* to the substituent are largely predominant. Electron-attracting substituents induce a distinct shift toward the 6-*anti* isomer, with the remarkable exception of the halogens. Indeed, with 3-chlorocyclopentene the cycloaddition is nearly devoid of regioselectivity, whereas with the 3-bromoderivative a reversal of orientation is observed.[5/75] Another interesting feature of this cycloaddition is the possibility of hydrogen-bonding between the oxygen atom of the nitrile oxide and a substituent having a relatively acidic proton. The presence of a 3-hydroxy group increases the amount of the 8-*syn* isomer,[13/74] but the effect is far more striking with secondary amido groups, which favor almost exclusive (up to 95%) formation of the 8-*syn* isomer. Evidence for the existence of hydrogen-bonding in the transition state is provided by the effects exerted by solvents capable of hydrogen capture. Solvents such as hexamethylphosphoric triamide (HMPA), reverse the regio- and stereoselectivity back to the predominance of the 6-*anti* isomer. Moreover, tertiary amido groups, lacking the hydrogen atom, strongly decrease the reactivity of the dipolarophile and suppress the solvent effect.[7/90]

It is well known that cyclohexene is less reactive as a dipolarophile than cyclopentene, and this difference in reactivity has been attributed to the higher distortion strain necessary for the cyclohexene molecule to comply with the Felkin-Anh staggering effect in the cycloaddition transition state.[16/81] Cyclohexene and 1-methylcyclohexene do not react with nitrile oxides in dilute

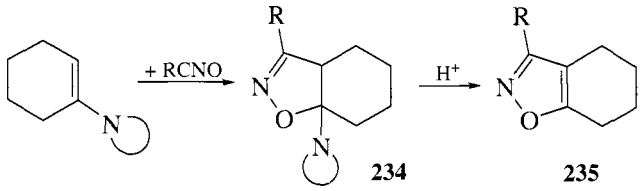
ethereal solution,[12/61,11/61,7/62,17/65] but 1,3-dipolar cycloaddition takes place (although in low rate and yields), when the nitrile oxides are slowly generated in cyclohexene as solvent.[19/65,11/73,3/75]

Sometimes the monoadduct **231** (e.g., R = Ph, 9-phenyl-7,8-oxazabicyclo[4.3.0]non-8-ene) is accompanied by minor amounts of the bisadduct **233**, arising from the regiospecific cycloaddition of a second molecule of nitrile oxide to the isoxazoline C=N bond.[11/72] The yields reported for cycloadditions with aliphatic nitrile oxides (**231**, R = Me, Et, Me_3C, $Me_2COSiMe_3$) are highly variable, and possibly depend on the preparation method used for the 1,3-dipole.[13/70,7/83,4/84,31/91] On the contrary, good to excellent yields of **231** or **232** (R = SO_2Ph or EtOOC) have been reported for the reaction of highly reactive nitrile oxides, such as benzenesulfonylcarbonitrile oxide[7/79,17/81,18/81] or ethoxycarbonyl (or cyano)formonitrile oxide[5/83,6/84] with cyclohexene or 1-methylcyclohexene, respectively. Moreover, generation of nitrile oxide under thermal conditions also seems to lead to excellent results[14/67] (see the reactivity of α-pinene under these conditions[12/68]).



231 **232** **233**

The presence of a tertiary amino group strongly enhances the dipolarophilicity of the cyclohexene double bond. Indeed, the enamines of cyclohexanone (and its substituted derivatives) cycloadd nitrile oxides regiospecifically to give the substituted oxazabicyclo[4.3.0]nonenes **234**, which easily loose the amine molecule by acidic treatment to yield the condensed isoxazoles **235**:[10/63,4/64,14/66, 9/68,13/69,9/71,13/71,7/75,1/78,9/80]



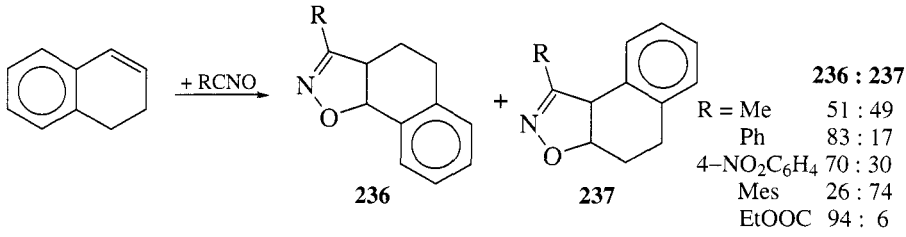
234 **235**

Enamines from α- or β-tetralone react analogously.[14/66] Substitution of the amino residue by the trimethylsilyloxy group remarkably lowers the yield, but preserves the regiospecificity.[5/78] Similar behavior is known for some dienamines from 2-octalones.[12/72]

Monosubstitution on the alicyclic ring brings about problems of regio- and stereochemical complexity. Thus, for example, cycloaddition of benzonitrile

oxide to 3-benzoyloxycyclohexene furnished, in addition to minor amounts of bisadducts, a nonisolable mixture of monoadducts, whose hydrolysis led to all four possible regio- and stereoisomeric alcohols. A feeble level of regioselectivity, which favors the 5-hydroxy-7-phenyl-8,9-oxazabicyclo[4.3.0]non-8-ene, and high stereoselectivity in favor of the *anti* isomer have been observed.[11/72] A somewhat higher selectivity has been reported for the cycloaddition of (1*R*,5*R*)-7-oxabicyclo[3.2.1]oct-2-en-6-one to pyruvonitrile oxide, a key passage in the enantioselective total synthesis of (+)-phyllanthocin.[8/89]

3,4-Dihydronaphthalene readily undergoes cycloaddition with nitrile oxides, yielding a mixture of the two regioisomers **236** and **237**.[11/72,13/76,13/85] The regioselectivity expressed here is less pronounced than in the above-reported case of indene, and with several nitrile oxides the major product is **236**. With acetonitrile oxide the reaction is unselective, and with mesitonitrile oxide the isomer ratio is even reversed. Frontier orbital theory has been invoked in order to explain the results.[13/76]



236 **237**

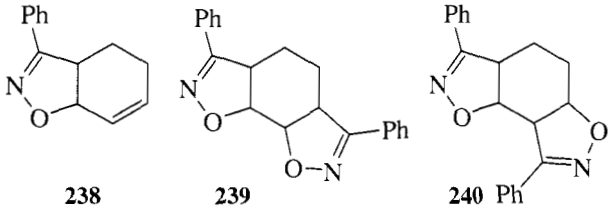
	236 : 237
R = Me	51 : 49
Ph	83 : 17
4–$NO_2C_6H_4$	70 : 30
Mes	26 : 74
EtOOC	94 : 6

The insertion of a methyl group on the double bond of 3,4-dihydronaphthalene lowers the yield and requires that more drastic conditions be employed. Moreover, the presence of the substituent shifts the selectivity toward the isomer bearing the methyl group in the isoxazoline 5 position; the shift is complete in the case of the 1-methyl derivative, and still high (ratio 90 : 10) for the 2-methyl derivative.[13/85]

It should be added that a total synthesis of the lignan epipodophyllotoxin takes advantage of the regiospecific cycloaddition of bromoformonitrile oxide to a suitably substituted dihydronaphthalene.[21/86]

1,4-Dihydronaphthalene, which contains an unconjugated double bond, reacts more sluggishly, furnishing the cycloadduct in moderate or poor yield.[12/88]

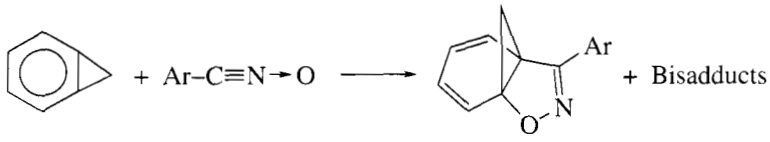
Similar results have been reported for the two isomeric cyclohexadienes. 1,3-Cyclohexadiene reacts with benzonitrile oxide to yield a complex mixture, containing both the homogeneous monoadduct **238** and the two possible bisadducts **239** and **240**, besides minor amounts of another bisadduct (at the C=N double bond) and of two tetraadducts.[17/70] Only monoadducts of type **238** have been reported for other nitrile oxides. The cycloaddition is far slower in the case of 1,4-cyclohexadiene, although under appropriate conditions good yields of the monoadduct can be reached, occasionally accompanied by minor amounts of bisadducts.[17/65,11/79,9/85]



238 239 240

Aromaticity suppresses or strongly reduces the dipolarophilicity of olefins. Benzene and naphthalene are known to be totally unreactive toward nitrile oxides. Phenanthrene has been reported to be unreactive toward benzonitrile oxide,[11/61,7/62] whereas reaction is reported to slowly occur with mesitonitrile oxide.[9/84]

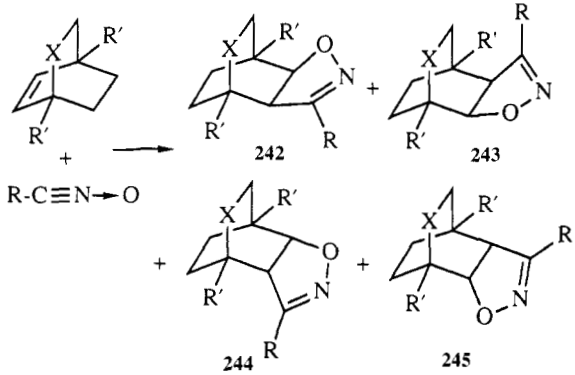
By contrast, benzocyclopropene enters, although slowly, cycloaddition with benzo- and mesitonitrile oxide to give low yields of the monoadduct **241**, along with higher amounts of bisadducts, arising from the relatively easier reaction of the cyclohexadiene moiety of **241** with a second molecule of 1,3-dipole.[12/79]



241

R = Ph	10%	53%
R = Mes	27%	39%

As already mentioned, the bicyclo[2.2.2]oct-2-ene system is relatively unreactive; nevertheless, its cycloaddition to reactive nitrile oxides gives good yields of the corresponding cycloadducts.[13/85,42/90] Heterocyclic analogs of bicyclo[2.2.2]oct-2-ene exhibit some degree of regio- and stereoselectivity in



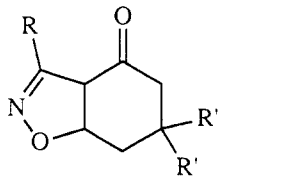
242 243 244 245

R	R′	X	242:243:244:245
(*)	H	O	47 : 8 : 26 : 19
(*)	Me	O	28 : 8 : 36 : 28
EtO_2C	Me	O	37 : 11 : 28 : 24
(*)	H	NMe_2	24 : 0 : 34 : 42
(*)	H	S	6 : 2 : 30 : 62
EtO_2C	H	S	5 : 0 : 18 : 77
(*)	H	SO_2	4 : 0 : 51 : 45

(*) $Me_3SiOC(CH_3)_2$.

their reactions with 2-(trimethylsilyloxy)-2-methylproprionitrile oxide (or ethoxycarbonylcarbonitrile oxide). The *endo–anti* isomer **242** prevails only when X = O, but with X = NMe, S, **or** SO_2 the *exo*-products **244–245** become increasingly predominant, although only slight regioselectivity is observed.[42/90]

Cyclohex-2-enone and its derivatives are active dipolarophiles, and the course of the cycloaddition seems to depend on the structures of both the 1,3-dipole and the dipolarophile. Aliphatic nitrile oxides are reported to furnish exclusively the regioisomer with the carbonyl group α to the isoxazoline 4-position (**246**).[14/74,14/76,13/79,8/88] Although 5-methylcyclohexenone reacts stereospecifically, in an *anti* fashion, with acetonitrile oxide to give as the major product the cycloadduct corresponding to **246**, the small quantities of the other regioisomer are sufficient to permit the total synthesis of bisanbolangelone to be undertaken.[9/89] The cycloaddition of cyclohexenone to benzonitrile oxide,[11/61,7/62] has been reported to yield a 75:25 ratio of the two regioisomers **247** and **248**, whereas with mesitonitrile oxide only **247** could be detected.[15/73]



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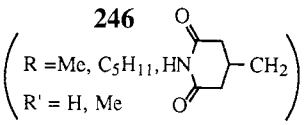

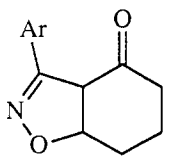

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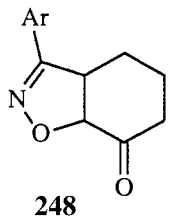
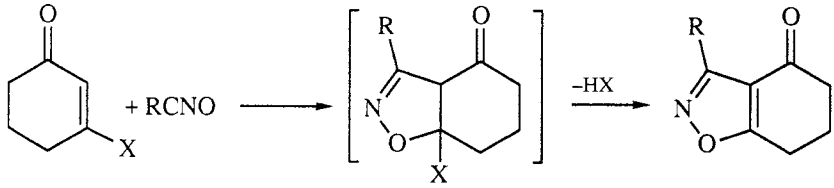


248

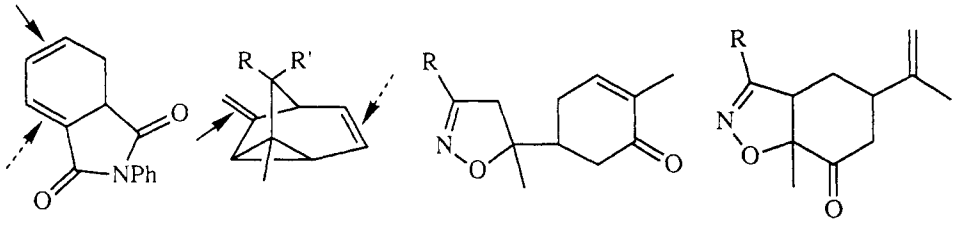
Cyclohexenones that bear heteroatom-containing substituents, such as OH, OR, Cl, and NR_2 in the β position react regiospecifically to give isoxazoles via nonisolable condensed 2-isoxazoline intermediates.[15/76,6/78]



Some special cases require mention. Diene **249** reacts primarily on the terminal double bond.[34/87]

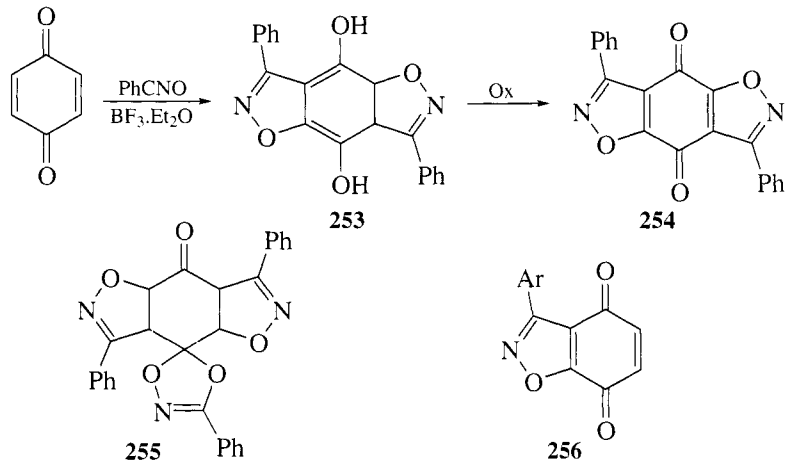
Cycloaddition with tricyclic systems such as **250** usually takes place at the exocyclic double bond, but sometimes also at the endocyclic cyclohexene bond.[52/84] Acetonitrile oxide reacts with limonene to yield only one monocyclic

isoxazoline, but with carvone a mixture of the two positional isomers **251** and **252** is formed with a 1.7 : 1 ratio, respectively. In contrast, benzonitrile oxide cycloadds on the exocyclic double bond only.[16/76] Steroidal isoxazolines condensed on the A or B rings have been occasionally prepared by the nitrile oxide route.[16/66,43/90]



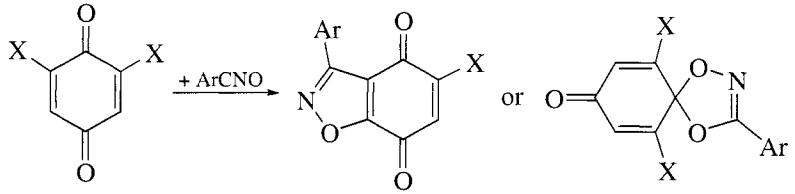
249 **250** **251** **252**

Although both the olefinic double bond and the carbonyl group of quinones are reactive towards nitrile oxides, the mode of attack depends on both dipolarophile structure and on the experimental conditions. Cycloaddition of 1,4-benzoquinone with benzonitrile oxide in basic media yields a bisadduct,[3/50] which cannot be isolated, but oxidizes to the bisisoxazolo-quinone **254**. Subsequent studies have shown that the primary isoxazoline derivative **253** can be obtained if the reaction is carried out in the presence of Lewis acids such as boron trifluoride etherate.[13/68,17/69] In addition to the bisadduct, minor amounts of the trisadduct **255** and/or its oxidation product have been identified in the mixture, indicating that one carbonyl group has also reacted. Analogous results have been reported for 1,4-naphthoquinone,[13/68,17/69,15/74,14/79,19/81] which affords a mono-adduct, and other nitrile oxides,[18/65,12/68] which on occasion afford adducts of type **256**.[12/68,10/84,8/90]



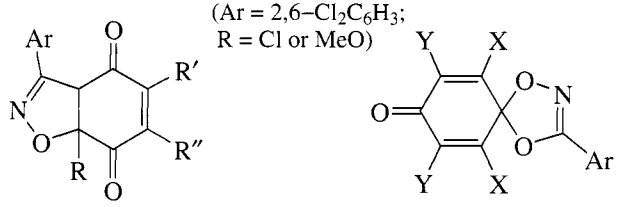
253 **254** **255** **256**

The presence of substituents in the quinone ring strongly affects positional and regioselectivity. Thus, 2-methylbenzoquinone reacts both at the methylsubstituted and at the unsubstituted double bond, yielding a mixture of two positional isomers;[10/84] 2-methoxybenzoquinone reacts only on the unsubstituted double bond, yielding a mixture of the two oxidized regioisomeric monoadducts.[11/84] 2,6-Dichloro- and 2,6-dimethoxyderivatives furnish different results depending on the nitrile oxide employed; 2,6-dichlorobenzonitrile oxide favors cycloaddition on the C=C bond, and immediate loss of HX (hydrochloric acid or methanol) promotes formation of the isoxazoloquinone **257**.[10/84,11/84] Conversely, other aromatic nitrile oxides, such as benzo-, mesito-, or 2,3,5,6-tetramethylbenzonitriloxide, yield the corresponding spiro[1,4,2]dioxazole derivative **258** as the sole product, showing exclusive addition on the C=O group of the chlorine-substituted side.[7/78] Other di- or trisubstituted benzoquinones react with nitrile oxides to give cycloadducts **259** in good to excellent yields.[7/78,10/83,11/83,53/84] Tetrasubstituted 1,4-benzoquinones usually furnish only C=O adducts (**260**), with the exception of the methyl and methoxy derivatives, which yield a mixture of C=C and C=O cycloadducts.[7/78,10/84] Selectivity is controlled by FMO interactions such that cycloaddition onto the C=O bond is chiefly governed by HOMO(quinone)–LUMO(dipole) interaction, a correlation that has been corroborated by kinetic measurements.[10/84]



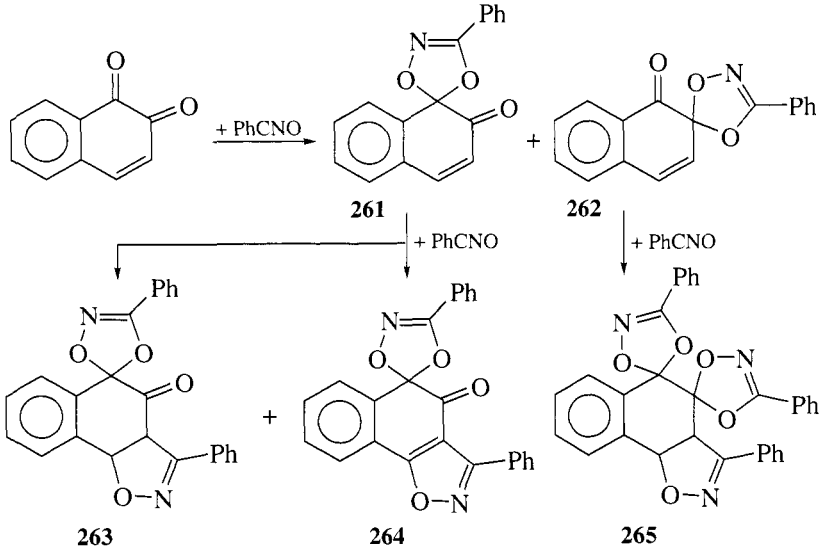
(X = Cl or MeO) **257** **258**

(Ar = 2,6-$Cl_2C_6H_3$; R = Cl or MeO)

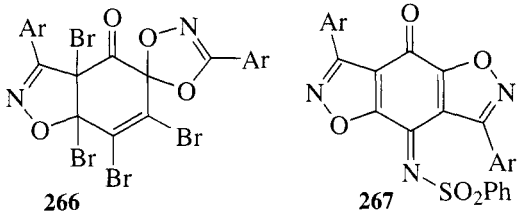


259 (R = alkyl) **260**

The results obtained in the cycloaddition of 1,2-naphthoquinone show that the two C=O bonds are more reactive than the C=C bond. In the presence of excess dipolarophile, a mixture of the isomeric dioxazole monoadducts can be obtained; excess nitrile oxide favors formation of the bisadduct **263** and its oxidation product **264**, as well as trisadduct **265**.[18/69]

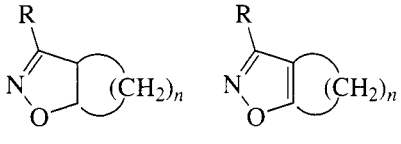


In the case of *o*-benzoquinone both C=C bonds and one C=O bond are reactive;[18/69] the tetrabromoderivative gives exclusively the bisadduct **266**.[19/69]



Cycloaddition of 1,4-benzoquinone-*N*-benzenesulfonylmonoimine to nitrile oxides leads to the tricyclic cycloadduct **267**.[19/73]

Seven-,[13/70,7/75,8/78] eight-,[14/67,11/72,9/77,8/79,14/85] and twelve-membered[7/75, 54/84,14/85] cycloalkenes have been reported to react with aliphatic and aromatic nitrile oxides to give the condensed isoxazolines **268**. The kinetics of the cycloaddition showed that *cis*-cyclooctene reacts more slowly than the *trans*-isomer.[17/76] The



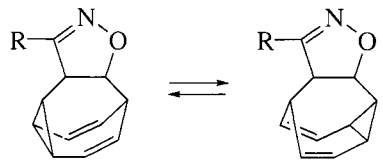
corresponding condensed isoxazoles **269** could easily be obtained either by NBS oxidation of the isoxazoline[13/70,12/84] or through the cyclanone enamine cycloaddition followed by deamination,[10/63,4/64,13/71,56/85] or even by direct reaction of nitrile oxides with cycloalkynes such as cyclooctyne.[12/83]

The activating influence of an endocyclic oxygen atom on the reactivity of 3-methoxy-*trans*-cyclooctene has been evaluated; an unequal mixture of the two regioisomeric cycloadducts is obtained both with the dioxaderivative and its carbocyclic analog.[13/83]

In the case of cyclooct-1-en-3-yne only the triple bond is reactive, and an equimolar mixture of the two regioisomeric 3-mesityl-tetrahydrocycloocta[*d*] isoxazoles with mesitonitrile oxide has been obtained. Analogous results have been reported for large-ring cycloalkenynes.[12/83]

Cyclic dienes and polyenes, such as 1,5-cyclooctadiene or 1,5,9-cyclododecatriene, afford monoadducts only.[12/68,13/84] Only the endocyclic double bond of dibenzoheptafulvenes, as expected, is reactive toward nitrile oxides; with asymmetrically disubstituted derivatives, the two regioisomeric cycloadducts are obtained.[14/84]

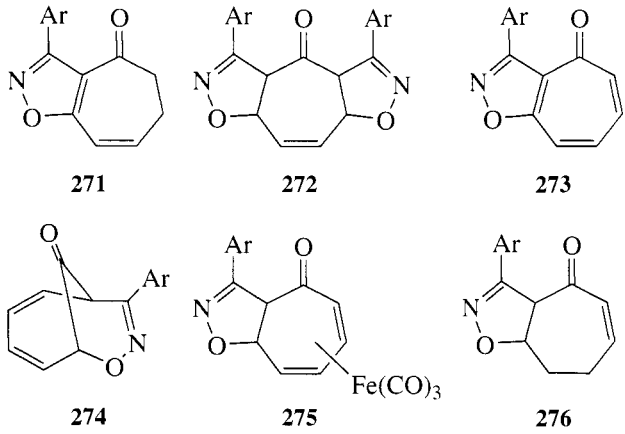
A special case of cyclic polyene is bullvalene, which enters the normal [3+2] cycloaddition with nitrile oxides, leading to the monoadduct **270**. The balance between the two valence tautomers possibly depends on steric interactions.[16/74]



270

Cyclic enones or dienones with seven carbon atoms react with nitrile oxides to give one regioisomer[12/85,19/86] or a mixture of the two regioisomers, where the isomer having the carbonyl α to the isoxazoline 4 position is more or less largely prevalent.[15/73,12/81]

The behavior of tropone and its derivatives toward nitrile oxides is of some interest. Tropone itself reacts sluggishly with benzonitrile oxide, yielding a complex mixture of at least eight products. Secondary products, derived from an attack of the 1,3-dipole on the highly polarized C=O bond, largely prevail, but mono- and bisadducts, derived from the initial regiospecific attack on the α,β C=C double bond (e.g., **271–273**) are present, besides smaller amounts of the [6+4] cycloadduct **274**. By contrast, mesitonitrile oxide practically fails to react with the C=O bond, giving very low yields of **271** and **274** and remarkably good yields of **273**.[17/74] A predominant HOMO (tropone)–LUMO(dipole) interaction explains the site and regioselectivity of the [4+2] processes.



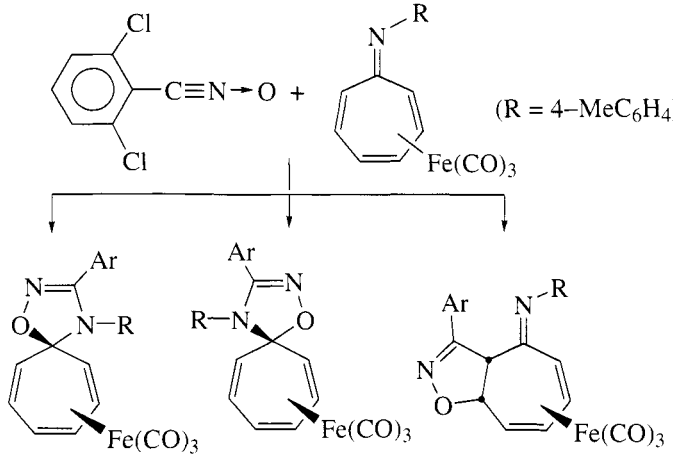
271 **272** **273**

274 **275** **276**

Geometric factors and coulombic repulsions may be involved in determining the observed periselectivity. Tricarbonyltroponeiron undergoes fast regio- and site-selective cycloadditions with aromatic nitrile oxides to yield monoadducts (**275**) that are easily decomplexed and dehydrogenated to the isoxazolotropones **273**.[10/77,54/86]

Perhaps not unexpectedly, the cycloaddition of nitrile oxides to cyclohepta-2,6-dienone permitted isolation of the primary isoxazoline cycloadduct **276**,[17/74] along with small amounts of the regioisomer.[12/81]

The related azaheptafulvenes show a remarkable site selectivity shift toward cycloaddition at the carbon–nitrogen double bond. Indeed, in methanol only this bond is reactive, whereas in cyclohexane some attack at the other position is

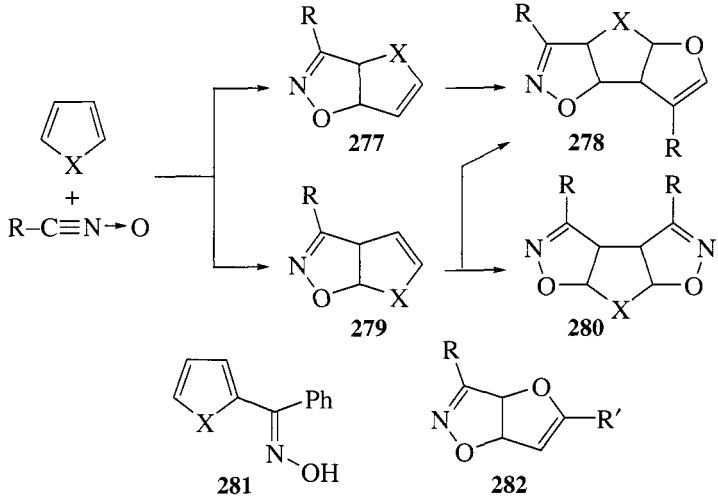


in Methanol:	27.0	:	69.4	: 3.6
in Cyclohexane:	3.0	:	20.5	: 76.5

observed. Tricarbonyliron complexation does not change the site of attack with benzonitrile oxide, but with 2,6-dichlorobenzonitrile oxide an unusually high solvent effect was observed. In methanol the dominant attack was again at the C=N bond, but in cyclohexane the preferred site of attack was the C2–C3 double bond.[48/83]

Extensive studies have been devoted to the dipolarophilic activity of heteroaromatics. As is well known, the loss of resonance energy that results during cycloadditions to aromatic dipolarophiles greatly reduces their reactivity. Although benzene and naphthalene do not enter cycloadditions with nitrile oxides, five- and six-membered heteroaromatics, are prone, because of their reduced aromaticity, to react with 1,3-dipoles.

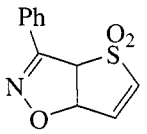
Cycloadditions of nitrile oxides with furan[18/76] and thiophene[10/78] occur with high regioselectivity to give as the predominant products, **277** and **279**; trace amounts of the bisadducts **278** and **280** are occasionally formed. In many cases only **277** (and/or **279**) has been reported.[17/66,11/77,13/82,55/84,16/85,38/88] In the reaction of benzonitrile oxide with furan competing 1,3- addition, to give oxime **281** (X = O), was found to be about 100 times slower than cycloaddition.[18/76]



Reaction of monosubstituted furans gives monoadducts (**282**) exclusively.[13/82,16/85] The reaction of pyrrole and its *N*-methyl derivative seems to be more complex, and monocycloadducts have not been isolated. A 90 : 10 mixture of oxime **281** (X = NH) and its 3-regioisomer has been reported from the cycloaddition of pyrrole to benzenesulfonylcarbonitrile oxide.[55/84] Mixtures of **281** (X = NH) and bisadducts **278** and **280** (X = NH) have been claimed to result when other nitrile oxides are employed; the symmetrical bisadduct **280** (X = NMe) dominates in the case of *N*-methylpyrrole.[9/84] A rough evaluation of the relative dipolarophilicities of the five-membered heteroaromatics toward

benzonitrile oxide compared with cyclopentadiene shows the following sequence: cyclopentadiene (1.00) > *N*-methylpyrrole > furan (0.001) > thiophene.[18/76,9/84]

The loss of aromaticity due to oxidation strongly enhances the reactivity of thiophene-1,1-dioxide, which undergoes cycloaddition with benzonitrile oxide 25 times faster than does cyclopentadiene, giving an almost quantitative yield of the monocycloadduct **283** with remarkably high regioselectivity. The second double bond reacts more slowly, and the bisadduct **284**, along with minor amounts of the regioisomer, is obtained.[14/82] Analogous results have been reported for mesitonitrile oxide, although the cycloadducts are obtained in lower yields.[20/81,14/82]



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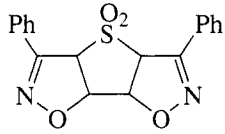
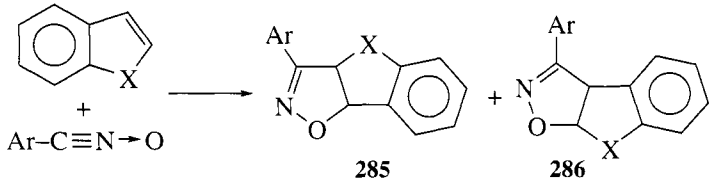


284

Cycloaddition of nitrile oxides to the benzo-fused five-membered heteroaromatics follows a somewhat similar pattern and the same order of reactivity. As shown in Table 4.7, the regioselectivity is very high for indoles and less pronounced for benzofuran and benzothiophene. In these latter cases, reversal of regioselectivity has been observed when benzonitrile oxide is replaced by mesitonitrile oxide. This result has been attributed to a change in frontier orbital interactions, from LUMO(dipole)–HOMO(dipolarophile) in the first case to HOMO(dipole)–LUMO(dipolarophile) interaction for the more nucleophilic mesitonitrile oxide.[9/78]



285 **286**

TABLE 4.7. CYCLOADDITION OF NITRILE OXIDES TO FIVE-MEMBERED BENZO-HETEROAROMATICS

X	**285 : 286** ratio (total yield %)		References
	Ar = Ph	Ar = Mes	
O	70 : 30 (10.5)	26 : 74 (89)[a]	9/78
S	78 : 22 (1.8)	26 : 74 (30)[b]	10/78
NCOOEt	4 : 96 (14)	5 : 95 (56)	15/82

(*continued*)

TABLE 4.7. (*continued*)

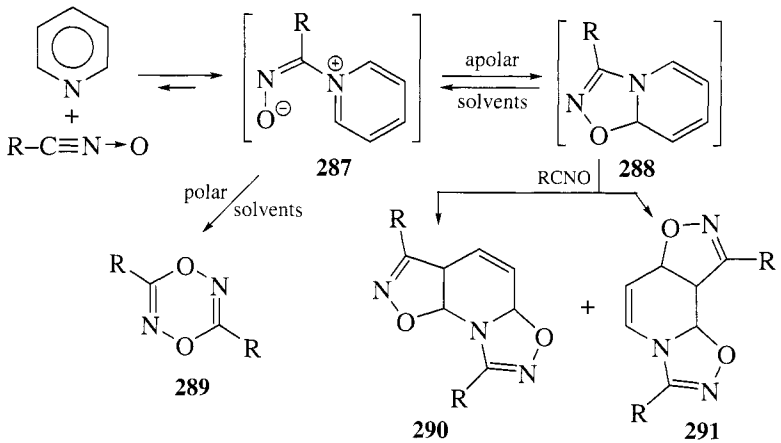
X	**285 : 286** ratio (total yield %) Ar = Ph	Ar = Mes	References
NH	0 :100 (15)	5 :100 (28)	15/82
NMe	0 :100 (19)	0 :100 (62)	15/82
NCOMe	0 :100 (5)	2 : 98 (74)	15/84
$NSO_2C_6H_4Me$	0 :100 (1)	0 :100 (41)	15/84

[a] 39 : 61 ratio (51% total yield) for Ar = 3,5-Cl_2-2,4,6-Me_3C_6.[11/77]
[b] 40 : 60 (25) for Ar = 3,5-Cl_2-2,4,6-Me_3C_6.[11/77]

The monocycloadducts formed from unsubstituted indoles are sensitive both to acids and to bases, and if the cycloaddition is not carried out using special precautions, ring opening to the isomeric oximes may occur.[15/82,14/83,55/84] A similar ring–chain tautomerism was observed in the reaction mixture from the cycloaddition of 3-pyrrolidinobenzo[*b*]furan to nitrile oxides.[18/74]

Oxidation of the sulfur atom of benzo[*b*]thiophene produces a more reactive dipolarophile, which often exhibits regioselective behavior. Regioisomers of type **285** (X = SO_2 or SO) are usually the only reported products from the cycloaddition of benzo[*b*]thiophene-1,1-dioxide, or -1-oxide, with nitrile oxides.[19/74,16/79,16/82,6/91] Kinetic measurements indicate that benzo[*b*]thiophene-1,1-dioxide is 7 times more reactive toward benzonitrile oxide than indene, and that a mixture of cycloadducts **285** and **286** (X = SO_2) are formed in the cycloaddition with benzo- and mesitonitrile oxide, in a 99.2 : 0.8 and 95 : 5 ratio, respectively.[14/82]

Equally interesting is the reactivity of pyridine derivatives toward nitrile oxides, which greatly depends on solvent polarity and structural features both of the heterocycle and of the dipole. Pyridine itself in polar solvents is known to catalyze the dimerization of nitrile oxides to 1,4,2,5-dioxadiazines (**289**). In



apolar solvents, however, aromatic nitrile oxides react to give a mixture of the two site-isomeric biscycloadducts **290** and **291** in yields of up to 50%.[23/86,10/89] The reaction presumably proceeds through the mechanism depicted in the scheme. The intermediacy of the zwitterion **287** has been established by its isolation from the reaction involving benzoylcarbonitrile oxide (R = COPh).[75/88] The intermediacy of the monoadduct **288** has been established by trapping experiments, using a variety of aromatic nitrile oxides.[10/89]

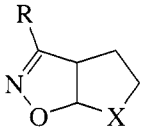
Whereas 2- and 3-picolines react in the same manner, 4-picoline does not participate in cycloadditions, instead affording products of condensation with the methyl group.[70/90]

Quinoline and isoquinoline react with benzonitrile oxide to furnish isolable monocycloadducts, which are the corresponding benzoderivatives of **288**.[1/86,75/88]

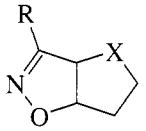
A wide variety of 2-isoxazolines condensed with partially hydrogenated heterocyclic rings have been prepared. The bicyclic systems described in the following paragraph have been prepared, usually in good to excellent yields.

4-Substituted 2,8,3-dioxazabicyclo[3.3.0]oct-3-enes **292a** by highly regioselective cycloaddition of nitrile oxides to the cyclic ether 2,3-dihydrofuran;[8/62,13/63,14/68,16/80,51/84,9/86,5/87,7/87,10/88] a more accurate product analysis discovered the presence of very low amounts of the isomeric 2,6,3-dioxazabicyclocyclooctenes **293a**.[16/84] 2-Methyl-[14/68] or 3-ethoxycarbonyl-[51/84] substituted 3,4-dihydrofurans do not change the preferred direction of cycloaddition, leading to **292a**-type of products.

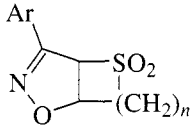
2,3-Dihydrothiophene reacts analogously, but with lower regioselectivity, to yield as main cycloadduct 4-substituted 2,8,3-oxathiazabicyclo[3.3.0]oct-3-enes **292b**, along with minor amounts of the regioisomers **293b**.[16/84] This decrease in regioselectivity on passing from the enol ether to its sulfur analog has been observed for the acyclic analogs and has been attributed to the reduced polarization of the double bond.[16/84]



292 a: X = O
b: X = S



293 a: X = O
b: X = S



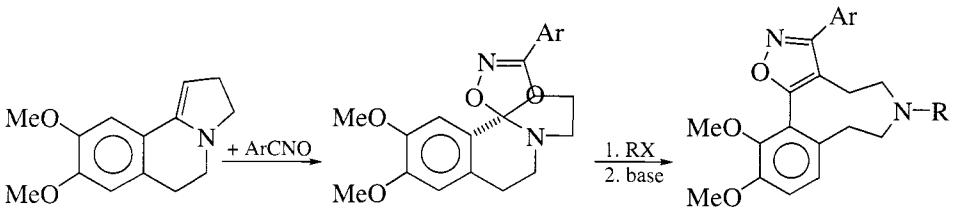
294 a: $n = 1$
b: $n = 2$

R	X	**292:293** ratio	tot.yield %
Ph	O	99.4 : 0.6	98
Mes	O	99.5 : 0.5	96
Ph	S	88 : 12	63
Ph	S	89 : 11	61

4-Aryl-2,6,3-oxathiazabicyclo[3.2.0]hept-3-ene-6,6-dioxides **294a** are obtained from the cycloaddition of arenonitrile oxides to thiete-1,1-dioxide; in the case of mesitonitrile oxide a small amount (isomer ratio 97 : 3) of the regioiso-

meric cycloadduct was obtained.[17/82] In five-membered rings the SO_2 group maintains its control on regiochemistry; both unsubstituted and 3-substituted 2,3-dihydrothiophene-1,1-dioxides cycloadd benzo- or mesito-nitrile oxide to yield 98 : 2 mixtures of the cycloadduct **294b** with their regioisomers.[14/82] Only the major regioisomer **294b** has been identified in another case.[20/81] Lower yields have been reported for the cycloaddition of nitrile oxides to 2,5-dihydrothiophene-1,1-dioxide.[16/67,30/71,7/75]

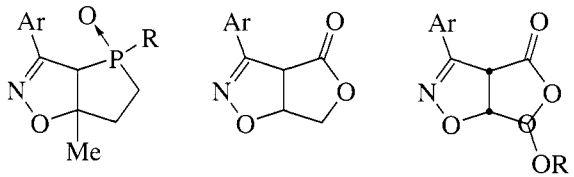
Nitrogen analogs of cycloadducts **292** are not well known, yet may be prepared from lactam acetals.[24/86] More interesting is the tricyclic enamine **295** as starting material for a regiospecific synthesis of aza macrocyclic rings. Cycloaddition of nitrile oxides easily yields the tetracyclic 2-isoxazoline **296**, which undergoes a quaternization–elimination sequence to give the macrocyclic **297**.[49/89,7/91]



295 **296** **297**

No problem of regioselectivity is raised by 2,5-dihydrofuran or its sulfur or nitrogen analogs. Good yields of cycloadducts have been obtained from the reaction of 2,5-dihydrofuran with a variety of nitrile oxides.[8/62,51/84,72/84,17/85,9/86,5/87,7/87,10/88,13/88,14/88,3/90,5/91] Analogous results have been reported for 2,5-dihydrothiophene[9/86] and for 2,5-dihydropyrrole derivatives.[7/75,8/87] Substituted derivatives, such as 2,5-dimethoxy-2,5-dihydrofuran, have also been used as dipolarophiles to afford primarily the *anti* cycloadduct.[14/71,13/72,25/86,9/87]

Low reactivity but high regioselectivity have been observed in the synthesis of the 2,3,6-oxazaphosphabicyclo[3.3.0]oct-3-ene system **298** via nitrile oxides and the suitable dihydrophosphole.[17/67] A phosphorinanone-4-enamine also cycloadds benzonitrile oxide to give the expected condensed isoxazole derivative regioselectively.[32/72]

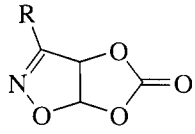


298 **299** **300**

As already cited in Part 1, § 2.2.2.2, p. 517, maleic anhydride and maleic *N*-arylimides are highly active dipolarophiles, and afford high yields of the corresponding bicyclic 2-isoxazolines. The reaction will not be further examined, apart from an updating of relevant literature references.[14/85,13/86,26/86,8/91]

Cycloaddition of nitrile oxides to the 2-butenolide, 5*H*-furan-2-one, gave moderate to good yields of 4-aryl-2,7,3-dioxazabicyclo[3.3.0]oct-3-en-6-ones **299**, commonly referred to as 3-aryl-4-oxo-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazoles.[18/70,27/86] The reaction is always regiospecific and use of chiral butenolides (5-alkoxy- or 5-acyloxy-furanones) leads stereoselectively to the *anti*-cycloadducts.[10/87,9/91] The reaction with 5-hydroxyfuranone exhibits no π-facial diastereoselectivity, due perhaps to the intervention of hydrogen bonding in the transition state, and gives a 52:48 mixture of **300** (R = H) with its diastereomer.[10/87] With *l*-menthyloxyfuranone and benzonitrile oxide the diastereofacial control is excellent.[15/88]

The bicyclic 2-isoxazolines **301**, obtained by cycloaddition of vinylene carbonate to nitrile oxides, are interesting because of their easy transformation into 4-hydroxyisoxazoles **302** through hydrolysis and dehydration.[15/68,13/85]



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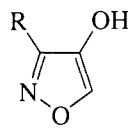

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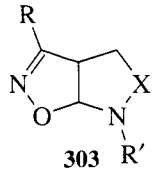
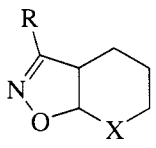


303

Other five-membered unsaturated heterocycles can be similarly employed to build bicyclic heterocyclic derivatives: thus, both pyrazolines and 3-isoxazolines react regiospecifically to give 2-oxa-3,7,8-triaza- (or 2,7-dioxa-3,8-diaza-, respectively[11/78]) bicyclo[3.3.0]oct-3-enes **303**.[20/74] Substituted 3-pyrazolines show moderate stereoselection.[19/76,12/77] Isothiazol-3(2H)-one 1,1-dioxide reacts regiospecifically with *p*-chlorobenzonitrile oxide to give 3-aryl-7-alkyl-2-oxa-6-thia-3,7-diazabicyclo[3.3.0]oct-3-en-8-one 6,6-dioxide.[11/89]

2,9-Dioxa-8-azabicyclo[4.3.0]non-7-enes **304** (X = O) have been synthesized regioselectively in variable yields by cycloaddition of nitrile oxides to 2,3-dihydropyran.[8/62,14/68,7/75,16/80,51/84,5/87,7/87,10/88] An analogous reaction has been reported for 2,5-dihydropyran: despite a previous claim,[13/69] regioselectivity is very low; both regioisomers are obtained in a 54:46 ratio.[42/90] Conjugation of the



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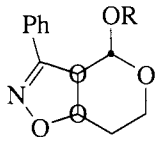

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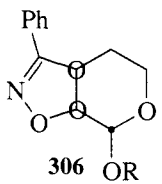


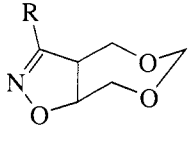
306

dihydropyran double bond with a benzo-[21/81] or carbonyl group[19/85,20/85,16/88] induces a high degree of regioselectivity in the cycloaddition. The presence of an allylic methoxygroup controls both regio- and stereoselectivity and a mixture of the regioisomeric cycloadducts **305** and **306** are produced, with prevalence of the former one and along with minor amounts of the stereoisomer of **305** and of several bisadducts when R = Me.[46/88] Hexenopyranosides enter cycloaddition with low regioselectivity but high face selectivity.[18/82,19/85,18/88]

The nitrogen atom in a heterocyclic dipolarophile controls the regioselectivity, in both α and in β positions, and directs the 1,3-dipolar cycloaddition toward the formation of the 9-oxa-2,8-diazabicyclo[4.3.0]non-7-ene system **304** (X = NR or NCOR)[14/68,11/87,2/89,44/90] or of the 9-oxa-3,8-diazabicyclonon-7-ene analog.[4/64] Even 1,2-dihydroquinoline[47/89] and 1,2-dihydroisoquinoline[21/74] derivatives follow the same pattern. Substituted 1,2-dihydropyridine derivatives react with nitrile oxides either on the α,β-[68/86] or on the γ,δ-double bond,[17/84] always regiospecifically. An exception seems to be the cycloaddition of methyl 2,3-dehydroquinuclidine-3-carboxylate (1-azabicyclo[2.2.2]oct-2-ene-3-carboxylate), which is reported to yield a condensed 2-isoxazoline having the nitrogen bound to the 4-position.[18/67]

A regio- and site-specific cycloaddition is known for substituted pyridazin-3-ones, as predicted by a dominant HOMO(dipole)–LUMO(dipolarophile) interaction.[13/89]

The 8-substituted 3,5,10-trioxa-9-azabicyclo[5.3.0]dec-9-ene system **307** is readily obtained by cycloaddition of nitrile oxides to 2*H*,4*H*,7*H*-1,3-dioxepine.[18/84,51/84,65/85,9/86,5/87,7/87,12/87,10/88,13/88,3/90,45/90,5/91] 2-Substituted dioxepines afford a mixture of the two stereomeric cycloadducts, in which the *anti* isomer usually predominates.[51/84,65/85,28/86,29/86,5/87,7/87,12/87,10/88,13/88,56/89] Bicyclic sulfur analogs are also known.[56/84,9/86] The situation is completely different with nitrogen analogs, such as 1,2- or 1,4-diazepine derivatives, where the C=N double bond is more dipolarophilic than the C=C double bond, thus leading preferentially to oxadiazolodiazepines, such as **308**.[13/77] The bisadduct is usually absent or present in very low amount, except for **309**, obtained in 60% yield along with 30% yield of the monoadduct on the C=N bond.[10/91] 2*H*,5*H*-1,6-Benzodioxocine[19/88] and the analogous benzodiazocines[12/88] have also been recorded as successful dipolarophiles, as well as an oxygenated macrocycle.[19/88]



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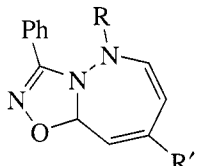

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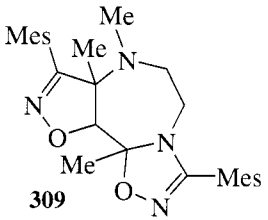
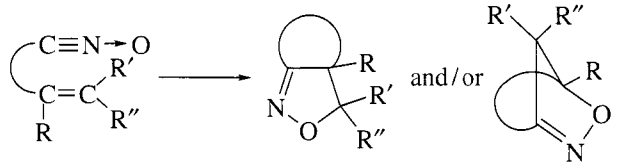


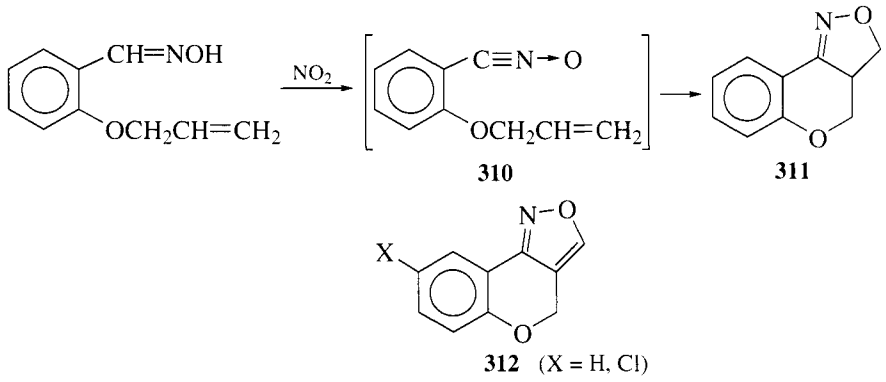
309

4.2.2.2. Intramolecular Cycloadditions of Unsaturated Nitrile Oxides

Substrates that contain both a nitrile oxide moiety and a double or triple bond on the same chain can undergo an intramolecular 1,3-dipolar cycloaddition, which has been abbreviated INOC (intramolecular nitrile oxide cycloaddition) reaction. In principle one of two regioisomeric cycloadducts, i.e. a 3,4- or a 3,5-condensed 2-isoxazoline (or isoxazole), can be expected:



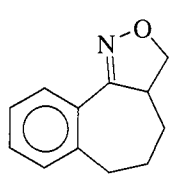
The first INOC reaction was discovered by oxidizing 2-allyloxy benzaldoxime with nitrogen dioxide. The corresponding nitrile oxide **310**, generated *in situ*, immediately cyclizes to the 3,4-fused isoxazoline **311**. Analogously, the 2-propynyloxyderivative was shown to give rise to the condensed isoxazole **312**:[8/75]



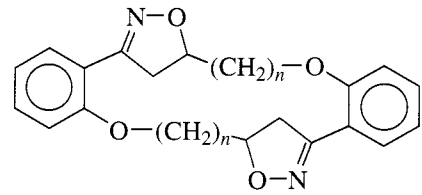
The yields of **311** can be improved (up to 90%) when other methods of generating the nitrile oxide are employed.[19/82, 9/90,47/91]

The most striking feature of the intramolecular cycloaddition of nitrile oxides in comparison with the intermolecular version is the complete inversion of regiochemistry. Whereas in the latter reaction monosubstituted olefins (and in most cases acetylenes, too) furnish the 5-substituted 2-isoxazolines exclusively, the INOC reaction almost always leads to the 4-substituted (isoxazoline numbering) regioisomers, clearly because of steric constraints in the transition state. In fact, increase of the chain length between the nitrile oxide moiety and the termi-

nal double bond can change this preferred orientation. Thus, the next higher homologs cyclize more sluggishly; the seven-membered ring still yields the intramolecular cycloadduct **313** as predominant product, along with small amounts of the macrocyclic compound **314a**, but the next-higher homologs furnish **314b-c** only, although in low yields. These 5-substituted large-ring cycloadducts derive from an initial intermolecular reaction, followed by an intramolecular closure, which can conform to the "normal" regiochemistry.[9/75]

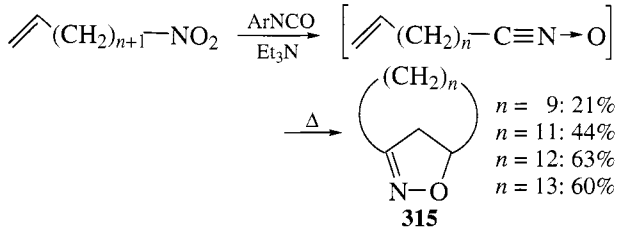


313 (17%)



314 a: $n = 3$ (2%)
b: $n = 4$ (13%)
c: $n = 5$ (19%)

Increasing chain length allows a shift toward formation of the 3,5-fused isoxazoline product. Thus, nitrile oxides generated from nitroalkanes, in which the terminal double bond and the nitro group are separated by 10 or more carbon atoms, furnish isoxazoline-fused macrocycles (**315**) in fair to good yields:[21/85]

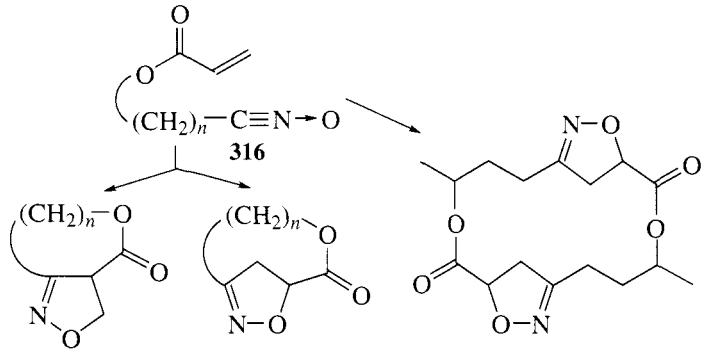


$n = 9$: 21%
$n = 11$: 44%
$n = 12$: 63%
$n = 13$: 60%

315

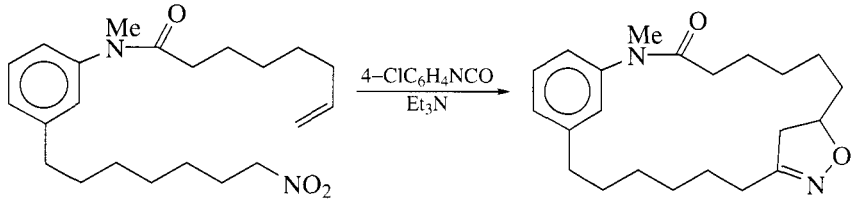
The dependance of the regiochemical outcome on the length of the tether between the two reactive centers is nicely illustrated by the type of lactone rings obtainable from nitrile oxides (**316**).

When the two reactive centers are close together, steric demands dictate the formation of either a 3,4-fused 9-membered monolactone[20/82] or a 16-membered dilactone, the products of inter- and intramolecular cycloadditions respectively.[22/81] With increasing separation, the monolactones with "normal" regiochemistry (3,5-condensed isoxazolines) predominate or are the exclusive products.[20/82] A 3,4-condensed five-membered lactone is also known in the 2-isoxazoline series, whereas a six-membered lactone has been reported for the isoxazole series only, possibly because of the higher tendency of acetylenes to yield 4-substituted cycloadducts.[17/80]



n = 3:	==	==	34%
n = 5:	44%	==	==
n = 8:	14%	68%	==
n = 10:	10%	64%	==
n = 11:	==	67%	==

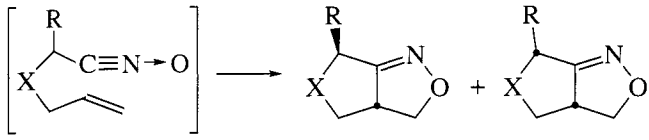
In a similar way, synthesis of a 19-membered lactam containing a 3,5-condensed 2-isoxazoline ring has been achieved in excellent yields.[19/84]



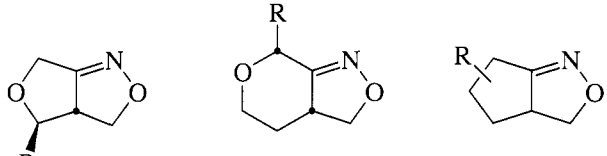
Several other 2-isoxazolines 3,4-fused with nitrogen-containing[29/88,21/88,22/88,14/89,10/90,46/90,11/91] or sulfur-containing[11/90,12/91] five- or six-membered rings are known; higher rings imply lower yields.[10/90] Carbocyclic six-[14/77,47/90] and nine-membered rings[21/88] fused at the isoxazoline 3,4-positions have been obtained without difficulty.

If the connecting tether contains one or more substituents, stereoisomerism must be expected, and often mixtures of isomers are obtained. Thus, for instance, the α-alkyl-(or phenyl-) substituted ethylenic nitrile oxides **317**, generated as usually in situ from the nitrocompound, yield a mixture of the two stereoisomers **318** and **319** in the ratio 2.5-9 : 1 when X = O, and 1.2-2 : 1 if X = S.[23/88,15/89,11/90,12/90,13/91,14/91]

Complete (or very high) facial selectivity has been observed when the isomeric bicyclic compounds **320** or the higher homologues **321** are produced.[23/88,15/89,13/91,14/91] Only limited selectivity was observed for the carbocyclic analogs **322** or for the sulfur analogs of **321**.[11/90]

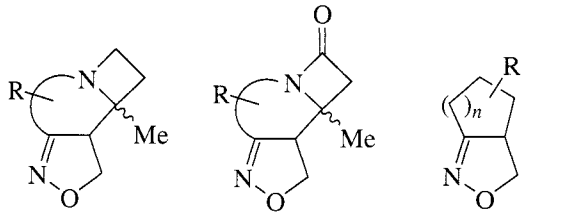


317 318 319



320 321 322

A number of azetidine or azetidinone condensed compounds corresponding to the general structure **323/324** (the central ring can be five-, six- or seven-membered) have been prepared through INOC reactions of the 4-vinyl *N*-substituted azetidines or *β*-lactams.[13/87,38/87,39/87,24/88] The stereochemical pathway depends on the tether length, the nature of the substituents, and the product stabilities. Theoretical calculations correlate well with experimental results.[24/88]

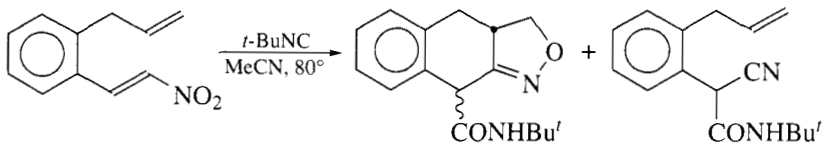


323 **324** **325 a:** $n = 1$ **b:** $n = 2$

3,4-Substituted isoxazolines fused with five-membered carbocyclic (general structure **325a**) rings containing chiral centers have been prepared by utilization of intramolecular cycloadditions. The degree of stereoselectivity in these systems has been clearly linked to steric requirements in the transition state.[21/82,20/84,68/88]

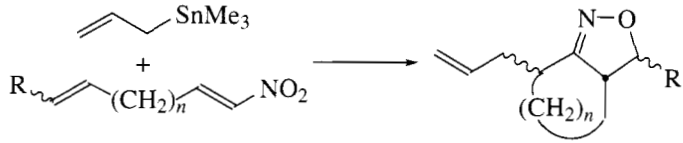
When the vinyl group and the nitrile oxide component (generated *in situ* from CH_2NO_2 or CH=NOH) are linked by four, variously substituted, carbon atoms, the cycloadducts **325b** are produced with high stereoselectivities.[22/85,23/85,16/89,13/90,14/90,15/91] The stereochemical control exhibited in these instances has been attributed to the adoption of a strain-minimizing, chair-like structure in the transition state.

Generation of a nitrile oxide by dehydration of a terminal nitroolefin with *t*-butylisocyanide affords the tricyclic 2-isoxazoline **326**, along with minor amounts of an open-chain *α*-cyanoamide:[40/87,17/89]



326 (2 : 1 *trans/cis*; 48%) (34%)

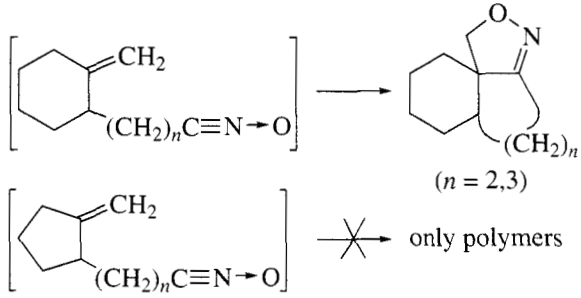
Another source of 3,4-fused isoxazolines is the Lewis acid–promoted reaction of 1-nitro-1,5-(or 1,6-)alkadienes with allylic stannates:[14/87,18/89]



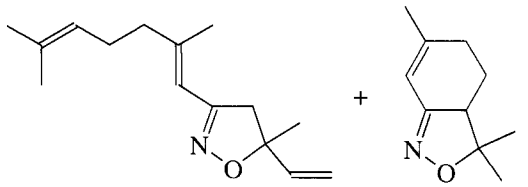
(n = 1,2; R = H, Ph, Me)

Here, too, mixtures of diastereomeric cycloadducts are obtained. The nature of the Lewis acid is also important: $TiCl_4$ promotes cyclization, whereas $AlCl_3$ gives an open-chain adduct. The 1-nitro-1,6-dienes furnish the bicyclic isoxazolines with high stereoselectivity, irrespective of the Lewis acid employed, and a two-step cycloaddition has been postulated in this case.

The nitrile oxide (generated *in situ* from the suitable nitroalkene) can cycloadd intramolecularly to a methylene cyclohexane moiety, but not to the methylene cyclopentane homolog:[26/88]

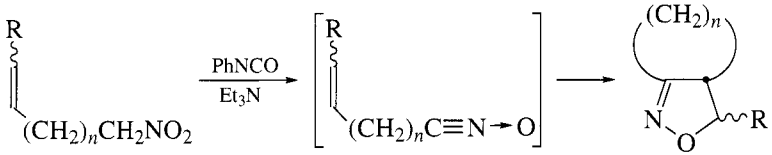


Sometimes the INOC reaction can compete with the intermolecular cycloaddition, as observed in the oxidation of crude citral oxime in the presence of isoprene. In this case both the intermolecular cycloadduct **327** and the intramolecular product **328** are formed:[69/90]



327 (32%) **328** (20%)

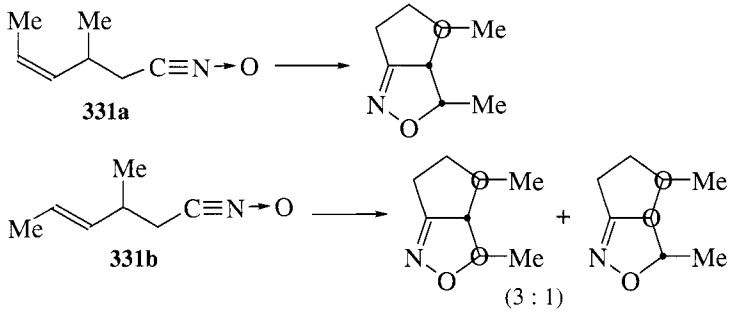
Regio- and stereospecificity has been encountered when the double bond at one end of the chain is 1,2-disubstituted: *E/Z* mixtures of **329**, dehydrated by Mukaiyama procedure, cyclize intramolecularly to yield *E/Z* mixtures of the corresponding bicyclic 2-isoxazolines **330**.[15/83]



329 (n = 3, 4; R = Me, Ph) **330**

An example of similar specificity is known.[15/90]

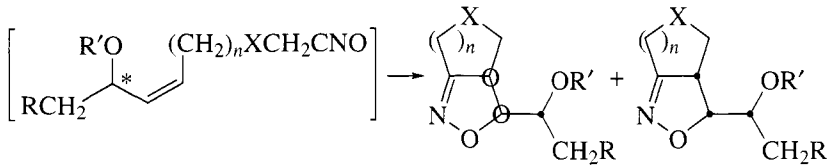
High diastereofacial selection is possible in the INOC reaction of olefinic nitrile oxides having an allylic stereogenic center, as in **331**:[22/82]



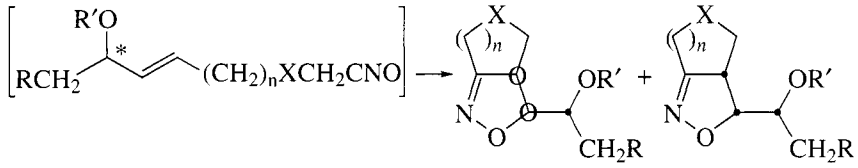
The varying levels of stereocontrol in the two cases (*Z* or *E* educts) have been attributed to different types of $A^{1,3}$ strain present in the two possible transition states. In another case the diastereofacial selectivity has been reported to be very low.[23/81,21/84]

A thorough study of the INOC reaction of nitrile oxides containing a chiral allyl ether moiety at the other end of the chain has been conducted. The diastere-

ofacial control varies from poor to excellent, depending on the nature and length of the chain, the geometry of the double bond, and the substituents at the allylic stereocenter. The following results are reported as typical examples:[15/87,16/87,68/87]

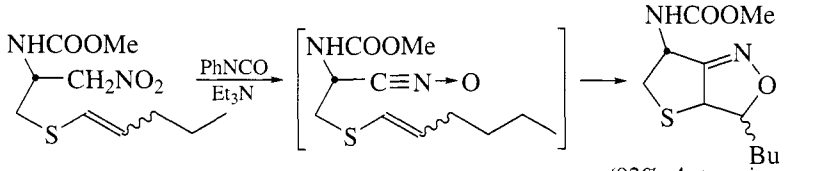


n	X	R	R′	Isomers ratio	Total yield (%)
1	CH_2	H	CH_2Ph	75:25	57
1	CH_2	$-OC(CH_2)_5-$		81:19	58
1	S	OCH_2Ph	CH_2Ph	63:37	72
1	S	$-OC(CH_2)_5-$		95:5	72
2	CH_2	H	CH_2Ph	80:20	62
2	CH_2	$-OC(CH_2)_5-$		86:14	63



n	X	R	R′	Isomers ratio	Total yield (%)
1	CH_2	H	CH_2Ph	58:42	26
1	CH_2	$-OC(CH_2)_5-$		78:22	43
1	S	OCH_2Ph	CH_2Ph	63:37	78
1	S	$-OC(CH_2)_5-$		83:17	71
2	CH_2	H	CH_2Ph	60:40	70
2	CH_2	$-OC(CH_2)_5-$		86:14	84

No stereoselection was exhibited in the following INOC reaction:[18/80,24/81,17/87]

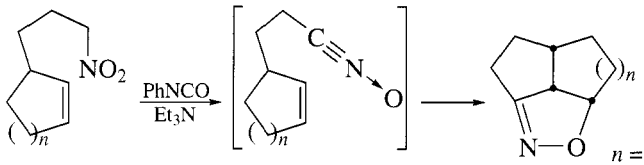


(92%; 4 stereoisomers in ~ equal amounts)

An example of the ability of trisubstituted double bonds to participate in the intramolecular cycloaddition involves NaClO oxidation of farnesyl oxime to give the corresponding 3,4-condensed 2-isoxazoline.[19/89,48/90]

Irradiation of (*E*)-5α-cholest-1-en-3-one oxime in protic or aprotic solvents furnishes a mixture of products, among which 4α′,5α′-dihydro-*A*-nor-5α-cholestano[2,1-*c*]isoxazole was isolated, in 20% yield. The formation of this product has been attributed to a ring opening of the photoexcited (*Z*)-oxime leading to an unsaturated nitrile oxide, which undergoes intramolecular cycloaddition.[18/87]

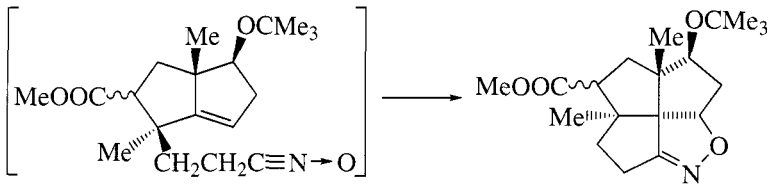
If the reactive double bond belongs to an alicyclic ring, a route is opened toward tricyclic 2-isoxazolines. Thus the nitrile oxides, generated *in situ* from several nitro cycloalkenes, give rise to stereochemically pure cycloadducts **332** in high yields:[19/80]



332 (yields 81–96%)

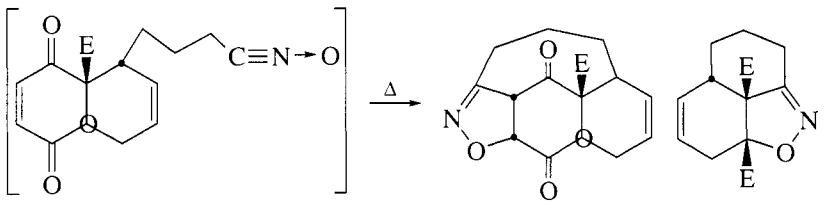
The presence of substituents on either the carbocyclic ring or the lateral chain does not affect the stereochemical outcome of the reaction.[16/83,22/84,24/85,30/86,66/86,41/87,57/87,27/88,20/89,75/90] Theoretical calculations have also been performed, and corroborate the experimental results.[41/87] Yields are generally high, and a high degree of stereoselectivity is usually observed if other chiral centers are positioned close to the two reactive moieties. A decrease in stereochemical control has been noted in the cyclization of (*E*)-3-(3-nitroallyl)cyclohexene with *t*.butylisocyanide, which is reported to furnish four isomeric tricyclic isoxazolines.[40/87,17/89]

The tetracyclic isoxazoline **333** could also be produced in excellent yields by INOC reaction from the suitable nitrile oxide.[16/91]



333

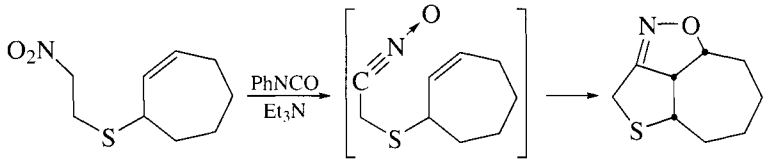
Also worthy of mention is the cyclization of **334** in which the 8-membered ring is formed in preference to the less strained six-membered ring, presumably owing to the higher dipolarophilicity of the carbonyl-conjugated double bond in comparison to the non-conjugated one.[22/84]



334 E = COOMe **335**

Similarly, the nitrile oxide derived from dimethyl 3-(4-nitrobutyl)cyclohexa-1,4-diene-1,2-dicarboxylate reacts in an intramolecular fashion to afford adduct **335** as the only isolated product .[22/84]

Condensed heterocyclic compounds are readily available by extension of the stereocontrolled annulation illustrated above. Cycloaddition of tethered nitrile oxides to unsaturated heterocycles, such as dihydropyrans[24/85,25/85,42/87,28/88] or di- and tetrahydropyridine[58/85,26/85, 16/90] derivatives. The heteroatom can also belong to the chain that links an unsaturated carbocyclic ring with the pendant nitrile oxide precursor. A useful example is the following well-known key step in the total synthesis of biotin:[12/78,20/80]



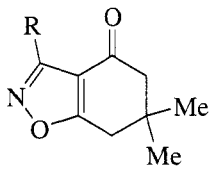
In addition to sulfur, other heteroatoms commonly present as components of the tether are oxygen[17/91] or nitrogen.[27/85]

As mentioned previously, nitrile oxides can undergo cycloadditions with heteroaromatic compounds. The intramolecular version of this kind of reaction has been exemplified by the so-called INHC (intramolecular nitrile oxide-heterocycle cycloaddition) reaction to the double bond of furan,[23/84,29/88,15/89, 21/89,18/91,19/91] thiophene,[30/88,15/89] pyrrole and indole.[19/91] The process seems to be highly regioselective but poorly diastereoselective. In some cases even bis-cycloadducts are produced, although in minor amounts,[23/84] while in other cases the cycloadduct may be unstable, leading to ring opening of the isoxazoline ring.[19/91]

4.2.2.3. Cycloaddition of Nitrile Oxides to Cyclic β-Diketones or Analogous Compounds

The well-known cycloaddition of nitrile oxides (or hydroxamic acid chlorides) to β-diketones (see Part 1, § 1.3.2.3, pp. 203–207) has been extended

to cyclic derivatives, such as cyclopentane-1,3,dione,[31/88] cyclohexane-1,3-dione,[6/78,25/81] dimedone,[22/74,10/75,23/82], and indandione.[23/82] Condensed isoxazoles that have general structure **336** are obtained regiospecifically. The intermediate 5-hydroxy-2-isoxazolines (derived from the enol form of the β-diketone) are never isolated, except in the case of indandione, where the cycloadduct **337** is reported to be relatively stable.[23/82] In the cycloaddition of 3-nitrobenzonitrile oxide to dimedone the cycloadduct **336** is accompanied by a significant amount of the product of 1,3-addition **338**.[22/74]



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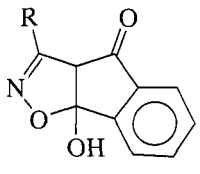

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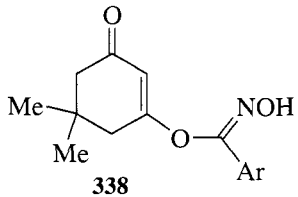
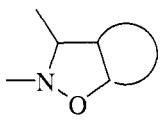


338

4.2.2.4. Cycloaddition of Acyclic Nitrones to Unsaturated Cyclic Compounds

As summarized in Scheme 4.4 , acyclic or cyclic nitrones can react with either olefinic or acetylenic acyclic or cyclic dipolarophiles. The resulting 1,3-dipolar cycloaddition opens the route to the formation of 4,5-fused isoxazolidines **339** or 4-isoxazolines **340** when starting from an acyclic nitrone, and to the 2,3-fused isoxazolidines **341** or 4-isoxazolines **342** when starting from a cyclic nitrone.



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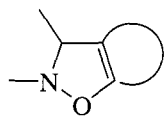

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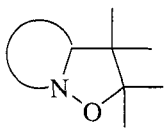

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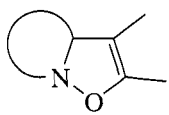

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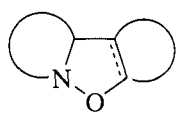


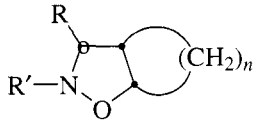
343

The two cases will be separately reviewed, first considering the structure of the dipolarophile and then the structure of the nitrone. Finally, the cycloaddition of cyclic nitrones to cyclic dipolarophiles to form polycyclic isoxazolidines or 4-isoxazolines of general structure **343** will also be illustrated.

Cycloaddition of 1,3,3-trimethylcyclopropene[24/82] and 1-methylcyclobutene[25/82] with *N*-phenyl-*C*-phenylamidonitrone is reported to afford the expected fused

isoxazolidines in excellent yields, and although the regiochemistry of the products has been deduced, their relative stereochemistry is still uncertain.

Several symmetrically substituted, cyclic olefins, such as cyclopentene,[17/68,20/69, 13/76,24/84] cyclohexene,[19/67,17/68,18/68,15/71,20/73,15/77,24/84] cycloheptene,[24/84] *trans*-cyclooctene,[15/71,7/75,9/77] 1,4-cyclohexadiene,[26/82] 1,5-cyclooctadiene,[20/68,26/82] and acenaphthylene,[19/68,20/69,12/74,17/83,17/90] are very reactive toward acyclic nitrones and yield 4,5-ring-fused isoxazolidines with *cis*-stereospecifity. Two of the expected products, stereoisomers **344** and **345** (epimers at C3), have been indeed isolated and their relative proportions measured in some cases. Thus, *C*-phenyl-*N*-methylnitrone reacts with cyclopentene, cyclohexene, *trans*-cyclooctene and acenaphthylene to give **344**:**345** (*trans*:*cis*) ratios = 81:19, 87:13, 50:50, 80:20, respectively.[13/76, 15/71,12/74] Conversely, *C*-benzoyl-*N*-phenylnitrone is reported to furnish only the 3,4-*trans*-cycloadduct .[17/83]



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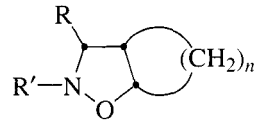
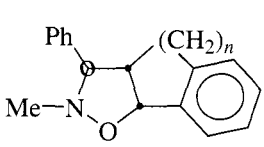
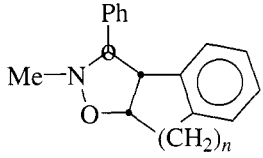


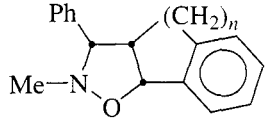
345

Nitronic esters are also known to react with cycloalkenes, yielding 2-alkoxy-isoxazolidines.[20/65,19/70,16/71]

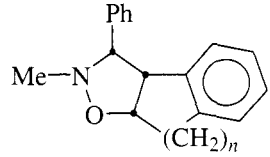
With asymmetrically substituted cyclic olefins, such as indene[18/68,19/68,20/69,13/76, 17/83] or 1,2-dihydronaphthalene,[19/68,13/76] regioselectivity must be taken into account since up to four isomeric cycloadducts are possible and have in fact sometimes been isolated. As an example, the cycloadducts arising from reaction of *C*-phenyl-*N*-methylnitrone with indene or 1,2-dihydro-naphthalene are reported.







Isomers ratio: $n = 1$, 74 : 12 : 11 : 3
$n = 2$, 26 : 59 : 4 : 11

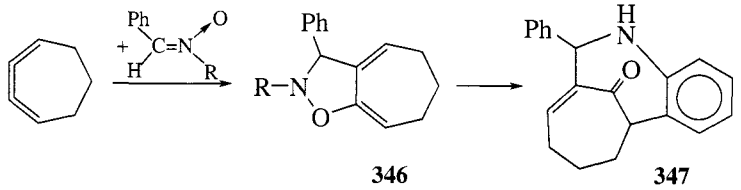


1-Substituted indenes (or dihydronaphthalenes) react with *N*-methylnitrone regiospecifically.[23/74]

Conjugation with another endocyclic double bond induces a high degree of regioselectivity, as demonstrated by the cycloaddition of nitrones to 6,6-diphenylfulvene[22/89] and to 1,3-cyclohexadiene.[26/82] Curiously, the cycloaddi-

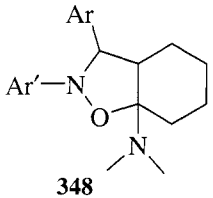
tion of *C*,*C*-dinitro-*N*-methoxynitrone with cyclopentadiene seems to contradict the rule, and a mixture of the two regioisomers is obtained instead.[21/68]

Trapping of the highly unstable species, 1,2,3-cycloheptatriene, by *C*-phenyl-*N*-methylnitrone affords the isolable cycloadduct **346** (R = Me). The corresponding adduct (**346** R = Ph) formed from *C*,*N*-diphenylnitrone rearranges to the anti-Bredt olefin **347**.[18/83]



346 **347**

Functionalized cyclohexenes exert a marked degree of control on the regiochemistry of their cycloadditions with nitrones. Thus, carvone and eucarvone furnish unique monoadducts, where only the carbonyl-conjugated double bonds are reported to be reactive.[22/68] Enamines derived from cyclohexanone and cyclopentanone are also known to react regiospecifically to afford the 5-substituted isoxazolidines **348**, albeit in low to moderate yields.[20/67,21/67,23/68, 20/70,21/73] Nevertheless, a reversal of regiochemistry has been observed when 1-pyrrolidino-*cis*-3,5-dimethylcyclohexene was employed as the dipolarophile.[21/70] Sometimes, especially with 1-morpholinylcycloalkenes, the amino residue in the product can be substituted by the phenylhydroxylamino group.[21/67,20/70,17/71,20/76] Occasionally, two epimers have been isolated; the *cis*-configuration is claimed to be largely prevalent.[21/67] Benzoquinones are reported[43/87] to be unreactive toward *C*-phenyl-*N*-methylnitrone.



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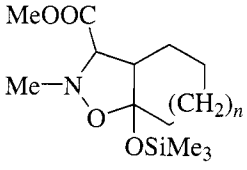
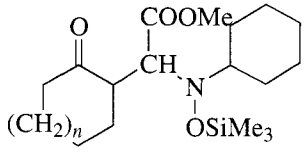


349 (n = 0, 1)

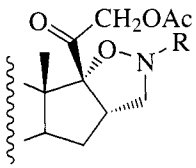


350 (n = 0, 1)

Dipolar cycloadditions can be highly sensitive to small variations in steric and electronic patterns. A pertinent example is offered by the cycloaddition of *C*-methoxycarbonyl-*N*-methylnitrone to cyclopentanone or cyclohexanone lithium enolate to give, after silylation, a mixture of diastereoisomeric cycloadducts **349**, a product not accessible by direct reaction of the nitrone with 1-trimethylsilyloxycycloalkene. Nitrones bearing a bulkier substituent, such as phenyl or cyclohexyl, on nitrogen either fail to react or divert the reaction toward

a simple addition product, such as **350**. Moreover, the presence of the activating ester group is essential, since differently substituted nitrones are unreactive.[62/85]

Several studies have been devoted to the synthesis of fused heterocyclic steroid derivatives by 1,3-dipolar cycloadditions. 1,4,16-Pregnatriene-3,20-diones undergo cycloaddition with *N*-methyl- (or benzyl)nitrone, to yield, regio- and stereoselectively, [16α,17α]isoxazolidines of partial structure **351**.[27/82] Cycloaddition of *C*,*N*-diphenylnitrone to 16-dehydropregnenolone acetate is reported to give both possible regioisomeric adducts.[11/64] The reaction of several analogous 16-dehydro-20-oxosteroidal derivatives must be induced either by high pressure or by boron etherate catalysis.[24/74,11/75,12/75,16/77,17/77,18/77,13/78, 21/80,22/80] In the latter case the primary adduct **352** directly undergoes elimination to the [16α,17α]isoxazoline **353**. Here, too, the cycloaddition is regiospecific and often highly stereoselective.



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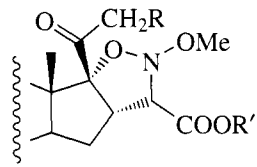

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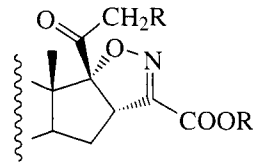


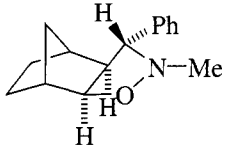
353

Polycyclic olefins with diastereotopic faces, such as norbornene,[17/68,24/68,20/69, 15/71,23/80] norbornadiene[17/68,24/68,12/76,8/77] (and their 7-oxaanalogs), bicyclo[4.2.0]oct-7-ene,[15/71] dicyclopentadiene,[17/68,20/68,21/69] and dialkyl bicyclo[2.2.1]hept-2-en-5,6-dicarboxylate[17/68] (and its 5,6-diaza analog[17/68] or 7-oxa analog[17/83]), as well as the analogous bicyclohepta-2,5-dienedicarboxylates,[14/81,17/83] are also active dipolarophiles. The regio- and stereoselectivities of their cycloadditions to acyclic nitrones have been thoroughly studied, leading to results widely in accordance with expectations on the basis of qualitative perturbation treatment, considering frontier orbital interactions only.

Diene derivatives generally offer only one double bond for cycloaddition, although sometimes bisadducts can be isolated in yields that do not exceed 3–4%. Furthermore, it should be noted that norbornene exclusively yields *syn*-methano bridge products,* thus confirming the *syn* (previously the *exo*) rule to be generally valid for 1,3-dipolar cycloadditions to norbornenes. Here, too, a clear prevalence or even an exclusive formation of the *trans* isomer has been reported. For instance, with *C*-phenyl-*N*-methylnitrone a 9:1 or 7:1 mixture of *syn*-adducts **354/355** has been observed;[24/68,15/71] an *exo*-transition state **356** involving the less favored, but highly reactive, *E* configuration of the nitrone, has

Syn/anti descriptors (with respect to the methano bridge) for stereofacial selectivity have been adopted throughout for the final products instead of *exo/endo* (reserved to transition states),[19/77] although the latter prefixes are still widely present in the chemical literature. Moreover, the *trans/cis* terminology indicates the relative configuration at the 3 and 4 centers of the isoxazolidine moiety.

been proposed for the formation of **354**. Similar results have been observed by using norbornene 2,3-dicarboxylate (or its 7,7-dimethyl or 7-oxa analogs).[18/71,14/81,17/83]



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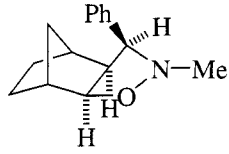

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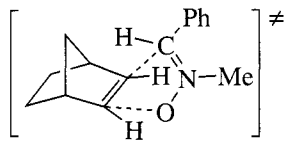


356

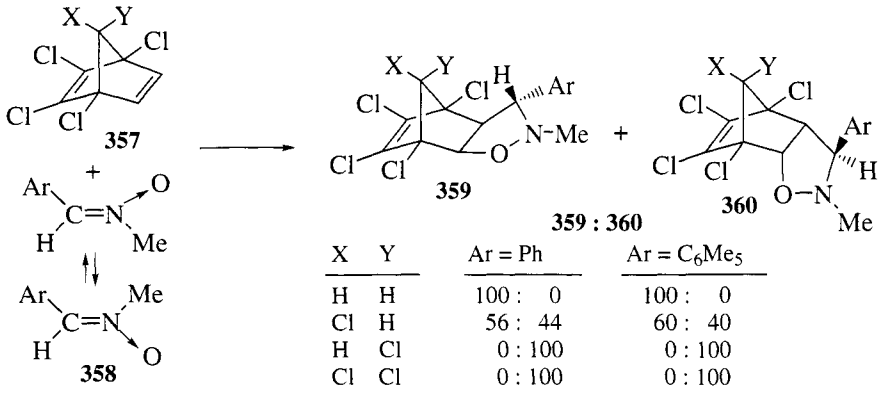
However, the stereochemical fate of the reaction, as for *trans/cis* ratio of cycloadducts, seems to also depend on the structure of the dipole. Thus, the reaction of *C,N*-diphenylnitrone with norbornene is devoid of diastereoselectivity and the two epimeric *syn*-cycloadducts are produced in almost a 1:1 ratio.[25/68]

Cycloaddition of *C,N*-diphenylnitrone to asymmetrically substituted 7-oxanorbornene is characterized by *syn*-oxabridge facial selectivity, no regioselectivity and moderate diastereoselectivity (the *trans* isomer is the major product).[65/88] Other dipolarophiles studied are 7-oxa- and 7-azabenzonorbornadienes, and here, too, the *trans/cis* ratio strongly depends on the structure of the reactants.[11/80,57/84]

Cycloadditions of norbornadiene, its derivatives and analogs to acyclic nitrones follow a pattern somewhat different from those of norbornenes, thus paralleling the results already illustrated (this volume, § 4.2.2.1) for cycloadditions to nitrile oxides. Indeed, variable amounts of the two epimeric *syn*-monoadducts have been produced by cycloaddition of acyclic nitrones to the unsubstituted norbornadiene. A preference toward the *trans* configuration is observed with *C*-phenyl-*N*-methylnitrone, whereas the stereoselectivity is reversed with *C,N*-diphenylnitrone. Use of *C*-*p*-nitrophenyl-*N*-phenylnitrone permits the isolation, along with the *syn* epimers and some bisadducts, of one *anti* (= *endo*) isomer in low yield.[8/77]

Steric constraints and electronic factors, which result from substitution at the methano bridge, can dramatically shift the reaction path toward an *endo* transition state. The reactions of polychloronorbornadienes **357** with nitrones **358** clearly illustrate the switch from a *syn* to an *anti* attack.[17/79] The dipolarophile in this instance is more reactive than norbornadiene itself, owing to the increased LUMO(alkene)–HOMO(nitrone) interaction; the preference of the 7-chlorine substituted terms toward *anti* attack has been attributed both to steric and electronic factors, whereas the exclusive *trans* configuration observed in all cycloadducts should most probably be ascribed to a $Z \rightarrow E$ conversion of the starting nitrone, followed by attack of the reactive *E* form to the dipolarophile via an *exo* transition state.

Consistent with the proposal stated above is the cycloaddition of nitrones to dicarboxylated norbornadiene and its 7-oxa analog. Contrary to what happens in



359 : 360

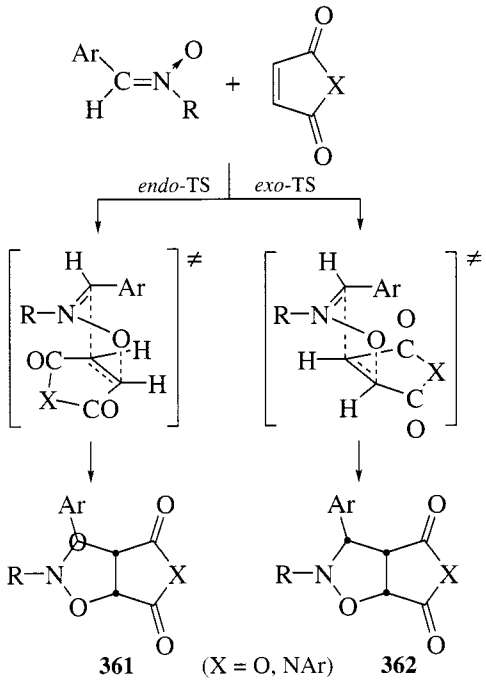
X	Y	Ar = Ph	Ar = C_6Me_5
H	H	100 : 0	100 : 0
Cl	H	56 : 44	60 : 40
H	Cl	0 : 100	0 : 100
Cl	Cl	0 : 100	0 : 100

the case of the nitrile oxides, the monoadducts are stable and can be easily isolated. The reaction with *C*-phenyl-*N*-methylnitrone is site-specific and stereoselective; only the adducts on the electron-poor tetrasubstituted double bond are obtained, as expected because of the dominant HOMO(nitrone)–LUMO(dipolarophile) interaction.[14/81] With electron-poor nitrones, such as *C*,*N*-diphenylnitrone or *C*-benzoyl-*N*-phenylnitrone, reduced site selectivity is observed, since the HOMO(dipolarophile)–LUMO(nitrone) interaction, favoring attack on the disubstituted double bond, becomes important.[17/83] The diastereoisomer having a *cis* relationship between the phenyl and the ester group is formed exclusively; a stereochemical preference, that is diminished in reactions of a 7-oxaderivative.

Various unsaturated heterocyclic compounds have been evaluated for their reactivity toward acyclic nitrones.

As already mentioned in Part 1, both maleic anhydride and *N*-aryl (or *N*-alkyl) maleimides are very active dipolarophiles and easily cycloadd nitrones. *C*-Unsubstituted nitrones (i.e., formaldehydonitrones) do not present stereochemical problems, and yield 3-unsubstituted 4,5-fused isoxazolidines.[21/69,18/79,49/90] *C*,*N*-Disubstituted nitrones can lead to two diastereoisomers, having C3 and C4 isoxazolidine hydrogens in *trans* or *cis* relationship. Adopting the two-plane orientation complex approach, generally accepted for 1,3-dipolar cycloadditions of allyl type 1,3-dipoles,[25/84] and supposing to start from a *Z*-nitrone (= *anti* form, corresponding to the most stable configuration for aldonitrones), an *exo* transition state, sterically favored, should yield a 3,4-*cis*-isoxazolidine **361**. An *endo* transition state, favored by mutual orientation of dipolar moments, should furnish a 3,4-*trans*-isoxazolidine **362**. Both the *endo* and (in special cases) the *exo* attacks have been determined to be favored by secondary orbital interactions.

For an aldonitrone having the *E* configuration (*syn* form), the opposite result should be obtained. Of course, the possibility of $Z \rightarrow E$ isomerization prior to cyclization could affect the outcome. It is particularly important to realize that the viability of *E*/*Z* isomerization (even for nitrones for which only one form is

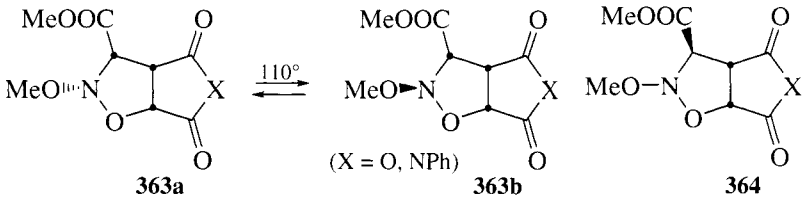


actually detectable by spectroscopic techniques) overshadows the link between *endo/exo* geometry of the transition state and 3,4-*cis/trans* relationship in the final products. In fact, it has been argued that even the major epimer in the reaction of an acyclic nitrone can derive from the "undetectable" *E* form. In short, the claim that the stereochemistry of the final adduct of an acyclic nitrone demonstrates an *endo* (or *exo*) disposition in the transition state leading to it should be considered with much reservation.

With *C,N*-diarylnitrones, where the *Z* configuration is assured and less prone to isomerization, especially under mild experimental conditions, mixtures of the two epimeric isoxazolidines **361** and **362**, have been obtained and are readily identified by NMR spectroscopy.[22/69,22/73] The *trans* isomer **361** has been reported to be more or less predominant.[23/69,14/72,19/83,32/86,23/89] Assuming that only the *Z* form is reactive, moderate substituent effects appear to support the assumption that the *endo* transition state of the reaction is favored by a better dipole orientation and by π–π interaction between the two N-aryl groups.[14/72] In another case a prevalence of the *cis* isomer has, however, been claimed.[76/84] Catalysis by $AlCl_3$ decreases the reactivity and slightly increases the amount of *cis* isomer[32/86], whereas use of $GaCl_3$ as catalyst provokes a huge increase in reactivity[20/83]. Kinetic evaluation of the cycloaddition has been carried out.[14/78,19/79] It is also interesting to note that the *cis*-isoxazolidines are converted to the thermodynamically stable *trans* isomers by heating in boiling *p*-xylene.[19/83,32/86].

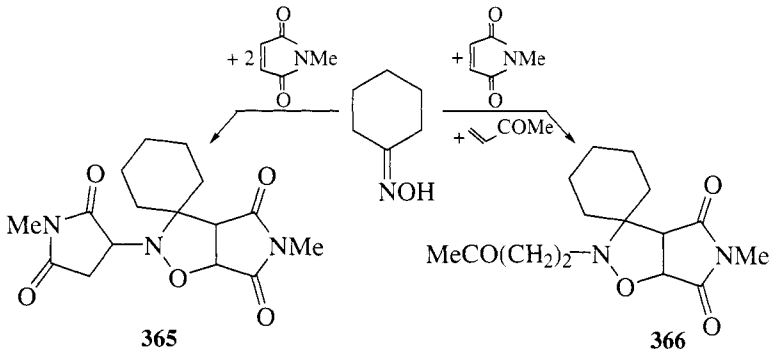
Almost equimolecular mixtures of the two epimeric isoxazolidines have been reported for the cycloadditions of *C*-methoxycarbonyl-*N*-methylnitrone, where the *E* and *Z* forms are both present in fast equilibrium.[17/90] With *C*-carbamoyl[35/66,20/79] or *C*-benzoyl,[22/73] as well as with *C*-alkyl-*N*-aryl nitrones,[18/66,22/70,21/79] a single cycloadduct is usually obtained, sometimes identified as the *trans* isomer.

Owing to the possibility of starting from the two geometric isomers, unconvertible under reaction conditions, nitronic esters are particularly valuable 1,3-dipoles. Their cycloadditions to maleic anhydride or *N*-phenylmaleimide, believed to be under HOMO(dipole)–LUMO(dipolarophile) control,[6/75] are completely diasteroselective, and likely pass through an *endo* transition state that is favored by secondary orbital interactions. Thus, the more reactive *Z*-nitronic ester yields the single invertomer **363a**, which at high temperature equilibrates with **363b**. The *E*-nitronic ester likewise gives the single adduct **364**, stable on heating.[19/71,15/72,13/75,22/76]



363a **363b** **364**

A tandem Michael addition—1,3-dipolar cycloaddition allows the transformation of aldo- or ketooximes directly into *N*-substituted condensed isoxazolidines. Thus, cyclohexanone oxime can react with *N*-methylmaleimide, acting both as Michael acceptor and dipolarophile, to give **365**, or with a mixture of *N*-methylmaleimide and another Michael acceptor to give **366**:[20/91]

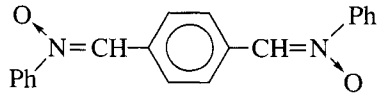


365 **366**

The *N*-substituted nitrone is a logical intermediate of the reaction. Similar results have been achieved starting from oxime *O*-allyl ethers, which are converted by Pd(II) catalysis, to the isomeric *N*-allyl nitrones. This latter inter-

mediate promptly cycloadds *N*-methylmaleimide to furnish the corresponding condensed isoxazolidine.[21/91] Several other examples of *N*-alkylation/cycloaddition are known.[26/84] Starting from 1,2,3-tricarbonyl-2-monoximes the *N*-unsusbtituted isoxazolidine is achieved.[27/84]

The obtention of polymeric material, possibly of a structure such as **368**, has been described, using **367** or the isomeric *meta*-bisnitrone or glyoxal-bis(*N*-phenyl) nitrone as dipole and *m*- or *p*-phenylene-bismaleimide as dipolarophile.[21/65,22/67,18/68]



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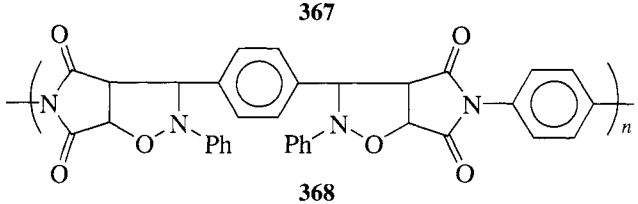
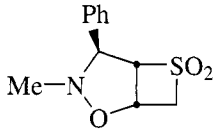


368

Other unsaturated heterocyclic rings are active as dipolarophiles in cycloaddition reactions with acyclic nitrones. Thus, thiete-1,1-dioxide reacts with *C*-phenyl-*N*-methyl nitrone, furnishing the sole cycloadduct **369** regiospecifically and with complete stereoselectivity.[17/82] The cycloaddition of nitrones to 2,3-dihydrofuran[23/67] or to 2,3-dihydrothiophene,[21/83] is also regiospecific, although in the latter case a mixture of the two epimeric cycloadducts **370** is obtained.[28/82] No regiochemical problem arises with 3,4-dihydrofuran (or thiophene) and derivatives, but mixtures of epimeric cycloadducts **371** are obtained with a 100% π-facial *anti* selectivity, the results are summarized below:[28/82,21/83]



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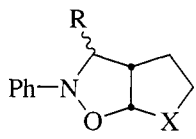

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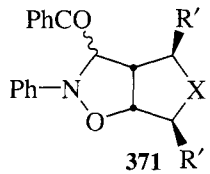


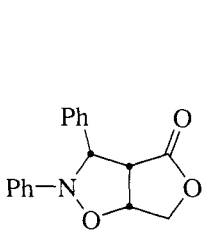
371

X	R	*trans : cis*
O	Ph	22 : 78
O	COPh	52 : 48
S	COPh	76 : 23

X	R	*trans : cis*
O	H	44 : 56
O	OAc	70 : 30
O	OMe	54 : 46
S	H	34 : 66

The lack of reaction of dihydropyran[23/67] exemplifies the lower reactivity of nitrones in comparison with nitrile oxides, which yield the corresponding condensed 2-isoxazolines (see § 4.2.2.1).

Regiospecificity is observed in the 1,3-dipolar cycloadditions of *C,N*-diarylnitrones to 2(5*H*)furanone, which leads stereoselectively to the single *cis*-monoadduct **372**, indicating an *exo* approach of the *Z*-1,3-dipole to the dipolarophile.[26/81] Analogous results have been reported from the cycloaddition to a pyrrolinone[50/90] and to the chiral 5-menthyl-2(5*H*)furanone.[15/88,51/90] A chiral substituent on the nitrone carbon atom induces diastereofacial selectivity; cycloaddition of the appropriate nitrone to vinylene carbonate furnishes a mixture of diastereomeric isoxazolidines **373** and **374**, as both have 3,4-*trans* relationship, involving, according to the authors, an *endo* transition state of the *Z*-nitrone, favored possibly by developing anomeric stabilization.[75/84,22/91]



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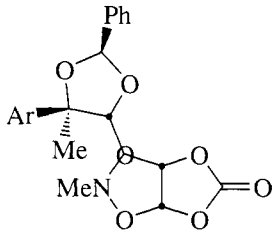

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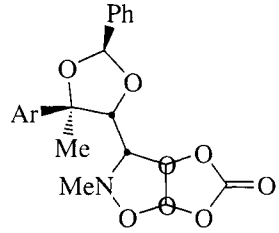


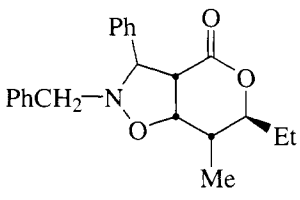
374

Alternatively, the slight prevalence of the *trans* isomer in the cycloaddition of *C*-methoxycarbonyl-*N*-methylnitrone to vinylene carbonate has been attributed to an *exo* transition state from the nitrone *E* form.[17/90]

Whereas cycloaddition of *C,N*-diphenylnitrone to vinylene carbonate under thermal conditions yields a 1 : 1 mixture of *trans/cis* monoadducts, use of high pressure has been reported to shift the stereoselectivity toward the *trans* isomer, giving a >2 : 1 ratio but not improving the reaction yields.[29/82]

Other pentaatomic heterocyclic systems reactive toward nitrones are some 4-isoxazolines prepared *in situ*,[24/69,28/84] some 1,3-oxazolin-2-ones,[25/74] as well as 1-ethoxyphosphindole.[24/89] Regiospecificity has always been observed, and the latter two cases proceed with complete stereoselectivity.

Six-membered heterocycles are also reactive, provided the endocyclic double bond is suitably activated, for instance by a carbonyl group. Thus, cycloaddition



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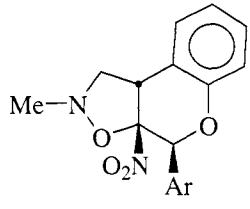
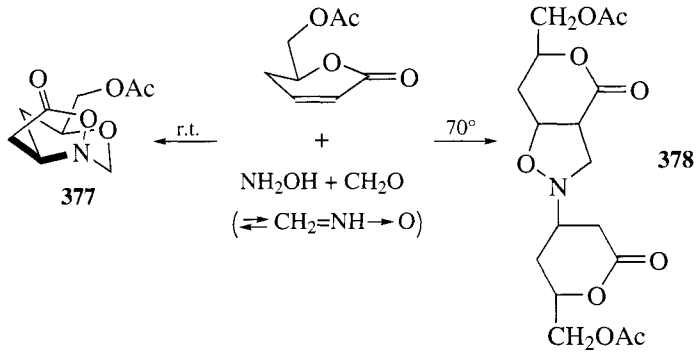


376

of 6-ethyl-5-methyl-5,6-dihydro-2*H*-pyran-2-one to *C*-phenyl-*N*-benzylnitrone takes place regiospecifically and stereoselectively *syn* to the allylic methyl group, leading to a mixture of the two epimeric monoadducts **375**.[20/85]

[1]Benzopyrano[4,3-*d*]isoxazoles of structure **376** are reported to arise regiospecifically from the cycloaddition of *N*-methylnitrone to 3-nitroflavenes.[32/88]

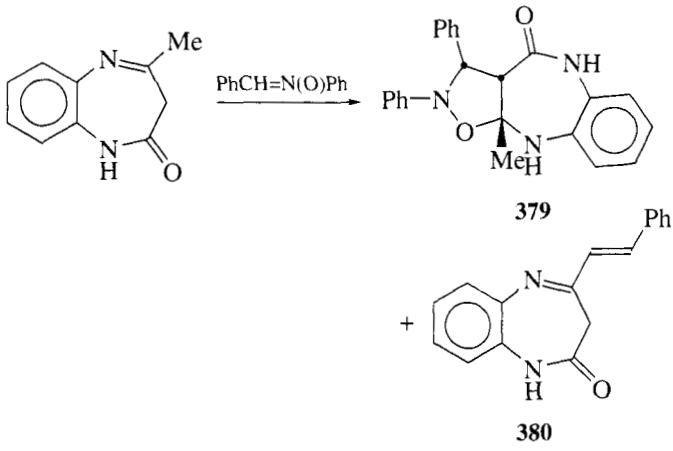
An interesting competition between Michael addition and 1,3-dipolar cycloaddition has been observed in the reaction of unsaturated pyranose derivatives with a mixture of formaldehyde and hydroxylamine. The formation, at room temperature, of isoxazolidinone **377** is presumed to arise from an initial Michael addition of hydroxylamine, followed by ring opening. Subsequent cyclization to a five-membered ring intermediate is then followed by cyclization with formaldehyde. Conducting the reaction at higher temperature suppresses the Michael addition and favors a 1,3-dipolar cycloaddition involving the nitrone tautomer of formaldoxime. The resulting bisadduct **378** is obtained as a mixture of two diastereomeric racemates. The 4-acetoxyderivative reacts via cycloaddition, giving the expected monocycloadduct.[25/89]



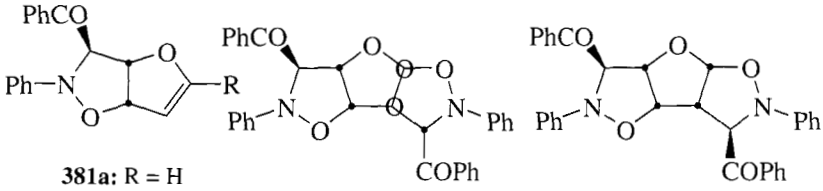
Cycloaddition of *C,N*-disubstituted nitrones to α,β-unsaturated sugar carbonyl compounds at high temperature exclusively furnishes the isoxazolidine adduct in which the carbonyl group is α to the 4-position of the isoxazolidine. The pronounced stereoselectivity results in the formation of isomers in which the protons at the 3 and 4 positions are in a *cis* relationship.

Heterocycles with larger rings can also undergo 1,3-dipolar cycloaddition with nitrones. Thus, *N*-carboxy-1*H*-azepine and 1*H*-1,2-diazepine add to *C,N*-diphenylnitrone in a regiospecific manner, at the 4,5-double bond, to give a mixture of the two epimeric monocycloadducts.[23/91] Catalysis with boron trifluoride etherate promotes the regio- and stereospecific reaction of 4-methyl-1,3-dihydro-1,5-benzodiazepin-2-one with diphenylnitrone, leading to the cycloadduct **379** along with the styrylderivative **380**.[24/91]

The macrolide elaiophylin has been reported to react with nitrones to give biscycloadducts in a regio- and stereoselective manner.[52/90]



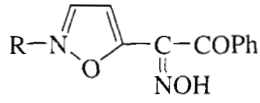
Five-membered heteroaromatic rings can act as dipolarophiles in cycloadditions with activated nitrones. While *C,N*-diphenylnitrone is reported to be unreative toward furan,[24/80] *C*-aroyl-*N*-phenylnitrone reacts with an excess of furan in an autoclave to yield a complex mixture of products, among which the monocycloadduct **381a** and both diasteromeric bisadducts **382** and **383** could be isolated in moderate yields.[24/80] In line with the assumption of a governing LUMO(nitrone)–HOMO(furan) interaction,[27/81] 2-alkylfuran and other monosubstituted furans are more reactive: with a large excess of dipolarophile only the monocycloadduct **381b** could be isolated, accompanied under suitable conditions by the bisadduct and sometimes by small amounts of the product **384** of 1,3-addition.[22/79,25/80]



381a: R = H
b: R = Me,Et,CH_2OH, CH_2OAc,CH_2SH

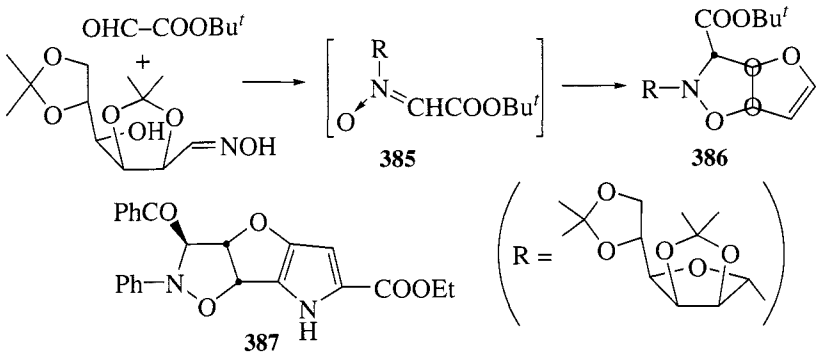
382

383



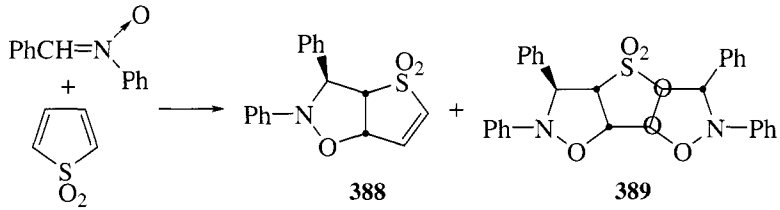
384

Preparation of bicyclic isoxazolidine **386**, by *in situ* generation of nitrone **385** and the use of furan as solvent, is the first step of a total synthesis of nojirimycin.[30/82]



C-benzoyl-*N*-phenylnitrone reacts with benzofuran and 5-ethoxycarbonyl-4*H*-furo[3,2-*b*]pyrrole. In the case of the latter, *endo* attack of the *Z*-nitrone on the furan endocyclic double bond gives **387** exclusively.[23/79,28/81] Similar results are also obtained with *C*,*N*-diphenylnitrone.[28/81]

Thiophene S,S-dioxide reacts regio- and stereospecifically, yielding the monocycloadduct **388** and, with excess nitrone, the bisadduct **389**; an *endo* transition state has been suggested as the preferred mode in this instance as well.[20/81,10/86]



The reactivity of benzothiophene *S*-oxide and *S*,*S*-dioxide has also been studied. In the latter case the same regio- and stereochemistry observed with thiophene *S*,*S*-dioxide has been ascertained.[19/74,29/84] The *S*-oxides generally follow the identical pathway, except for the 2-methylderivative, which leads to a preponderance of the cycloadduct having a regiochemistry opposite that of cycloadducts obtained from the *S*,*S*-dioxide.

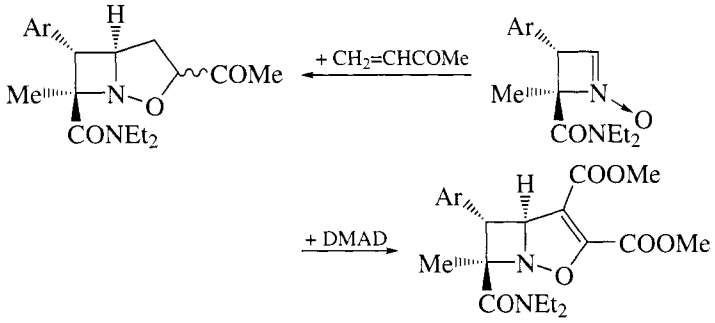
The reaction of *C*-benzoyl-*N*-phenylnitrone with indole and its *N*-alkylderivatives is more complex.[22/83]

Highly strained cyclic acetylenes are reactive dipolarophiles whose cycloadducts offer a route toward condensed 4-isoxazolines. Generation of benzyne in the presence of *C*-aryl-*N*-methyl (or *N*-phenyl) nitrones gives the corresponding 2,3-dihydro-benz[*b*]isoxazoles.[14/61,25/69] 1,4-Benzodiyne, generated *in situ* by treatment of 1,5-diaminobenzo[1,2-*b*: 4,5-*d'*]bistriazole with lead tetraacetate reacts to give the biscycloadduct regiospecifically.[30/84,33/86]

4.2.2.5. *Cycloaddition of Cyclic Nitrones to Unsaturated Compounds*

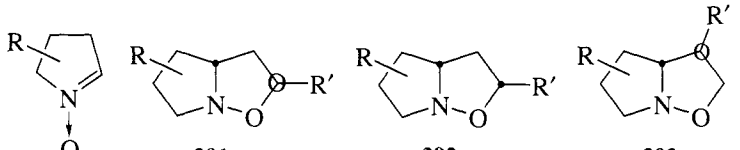
The cycloaddition reactions of cyclic nitrones have been thoroughly studied. Since this class of dipoles exists in a fixed configuration, the *E* structure, the complications associated with a configurational equilibrium are avoided. Five- and six-membered cyclic nitrones have generally been utilized for such studies, because of their ready availability through oxidation of cyclic secondary amines.

Nevertheless, some examples of heavily encumbered four-membered cyclic nitrones are known to participate in cycloadditions with activated alkenes and alkynes to afford the expected bicyclic adducts.[33/88]



Approach of the dipolarophiles to the cyclic nitrone occurs from the sterically less hindered face, resulting in a highly regio- and stereoselective process. Reaction with monosubstituted dipolarophiles usually yields a single regioisomer, in which the resulting substituent occupies the 5 position of the isoxazoline ring. An exception to this trend occurs in the case of methyl propynoate, which gives, as a minor product, the 4-substituted regioisomer.

Cycloaddition reactions of 1-pyrroline-1-oxide (**390**) and its derivatives to monosubstituted alkenes are well known,[4/60,5/60,6/60] due, in large part, to the utility of the cycloadducts as intermediates in the synthesis of alkaloids (see this volume, §4.3.3, and Part 1, §3.4.10.1, pp. 754–760). As outlined in Table 4.8, where some examples of this type of cycloaddition reaction are collected, the reaction is usually regiospecific when nonconjugated, electron-rich olefins are



390 **391** **392** **393** (+ *cis* isomer)

TABLE 4.8. CYCLOADDITION OF CYCLIC NITRONES **390** TO MONOSUBSTITUTED ALKENES

R	R′	Experimental conditions	Cycloadduct	Total yield(%)	References
H	n-C_3H_7	110°C, sealed tube	**391**	72	24/79
	n-C_5H_{11}		**391**	87	34/86
	OEt	60°C, CH_2Cl_2	**391** + **392** (92:8)	70	74/88
		50°C, 2000 atm	**391**		29/82
	CH_2OH	98°C	**391** + **392** (76:24)	79	74/88
	CH_2OAc	110°C, toluene	**391** + **392** (88:12)	78	74/88
	$CH_2OSiBu^tMe_2$	90°C, toluene	**391**+ **392** (92:8)	61	74/88
	COOMe	25°C, $CHCl_3$	**391**+**392**+**393**+ **393cis**(43:37:11:9)	89	74/88
	COOEt	100°C	**393**	59	23/83
	CN	25°C, CH_2Cl_2	**391**+**392**+**393**+ **393cis**(49:24:21:6)	83	74/88
	CHO	25°C, CH_2Cl_2	**391**+**392**+**393**+ **393cis**(5:62:8:25)	58	74/88
	CH_2COOMe	110°C, toluene	**391**+ **392** (50:50)	96	15/78
	CH_2CN	110°C, toluene	**391**	81	25/79
	Ph	110°C	**391**	73, 59	23/83; 15/78, 25/79
		110°C, toluene	**391**+**392**+**393** (91:8:1)	81	74/88
	3,4-$(MeO)_2C_6H_3$	110°C, toluene	**391**+ **392** (71:29)	93, 88	24/83, 31/84
	2-MeO,6-MeC_6H_3	95°C, toluene	**391**	85	26/79
	$CH_2C_6H_4OMe$(p)	110°C, toluene	**391**	70	25/83, 29/85
	CH=CHPh	r.t., 10 days	**391**+ **392** (81:19)	50	16/78, 35/86
		110°C, toluene	**391**+ **392** (57:43)	91	35/86
	CH=CHCH(OH)Ph	80°C, benzene	**391**	70	58/84, 28/85
	CH_2CH_2Ph	110°C, toluene	**391**	73	35/86
5,5-Me_2	CN	r.t., 24 h	**391** (or **392**)	100	14/63
	CH_2OH	100°C, 12 h	**391** (or **392**)	84	14/63
	$CH(OEt)_2$	100°C, 24 h	**391** (or **392**)	59	14/63
	COOEt	r.t., 24 h	**391** (or **392**)	100	6/60, 14/63
		100°C, 4 days	**393**	98	14/63
	$CONH_2$	35°C, 2 days	**391** (or **392**)	89	19/66
	$CONHBu^t$	30°C, 2 days	**391** (or **392**)	86	19/66
	PPh_2	r.t., benzene, 6 days	**392** + **393** (86:14)	62	26/89
	P(=O)Ph_2	r.t., $CHCl_3$, 7 days	**391** + **393** (86:14)	90	27/89
		110°C, 1 day	**391** + **392** + **393** (45:13:42)		74/90
	$PO(OEt)_2$	r.t., $CHCl_3$	**391** + **393** (72:28)	84	74/90
		110°C, toluene	**391** + **393** (28:72)	75	74/90
	$Ph_3P^+Br^-$	r.t., $CHCl_3$	**391**	63	74/90
4,5,5-Me_3	SO_2F	80°C, benzene	**393**	67	44/87
	SO_2NEt_2	80°C, benzene	**393**	62	44/87
5-COOMe	COOMe	r.t., $CHCl_3$	**391** + **392** + **393**[a]	92.5	26/83, 59/84
5-n-Pr	$CH_2CH(OH)Pr$	110°C, toluene	**391**[b]	61	28/89
5-CH=CH_2	Ph	70°C	**391**[c]	42	30/85
5-$CH_2CHOHAm$	Et	110°C, toluene	**392**	66	34/86
5-$CH_2CHOHCH_2CO_2Me$	COOMe	80°C, benzene	**391** + **392**	77	15/78, 25/79
5-$CH_2CHOHCHCN$	COOMe	80°C, benzene	**391** + **392**	100	25/79

[a] Not separated.
[b] Two epimers (1:1).
[c] 6-H *trans* to 3a-*H*.

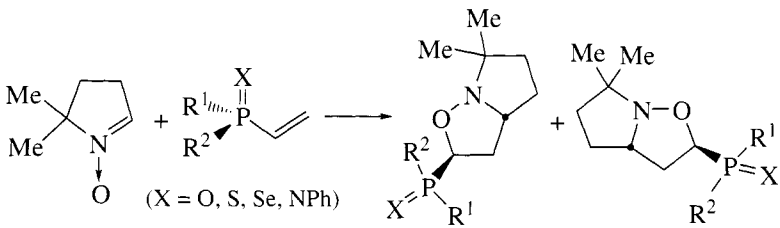
employed. The 2-substituted hexahydropyrrolo[1,2-*b*]isoxazole **391** is obtained, with exclusive or preponderant formation of the 2,3a-*trans* isomer, at least under kinetic control, suggesting a preference for the *exo* transition state over the *endo*. Higher reaction temperatures favor production of an equilibrium mixture of the two stereoisomers **391/392**. In agreement with predictions based on frontier orbital considerations, electron-poor olefins, such as methyl (or ethyl) acrylate,[14/63,23/83,74/88] acrylonitrile,[74/88] and acraldehyde,[74/88] show a tendency to yield the 3-substituted hydrogenated pyrroloisoxazole, usually as minor product. A mixture of all four possible stereo- and regioisomers has been isolated, where the stereoisomers proceeding from the *endo* mode of attack are notably abundant and even, in the case of acrylaldehyde, largely predominant.[74/88]

Complete reversal of regiochemistry occurs in the case of some ethenesulfonic acid derivatives,[44/87] whereas in the case of diethyl vinylphosphonate the influence of the reaction temperature suggests the involvement of a cycloreversion/cycloaddition process.[74/90]

Kinetic measurements have revealed that the reactivity of dipolarophiles toward 1-pyrroline-1-oxide sharply decreases along the following series: ethyl acrylate > ethyl vinyl ether > 1-hexene.[36/86]

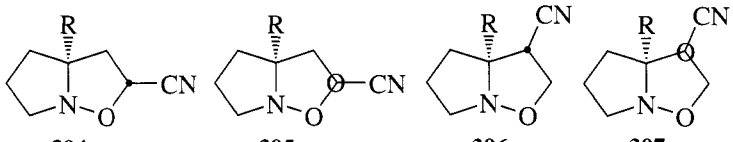
In the reaction of pyrroline-1-oxide with methyl 2-phenyl-3-butenoate, the nitrone partially catalyzes isomerization of the dipolarophile to the 2-butenoate and a mixture of the 2-monosubstituted pyrroloisoxazolidine and the two regioisomeric trisubstituted cycloadducts results. Complete migration of the double bond prior to cycloaddition occurs when the 4,4-dichlorobutenoate derivative is used as dipolarophile.[31/85]

Impressive levels of diastereofacial selectivity, in some cases in excess of 90:10, have been observed in the cycloaddition of 5,5-dimethyl-1-pyrroline-1-oxide to chiral (or prochiral) vinylphosphine derivatives, where the phosphorous substituents are chosen for their steric differentiation.[25/91]



X	R^1	R^2	isomer ratio
O	Me	Ph	71 : 29
NPh	Me	Ph	76 : 24
S or Se	Me	Ph	80 : 20
O	Me	Mes	90 : 10
S	$CH{=}CH_2$	*t*.Bu	96 : 6

2-Substituted 1-pyrroline-1-oxides react with acrylonitrile to yield a mixture of the four possible regio- and stereoisomers **394–397**. The structures of the products reveal that the process leading to the 5-substituted (isoxazolidine numbering) cycloadduct prefers an *exo* transition state, whereas the 4-substituted isomer arises from an *endo* transition state, likely dictated by the steric effect of the nitrone 2-substituent.[29/89]

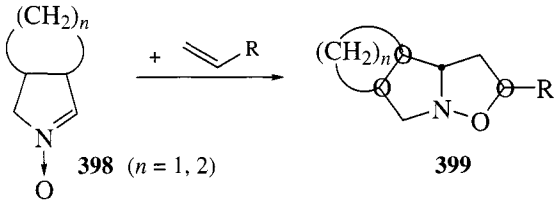


394 **395** **396** **397**

R	**394:395:396:397**	total yield %
Me	56 : 16 : 5 : 23	91
$CH_2CH_2CO_2Me$	50 : 15 : 5 : 30	85

Somewhat different results have been reported for the cycloaddition of acrylonitrile with 2,5,5-trimethyl-1-pyrroline-1-oxide. Under conditions that favor kinetic control, only the 5-substituted cycloadduct is obtained while at higher temperature, equilibration between the two regioisomers can occur, shifting the product distribution toward the 4-substituted isomer. Cycloaddition of 2,5,5-trimethyl-1-pyrroline-1-oxide with methyl acrylate afforded a mixture of all four possible regio- and stereoisomers.[60/84] Similar results are described for 2,4,4-trimethyl-1-pyrroline-1-oxide.[23/76]

Facial selectivity, and regiospecificity, are observed when bicyclic nitrones, such as **398**, undergo 1,3-dipolar cycloaddition with monosubstituted alkenes. In these instances, products arising from addition to the α-face (**399**) tend to predominate.[20/87,45/87]

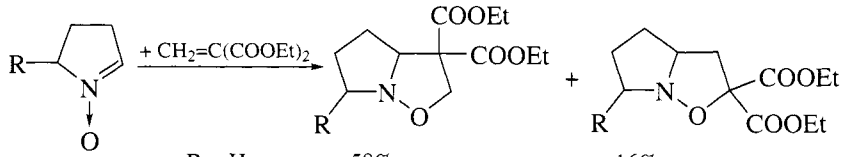


398 (n = 1, 2) **399**

1,1-Disubstituted olefins, such as methylenecyclobutane[37/86] or methylenecyclopropanes,[33/90] react with pyrroline oxides to give primarily the 5,5-spirobicyclic isoxazolidines. Cycloaddition of 2,3-diaryl-1,3-butadienes with 1-pyrroline-1-oxide gives a 2 : 1 *exo* : *endo* (with respect to the arylvinyl moiety) mixture of the two isomeric 5,5-disubstituted monocycloadducts.[26/80] α-

Methylstyrene reacts regiospecifically but with virtually no stereoselection. Formation of the cycloadduct arising from an *endo* (with respect to the group of higher priority) transition state is observed in the cases of α-methylallylic alcohol and its derivatives, stereoselectivity is higher with methyl methacrylate and methacrylaldehyde.[74/88]

The presence of two electron-withdrawing groups on the double bond, as in diethyl methylenemalonate, shifts the cycloaddition toward the formation of the 4,4-disubstituted bicyclic isoxazolidine:[59/84,74/88]

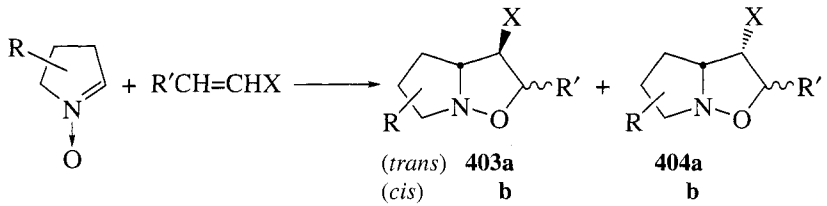


R = H : 58% 16%
R = COOMe : 63% 28%

Analogous results have been reported when α-bromoethenesulfonic acid derivatives are used as dipolarophiles.[44/87]

Cycloaddition of 1-pyrroline-1-oxide to several 1,2-disubstituted alkenes, having at least one electron-withdrawing substituent, proceeds regiospecifically. The electron-withdrawing substituent always ends up in the 4 position of the isoxazolidine ring in the bicyclic cycloadduct, as illustrated in Table 4.9. When both substituents are electron-withdrawing, a mixture of two regioisomers can arise, as when diphenyl (α-phenylsulfonyl)vinylphosphine oxide is used as dipolarophile.[74/90] Frequently a mixture of the two stereoisomeric cycloadducts is obtained, especially when the configuration of the starting olefin is *trans*. The predominant product derives from an *endo* (relative to the electron-withdrawing group X) transition state, leading to a 3,4-*cis* substituted isoxazolidine of type **404**. On the contrary, *cis* olefins show a tendency to favor an *exo* transition state, in some cases even leading to an exclusive formation of the *exo* adduct.[21/87,17/90,74/90] A remarkable exception is provided by maleonitrile, where a dipole–dipole interaction has been proposed as *endo*-favoring factor.[17/90] Other factors suggested to control the stereoselectivity of the cycloaddition are steric factors and secondary orbital interactions. The latter are usually considered to favor *endo* attack. However, it has also been claimed, on the basis of MO calculations, that secondary orbital interactions as a whole slightly destabilize the *endo* transition state.[17/90] However, special caution should be exerted in evaluating the experimental results, owing to the possibility of thermodynamic equilibration of the educts through cycloreversion processes[17/90] or base catalysis.[21/87] Kinetic measurements have confirmed the higher reactivity of the *trans* isomer in the case of fumarates and maleates,[30/89] but have revealed an interesting inverted reactivity scale for the *E/Z* isomers of β-nitrostyrene.[21/87]

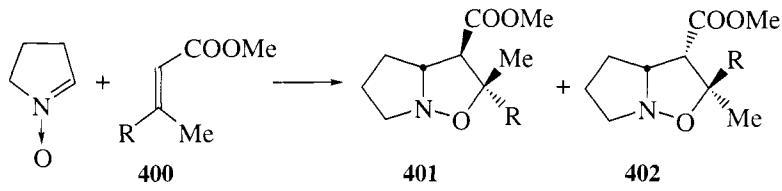
TABLE 4.9. CYCLOADDITION OF CYCLIC NITRONES **390** TO 1,2-DISUBSTITUTED ALKENES



R	R′	(O)[a]	X	Conditions	Cycloadduct	Total yield %	References
H	Me	(T)	COOMe	$CHCl_3$, 25°C, 24 h	n.d.	87	14/75
				CH_2Cl_2, 40°C	**403a+404a** (7:93)	72	30/89
	CH_2OH	(T)	COOMe	CH_2Cl_2, r.t., 36 h	**403a+404a** (15:85)	95	30/89
				$CHCl_3$	**403a** or **404a**	80	20/71, 14/75
				$CHCl_3$	**403a+404a**	62	14/75
		(C)		CH_2Cl_2,50°C, 4 h	**403b+404b** (83:17)	88	30/89
				Benzene, 20°C	**403a+404a** (85:15)		17/90
	COOEt	(T)	COOEt	$CHCl_3$	**403a+404a** (1:2)	90	14/75, 38/86
		(C)		$CHCl_3$, 25°C	**403b+404b** (1:2)	24	14/75
	CN	(C)	CN	Benzene, 20°C	**403b+404b** (23:77)		17/90
				MeCN, 20°C	**403b+404b** (39:61)		17/90
	$(CH_2)_2$ OTHP	(T)	COPr	Toluene, 110°C	**403a+404a** (2:3)	91	31/82, 32/82
		(C)		Toluene, 110°C	**403b+404b**	90	32/82
	Ph	(T)	COOMe	Benzene, 80°C	**403a+404a** (8:92)	73	30/89
	COPh	(C)	COPh	Benzene, 20°C	**403b+404b** (70:30)		17/90
	SO_2Ph	(C)	SO_2Ph	Benzene, 20°C	**403b**		17/90
	3-Furyl CH=CH	(T)	COOMe	Benzene, 80°C	**403a+404a**	73	22/87
5,5-Me_2	Me	(T)	NO_2	Benzene, r.t.	**403a+404a** (6.5:93.5)	93	21/87
	Me	(T)	$P(O)Ph_2$	Toluene, 110°C	**403a+404a** (43:57)	80	74/90
	Me	(C)	$P(S)Ph_2$	$CHCl_3$, 60°C	**403b**	86	74/90
	Me	(C)	$P(O)Ph_2$	Benzene, 80°C	**403b**	70	74/90
	COOMe	(C)	COOMe	Benzene, 20°C	**404b**		17/90
	CN	(C)	CN	Benzene, 20°C	**403b+404b** (52:48)		17/90
				MeCN, 20°C	**403b+404b** (63:37)		17/90
	Ph	(T)	NO_2	C_6D_6, 33°C, 9 h	**404a**	50	21/87
		(C)		Benzene, 33°C, 24 h	**403b**	90	21/87
	COPh	(C)	COPh	Benzene, 20°C	**403b**		17/90
	SPh	(T)	$P(O)Ph_2$	Toluene, 110°C	**403a+404a** (62:38)	37	74/90
	SO_2Ph	(C)	SO_2Ph	Benzene, 20°C	**403b**		17/90
3,3-$(OMe)_2$	CH_2OH	(T)	COOMe	$CHCl_3$, 45°C	**403a+404a**	86	27/79, 27/80
4,4,5-Me_3	$[CH(OAc)_2]$ $CHMeCH_2OAc$	(T)	COOMe	Benzene, 80°C	**404a**	80	26/91

[a] Orientation: T = *trans*; C = *cis*.

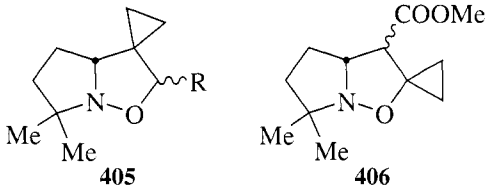
1,3-Dipolar cycloaddition of 1-pyrroline-1-oxide to trisubstituted alkenes of type **400** is regiospecific, leading to the fused isoxazolidine having the ester group in the 4 position.



400 **401** **402**

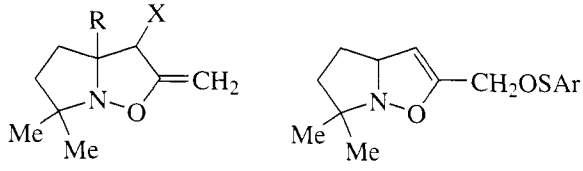
The degree of stereoselectivity depends on the nature of the R group in **400**. When dimethyl mesaconate (R = COOMe) is employed adduct **401** is obtained as the sole product but with methyl 3,3-dimethylacrylate (R = Me) **401** and **402** are formed in equal proportions. Stereoselection in favor of the *endo* adduct is reported for dimethyl citraconate and citraconic anhydride. The expected reversal of regiochemistry has been observed with dimethyl ethoxymethylenemalonate. All the above results have been rationalized in terms of frontier orbital and steric effects.[18/90] Some degree of stereoselection has been reported also with methyl 3,3-dimethylacrylate in its cycloaddition to the 5,5-dimethylderivative of the cyclic nitrone.[17/78]

The use of methylenecyclopropanes substituted on the exocyclic double bond gives exclusively the 4-spirocyclopropane isoxazolidines **405** when the substituent is an aryl or an alkyl group, and 5-spirocyclopropane isoxazolidines **406** when the substituent is an electron-withdrawing group, such as methoxycarbonyl.[34/88]



405 **406**

Electron-deficient allenes are activated toward cycloaddition with cyclic nitrones and react regiospecifically to produce 5-exomethylene substituted

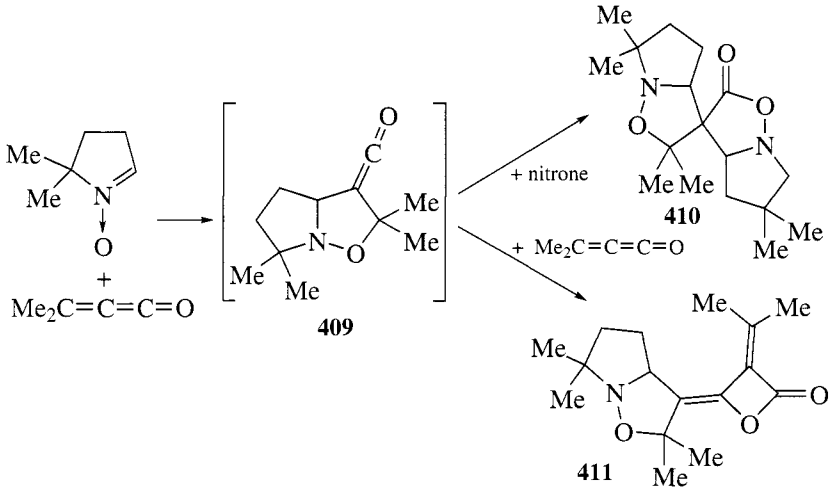


407 **408**

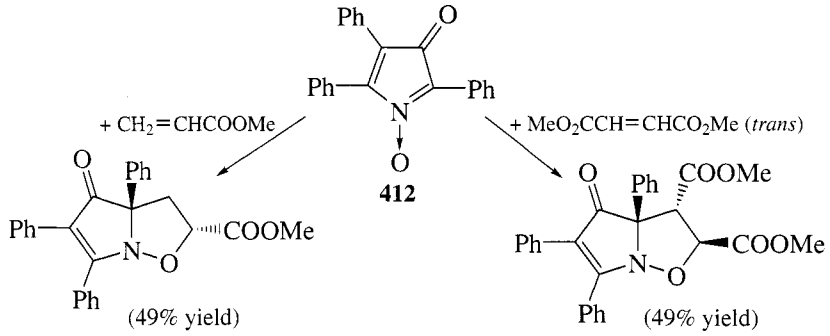
(R = H, Me; X = CN, COOMe) (Ar = 2,4-$(NO_2)_2C_6H_3$)

isoxazolidines. Substituted 1-pyrroline-1-oxides, when treated with methoxycarbonyl or cyano substituted allenes, produce monoadducts of type **407**.[46/87] The use of (nitroaryl)sulfinyl-substituted allenes $CH_2=C=CHS(O)Ar$ as dipolarophiles directly yields condensed 4-isoxazolines such as **408**, the products of formal cycloaddition to propargylic alcohols.[27/91]

Isopropylideneketene reacts with 5,5-dimethyl-1-pyrroline-1-oxide to yield the nonisolable monoadduct **409**, which is further transformed into **410** or **411**, depending on which reagent is used in excess.[17/78]

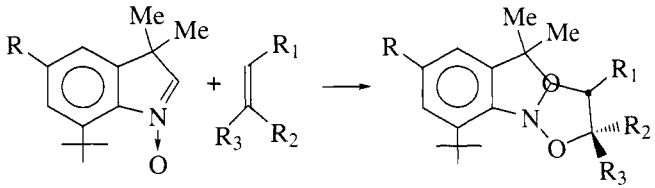


1-Pyrroline-1-oxides are not the only five-membered cyclic nitrones capable of participating in 1,3-dipolar cycloadditions; the acyl nitrone 2-phenylisatogen[9/62,20/69,28/79] and its monocyclic analogue (2,4,5-triphenyl-3*H*-pyrrol-3-one 1-oxide),[24/76,28/79] although less reactive than their acyclic counterparts, such as *C*-benzoyl-*N*-alkyl (or aryl) nitrones, cycloadd mono- and disubstituted activated olefins. As illustrated in the following example, the reaction seems to be regiospecific and highly stereoselective:[24/76]



Replacement of one or two phenyl groups of **412** with alkyl groups results in a destabilization of the compound, which is partially converted to a dimer.[32/84]

Cycloaddition of 2*H*-pyrrole-1-oxides with monosubstituted olefins leads to a mixture of regio- and stereoisomeric cycloadducts.[28/80] The sterically encumbered 3*H*-indole 1-oxides **413** react regiospecifically with activated olefins to give *exo* (with respect to the eventual 4-substituent) adducts. Although cycloadducts **414a** (R = H) are stable, those for which R = *t*-Bu (**414b**) are unstable under the reaction conditions and rearranged products are isolated.[33/82,32/85]



413 (**a**: R = H; **b**: R = Bu^t) **414**

R	R_1	R_2	R_3	% Yield
H	COOMe	H	COOMe	90
Bu^t	COOMe	H	COOMe	74
H	COOMe	COOMe	H	85
Bu^t	COOMe	COOMe	H	56
H	CN	H	CN	79

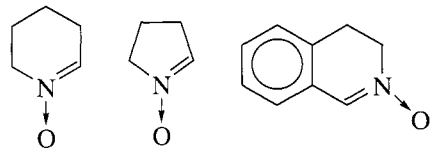
With tetracyanoethylene, isomerization of the cyclic nitrone occurs to give predominant formation of the lactam, along with minor amounts of products probably derived from the unstable cycloadduct.[18/78] The cycloaddition reaction has been also carried out on thin-layer chromatography plates.[27/83]

Frequently used nitrones derived from six-membered rings include 2,3,4,5-tetrahydropyridine-1-oxide (**415**), of value as starting material in the synthesis of piperidine alkaloids, and 3,4-dihydroisoquinoline *N*-oxide (**417**), because of its suitability for mechanistic studies. Both nitrones are prepared by oxidation of the cyclic secondary amine or its *N*-hydroxyderivative, and have been utilized as isolated reagents or by generation *in situ*. Although the 1,3-dipolar nature of these cyclic nitrones is well documented,[4/60,20/66,17/68,19/68,22/68,26/68,22/69] detailed study of the regio- and stereoselectivities of the cycloaddition process is relatively more recent.

Six-membered cyclic nitrones are known to be more reactive dipoles than the five-membered analogues, which, in turn, are far more reactive than the acyclic nitrones, with the exception of *C*-benzoyl-*N*-phenyl nitrone. Thus, for example, the following nitrones undergo cycloaddition with ethyl crotonate in toluene at 100°C with the nearby reported relative reactivities (k_{rel}):[26/69]

C-*n*-propyl-*N*-cyclohexyl nitrone	1.0
C,*N*-diphenyl nitrone	5.7
C-benzoyl-*N*-phenyl nitrone	642
2-phenyl-1-pyrroline-1-oxide	2.1
1-pyrroline-1-oxide	166
3,4-dihydroisoquinoline N-oxide	248

According to Sustmann's classification,[21/71,26/74] and as already illustrated in Part 1 (§ 3.3.1.1, p. 687), nitrones are type II dipoles, and therefore both HOMO–LUMO interactions are important in controlling reactivity and regiochemistry. Cyclic nitrones react better with electron-poor than with electron-rich alkenes, as the following rate constants ($10^5 k_2$/l mol^{-1} s^{-1}) for the cycloadditions of nitrones **415** and **416** to several dipolarophiles at 36°C in deuterochloroform show:[36/86,35/88,30/89]

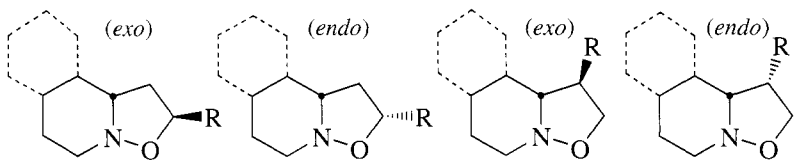


415 **416** **417**

Dimethyl fumarate	3370	178
Dimethyl maleate	207	13.8
Methyl acrylate	340	62
Methyl crotonate	22.4	1.85
Ethyl vinyl ether	8.10	0.295
1-Hexene	—	0.193 (at 46°C)

The lower reactivity of the five-membered nitrone in comparison to the six-membered counterpart has been attributed to the greater eclipsing strain introduced in the transition state.[36/86] As a consequence of the concertedness of the process, the rate of cycloaddition is not significantly influenced by solvent polarity. Interestingly enough, the general rule, stating that *E*-alkenes are always more reactive than *Z*-alkenes in 1,3-dipolar cycloadditions, suffers some exceptions with cyclic nitrones. Thus, both (*Z*)-*β*-nitrostyrene[21/87] and (*Z*)-stilbene[36/88] react with **417** faster than do their (*E*)-counterparts, owing possibly to the formation of secondary repulsive interactions in the transition states of these latter cycloadditions.

Although often highly regio- and stereoselective, cycloaddition of **415** and **417** to monosubstituted alkenes CH_2=CHR can a priori lead to four possible regio- and stereoisomeric cycloadducts **418**–**421**.



5-*trans* 5-*cis* 4-*trans* 4-*cis*

418 **419** **420** **421**

TABLE 4.10. CYCLOADDITION OF SIX-MEMBERED CYCLIC NITRONES TO MONOSUBSTITUTED ALKENES

R	Experimental conditions	**418:419:420:421** ratio[a]	Total yield (%)	References
		a. 3,4,5,6-Tetrahydropyridine-1-oxide (**415**)		
Me	Toluene, 110°C	100 : 0 : 0 : 0	53	19/78, 29/79, 37/88
n-Pr	$CHCl_3$, 35°C	98 : 2 : 0 : 0	65	29/81
n-Bu	CH_2Cl_2, 40°C	100 : 0 : 0 : 0	67.5	36/86, 53/90
n-Am	$CHCl_3$, 62°C	100 : 0 : 0 : 0	94	73/88, 29/91
$(CH_2)_2C_6H_3OCH_2Ph$	$CHCl_3$, 62°C	100 : 0 : 0 : 0	81	30/91
CH_2OH	Toluene, 80°C	83 : 17 : 0 : 0	84	37/88
CH_2O(THP)	Toluene, 110°C	100 : 0 : 0 : 0	66	23/83
CN	CH_2Cl_2, 25°C	61 : 20 : 13 : 6	92	35/88, 37/88
COOMe	CH_2Cl_2, 0°C	69 : 15 : 10 : 6[b]	96	19/78, 29/79, 35/88, 37/88
CHO	CH_2Cl_2, 25°C	3 : 5 : 24 : 68	96	37/88
OEt	CH_2Cl_2, 40°C	93 : 7 : 0 : 0	67	35/88, 37/88, 36/86
OBu^n	water, 100°C; 90°C	100 : 0 : 0 : 0	64; 69; 54	23/83, 61/84, 23/87, 19/90
OBu^i		100 : 0 : 0 : 0	30	70/88
$P(O)Ph_2$	CH_2Cl_2, 40°C	50 : 26 : 12 : 12	93	74/90
Ph	CHCl, 62°C	98 : 5 : 0 : 0[c]	>95	47/87, 31/89, 53/90
$(MeO)_2C_6H_3$	Toluene, 110°C	95 : 5 : 0 : 0	93	30/81, 31/84
		b. 3,4-Dihydroisoquinoline-2-oxide (**417**)		
NO_2	Benzene, r.t.	0 : 0 : 60 : 40	84	21/87
CH_2OH	65–80°C	100 : 0	75	17/68
CN		20 : 80		20/77
COOMe	Benzene, 20°C	24 : 13 : 12 : 51		66/82
OBu^n	Water, 90°C	100 : 0	77	19/90
$P(O)Ph_2$	$CHCl_3$, r.t.	53 : 33 : 11 : 0	83	74/90
Ph	95°C; 110°C	100 : 0 : 0 : 0	82; 55	26/68, 23/83

[a] A binary ratio corresponds to **418** + **419**/**420** + **421**.

[b] The obtention of pure **420** (ethyl ester) is reported under different conditions (100°C, 73% yield).[23/83]

[c] Different proportions have been reported in refs. 35/88 and 37/88.

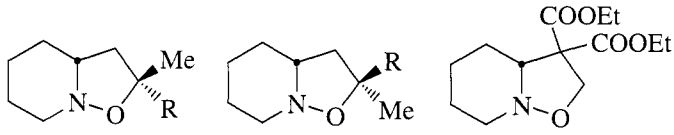
In some cases the composition of the reaction mixture is often difficult to evaluate, and the possibility of a cycloreversion process, obscuring the results of the kinetically controlled process, should always be kept in mind. Indeed, cycloreversion appears to be particularly facile for isoxazolidines prepared from cyclic nitrones and dipolarophiles carrying electron-attracting conjugating substituents.[36/88] Table 4.10 reports some examples of cycloadditions of **415** and **417** to monosubstituted alkenes.

In accordance with frontier orbital (FO) treatment, the regioisomer bearing the substituent in the 5-position of the isoxazolidine ring is obtained exclusively or almost exclusively with electron-rich alkenes. Electron-attracting substituents on the double bond promote the formation of increasing amounts of the regioisomer with the substituent in the 4 position, which even becomes the predominant product when acrylaldehyde is employed as dipolarophile. Insofar as the stereocontrol is concerned, a significant preference for the *exo* approach in the transition state, leading to the *trans* isomer **418**, has

been observed, suggesting a strong influence of steric factors on the cycloaddition process.

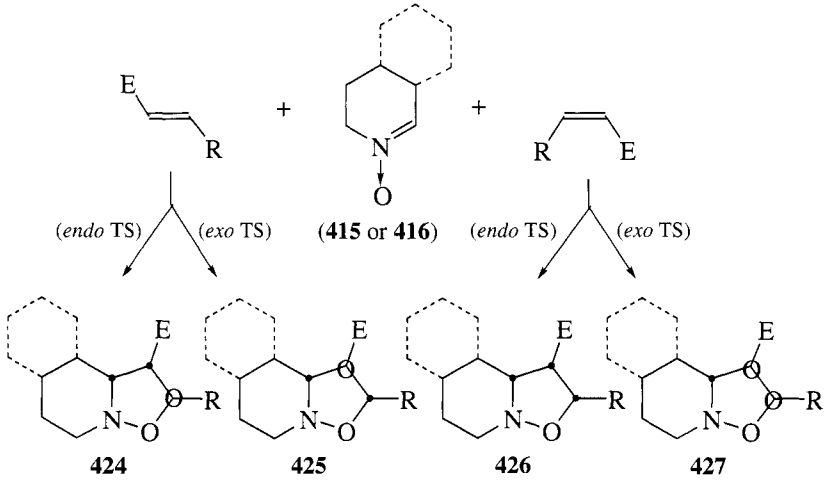
The use of several opticaly active vinyl ethers as dipolarophiles in the cycloaddition to **415** revealed moderate to high [> 95% enantiomeric excess(ee)] degrees of chiral induction and represents a useful route to optically pure piperidine derivatives.[28/91]

Reaction of cyclic nitrones with 1,1-disubstituted alkenes of type CH_2=CHRMe is regiospecific and stereoselective, leading to a mixture of disubstituted condensed isoxazolidines **422**. Exclusive formation of isomer **422a** is noted when R = CHO, and isomers of this type predominate when R is an electron-attracting group. This selectivity progressively diminishes until reaching a practically unselective cycloaddition when R = Ph.[37/88] An analogous regiospecificity is observed when isobutene,[39/86,39/88] 1,1-diphenylethylene[19/68] or 1,1-diethoxyethylene[19/68] are used as dipolarophiles. Conversely, an opposite regiochemical preference was found with diethyl methylenemalonate, which cycloadds **415** to yield **423** only.[29/79]



422a **422b** **423**

1,2-Disubstituted alkenes, having at least one electron-attracting substituent (alkoxycarbonyl, nitro, cyano, sulfonyl), are active dipolarophiles, and react with six-membered cyclic nitrones regiospecifically and stereoselectively. As illustrated by the selected examples reported in Table 4.11, the electron-attracting group almost always resides at the 4 position of the isoxazolidine



424 **425** **426** **427**

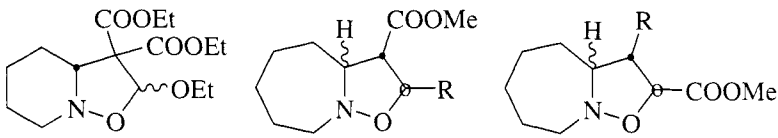
TABLE 4.11. CYCLOADDITION OF SIX-MEMBERED CYCLIC NITRONES TO 1,2-DISUBSTITUTED ALKENES R–CH=CH–E[a]

R	E	424:425 ratio	Total yield(%)	References	426:427 ratio	Total yield(%)	References
			a. 3,4,5,6-Tetrahydropyridine 1-oxide (**415**)				
Me	COOMe	90:10	94	35/88, 37/88, 30/89			
Me	COOEt	0:100	56; 85	23/83, 23/87			
CH_2OH	COOMe	77:23	88	30/89			
Ph	COOMe	87:13	79	37/88, 30/89			
Me	CHO	100:0	87	37/88			
Ph	CHO	100:0	82	37/88			
COOMe	COOMe	60:40	89	35/88, 37/88, 30/89	16:84	93	37/88, 30/89
			b. 3,4-Dihydroisoquinoline 2-oxide (**417**)				
NO_2	Ph	K 85:15 T 13:87		21/87	K 0:100	≥ 75	21/87
CN	CN	K 50:50 T 20:80		36/88	K 60:40 T 15:85		36/88
COOMe	COOMe	K 77:23 T 7:93	77	36/88	K 52:48 T 0:100	80	36/88
COPh	COPh	K 50:50 T 0:100		36/88	K 25:75 T ≤ 2:≥ 98		36/88
SO_2Ph	SO_2Ph	K 0:100 T 0:100	100	36/88	K 17:83 T 0:100		36/88
Ph	Ph	K 0:100 T 0:100	30	36/88	K ≤ 5:>95 T 0:100	8	36/88

[a] Key: E = electron-withdrawing substituent; K = under kinetic control (r.t., ~ 35°C); T = under thermodynamic control (80°C, or even r.t. after several days).

cycloadduct and with *trans*-alkenes the predominant stereoisomer is usually the one resulting from an *endo* attack (with respect to the electron-withdrawing substituent). The observation that *cis*-alkenes prefer an *exo* process suggests that steric repulsion counteracts the stabilizing effects of secondary orbital overlap and is a more important factor in the control of *exo/endo* selectivity.[36/88] In a study on the cycloaddition–cycloreversion process of **417**, equilibrating conditions (heating in boiling benzene or standing at r.t. for several days) were found to afford the thermodynamically more stable 3,4-*trans* isomers **425** and **427** (isoxazolidine numbering) as the predominant products.[36/88]

Cycloadditions that employ trisubstituted alkenes have also been studied.[22/68,18/90] The reaction of **415** with diethyl ethoxymalonate is regiospecific yet yields a mixture of diastereoisomers **428**.[18/90]



428 **429** (R = Me, Ph) **430**

1-Substituted butadienes[16/78,28/83,33/84] also react regio- and site-specifically. Methyl sorbate yields a complex mixture of mono- and dicycloadducts.[32/89] Several substituted tetrahydropyridine-1-oxides (e.g., 2-alkyl-,[23/89,20/90,53/90] 4-alkyl-,[29/81] 6-alkyl-,[29/80,30/80,40/86,34/89,20/90] 6-vinyl,[30/85,33/89] 3-oxo-,[35/88] 3,3-dimethoxy-,[35/88] and polysubstituted[54/89] derivatives) have been used as 1,3-dipoles, without sensibly diverging from the results obtained with the unsubstituted term. Substitution at the 2 position retards the reactivity of the 1,3-dipole; therefore, it is not surprising that in a mixture of 2- and 6-butyl-3,4,5,6-tetrahydropyridine-1-oxides only the latter nitrone has been found reactive toward 1-pentene.[29/81] Diminished reactivity has also been noted in reactions of 3-oxo-tetrahydropyridine-1-oxide.[35/88]

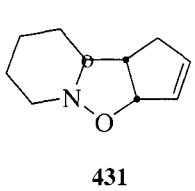
A systematic study of the 1,3-dipolar cycloaddition of 3,4,5,6-tetrahydro-2*H*-azepine-1-oxide to a series of di-and trisubstituted alkenes has been conducted. The absence of regiospecificity has been observed in reactions with methyl crotonate and methyl cinnamate; along with the two diastereomeric adducts **429**, increasing amounts of **430** are isolated.[77/90] Other examples of seven-membered cyclic nitrones as participants in cycloaddition reactions have been noted.[23/83,38/86,25/87,32/91] The (*E*,*Z*)-1-azacyclodeca-1,6-diene-1-oxide generated in situ can either undergo intramolecular cycloaddition (see § 4.2.2.6) or be trapped intermolecularly by styrene.[43/85]

Heteroaromatic *N*-oxides are feeble 1,3-dipoles and only 3,5-lutidine-*N*-oxide[47/83,63/87] and phenanthridine-*N*-oxide[15/63,27/69] are known to react with *N*-substituted maleimides or methyl acrylate, respectively. However, the corresponding cycloadducts are unstable and isomerize to cyclic or acyclic products. Although quinoline *N*-oxide[23/89] generally gives only charge-transfer complexes with dipolarophiles, it, and some substituted pyridine *N*-oxides, have been reported to enter cycloaddition with the activated double bond of 1,4-epoxy-1,4-dihydronaphthalene.[14/64,21/90]

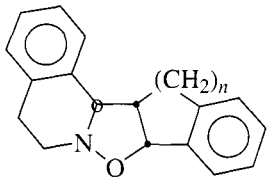
Similarly, while isoquinoline *N*-oxide is reported to give cycloadducts with methyl acrylate[15/63] and 3,4-dimethylthiophene-1,1-dioxide,[51/74] it yields only zwitterionic adducts from its reactions with methyl propriolate or other acetylenic esters.[27/69] Both quinoxaline *N*-monoxide and *N*,*N*′-dioxide are reported to enter cycloaddition with active dipolarophiles, such as dimethyl maleate, *N*-phenylmaleimide, and dimethyl acetylenedicarboxylate.[27/74] It is presumed that pentachloropyridine *N*-oxide enters cycloaddition with cyclic enamines, but ring opening and rearrangement of the hypothetical cycloadduct lead only to substitution products.[31/79]

Cycloaddition of five- and six-membered cyclic nitrones to cycloalkenes represents an easy method for synthesizing polycyclic isoxazolidines. Cyclopentene,[20/69] cyclohexene,[15/71,5/60] bicyclo[4.2.0]oct-7-ene,[15/71] and acenaphthylene[17/90] give tricyclic or tetracyclic derivatives. Cycloalkenones, as well as tricarbonyltroponeiron and cyclopentenone ketal, react with 3,4-dihydroisoquinoline *N*-oxide in a regiospecific manner.[32/79] Whereas cyclohept-2-enone ketal yields a mixture of two regioisomeric cycloadducts, free tropone or 8-aryl-8-azaheptafulvenes do not react at all.[32/79] Cyclopentadiene reacts with tetrahydropyridine *N*-oxide at r.t. to give the monoadduct **431** regio- and stereospecifically; at 110°C a mixture of two regioisomeric bis-adducts is

formed.[54/90] Cycloaddition of indene with dihydroisoquinoline *N*-oxide occurs regio- and stereoselectively.[19/68] The major products of this reaction, regioisomers **432a** and **433a**, which are presumed to arise from an *exo* transition state, are formed along with traces of the two corresponding epimers (from an *endo* transition state).[13/76] 3,4-Dihydronaphthalene reacts similarly, yet affords only the products of an opposite regiochemistry, the 3,4-*trans* stereoisomers **432b** and **433b**.[13/76]



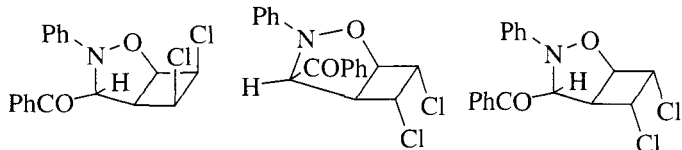
431



432 **a:** (n = 1): 56 : 36 (4 : 4) **433**
b: (n = 2): 8 : 92

The results of a study of *syn-anti* isomerism in the 1,3-dipolar cycloaddition of cyclic and acyclic nitrones to *cis*-3,4-disubstituted cyclobutenes parallel those obtained with nitrile oxides (see § 4.2.2.1) and with other 1,3-dipoles. Thus, high *syn*-selectivity, which even reaches 100% in the case of the 3,4-dihydroxyderivatives, has been observed when dichloro-, dimethoxy-, diacetoxy-, and dimesyloxycyclobutenes are employed, whereas in the case of dimethoxycarbonyl or of a cyclic disubstitution, even with heteroatoms, the *anti* cycloadduct is always obtained as the predominant or exclusive product. The stereochemical junction with cyclic (and probably with acyclic) nitrones invariably originates from an *exo* approach of the two reactants.[15/75,8/76,33/79,40/88,71/90,3/91]

The obtention of three isomeric cycloadducts (**434**–**436**) from the reaction between *C*-benzoyl-*N*-phenylnitrone and 3,4-dichlorocyclobutene may be explained by steric factors (formation of the *anti* isomer **435** from the *trans* form of the nitrone) and by a *Z*–*E* isomerization of the starting nitrone prior to cycloaddition, leading to **434** and **436** (ref. 19/77, p. 491):

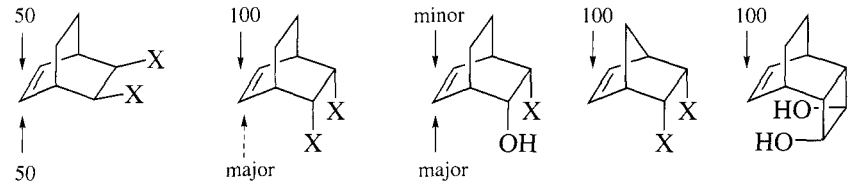


434 **435** **436**

Isomers ratio: 38 : 60 : 2

Norbornene,[7/60,17/68,20/69,15/71] norbornadiene,[17/68,17/79] polychloro-norbornadienes[17/79] easily react with cyclic nitrones without notable variations in comparison to the results obtained with acyclic nitrones (see § 4.2.2.4).

For the sake of comparison with the abnormal *syn*-selectivity of some 3,4-*cis*-disubstituted cyclobutenes, the cycloadditions of 3,4-dihydroisoquinoline-2-oxide (and of other nitrones) to some appropriate substrates, such as **437**–**441**, have been thoroughly studied.[60/87] Whereas practically no stereoselectivity is observed with the *exo*-disubstituted compound **437**, *endo*-disubstituted bicyclo[2.2.2]oct-2-enes **438** show complete *anti* stereoselectivity with all substituents, except the dihydroxyderivative, which gives a 93 : 7 mixture of *syn* : *anti* cycloadducts with increased reactivity. The *syn* selectivity is promoted by hydrogen bonding effects in the transition state, as confirmed by the high *syn* selectivity (80 : 20 for X = H, 72 : 28 for X = OMe) achieved with the monohydroxy derivative **439**. The major product is regiohomogeneous with the isoxazolidine oxygen atom facing the OH group, whereas the minor product (from the *anti* attack) is a mixture of the two regioisomers. By constrast, only *anti* cycloadducts are obtained from compounds **440** and **441**. Indeed, in **440** the norbornene skeleton imposes its *syn*-methano bridge selectivity, whereas in **441** the two OH groups sterically shield the *syn* face from cycloaddition.



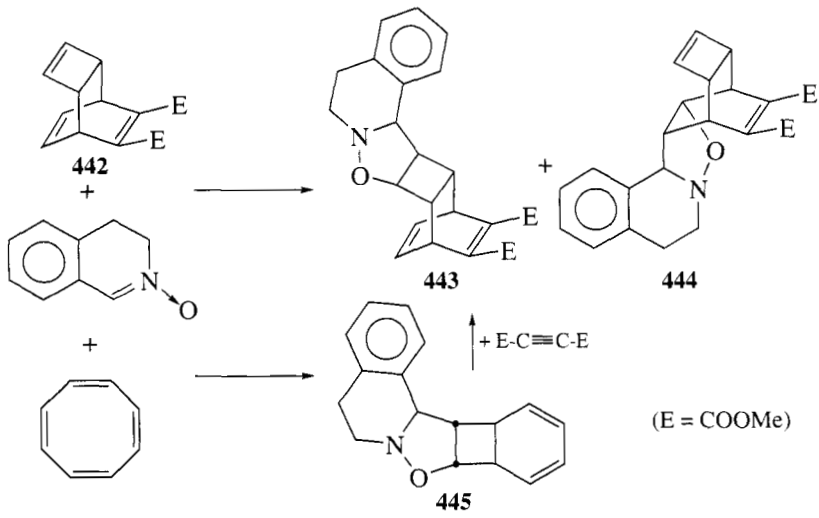
437 **438** **439** **440** **441**

(X = OH,Ac) ⟶ (X = CO_2Me,CH_2OH, OCOO,CN,OMe,OAc) (X = H,OMe) (X = OH,OAc)

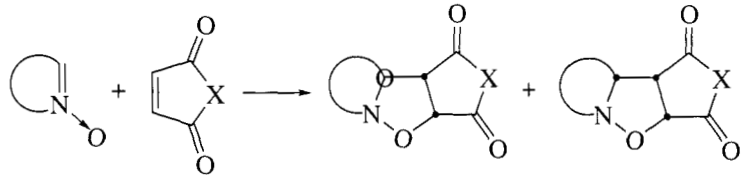
⇢ (X = OH)

Competition between different double bonds has been exhibited in polyunsaturated systems, such as dimethyl tricyclo[4.2.2.$0^{2,5}$]deca-3,7,9-triene-7,8-dicarboxylate (**442**); indeed, both the cyclobutene and the unsubstituted cyclohexadiene double bond enter cycloaddition with acyclic and cyclic nitrones to yield monocycloadducts, such as **443** and **444**. The former compound can also be synthesized through cycloaddition of the nitrone to cyclooctatetraene and subsequent Diels–Alder reaction of the cycloadduct **445** with dimethyl acetylenedicarboxylate.[27/72]

The cycloaddition of maleic anhydride and of *N*-aryl (or *N*-alkyl) maleimide to cyclic nitrones has been thoroughly studied. A mixture of the two possible stereoisomeric cycloadducts is usually obtained, where the isomer proceeding from an *exo* transition state predominates. This stereochemical result has been attributed to the dominance of steric factors over possible secondary orbital interactions in the transition states.[37/88]



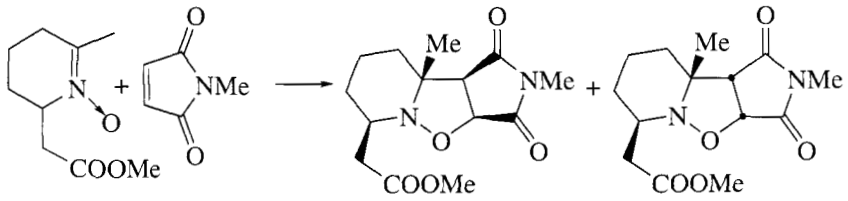
Thus, maleic anhydride reacts with pyrroline *N*-oxide,[30/89] tetrahydropyridine *N*-oxide,[37/88] and 3-oxotetrahydropyridine *N*-oxide[35/88] to yield **446**:**447** ratios of 63 : 37, 81 : 19, 70 : 30, respectively. Excellent yields of cycloadducts at room temperature are also reported for the reactions of *N*-methyl- or *N*-phenylmaleimide. The former compound reacts with 5,5-dimethyl-pyrroline-1-oxide and with 3,4-dihydroisoquinoline-2-oxide to yield **446** : **447** ratios of 86:14 and of 98 : 2, respectively; the latter compound gives with pyrroline-1-oxide, its 5,5-dimethylderivative and 6-*tert*-butyl-3,3-dimethyl-3*H*-indole-1-oxide **446** : **447** ratios of 55 : 45, 94 : 6,[17/90] and 73 : 27,[32/85] respectively. Substituted 2*H*-pyrrole-1-oxides also cycloadd *N*-phenylmaleimide to yield the 3,4-*trans* (isoxazolidine numbering) isomer only.[31/80]



With 2-methylpyrroline-1-oxide a mixture of the two stereoisomeric cycloadducts is reported, in which the product of an *endo* transition state seems to be predominant.[22/90]

The 2,6-disubstituted nitrone **448**, resulting from an intramolecular Michael addition of the suitable 5-alkenyl ketoxime, reacts at r.t. with *N*-methyl-

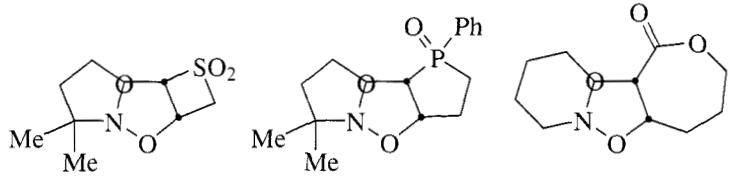
maleimide to give a 3:1 mixture of the isomeric cycloadducts **449** and **450** through a diastereofacially specific cycloaddition:[24/87]



448 **449** (100%) **450**

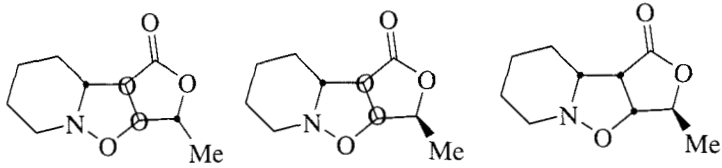
At higher temperature (110°C) only isomer **449** is formed, and the Michael addition and the cycloaddition can also be carried out in a one-pot procedure.

Several other heterocyclic dipolarophiles exhibit reactivity toward cyclic nitrones. Sometimes the cycloaddition is both regiospecific and completely stereoselective; thiete-1,1-oxide[17/82] yields **451**, phospholine oxide[74/90] affords **452**, hept-2-en-7-olide[55/90] gives **453**, 4*H*-pyran and 4-pyrone[29/83,54/90] yield monoadducts and/or bisadducts.



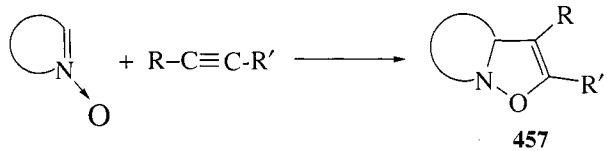
451 **452** **453**

Occasionally, the cycloaddition is regiospecific, but only stereoselective; the isomer derived from the *exo* approach is always more or less highly predominant. Thus, 2,3-dihydrofuran reacts with pyrroline-1-oxide to give a 97:3 mixture of *exo*:*endo* products,[60/79,62/82] and vinylene carbonate reacts with the same nitrone or its 5,5-dimethylderivative to yield a 74:26 or >95:<5 ratios, respectively, of *exo* : *endo* cycloadducts.[17/90] Although the stereochemistry has not been assigned to the regiospecific cycloadduct obtained from the unsubstituted butenolide,[14/75] the kinetically controlled reaction of tetrahydropyridine-1-oxide with 5-methyl-2(5*H*)-furanone leads to a mixture of the three isomeric cycloadducts **454**–**456** on the ratio 18.6:2.3:1.[32/89]



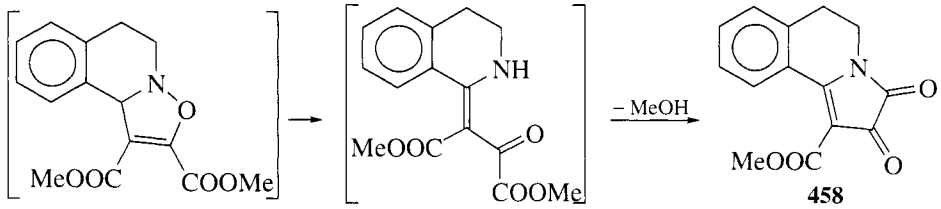
454 **455** **456**

Cyclic nitrones react with alkynes as well as alkenes, although the primary cycloadduct, a 2,3-fused ring 4-isoxazoline having structure **457**, is relatively unstable, and not always can be isolated.



457

Dimethyl acetylenedicarboxylate (DMAD) reacts with a variety of nitrones to give cycloadducts **457** (R = R′ = COOMe), in moderate to high yields. Participants in this reaction include four-membered,[34/82,30/83,48/87,41/88] five-membered,[21/66,22/66,23/76,31/83,71/85,49/87,29/89,36/89] six-membered,[41/86] and higher[35/89] cyclic nitrones. The stability of the cycloadduct seems to decrease with increasing ring dimension and complexity. In some cases the primary monoadduct spontaneously isomerizes and leads to other heterocyclic derivatives; thus, for example, 3,4-dihydroisoquinoline *N*-oxide reacts with DMAD to give **458** directly.[16/63,25/69]



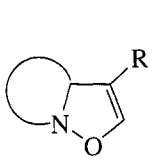
458

Other cycloaddition reactions of DMAD that lead to rearranged products are those carried out with 2,4,5-triphenyl-3*H*-pyrrol-3-one-1-oxide,[24/76,32/80] 3-bromo-4-methoxyquinoline-1-oxide,[32/83] 2,2-dimethyl-2*H*-pyrrol-1-oxide,[31/80] benzo[*c*]cinnoline-1-oxide,[23/73] and phenanthridine *N*-oxide.[22/66,36/67]

Another symmetrically disubstituted alkyne, dibenzoylacetylene, reacts in the same manner as DMAD, yielding either stable[31/81,34/85] or unstable[35/82] 4-isoxazolines.

Monosubstituted alkynes, such as phenylacetylene, cycloadd cyclic nitrones regiospecifically, yielding the 5-substituted (isoxazoline numbering) cycloadducts, which either are stable[34/84,42/88] or rearrange spontaneously.[16/75,20/78] Substitution with an electron-withdrawing group reverses the regiochemistry, leading predominantly to the 4-substituted isoxazolines **459**. This is the sole monoadduct when 3,4-dihydroisoquinoline-2-oxide and alkyl propiolate[16/63,25/69, 36/82] or cyanoacetylene[20/77] are employed, whereas a regioisomeric mixture is obtained when starting from four-membered cyclic nitrones and methyl propio-

late.[34/82] When phenylpropiolates or tetrolates are employed, products exhibiting the expected regiospecificity (the ester group in the isoxazoline 4 position) has always been obtained.[16/63,25/69,20/78,34/84,60/84]



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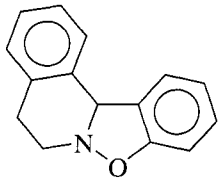


460

2-Arylisatogens are known to react with alkynes, such as phenylacetylene, its copper salt, or phenylpropiolic acid, to yield quinolone derivatives; the 4-isoxazoline has been proposed as primary intermediate in the reaction mechanism.[15/64,28/69] However, the cycloadduct from the same dipole and ethyl phenylpropiolate has been isolated.[25/69]

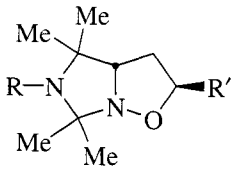
Cycloadducts arising from aromatic nitrones, such as pyridine *N*-oxides, are highly unstable, and have been hypothesized as intermediates in the reaction with benzyne[29/74] or with 5-thiacycloheptene.[34/79]

On the contrary, the stable cycloadduct **460** has been obtained from cycloaddition of 3,4-dihydroisoquinoline-2-oxide to benzyne.[14/61,25/69]

4.2.2.6. Cycloaddition of Heterocyclic Nitrones to Unsaturated Compounds

The reactivity of heterocyclic *N*-oxides often parallels that of the carbocyclic nitrones discussed previously, although the presence of a second heteroatom may influence both the reactivity and selectivity exhibited as a 1,3-dipole.

Several five-membered heterocyclic nitrones and nitronic esters are known to behave as 1,3-dipoles: 3-imidazoline-3-oxides react with monosubstituted alkenes to furnish cycloadducts (**461**) regio- and stereoselectively. When R = O', stable nitroxides are obtained in good yields.[35/85,43/88]



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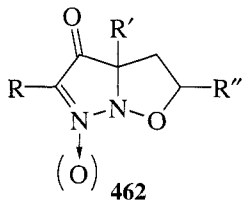

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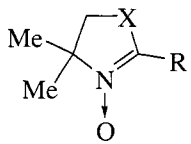
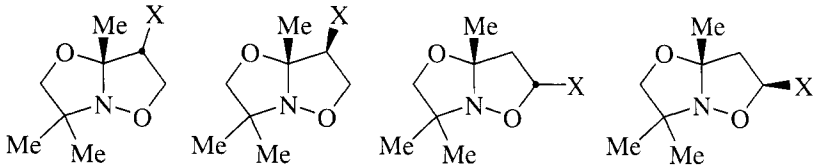


463 **a:** X = O
b: X = S
c: X = NMe

Owing to their structural similarity with isatogen, the 2,5-disubstituted 3,4-diazacyclopentadienone *N*-oxide and *N,N'*-dioxide have been thoroughly studied. Cycloaddition of these compounds with activated monosubstituted alkenes is regiospecific, and both electron-rich and electron-poor olefins afford cycloadducts having structure **462**. It is also noteworthy that with *N,N'*-dioxides having one aromatic and one aliphatic substituent, cycloadducts are obtained that result from reaction of the nitrone component bearing the aliphatic group (**462**, R' = alkyl).[22/71,28/79]

According to FMO theory, the presence of a heteroatom in the α position of the nitrone moiety, as in **463**, alters both the frontier orbital energy levels and coefficients and can influence the reactivity. For instance, the trisubstituted oxazoline *N*-oxides (**463a**) are about 160 times more reactive than the corresponding pyrroline *N*-oxides in competitive cycloadditions with dimethyl acetylene dicarboxylate. A slightly different regiochemical distribution has been observed with methyl acrylate and with acrylonitrile, which react under kinetic control with **463a** (R = Me) to yield a mixture of all four possible isomeric cycloadducts **464**–**467**, in which the 4-substituted (**464** and **465**) products dominate.[60/84]



464 **465** **466** **467**

X = COOMe, isomers ratio =38 : 15 : 12 : 35
X = CN, " " 56 : 19 : 7 : 18

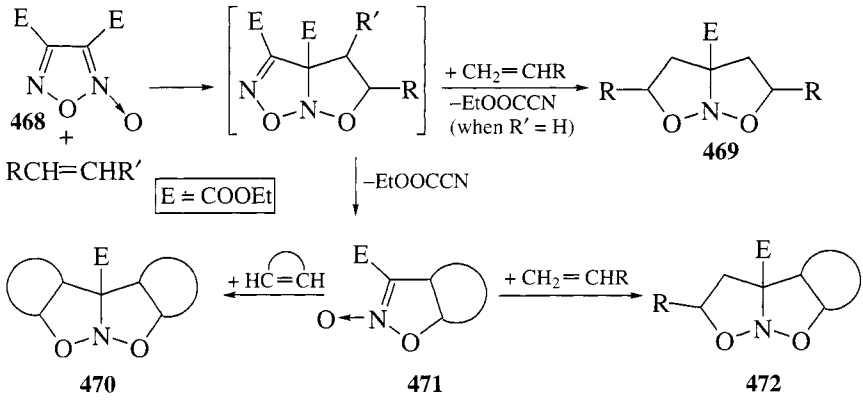
Although the reaction of maleic anhydride with **463a** (R = H) produces the *exo*-cycloadduct exclusively, methyl propiolate gives a rearranged product that is presumed to arise from rearrangement of a 4-substituted isoxazolidine intermediate[33/83]. Alternatively, cycloadducts derived from an *endo* transition state result when 2-substituted derivatives of **463a** (R = Me or Et) are treated with *N*-phenylmaleimide.[23/89]

Less frequently studied have been five-membered cyclic nitrones bearing other α-heteroatoms, as in **463b** and **463c**. The cycloaddition products obtained from benzothiazole *N*-oxides and dimethyl acetylenedicarboxylate are stable and isolable,[36/73] whereas those derived from benzyne or tetracyanoethylene give only rearrangement products.[23/70] The presumed primary cycloadducts from 1-methylbenzimidazole *N*-oxides and acetylenic compounds have never been isolated,[16/64,22/65,27/68] but several imidazolinone *N*-oxides have been reported to undergo cycloaddition with substituted alkenes.[62/84]

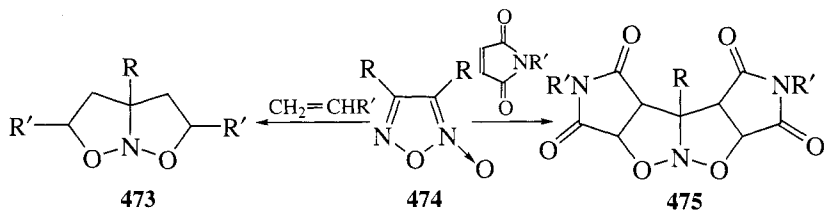
1,2,5-Oxadiazole-2-oxides (furoxans) react with dipolarophiles at high temperatures. Under conditions such as refluxing xylene, temperatures up to

260°C and flash-vacuum pyrolysis, symmetrically substituted furoxans decompose into two nitrile oxide molecules or rearrange intramolecularly to a substituted nitrile oxide. Reactions of this type enable the synthesis of isoxazoles or 2-isoxazolines and have been discussed in Part 1 (§ 2.2.2.2a, p. 481).

Furoxans may also be formally considered as cyclic masked bisnitrones, and do indeed behave as nitrones under suitable conditions. In one example of this behavior, readily available 3,4-bis(ethoxycarbonyl)furoxan (**468**) reacts, in refluxing xylene, with a large variety of monosubstituted or cyclic olefins to yield the corresponding 5-ethoxycarbonyl-2,8-dioxa-1-azabicyclo[3.3.0]octanes **469** or bis-condensed derivatives (**470**). Using cyclododecene as dipolarophile the intermediate monoadduct **471** can be isolated, thereby allowing the formation of asymmetrically substituted derivatives **472**.[34/83]

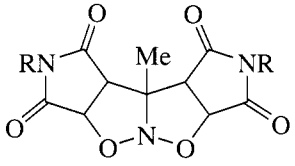


A variety of other symmetrically or unsymmetrically 3,4-disubstituted furoxans, bearing both electron-withdrawing and electron-releasing substituents participate in nitrone-like cycloadditions which have opened a convenient synthetic route to the so-called *isoxazolizidines*, namely, 2,8-dioxa-1-aza-bicyclo[3.3.0] octanes.[36/85] The nature of the substituents on furoxan ring and on the dipolarophile often determines the fate of the reaction. In only a limited number of cases have the intermediate 3-substituted 2-isoxazoline *N*-oxides been isolated when 3,4 symmetrically disubstituted (R = CN, SO_2Ph, RNHCO) furoxans (**474**) are treated with cycloalkenes (even norbornene). As a rule, the trisubstituted isoxazolizidines **473** are obtained when the furoxan is treated with mono-



substituted alkenes; derivatives of **475** result when maleimides are employed as dipolarophiles.

The reactions of 3,4-di-unsymmetrically substituted furoxans are more complex, as illustrated by 3-methyl-4-nitrofuroxan, which reacts with maleimide to yield 5-methylisoxazolizidines **476**. Other electron-rich olefins, such as norbornene, styrene, and 2-naphthyl vinyl ether, afford the 5-nitro derivatives **477**. The choice of solvent may also be important, as in the case of 3,4-dicyano furoxan, which, in refluxing toluene or xylene, participates in a nitrone-type cycloaddition, but rearranges to cyanogen *N*-oxide and ultimately gives a 2-isoxazoline when a dipolar protic solvent is added.



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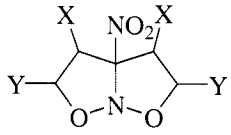
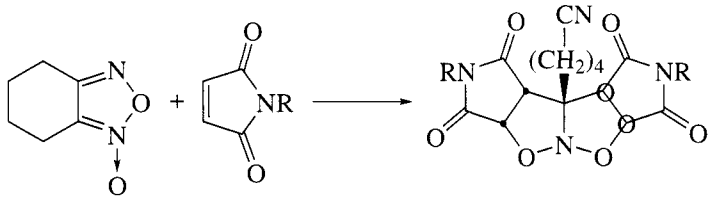


477

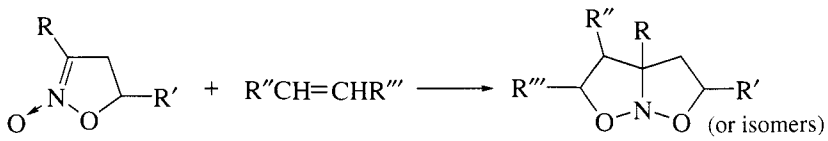
Often mixture of stereoisomers is produced that exhibits a preference for the product of *exo* attack. Diacyl- or disulfonyl-substituted furoxans have a strong tendency to behave as source of nitrile oxides, although dicarbamoyl furoxans behave differently.

Another furoxan system that exhibits nitrone-like behavior is the tetrahydrobenzo derivative **478**; its reaction with maleimides in refluxing toluene gives bisadduct **479** presumably through opening of the six-membered carbocyclic ring:[44/88]



478 **479**

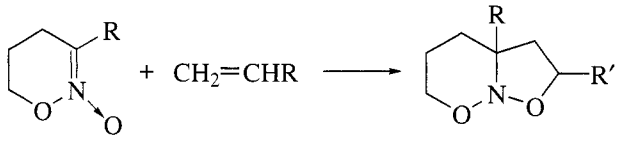
A convenient entry into the 2,8-dioxa-1-azabicyclo[3.3.0]octane system is offerred by nitrone-type cycloaddition of 2-isoxazoline *N*-oxides with a large variety of olefinic substrates, including those with electron-withdrawing and electron-donating substituents and even ethylene.



The requisite precursors are obtained by synthetic methods illustrated in Part 1 (§ 2.3.2, pp. 607–614), and can be formally considered as cyclic nitronic esters. Commonly-utilized derivatives include 3-nitro,[17/64,23/65,23/66,24/66,24/67,25/67,29/69,16/72,17/72,24/73,30/74] 3-ethoxycarbonyl,[30/69,31/74] 3-phenyl-,[30/69] and 3-methylisoxazoline *N*-oxides.[37/89] In order for ethylene to function as an efficient substrate, high pressures (20–30 atm) are required.[23/65,24/66] Rates and activation parameters of the cycloaddition have been determined.[26/67,28/68]

Monosubstituted alkenes react regiospecifically, such that the substituent group is always located at the 7 position of the dioxazabicyclo[3.3.0]octane system. Mixtures of stereoisomers are often encountered and 3-methyl-5-phenyl-2-isoxazoline *N*-oxide routinely gives a mixture of all four possible stereoisomers in which the product of the least sterically-hindered approach often predominates.[37/89]

Similarly, 1,3-dipolar cycloaddition of 3-substituted-5,6-dihydro-4*H*-1,2-oxazine *N*-oxides to alkenes affords derivatives of 2,9-dioxa-1-azabicyclo [4.3.0]nonane in which the product of *exo* approach results.[24/70, 25/70,25/73,32/74,17/75,25/76,21/77,21/78]

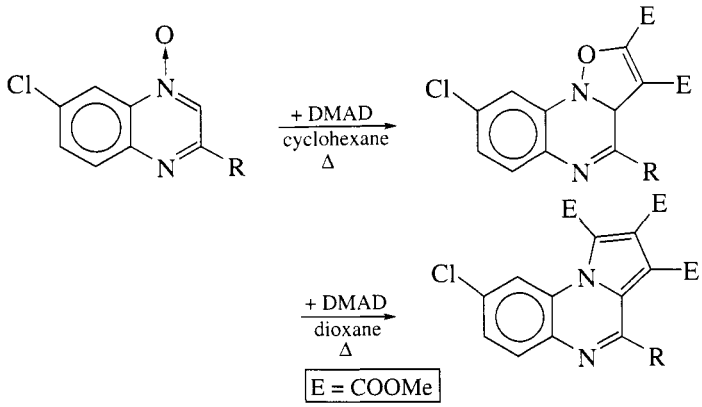


More complex substituted 1,2-oxazine *N*-oxides are often unstable, but can be trapped with acrylonitrile or, less easily, with ethyl vinyl ether.[45/88] Condensed oxazine *N*-oxides also exhibit high stereoselectivity in their cycloadditions.[15/85,19/87]

Reaction of 3-nitro-5,6-dihydro-4*H*-1,2-oxazine *N*-oxide with acetylenes gives rise to products that are presumed to arise from the ring opening of an unstable cycloadduct.[33/74,34/74]

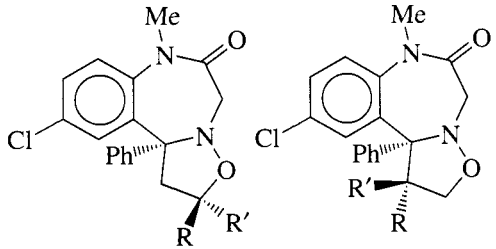
Other six-membered heterocyclic compounds in which a nitrone moiety has been embedded have been evaluated as 1,3-dipoles. Cycloadducts have been obtained from 2,3-dihydro-1,4-oxazine-4-oxide[29/68,38/86,25/87, 19/90,56/90] or its substituted derivatives,[18/75] 3-phenyl-2*H*-1,4-benzoxazine-4-oxide,[35/79] polysubstituted 1,2,5,6-tetrahydropyrimidine-3-oxides,[37/82] 3,6-dihydro-2(1*H*)-pyridazinone-4-oxides,[32/81] 3-ethoxycarbonyl-3,4-dihydro-β-carboline-2-oxides,[39/86,47/88] and 2-substituted 6-chloroquinoxaline-4-oxides. In the last case, 4-isoxazoline-derived cycloadducts from the reaction with dimethyl acetylenedicarboxylate (DMAD) could be isolated only from reactions that employed equimolar quantities of reactants; an excess of the dipolarophile drives the reaction toward formation of pyrrolo[1,2-*a*]quinoxalines.[38/89,57/90]

In other cases, especially when acetylenic compounds are involved, the formation of a primary cycloadduct is only presumed, and rearranged products are obtained.[18/72,36/79,33/81,35/83]



Although it has been reported that the α-dinitrone, hexamethyl-2,3-dihydropyrazine-1,4-dioxide, is unreactive as a 1,3-dipole, the product of its photo rearrangement, which has an oxaziridine–nitrone structure, reacts with acrylonitrile to give a mixture of regio- and stereo-isomeric monocycloadducts.[30/68]

Because of the pharmacological importance of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (diazepam), its 4-oxide has been the object of several studies intended to evaluate the dipolarophilicity of the cyclic nitrone moiety. Acrylic esters and crotonates[38/82,35/84] were shown to cycloadd easily in the absence of solvents; under conditions (70°C, excess alkene), that favored kinetic control, a mixture of the two regioisomers **480** and **481** was obtained.[58/89]

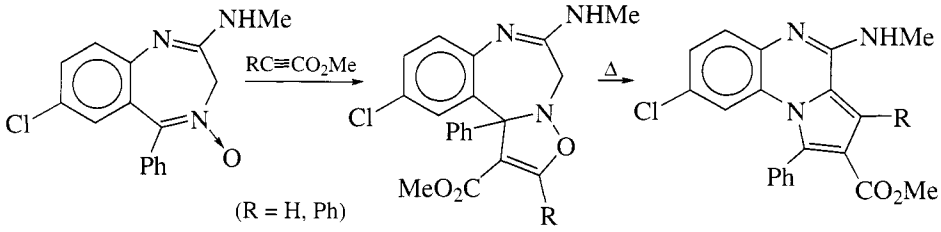


480 **481**

R	R′	**480:481** ratio	% total yield
H	COOMe	30 : 70	54
H	CN	42 : 58	60
Me	COOMe	70 : 30	50

Longer reaction times and/or higher temperatures were reported to push the ratio toward a neat prevalence of the thermodynamically more stable isomer **480**.

In accord with the higher propensity of acetylenic dipolarophiles to furnish 4-substituted 4-isoxazolines, both diazepam *N*-oxide[39/82] and the related chlordiazepoxide[37/85,42/86,43/86] react regiospecifically with methyl propiolate and with alkyl phenylpropiolates. When the latter dipole is employed, the reaction can proceed further, yielding a pyrroloquinoxaline system:[42/86]



Dimethyl acetylenedicarboxylate is also reactive, but the primary cycloadduct does not seem to be isolable, and quinoxalinone or pyrrolo quinoxalines are directly obtained.[22/77,42/86]

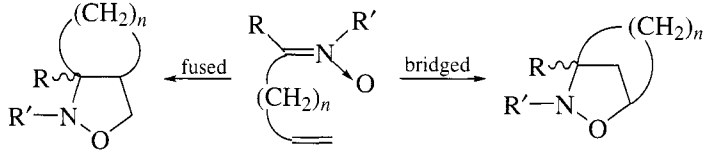
4.2.2.7. *Intramolecular Cycloaddition of Unsaturated Nitrones*

The intramolecular versions of many 1,3-dipolar cycloadditions involving nitrones are known and are referred to by the acronyms IMNC or INC.[24/65] The importance of this reaction, first disclosed in the pioneering work of Le Bel and his group, has increased along with its growing utilization in the stereoselective syntheses of complex molecules and natural products.

In general, the nitrone moiety is generated *in situ* within a structure already possessing a site of unsaturation and immediately cyclizes without the possibility for its isolation.

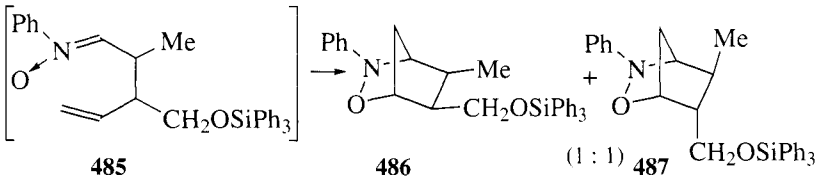
The dipolarophilic center can be linked to either the carbon-atom or the nitrogen atom of the nitrone, and the two cases will be here separately illustrated.

C-Alkenyl nitrones **482**, generated by condensation with either an aldehyde or a ketone, can either give rise to a fused isoxazolidine of type **483** or to a bridged isoxazolidine of type **484**, depending on the tether length and on the substitution pattern of the nitrone and of the double bond.

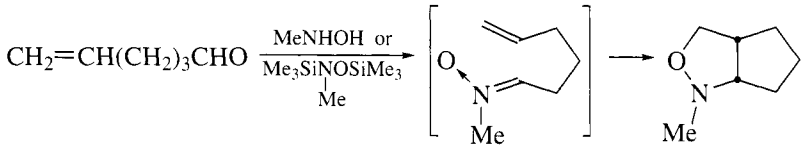


483 **482** **484**

C-(3-Alkenyl)aldonitrones **485**, generated *in situ* from the corresponding aldehyde and N-phenylhydroxylamine, cyclize to give a 64% yield of a 1:1 mixture of the two bridged bicyclic isoxazolidines, 2-oxa-3-azabicyclo [2.2.1]heptane derivatives **486** and **487**.[44/86,39/89]

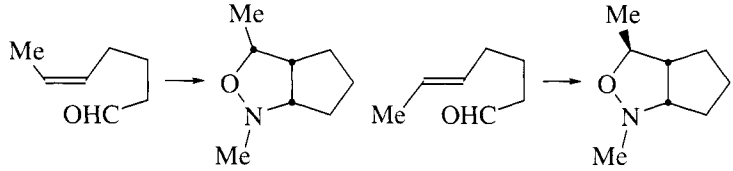


In an example that illustrates the reversal of regiochemistry that further distinguishes the intramolecular process from the intermolecular process, the unsubstituted *C*-(4-alkenyl)nitrone cyclizes to yield the 3,4-fused (hence, 4-substituted) bicyclic isoxazolidine.[3/59,18/64,69/85]

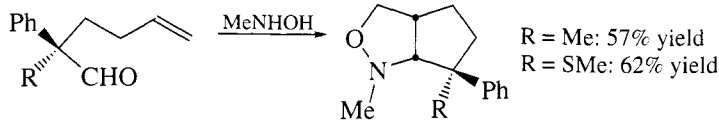


The normal orbital control, which favors formation of the 5-substituted products (see Part 1, § 3.3.1.1, pp. 686–710), appears to be overridden by steric constraints that also dictate a *cis*-fusion of the two rings.

The stereospecificity of the cycloaddition is illustrated by the cyclization of nitrones derived from *cis*- and *trans*-5-heptenal, in which the configuration of substituents about the double bond is retained in the bicyclic products.[18/64]

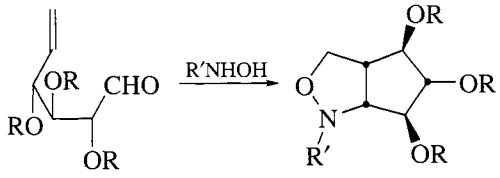


Substitution in the α-position of the chain also influences the stereochemical outcome and cyclization of nitrones derived from α,α-disubstituted hexenals furnishes a single bicyclic product, bearing three contiguous chiral centers, and in which the more bulky phenyl group occupies the *exo* position:[23/77]



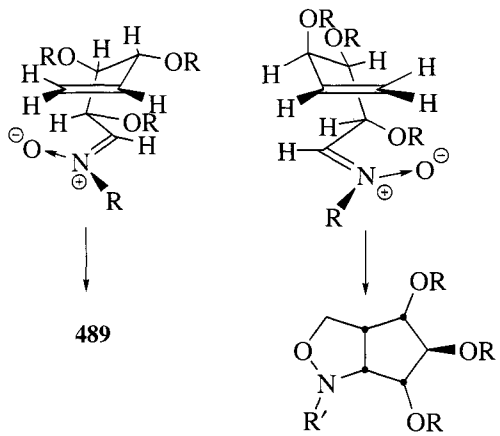
Unsaturated monosaccharides are suitable starting materials for the preparation of cyclopentanoisoxazolidines (3-oxa-2-aza-bicyclo[3.3.0] octane deriva-

tives, **489**). In one instance, optically active 5,6-dideoxy-hex-5-enoses of type **488** react with *N*-substituted hydroxylamines to give bicyclic isoxazolidines (**489**) with high stereoselectivity.[37/79,34/81,36/83]



488 **489**

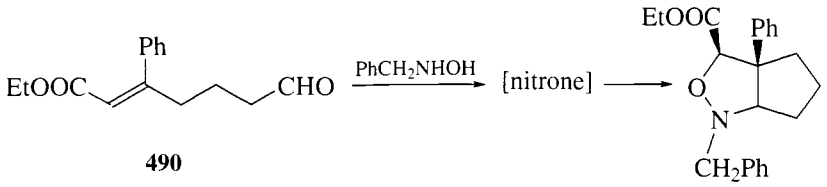
Analogous bicyclic isoxazolidines have been prepared from mannose,[38/79,58/90] galactose,[39/79] and allose,[40/89] derivatives. Sometimes other minor by-products are also obtained in the cyclization reactions shown above, but the bicyclic products predominate and show a *cis* configuration at the ring fusion and a *trans* relationship between the hydrogen atoms at C1 and C8 of the bicyclo[3.3.0]octane ring. This stereochemical result has been shown to depend on kinetic control, and has been attributed to the destabilizing synperiplanar interaction between the nitrone group and the α-OR group in the transition state leading to the 1,8-*cis* isomer. This interaction is absent in the transition state leading to the *trans* isomer:[39/79]



489

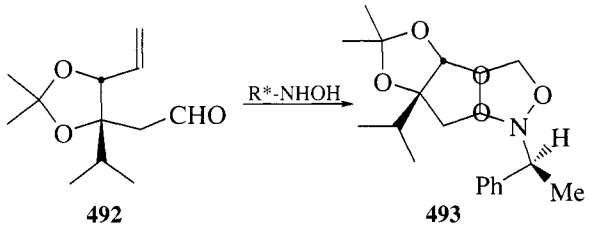
Less highly substituted derivatives of **489** are also known.[34/91]

Regiospecificity with "reversed" orientation, and maintenance of the double-bond stereochemistry, are also observed when the starting aldehyde bears aryl and ester functionalities on the terminal alkene. For example, the nitrone derived from aldehyde **490** and *N*-benzylhydroxylamine cyclizes to the fused product **491** exclusively:[38/85]



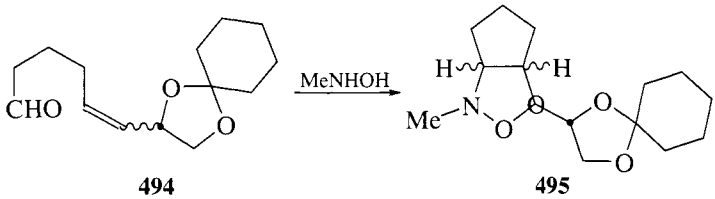
490 **491** (77% yield)

Reaction of substituted 5-hexenals with chiral hydroxylamines induces a high degree of double diastereoselection in the intramolecular cycloaddition process.[34/91,35/91,36/91] The configuration of the chiral atom also seems to be important in determining the degree of diastereoselectivity since aldehyde **492** reacts with (*S*)-α-methylbenzyl hydroxylamine to give the tricyclic *anti* isomer **493** with only traces of the *syn* isomer (mixture 20:1). By contrast, (*R*)-α-methylbenzyl and methyl hydroxylamine yield 4.1 : 1 and 4.6 : 1 mixtures of *anti* : *syn* diastereoisomers, respectively:[34/91]



492 **493**

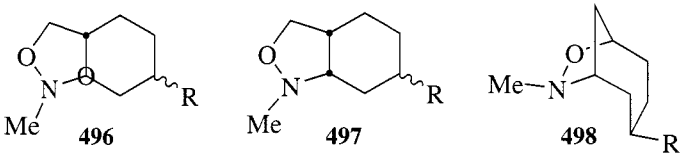
Good to excellent stereocontrol has also been observed when the chiral center is linked to the terminus of the double bond. Thus, cyclization of C-4-alkenyl nitrones generated from the chiral allyl ethers (*Z* and *E*) **494** furnishes the stereoisomer **495** having a C5/C5′ *anti* structure with large predominance (*anti*: *syn* = 96 : 4 from *Z* and 92 : 8 from *E*)[26/87]:



494 **495**

The lengthening of the tether linking nitrone and alkene functionalities by one more carbon atom induces some variations in the regio- and stereo-chemistry of the cyclization. Nitrones derived from 6-heptenal or its 3-methylderivative react with *N*-methylhydroxylamine to yield three (or four) isomeric cyclic products: a

major *trans*-fused isomer **496**, along with minor amounts of the *cis* isomer **497** (when R = Me, 2 epimers) and of the bridged 7-oxa-8-azabicyclo[4.2.1]nonane derivative **498**:[18/64,23/71,23/90]

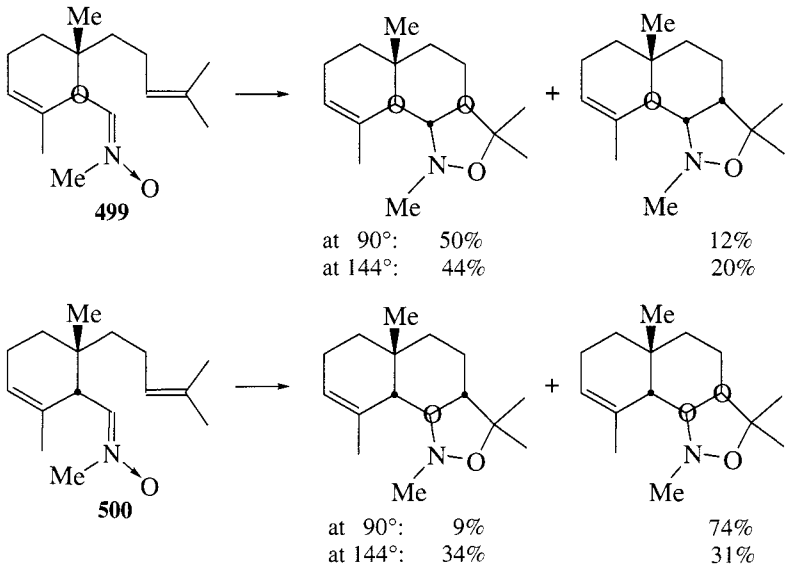


R = H	at 110°	**496 : 497 : 498** = 57 : 35 : 8	(44% total yield)
R = Me	at 76°	74 : 22.5 : 3.5	(69% " ")
	at 110°	60 : 35 : 5	(80.5% " ")

The *trans* isomer equilibrates with the *cis* isomer at higher temperatures,[31/66,23/71] presumably through a retrocycloaddition.

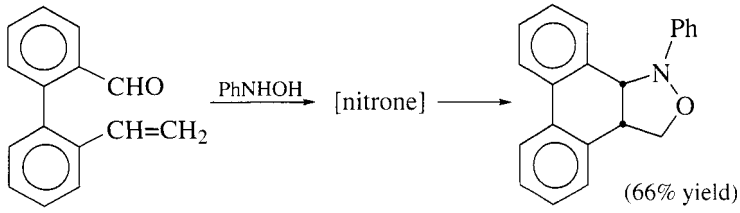
The degree and nature of substituents along with the lenght of the chain can markedly influence the structure of the resulting cycloadducts. *N*-Methyl-*C*-(6-methyl)hepten-5-yl nitrone, generated *in situ* from the corresponding aldehyde derivative, furnishes low yields of a mixture of the fused isoxazolidines (*trans/cis* = 85:15).[23/71] Likewise, (+)-citronellal reacts with *N*-alkylhydroxylamines to furnish predominantly the *trans*-fused cycloadducts, which isomerize to the *cis*-fused isomers at 280°.[24/65,22/78] By contrast, citral (or neral)[40/79] as well as farnesal,[40/79,41/79] are reported to afford, on treatment with *N*-methylhydroxylamine, fused cycloadducts in which the *cis* isomer predominates.

A remarkable change in stereochemistry has been observed with the two isolable isomeric nitrones **499** and **500**: whereas the *trans*-fusion predominates

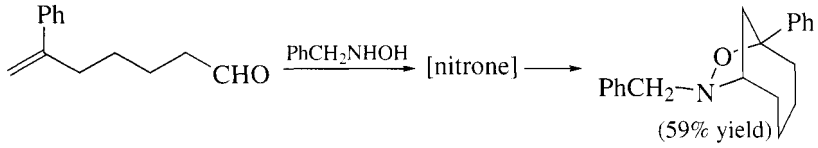


with the former starting material, a large majority of the *cis*-fused cycloadduct is obtained from the latter nitrone. A rise in reaction temperature increases the amount of the minor product.[39/85]

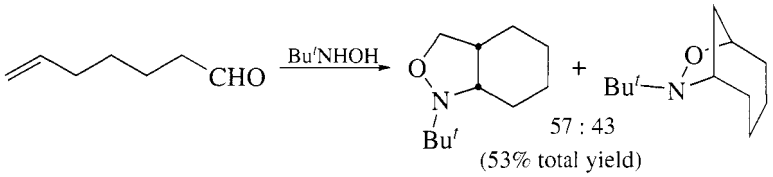
In reactions of 2′-vinyl-2-biphenylcarboxaldehyde with *N*-phenylhydroxylamine, steric factors, rather than orbital interactions, control the regiospecificity and diastereoselectivity such that only the *cis*-fused cycloadduct is isolated.[23/78]



In the reaction of 6-heptenals with *N*-substituted hydroxylamines, the presence of a phenyl group on the double bond reverses the regiochemistry of the cycloaddition to afford the bridged isoxazolidine as single product:[38/85]



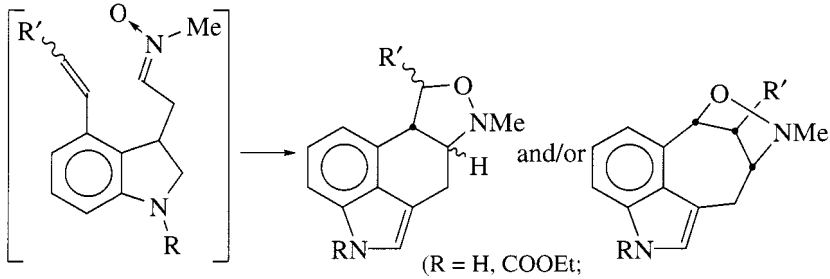
Similarly, the presence of a bulky substituent on the nitrone nitrogen sharply increases the amount of the bridged isoxazolidine (compare **496** + **497/498** ratio!):[23/90]



A fused isoxazolidine containing the 8-oxa-7-azabicyclo[4.3.0]nonane skeleton is formed with high stereoselectivity and in favor of a *cis* ring junction by cyclization of a vinylcarbohydrate derivative.[40/89] A high level of diastereocontrol is achieved in the intramolecular cycloaddition of the *C*-(5-alkenyl)nitrones derived from chiral allyl ethers. As with the lower homologues, the C5/C5′ *anti* products are largely predominant. The stereoselectivity at the ring junction is still largely in favor of the *trans* fusion only for the *cis*-alkene, but is practically absent for the *trans*-alkene.[26/87]

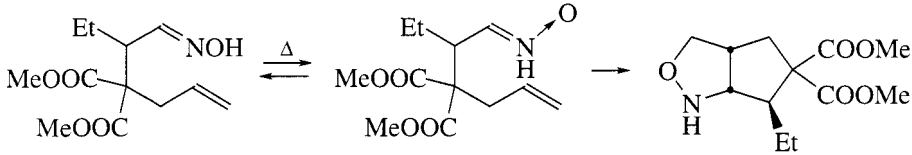
Owing to its importance as key step in the synthesis of indole alkaloids, the cyclization of *C*-(3-indolylmethyl)nitrones of general structure **501** has been

thoroughly studied. The substitution pattern on the double bond largely controls the regiochemistry of the reaction. Thus, the unsubstituted vinyl group in the indole 4-position leads to formation of the bridged isoxazolidine **503** only.[37/83] Substitution with an electron-releasing (e.g., methoxy) group shifts the cyclization toward the fused isoxazolidine **502** (*cis* or *trans/cis* mixture) as unique cycloadduct.[37/83,40/85] Starting from a compound having an electron-withdrawing group on the terminal double bond, a mixture of *cis*-fused and bridged cycloadducts is obtained whose composition is temperature-dependent. At 70°C the kinetically preferred fused product is favored (4:1), at higher temperature (180°C) the thermodynamically more stable bridged isoxazolidine prevails (1:4).[33/80,37/83]



501 **502** **503**

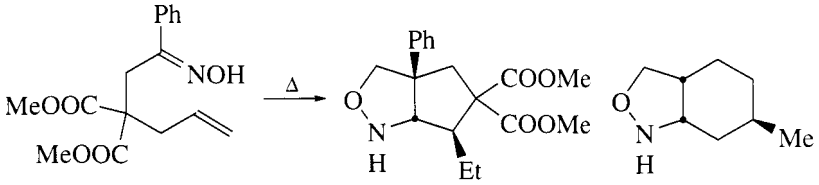
It is well known that at high temperatures oximes can equilibrate with the tautomeric form of *N*-unsubstituted nitrone and thus undergo cycloadditions with activated alkenes to yield isoxazolidines. Suitably disposed unsaturated oximes can give rise to an intramolecular oxime–olefin cycloaddition (the so-called IOOC reaction).[55/89] Indeed, oxime **504**, heated in toluene at 190°C in a sealed tube, cyclizes to the fused isoxazolidine **505** stereospecifically with 81% yield:[55/89]



504 **505**

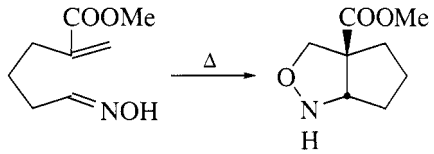
Similar results have been achieved with ketoxime **506**, which yields a single stereoisomer **507**,[55/89] and with citronellal oxime, which cyclizes to give **508**. In the latter case the influence of the temperature is evident; heating for 2 days at 80°C gave a 22% yield of cyclized product, heating in the presence of $ZnCl_2$ improved the yield to 60%, and heating at 180°C for 5 h furnished **508** in 80% yield.[55/89]

The presence of a methoxycarbonyl group on the double bond seems to assist this type of reaction and, as in the following example, permits cyclization in a

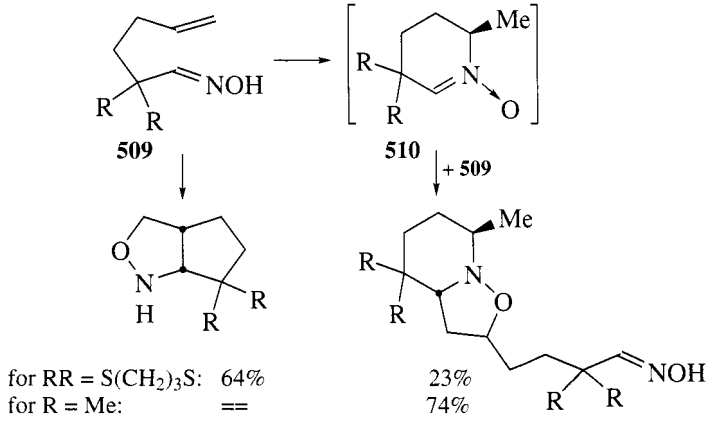


506 (75% yield) **507** **508**

fashion analogous to **506** at 80°C in 80% yield. The product of an alternative 7-*endo*-trig-cyclization was not observed.[24/90,37/91]

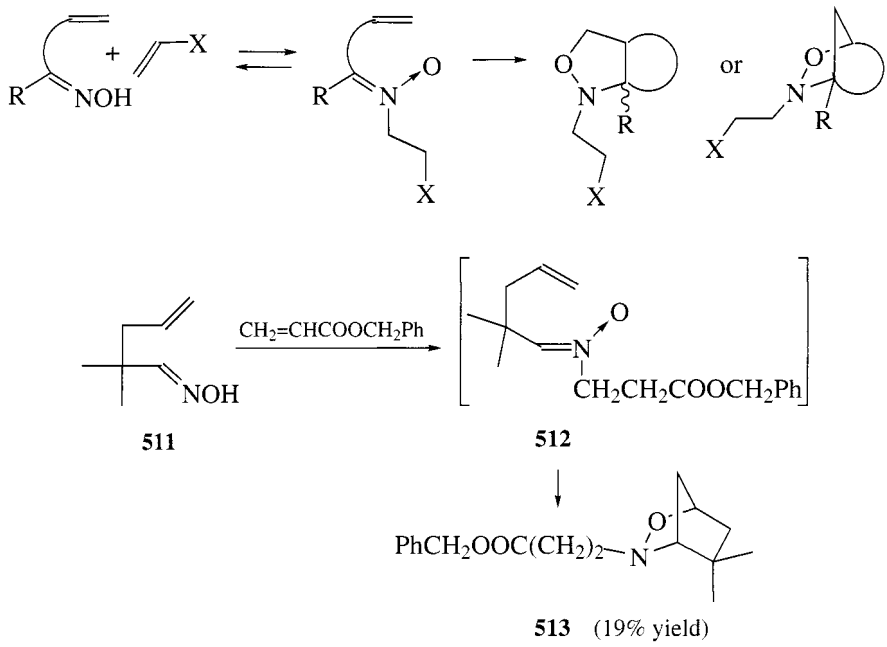


Although disubstitution at both the β and γ positions of 4-alkenyl oximes does not adversely affect the cyclization process, α,α-disubstituted oximes of type **509** tend to follow a cyclization–intermolecular cycloaddition process in which the intermediacy of a cyclic nitrone (**510**) has been postulated.[24/90,37/91]



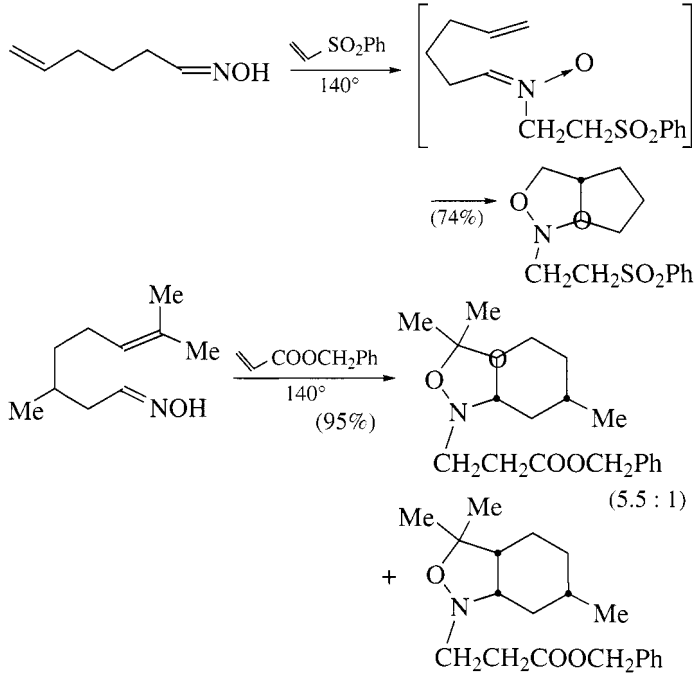
N-Substituted nitrones can be prepared by Michael addition of oximes to alkenes bearing electron-withdrawing groups and by reaction with epoxides.[54/89] Generation of a *C*-alkenyl nitrone *in situ* from an alkenyl oxime initiates an intramolecular cycloaddition along the following scheme.[38/91]

The 3-alkenyl oxime **511** reacts with benzyl acrylate to generate the *C*-(3-alkenyl)nitrone **512**, which cyclizes, as expected, to the bridged isoxazolidine **513**.[38/91]



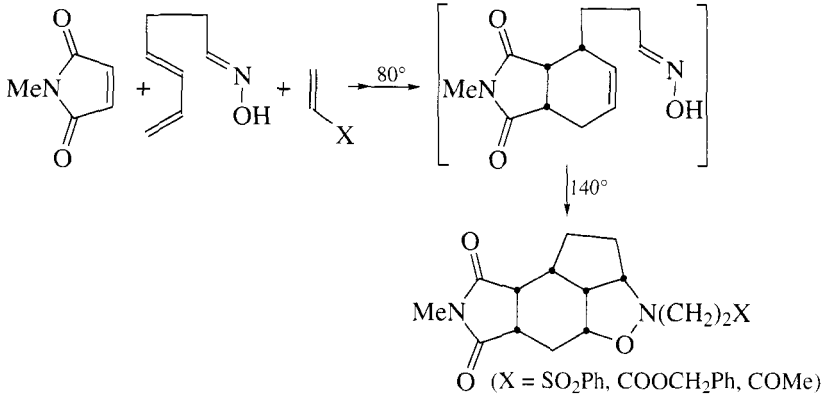
511 **512** **513** (19% yield)

C-(4-Alkenyl) and *C*-(5-alkenyl) nitrones furnish the fused isoxazolidines only, as following examples show:[38/91]



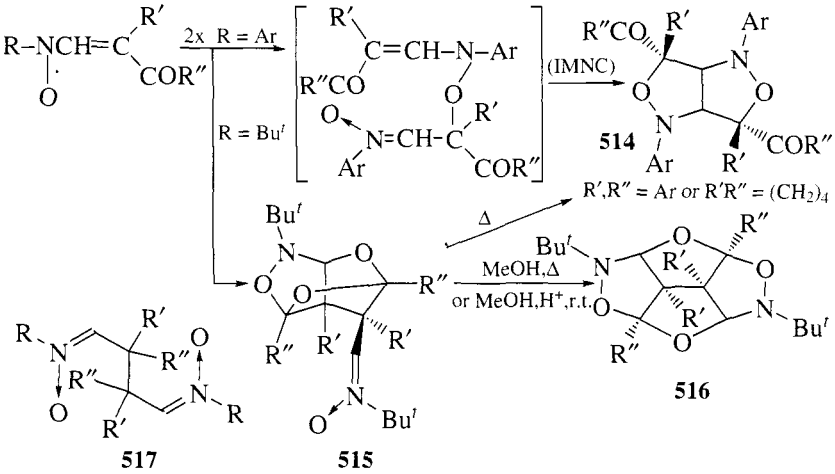
In the former example the formation of the *trans*-fused isomer is a remarkable exception to the general trend of *cis*-fused isoxazolidine formation from *C*-(4-alkenyl)nitrones.

The consecutive Diels–Alder addition→Michael addition→nitrone cycloaddition is illustrated by the following example, where six adjacent chiral centers are generated all-*syn* with a one-pot procedure.[41/89]



Fused and bridged polycyclic isoxazolidines are formed as minor products from the thermolysis of *cis*-laudanosine *N*-oxide, presumably through the intermediacy of a *C*- and an *N*-alkenyl nitrone.[34/80]

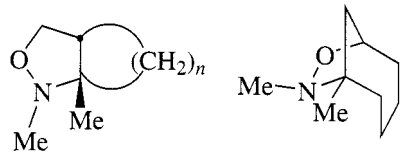
Several fused isoxazolidine systems have been obtained through dimerization of the vinylaminyl oxides, generated *in situ* by oxidation of the corresponding nitrones or hydroxylamines. Their formation depends on the nature of the substituents and on the experimental conditions. Thus, *N*-arylsubstituted



vinylaminyl oxides (vinyl nitroxides) dimerize to afford the 3,7-dioxa-2,6-diazabicyclo[3.3.0]octane system **514**, presumably arising from an initial βC–O bond formation, followed by an intramolecular nitrone cycloaddition (IMNC reaction).[36/84,45/86,48/88,25/90]

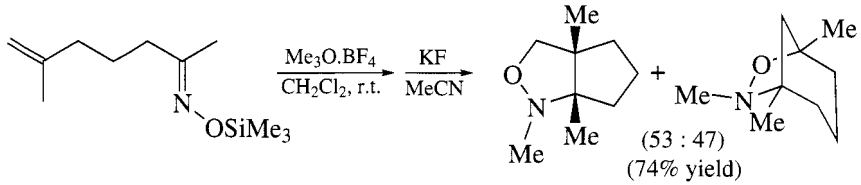
By contrast, *N-tert*-butyl vinyl aminyl oxides usually dimerize to the tricyclic system **515**, which either thermally converts to the thermodynamically more stable bicyclic dimer **514** or isomerizes in protic solvents to the tetracyclic dimer **516.**[45/86,48/88] With other substitution patterns only the linear *CC* dimers of type **517** are formed[57/89,25/90] or the dimerization is blocked entirely.[57/89]

The behavior of unsaturated ketonitrones is similar to that of the corresponding aldonitrones. Reaction of hept-6-en-2-one with *N*-methylhydroxylamine in refluxing toluene gives the *cis*-fused cycloadduct **518a** as the exclusive product, where the presence of the two nitrogen invertomers (*exo* and *endo*) could be evidenced by low-temperature PMR analysis.[18/64,26/70] The *cis*-fused homologue **518b**, obtained by cyclization of the nitrone derived from oct-7-en-2-one, is accompanied by a notable amount of the bridged isoxazolidine **519** (**518b**:**519** = 62 : 38), which, however, at higher temperatures converts into the thermodynamically more stable **518b**.[23/71]



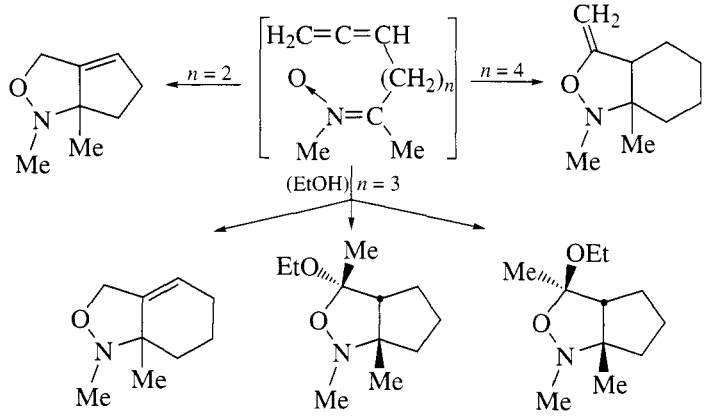
518a: $n = 3$ **519**
b: $n = 4$

Similar results are reported for nitrones derived from unsaturated α-ketoesters.[37/84] A mixture of *cis*-fused and bridged isoxazolidines is also obtained when an unsaturated nitrone is generated from a ketoxime *O*-trimethylsilyl ether, as in the following example:[41/85]

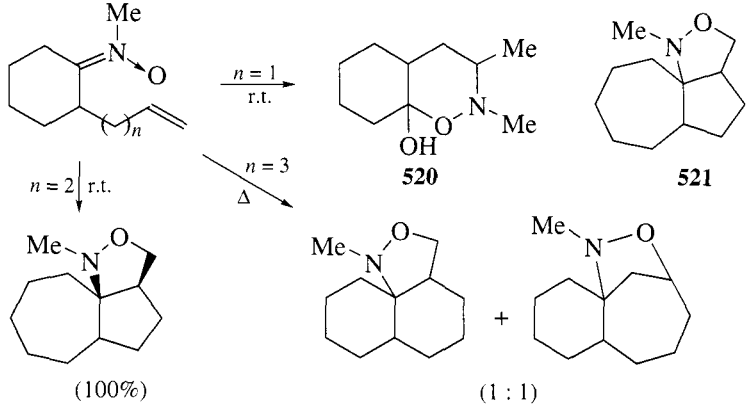


Cyclization of ketonitrones having an allenic group at the end of the chain can occur at either the terminal or the internal double bond to give fused isoxazolidines; the regiochemistry of attack depends on the chain length. The former cyclization mode is followed exclusively with the nitrone derived from hepta-5,6-dien-2-one, the latter route is followed by 7,8-nonadien-2-one,

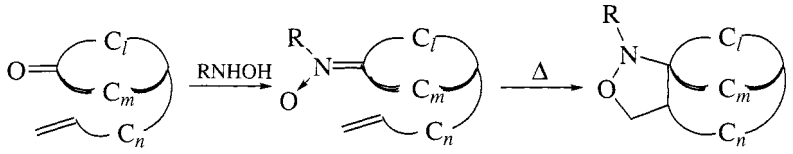
although with lower yields. Starting from 6,7-octadien-2-one the reaction leads to a mixture of the two types of products:[27/70]



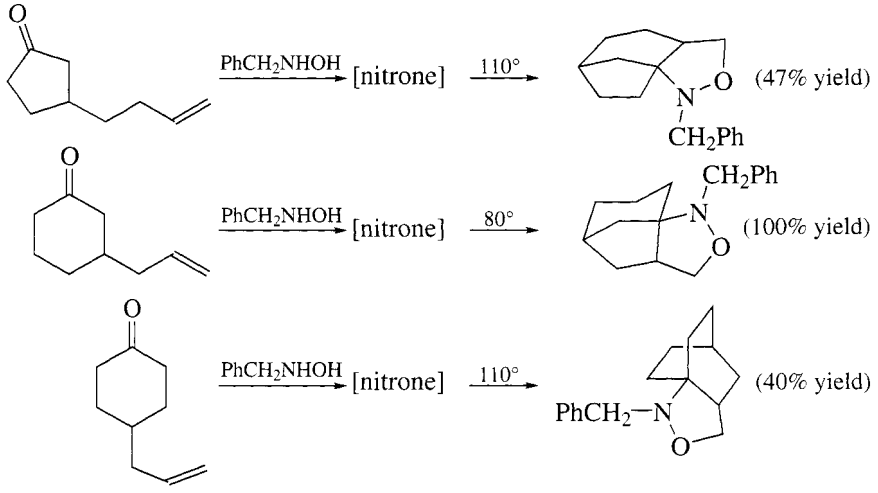
2-Alkenylcyclohexanones react with *N*-methylhydroxylamine to give the corresponding nitrones, although the ultimate fate of the reaction depends on the length of the unsaturated chain. The nitrone derived from 2-allylcyclohexanone does not enter the 1,3-dipolar intramolecular cycloaddition, but diverts toward the formation of the oxazine **520**. By contrast, condensed isoxazolidines are regularly produced starting from 2-(3-butenyl)- or from 2-(4-pentenyl)-cyclohexanone. The perhydroazulene-condensed isoxazolidine **521** has been obtained from 2-(3-butenyl)cycloheptanone.[24/78,35/81]



Still more interesting, because of its versatility, is the synthesis of polycyclic fused isoxazolidines, starting from β- or γ-substituted cycloalkanones along the following general scheme:[38/83,67/85]

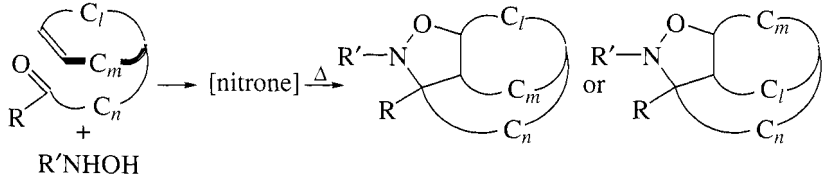


Some selected examples of the reaction are depicted below:

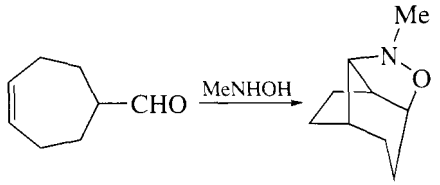


The tandem intermolecular Michael addition–intramolecular nitrone cycloaddition sequence has been also applied to ketoximes, both acyclic and cyclic.[28/87,38/91] In the former case the usual *cis*-fused isoxazolidine are obtained, in contrast to what happens with the corresponding aldoximes (see above).

When the intramolecular cycloaddition is extended to *C*-cycloalkenyl nitrones, a tricyclic (or polycyclic) isoxazolidine can be produced, along the following general scheme, where $C_n + C_l$ and $C_n + C_m$ must be ≥ 2:

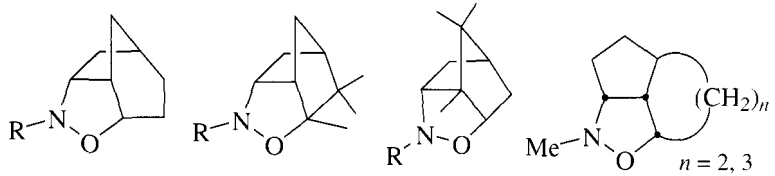


In this manner 4-cycloheptenecarboxaldehyde reacts with *N*-methyl-hydroxylamine to give a 60% yield of the tricyclic cycloadduct:[10/62]



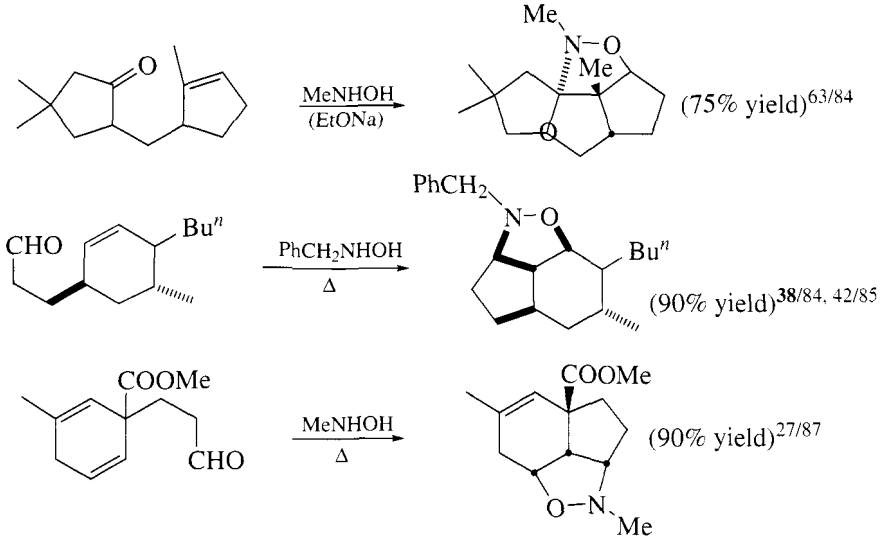
The dibenzoanalog is also known, as well as its higher homolog with the corresponding aza derivative.[39/83]

A high degree of regiospecificity is observed in the case of the nitrone derived from 3-cyclohexen-1-acetaldehyde, which gives a single cycloadduct (**522**).[19/72] Conversely, the nitrone derived from campholenic aldehyde gives both regioisomeric cycloadducts (**523** and **524**) in a 3 : 2 ratio.[10/62]



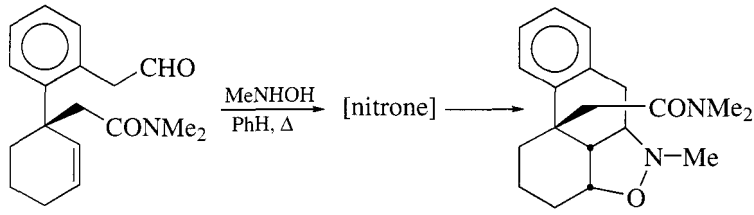
522 **523** **524** **525**

Fused tricyclic products of type **525** are obtained when starting from 3-(2-cyclopentenyl- or 2-cyclohexenyl)propionaldehyde or ketones of similar structure, usually with complete *cis* ring junction stereoselection, although the



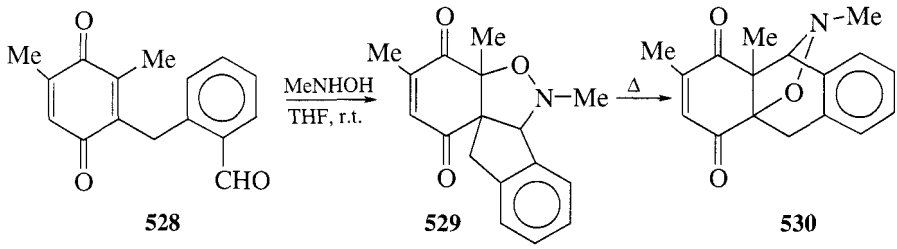
stereochemistry of the cycloadduct from the simple 3-(2-cyclohexenyl)propionaldehyde was unspecified.[24/65] Representative examples are reported on p. 595.

The high degree of positional slelectivity in the latter example is attributed to steric interactions in the transition state, factors that cause trisubstituted alkenes to always exhibit a lower reactivity than disubstituted derivatives in nitrone as well as nitrile oxides cycloadditions. A variation involving a chiral auxiliary has been carried out on a similar substrate.[75/90] The presence of a benzo group on the chain connecting the nitrone and the cyclohexenyl double bond seems to cancel the stereoselectivity of the cycloaddition; a 1 : 1 mixture of the two epimers **527** was obtained from aldehyde **526**:[39/84]



526 **527** (72% yield)

The enhancement of reactivity that is attainable on moving from an intermolecular process to the corresponding intramolecular process is nicely illustrated by the case of substituted benzoquinones. Whereas benzoquinones do not participate in cycloadditions with *N*-methyl-*C*-phenyl nitrone, the quinone-substituted aldehyde **528** readily reacts with *N*-methylhydroxylamine under mild conditions to afford the polycyclic isoxazolidine **529**, which on heating is converted into the more stable **530**, presumably through a 1,3-dipolar cycloreversion. When the corresponding 2,3-dimethylbenzoquinone derivative is employed, the thermodynamically favored regioisomer is obtained directly.[43/87]

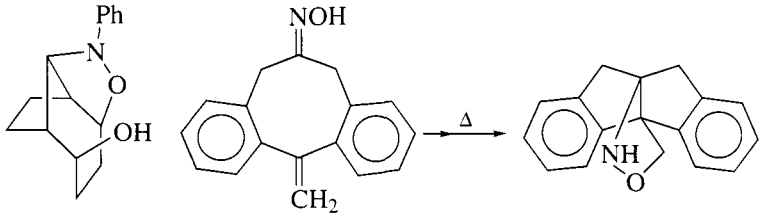


528 **529** **530**

Some related quinone methide derivatives also react regioselectively.[24/71]

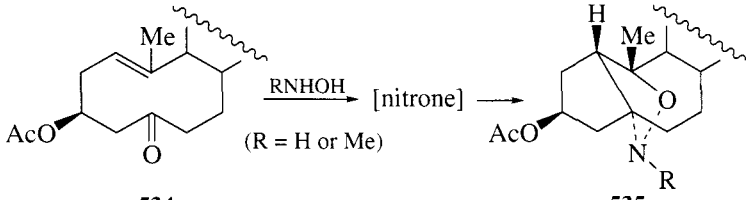
Examples are known in which the site of unsaturation belongs to a larger ring. The *N*-phenylnitrone of 2-hydroxycyclooct-5-enecarboxaldehyde cyclizes regiospecifically to the tricyclic compound **531**.[26/82] The exocyclic double bond

of **532** enters cycloaddition with the nitrone tautomeric form of the oxime by heating at 75°C, affording the pentacyclic isoxazolidine **533**.[42/79]



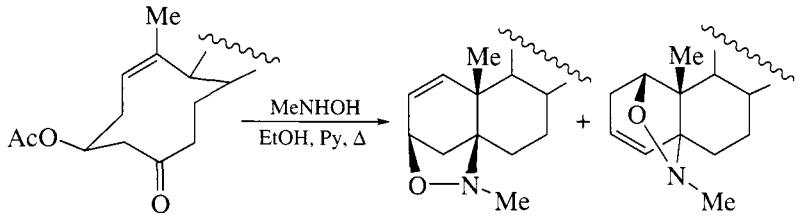
531 **532** **533**

Transannular cycloaddition of nitrones of unsaturated 5-oxo-5,10-secosteroids of general structure **534** (*E* configuration at the double bond), promoted by reaction with hydroxylamine or *N*-methylhydroxylamine, are known to furnish isoxazolidino steroids such as **535** under acidic catalysis:[26/73,58/88]



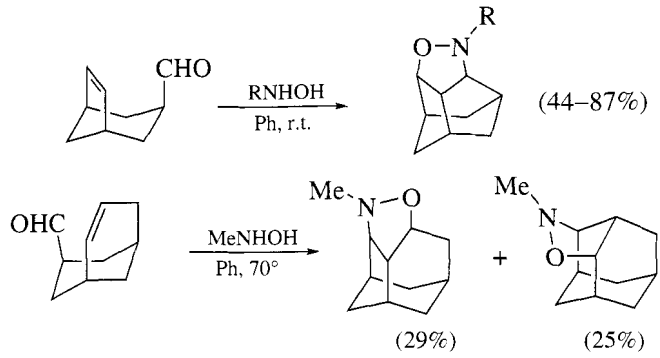
534 **535**

The corresponding (*Z*)-stereoisomeric 5,10-secoketones **536** do not proceed beyond the oxime stage when treated with hydroxylamine. However, *N*-methylhydroxylamine in the presence of pyridine promotes elimination of the elements of acetic acid, leading to intramolecular 1,4-cycloaddition, which gives isoxazolidino steroid **537**, and 1,2-cycloaddition, which yields **538**.[42/89]

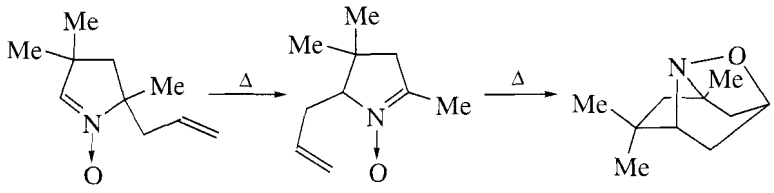


536 **537** (48–56%) **538** (23–30%)

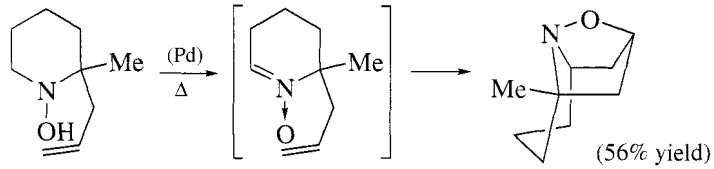
C-Bicycloalkenyl nitrones are useful sources of noradamantane, protoadamantane, and adamantane derivatives, since they cyclize under very mild conditions.[43/79,40/82] The following examples are illustrative:



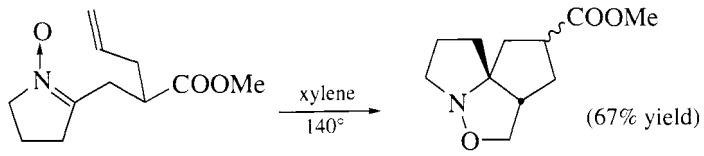
Cyclic nitrones with a suitably positioned double bond in the side chain can also undergo thermally induced intramolecular cycloaddition. Thus, 5-allyl-3,3,5-trimethyl-1-pyrroline-1-oxide, when heated in refluxing toluene, first isomerizes via a Cope rearrangement, and then cyclizes to 1,6,6-trimethyl-9-oxa-8-azatricyclo[3.2.1.1^{8,3}]nonane:[34/72]



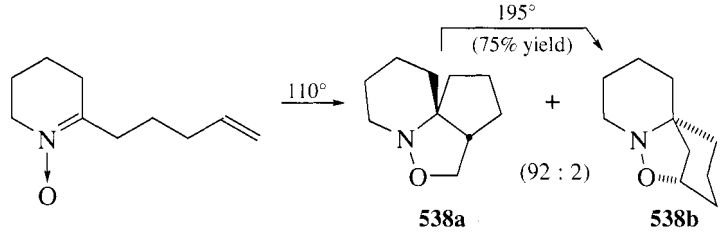
A differently substituted compound,[15/78] as well as their higher homologs,[58/84,28/85] have been prepared in an analogous fashion. An isomeric 10-oxa-9-azatricyclo[3.3.1.1^{3,9}]decane system has been constructed from 2-allyl-1-hydroxy-2-methylpiperidine through the nonisolable intermediate cyclic nitrone:[61/84,19/90]



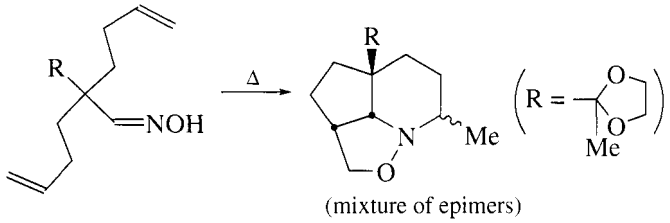
Starting from 2-(4-pentenyl)-1-pyrroline-1-oxides, either prepared as such[29/89] or generated *in situ* by tandem intramolecular Michael addition–nitrone cycloaddition,[24/87] a hexahydrocyclopenta[*c*]pyrrolo[1,2-*b*]isoxazole derivative is procured, as in the following example:[29/89]



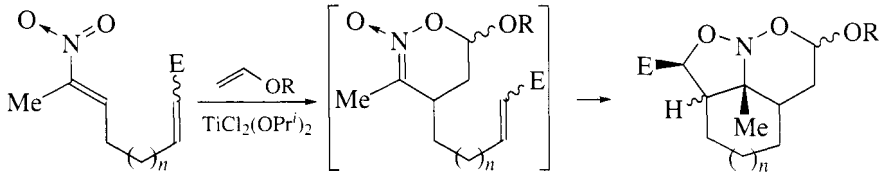
The analogous cyclization of 2-(4-pentenyl)-3,4,5,6-tetrahydropyridine-1-oxides is highly regioselective and provides a route to the octahydrocyclopent[3,4]isoxazolo[2,3-*a*]pyridine ring system **538a**.[35/74,54/89] Thermal rearrangement yields the thermodynamically more stable isomer **538b**:[20/75]



Another tricyclic isoxazolidine has been obtained stereoselectively through tandem intramolecular Michael addition–nitrone cycloaddition:[24/90]



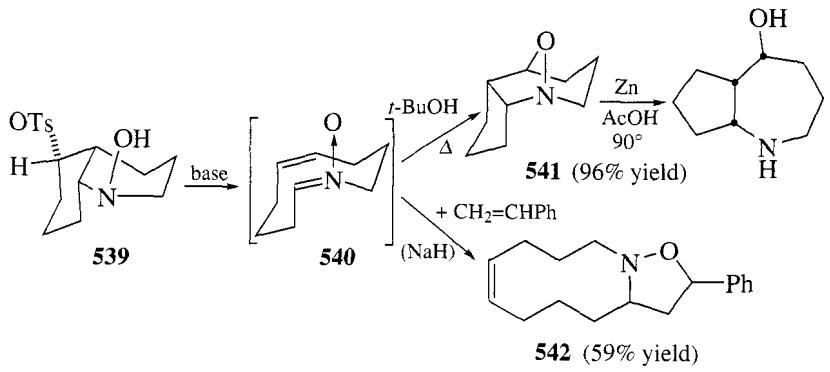
An interesting tandem [4+2]/[3:2] cycloaddition of funtionalized nitroalkenes with olefins or enol ethers involves an intermediate cyclic nitronate incorporating an α,β-unsaturated ester (or nitrile) moiety in the lateral chain, as in the following example:[26/90]



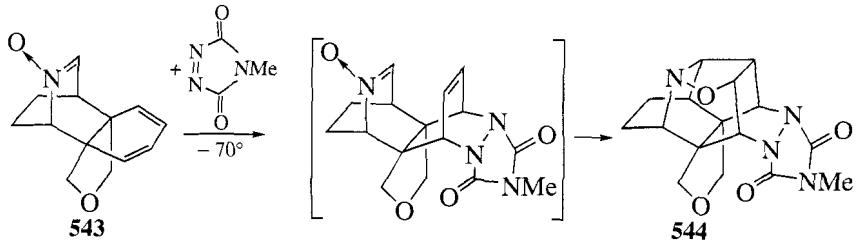
(*n* = 1, 2; E = COOMe)

A highly stereoselective (90% ee) variant of this reaction has been studied with an appropriate chiral vinyl ether.[59/90]

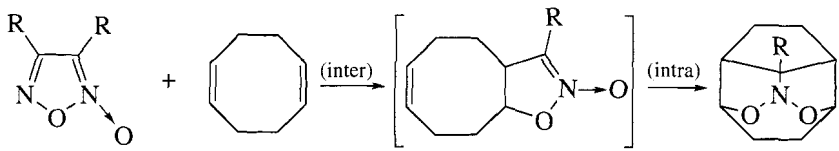
Intramolecular nitrone cycloaddition is facilitated by the inclusion of nitrone and alkene moieties in relatively rigid structures, thereby increasing their proximity. Under basic conditions, cyclic hydroxylamine **539** undergoes a concerted fragmentation to give nitrone **540**, which either cyclizes intramolecularly to **541**, and represents a convenient source of perhydroazaazulene; or cycloadds intermolecularly to **542**.[43/85]



A similar example occurs in the formation of cage isoxazolidine compound **544** in one-pot reaction from the cyclic nitrone **543**:[46/86]

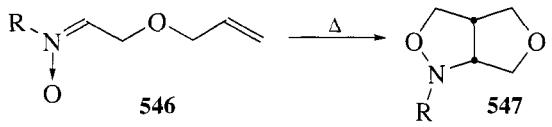


A special case of consecutive intermolecular–intramolecular nitrone cycloadditions is represented by the reaction of a furoxan with 1,5-cyclooctadiene to give **545**:[36/85]



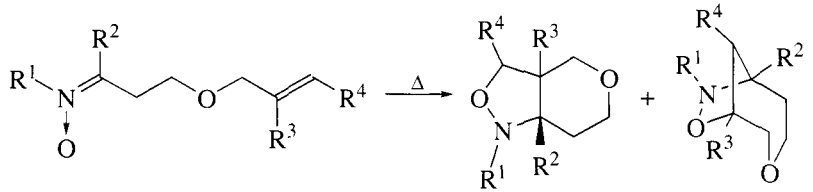
545 (R = CN, SO_2Ph; 15–30% yields)

Intramolecular nitrone cycloadditions in systems where the chain connecting nitrone and alkene moieties incorporates a heteroatom have been widely studied, without remarkable differences observed between the corresponding carbocyclic counterparts. Thus, acyclic oxygen-containing unsaturated nitrones of type **546** cyclize to *cis*-fused isoxazolidines **547**:[23/90]



546 **547**

The insertion of a chiral substituent promotes asymmetrical induction.[39/91] The higher homolog derivatives **548** give a mixture of *cis*-fused **549** and/or bridged cycloadducts **550**, depending on the substituent pattern:[23/90]

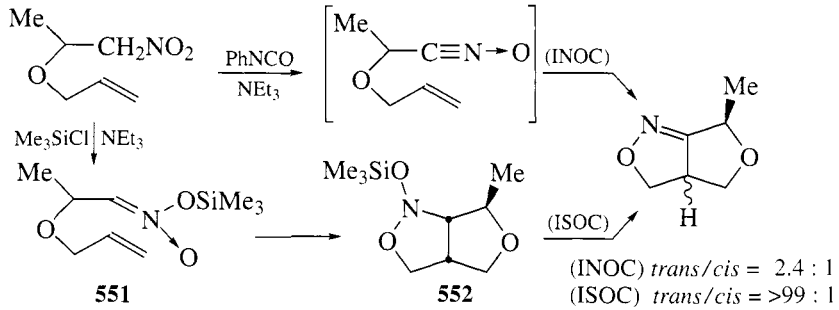


548 **549** **550**

R^1	R^2	R^3	R^4	**549:550**	total yield (%)
Bu^t	H	H	H	45:55	68
4-Bu^t C_6H_4	Me	H	H	30:70	30
Bu^t	H	Me	H	0:100	92
Bu^t	H	H	Me	100:0	50

3-*O*-Allyl-D-(+)glucose reacts with *N*-benzylnitrone to yield a bridged isoxazolidine only,[60/90] whereas a pyranoside aldehyde affords a 2 : 1 mixture of fused and bridged cycloadducts.[27/90]

The intramolecular silyl nitronate–olefin cycloaddition (ISOC reaction) of compound **551** leads with high stereoselectivity to the *cis*-fused isoxazolidine



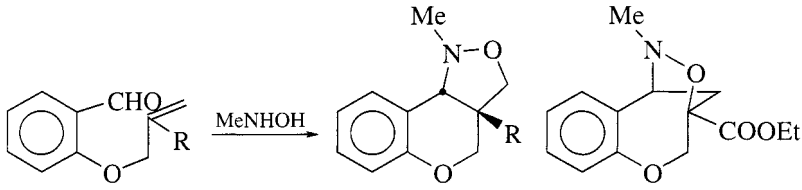
551 **552**

(INOC) *trans*/*cis* = 2.4 : 1
(ISOC) *trans*/*cis* = >99 : 1

552, whereas the selectivity is far lower with the corresponding INOC reaction.[12/90]

Sulfur analogs behave similarly, but with higher homologs the ISOC reaction is much slower, far less stereoselective, and often in favor of the *trans* cycloadduct, a result that is contrary to what happens with the INOC reaction.

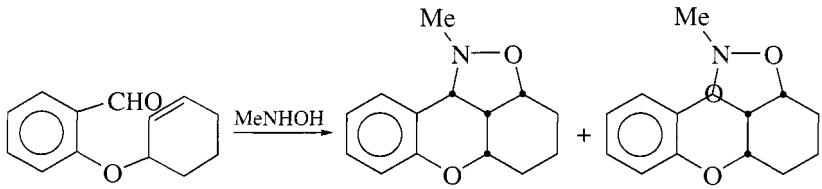
2-Allyloxy aromatic aldehydes of type **553** react with *N*-methylhydroxylamine usually to give the *cis*-fused isoxazolidines **554**.[28/70,29/70,22/88]



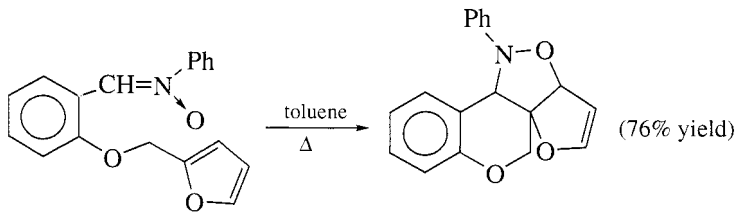
553 (R = H, Me, Br) **554** **555**

The intermediate nitrone can also be generated by thermolysis of 2-allyloxyoxaziridines.[47/86]

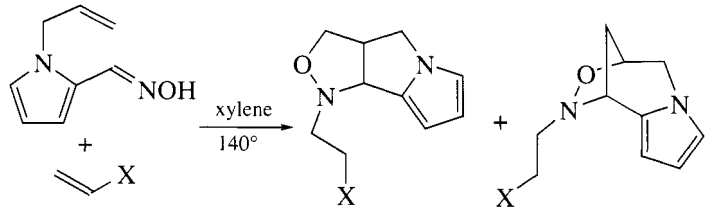
In some cases a bridged cycloadduct can be produced: starting from **553** (R = COOEt), along with **554** (R = COOEt) in 64% yield, a 26% yield of **555** is also isolated. *O*-Vinyloxybenzaldehyde even leads to a bridged cycloadduct as major product.[28/70] Moreover, sometimes a mixture of stereoisomers (*cis*- and *trans*-fused) can arise, such as in the following example:[28/70]



Cycloaddition is also readily accomplished when the double bond belongs to a furan ring, as in the following example:[23/84]

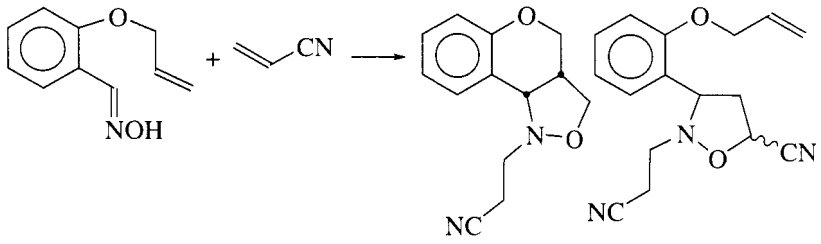


The related aryl aldoximes can cyclize thermally or under acidic catalysis, although in some cases the Claisen rearrangement prevails over the intramolecular cycloaddition.[44/85,23/88,15/89,37/91] This drawback can be easily overcome either by prior trimethylsilylmethylation of the oxime[49/87,36/89] or by the *in situ* generation of an *N*-substituted nitrone through the tandem Michael addition–1,3-dipolar cycloaddition process,[49/88,38/91,40/91] which sometimes leads to mixtures of cycloadducts.



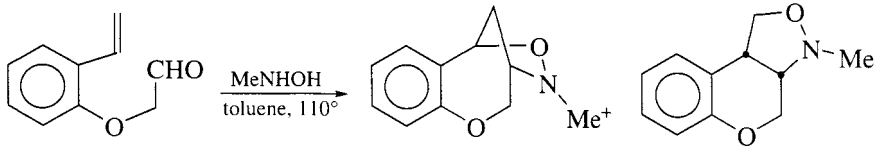
(X = SO_2Ph - ratio 53 : 47– 75% yield;
X = COMe - " 46 : 54– 81% ")

Sometimes the intermolecular cycloaddition can compete with the intramolecular process, as illustrated in the following example:[26/84]



(65 : 35; 79% yield)

Starting from the aldehyde **556**, a mixture of bridged **557** (major) and *cis*-fused **558** (minor) cycloadducts has been obtained:[30/70]



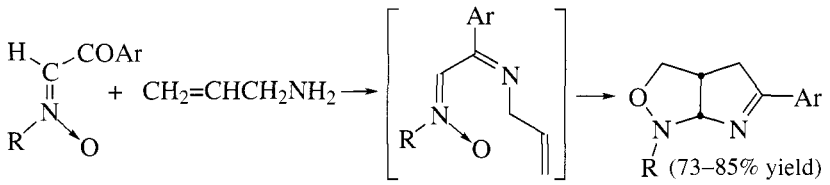
556 **557** (40% yield) **558** (10% yield)

When the vinyl group carries an ethoxycarbonyl substituent, only the fused isoxazolidine is isolated.

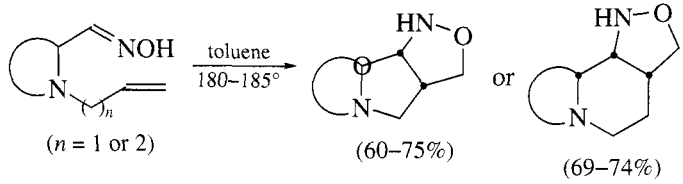
Intramolecular cycloadditions, similar to those reported above, are known for compounds having an ester[36/81,37/81,45/85,48/86,28/87,50/88,43/89] or an amide[51/81,28/87,67/87,61/90] function in the chain connecting the dipole and dipolarophile moieties.

A thorough study has been carried out on the influence of chiral centers on the stereoselectivity of the intramolecular cycloaddition of unsaturated nitrone esters, where fused cycloadducts have been isolated exclusively. Whereas the presence of a stereocenter inside the connecting chain always induces some degree of stereoselectivity, the level of stereocontrol is higher when the allylic stereocenter is located on the double bond in a terminal position than for chiral auxiliaries situated on the nitrone nitrogen atom. (*Z*)-Alkenyl nitrones show higher stereoselectivity than do their *E* counterparts, all other structural parts being equal. Of the different chiral allyl ethers tested, those derived from glyceraldehyde are the most effective for inducing stereocontrol.[28/90]

Several other terminally unsaturated nitrones or oximes, having a nitrogen atom in the connecting chain, are known to readily cyclize to polycyclic (generally fused) isoxazolidines.[28/70,25/78,22/88,29/88,48/89] The connecting chain can sometimes be assembled *in situ*, as in the following example:[25/78]



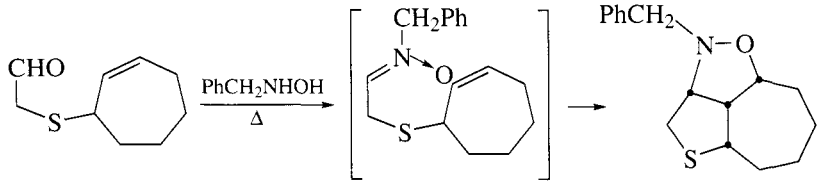
When the nitrogen atom belongs to a pyrrolidine or piperidine ring, the stereoselectivity of the thermal intramolecular oxime–olefin cycloaddition (IOOC reaction) is high; the *cis–anti* isomer is preferred if the cyclization leads to a five-membered ring, with the *cis–syn* isomer predominating in the cyclization to six-membered products.[41/91]



(*n* = 1 or 2) (60–75%) (69–74%)

Bicyclic sulfur-containing isoxazolidines have also been prepared through INC reactions.[26/78,41/82,42/82,51/88,57/89,23/90,62/90] As already illustrated with the oxygen analogs, the stereochemical outcome depends on the tether length, the position of the sulfur atom (or sulfonyl group), and the nature and position of the substituents. Generally *cis* fusion is the rule in the synthesis of thiaderivatives of

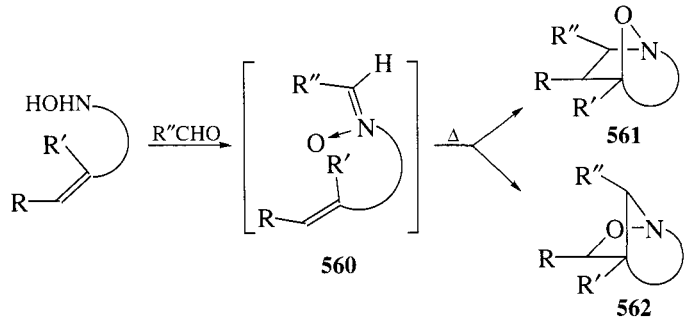
oxazabicyclo[3.3.0]octanes, whereas both bridged and/or fused (*cis* and *trans*) cycloadducts (i.e., oxathiazabicyclo[4.2.1]nonanes and oxathiazabicyclo[4.3.0] nonanes, respectively) are formed with the higher homologues. Notable for its key position in a stereospecific total synthesis of biotin, the cyclization of nitrone **559** effects the installation of four contiguous stereocenters in one-step.[12/78,20/80,35/80]



559

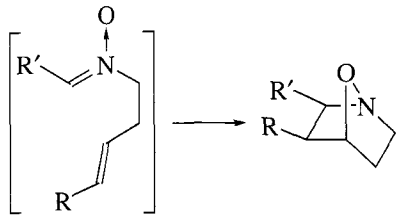
N-Alkenylnitrones are a convenient source of bridged or polycyclic isoxazolidines, which are highly useful intermediates in the synthesis of alkaloids. Three different types of alkenylnitrones can be envisaged: acyclic *N*-alkenylnitrones, *N*-cycloalkenylnitrones, cyclic nitrones having an unsaturated chain in the α-position.

Acyclic (*Z*)-N-alkenylnitrones **560**, usually prepared *in situ* from an *N*-alkenylhydroxylamine and an aldehyde (or ketone) can cyclize thermally to yield the bridged isoxazolidines of general structure **561** and/or **562**. The formation of one or the other cycloadduct strongly depends on the tether length and on the nature of the substituents.[46/85]



560

N-(3-Alkenyl)nitrones with a terminal vinyl group invariably cyclize regio- and stereospecifically to the 7-oxa-1-azabicyclo[2.2.1]heptane (oxazanorbornane) ring system of type **561**, which is highly favored over the 2-oxa-1-azabicyclo[2.2.1]heptane isomer (**562**) both sterically and electronically.[31/69,44/79,46/85,44/89,22/90] As a consequence, high yields of cycloadduct **564** are obtained from nitrones **563**.

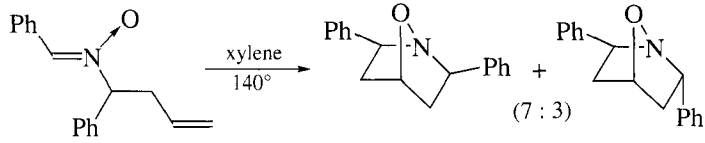


563

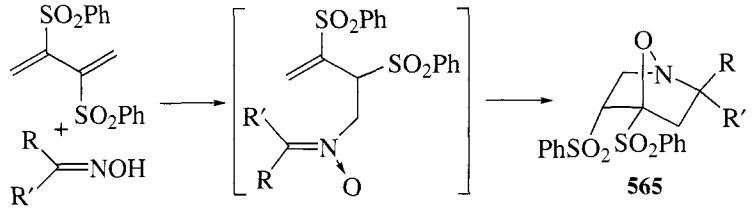
564a: R = H, R′ = Me, 76% yield[46/85]
b: R = H, R′ = Ph, 72% yield[31/69]
c: R = Ph, R′ = H, 56% yield[46/85]

When the terminal alkene is a styryl group (**563**, R = Ph, R′ = H), along with a 56% yield of **564**, a minor amount (9%) of the isomer of type **562** was isolated.[46/85] When the terminal alkene carbon atom is dimethylsubstituted, no reaction occurs.[31/69]

Substitution on the tether connecting dipole and dipolarophile introduces stereoselectivity,[65/86,52/88] and mixtures of diastereoisomeric cycloadducts are obtained, where the *exo,exo* isomer is more or less strongly favored over the *exo,endo* one, for instance:[65/86]



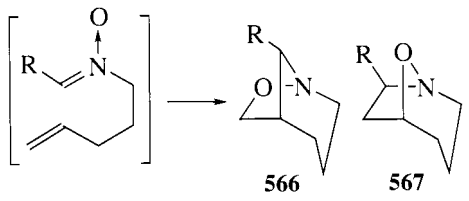
Tandem intermolecular Michael addition–intramolecular nitrone cycloaddition reactions between aldoximes or ketoximes and 2,3-bis(phenylsulfonyl)-1,3-butadiene always lead to a single cycloadduct **565**, a reaction whose stereoselectivity is consistent with theoretical calculations.[49/88,40/91]



565

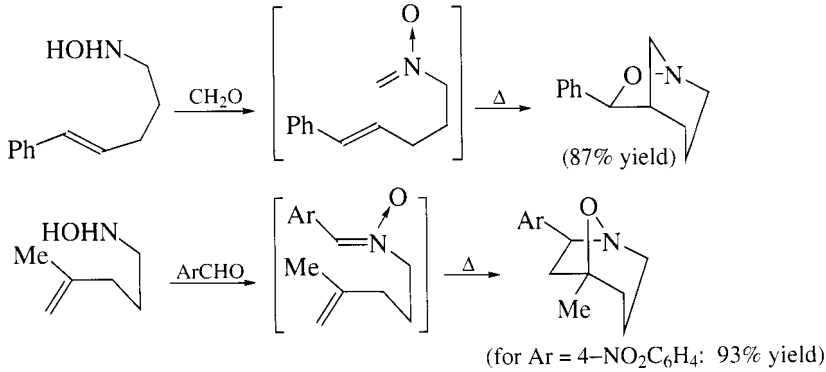
Heating of *N*-(4-butenyl)nitrones gives a mixture of two regioisomeric cycloadducts in which the ratio **566 : 567** always favors the former compound.[44/79,46/85,50/86,50/87,45/89,22/90,63/90,42/91]

Similar results have been reported for nitrones generated *in situ* from oximes and divinyl sulfone.[49/88,53/88,40/91]

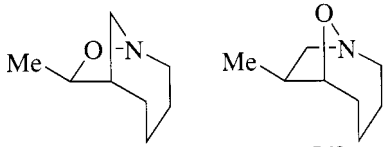


R	566/567	% yield	ref.
H	2.0	70	46/85
4-$MeOC_6H_4$	4.0	61	22/90
Ph	2.3	69	45/89
4-BrC_6H_4	2.2	71	45/89
4-$NO_2C_6H_4$	2.0	80	45/89
PhCH=CH	2.1	78	45/89
2-Pyrrolyl	7.0	35	45/89
2-Thienyl	2.8	62	45/89
2-Furyl	2.0	79	45/89
$C_{11}H_{23}$	6.2	72	45/89

A substituent at the terminal atom of the double bond shifts the cycloaddition toward the formation of the single cycloadduct **566**; by contrast, substitution at the internal carbon atom causes exclusive or preponderant formation of cycloadduct **567**, as shown by the following examples:[44/79,46/85]

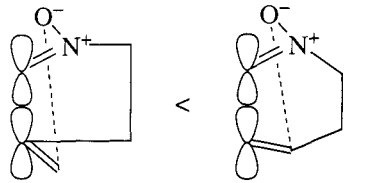


The higher homolog, *N*-(5-heptenyl)nitrone, yields a 3 : 1 mixture of the two isomers **568** and **569**:[46/85]

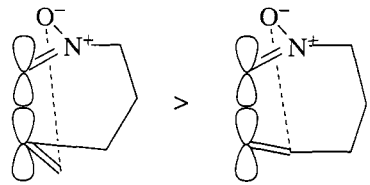


The various results reported above have been nicely rationalized by assuming that in the transition state the new C–C bond is more developed than the C–O

bond. Thus, with *N*-(3-alkenyl)nitrones, the predominant regioisomer arises from transition state **571**, which is lower in energy than transition state **570**, in which additional angle strain is present. In the case of *N*-(4-alkenyl)nitrones, both transition states **572** and **573** are free of strain, but the observed dominance of one product over the other suggests that a preference for transition state **572** may originate in the more entropically favored closure to a six-membered ring.



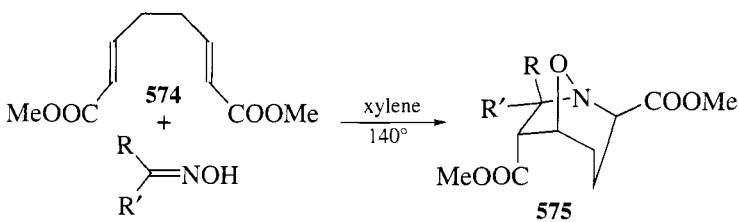
570 **571**



572 **573**

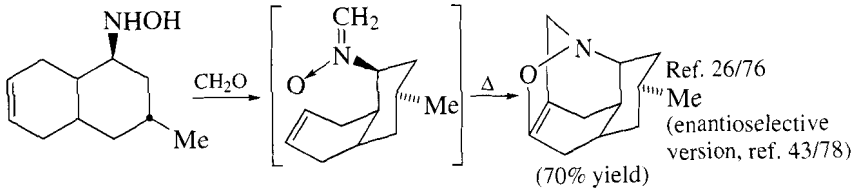
The high degree of stereoselectivity that may be attained has been explained by the severe strain imposed by the short bridge (four or fewer atoms linking nitrone nitrogen and alkene) on the *exo* transition state, thus allowing only cycloaddition of the (*Z*)-nitrone through the unstrained *endo* transition states.

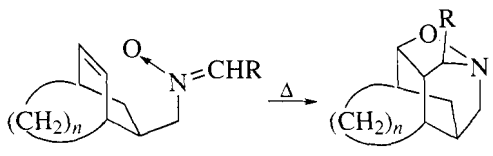
The influence of the substituents along the connecting chain is minimal: α-substitution accentuates the tendency to yield 2-substituted 7-oxa-1-azabicyclo[3.2.1]octanes.[51/86,54/88,46/89,42/91,43/91] Some exceptions to the rule are known; in one, *C*-phenyl-*N*-(2-hydroxyhexen-5-yl)nitrone cyclizes to give a mixture of three stereoisomeric 3-hydroxy-8-phenyl-9-oxa-1-azabicyclo[4.2.1]nonanes, along with minimal amounts of the regioisomeric 3-hydroxy-9-phenyl-8-oxa-1-azabicyclo[4.2.1]nonane.[22/90] A sequence of intermolecular Michael addition followed by intramolecular nitrone cycloaddition involving oximes and 1,5-diene derivative **574** has been reported, yielding cycloadducts **575**.[53/88]



575

Cyclization of *N*-cycloalkenyl nitrones is an extremely useful process for synthesizing polycyclic bridged isoxazolidines, precious key intermediates for building complex alkaloid skeletons. Often when the double bond is endocyclic to a six-membered ring the cycloaddition is regiospecific, as in the following examples:

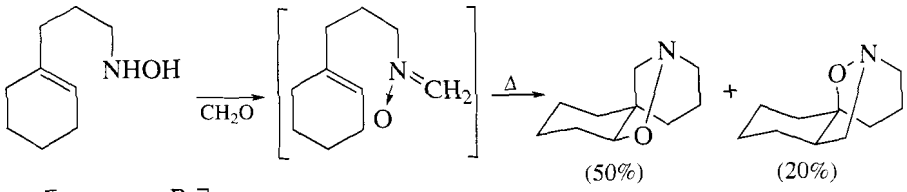




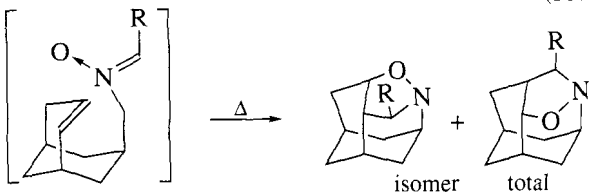
R	n	% yield
H	1	86
Ph	1	99
H	2	49
Ph	2	59

Ref. 47/85

Further examples of this behavior are known,[48/85,10/86] whereas in other cases mixtures of regioisomeric polycyclic isoxazolidines are obtained:[26/82,40/84,5/88,55/88, 1/90]

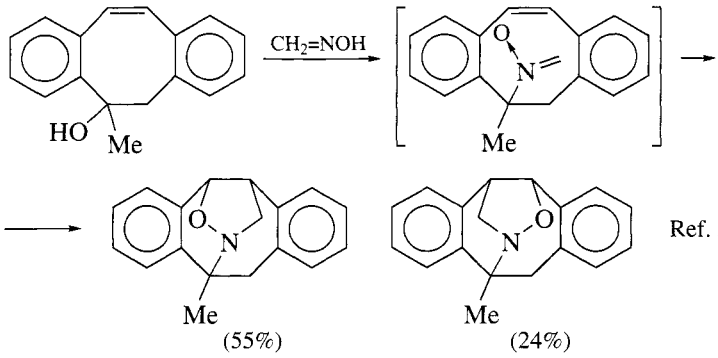


Ref. 40/84

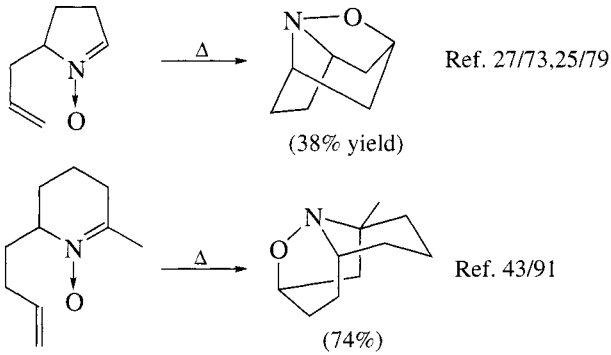


Ref. 55/88

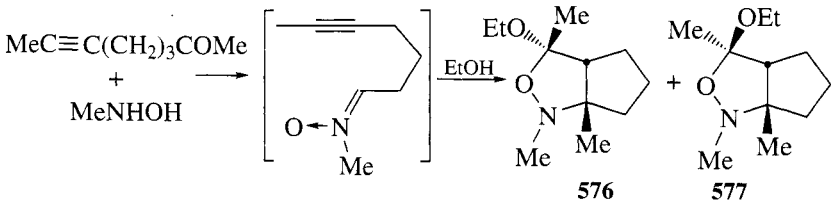
R	isomer ratio	total yield %
H	62 : 28	76
Ph	74 : 26	60
a-furyl	95 : 5	45



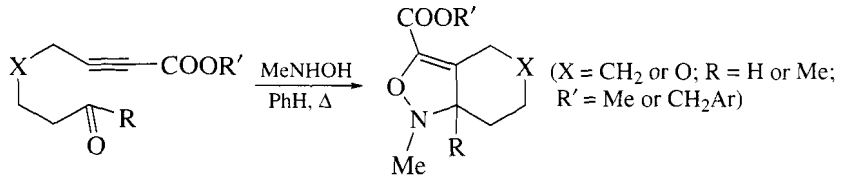
The cyclization of cyclic (five- or six-membered) nitrones, carrying an unsaturated chain at the α position near the nitrogen atom, is also regiospecific and 100% diastereoselective, and opens other potentially interesting routes to alkaloids.[27/73,28/78,25/79,36/80,43/91] The following examples are illustrative:



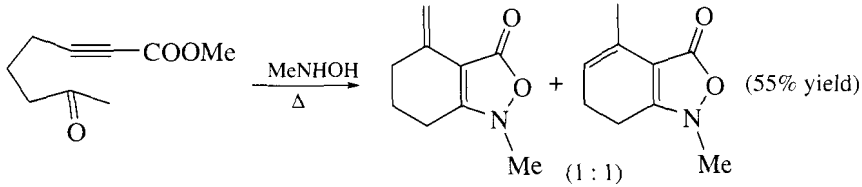
The intramolecular cycloaddition of acetylenes with *in situ*–generated nitrones has received very little attention. An earlier short account on the reaction of oct-6-yn-2-one with *N*-methylhydroxylamine hydrochloride in ethanol reported the formation of the two epimeris cycloadducts **576** and **577** in a 92 : 8 ratio and unreported yields:[27/70]



Recently a more detailed study on the intramolecular nitrone–alkyne cycloaddition showed that cyclization can occur (under strictly controlled experimental conditions) only when the triple bond is separated from the nitrone by four atoms and is substituted with an electron-withdrawing group. Thus, the following reaction takes place with reasonable yield:[50/91]

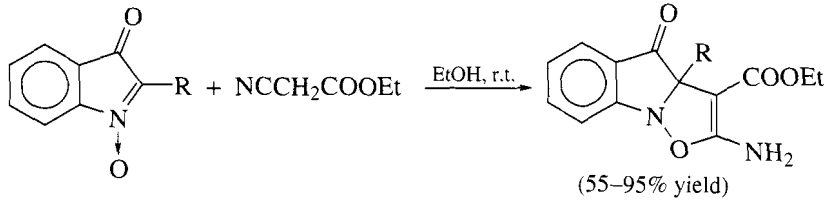


By contrast, the reaction of the lower homolog takes another course and furnishes a mixture of the two condensed isoxazolinones:[51/91]



4.2.2.8. Miscellaneous Cycloadditions

The substituted isatogens have been found to react with ethyl cyanoacetate to yield the corresponding 5-amino-4-isoxazoline derivative, presumably through a two-step pathway:[25/66]

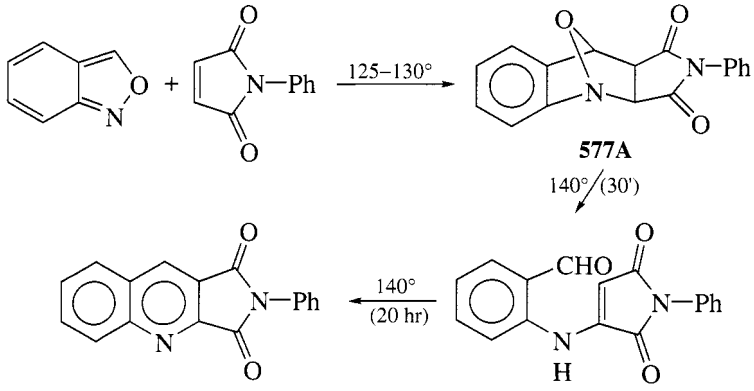


C,N-Diphenylnitrone does not react at all.

4.2.3. [NOC + CC] Process

As described in Chapter 2, the Diels–Alder cycloaddition of anthranil with ethylenic compounds gives rise to *exo*-1,4-epoxy-1,2,3,4-tetrahydroquinolines.

The following example, involving *N*-phenylmaleinimide as the dipolarophile, [28/67] rectified an erroneous report.[2/58] The bridged isoxazoline **577A** is formed by heating the two reactants without solvent and, once isolated, undergoes ring opening in hot xylene solution to give (2-formylanilino)-*N'*-phenylmaleimide, which, in turn, gives rise to a quinoline derivative by longer heating.[28/67] *N*-Alkylmaleinimides give similar results.[27/76]

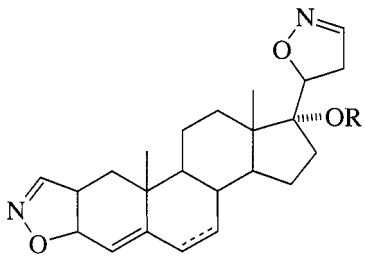


Analogous intermediates have been proposed in the cyclization reaction of anthranil with cycloalkenes and cycloalkanones.[26/66]

1,4-Cycloaddition with dimethyl acetylenedicarboxylate is possible only if electron-withdrawing groups are present in the carbocyclic ring of the anthranil.[58/81]

4.2.4. [OCC + NC] Process

The somewhat peculiar method of synthesizing 2-isoxazolines by cyclocondensation of acetophenones with urea under severe conditions (see Part 1, § 2.2.2.7) has been extended to 17α-hydroxyprogesterone.[45/79] Use of formamide in the presence of perchloric acid furnishes the corresponding 3-unsubstituted isoxazoline derivatives of dihydrotestosterone and other steroidal compounds. [50/74,35/75] Application of the same reaction to 17α-hydroxy (or -acetoxy)progesterone or their dihydro derivatives gave the bisisoxazoline compounds **578**:[45/79]

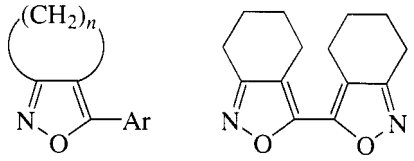


578

4.2.5. [CCNO + C] Processes

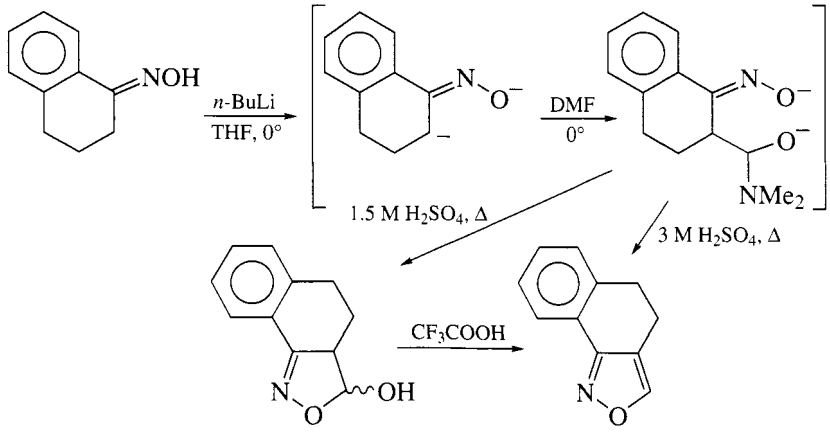
The reaction of oxime dilithium salts with carboxylic acid derivatives offers a convenient method for the regiospecific synthesis of isoxazoles, and has already been illustrated in Part 1, § 1.3.4.1.

The original procedure, from which only moderate yields of product were realized, utilizes carboxylic esters as acylating agents. The reaction has been applied to cyclopentanone or cyclohexanone oximes, which, after formation of the dilithium salts with 2 mole equivalents of butyllithium, were condensed with benzoate esters (or heteroaromatic carboxylates) and cyclized under acidic conditions, to 5-aryl- and 5-heteroaryl- fused derivatives **579**.[16/70,28/76] Use of diethyl oxalate allows the preparation of bisisoxazoles, such as **580**.[21/75] Better yields have been achieved by using lithium diisopropylamide instead of *n*-butyllithium.[13/80]



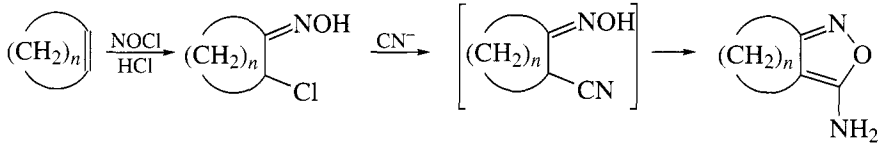
579 (n = 3,4) **580**

A far more convenient procedure involves the use of dimethylformamide as the acylating agent. Good to excellent yields of 3,4-condensed isoxazoles, both 5-unsubstituted and 5-arylsubstituted, have been obtained.[29/78,41/84] Depending on the conditions employed for the final cyclization step, the intermediate 5-hydroxy-2-isoxazoline can be isolated, as shown in the following example:[29/78]



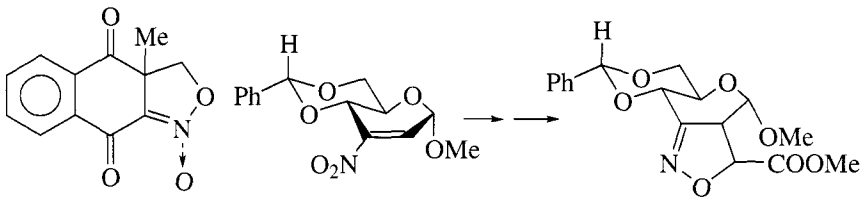
A modification of the preceding method leads to 5-alkylsubstituted 3,4-condensed isoxazoles.[43/82]

A simple and convenient method for synthesizing 5-aminocycloalka[*c*]isoxazoles starts from the α-chlorocycloalkanone oxime, obtained by acidic treatment of the corresponding cycloalkene with nitrosyl chloride. Subsequent treatment with potassium or sodium cyanide in dimethylsulfoxide or ethanol affords the product of substitution and cyclization in one step and in excellent yields,[19/64, 27/66,29/67] as exemplified in the following sequence:



α-Acetoxycycloalkanone oximes can be used instead of the chloroderivatives.[32/69] The same reaction fails with aliphatic chlorooximes or with the chlorooxime derived from norbornene.[27/66] It should be also mentioned that the isolated α-cyanocyclohexanone oxime cyclizes easily under basic conditions (see § 4.2.7). 2-Chloro-1-nitrosocyclohexane behaves analogously, although an unstable intermediate has been reported here.[36/74]

The reaction of nitroalkenes with diazoalkanes or sulfonium ylides is a source of 2-isoxazoline *N*-oxides in all cases where 1,4-addition prevails over 1,2-addition (see Part 1, §§ 2.3.2.3–2.3.2.4). Thus, structure **581** has been proposed for the product of the cycloaddition of diazomethane to 2-nitro-3-methyl-1,4-naphthoquinone,[42/84] whereas the condensed isoxazoline **583** has been obtained from the reaction of the nitrohexenopyranoside **582** with dimethylsulfonium ethoxycarbonylmethylide and subsequent deoxygenation:[25/77,30/78]

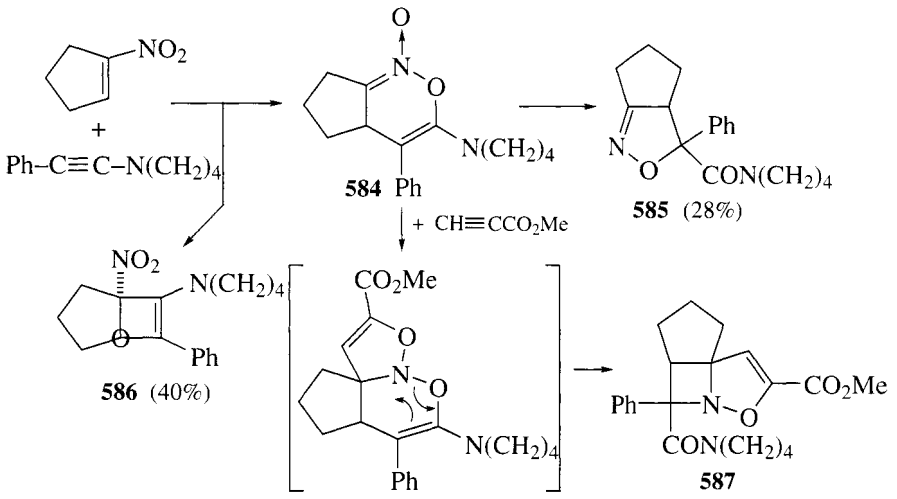


581 **582** **583**

Another condensed 2-isoxazoline *N*-oxide derives from the action of diazomethane on 5,5-dimethyl-2-nitro-1,3-cyclohexadienol, but it is unstable even at room temperature and decomposes to 5,5-dimethyl-3-cyclohexene-1,2-dione monoxime.[40/83] A 3,4-fused isoxazoline *N*-oxide could also be isolated from the low-temperature reaction of 1,3,5-trinitrobenzene with diazomethane.[31/71]

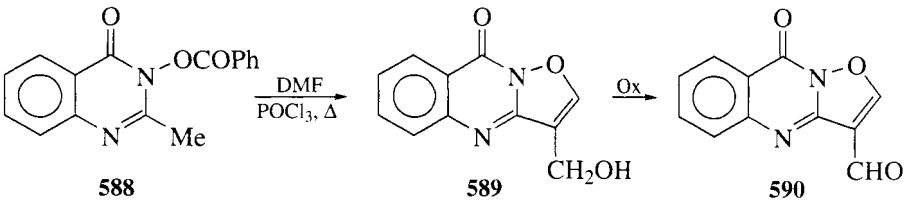
3-Nitrochromone gives mainly the cyclopropabenzopyran, although the condensed isoxazoline-*N*-oxide is also isolated in small amounts.[44/76,59/80]

Electron-rich ynamines react with some cyclic nitroalkenes to give, via an unstable 1,2-oxazine 2-oxide, a 3,4-fused isoxazole derivative, among other products, which may include four-membered cyclic nitrones or cyclobutene [2 + 2] cycloadducts. The procedure is here exemplified by the condensation of 1-nitrocyclopentene with 1-phenyl-2-(1-pyrrolidinyl)acetylene.[37/80,64/82] In addition to the [2+2] cycloadduct **586**, the [4+2] cycloadduct **584** is formed, which is thermally unstable and rearranges to the fused 2-isoxazoline **585**. Moreover, its interception with methyl propiolate produces the fused 4-isoxazoline **587**.



In the reaction of 1-nitrocyclopentene and 1-phenyl-2-dimethylaminoacetylene, homolytic N–O bond cleavage of the intermediate of type **584** has been invoked to account for the exclusive formation of an isoxazoline derivative analogous to **585** in which the $CONMe_2$ has replaced $CON(CH_2)_4$.[76/88] Analogous reactions have been reported for 2-nitrobenzofuran and the same ynamine [38/81] or 1-(diethylamino)propyne.[38/80]

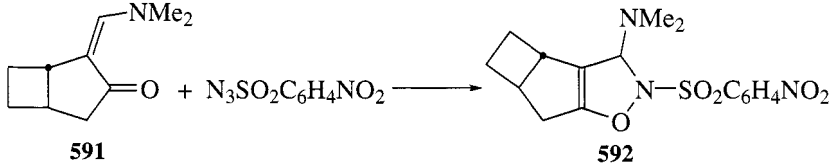
An unprecedented condensation leads to the formation of 3-hydroxymethylisoxazolo[3,2-*b*]quinazol-9-one (**589**) by Vilsmeier–Haack reaction on



3-benzoyloxy-2-methyl-4-quinazolone (**588**); the expected aldehyde **590** is produced from the carbinol **589** only by subsequent oxidation with Jones' reagent.[52/86]

4.2.6. [CCCO + N] Process

A condensed 4-isoxazoline structure **592** has been suggested for the product obtained by condensation of the bicyclic enamino ketone **591** with 4-nitrophenylsulfonylazide,[46/79] although the proposed structure needs further confirmation.



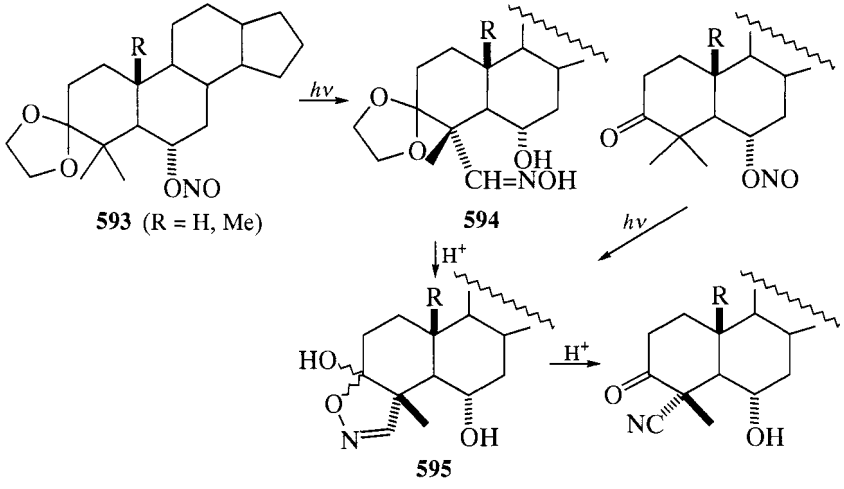
591 **592**

4.2.7. [CCCNO] Processes

4.2.7.1. Cyclization of β-Diketone Monoximes and Related Compounds

Oximation of β-diketones has already been addressed in § 4.2.1.1; the intermediate monoxime, or its cyclic 5-hydroxy-2-isoxazoline tautomer is not usually isolated but can be cyclized in a subsequent step, generally in acidic media.

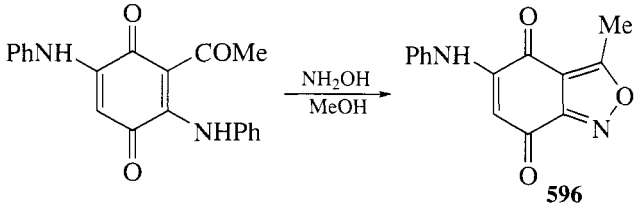
Barton reaction has been employed to prepare monoximes in the lanostane series. Photolysis of the 6α-nitrite **593** leads to monoxime **594**, which cyclizes



593 (R = H, Me) **594**

in acidic media to the A ring condensed 5-hydroxyisoxazoline **595**. The latter compound can be directly prepared by photolysis of the nitrite of the free 6-hydroxy-3-keto derivative.[31/70,26/77]

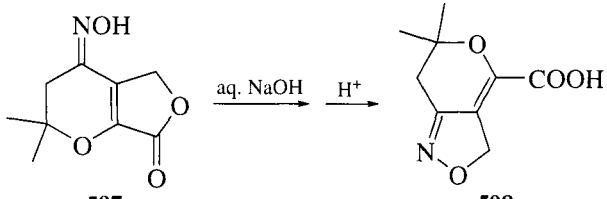
The intermediacy of a β-diketone monoxime is presumed in the quantitative preparation of 2,1-benzisoxazolequinone **596** by oximation of 2-acetyl-3, 6-bisanilino-1,4-benzoquinone.



596

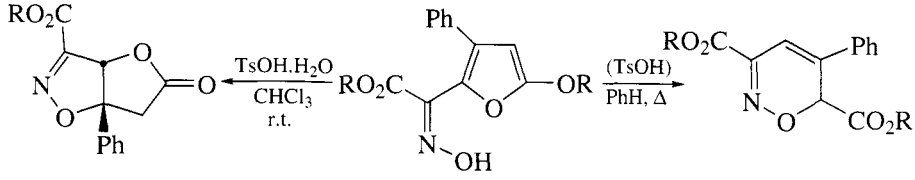
4.2.7.2. *Cyclization of α,β-Unsaturated Oximes*

In the acyclic series, cyclization of α,β-ethylenic ketoximes is one of the oldest, although far from the most straightforward, methods for preparing 2-isoxazolines (see Part 1, § 2.2.2.1a). A few scattered examples have also been reported in the condensed series. Thus, dimethylisopatuline oxime (**597**) rearranges under basic conditions to the pyrano[4,3-*c*]isoxazoline **598**.[64/87]



597 **598**

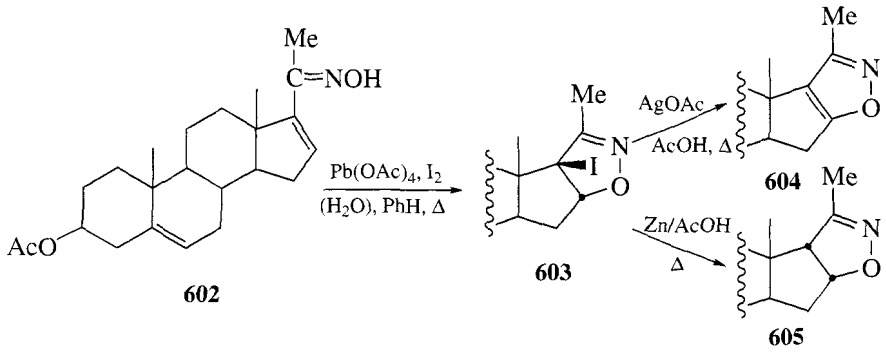
Treatment of the furanylglyoxylate oxime **600** with excess $TsOH.H_2O$ yields the isoxazoline lactone **599**, whereas catalytic amounts of TsOH effect rearrangement to the 6*H*-1,2-oxazine dicarboxylate **601**:[39/81]



599 **600** **601**

Cyclizations of this type are often effected with an oxidizing agent, as with the oxime derived from 2-benzylidene-3-oxoquinuclidine[40/81] and, in the steroid

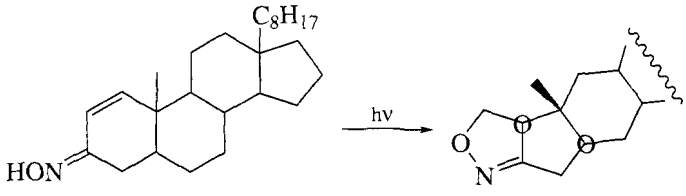
field, the oxime of 3β-acetoxypregna-5,16-dien-20-one (**602**). While lead tetracetate in anhydrous medium led to a dimeric product, use of a mixture of the same oxidant and iodine in the presence of water allowed the isolation of the 4-iodoisoxazoline **603**, which can easily be either deiodinated to **605** or aromatized to **604**:[33/69]



602 **603** **604** **605**

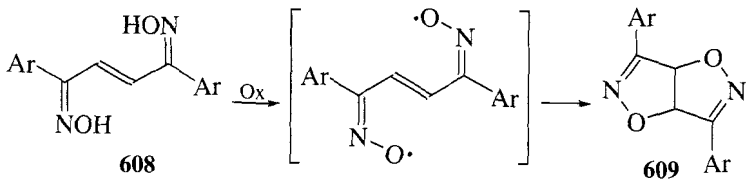
An analogous compound (**605**) has been reported to result from photolysis of oxime **602**.[34/69]

Irradiation of cholest-1-en-3-one oxime (**606**)[18/87] and of its 4,4-dimethyl derivative[77/88] promotes an A-ring contraction with formation of the 3,4-fused isoxazoline **607**.



606 **607** (28% yield)

A peculiar double cyclization of some 2-unsaturated 1,4-dioximes **608** to the interesting dihydroisoxazoloisoxazole system **609** is promoted by iminoxyl-generating oxidants, such as phenyliodoso bistrifluoroacetate (PITFA) or lead tetracetate (LTA):[31/78,47/79,45/82]

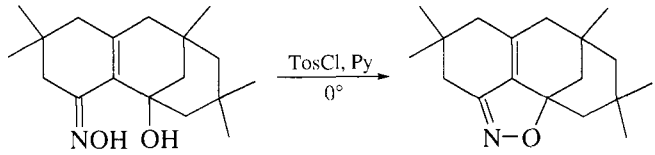


608 **609**

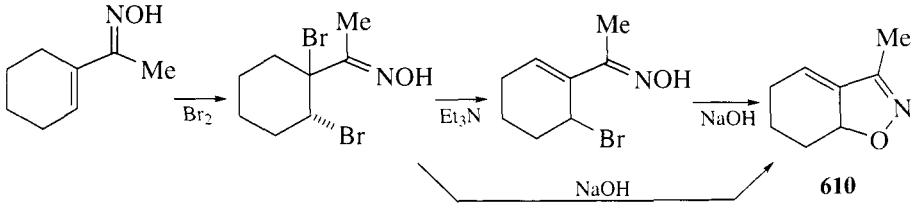
Along with **609**, minor amounts of 3,6-disubstituted pyridazine 1,2-dioxides are formed. This last compound is the only product that results when aliphatic dioximes, such as hex-3-ene-2,5-dione dioxime, are used.[29/76,47/79]

4.2.7.3. Cyclization of Ketoximes β-Substituted with Electron-Withdrawing Groups

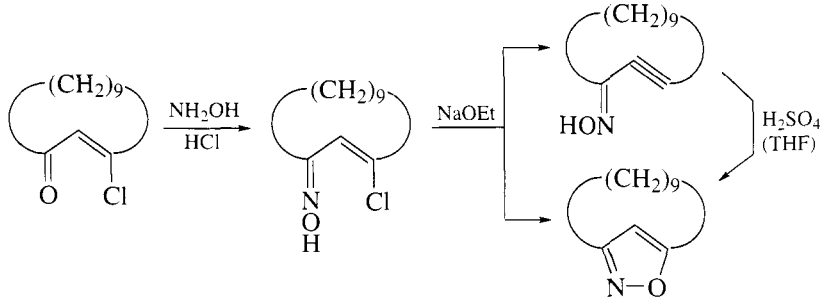
Cyclization of β-hydroxyketoximes to condensed 2-isoxazolines is promoted by acylating agents, such as tosyl chloride or acetic anhydride in the presence of pyridine, and is known in the steroid field;[20/64,28/66] the method is exemplified here with 3-oximinodiisocamphor-2(7)-en-1-ol:[78/90]



The oximes of 1-acetyl-1,2-dibromocyclohexane (or -cycloheptane) can be dehydrobrominated in two steps under the influence of bases to obtain fused-ring isoxazolines of type **610**.[13/70] The failure of the homologous cyclopentane derivative to undergo cyclization conforms to Brown's I-strain theory.

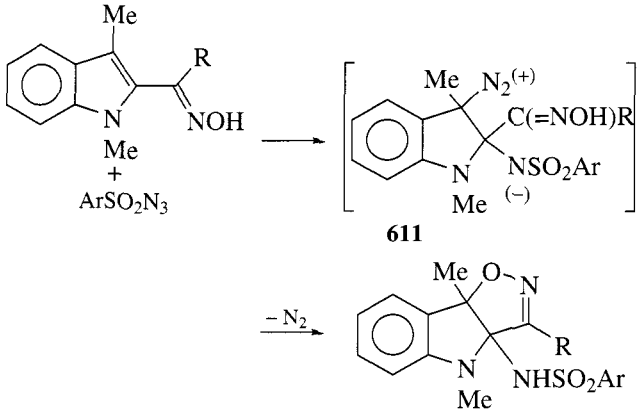


The first example of an isoxazolophane, specifically, (3,5)[9]isoxazolophane, has been prepared from a mixture of isomeric 3-chlorododec-2-enone oximes:[32/70]



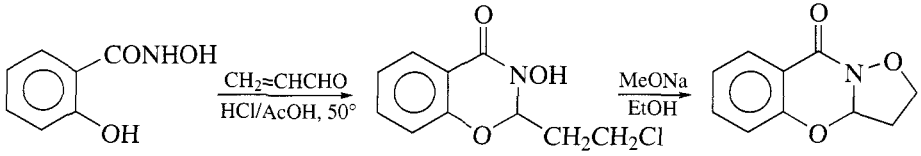
The cyclization of a steroidal β-dimethylaminomethiodide ketoxime is deceiving: only a 3% yield of the D-ring condensed isoxazoline has been obtained.[14/65] Better results have been achieved by cyclization of analogous α,β-oxido ketoximes.[21/64]

The 1,3-dimethyl-2-acylindole oxime cyclizes by reaction with arenesulfonyl azides; the intermediacy of the diazonium internal salt **611** has been proposed.[37/74]



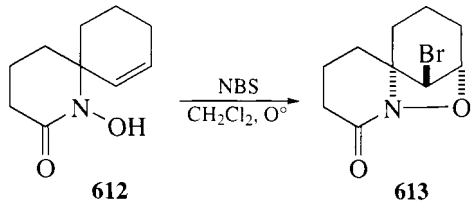
4.2.7.4. *Cyclization of γ-Substituted Cyclic Hydroxylamines*

A large number of antiinflammatory agents belonging to the class of 3,3a-dihydro-2*H*,9*H*-isoxazolo[3,2-*b*][1,3]benzoxazin-9-ones have been prepared starting from salicilohydroxamic acids and α,β-ethylenic aldehydes through base-promoted cyclization of the intermediate cyclic hydroxylamines.[35/69,33/70,22/75,27/77]



With suitably modified methods, a series of isoxazoloquinazolinones have subsequently been prepared.[28/77]

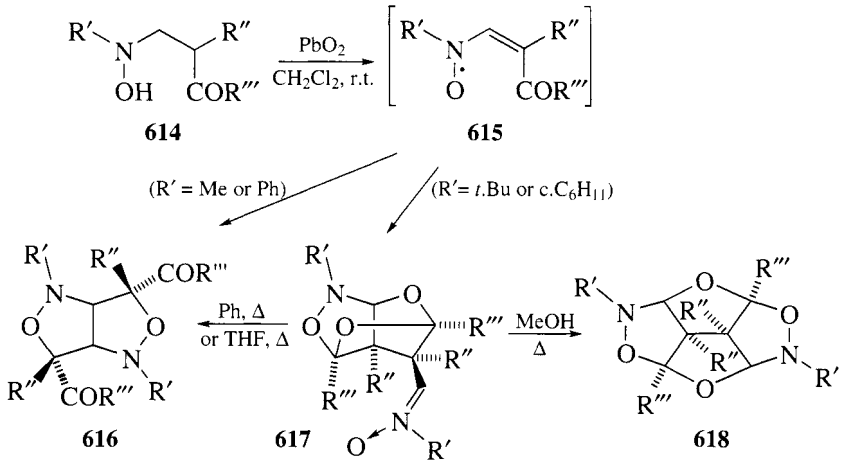
A key intermediate in a synthesis of (±)perhydrohistrionitoxine is the spirocyclic hydroxamic acid **612**, which can easily cyclize by reaction with NBS to give the tricyclic bromoisoxazolidine **613**:[46/82]



612 **613**

4.2.7.5. Cyclization of γ-Ketohydroxylamines

A general synthesis of the tetracyclic isoxazolidine system **618** is based on the oxidation of γ-ketohydroxylamines **614** with lead dioxide. The intermediate unstable vinylaminyloxide **615** promptly dimerizes to the isoxazolidine nitrone **617**, which may thermally isomerize, according to solvent and temperature, either to **618** with good to excellent yields, or to the bicyclic compound **616**. With suitable substituents, this is also the preferred dimerization product.[43/84,48/88,59/89]

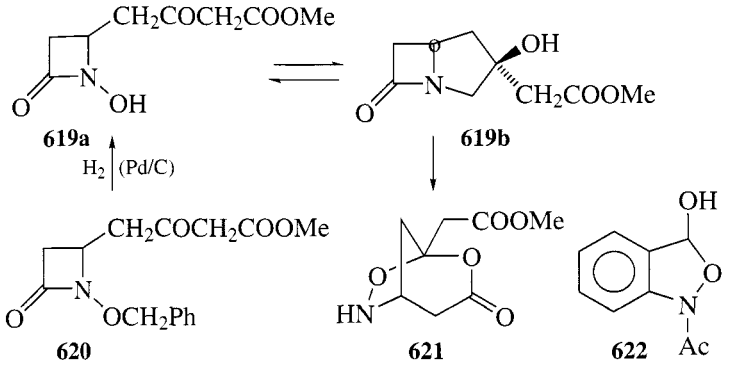


614 **615**

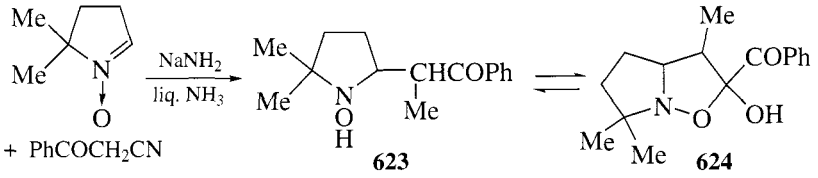
616 **617** **618**

The ring–chain isomerism of cyclic γ-ketohydroxylamines usually disfavors the hemiketal 5-hydroxyisoxazolidine form.[60/89] Nevertheless, starting from *N*-benzyloxy-β-lactam **620**, isoxazolidine **619b**, obtained by catalytic reduction, converts to the stable bicyclic isoxazolidine compound **621**.[49/91]

The hemiacetal form **622** results from the acetylation of the so-called agnotobenzaldehyde, obtained in an older research from the zinc-promoted reduction of 2-nitrobenzaldehyde, whose first step is reported to be 2-hydroxylaminobenzaldehyde.[32/78]

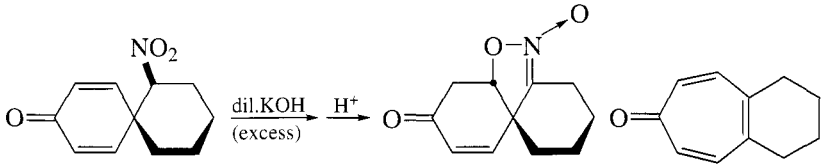


The γ-ketosubstituted 1-hydroxypyrrolidine **623**, easily obtainable from dimethylpyrroline 1-oxide, is reported to exist in the solid phase as the isomeric condensed 5-hydroxyisoxazolidine **624**:[30/76]



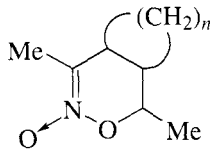
4.2.7.6. Cyclization of Nitroderivatives

The importance of unsaturated and partially unsaturated nitro- or dinitrocompounds in the synthesis of 2-isoxazoline *N*-oxides is well-known (see Part 1, § 2.3.2). Some cyclic derivatives of unusual structure have been reported. Thus, the tricyclic spiroisoxazoline *N*-oxide **626** has been prepared by treatment of the spirocyclohexadienone **625** with dilute KOH:[60/86]

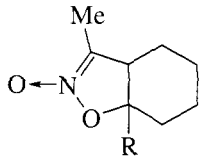


Treatment of both **625** and **626** with more concentrated base (or, better, with DBU) promotes the formation of condensed tropone **627**.

Intramolecular cyclization of 2-nitrodeca-2,8-diene, catalyzed by tin tetrachloride, gives the corresponding condensed 1,2-oxazine-*N*-oxide **628b** as main product, and the condensed isoxazoline-*N*-oxide **629a** as secondary product. The same reaction with 2-nitronona-2,7-diene is reported to yield different products depending on the stereochemistry of the starting compound. The *cis*-nitrodiene is 20-fold more reactive than the *trans* isomer; the former compound gives the oxazine-*N*-oxide **628a** in good yield, whereas only the isoxazoline-*N*-oxide **629b** is obtained in 11% yield from the latter compound.[79/90]

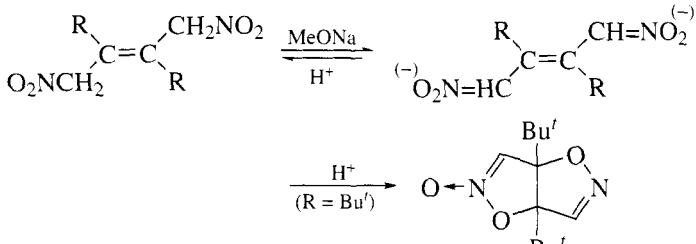


628a: $n = 3$
628b: $n = 4$



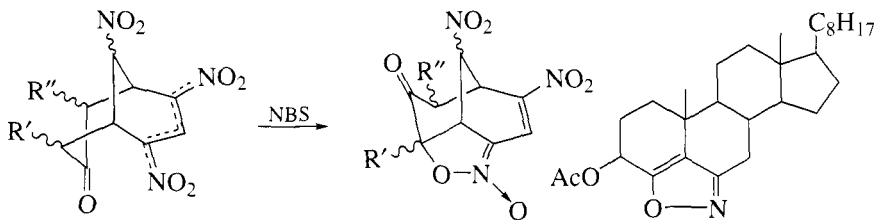
629a: R = Et
629b: R = Me

1,4-Dinitro-2,3-dialkyl-2-butenes are easily transformed into the corresponding dianions; the dimethylsubstituted salt reverts to the starting dinitrocompound by acidification. By contrast, the bulky 2,3-di-*tert*-butylderivative cyclizes under the same conditions to 3a,6a-di-*tert*-butyl-3a,6a-dihydroisoxazolo[5,4-*d*]isoxazole-*N*-oxide (**630**):[34/70]



630

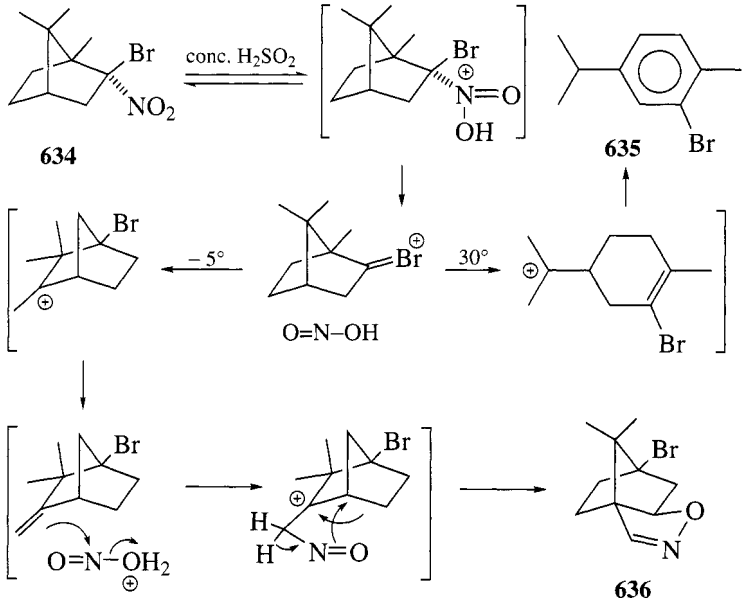
The isoxazoline-*N*-oxide structure **632** has been attributed to one of the products of NBS oxidation of the stable bicyclic anions **631**, prepared from suitably substituted Meisenheimer complexes.[25/71]



631 **632** **633**

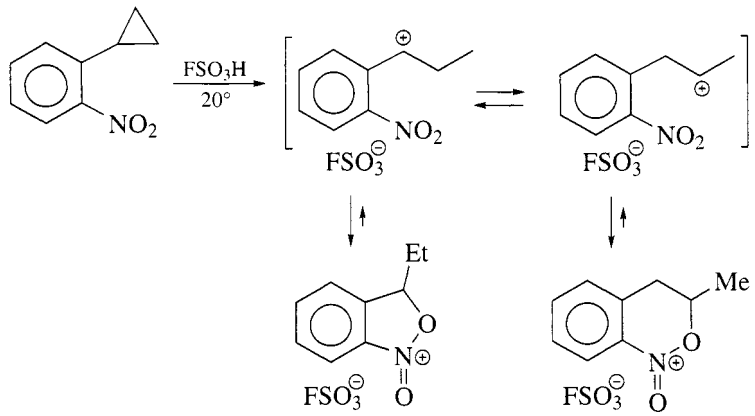
Irradiation of 6-nitrocholesteryl acetate promotes deconjugation to 6-nitrocholest-4-en-3-yl acetate and, to a lesser extent, cyclization to the condensed steroidal isoxazole **633** as secondary product.[4/65]

An interesting mechanistic problem is offered by the low-temperature acid-promoted formation of the so-called "anhydrobromonitrocamphane" derived from 2-bromo-2-nitrocamphane **634**, in turn, easily prepared from camphor oxime and hypobromite. This venerable reaction,[1/899,1/01] was reconsidered when the structure of the product was demonstrated to be the tricyclic isoxazoline **636** by chemical studies,[2/57] spectroscopic data[5/74] and X-ray analysis.[20/72] The reaction mechanism must take into account the fact that treatment with acid at room temperature leads to 2-bromo-*p*-cymene (**635**) instead of **636** (Scheme 4.5).[12/69,5/74] The transformation involves three stages: an initial loss of the nitro group as nitrous acid to give a bornane cation, which rearranges to 4-bromocamphene, followed by recombination with the elements of the lost nitro group.



Scheme 4.5

Although this does not have any preparative value, solutions of 2-nitrophenylcyclopropanes in fluorosulfonic acid contain the cyclic *N*-oxo-3-alkylsubstituted benz[2,1]isoxazolium ions in admixture with six-membered *N*-oxo-3-alkyl-substituted 3,4-dihydro-benz[2,1]oxazinium ions, as illustrated below for the unsubstituted starting material:

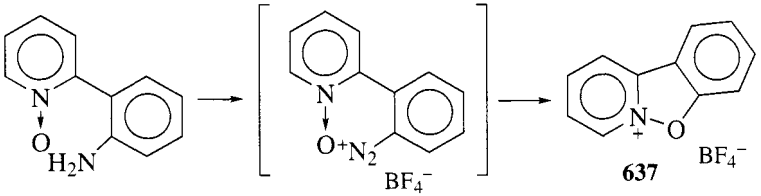


Substitution in the cyclopropane ring results in a mixture of three or four isomeric ions. The isomerization rate and the ratio of isomeric ions strongly depend on the substitution pattern on both the cyclopropane and the phenyl rings.[39/74,40/74,31/76,78/88,79/88,61/89,62/89]

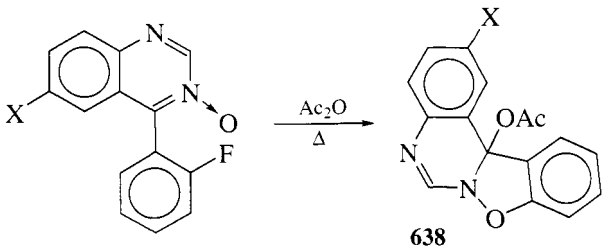
4.2.7.7. *Cyclization of Aromatic N-Oxides*

Pyridinium *N*-oxides or analogous compounds can cyclize to polycondensed isoxazolium or aromatic isoxazolium salts if a group prone to intramolecular nucleophilic attack is present in a suitable position.

Thus, the benzisoxazolo[2,3-*a*]pyridinium system **637** has been prepared from 2-*o*-aminophenylpyridine 1-oxide via the diazonium salt[33/78] and benzisox-



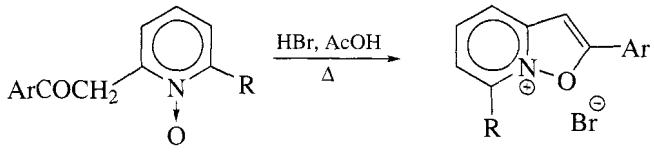
637



638

azolo[2,3-*c*]quinazolines **638** have been obtained from 4-*o*-fluorophenylquinazoline 3-oxides:[41/74]

Moreover, a general synthesis of 2-arylisoxazolo[2,3-*a*]pyridinium salts is based on the acid-catalyzed cyclization of 2-(aroylmethyl)pyridine 1-oxides:[29/77,30/77]

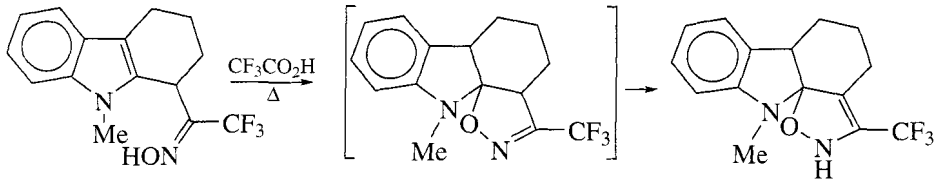


The unsubstituted 2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromide was formed by refluxing 2-(2-pyridyl) ethanol *N*-oxide with 48% hydrobromic acid.[26/58]

For syntheses involving rearrangements of heteroaromatic *N*-oxides, see § 4.2.11.4.

4.2.7.8. Miscellaneous Cyclizations

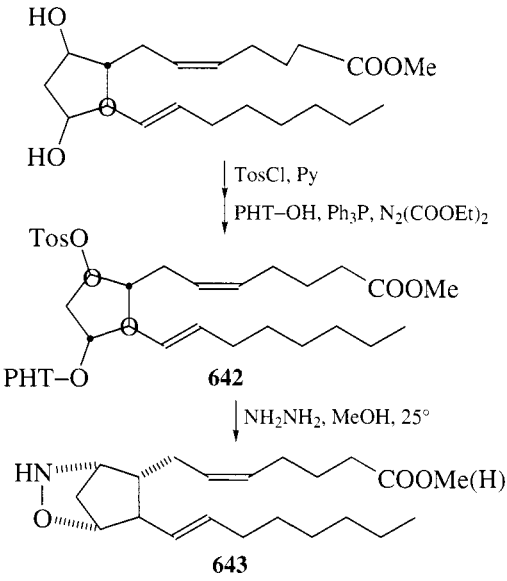
An acid-promoted isomerization transforms oxime **639** into tetracyclic 3-isoxazoline **641**, less strained than the expected 2-isoxazoline compound **640**:[111/81]



639 **640** **641**

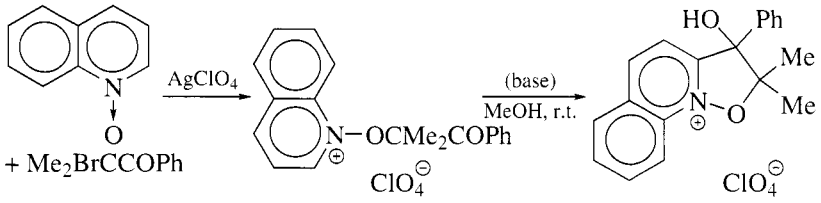
4.2.8. [CCCON] Process

During the synthesis of 15-deoxy-9,11-(epoxyimino)prostaglandins (e.g., **643**), potent thromboxane synthetase inhibitors, the key step was deprotection of the masked *O*-alkylhydroxylamine **642** (PHT = phtalimido) with hydrazine, as illustrated by the following sequence:[34/78]



4.2.9. [CNOCC] Process

N-Alkoxyquinolinium (or isoquinolinium) salts, which have a β-keto group in the alkoxy chain, undergo facile intramolecular cyclization in the presence of a base (preferably 2,2,6,6-tetramethylpiperidine) to give hydroxylated isoxazolo[2,3-*a*]quinolinium (or isoquinolinium) salts, as illustrated in the following example:



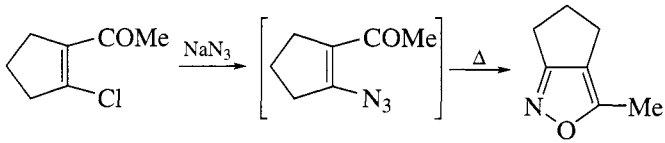
Further action of a base (preferably a cyclic secondary amine) results in a convenient synthesis of 2-acylquinolines (or 1-acylisoquinolines), a procedure that will be discussed in section § 4.3.2.7.[29/87,36/87]

Similarly substituted *N*-alkoxypyridinium salts behave analogously, but subsequent treatment of the isoxazolopyridinium salts thus obtained with pyrrolidine provokes opening of the pyridinium ring, leading to 3-butadienyl-2-isoxazoline derivatives.[69/86,50/89]

4.2.10. [OCCCN] Processes

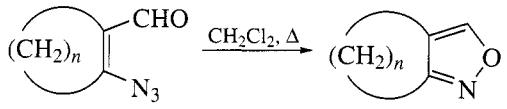
4.2.10.1. Decomposition of β-Azidocarbonyl Compounds

Thermolysis of β-azidovinyl ketones gives fairly good yields of isoxazoles (see Part 1, § 1.3.6.1). Some fused isoxazoles have also been prepared by this route; 3-methylcyclopenta[1,2-*c*]isoxazole (**644**) has been obtained, 58% yield, from the crude azide in dimethylformamide at 50°C.[29/66]



644

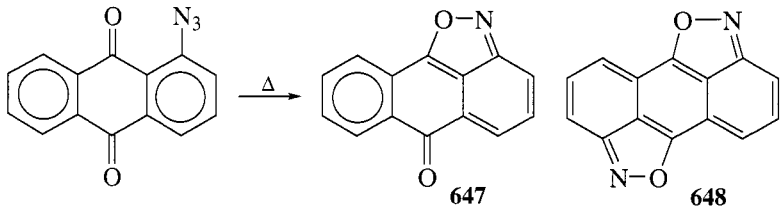
In a similar fashion, cyclic β-azido-unsaturated aldehydes **645** give the unsubstituted fused compound **646**.[80/88]



645 **646**

Polycyclic isoxazoles, such as naphtho[1,2-*c*]-, phenanthro[1,2-*c*]-, and acenaphtho[1,2-*c*]isoxazoles, have been prepared by the same method.[45/91]

The carbonyl group of 1-azidoanthraquinone is perfectly situated to assist in thermal decomposition, and a pericyclic process has been proposed for the pyrolysis.[31/77] Excellent yields of anthra[1,9-*cd*]isoxazol-6-ones of type **647** have been obtained from a large number of azidoanthraquinones bearing substituents in one or both aromatic rings.[1/16,1/21,31/68,15/79,39/80,40/80,47/82,48/82,41/83,44/84,64/84,65/84,49/85]

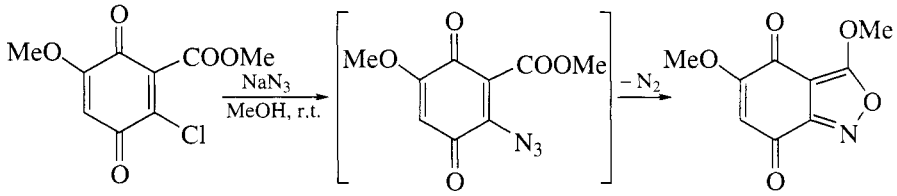


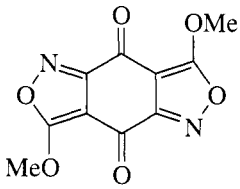
647 **648**

In an extension of this methodology, anthra[1,9-*cd*:5,10-*c'd'*]bisisoxazole **648** has been prepared from the corresponding bisazide.[47/82]

In general, nonpolar solvents such as benzene, toluene, xylene, *o*-dichlorobenzene, and nitrobenzene have been used to effect this transformation, which occurs at temperatures between 80 and 160° C. In isolated cases the cyclization takes place under brief irradiation in dioxane.[15/79] When a suitable substituent is present in the 2 position of both the starting azidoanthraquinone and the anthraisoxazolone, thermolysis in polar solvents, such as DMF, can lead to recyclization and subsequent formation of different polyheterocyclic systems (see this volume, Chapter 2).

β-Azidocarboxylic esters are also candidates for thermal cyclization. For example, the azidoquinone **649** is unstable even at room temperature, and the bicyclic isoxazole system **650** is directly obtained when 2-chloro-5-methoxy-3-methoxycarbonyl-*p*-benzoquinone is treated with sodium azide:[31/67,42/74]

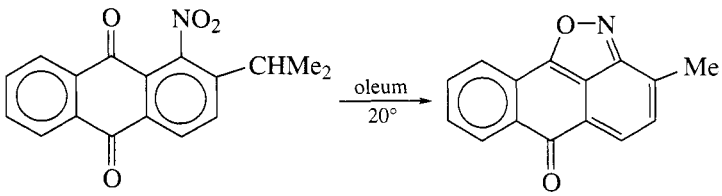




The tricyclic bisisoxazole **651** has been similarly prepared.[58/80]

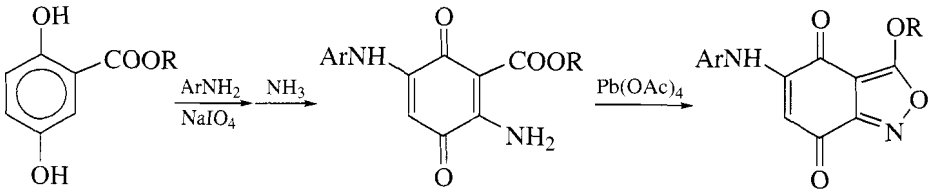
4.2.10.2. Other Cyclizations

An interesting variation of 1-azidoanthraquinone decomposition is its use in the formation of 3-methylanthra[1,9-*cd*]isoxazole by treatment of 2-isopropyl -1-nitroanthraquinone with oleum at room temperature:[31/68]



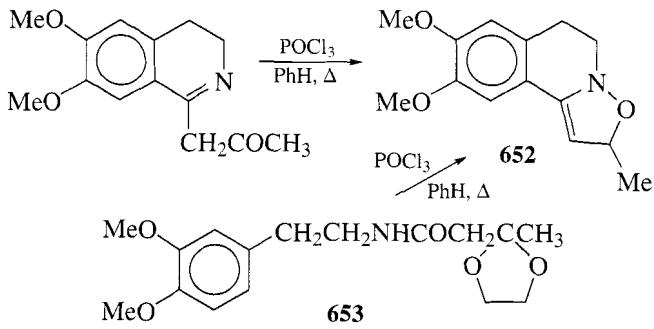
Taking into account the formation of anthra[1,2-*c*]isoxazole-6,11-diones by the action of oleum on 2-alkyl-1-nitroanthraquinones (see Chapter 2), a mechanism has been proposed that involves initial formation of an anthra[1,2-*c*]isoxazole cation, 1,2-methyl-shift, and loss of an acetyl cation with simultaneous closure on the oxygen of the 9-carbonyl group.

Alkoxyisoxazolequinones can be also prepared from gentisic esters through the following three-step sequence, involving as the final step an oxidative cyclization of 2-aminoquinonecarboxylates:[42/74,72/85]



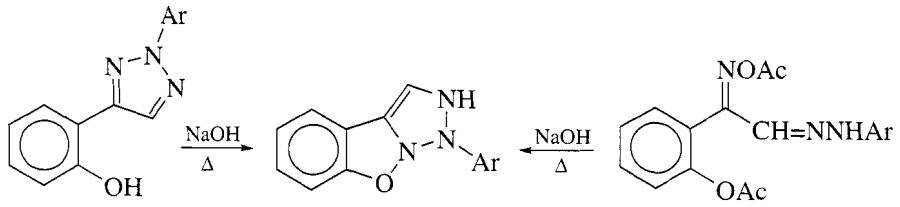
3-Methoxynaphth[2,3-*c*]isoxazole-4,9-dione has also been prepared by a similar route.[72/85]

Cyclization of 1-acetonyl-6,7-dimethoxy-3,4-dihydroisoquinoline to the condensed isoxazole derivative **652** is effected by refluxing with phosphoryl chloride:[8/60]

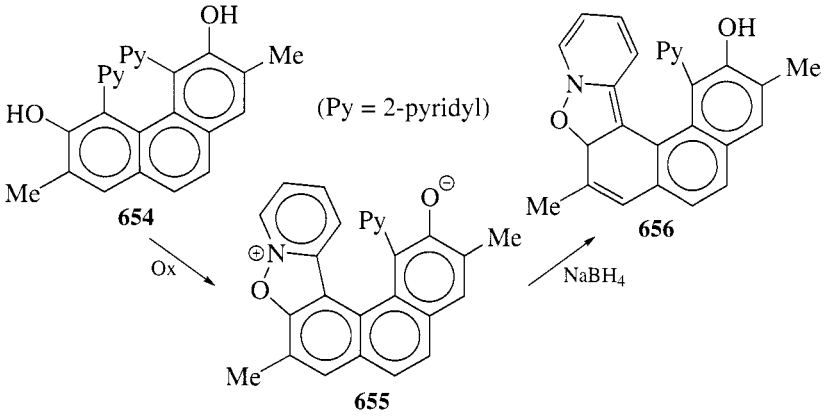


The same product can be obtained directly from amide derivative **653**.

Some 1,2,3-triazolo[3,4-*b*]benzisoxazoles are formed by base-promoted isomerization of 4-(*o*-hydroxyphenyl)-1,2,3-triazoles or of their acyclic precursors, as in the following example:[36/69]



Intramolecular oxidative cyclization enables the synthesis of isoxazolium betaines **655** by treatment of the highly congested bispyridylphenanthrenediol **654** with *N*-chlorobenzotriazole; subsequent reduction under mild conditions formed the neutral pentacyclic 3-isoxazoline **656**:[28/73]



Analogous polycyclic isoxazolium salts could be obtained by using cupric chloride as oxidant.[28/73,29/73]

4.2.11. Syntheses from Monocyclic Heterocycles

Condensed bi- or polycyclic isoxazole systems have also been prepared from either monocyclic isoxazole derivatives provided with a suitable functionalized side chain, or, less frequently, from other heterocyclic rings by ring opening and subsequent reclosing in different way.

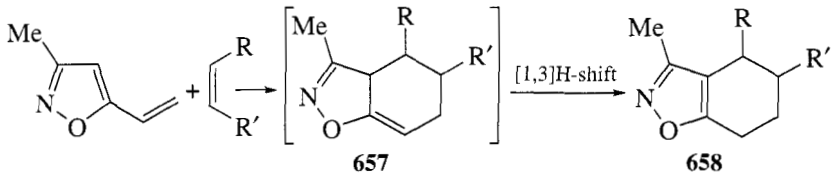
Methods based on the former process are illustrated separately here, depending on whether the starting ring belongs to an isoxazole, an isoxazoline, or an isoxazolidine system.

4.2.11.1. Syntheses from Isoxazole Derivatives

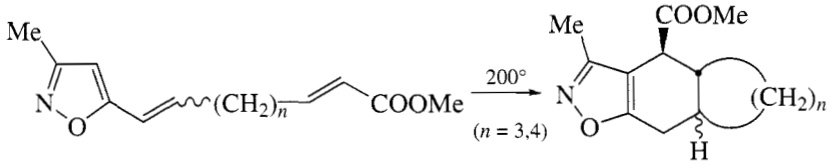
Diels–Alder reactions that involve isoxazole derivatives in the capacity of diene or dienophile have been discovered quite recently; examples are provided below.

5-Vinylisoxazole can enter reaction with electron-poor dienophiles only with difficulty, whereas maleic anhydride reacts easily at 120°C in a sealed tube. Lower yields are obtained with methyl vinyl ketone or with methyl acrylate under the same conditions owing in large part to polymerization of the dienophiles. In one case the primary cycloadduct **657** has been detected as a

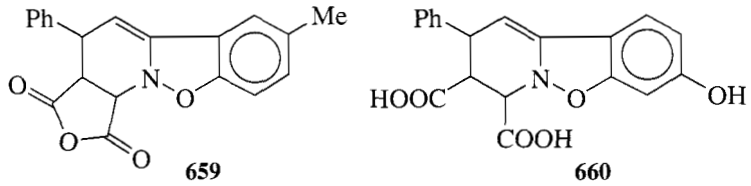
transient species by NMR spectroscopy, but the isolated products are the aromatized tetrahydrobenzisoxazoles **658**. The regioselectivity observed in the latter case is consistent with frontier orbital considerations.[50/85]



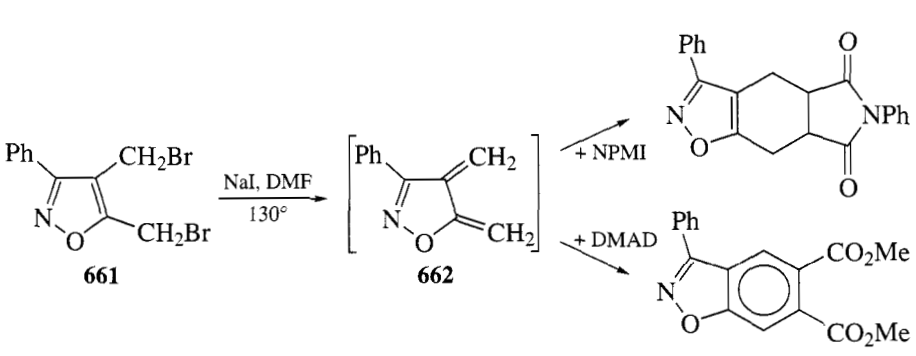
Intramolecular versions of the same reaction that exhibit moderate stereoselectivity, have been reported, as illustrated by the following example:[65/87]



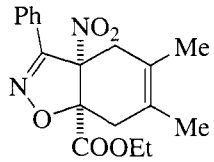
3-Styryl-1,2-benzisoxazoles and related compounds have been reported to enter 1,4-cycloadditions with maleic anhydride or maleic acid to generate condensed systems such as **659** or **660**.[41/80]



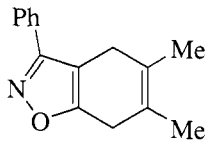
The isoxazole 4,5-diene **662**, generated *in situ* by sodium iodide–induced 1,4-elimination from dibromide **661**, can be trapped by a variety of dienophiles, as the following examples show:[52/91]



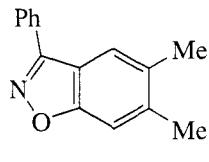
The presence of a nitro group in the 4 position and of another electron-withdrawing group (ethoxycarbonyl, benzoyl) in the 5 position enables the isoxazole nucleus to serve as a dienophile in Diels–Alder reactions under rather severe conditions (toluene, sealed tube, 110–115°C, 48 h). Adduct **663** was obtained, in 87% yield, by reaction of ethyl 4-nitro-3-phenylisoxazole-5-carboxylate with 2,3-dimethylbutadiene (DMB).[53/86,29/90] Prolonged heating of **663** in xylene at 150°C led to formation of **664** by Grob-like fragmentation; subsequent aromatization to **665** occurred on treatment with DMB.[53/86]



663

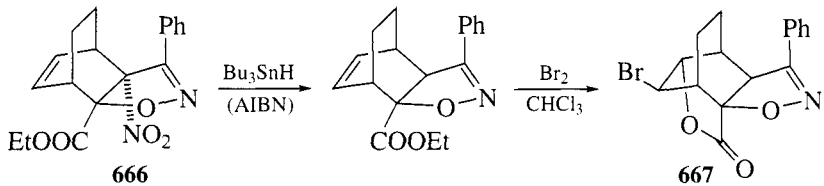


664



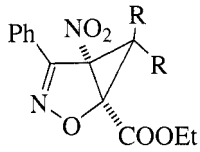
665

Other dienes employed in this sequence are isoprene, which gives a 5:1 mixture of the two possible regioisomers, and cyclohexa-1,3-diene, whose cycloadduct (**666**) undergoes facile denitration and bromination to give the polycyclic isoxazoline **667**:[29/90]

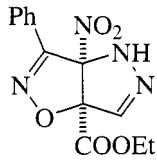


666 **667**

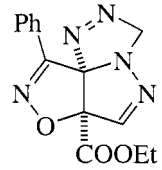
The C4–C5 double bond of ethyl 4-nitro-3-phenylisoxazole-5-carboxylate is also reactive toward 1,3-dipoles, such as diazomethane or 2-diazopropane. The initial 1,3-dipolar cycloadduct is not isolable, but its presence has been inferred both from spectroscopic evidence and from the nature of the resulting products. Thus, diazomethane in equimolar amount yields a mixture of the stable bicyclic cyclopropaisoxazole **668a** and of the dihydropyrazole[3,4-*d*]isoxazole derivative **669**,which is unstable and can be detected only by chemical and spectroscopic methods. The use of excess diazomethane gives rise to a mixture of **668a** and of the 1:2 adduct **670** and 1:3 adduct **671**. Cycloaddition of 2-diazopropane forms **668b** as the main product.[66/87,63/89] Similar results have been obtained starting from 5-benzoyl-4-nitro-3-phenylisoxazole; in this case, the bicyclic cyclopropaisoxazole is accompanied by **672**, which arises from a 1,5-sigmatropic shift of the benzoyl group.[56/88]



668a: R = H
668b: R = Me



669



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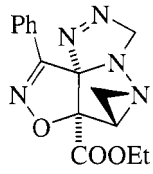

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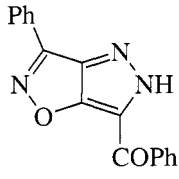
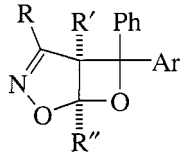


672

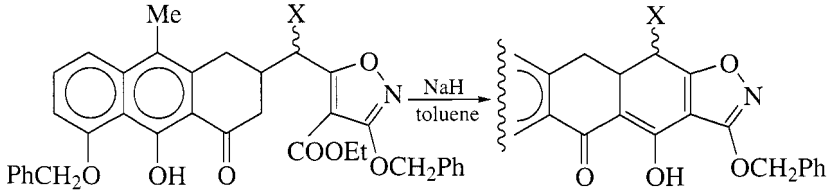


673

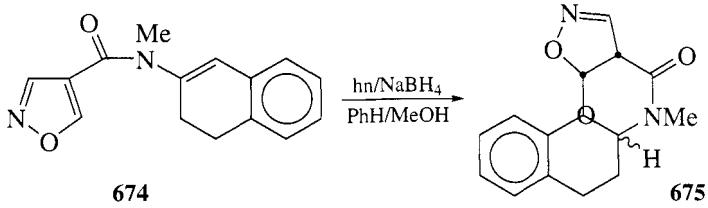
The oxetane products (**673**) of [2 + 2] photocycloaddition between the 4–5 double bond of isoxazole derivatives and the carbonyl groups of benzophenone and 3-benzoylpyridine have been obtained in moderate yields.[42/80]

The [2 + 2] photodimerization of 5-styrylisoxazoles in solution is known to yield a mixture of isomeric 1,2,3,4-tetrasubstituted cyclobutanes in addition to very minor amounts of the products of [2 + 2] cycloaddition between the styryl group and the 4,5 position of the isoxazole ring.[48/79] The intermediacy of an initial [2 + 2] cycloadduct has been proposed for the formation of pyridine derivatives when an isoxazole is heated with an acetylenic ester in the presence of hexacarbonylmolybdenum.[51/85]

In the Stork approach to tetracyclines, formation of ring A is accomplished by attack of a B-ring enolate anion on the 4-ethoxycarbonyl group of an isoxazole ring:[35/78]

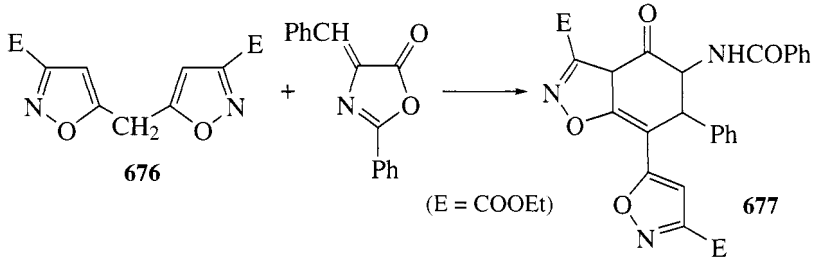


A mixture of the two epimeric lactams **675**, having an isoxazoline [4,5-*c*]fused with a benzo[*f*]quinolinone ring, is formed by reductive photo-cyclization of the enamide **674**. Photochemical electrocyclic closure followed by reduction has been suggested to account for the product formation.[66/84]



674 675

The shared 5,5′-methylene group in **676** is activated toward attack by various electrophiles and reacts with 4-benzylidene-2-phenyl-2-oxazolin-5-one to yield the condensed polyfunctionalised isoxazole derivative **677**:[21/72]

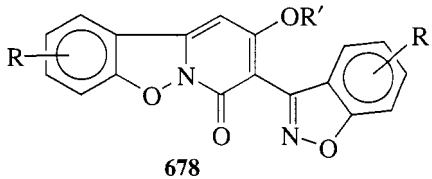


676 677

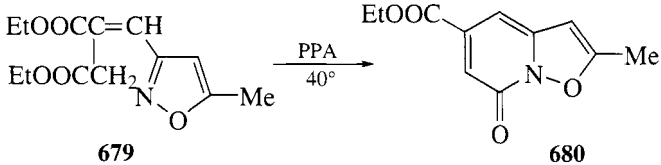
An isoxazole fused with a hetero- or carbocyclic seven-membered ring at either the 4,5 or 3,4 positions has been prepared from a suitable substituted isoxazole-4-carboxylic acid.[52/85] The same process has been extended to the higher homologs.[70/86]

Carbocyclic or, more frequently, heterocyclic six-membered rings can also be fused to the 2,3 positions of the isoxazole ring, provided a suitable electrophilic center is present in the side chain which adorns the 3 position. In some instances the condensed isoxazolium salts are formed.

Acylation or tosylation of 1,2-benzisoxazole-3-acetic acid in pyridine furnish the 4-oxo-4*H*-benzisoxazolo[2,3-*a*]pyridines **678** (see also Chapter 1, § 1.3.9.2).[49/82] However, very low yields are reported for the acid-promoted cyclization of **679** to **680**.[43/80]

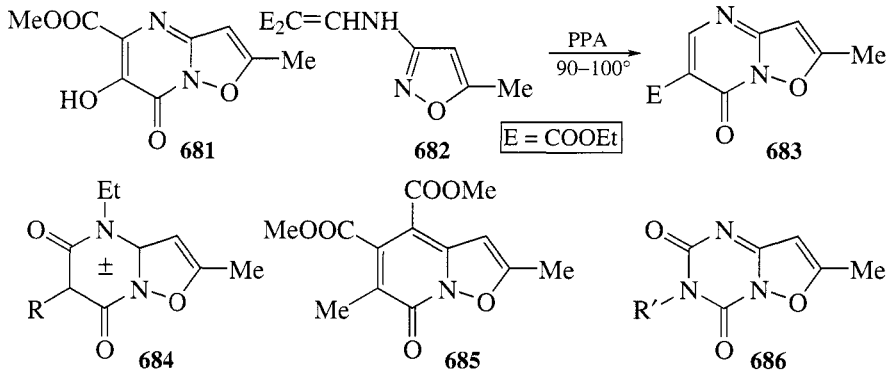


678

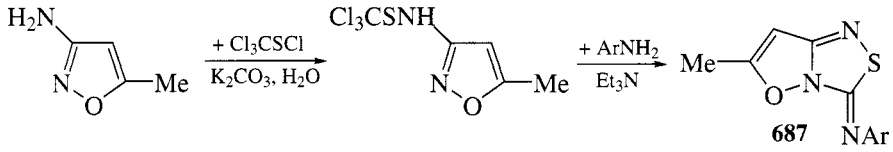


679 680

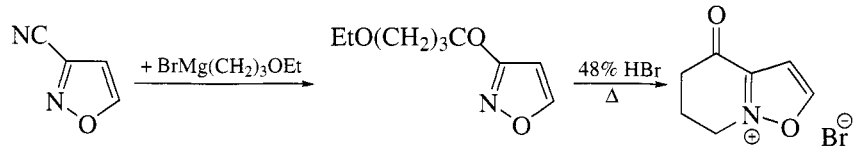
3-Aminoisoxazole derivatives are suitable starting materials for preparation of the isoxazolo[2,3-*a*]pyrimidinones. Condensation of 3-amino-5-methylisoxazole with dimethyl diacetoxyfumarate yields compound **681**,[80/90] while diethyl ethoxymethylenemalonate affords the substitution product **682,** which cyclizes to **683** under acidic conditions.[53/91] 3-Ethylamino-5-methylisoxazole reacts with carbon suboxide or with perchlorophenylester malonates to yield the relatively unstable zwitterion **684**, which can, in turn, be condensed with diethyl acetylenedicarboxylate to give the stable **685** (when R = Me).[30/87] The isoxazolo[2,3-*a*]triazinedione system **686** has also been prepared by routine cyclizations that commence with either a 3-amino-[73/85] or a 3-carbazido-isoxazole derivative.[81/90] A mixture of two isomeric oxopyrimido[1,2-*b*]benzisoxazoles has been obtained by condensation of 3-amino-1,2-benzisoxazole with methyl propiolate.[22/72]



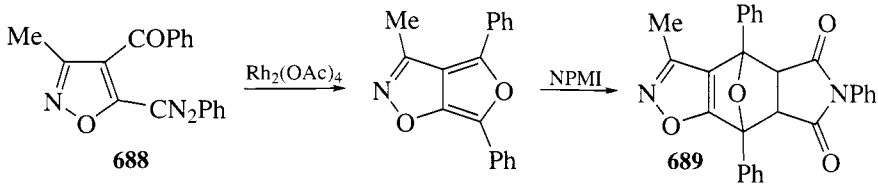
The 3*H*-isoxazolo[3,2-*c*][1,2,4]thiadiazole system **687** has been prepared starting from 3-amino-5-methylisoxazole by the following sequence of reactions:[23/75]



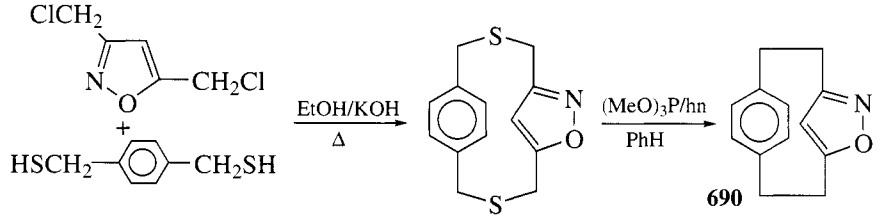
Acid-promoted cyclization of 3-(4′-ethoxybutyryl)isoxazoles represents an easy method for preparing isoxazolo[2,3-*a*]pyridinium salts,[26/71,23/72] as the following example shows:



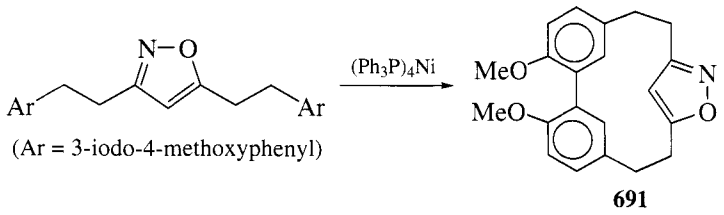
The 3-methyl-4,6-diphenylfuro[3,4-*d*]isoxazole system has been prepared by metal-catalyzed nitrogen extrusion from the diazocompound **688** in low yields; the strained bicyclic heterocycle undergoes Diels–Alder reaction to yield **689**:[54/91]



The isoxazole ring has been incorporated into macrocyclic compounds by two different methods. Low yields of [2.2](3,5)isoxazoloparacyclophane **690** have been obtained by photochemical sulfur extrusion of the corresponding 2,11-dithia[3.3]derivative:[42/83]



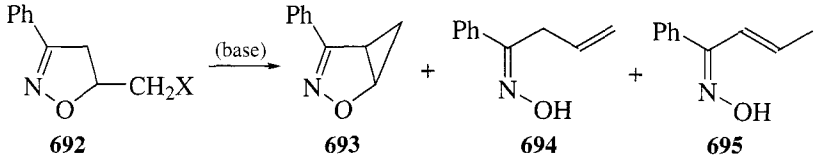
Aryl–aryl coupling of a suitable isoxazole precursor leads to the macrocycle **691**:[43/83]



4.2.11.2. Syntheses from Isoxazoline Derivatives

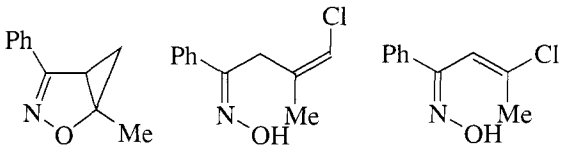
Fusion of a cyclopropane ring to the 4,5 positions of the isoxazole ring can be achieved by intramolecular alkylation of 5-halogenomethyl-2-isoxazolines **692**. Cyclization to **693** competes with ring opening, and mixtures of **693** are obtained along with isomeric unsaturated ketoximes **694** and **695**; the product ratios depend on the nature of the base employed and the halogen involved.

Starting from 5-halogenomethyl-3-phenyl-2-isoxazoline, use of potassium *tert*-butoxide in dimethyl sulfoxide at r.t. with both chloro and bromo derivatives is reported to furnish the bicyclic product (4-phenyl-2-oxa-3-azabicyclo[3.1.0]hex-3-ene) only.[32/77] Use of butyllithium in tetrahydrofuran at −78°C on the chloromethylisoxazoline gives the same result; by contrast, the same reaction carried out on the bromo derivative yields a 6:1 mixture of the two isomeric oximes:[49/79]



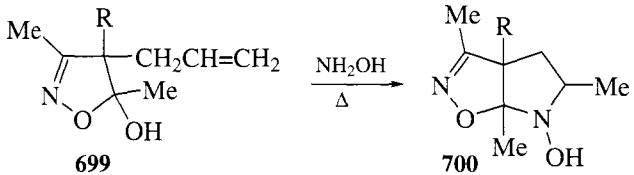
692 **693** **694** **695**

Depending on the nature of the base and the experimental conditions employed, deprotonation of 5-chloromethyl-5-methyl-3-phenyl-2-isoxazoline furnishes either the bicyclic isoxazoline **696** or a mixture of this latter compound with the two chlorinated oximes **697** and **698**.[49/79]



696 **697** **698**

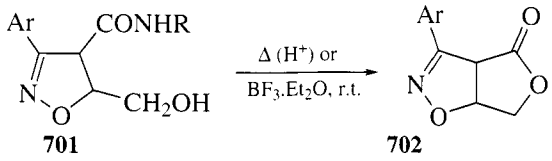
An *N*-hydroxypyrroline nucleus has been fused on isoxazoline 4,5 positions by cyclization of the 5-hydroxyisoxazoline **699** (or of its precursor 1,3-diketone) with excess hydroxylamine: compounds **700** are obtained in moderate yields.[32/76]



699 **700**

A [1,3]dioxolo[4,5-*d*]isoxazoline derivative has been prepared by ketalization of a 3-aryl-2-isoxazoline-4,5-diol.[15/68]

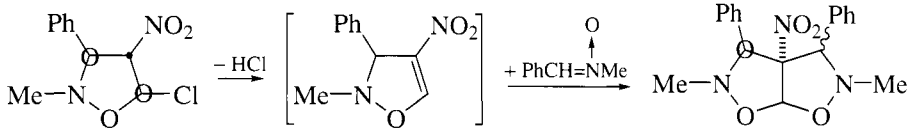
The furo[3,4-*d*]isoxazole derivative **702** has been obtained by acid-catalyzed ring closure of **701**:[57/86,8/87]



701 **702**

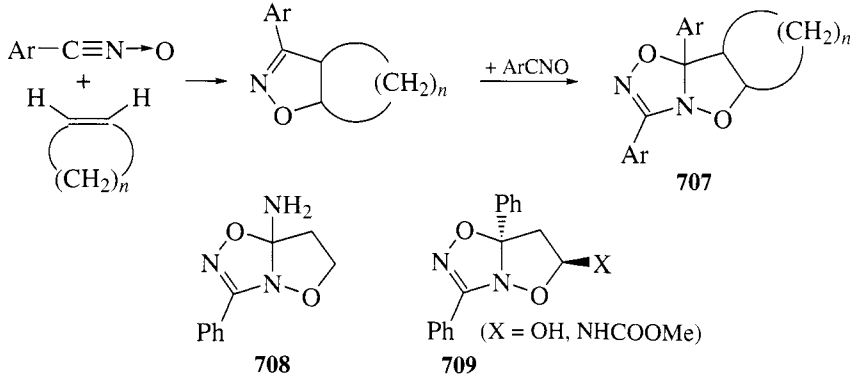
The homologous pyrano[3,4-*d*]isoxazole system has been accessed by a similar closure.[73/84]

The presence of a 4-nitro substituent activates the 4,5 double bond of 4-isoxazolines toward nitrone 1,3-dipolar cycloaddition; thus, heating the isoxazoline **703** with excess *N*-methyl-*C*-phenylnitrone gave rise to the bicyclic adducts **705** and **706** in excellent yields. The reaction clearly involves the intermediacy of the 4-isoxazoline **704**.[28/84]



703 **704** **705:** *cis*-Ph_2 **706:** *trans*-Ph_2

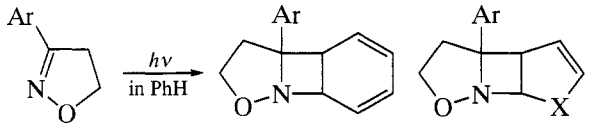
The strained C=N double bond of 2-isoxazolines, especially those fused in the 4,5 positions with another carbo- or heterocyclic ring, can enter 1,3-dipolar cycloadditions with nitrile oxides. Tricyclic systems, such as **707**, have been prepared or have frequently been isolated as by-products in the cycloaddition reaction between nitrile oxides and cycloalkenes.[17/70,12/71,11/72,16/73,18/76,10/78]



707 **708** **709**

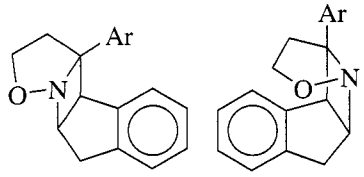
Bicyclic systems, such as **708** or **709**, have also been prepared by the same route.[56/79,50/80]

In a process that is thermally reversible, the isoxazoline C=N double bond can enter a [2 + 2] photocycloaddition with some aromatics (benzene, indene) or heteroaromatics (furan, thiophene, even dihydrofuran), provided that an electron-withdrawing group (X = CN or COOEt) is present in the 4 position of the 3-arylsubstituent.[50/79,42/81,43/81,44/83]



710 **711** (X = O or S)

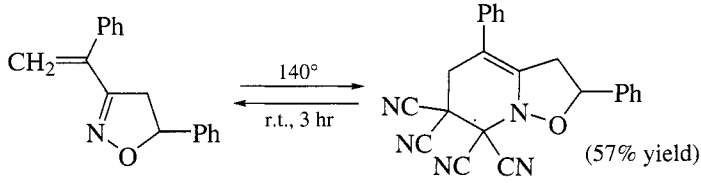
The [2 + 2] adducts **710** and **711** have been assigned the *anti* configuration. Reaction with indene gives rise to both the *anti* (major) **712** and the *syn* (minor) **713** cycloadducts.[74/85]



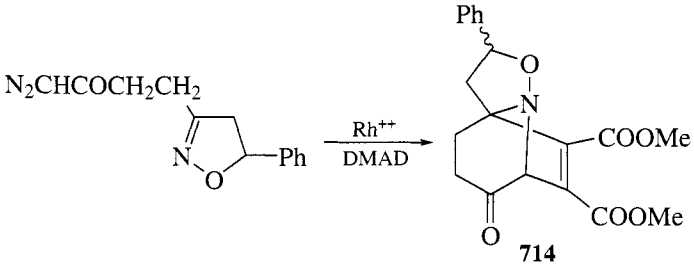
712 **713**

	712	**713**
Ar = 4-NC-C_6H_4:	64%	11%
Ar = 4-MeOOCC_6H_4:	57%	4%

Conjugation of the C=N bond with an external double bond creates an 1-azabutadiene moiety, which can enter Diels–Alder reaction with tetracyano ethylene (TCNE) to give a thermodynamically disfavored cycloadduct.[6/84]

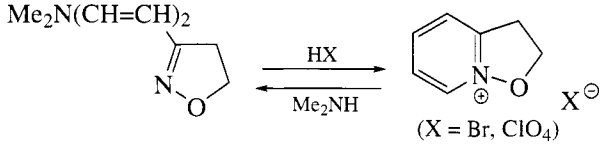


Generation of a rhodium-carbenoid species from a diazoketone moiety appended to the 3 position ultimately gives rise to cycloadduct **714** as a mixture of diastereomers.[82/90]

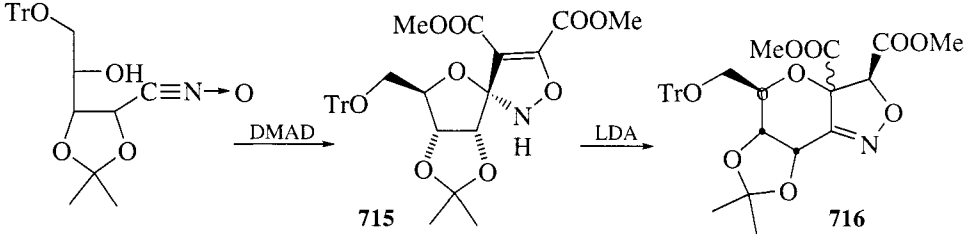


714

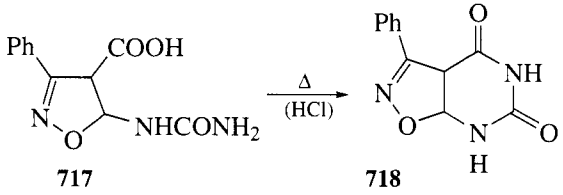
3-ω-Dimethylaminobutadienyl-2-isoxazoline, prepared by the attack of dimethylamine on 2,3-dihydroisoxazolo[2,3-*a*]pyridinium bromide(§ 4.2.7.7), reverts to the same cyclic cation under strong acid treatment:[30/67]



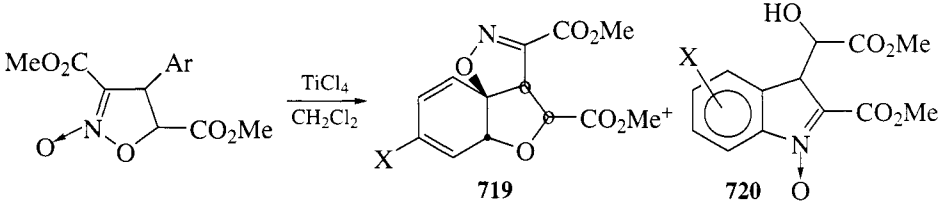
The unstable spiroisoxazoline **715** isomerizes to the bicyclic isoxazoline **716** (mixture of the two diastereoisomers) by action of lithium dimethylamide:[64/89]



Acid-catalyzed ring closure of isoxazoline **717** yields the dihydroisoxazolo[5,4-*d*]pyrimidine-4,6-dione **718**:[31/72]



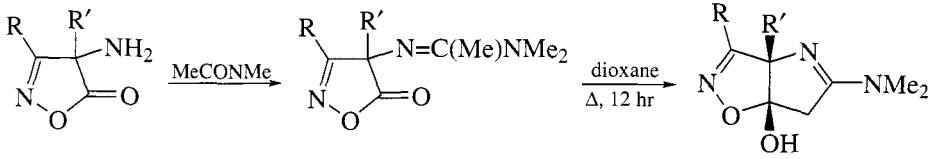
2-Isoxazoline-*N*-oxides are starting materials for an interesting ring transformation, promoted by Lewis acids such as titanium tetrachloride in dichloromethane. Starting from the easily available 3,4-bis(methoxycarbonyl)-4-aryl-2-isoxazoline-2-oxides, either benzofuro[3,3a-*d*]isoxazole-3,4-dicarboxylates **719** or 3*H*-indole-3-acetate 1-oxides **720** can be obtained. The course of



the reaction is strongly affected by the substitution pattern of the aryl group; *para* substitution directs the rearrangement toward **719** as largely prevalent product, whereas *meta* or *ortho* substitution exclusively furnishes **720**.[45/83, 45/84,46/84, 53/85]

A mechanism involving an N–O ring opening followed by an ipso attack has been postulated for the formation of **719**.[45/84] Similar results have been achieved when the isoxazoline oxide 4-substituent is a di- or trisubstituted phenyl[74/86] or a naphthyl residue.[46/84]

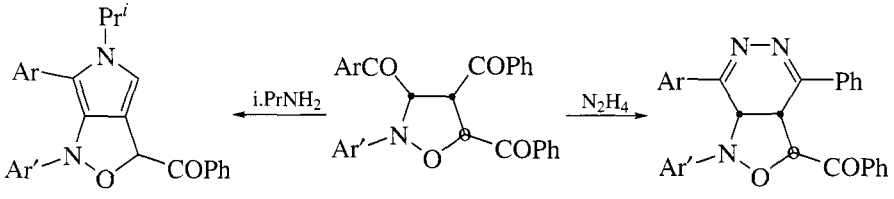
Even 4-amino-2-isoxazolin-5-ones have been the source of bicyclic pyrrolo[2,3-*d*]isoxazoles, as in the following example:[55/91]



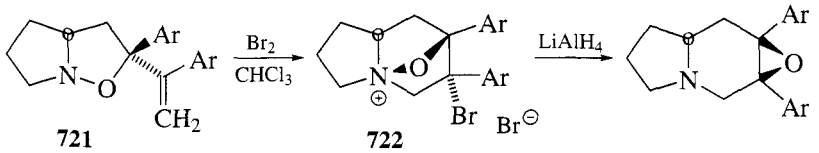
(43–84% yield)

4.2.11.3. Syntheses from Isoxazolidine Derivatives

The 3,4,5-triaroylisoxazolidines, obtained by nitrone cycloaddition to *trans*-diaroylethylene, are a source of 3,4-heterocycle fused systems, as the following example shows:[28/74]

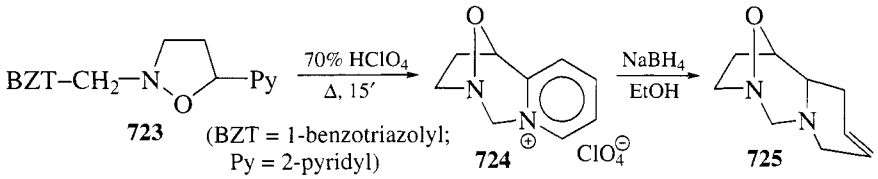


During the synthesis of *dl*-septicine tricyclic isoxazolidine **722** was prepared by bromine-promoted cyclization of the unsaturated bicyclic isoxazolidine **721**:[26/80]

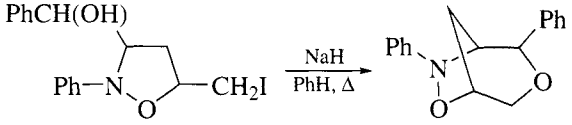


721 **722**

The lability of the benzotriazole moiety in **723** enables intramolecular displacement by the pyridine nitrogen. Reduction of the unstable salt **724** can affords the 12-oxa-1,3-diazatricyclo[7.2.1.$0^{3,8}$]dodec-5-ene **725**. Prolonged exposure to acid yields a dimeric product instead.[49/90]

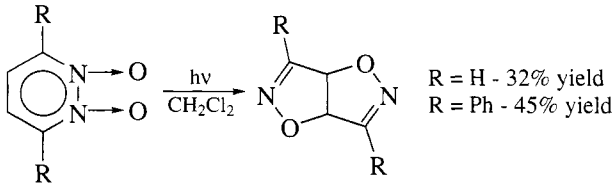


Base-promoted dehydroiodination of 3-α-hydroxybenzyl-5-iodomethyl-2-phenylisoxazolidine provokes cyclization to the 3,6-dioxa-7-azabicyclo[3.2.1] octane system:[54/85]



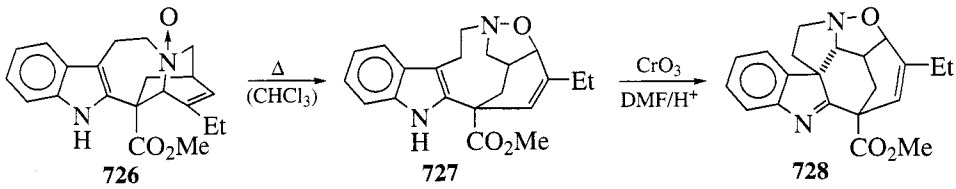
4.2.11.4. Syntheses from Other Heterocyclic Derivatives

Heteroaromatic *N*-oxides are particularly prone to photo- and thermally induced rearrangements and in some cases condensed isoxazole derivatives, difficult to prepare in other ways, are obtained. Thus, pyridazine 1,2-oxide is photoisomerized to 3a,6a-dihydroisoxazolo[5,4-*d*]isoxazole:[33/77,51/79]



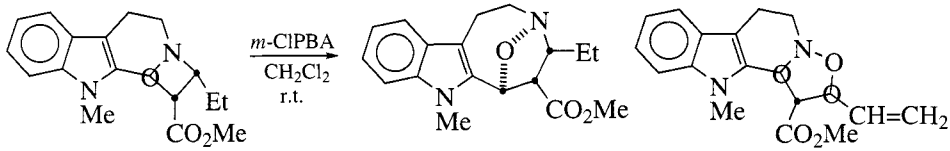
Although without any apparent preparative value, small amounts of a labile benzazete[1,2-*b*]benzisoxazole derivative are formed by photoisomerization of 5-methylacridine-10-oxide.[24/75,52/79]

A [2,3]sigmatropic rearrangement has been invoked for the thermal transformation of catharanthine *N*-oxide **726** into the pentacyclic indoleisoxazolidine compound **727**, which can further cyclize to **728** by oxidation:[33/76]



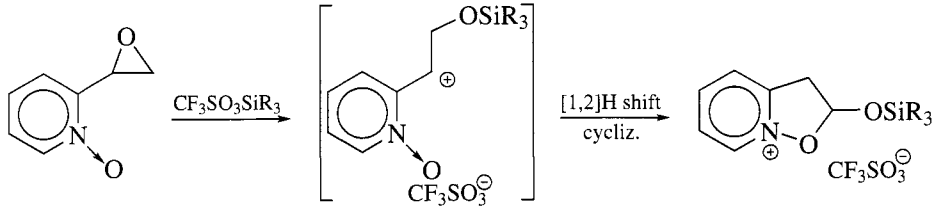
726 727 728

Alternatively, the *N*-oxide may be produced *in situ*, as in the case of azetopyridoindole derivative **729**, which is oxidized by *m*-chloroperbenzoic acid and rearranges to the 3,6-epoxyhexahydroazocino[5,6-*b*]indole **730**.[44/91]

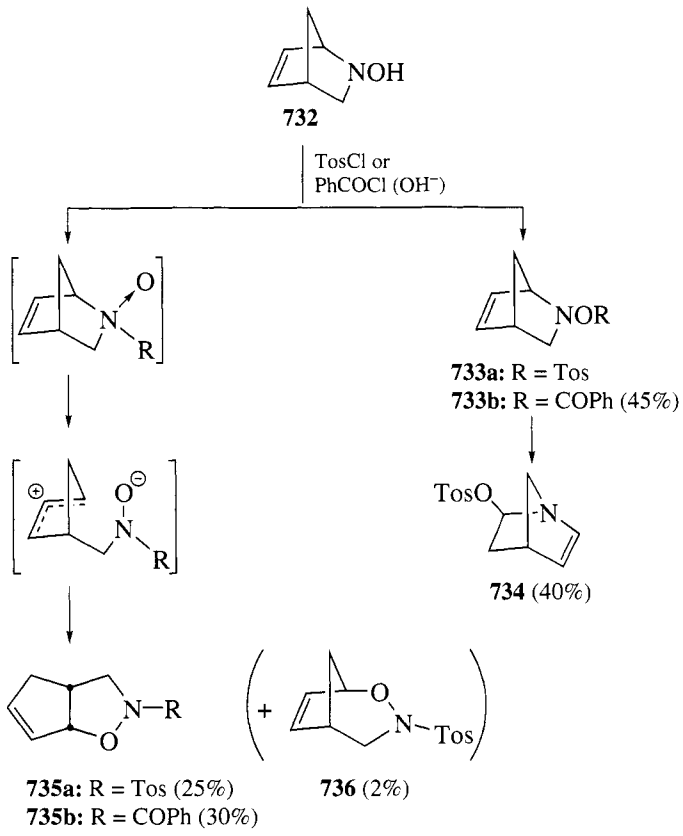


729 730 731

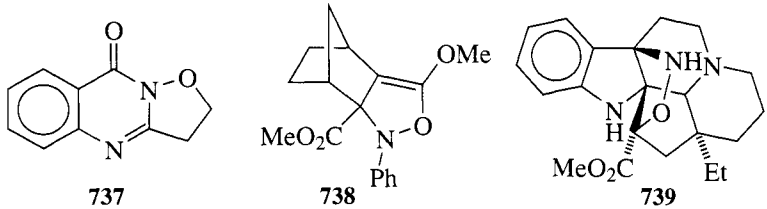
Interestingly, when a vinyl group is present instead of the ethyl group in **729**, *N*-oxidation of the *cis*-isomer (stereochemistry relative to the vinyl/methoxycarbonyl groups) gives a tetrahydropyridooxazepine, whereas *N*-oxidation of the *trans* isomer leads to the tetracyclic isoxazolidine derivative **731**.[56/91] Also of interest is the formation of an isoxazolo[2,3-*a*]pyridinium salt by action of trialkylsilyl triflate on 2-oxiranylpyridine *N*-oxide:[44/81]



Although generally difficult to obtain otherwise, bicyclic isoxazolidines of structure **735**, are produced by *N*-acylation of the bridged *N*-hydroxy-2-azabicyclo[2.2.1]hept-5-ene (**732**). The more abundant *O*-acylation product **733b** or the rearranged compound **734** are also obtained together with minor amounts of **736** in the case of the tosyl derivative.[46/81,46/83]



A low yield of 2,3-dihydro-9*H*-isoxazolo[3,2-*b*]quinazolin-9-one (**737**) was obtained by reaction of isatic anhydride with 3-chloropropiohydroxamic acid in basic medium.[31/87]



Furthermore, the unstable polycyclic bridged isoxazole derivatives **738** and **739** have been reported to be formed by thermolysis of a 3,4,5-triazatricyclo[5.2.1.$0^{2,6}$]dec-4-ene-2,6-dicarboxylate,[25/75] and by acidic treatment of the zwitterionic compound obtained from the alkaloid vincadifformine and Fremy's salt,[57/88] respectively.

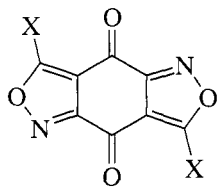
4.3. CHEMICAL PROPERTIES

4.3.1. Reactions without Ring Cleavage

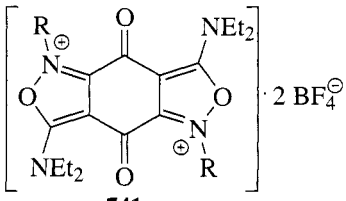
4.3.1.1. Salt Formation

Like their monocyclic counterparts, condensed isoxazoles readily undergo quaternization (see Part 1, § 1.4.1, pp. 265–268). The reagent of choice for the preparation of *N*-methyl- or *N*-ethylderivatives is usually a trialkyloxonium tetrafluoborate, which affords the desired materials in good yields under mild conditions.[32/68,2/70] However, methyl trifluoromethanesulfonate or ethyl fluorosulfonate have sometimes been utilized,[41/84] as well as methyl iodide[1/76] or methyl sulfate[2/74] under more severe conditions. Bulkier substituents (*tert*-butyl or adamantyl) can be introduced by using a tertiary alcohol in the presence of perchloric acid.[4/71,41/84]

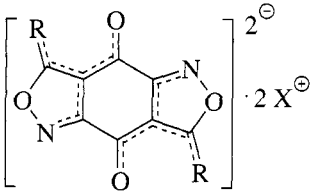
Interesting behavior has been reported for the peculiar system of 3,7-diethoxy (or 3,7-dialkylamino)-4*H*,8*H*-benzo[1,2-*c*,4,5-*c*′]diisoxazol-4,8-diones (**740**), which can react with either electrophiles or nucleophiles. Starting from **740a** in the former case, the expected bisisoxazolium salts **741** are obtained.[45/80,48/91] Reaction of **740b** with the salts of active methylene compounds (such as malononitrile) or of arylsulfonylamides leads to salts of type **742**.[45/81] Replacement of the ethoxy groups is promoted by the reaction of **740b** with tertiary amines (or with other nucleophiles), which furnishes salts of type **743**.[50/82]



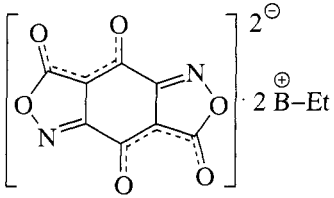
740a: X = NEt_2
b: X = OEt



741
(R = Me, Et)

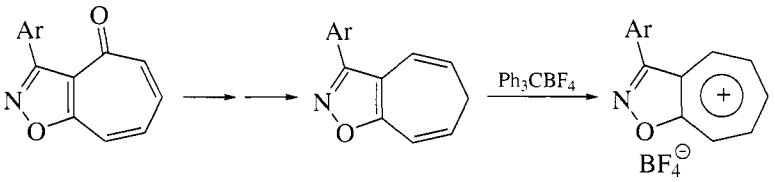


742
(R = $C(CN)_2$, C(CN)COPh, C(CN)COOEt, NSO_2Ar; X = RNH_3, Na, K)



743
(B = NEt_3, Py)

Green or red crystals of 3-arylcyclohepta[*d*]isoxazolium tetrafluoborates have been prepared by hydride abstraction from the corresponding 6*H*-cyclohepta[*d*]isoxazoles by reaction with triphenylmethyl tetrafluoroborate:[54/86]



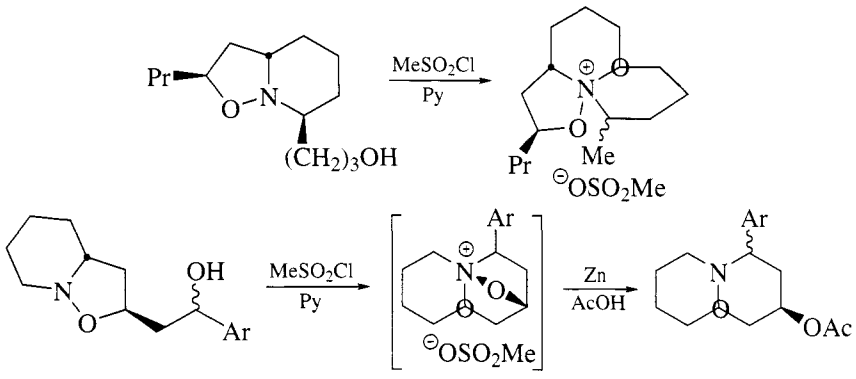
The pK_R+ values suggest that the isoxazole ring sharply decreases the stability of the tropilium ion in comparison with the benzo group.

Salts of tetramethylene isoxazoles with mercuric chloride have been described as crystalline compounds. They regenerate the condensed isoxazole on heating at 140°C.[6/70]

Although dimethyl sulfate and sodium perchlorate are also effective,[30/73] trimethyloxonium tetrafluoroborate is the usual reagent for the quaternization of condensed 2-isoxazolines. 2-Isoxazolinium salts are useful intermediates for preparing *N*-methylisoxazolidines[12/74,44/80] (see also Part 1, § 2.2.3.1, pp. 541–543). A dication is formed when 3(4′-piperidinyl-1′,3′-butadienyl)-2-isoxazoline is treated with concentrated sulfuric acid.[30/67]

The higher basicity of the isoxazolidine nitrogen atom makes isolation of stable hydrochlorides possibile, and quaternization quite easy, as already described for monocyclic derivatives (see Part 1, § 3.4.1, p. 733). Alkylation with methyl iodide (or other alkyl halides) occurs without any difficulty with 2,3-fused,[35/74,19/78,26/79,29/81,31/89,33/89,28/91] 3,4-fused[40/79,41/79] and 4,5-fused[20/73,26/75,62/85,81/88] isoxazolidines, as well as with polycyclic bridged isoxazolidines.[27/73,28/78,25/79]

Of greater interest is the intramolecular quaternization of 2,3-fused isoxazolidines. When a mesyloxy group is located at suitable distance, ring closure can



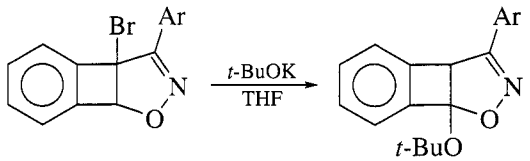
occur, leading to polycyclic fused[29/80] or bridged[47/81,31/82,51/82] isoxazolidinium mesylates, as the above reported two examples illustrate. The salts are usually not isolated, but directly submitted to reductive ring opening.

4.3.1.2. Substitution Reactions at the Isoxazole Ring

The dehydrogenation of 2-isoxazolines to isoxazoles by treament with *N*-bromosuccinimide is a well-known process (see Part 1, § 1.3.7.1a, p. 229), involving a 4-bromo or 5-bromoisoxazoline as non-isolable intermediate. With fused 2-isoxazolines, a stable 4-bromo derivative can usually be isolated:

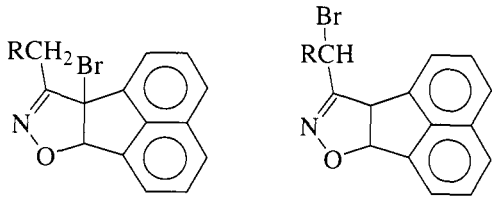
The reaction has general applicability; thus, bromination of 3-phenyl-5,6-dihydrocyclopenta[*d*]-2-isoxazoline,[11/66] 3-phenyl-, 3-methyl-, or 3-methoxycarbonyl-acenaphtho[1,2-*d*]-2-isoxazoline,[22/64,11/71] 3-arylbenzo[3,4]cyclobuta[1,2-*d*]-2-isoxazoline,[7/74] 3-methyl-4-oxo-5,6-dihydrocyclopenta-[*d*]-2-isoxazoline,[11/76] and 7-phenyl-9,8-oxazabicyclo[4.3.0]nona-2,7-diene and its cycloadducts with benzonitrile oxide[17/70] give the 4-bromo derivative (isoxazoline numbering) exclusively or almost exclusively.

In the case of the cyclobutaisoxazole system, the bromo derivative **744** cannot be dehydrobrominated by mild bases, but affords **745** on treament with *tert*-butoxide.[7/74]



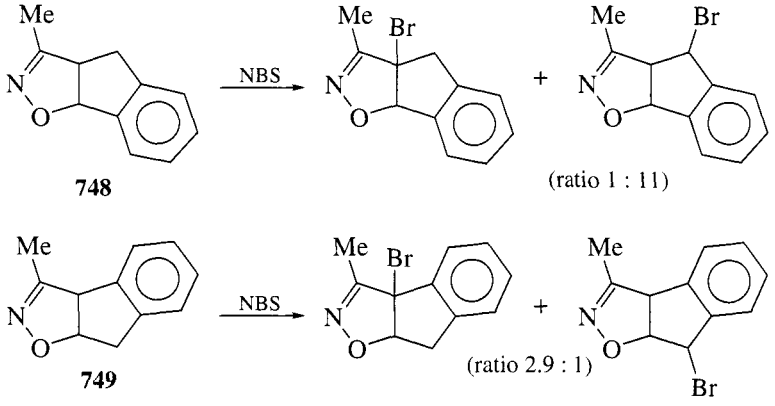
744 **745**

3-Ethyl- and 3-*n*-propyl-acenaphthoisoxazolines react at both the exo- and endocyclic allylic positions to give **746** and **747** in approximatively equal amounts along with minor amounts of the dibromo derivative.[11/71]



746 (R = Me, Et) **747**

Bromination of indenoisoxazolines has been studied in detail.[15/67] The two regioisomers **748** and **749**, obtained by cycloaddition of acetonitrile oxide to indene, react as expected to give the products of allylic and benzylic bromination.



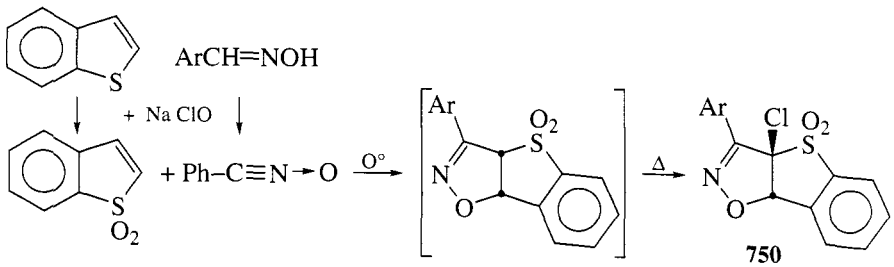
748 (ratio 1 : 11)

749 (ratio 2.9 : 1)

The 3-phenyl analog of **748** reacts by substitution at the benzylic position to furnish the 4α-bromoisoxazoline exclusively.

Benzylic bromination of the 5 position of the isoxazoline ring has been reported for an isoxazoloquinoline derivative.[47/89]

A simultaneous double oxidation and chlorination with sodium hypochloride under appropriate conditions furnishes the chloro derivative **750** regio- and stereospecifically:[6/91]

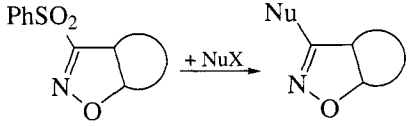


750

Replacement of a bromine atom at the 4 position of a tricyclic isoxazolidine with an allyl residue has been achieved by photochemical treatment with allyltributylstannane.[59/85]

Methylation at position 4 of a bicyclic isoxazolidine (polysubstituted 3,7-dioxa-8-azabicyclo[4.3.0]nonan-2-one) has been achieved using lithium diisopropylamide and methyl iodide.[20/85]

When the 3 position of the 2-isoxazoline ring is occupied by a strong electron-attracting group, such as phenylsulfonyl, nucleophilic substitution occurs in high yields according to the following general scheme:[7/79,49/83,17/84]

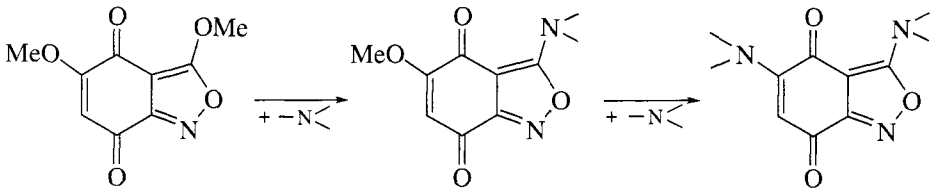


NuX: $NaBH_4$, MeLi, *n*-BuLi, MeOLi, KCN

A bromine atom in the same position has also been reported to undergo substitution by nucleophiles such as alkoxides, amines, and cyanides.[65/89]

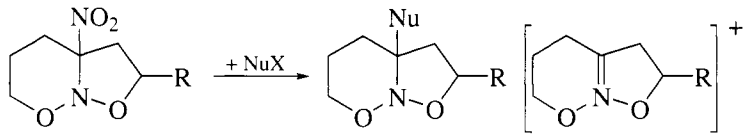
The 5 position of the isoxazole ring is also susceptible to substitution, and some examples employ condensed isoxazoles. Thus, methoxy groups can be replaced by amino groups in isoxazole quinones,[31/67,45/80] whereas a 5-aminoisoxazolesteroid undergoes the Sandmeyer reaction to give the corresponding 5-chloro derivative.[12/65] A 5-chloro derivative has also been reported to result from treatment of the condensed 5-mercaptoisoxazole with hydrogen peroxide and concentrated hydrochloric acid.[11/70]

With dimethoxyisoxazole quinones (**751**), selective amination to give **752** can be achieved with equimolar amounts of primary or secondary amines, whereas excess of amines leads to disubstitution with formation of **753**:[42/74]



751 **752** **753**

The nitrogroup in 6-nitro-2,9-dioxa-1-azabicyclo[4.3.0]nonane derivatives is easily displaced by a large variety of nucleophiles:[31/73,34/74,25/76,36/78,53/79,52/83]



754

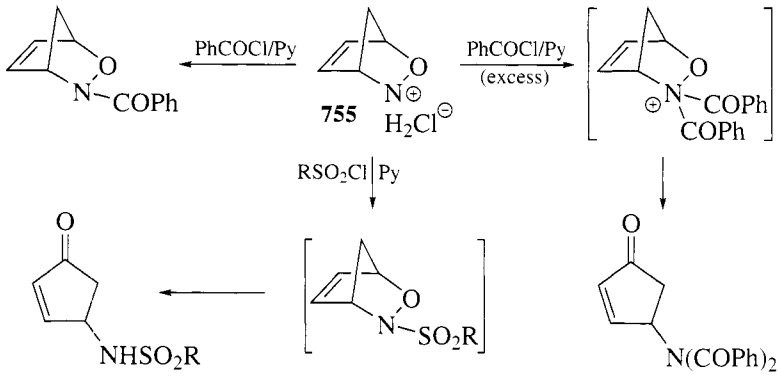
With sodium cyanide, a mixture of two stereoisomers is obtained and the intermediacy of the salt **754** has been postulated.[17/75,34/76]

The nitro group in the 4 position of a fused 2-isoxazoline has been removed by treatment with tributyltin hydride.[29/90] Reductive dehalogenation of a 5-iodo-2-isoxazoline fused with a steroidal skeleton can be accomplished with zinc and acetic acid.[33/69]

N-Unsubstituted fused isoxazolidines exhibit properties similar to those of the monocyclic derivatives (see Part 1, § 3.4.8, pp. 750–52), and can be *N*-methylated, preferably with methyl tosylate;[26/73,50/83,58/88] or *N*-acylated, with, for example, acetic anhydride,[26/73,33/77,32/78,37/79,51/79,50/83] benzoyl chloride[10/81,22/88,48/89,41/91] or phenyl chloroformate.[37/79] 2,2′-Bisisoxazolidinyl derivatives have been derived by treatment with formaldehyde and formic acid.[37/79]

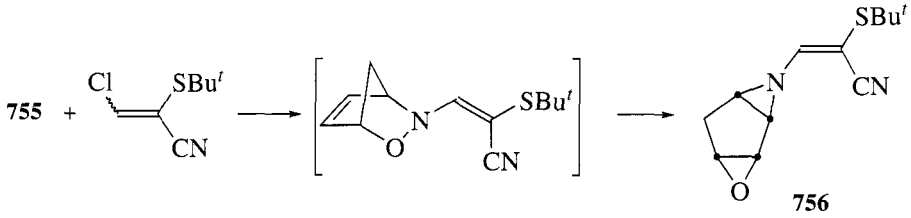
Conversely, *N*-substituted fused isoxazolidines have been conveniently produced by acid-promoted alcoholysis of their *N*-pyranyl derivatives.[24/84]

Several reagents have been evaluated on the simpliest bridged isoxazolidine, namely, 2,3-oxazabicyclo[2.2.1]hept-5-ene, and its stable hydrochloride **755**. The free base can be *N*-hydroxymethylated with formaldehyde, *N*-nitrosated with isoamyl nitrite, and *N*-thioamidated with phenyl isothiocyanate. Acylation and α-chlorobenzylation is more conveniently performed directly on the hydrochloride. It should be added that the *N*-sulfonyl derivative as well as the *N*,*N*-bisbenzoyl derivative, obtained by treatment with an excess of benzoyl chloride, are unstable and suffer immediate ring opening:[10/81]

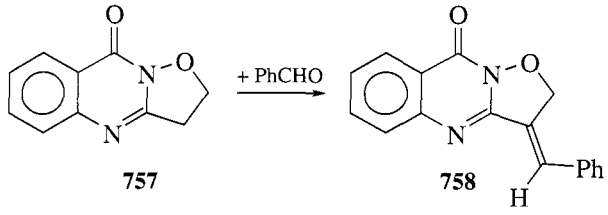


Preparation of an *N*-phenylcarbamoyl derivative has also been achieved by reaction with phenyl isocyanate.[49/91]

Vinylation of **755** also leads to an unstable *N*-substituted derivative, which spontaneously rearranges to the *syn*-epoxyepimine **756**:[59/88]



The 4 position (isoxazolidine numbering) of the dihydroisoxazolo[3,2-*b*] quinazolinone system **757** is activated and reacts with benzaldehyde to give the 4-(phenylmethylene) derivative **758** in moderate yields:[31/87]



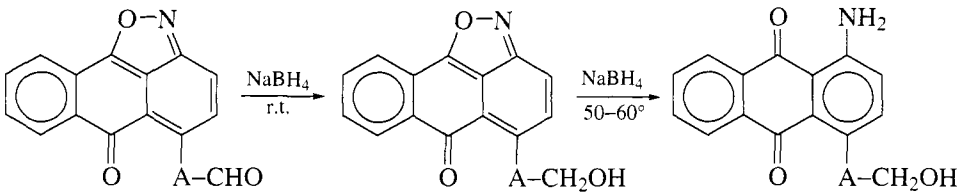
4.3.1.3 Reactions in Side Chains or Fused Homocyclic Rings

4.3.1.3a. Fused Isoxazoles

As with the monocyclic derivatives (see Part 1, § 1.4.3, pp. 273–85), sodium borohydride or lithium aluminum hydride easily reduce ester or carbonyl groups, located on a side chain or on the fused homocyclic ring, to the corresponding alcohol, without affecting the isoxazole ring.[1/63,1/69,2/69,24/72,25/72,43/74,44/74,2/75,64/90] This reactivity has been widely utilized in the multistep synthesis of complex molecules (see § 4.3.3).

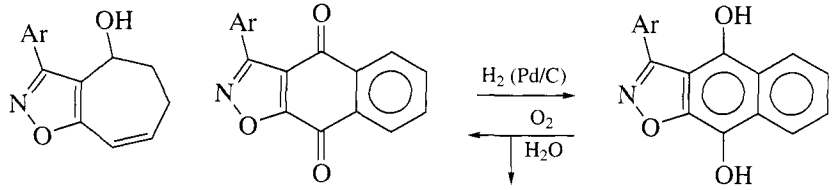
An α,β-unsaturated ketone moiety has been reduced by $NaBH_4$ to the corresponding saturated secondary alcohol.[54/86]

In the case of an anthra[1,9-*cd*]isoxazol-6-one derivative having an aldehyde group in a lateral chain, reduction with sodium borohydride at room temperature is limited to the carbonyl group only, whereas treatment at 50–60°C also opens the heterocyclic ring:[48/81]



Reduction of the entire α,β-unsaturated ketone moiety with sodium borohydride has been reported in the formation of the partially saturated alcohol **759** from the corresponding 3-arylcyclohept[*d*]isoxazol-4-one.[32/87]

Whereas catalytic hydrogenation generally effects ring opening (see § 4.3.2.1), reduction of naphthisoxazolequinone **760** to the corresponding hydroquinone **761** is accomplished catalytically in the presence of 10% Pd/C; reoxidation of the latter compound with air represents a convenient method for the generation of hydrogen peroxide:[19/81]



759 **760** **761**

The C=N bond of a hydrazone or Schiff base can be hydrogenated without affecting the isoxazole ring with either 10% Pd/C or by treatment with metal hydrides.[17/63,5/64,8/66]

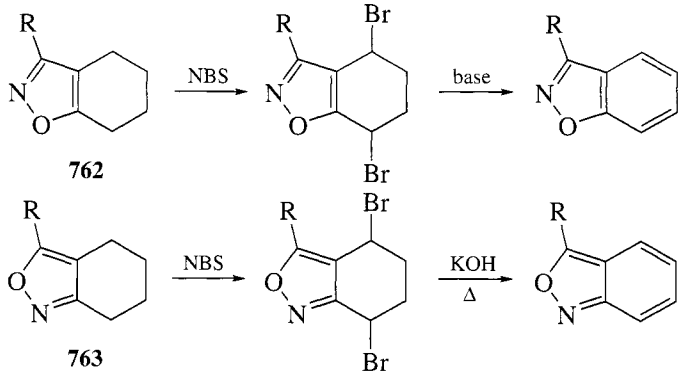
Deamination of the aromatic ring in anthra[1,9-*c*]isoxazol-6-one can be accomplished by treatment with lithium aluminum hydride.[54/79]

Oxidation of double bonds in side chains or in fused homocyclic rings can be accomplished by peracids to give peroxides;[33/68,34/68,35/70,1/79,55/79,53/82,2/87,60/88] periodic acid opens the epoxide ring.[13/84] Oxidation of hydroxyl groups to carbonyls is also carried out without difficulty with common oxidizing agents.[21/64,8/66,35/70,34/77,37/78,1/79]

Aromatization of partially saturated cyclohexene rings fused with an isoxazole has been accomplished with dichlorodicyanobenzoquinone,[36/66] *N*-bromosuccinimide,[17/70] or bromine.[3/72]

Addition of HCN to a double bond as well as hydration of a triple bond have been reported in the case of an isoxazole steroidal compound.[53/82] Conversely, formation of double bonds by alcohol dehydration,[35/70,53/82,54/86] eventually with rearrangement in the case of a tertiary alcohol,[8/64] is easily achieved with routine reagents.

Allylic halogenation, usually effected with *N*-bromosuccinimide followed by base treatment, allows a facile aromatization of fused isoxazoles **762** or **763** to 1,2-benzisoxazole[14/66] or to 2,1-benzisoxazole,[6/70] respectively.



Naphthisoxazoles have been obtained by similar route.[14/66,2/71,43/74,1/77] Aromatization of an isoxazolo[2,3-*a*]pyridinium salt by α-bromination and subsequent thermolysis has also been reported.[26/71]

Other reactions, easily carried out without affecting the isoxazole ring, include the following: (1) formation of halides from alcohols;[43/74,44/74,2/75,32/87,64/90] (2) acylation of alcohols[7/61,5/71,24/72,27/72,6/85,30/90] and of amines[8/66,37/69] or amides;[16/61,24/72,26/72] (3) alkylation of alcohols to form ethers;[30/90] (4) hydrolysis of ethers to alcohols;[5/71,2/79,47/84,52/86] (5) formation of carbonyl derivatives;[17/63,5/64,23/64,8/66,37/69,13/71,45/74,37/78,1/79,46/80,54/82,13/84] (6) Grignard reaction[34/77] and similar nucleophilic additions;[51/89] (7) hydrolysis of ketals,[3/60,5/72,4/73,54/82] esters,[1/46,1/63,11/71,43/74,2/75,37/78] or amides;[27/71,11/89] (8) formation of amides,[1/46,15/61,3/63,5/64,28/72] hydrazides,[17/63,5/64,23/64,28/71] or semicarbazides;[26/72] (9) formation of amines from amides;[2/59,11/62,5/64] (10) alkylation of amines;[2/25] (11) halogenation of terminal triple bonds.[61/88,36/90]

Benzisoxazolo[2,3-*b*]pyridinium tetrafluoroborate is nitrated on the benzenoid ring.[33/78]

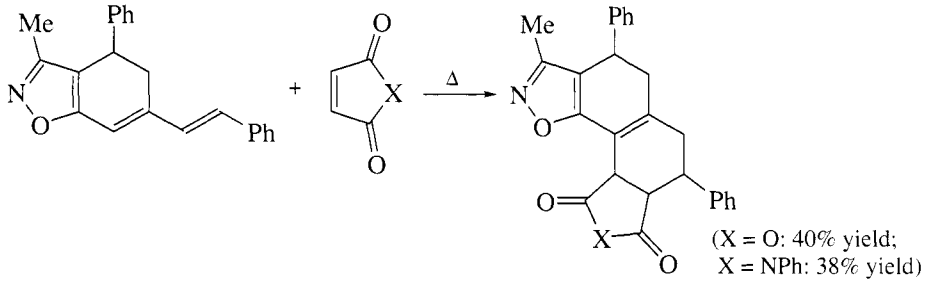
Nucleophilic replacement of a halogen atom on the carbocyclic ring or on a side chain by amines[54/82] or carbanions[27/71,43/74,47/84,64/90] is known, as well as base-promoted formation of a norcaradiene system fused with a 3-arylisoxazole.[32/87] α-Hydroxylation of a carbonyl group in the homocyclic ring of 3-substituted tetrahydro-1,2-benzisoxazol-4-ones has been reported.[1/88]

The methylene group of *N*-ethyl-3-phenylindeno[1,2-*d*]isoxazolium tetrafluoborate is strongly activated, and easily condensed with *p*-dimethylaminobenzaldehyde to yield the corresponding benzal derivative.[32/68]

Thorough studies have been devoted to the nucleophilic substitution of hydrogen and halogen atoms at positions 3 and 5 of anthra[1,9-*c,d*]isoxazol-6-ones by amines,[54/79,39/80,48/81,55/82,33/87] alkoxy,[51/83,31/90] azide,[55/86] or activated aryl residues.[69/84,51/87,62/88] The site of substitution depends on the experimental condi-

tions and on the substituents pattern. Kinetic correlations of this behavior have been performed.[59/81]

The lower reactivity of a diene that is partially comprised by an isoxazole ring is illustrated by the following example:[3/73]

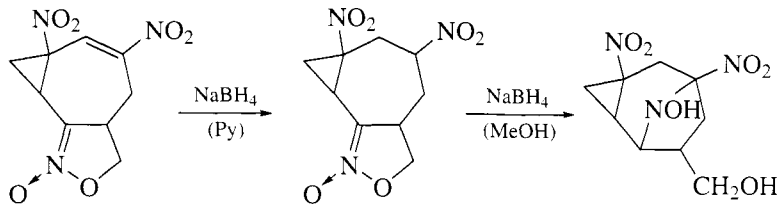


4.3.1.3b. Fused 2-Isoxazolines

The 2-isoxazoline ring is readily cleaved by treatment with lithium aluminum hydride, but remains unaffected by sodium borohydride. As a consequence, the latter reagent is often utilized for reducing carbonyl groups located outside the heterocycle, occasionally with a pronounced degree of stereoselection.[11/72,29/72,11/76,49/81,20/84,19/85,8/87,8/88,9/89] L-Selectride, employed during the late stages of the synthesis of (+)-phyllanthocin, has also proved effective for this purpose.[8/89] In one case lithium aluminum hydride was used to reduce an α,β-unsaturated lactam group without affecting the isoxazoline ring.[34/87]

Excess $NaBH_4$ reduces the ester group in the 3 position of an isoxazoline ring to a primary alcohol,[14/86] whereas an aluminate complex of Dibal and *n*-butyllithium has been employed to selectively reduce an α,β-unsaturated ester to the corresponding allylic alcohol during the synthesis of (−)-specionin.[42/87,28/88] A hydroxy group located in the fused cyclohexane ring was removed and substituted by hydrogen through subsequent treatments with ClC(=S)OPh and Bu_3SnH.[8/89]

Selective reduction of a fused 2-isoxazoline *N*-oxide, containing a nitroolefin moiety, with sodium borohydride has been observed. In pyridine only the activated CC double bond is hydrogenated, whereas in methanol hydrogenolysis of the heterocyclic ring occurs:[30/72]



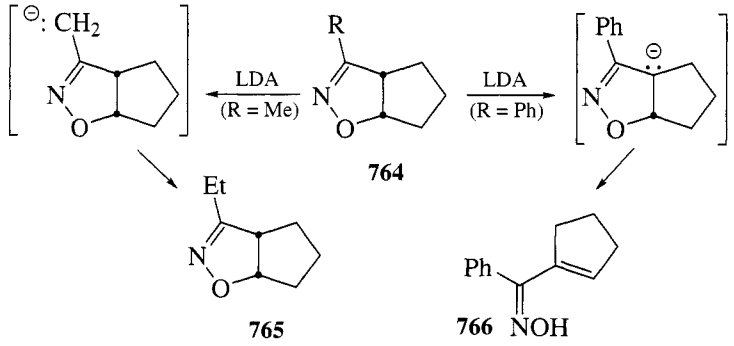
Although catalytic hydrogenation usually opens the ring, sometimes selective hydrogenation of a double bond in the homocyclic ring can be carried out by utilizing palladium on charcoal as catalyst.[12/70,17/74,18/76,14/82,16/84,46/84,15/86] In particular, the use of ethyl acetate/acetic acid as solvent allows this selective reduction to be achieved cleanly.

Oxidation of double bonds in an adjacent homocyclic ring can be safely carried out without affecting the 2-isoxazoline ring. The usual products include the epoxide or the cyclic 1,2-diol,[13/66,12/70,11/79,13/82,16/85,42/87,28/88] the open-chain diol resulting from double-bond rupture,[55/85,14/86] or, following treatment with stronger oxidants such as $KMnO_4$, the diacid.[12/67,12/70,11/71]

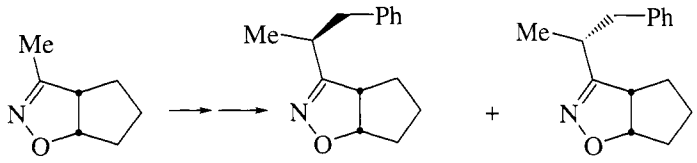
Oxidation of hydroxyl to carbonyl groups is also easily realized with Jones' reagent or other oxidants.[11/64,12/64,20/64,14/65,15/65,32/67,11/71,11/72, 29/72,50/83,20/84,30/86,52/86] In special cases, as with a steroidal 5-hydroxy-2-isoxazoline, enzymatic oxidation may be more convenient.[8/61]

Selenium dioxide oxidation regularly furnishes the α-diketo derivative, which can be submitted to routine reactions without affecting the 2-isoxazoline ring.[27/75] The azo group can be safely oxidized to azoxy group with peracids,[63/82] and the hydrazo to the azo group with various oxidants.[11/82]

Monocyclic 3-substituted 2-isoxazolines are known to undergo metallation with lithium diisopropylamide (or other strong bases) at low temperature. The 4-carbanion is preferentially formed, which can either promote ring scission to yield the ethylenic ketoxime (see Part 1, § 2.2.3.2c, p. 568), or be alkylated with alkyl halides (see Part 1, § 2.2.2.6, pp. 531–532 and § 2.2.3.1c, p. 550). With 3-alkyl substituents an appropriate choice of the solvent can sometimes favor the formation of the 3α-anion, with subsequent alkylation occurring in the side chain. Fused 2-isoxazolines, such as **764**, undergo *exo*-deprotonation more easily than *endo*-deprotonation. Thus, whereas the 3-phenyl-substituted derivative suffers ring opening to give the oxime **766**, the 3-methyl-substituted derivative can be easily alkylated at the 3α position with formation of the 3-ethylderivative **765**.[35/76,8/80]



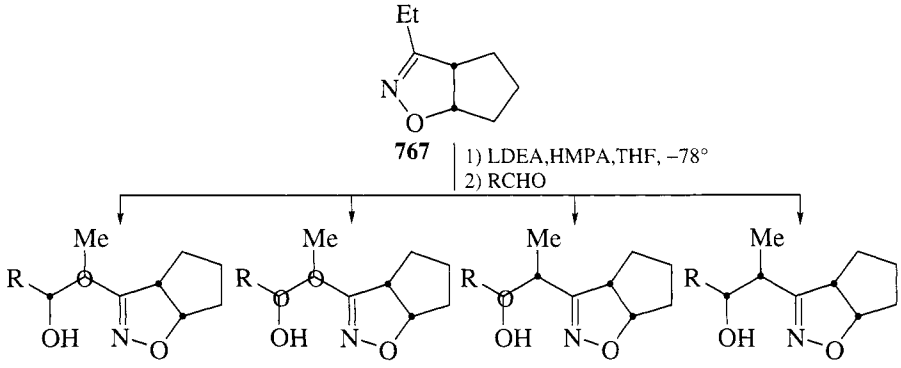
Curiously, 3α-alkylation is highly stereoselective, and the appropriate choice of reagents for the alkylating sequence can lead to good levels of diastereoselection, as shown in the following example:[52/87]



Route A [< 4 : >96 (total yield 61%)] (1) LDA, (2) MeI; then (3) LDA, (4) $PhCH_2Br$

Route B [87 : 13 (total yield: 71%)] (1) LDA, (2) $PhCH_2Br$; then (3) LDA, (4) MeI

The 3α-carbanion also attacks the carbonyl group, leading to an aldol reaction with high facial and *syn/anti* (Masamune nomenclature) selectivities.[67/90,83/90] Thus, deprotonation of the fused isoxazoline **767** with lithium diethylamide and subsequent condensation with aldehydes gives a mixture of all four possible diastereomers, as illustrated below:[67/90]



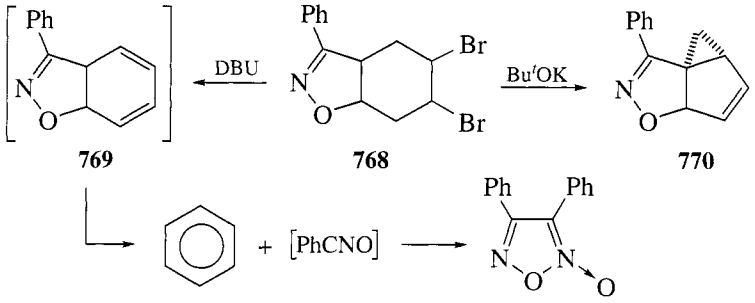
R = Et:	40 : 36 : 4 : 30	(total yield 46%)
Pr^i:	43 : 37 : 3 : 17	53%
Ph	44 : 35 : 8 : 13	58%
In the presence of $ZrCl_2Cp_2$:		
R = Et	= : = : 2 : 88	42%
Pr^i:	= : 4 : 8 : 89	39%
Ph	= : 1 : 6 : 93	58%

The Zr-promoted aldol reaction is characterized by high facial and *syn/anti* selectivity; deoxygenation of the products thus obtained furnishes the opposite diastereoisomer in comparison to the results obtained by direct alkylation.

An aldol condensation on the 3-acetyl substituent of a fused isoxazoline takes place without any notable selectivity.[8/89]

Electrophilic addition to endocyclic double bonds is easily accomplished,[7/62, 12/70,11/77,13/82,46/84,9/85] as is the formation of a bromolactone by reaction of a pendant carboxylate with the bromonium ion generated from a polycyclic isoxazoline.[29/90]

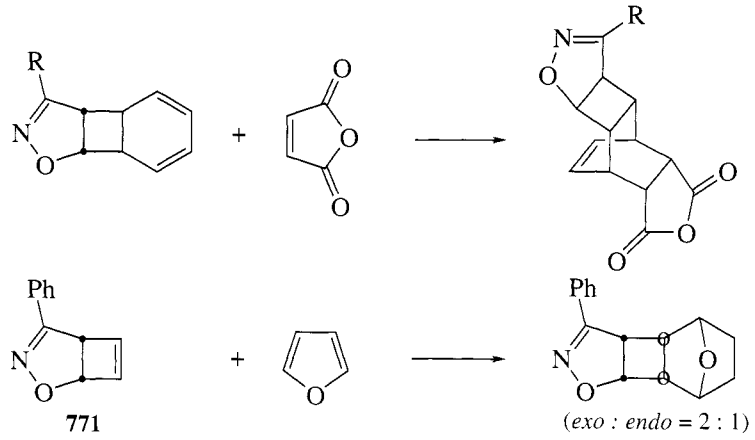
Conversely, dehalogenation[12/70] or dehydrohalogenation[14/82,22/84] can create endocyclic double bonds. An attempt to dehydrobrominate dibromide **768** in order to obtain the formal benzonitrile oxide–benzene cycloadduct **769** led to benzene and diphenylfuroxan (use of a stronger base led to the tricyclic derivative **770**):[9/85]



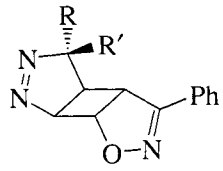
Epoxide opening in acidic conditions has been successfully performed in the presence of an isoxazoline ring.[12/70,11/7]

Reduction of a ketone to an olefin through degradation of an intermediate tosylhydrazone has been recorded.[16/73]

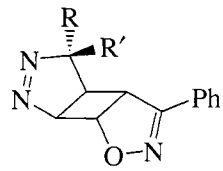
Diels–Alder reactions may involve either a diene contained within a fused homocyclic ring, or a similarly contained dienophile. Two examples are reported here:[12/67,12/70,6/77]



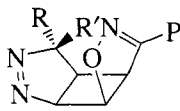
The bicyclic isoxazoline **771** readily undergoes 1,3-dipolar cycloadditions on the cyclobutene ring, leading to a complex mixture of regio- and stereoisomeric compounds. The reactions of this and other bi- and polycyclic isoxazolines with nitrile oxides has already been considered in § 4.2.2.1; cycloaddition of **771** with diazoalkanes gives mixtures of cycloadducts, whose composition depends on the dipole substituents, as here illustrated:[6/77]



772



773



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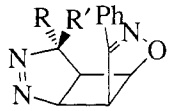


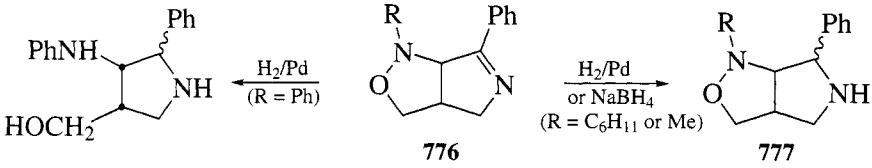
775

R	R′	**772:773:774:775**	Total yield (%)
H	H	47: 27: 3: 23	96
Me	Me	58: 42: 0: 0	95
H	Me	31: 20: 3: 17	98
Me	H	18: 10: 0: 0	

Other manipulations are also possible on the fused homocyclic rings and/or on the side chains, leaving unaltered the heterocyclic ring: (1) dehydration of alcohols,[23/81,21/84] (2) acylations of hydroxyderivatives[9/63,14/65,5/69,38/69,31/72,18/76,3/81] and of amines,[21/84,35/87,11/91] (3) ether formation[3/81,13/82,20/84,16/85,14/86,42/87,28/88,65/90] and ether hydrolysis,[21/84,20/84,83/90] (4) carbonyl group derivatizations,[7/62,16/65, 33/67,29/71, 27/75,20/84,30/86,8/89,65/90, 66/90] (5) hydrolysis of acetals,[20/84,30/86] and hydrolysis of esters [9/63,12/64,20/64,15/65,16/65,33/67,15/68,14/69,38/69,11/71,11/72,10/74,48/80,50/81,49/82,50/83,18/86,21/86,30/86,34/87,2/89, 8/89] and anhydrides,[7/62,12/70,9/85] (6) esterification[7/62,38/69,12/70,11/71,9/85,18/86,2/89,3/91] and formation of amides,[14/68,31/72,45/83,45/84,46/84,10/87,63/88] (7) formation of *N*-hydroxyimides,[31/72] (8) alcoholysis of imides,[8/87] (9) ammonolysis of lactones,[56/86,57/86], (10) Hoffmann degradation[14/68] and Schmidt reaction,[11/66] (11) alkylation of amines[11/91] or sulfonamides,[37/74] (12) oxidation of sulfides to sulfoxides[42/87,28/88,21/89, 12/91,18/91] or to sulfones,[16/79,14/82,16/84,11/90,12/91] and (13) acid-promoted aromatization of a 1,4-endoxocyclohexene moiety.[6/77]

4.3.1.3*c*. Fused Isoxazolidines

The isoxazolidine N–O bond is known to be easily cleaved by hydrogenolysis (see Part 1, § 3.4.2, pp. 734–737, and this volume, § 4.3.2.1). Nevertheless, selective hydrogenation of double bonds in fused or bridged polycyclic isoxazolidines is sometimes reported, usually when the catalyst is palladium on charcoal.[11/69,27/70,14/81,44/83] Even platinum as catalyst, or diimide or diborane have been sometimes successful.[7/76,46/82] Sometimes the selection depends on substitution. Thus, the C=N bond of the tetrahydropyrroloisoxazoles **776** is hydrogenated to



give **777** when R=cyclohexenyl or methyl; however, ring scission is observed when R = phenyl.[25/78]

Even different experimental conditions can lead to selective hydrogenation and hydrogenolytic ring opening.[46/83]

Hydrogenolysis of benzyl ethers can be accomplished without opening the heterocyclic ring by using hydrogen with Pd/C as catalyst;[37/79] however, in another case also the isoxazolidine ring is opened.[39/79] By contrast, use of platinum as catalyst opens the isoxazolidine N–O bond without affecting the benzyloxy group.[37/79] A partial hydrogenation of the fused pyridinium ring with $NaBH_4$ has been reported.[37/91] Diimide (prepared *in situ*) is the reagent of choice for hydrogenating the CC double bond of 2,3-oxazabicyclo[2.2.1]hept-5-ene or its *N*-benzoyl derivative.[10/81]

Reduction of an ester to methyl group in a fused isoxazolidine has been safely accomplished in three steps (reduction with $LiAlH_4$, mesylation, nucleophilic displacement with Super-Hydride), without affecting the heterocyclic system.[22/87]

Ester or carbonyl groups are reduced to alcohols with lithium aluminum hydride;[30/70,24/71,33/80,37/83,37/88,18/90,77/90,44/91] sodium borohydride[26/73,29/83,37/88] and diisobutylaluminum hydride[37/81] are also effective with carbonyl groups. A hydroxy group can be substituted by a hydrogen atom through reduction of the corresponding methyl xanthate by tributyltin hydride.[39/79]

Conversely, oxidation of hydroxy to keto groups is usually carried out with chromium trioxide.[24/71,26/73,56/80] Oxidation of a vinyl to a formyl group has been reported.[46/82] A stable radical from a hydroxylamino residue has been formed by oxidation with silver oxide.[20/76]

Additions of halogens to double bonds are known,[11/67,24/67,18/77] as well as formation of diols by treatment of the double bond with osmium tetroxide.[30/82,46/82]

Bromination in the *para* position of a phenyl ring has been achieved with *N*-bromosuccinimide.[24/71]

Diene and retrodiene syntheses are known for some polycyclic isoxazolidine systems.[27/72,42/81,43/81]

Double bonds in the side chains are most conveniently formed by mesylation of alcohols and subsequent treatment with DBN.[15/78,25/79] Formation of a keto group from an α-acetoxynitrile moiety has been reported.[65/88]

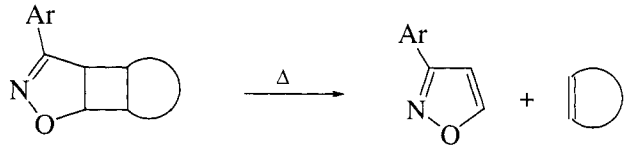
Other manipulations known for fused or bridged isoxazolidines are the following: (1) formation of ethers from alcohols[21/76,37/81,77/90] and hydrolysis of ethers,[39/79,29/80,27/90,77/90,62/90] (2) acylation of alcohols[30/70,20/71,25/79,33/79,37/79,38/79,27/80,29/80,36/83,43/89,77/90] and amines,[62/90] (3) Grignard reaction,[46/82] (4) functionalization of

carbonyl groups,[56/80,27/87] (5) formation of acetals,[30/82] (6) nucleophilic substitution,[21/76,46/82] (7) hydrolysis of esters[11/64,26/73,39/79,47/81,36/83,43/89,42/91] and anhydrides,[8/76,41/80,3/91] (8) mercury-promoted hydrolysis of thioethers,[36/83] (9) amination of alcohols,[62/90] (10) interconversion sulfide–sulfoxides,[29/84] and (11) epimerization in acidic[19/76] or basic conditions.[21/87]

4.3.1.4. Thermal Transformations

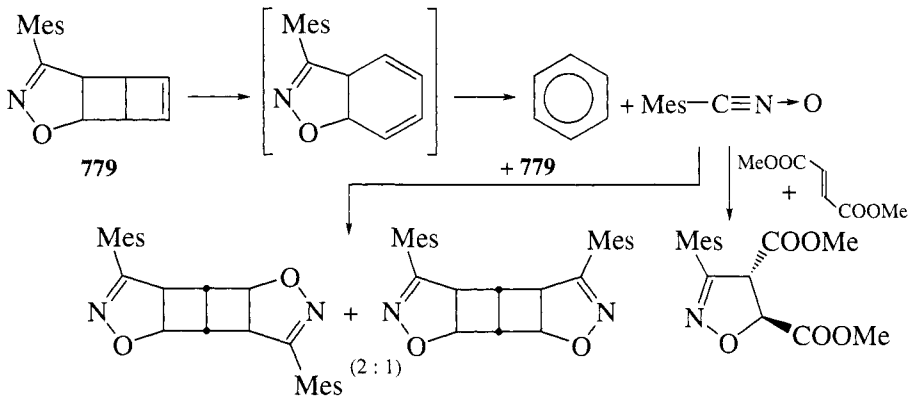
Polycyclic isoxazolines are often subject to thermal dienic cycloreversion, and some examples have already been dealt with in § 4.2.2.1.

Another example is the thermal decomposition of compounds such as **778**:[6/77,3/91]

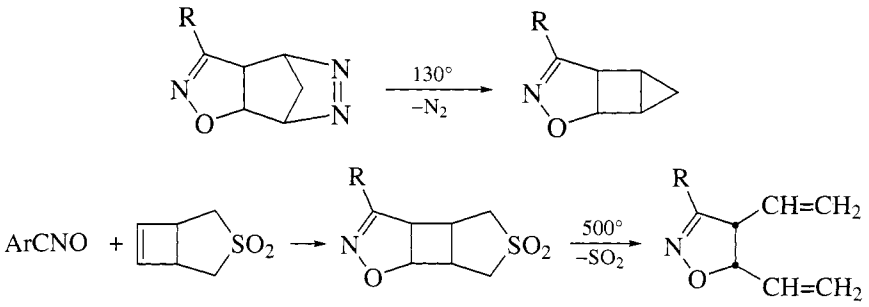


778

An attempt to isolate the formal cycloadduct of mesitonitrile oxide to benzene by thermal isomerization of **779** led to a 1,3-dipolar cycloreversion; the mesitonitrile oxide thus obtained can either react with the starting material to yield two regioisomeric bisadducts or be trapped with an active dipolarophile:[9/85]



Some fused isoxazolines can loose nitrogen or sulfur dioxide by thermal treatment; two examples are reported here:[9/82,56/82]



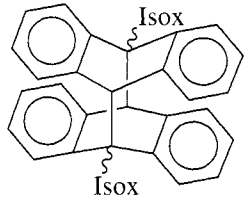
Isoxazolidines are known to readily undergo thermal cycloreversion (see § 4.2.2.5): under these conditions, the kinetically formed cycloadduct can be transformed into the regio-[14/63] or the stereoisomeric[2/58,31/66,23/71,35/74,39/79,37/83,32/85,21/87] more stable cycloadduct.

Some cases of thermal aromatization of isoxazoline or isoxazole derivatives to indoxazenes have also been reported.[4/80,53/86]

4.3.1.5. Photochemical Transformations

Isoxazoles and their hydrogenated counterparts are photolabile, owing to the presence of the weak N–O bond, and therefore photochemical reactions that leave the isoxazole ring intact are not well known.

Photodimerization is known for 3-anthranyl-2-isoxazoline derivatives, leading to compounds **780** in low yield.[67/86]

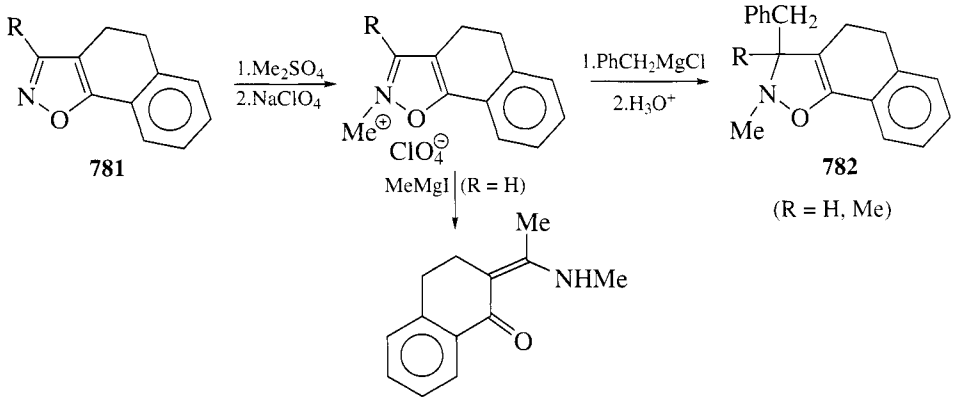


780

4.3.1.6. Interconversion between Isoxazole Derivatives

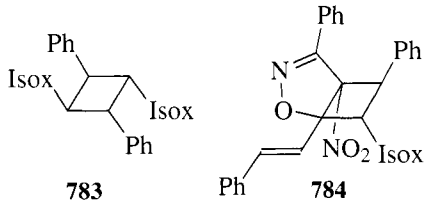
Several methods are known, which allow the conversion of dihydroisoxazoles (isoxazolines) to isoxazoles or tetrahydroisoxazoles (isoxazolidines); these latter compounds in turn can be dehydrogenated to isoxazolines or isomerized to other isoxazolidine derivatives.

Less frequently observed is the partial hydrogenation of the isoxazole nucleus to a dihydro derivative. The fused dihydronaphthisoxazole **781** is transformed into the fused 4-isoxazoline **782** through *N*-methylation and addition of benzylmagnesium chloride:[2/74]

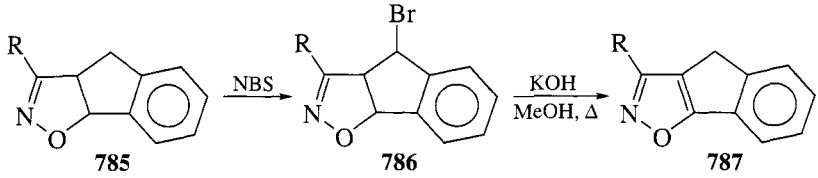


By contrast, methylmagnesium chloride provokes ring scission of the 3-unsubstituted **781**.

The isoxazole C=C bond can participate in [2+2] photocycloaddition; indeed, whereas irradiation of 3-methyl-4-nitro-5-styrylisoxazole in the solid state yields the dimer **783** of the α-truxillic type, irradiation in benzene solution or when absorbed on silicagel leads to the isolation of other three dimers as by-products, one of which has been assigned structure **784**.[48/79]



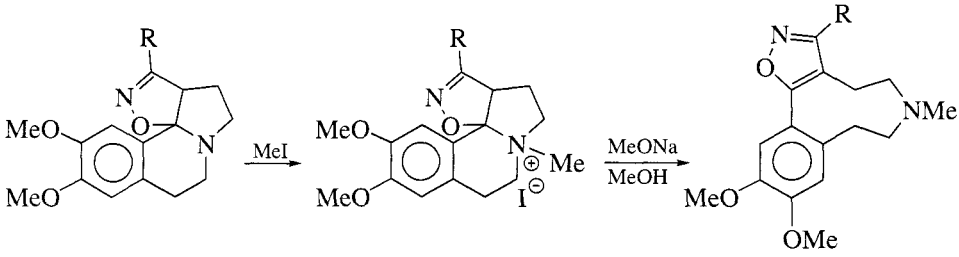
Fused isoxazolines may be (see also § 4.3.1.2) easily brominated in the 4 position by *N*-bromosuccinimide; coupling of this substitution stage with a treatment with a weak base (usually triethylamine) permits preparation of the corresponding condensed isoxazole, often in a one-pot procedure. Thus, several indeno-,[15/67] acenaphtho-,[22/64,11/71] or other fused isoxazole systems[17/70,9/75,34/83] have been prepared. When the indenoisoxazoline **785** is treated with NBS, the 4α-bromo derivative **786** is formed almost exclusively, and dehydrobromination to give the indenoisoxazole **787** requires a stronger base (usually potassium hydroxide):[15/67]



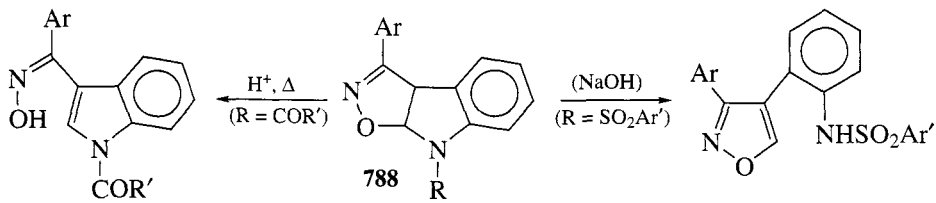
A steroidal isoxazole has been obtained by deiodination of the corresponding 5-iodoisoxazoline with silver acetate.[33/69]

However, the synthesis of isoxazoles fused with a five- or a six-membered ring is carried out most conveniently by deamination of the 5-amino-substituted fused isoxazolines available by 1,3-dipolar cycloaddition of nitrile oxides to the enamines of cycloalkanones. Deamination of the 4,5-tetramethylene derivatives is easily accomplished by heating with dilute mineral acids,[10/63,4/64,9/68,13/71, 32/72,49/80,56/84,56/85] whereas deamination of the fused five-membered ring analogs requires quaternization of the nitrogen atom and subsequent treatment with silver oxide or sodium hydroxide.[3/64,4/64,15/67]

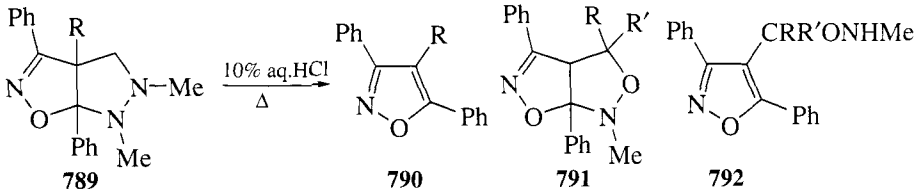
An internal deamination is known for a polycyclic pyrrolidinoisoxazoline, leading to an azamacrocycle:[49/89,7/91]



Cycloadducts **788**, obtained from mesito- or benzonitrile oxide and *N*-substituted indoles, undergo scission of the isoxazoline ring under acidic conditions. Under basic conditions the cleavage still concerns the isoxazoline ring predominantly when R is an acyl group, whereas the indole ring is exclusively opened when R is an arylsulfonyl group:[15/84]



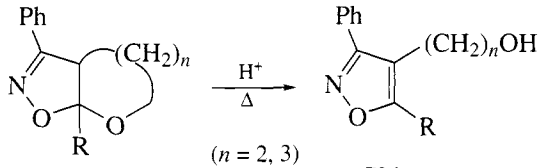
Under acidic conditions, pyrazolidino[4,3-*d*]isoxazolines (**789**) suffer ring scission to isoxazoles **790**:[20/74,19/76,12/77]



789 **790** **791** **792**

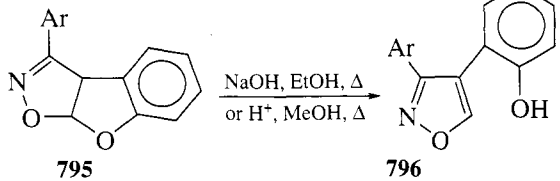
Quaternization of compounds such as **789** gives one of two regioisomeric methiodides, which, in turn, following scission of the quaternized pyrazolidine ring, furnish 3,4-di- or 3,4,5-trisubstituted isoxazole derivatives.[37/76] The analogous isoxazolidino[4,3-*d*]isoxazolines **791** under acid-promoted ring scission in chloroform yield the isoxazole **792**, whereas in aqueous solution a complex mixture of several isoxazole derivatives is formed.[11/78] A by-product of the Schmidt reaction on 3-phenyl-5-acylcyclopent[*d*]isoxazoline is the 3-phenyl cyclopent[*d*]isoxazole, possibly formed through an elimination process from the fused 5-acetamidoisoxazoline.[11/66]

Acid-promoted ring cleavage of 3-phenyltetrahydrofuro- or 3-phenyltetrahydropyrano[3,2-*d*]isoxazoles **793** leads to isoxazole 4-alkanols **794**:[17/66,14/68,39/69]



793 (*n* = 2, 3) (R = H, Me) **794**

Cycloadduct **795** is cleaved, under basic and acidic conditions, to give 3,4-diarylisoxazole derivative **796**:[11/77,9/78]



795 **796**

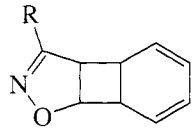
Similar acid-promoted cleavage of hydrofuran or hydrofuranone rings fused with the isoxazoline furnishes isoxazole derivatives.[18/76]

Ring opening of benzisoxazolo[2,3-*c*]quinazolines under acidic or basic conditions leads to 3-(*o*-aminophenyl)-1,2-benzisoxazole derivatives.[41/74]

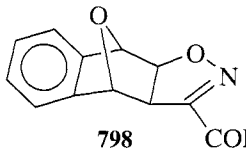
Dehydration of a 5-hydroxyisoxazolinosteroid occurs under acidic or basic conditions and leads to the corresponding isoxazole derivative.[5/69,6/69] Dehydration of 4-hydroxy-2-isoxazolines requires more drastic conditions.[17/66]

Transformation of isoxazolines to isoxazoles can sometimes be accomplished by direct dehydrogenation with oxidizing agents, such as activated γ-MnO_2,[13/84] chloranil,[14/74,17/74,10/75,14/76,13/79,54/86] NiO_2,[11/89] or even air.[19/85] Examples of base-assisted[23/81,21/84] or a silicagel-promoted[17/74] aromatization are also known.

Sometimes a thermal retrodiene scission transforms a fused isoxazoline derivative into a monocyclic isoxazole. This is the case for the 3-substituted 3a,3b,7a,7b-tetrahydrobenzo[3,4]cyclobuta[1,2-*d*]isoxazole **797**, which decomposes at 100–140°C into isoxazole and benzene.[12/67,12/70,11/73,35/77] Similarly, the cycloadduct **798**, of benzoylformonitrile oxide and 1,4-epoxydihydronaphthalene decomposes at 160°C to give benzoylisoxazole and benzoisofuran,[10/72] and the 5-substituted 8,9-azoxy-3-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]deca-4,8-diene **799**, thermally reverts into a 3-substituted isoxazole and 1-hydroxypyrazole[57/82,55/83] at 170°C. The tricyclic system **800** (R = H), decomposes at 140–160°C to isoxazole and cyclopentadiene,[13/67,12/73] but when R = Ph, heating at 170°C yields, along with 3-phenylisoxazole, the Diels–Alder adduct of cyclopentadiene to the CC double bond of **800**.[73/90]



797



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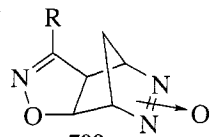

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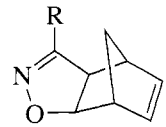
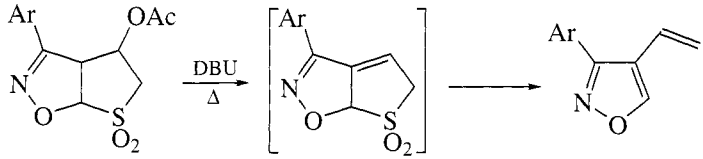


800

The spontaneous retrodiene decomposition of the regioisomeric cycloadducts from nitrile oxides and norbornadiene dicarboxylate (or its 7-oxa- and 7-aza-derivatives) has already been cited in § 4.2.2.1.

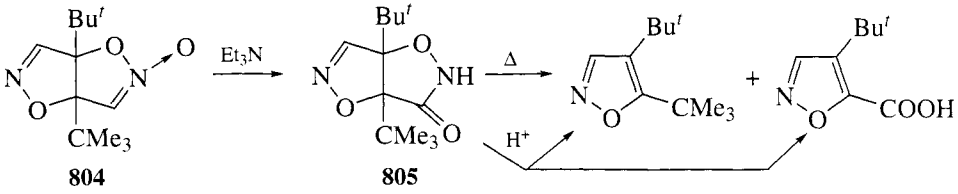
The minor cycloadduct **801** from arenonitrile oxide and 4-acetoxy-4,5-dihydrothiophene 1,1-dioxide, when treated with DBU, is decomposed to 3-aryl-4-vinylisoxazole (**803**) through the nonisolable fused isoxazoline **802**:[14/82]



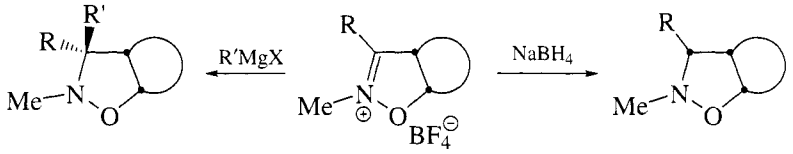
801 **802** **803**

Deoxygenation of fused 2-isoxazoline *N*-oxides to the corresponding isoxazolines is easily effected by triphenylphosphine.[25/77,30/78,34/83]

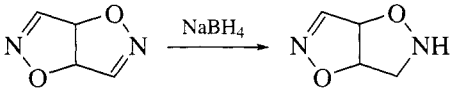
The fused diisoxazoline *N*-monoxide **804** has been reported to isomerize to **805** by base treatment; in turn, **805** decomposes to isoxazole derivatives by acid promotion or thermally:[34/70]



The conversion of 2-isoxazolines to isoxazolidines is most conveniently accomplished by quaternization and subsequent reduction with sodium borohydride:[12/74, 44/80,14/81,17/82,26/87]



The reaction sequence is highly stereoselective, usually leading to the 3,4-*cis* isomer. The presence of a methyl group in the isoxazoline 4 position makes the reduction practically unselective.[73/84] The reaction of the quaternary salt with Grignard reagents yields a 3,3-disubstituted fused isoxazolidine.[12/74] In one case, lithium aluminum hydride was also effective.[21/84] In other cases, especially with 3a,6a-dihydroisoxazolo[5,4-*d*]isoxazoles, treatment with $NaBH_4$ or DIBAL reduces one isoxazoline nucleus to *N*-unsubstituted isoxazolidine as in the following reaction:[32/66, 33/77,47/79,51/79,24/81]



The C=N bond of the fused 2-isoxazoline is reactive toward 1,3-dipoles, and isoxazolidino-condensed heterocycles are thus produced:[17/70,11/72,16/73,18/76,10/78, 50/80,15/82,46/88]

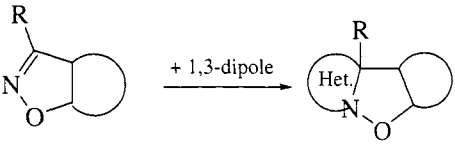
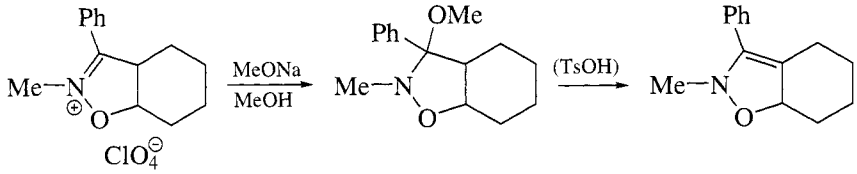


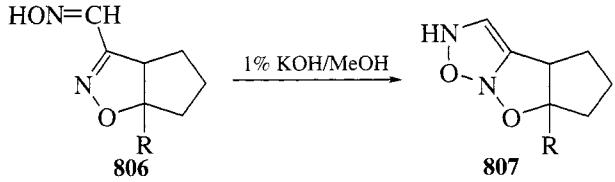
Photo-induced cycloaddition of benzene or indene or heteroaromatics to the C=N isoxazoline bond can produce [2+2] cycloadducts.[42/81,43/81] Thermal cycloreversion sometimes restores the 2-isoxazoline.[43/81]

Addition of ethanol to the double bond of a 3,4-fused 4-isoxazoline yields the corresponding 5-ethoxyisoxazolidine with high stereoselectivity.[27/70]

The transformation of a 2- into a 3-isoxazoline has been performed through quaternization and an addition/elimination sequence, such as the following:[46/74]

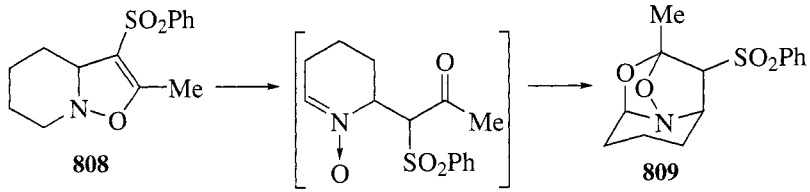


The oxime of 3-formyl-2-isoxazoline derivative **806** cyclizes to the isoxazolidino[2,3-*b*]-Δ^3-1,2,5-oxadiazoline **807** under treatment with base:[10/74]



806 **807**

A peculiar oxidative transformation of the fused 4-isoxazoline **808** to the tricyclic isoxazolidine **809** has been reported:[67/88]

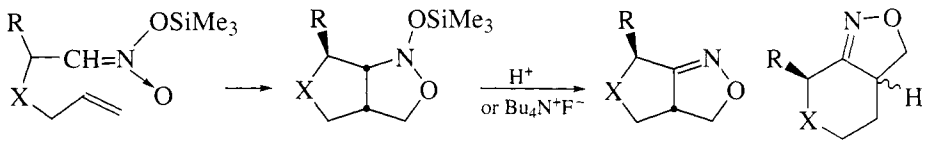


808 **809**

The isoxazolidine–isoxazoline conversion is less frequent than the reverse process.

Some steroidal isoxazolidines, obtained by high-pressure-induced 1,3-dipolar cycloaddition of nitronic esters to the 16,17-double bond of the steroid, easily lose methanol to give the corresponding 3-ethoxycarbonyl-2-isoxazoline under action of BF_3-etherate.[11/75,17/77]

The so-called ISOC (intramolecular silyl nitronate–olefin cycloaddition) is highly stereoselective, and thus elimination of trimethylsilanol furnishes the *trans*-2-isoxazoline derivative exclusively. The direct INOC process is far less stereoselective.[12/90]

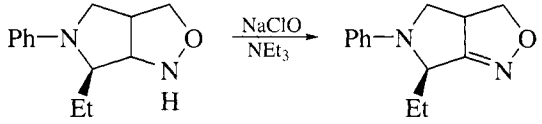


(X = O, S, C(COOMe)$_2$) **810** (X = O, S)

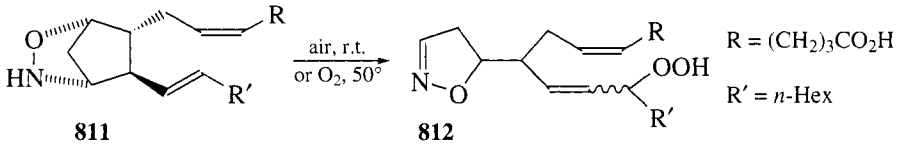
The formation of the higher homolog **810** is less stereoselective; when R = Me, the ISOC process furnishes a 5:3 mixture of *trans*:*cis* isomers, whereas the direct INOC process gives a 1:5 mixture.[12/90]

A low-yield dehydrogenation with DDQ has been performed on 2,3-dihydro-9*H*-isoxazolo[3,2-*b*]quinazolin-9-one, thus giving the 4-isoxazoline derivative.[28/77]

A simple dehydrogenation has been observed with a pyrrolidinoisoxazolidine:[22/88]

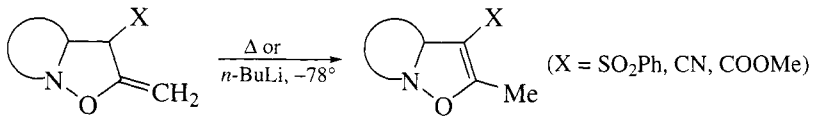


A rather peculiar air oxidation of the bridged isoxazolidine **811** yields the 2-isoxazolinyl hydroperoxide derivative **812**:[50/81,50/83]



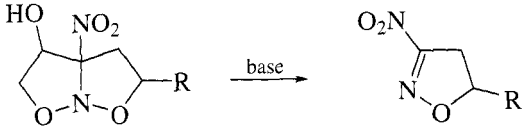
811 **812**

Thermal or base-induced isomerization of 5-methyleneisoxazolidines, bearing in the 4 position an electron-withdrawing substituent, to the corresponding 4-isoxazolines has been reported.[58/86,46/87]

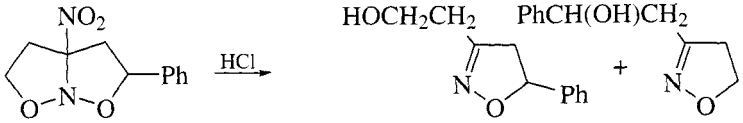


Isoxazolizidines or their higher homologs, such as 2,9-dioxa-1-azabicyclo[4.3.0]nonanes, are easily opened to give monocyclic or spiro-2-isoxazolines or isomerized to fused or spiroisoxazolidines. The product formation depends

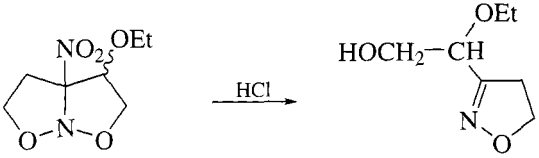
on the nature of the substituents and on steric effects, as well as on the reaction medium. The following examples are typical:



Ref. 23/66



Ref. 27/67



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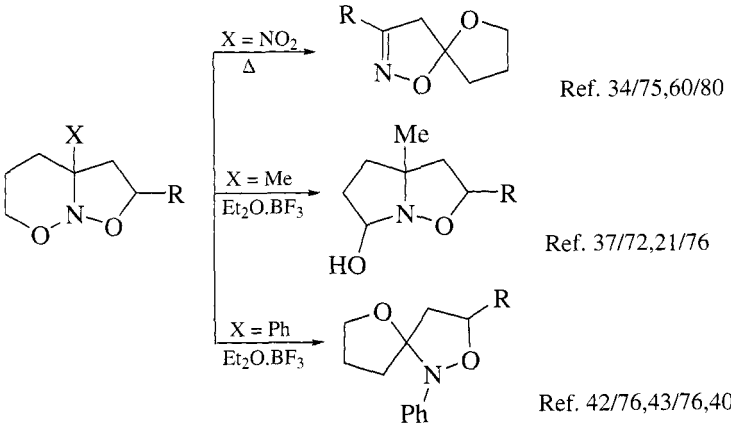
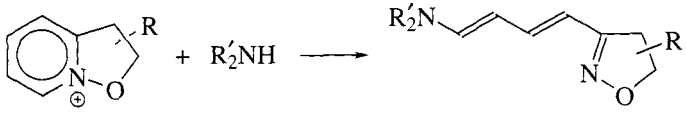


Ref. 34/75,60/80

Ref. 37/72,21/76

Ref. 42/76,43/76,40/77,40/78

The isoxazolidino–pyridinium cation is attacked by secondary amines, which open the pyridinium ring, leading to 3-aminobutadienyl-2-isoxazolines:[30/67,50/89]



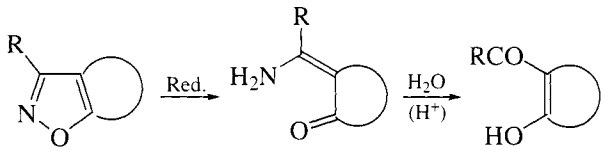
4.3.2. Reactions with Ring Cleavage

4.3.2.1. Reduction

Hydrogenolytic cleavage of the N–O bond is the most convenient method for opening both the isoxazole and its dihydro and tetrahydro derivatives. Both catalytic hydrogenation and chemical reductants have been utilized, and the best choice depends on the substrate and the product to be obtained. The following treatment is based on the nature of the substrate (fused or bridged isoxazole, 2-isoxazoline, or isoxazolidine).

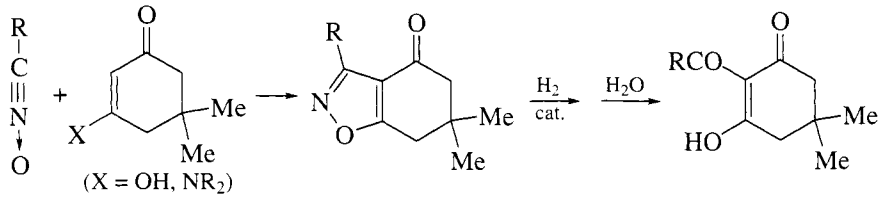
4.3.2.1a. Fused isoxazoles

As already illustrated in Part 1 (§1.4.3.1, pp. 273–281), the primary product of the reductive ring cleavage is the β-enamino ketone, which can easily be hydrolyzed, even *in situ*, to the corresponding β-diketone:

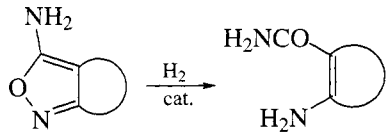


Catalytic hydrogenation in the presence of Raney nickel[15/67] or palladium on charcoal[52/85] or platinum[37/78,2/82] is the most common method of accomplishing the ring opening, but zinc and acetic acid[10/67] have proved equally effective.

Bearing in mind that the fused isoxazole is usually prepared by a regioselective 1,3-dipolar cycloaddition of a nitrile oxide to the cyclic β-diketone (or to its enamine), the whole sequence is equivalent to an α-acylation, such as the following:[22/74,10/75,14/76,15/76,13/79]

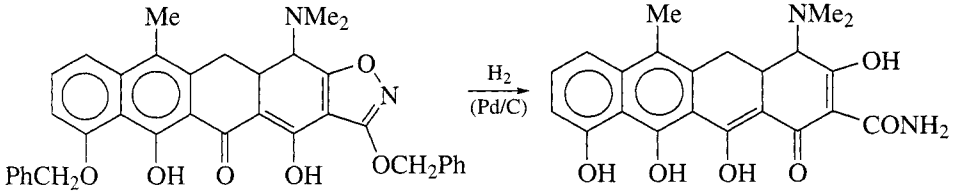


The presence of an amino group in the isoxazole 5- position leads to the formation of the corresponding enaminocarboxamide, as generalized here:[8/66, 27/66,9/67,10/67,31/67,33/72]



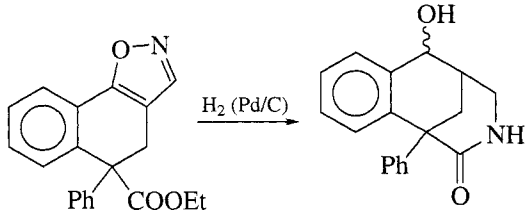
Analogously enamino esters are obtained by hydrogenolysis of 5-methoxy-isoxazole derivatives.[3/71]

The presence of a benzyloxy group in the isoxazole 3 position can furnish the corresponding β-ketocarboxamide, as illustrated by the last passage of a multi-step synthesis of 12a-deoxyanhydrotetracycline **813**:[35/78]



813

The presence of an ester group in the isoxazole 4β-position can be used to furnish a δ-lactam, as in the following example:[2/67]



Catalytic hydrogenolysis of the isoxazole ring in anthra[1,9-*cd*]isoxazol-6-ones proceeds regularly, giving the expected 1-aminoanthraquinones.[1/21,51/83,31/90] With 4- or 2-amino-substituted derivatives, reductions with sodium sulfide[54/79] or even sodium borohydride[48/81,57/85] have been reported, whereas lithium aluminum hydride is reported to deaminate the 4 or 2 position, leaving unaltered the isoxazole ring.[54/79]

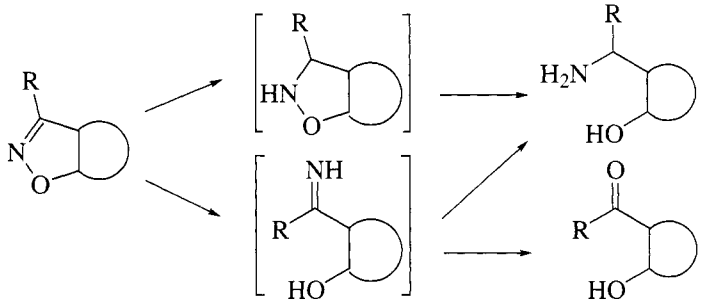
When suitably substituted, an enaminoketone can, in turn, spontaneously cyclize with its amino (or imino) group, giving rise to other nitrogen-containing heterocyclic systems. Illustration of these possibilities is postponed to § 4.3.2.6.

A selective hydrogenolytic method, which leaves side-chain double bonds unaffected, uses sodium borohydride and nickel chloride in DMF/THF containing 1-octene.[1/88]

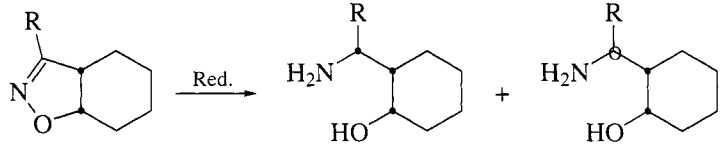
The structures of five metabolites, obtained by reductive biodegradation of danazol, have been studied and identified.[36/77]

4.3.2.1b. Fused 2-Isoxazolines

The reduction of 4,5-fused 2-isoxazolines has been studied in detail, in view of both the product obtainable and the stereochemical implications. As already summarized in Part 1 (§ 2.2.3.2b, pp. 561–565), hydrogenolytic cleavage of the isoxazoline ring can furnish either the γ-aminoalcohol or the β-hydroxy ketone, through the intermediacy of either an isoxazolidine, if the C=N bond is reduced first, or of a β-hydroxy imine, if the N–O bond is cleaved first. These two intermediates are seldom isolated.



Lithium aluminum hydride is the reductant of choice for preparing γ-aminoalcohols, and has been demonstrated to attack initially the C=N bond, whereas sodium in ethanol follows the hydroxyimine route.[51/80] Consequently, the stereoselection is very high for $LiAlH_4$ reduction, whereas practically no selectivity is observed with Na in methanol, as illustrated by the following example:[38/78,52/80]

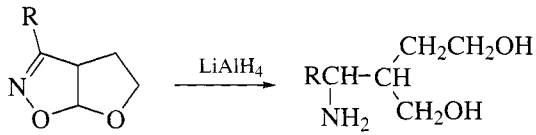


R	Red.	Isomer Ratio	Total Yield%
Me	$LiAlH_4$	97 : 3	87
	Na/EtOH	42 : 58	79
Et	$LiAlH_4$	97 : 3	81
Ph	$LiAlH_4$	>95 : <5	97

The same high stereoselectivity has been observed with other 2-isoxazolines fused at the 4, 5 or 3, 4 positions with five-membered rings.[15/70,12/78,20/80,3/81,13/82,16/85,

[55/85,11/90] A somewhat lower level of stereocontrol (~3 : 1) has been reported for isoxazolines fused with a tetrahydrofuran or a dioxepane ring.[12/87] Interestingly enough, whereas a very low selectivity is exhibited by a monocyclic isoxazoline bearing a free hydroxy group at the 4 position, the stereocontrol is again almost complete when the hydroxy group is blocked in a cyclic ketal ring.[55/85]

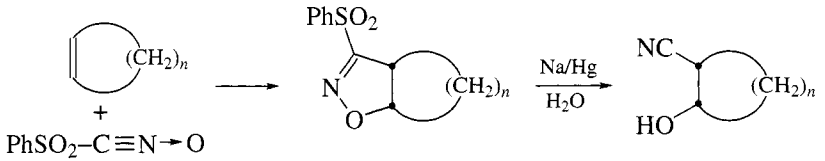
Not unexpectedly, reduction of the ketal-type bicyclic isoxazoline **814** opens both rings, giving the aminodiol **815**:[8/62]



814 **815**

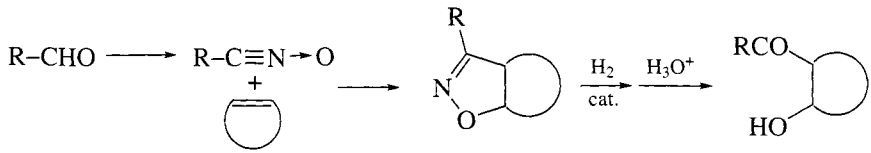
At variance with the aforementioned behavior, the ring scission of some 5-hydroxylated steroidal isoxazolines with lithium aluminum hydride is reported to yield a β-hydroxy aldoxime.[33/66,34/67,37/69]

3-Benzenesulfonyl-2-isoxazolines are reductively cleaved with 2% sodium amalgam to yield the β-hydroxynitrile; since the isoxazolines originate from the reaction of the cycloalkenes with the benzenesulfonylcarbonitrile oxide (prepared *in situ*), the whole sequence, which can be carried out without isolating the intermediate isoxazoline, represents a useful procedure for the stereospecific *syn*-cyanohydroxylation of cycloalkenes:[7/79,17/81]

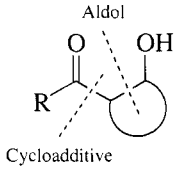


Sodium borohydride has been used for an analogous process, although with far lower yields.[17/84]

Catalytic hydrogenation leads to β-hydroxyketones, and, taking into account that the 2-isoxazoline ultimately arises from an aldehyde through the nitrile oxide methodology, the entire sequence is equivalent to an aldol synthesis:

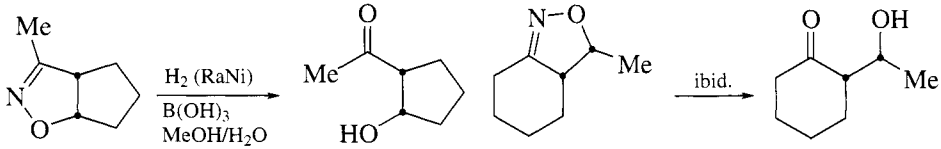


The so-called "cycloadditive strategy"[66/88] to β-hydroxyketones differs from the classic aldol condensation with its numerous variants mainly because of the C–C bond formed during the two processes. The aldol route involves the formation of the C–C(OH) bond, whereas the cycloadditive route involves the formation of the C–C(=O) bond:



The catalytic reduction step is based on a primary N–O fission, yielding the β-hydroxyimine, which is usually unstable and promptly hydrolyzes. Owing to the stereospecificity of the cycloaddition step, a complete stereocontrol is expected with formation of only one diastereoisomeric racemate. However, epimerization can occur, and retroaldol by-products can also be present in the reduction mixture, if the proper conditions are not adopted. An excellent review summarizes research devoted to maximize the stereocontrol in the cycloadditive strategy.[66/88]

The best results are attained when the hydrogenation is carried out with W2 Raney nickel as catalyst and in the presence of 2 equiv of boric acid in a 5:1 mixture of methanol/water. Under these conditions, for both 4,5- and 3,4-fused isoxazolines practically complete stereoselectivity has been observed, as the degree of epimerization is lower than 2%, as in the following examples:[58/82,15/83, 4/84,24/85]

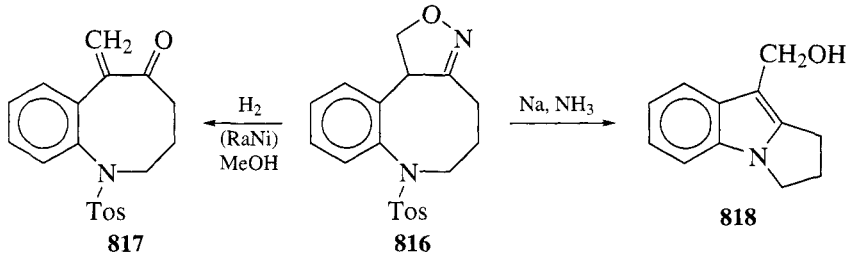


Other additives that may be used instead of boric acid are concentrated HCl or $AlCl_3$[65/82] or, with somewhat less straightforward results, trimethyl borate, which does not avoid some degree of epimeric hydroxyketone (4–15%) when the 3,4-fused ring is five-membered, boron trichloride, acetate or phosphate buffer, or acetic acid (this last method is often used in multistep synthetic strategy). In isolated cases the β-hydroxyimine could be isolated, and hydrolysis to the keto group requires stirring in the presence of silicagel.[30/86]

Other catalysts employed include palladium on charcoal,[58/85,17/89] platinum,[21/85] and rhodium on alumina,[42/87,28/88] with nonstereospecific results. Less concern

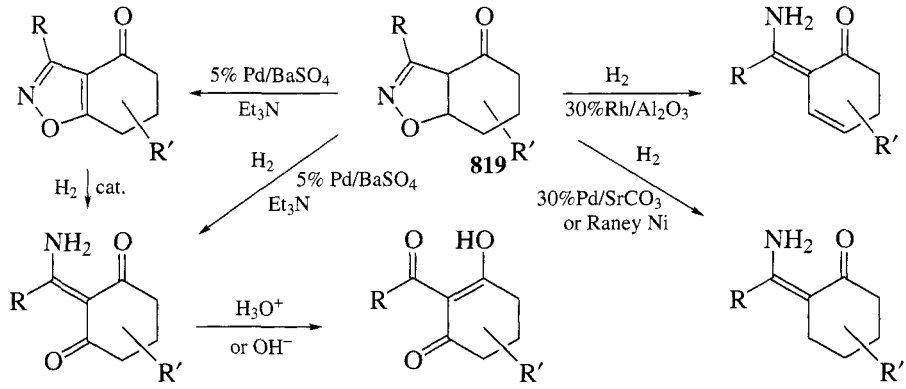
about stereocontrol is warranted when the formation of the aldol product is followed by dehydration to give the α,β-unsaturated ketone; this last process can be accomplished by mesylation and treatment with a base[19/80,21/82,20/84,21/85,68/88] or by trifluoroacetylation and subsequent treatment with triethylamine.[22/81,20/82]

Hydrogenation of the benzazocine condensed isoxazoline **816** on Raney nickel directly gave the unsaturated ketone **817**, whereas reduction with sodium–ammonia both removed the tosyl group and cleaved the isoxazoline N–O bond, giving rise to the tricyclic hydroxymethylindole derivative **818**.[21/88]



817 **816** **818**

Bicyclic isoxazolines of general structure **819** can be dehydrogenated in the presence of 5% $Pd/BaSO_4$ and Et_3N; consequently several products can be obtained by catalytic hydrogenation, depending on the catalyst adopted, as shown in the following scheme:[14/74,10/75,14/76,38/76,13/79]

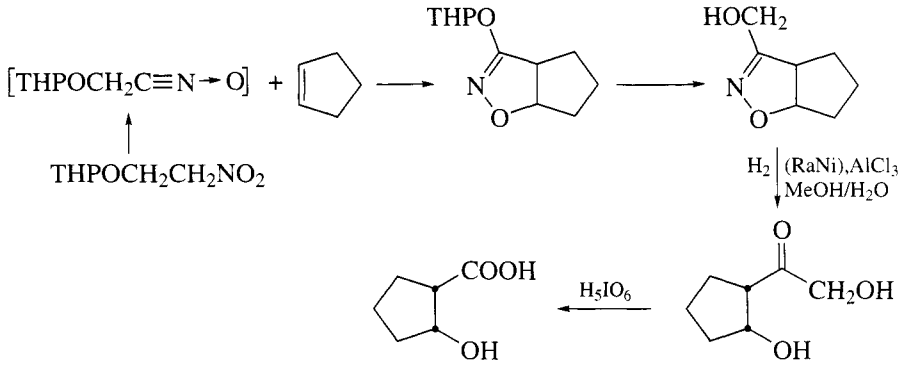


The corresponding bicyclic isoxazoline alcohols have been reported to give the 2-acylcyclohexane-1,3-diols or 2-acylcyclohex-2-enols by reaction with Raney nickel and strong acids.[39/78,57/79]

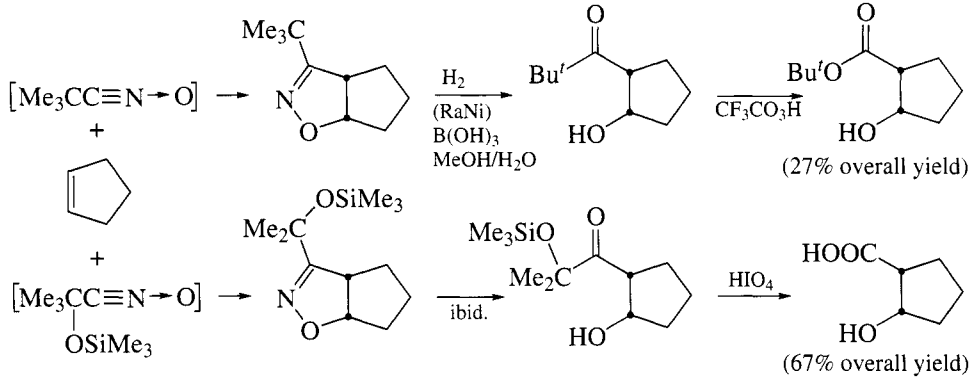
For oxidative methods of ring cleavage, leading also to β-hydroxyketones, see § 4.3.2.2.

At least four methods for accomplishing a stereoselective *cis*-hydroxycarbonylation of olefins involve a catalytic hydrogenation as key step. The first one

starts from the THP-protected β-hydroxypropiononitrile oxide, utilizes aluminum trichloride as Lewis acid additive to the Raney nickel–catalyzed hydrogenation mixture, and implies a final oxidative fission to furnish the β-hydroxy acid (or ester), as shown by the following example:[5/83]



The second and third methods commence with pivalonitrile oxide and, from 2-methyl-2-trimethylsilyloxypropiononitrile oxide, respectively, utilize the normal reduction mixture and involve appropriate terminal oxidative steps:[4/84]



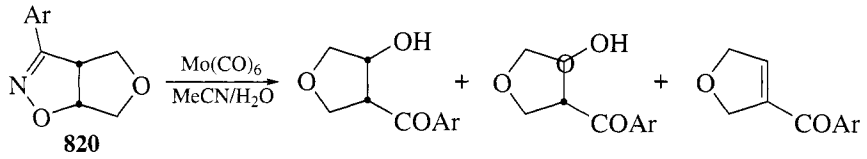
The latter method is based on the reduction of a 3-methoxyisoxazoline, obtained, in turn, by nucleophilic substitution of the easily available 3-benzenesulfonyl derivative.[4/84]

A 4,5-fused 3-chloro-2-isoxazoline has been hydrogenolyzed in the presence of Raney nickel or NiB to the β-hydroxynitrile.[21/86]

In isolated cases the catalytic hydrogenation can proceed to give the β-hydroxyamine or transformation products thereof, as for a steroidal 3-carboxy- or 3-ethoxycarbonyl-2-isoxazoline, which furnishes the corresponding

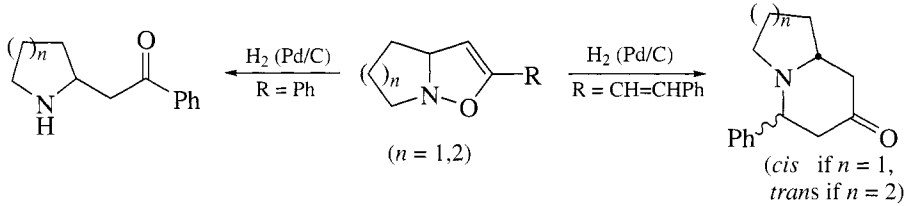
3′-amino[17α,16α]-γ-lactones,[48/80] or for a polycyclic isoxazoline, having in 4α position an ester group, whose reduction products are two γ-lactams.[46/84]

Few examples of other reductants for monocyclic 2-isoxazolines have been reported, although titanous chloride[23/85] or molybdenum hexacarbonyl in aqueous acetonitrile have been employed for this purpose. Application of the latter reagent to the furoisoxazoline **820** yielded, together with the expected *cis*-aldol, comparable amounts of the *trans*-epimer and of the corresponding enone:[69/88]



820

Catalytic hydrogenation of 2,3-fused 4-isoxazolines cleaves the N−O bond, leading to γ-aminoketones, which, when in possession of suitable substituents, can recyclize, as shown by the following example:[42/88]



The cycloadduct formed from *N*-methyl-*C*-phenylnitrone and benzyne is neatly reduced to the expected 2-(1′-methylamino)benzylphenol.[25/69]

Sometimes the hydrogenation can proceed further, and products arising from the absorption of 2 mol of hydrogen have been obtained.[25/69]

Conceivably, catalytic hydrogenation of a 3,4-fused 2-isoxazoline *N*-oxide can give either the β-hydroxy cyclic ketoxime or the corresponding γ-aminoalcohol, depending on the catalyst adopted (10% Pd/C for the former product, and Raney nickel for the latter one).[25/77,30/78]

4.3.2.1c. Fused Isoxazolidines

As already mentioned and illustrated for monocyclic isoxazolidines in Part 1 (§ 3.4.2, pp. 734–737), the N−O bond is easily cleaved by a large variety of reductants. This vast applicability extends to bicyclic and polycyclic, both fused and bridged, isoxazolidines. Stereocontrol is generally assured, and yields are always high to excellent, so that hydrogenolysis of fused isoxazolidines is now one of the most commonly used key passages in multistep synthetic strategy (see § 4.3.3).

The facile reductive ring cleavage of bicyclic isoxazolidines to give 3-amino- or 3-monoalkylamino alcohols has been known from the very beginning of research into nitrone cycloadditions,[3/59,10/62,14/63,18/64,24/65,30/91] and is a convenient structural proof for ascertaining the regio- and stereochemical outcomes of the cycloaddition. Zinc and acetic acid (often at 50–70°C),[20/80,51/81,41/82,42/82,52/88] lithium aluminum hydride,[19/78] catalytic hydrogenation in the presence of Raney nickel,[29/81,30/82,39/84] palladium on charcoal,[31/69,19/74,23/77,23/78,51/81,46/83,44/86] rhodium on charcoal,[37/84] or platinum,[20/66,34/72,37/79] in neutral or slightly acidic solution, sometimes under pressure, are the reductive agents most commonly used.

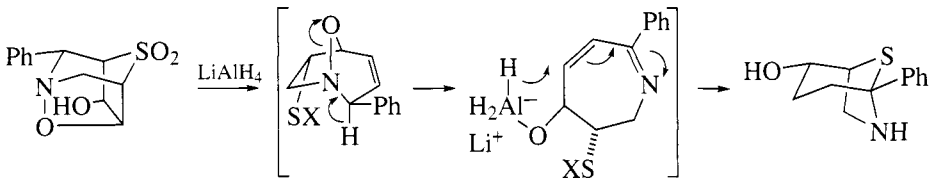
Catalytic hydrogenation of *N*-benzylisoxazolidines causes debenzylation to occur simultaneously with N–O cleavage. The same result has been achieved by palladium-catalyzed hydrogen transfer from cyclohexene in refluxing ethanol.[27/90]

As already mentioned in § 4.3.1.3, often $LiAlH_4$ selectively reduces a carbonyl group without opening the isoxazolidine ring, and, less frequently, catalytic hydrogenation of a side-chain double bond (with Pd/C or Pt as catalyst) has been selectively carried out.[24/68,46/83] Sometimes a diacetylated aminoalcohol has been obtained with zinc and acetic acid;[34/78] moreover, double bonds in side chains remain untouched.[26/80] *N*-Phenylisoxazolidines can occasionally yield the deaminated alcohol by catalytic hydrogenolysis; in this case use of a chromium (II) chloride solution in anhydrous acetic/hydrochloric acid afforded excellent yields of the expected *N*-phenylaminoalcohol.[24/71]

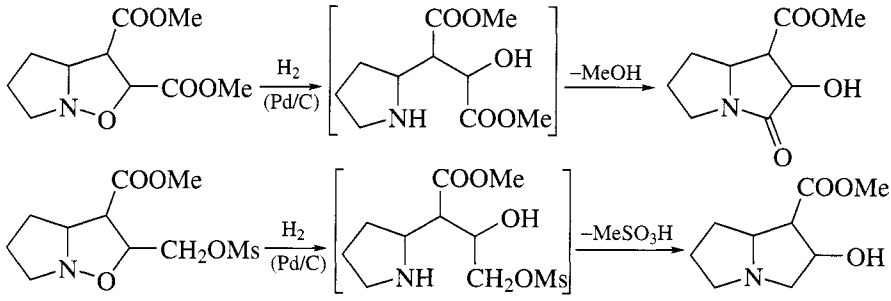
Less frequently utilized as reductants are aluminum amalgam in aqueous THF or ethanol,[58/79,23/81,21/84,48/86,32/90,1/91] titanium trichloride in refluxing ethanol,[35/81] sodium amalgam in isopropyl alcohol,[46/82] the complex hydride $NiCl_2$–$LiAlH_4$,[58/84,28/85] and isopropanol/acetone in the presence of sodium isopropoxide.[34/72]

An experimental comparison between three reductants—Al/Hg, $LiAlH_4$, and Zn/AcOH—on a tricyclic *N*-benzylisoxazolidine showed that zinc dust added to a preheated solution (50°C) of the substrate in 10*M* aqueous AcOH assured higher yields (95%) and faster rates than did the other two reagents. Moreover, sodium amalgam in ethanol was practically unreactive.[42/85] Other competitive data on the reduction of a bridged isoxazolidine are Zn/AcOH, 89%; $LiAlH_4$, 74%; H_2(Pd/C), 82%; and $TiCl_3/H_2O$, 76%.[46/89]

Sometimes unusual rearrangements can occur, especially with $LiAlH_4$, as in the following example, where the initial deoxygenation with elimination of the hydroxy group is followed by base-promoted N–O cleavage, intramolecular reduction of the azadiene, and reclosure of the thiol group on the C=N bond:[10/86]

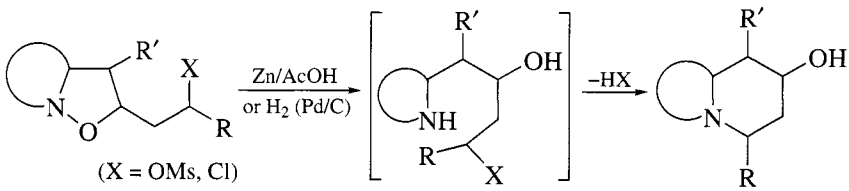


When the appropriate substituents are present on the isoxazolidine ring, the hydrogenolysis product can cyclize spontaneously, giving other heterocyclic compounds (see also § 4.3.2.6). One the most common patterns is when an ester or a mesyloxymethyl group is present at the isoxazolidine 5 position, which yields a hydroxy-γ-lactam[16/63,22/69,35/74,14/75,38/82,35/84,59/84,31/85,36/88,36/91] or a 3-hydroxypyrrolidine,[30/70,20/71,14/75,27/80,67/84] respectively.[14/75]



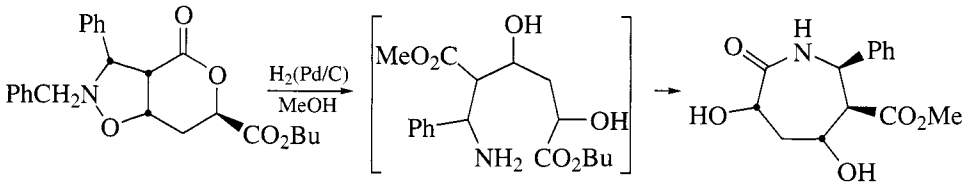
Seldom can the intermediate aminoalcohol be isolated.[27/79,26/83]

A mesyloxy group or a chlorine atom in the 5β position directs the reclosure toward the fused 4-hydroxypiperidine system:[32/82,28/83,33/84,40/85,28/89]

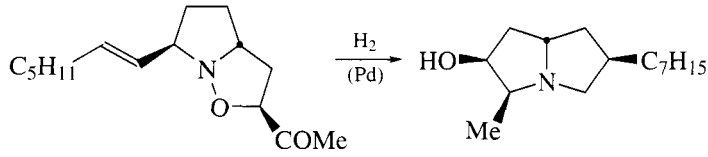


Moreover, a mesyloxy group in the 3γ position (isoxazolidine numbering) promotes the formation of a fused pyrrolidine compound,[42/91,43/91] whereas the presence of a 3α-tosyloxy group in a 3,4-fused isoxazolidine leads to the formation of a fused aziridine derivative.[34/81,56/83]

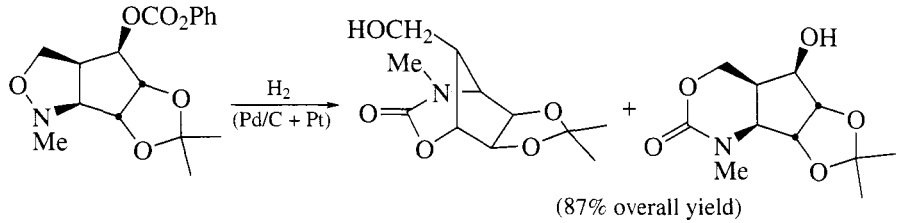
Even a seven-membered 3-hydroxylactam has been reported, where the free amino group, formed by hydrogenolysis, prefers to attack the ester in the 7 position rather that the one in the 3 position:[60/85]



An intramolecular reductive alkylation explains the formation of the 3-hydroxypyrrolizidine derivative in the following example:[33/89]

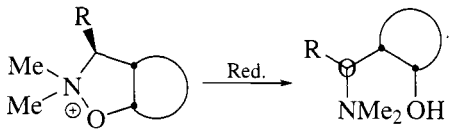


A *trans*-acylation process furnishes a mixture of the two isomeric products of ring opening followed by ring closure.[38/79]



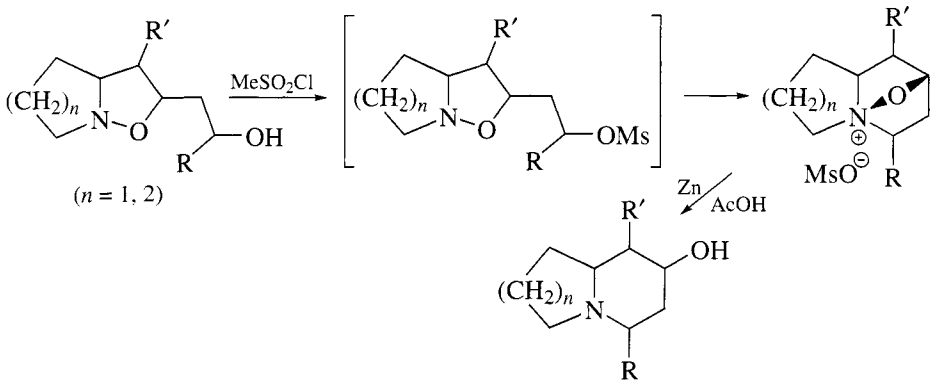
(87% overall yield)

Hydrogenolysis has been frequently accomplished also on the quaternary salts derived from fused isoxazolidines, leading to the expected 3-dialkylamino alcohols, usually with retention of stereochemistry:



In this respect the most commonly used reductants are zinc and acetic acid,[24/68,28/78,25/79,29/85,35/86] catalytic hydrogenation,[19/72,40/82,63/84,27/87] lithium aluminum hydride,[27/73,26/76,43/78,41/79,29/80,70/88,28/91] or lithium iodide.[31/89,81/88] However, some caution should be exerted, since the stereocontrol is not always complete and minor amounts of the epimeric product can be formed, especially with catalytic hydrogenation[40/82] or $LiAlH_4$.[29/81]

An "internal" quaternary salt, arising from the mesylation of a hydroxy group in the isoxazolidine 5β position, is perfectly suited for transforming a 2,3-fused isoxazolidine into an indolizidine or quinolizidine system, and this sequence has been frequently utilized for multistep alkaloid syntheses:[39/76,31/82,51/82,68/84,61/85]

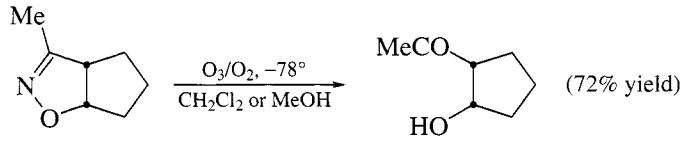


A slight variation implies bromination of a 5-vinyl group[26/80] and subsequent ring opening with $LiAlH_4$.

4.3.2.2. Oxidation

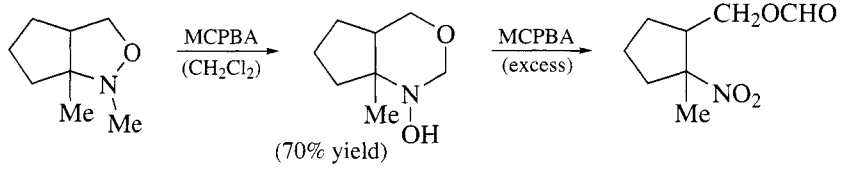
Two methods have been proposed for preparing β-hydroxy ketones from 2-isoxazolines through oxidative cleavage of the N–O bond.

Ozonolysis at low temperature is stereospecific, although the yields are somewhat lower than the appropriate hydrogenolytic cleavage.[65/82,16/83]

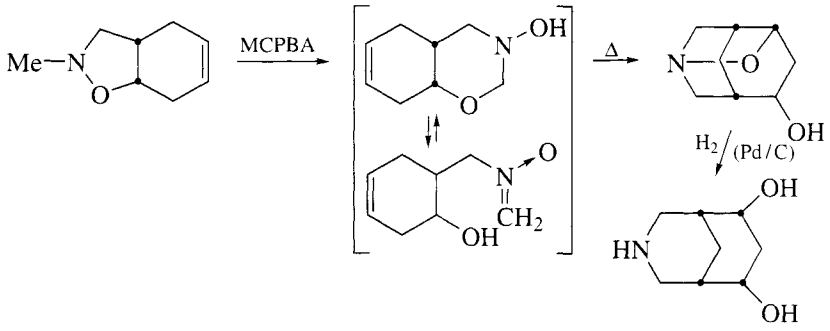


Peracids, such as 3,5-dinitroperoxybenzoic acid, oxidize 2-isoxazolines to give β–hydroxy ketones in moderate yields; longer treatment or use of trifluoroperoxyacetic acid causes further oxidation, and the corresponding diol monoester is furnished by a Bayer–Villiger process.[71/88,16/90]

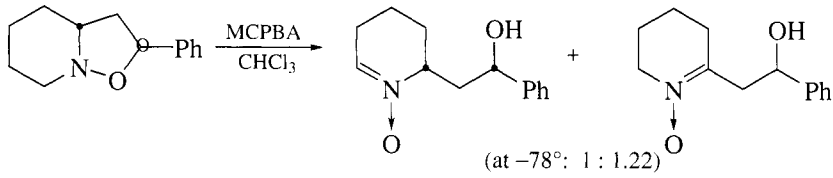
N-Methylisoxazolidines are known (see Part 1, § 3.4.3, p. 737) to be oxidized by *m*-chloroperbenzoic acid to *N*-hydroxy-1,3-tetrahydrooxazines;[24/65,59/79,51/81] an example of a fused isoxazolidine is described below.[59/79]



The intermediacy of the isomeric nitrone has been demonstrated; consequently, the presence of a double bond in a suitable position of the fused ring can diverge the reaction toward the formation of a bridged tricyclic isoxazolidine;[26/82,10/86] its hydrogenolysis furnishes azabicyclic diols, as shown in the following example:[26/82]



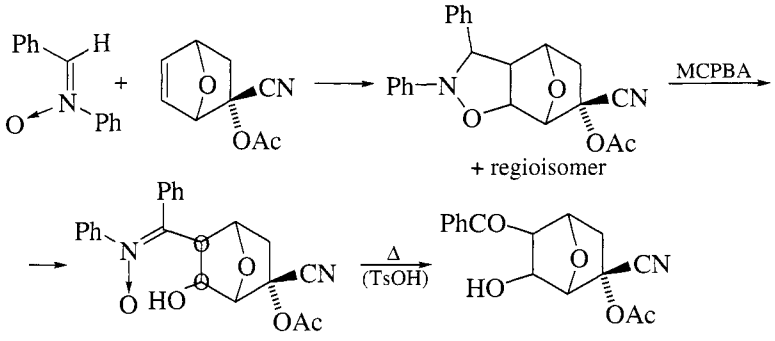
Peracid oxidation of 2,3-fused isoxazolidines, the cycloadducts of cyclic nitrone and olefins (see § 4.2.2.5), furnishes a new cyclic nitrone, which can, in turn, give rise to a new bicyclic isoxazolidine. Whereas previous researchers [15/78,34/86,45/87] claimed the regiospecific formation of the less substituted nitrone, subsequent studies have revealed that a mixture of the two possible isomeric nitrones is formed, whose composition depends on the substituents, the nature of the oxidant, and the reaction temperature.[53/90,33/91]



This reaction has been widely utilized for the synthesis of α,α′-dialkylpiperidines and related compounds (see § 4.3.3).

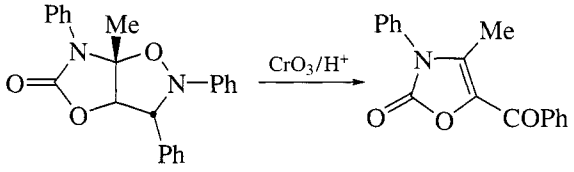
Similar peracid oxidation is known for 2,3-diphenyl-4,5-fused isoxazolidines, obtained by cycloaddition of *C,N*-diphenylnitrone to a 7-oxanorbornene derivative. Peracid fragmentation to nitrone and subsequent acidic hydrolysis represent an overall hydroxybenzoylation of the original double bond.[65/88]

Photoinduced oxidation of some bridged steroidal isoxazolidines by molecular oxygen leads to a complex mixture of products, whose composition varies with the nature of the solvent.[37/77]



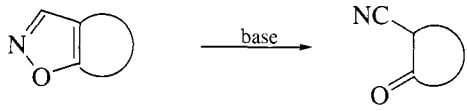
Nitrones have also been isolated by oxidative ring cleavage of furo-condensed isoxazolidines, promoted by dichlorodicyanobenzoquinone, as in the following example:[25/80, 28/81]

In one case the isoxazolidine ring was ascertained to be more susceptible to oxidative ring opening than the condensed oxazolidinone ring:[25/74]

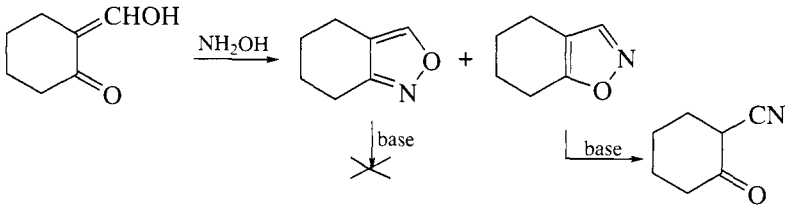


4.3.2.3. Base-Promoted Ring-Opening Reactions

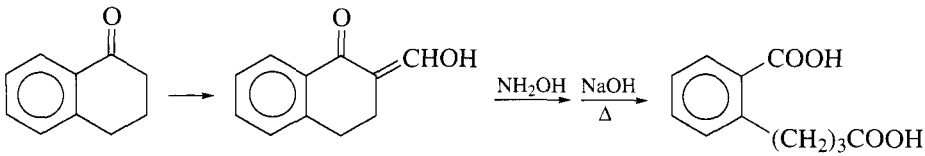
Isoxazoles bearing substituents at the 3 position (with exception of those that are strongly electron-withdrawing) are fairly stable toward alkoxides or aqueous bases. However, as discussed previously (Part 1, § 1.4.6, p. 298ff.), 3-unsubstituted derivatives undergo base-promoted cleavage to yield β-ketonitriles. Similarly, 4,5-fused isoxazoles undergo isomerization to 2-cyanocycloalkanones on treatment with aqueous sodium or potassium hydroxide as well as with alcoholic sodium or potassium alkoxides at room temperature or under light heating.[1/45,1/56,1/59]



The corresponding 3,4-fused isoxazoles are unaffected under the above-mentioned conditions.[1/25,1/45,1/62,1/68]



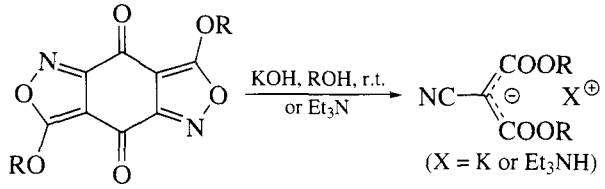
In a one-pot procedure that effects exhaustive hydrolysis 4-[(2′-carboxy) phenyl]butanoic acid has been prepared, in 80% yield, from 1-tetralone.[2/45,1/61]



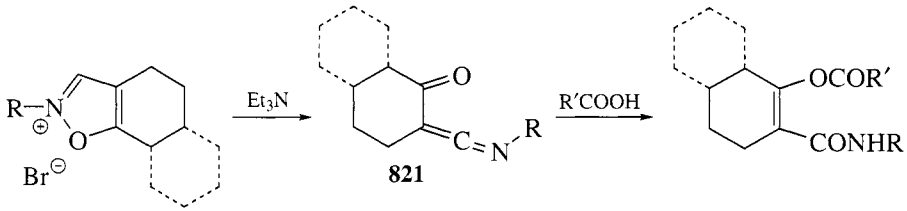
Anhydrous bases such as lithium diisopropylamide[53/80] or phenyllithium[51/89] have occasionally been used for the isomerization, which in one particular instance has been accomplished with W7 Raney nickel.[35/68]

Base-promoted isomerization of 4,5-fused 3-unsubstituted isoxazoles has been widely utilized in the steroid field,[2/60,3/60,6/61,3/62,6/62,5/63,1/84] and represents a key step in the syntheses of equilenin[1/47] and of estrone intermediates.[2/61,2/62]

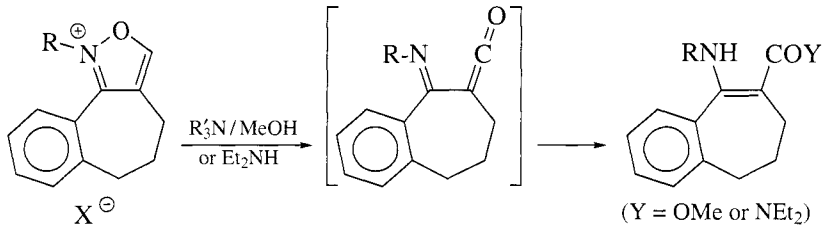
Base-promoted ring cleavage of 3,7-dialkoxy-4*H*,8*H*-benzo[1,2-*c*:4,5-*c*′] diisoxazol-4,8-diones is carried out with either alcoholic potassium hydroxide or bulky amines:[54/80]



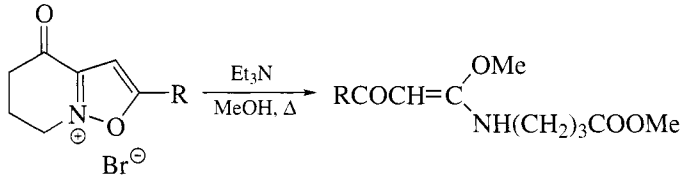
The importance of the Woodward–Olofson peptide synthesis, based on the ring cleavage of 3-unsubstituted isoxazolium salts, has been stressed in Part 1 (§ 1.4.6.1e, pp. 310–314). 4,5-Fused isoxazolium salts showed some advantages over other monocyclic salts, and their behavior toward bases has been studied in detail. The acylketenimines **821** are moderately stable in solution, and are transformed into the expected esters in the presence of the appropriate acids:[2/70]



With 3,4-fused isoxazolium salts, cleavage of the N–O bond is provoked by the attack on the 5-proton, as shown by the following example:[41/84]

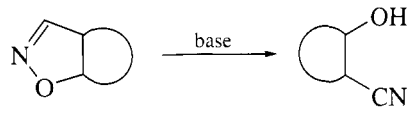


A different mechanism has been proposed for the ring opening of a 2,3-fused isoxazole, having a carbonyl group in the 3α position; cleavage of both rings has been reported:[40/76]



3-Unsubstituted 5-hydroxy-2-isoxazoline derivatives usually behave toward methanolic potassium hydroxide (or sodium methoxide) in the same way as the corresponding isoxazoles do, yielding α-cyanocycloalkanones.[8/61,9/65,3/67,31/70,26/77] Only once, the treatment with sodium methoxide has been reported to cause a simultaneous cleavage of the five-membered fused ring, providing a δ-cyanocarboxylic acid.[8/61]

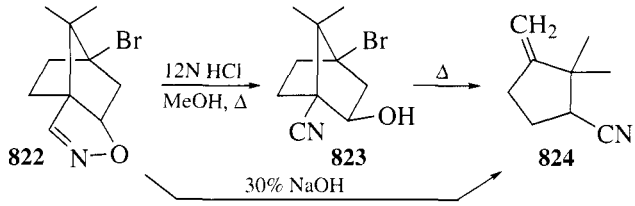
Other 3-unsubstituted 4,5-fused 2-isoxazolines are cleaved by various bases to give β-hydroxynitriles:[13/67,12/73,59/86]



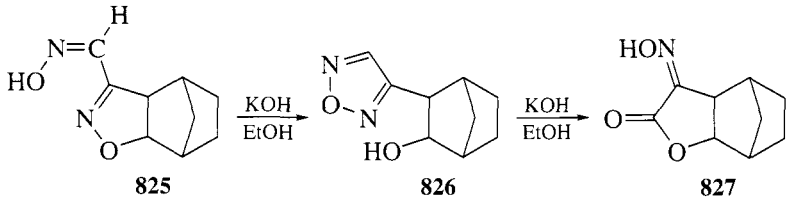
Occasionally ring cleavage can be followed by spontaneous dehydration and dehydrogenation.[66/84]

A slightly different process furnishes 2-cyanocyclohexanol by treatment of 3-bromo-4,5-tetramethylene-2-isoxazoline with methyllithium or methylmagnesium bromide.[65/89]

The strained isoxazoline **822** is opened to β-hydroxynitrile **823** under strongly acidic conditions, whereas vigorous alkaline treatment leads to the unsaturated nitrile **824**, the thermolytic final product from **823**:[2/57]

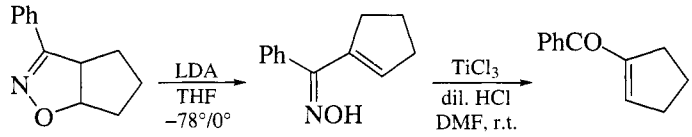


The cycloadduct of fulminic acid dimer and norbornene, *syn*-oxime **825**, is transformed by treatment with ethanolic potassium hydroxide into 1,2,5-oxadiazole derivative **826** and then into oximinolactone **827**.[11/85]

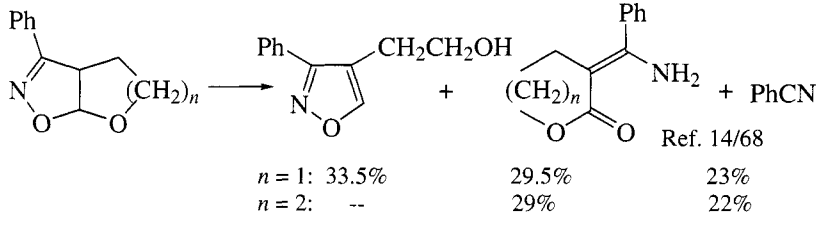


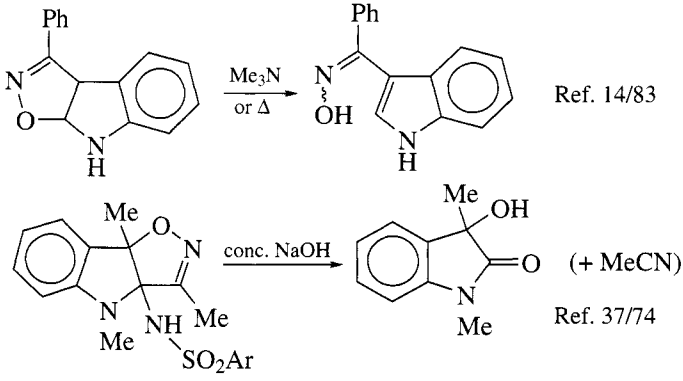
Similar transformations, although with different intermediate structures, have been described for simplier fused isoxazolines.[10/74]

Ring opening of 2-isoxazolines to α,β-unsaturated oximes with LDA in THF can be followed by hydrolysis to the corresponding ketones, a transformation that is best accomplished with titanous chloride in dilute hydrochloric acid.[35/76,8/80,19/80]

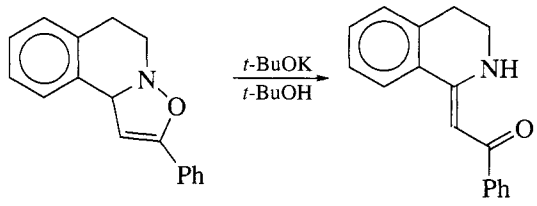


Fusion of the 2-isoxazoline with a heterocyclic ring favors the cleavage of the isoxazoline ring, as shown in the following examples:

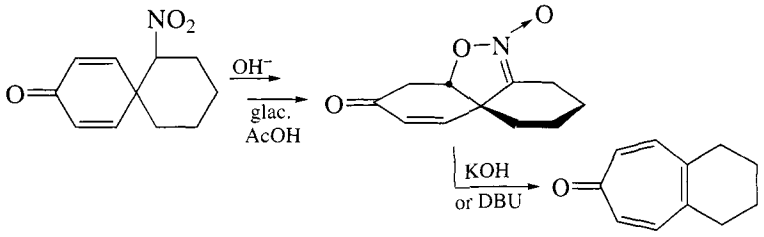




Fused 4-isoxazolines tautomerize to β-enaminoketones in the presence of base.[28/75, 52/81]

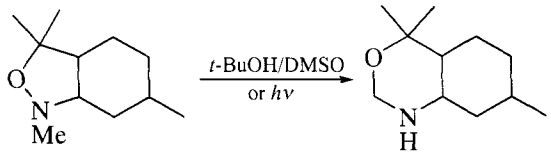


Base-promoted ring cleavage of a tricyclic 2-isoxazoline *N*-oxide with simultaneous ring enlargement has been reported:[60/86]



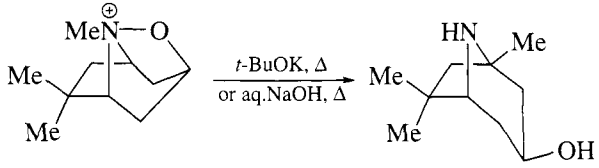
Discussion of the ring cleavage of 5-acylisoxazolines will be delayed until § 4.3.2.7.

Isoxazolidines are relatively stable toward aqueous bases (see Part 1, § 3.4.7, pp. 747–750); nevertheless, some examples of ring cleavage are known: 3,4-fused *N*-alkyl-substituted isoxazolidines isomerize by the action of potassium *tert*-butoxide or photolytically to 1,3-tetrahydrooxazines, as in the following example:[24/65,35/67]

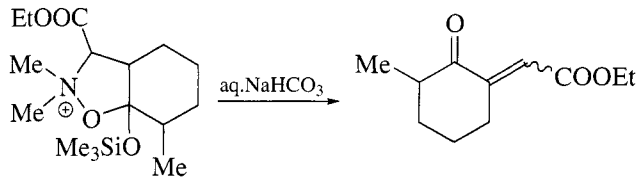


The reaction seems to be even easier if carried out on the quaternary salts.[40/79,39/85]

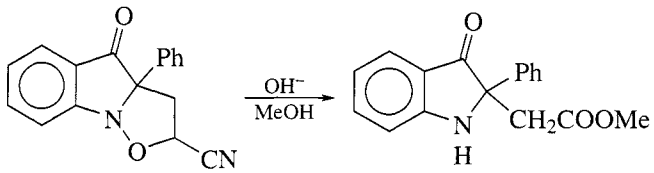
When recyclization is retarded by steric effects, the aminoalcohol is obtained owing to hydrolysis of the formiminium moiety, as in the following example:[34/72]



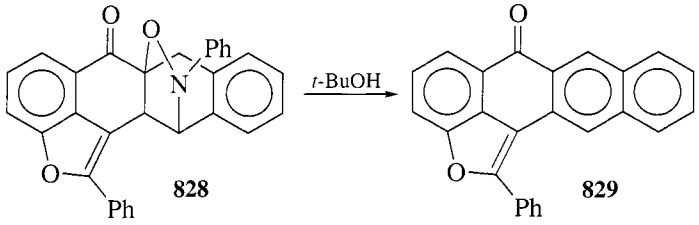
Another example of demethylation has been reported for a tetracyclic *N*-methylisoxazolidine.[59/82] The presence of a 3-carbethoxy group diverts the ring cleavage toward the α,β-unsaturated ketone:[62/85]



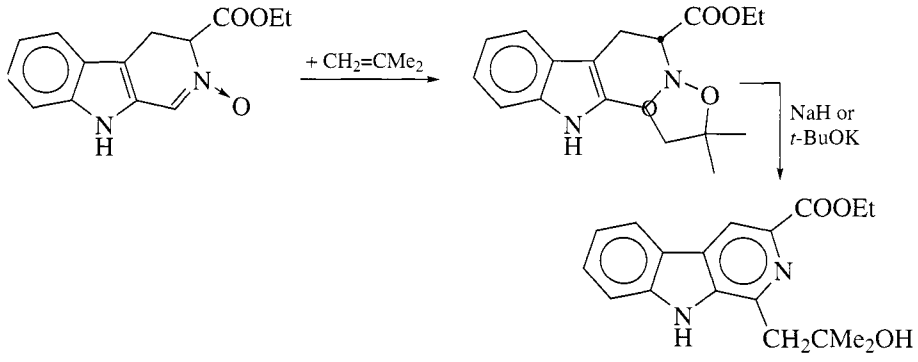
A cyano group in the isoxazolidine 5 position seems to favor ring cleavage and formation of an ester group, as shown by the following example:[9/62,22/71]



Base-promoted dehydration/aromatization has been reported for the *exo*-cycloadduct obtained from 2,1-benzisoxazole and *N*-phenylmaleimide.[2/58] Global aromatization of bridged isoxazolidine **828** to **829** results on treatment of the former with potassium *tert*-butoxide.[24/71]

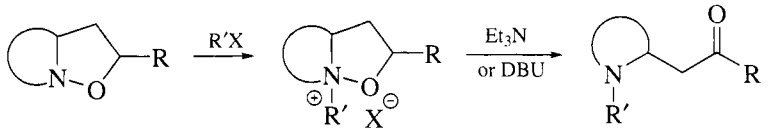


In the carboline series, treatment of an isoxazolidine tetrahydro-β-carboline-3-carboxylate with strong base induces ring opening and aromatization to the corresponding 1-hydroxyalkylated β-carboline:[39/88]



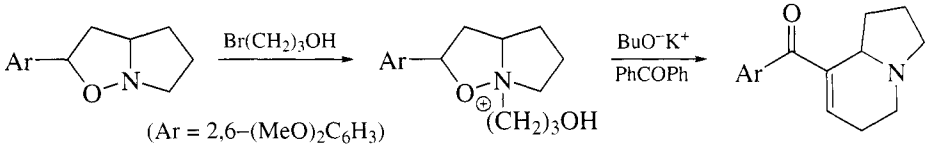
(75% yield)

A general synthesis of β-aminoketones or β-aminoesters utilizes the base-promoted ring cleavage of 2,3-fused isoxazolidinium salts in accord with the following scheme:[72/88]



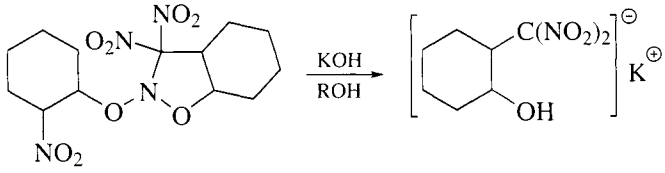
(R = Ph, COOEt, OEt; R′ = Me, CH_2Ph, $CH_2CH{=}CH_2$)

Alternatively, quaternization with 3-bromopropan-1-ol is a prelude to an interesting route toward indolizidine alkaloids in which base-promoted ring cleavage in the presence of benzophenone leads to reclosure and oxidation:[26/79]



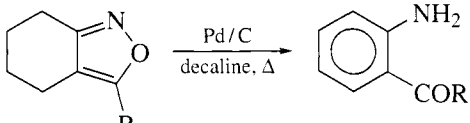
(Ar = 2,6-$(MeO)_2C_6H_3$)

As illustrated below, 3,3-dinitroisoxazolidines are cleaved by base at the C3–N bond, rather than the N–O bond, to give the potassium salt of the β,β-dinitrocarbinol.[19/67]



4.3.2.4. Thermolysis

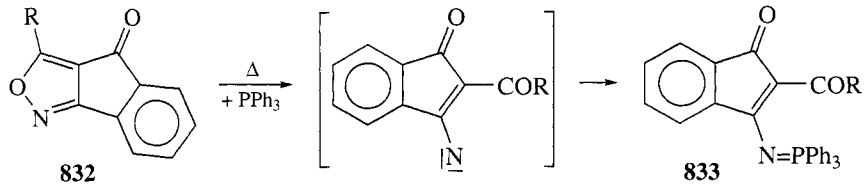
The thermal behaviour of fused isoxazoles does not differ substantially from that of monocyclic derivatives (see Part 1, § 1.4.5, pp. 285–293). Nevertheless, some special features should be mentioned. The tetrahydro-2,1-benzisoxazole



830 (R = Ph, Me, C_6H_{11}) **831** (65–75% yield)

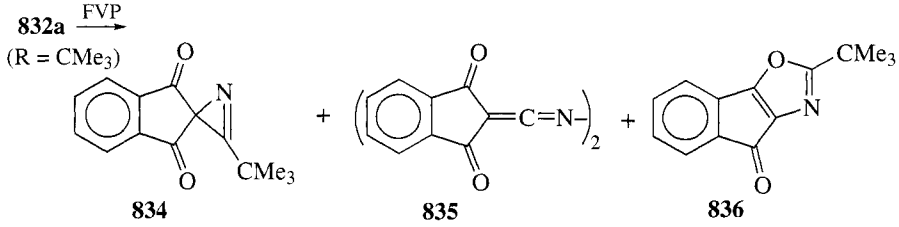
830, heated in boiling decaline in the presence of palladium on charcoal, is aromatized by hydrogenolytic ring cleavage to give **831**.[6/70]

The presumable primary ketonitrene can be trapped by appropriate reagents, and indeno[1,2-*c*]isoxazole **832**, when heated in boiling toluene in the presence of triphenylphosphine, yields **833**:[57/83]



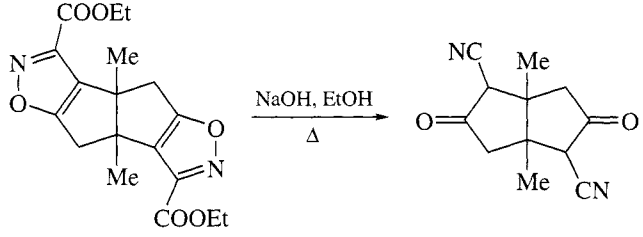
832 **833**

Flash-vacuum pyrolysis at 400–500°C of 3-*tert*-butylindeno[1,2-*c*]isoxazol-4-one (**832a**) has been reported to give a mixture of products, whose composition depends on the temperature employed. At 400°C, 35% of azirene **834** and 65% of azine **835** result while at 500°C 70% of **835** and 30% of the fused oxazole **836** are obtained.[55/87]

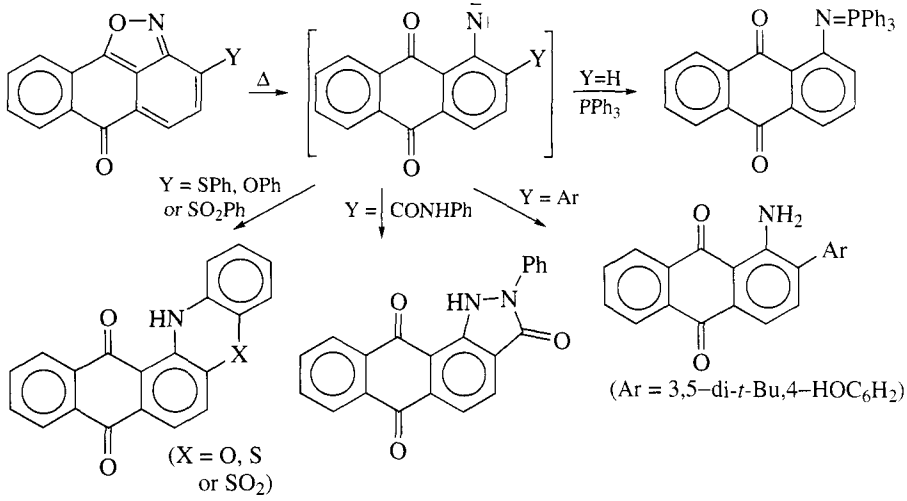


834 **835** **836**

The ready decarboxylation of isoxazole-3-carboxylic acids to *β*-cyano ketones is exemplified by the following reaction:[10/85]



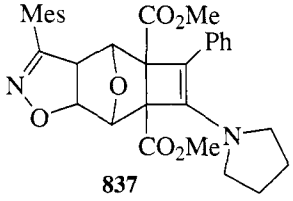
The thermolysis of 6*H*-anthra[1,9-*cd*]isoxazol-6-ones has been studied in detail. The fate of the primarily formed ketonitrene depends on the nature of the substituent at the 3 position. Interception of this intermediate with suitable reagents or reclosure to a heterocyclic ring are the reactions most commonly encountered,[15/79,40/80,53/81,47/82,44/84,65/84,69/84,49/85,57/85,33/87] as illustrated below:



The decomposition to the ketonitrene can also be accomplished photochemically.[63/85] The nitrenes generated from methoxy[2,1]benzisoxazole quinones were intercepted by dimethylsulfoxide or dialkylsulfides.[64/85]

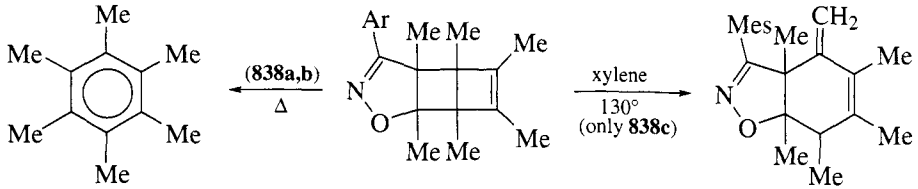
Thermal cycloreversion of fused 2-isoxazolines, leading to isoxazole derivatives, has already been illustrated in § 4.2.2.1 and § 4.3.1.6.

Occasionally cycloreversion can furnish the starting nitrile oxide, as in the case of the cycloadduct **837**, which when heated at 160°C *in vacuo*, gives mesitonitrile oxide in 90% yield.[10/76]



837

Decomposition of the tricyclic isoxazolines **838a,b** at 200°C in decalin furnishes hexamethylbenzene as the only identifiable product; by contrast, heating



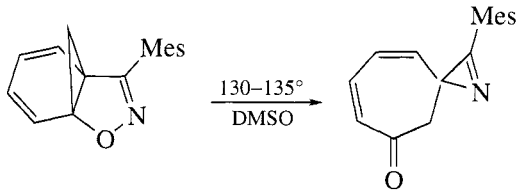
838 **a:** Ar = Ph
b: Ar = 4–$NO_2C_6H_4$
c: Ar = 2,4,6–$Me_3C_6H_2$ (Mes)

839

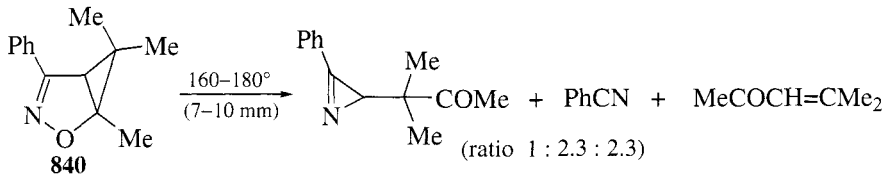
of **838c** at 130°C in xylene provokes valence isomerism, leading to the bicyclic isoxazoline **839**, along with very small amounts of a monocyclic nine-membered isomer.[32/73]

Other thermally induced aromatizations leading to other heterocyclic systems will be illustrated in § 4.3.2.7.

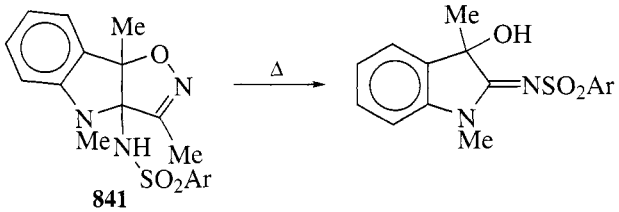
An example of valence tautomerism, in the case of the cycloadduct obtained from mesitonitrile oxide and benzocyclopropene, involves cleavage of both isoxazoline and cyclopropane rings, leading ultimately to ring expansion to a spirocycloheptadienone–azirine compound.[12/79]



The thermolysis of the cyclopropane-fused isoxazoline **840** can proceed by two routes; consequently a mixture of the isomeric azirine and the two decomposition products is formed.[29/75]

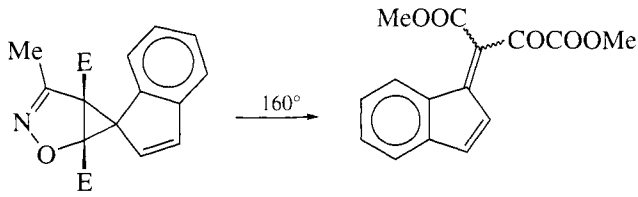


Extrusion of acetonitrile is observed during the sublimation of the indole-condensed isoxazoline **841**:[37/74]



A similar elimination has been observed in the pyrolysis of the spiro derivative **842**.[50/84]

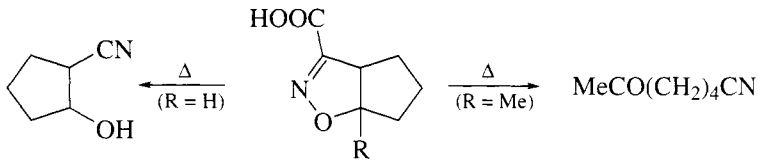
Pyrolytic decarboxylation of fused 3-carboxy-2-isoxazolines furnishes the expected β-hydroxynitriles.[15/65,16/65,33/67,14/69,40/69,5/83] This method of cyanohydroxylation of the double bond is more common than that involving the base-promoted ring opening of 3-unsubstituted isoxazoles, since the cycloaddition of



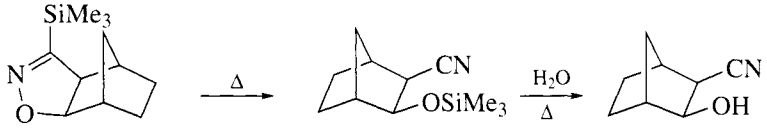
842 (E = COOMe)

the olefin to ethoxycarbonylfulmide is more convenient than the one to fulminic acid.

The presence of a methyl group in the isoxazoline 5 position favors further ring cleavage to give an open-chain ketonitrile.[5/83]

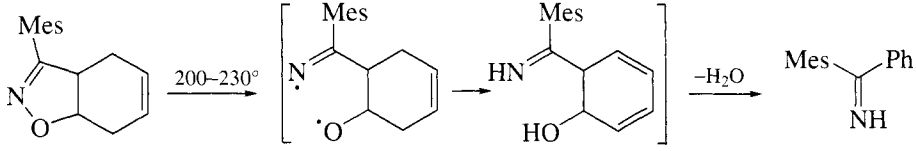


A slight variation exists in the cycloaddition of trimethylsilylcarbonitrile oxide to norbornene. The expected *exo*-cycloadduct **843** is unstable, and on heating in boiling benzene is isomerized to **844**, which may then be hydrolyzed to hydroxynitrile **845**.[8/83]



843 **844** **845**

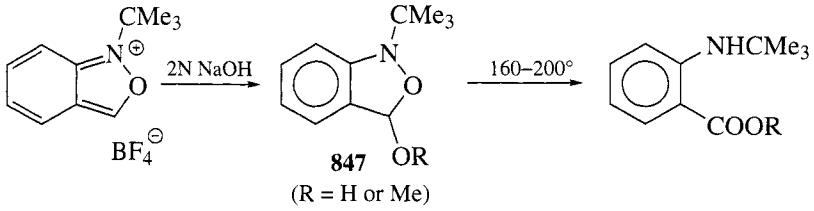
Cycloadduct **846** can be pyrolyzed to give mesityl phenyl ketimine, presumably through a sequence involving homolytic cleavage of the N–O bond, migration of two hydrogen atoms, and dehydration:[9/85]



846

Hydroxybenzisoxazoline **847** and its methyl ether, which are prepared by base-promoted hydration of the corresponding 2,1-benzisoxazolium salts,

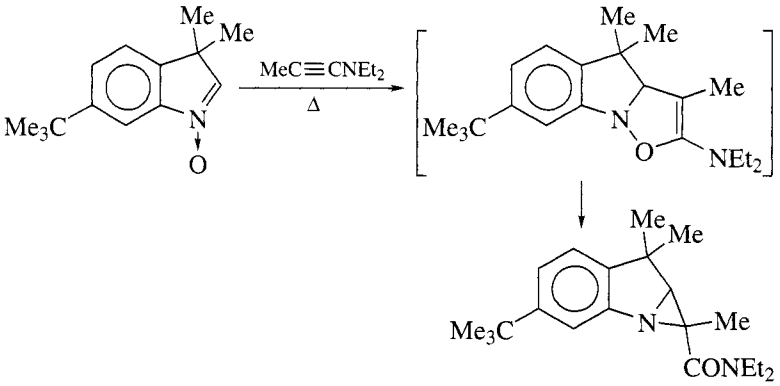
are pyrolyzed to *o*-t-butylaminobenzoic acid (R = H) or the methyl ester (R = Me).[38/77]



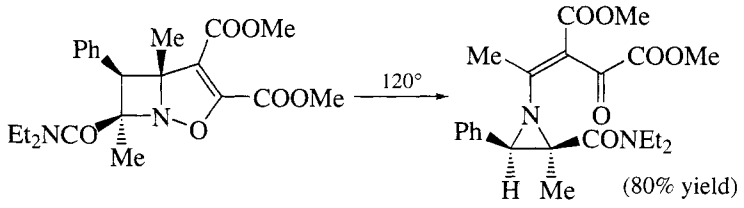
847
(R = H or Me)

The thermolysis of monocyclic 4-isoxazolines has been considered in Part 1 (§ 2.5.3.1). Depending on structural features and experimental conditions, 2-acylaziridines are the primary rearrangement products, although 4-oxazolines, azomethine ylides or cycloadduct thereof, pyrrole derivatives, or enaminoketones can be obtained; fused 4-isoxazolines behave in a similar fashion.

Thus, cycloaddition of indolenine oxide to alkynes affords the isomeric fused aziridine, through the intermediacy of a nonisolable 4-isoxazoline, as shown in the following example:[16/75,20/78]



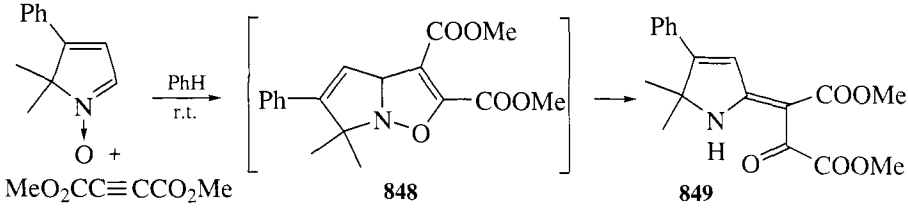
Thermolysis of 2,3-cyclobutane fused 4-isoxazolines leads to formation of an aziridine via cleavage of the four-membered ring:[34/82]



(80% yield)

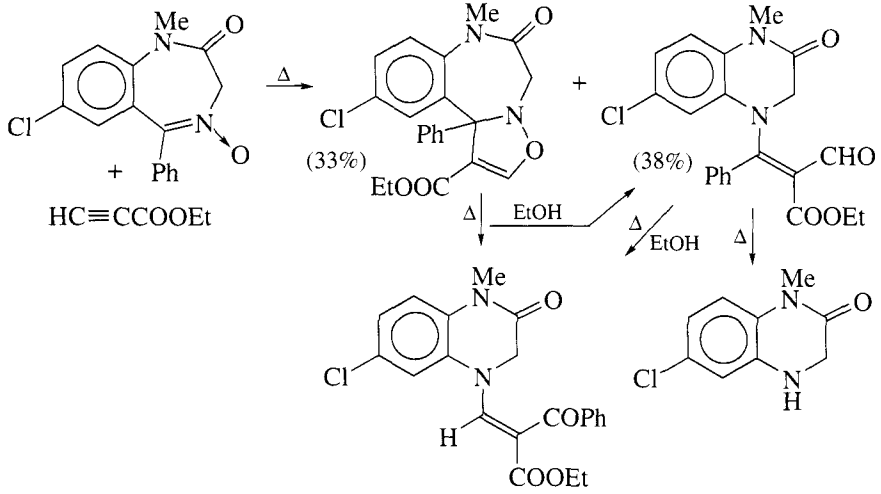
Isomerization to zwitterionic species, such as stabilized azomethine ylids, has been reported for the stable cycloadduct derived from isoquinoline *N*-oxide (or its dihydroderivative) and methyl propiolate,[15/63,25/69,27/69] and for the nonisolated cycloadducts from benzimidazole *N*-oxides[22/65,27/68] or phenanthridine *N*-oxide [22/66,36/67] and acetylene carboxylates. The azomethine ylide can also be isolated as dimer or trapped with dipolarophiles.[34/84,57/90]

In other cases an enaminoketone results from the isomerization of unstable fused 4-isoxazolines that are rarely isolated.[21/66,28/80,31/80,33/81, 35/82,33/83] Thus, pyrrole *N*-oxides react with dimethyl acetylenedicarboxylates to give, through the unstable 4-isoxazolines **848**, the enamino derivatives **849**:[31/80]



Similar results have been obtained starting from 1-methylbenzimidazole *N*-oxide.[16/64]

A simultaneous ring contraction has been observed with the diazepam *N*-oxide–ethyl propiolate cycloadduct:[39/82]

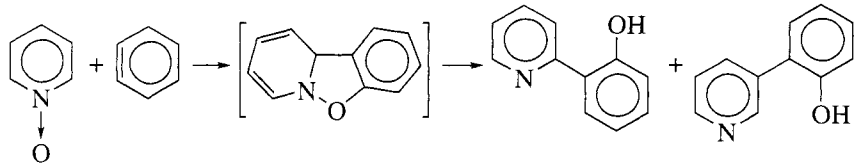


Slightly different results are reported for the cycloaddition with dimethyl acetylenedicarboxylate.[22/77] Ring contraction with concomitant loss of nitrogen has been reported for the cycloaddition of fervenulin 4-oxide to the same dipolarophile.[36/79]

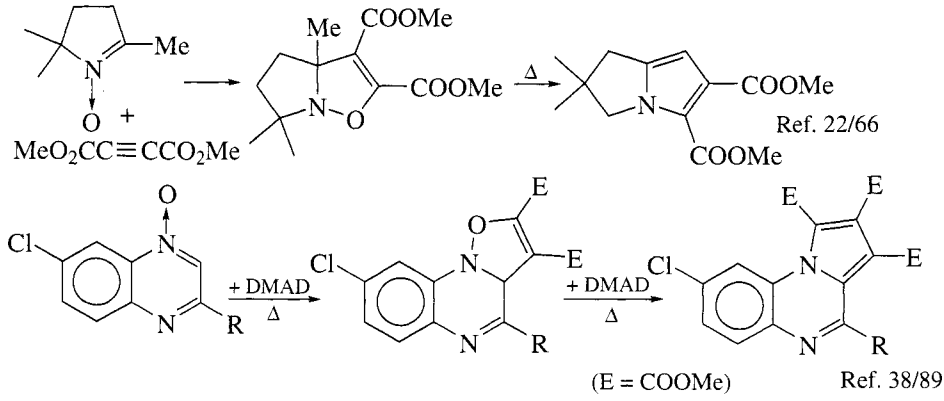
Ring-expanded products result from the following cycloadditions involving a presumable 4-isoxazoline intermediate: (1) conversion of 2-arylisatogens into 3-aryl-4-quinolones with acetylenes in boiling xylene;[15/64] (2) conversion of 2,4,5-triphenyl-3*H*-pyrrol-3-one *N*-oxide into either 4-pyridone or pyridine derivatives;[24/76] (3) the reaction of pyridine *N*-oxide with 3,3,7,7-tetramethyl-5-thiacycloheptyne to give an azacycloheptatriene–thiacycloheptanone spiro derivative, which, in turn, rearranges by heating to 2,2,6,6-tetramethyl-7-(*o*-pyridyl)-4-thiacycloheptan-one.[34/79]

Mixtures of a zwitterion, an enamino derivative, and a degradation product are obtained from the cycloaddition of 3-bromo-4-methoxyquinoline *N*-oxide to dimethyl acetylenedicarboxylate; the composition depends on solvent and temperature.[32/83]

When benzyne is the dipolarophile, the presumed cycloadduct readily isomerizes to the corresponding hydroxyphenyl heterocycle, as in the following reaction:[16/64,23/70,29/74]



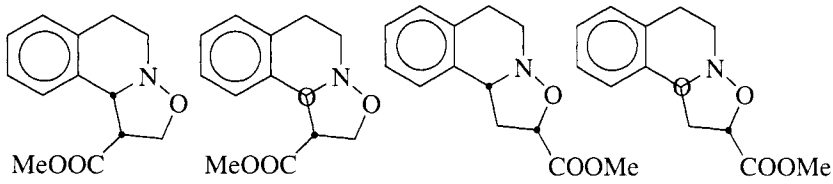
Sometimes the intermediate zwitterion cyclizes to give a stable 1,2-fused pyrrole derivative,[21/66,22/66,22/77] or it can react with an excess of dipolarophile to yield a completely substituted pyrrole derivative.[36/82,38/89] Two examples are here reported in order to illustrate these processes:



The thermal behavior of isoxazolidines has been studied in detail, since the ring is fairly unstable; a summary on monocyclic derivatives is presented in Part

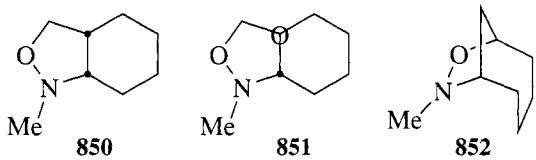
1, (§ 3.4.4, pp. 738–743). Fused derivatives follow an analogous pattern, and the points discussed in the following paragraphs must be noted.

The ease of 1,3-dipolar cycloreversion has been ascribed to the remarkable stability of nitrones in comparison to other 1,3-dipoles.[14/63,31/66] Nitrones formed by this process can either react with the same dipolarophile, yielding the thermodynamically more stable cycloadduct (see also § 4.2.2.5), or can be trapped by another more active dipolarophile. Thus, the cycloaddition of dihydroisoquinoline *N*-oxide to methyl acrylate at r.t. yields a mixture of four regio- and stereo-isomeric cycloadducts, whereas at 90°C an equilibrium mixture of three products is reached:[66/82]



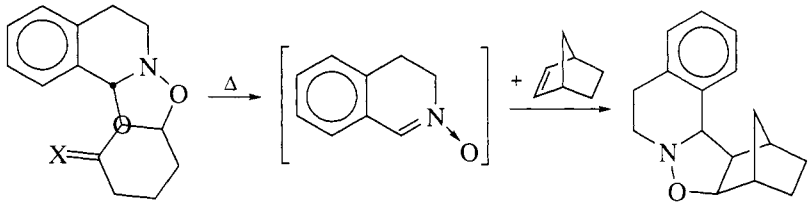
at 20°:	51%	12%	13%	24%
at 90°:	---	46%	27%	27%

Even more evident is the influence of temperature on the intramolecular nitrone–olefin cycloaddition, which at 110°C affords the three cycloadducts **850–852**. Heating at 200°C quantitatively transforms both **851** and **852** into the thermodynamically more stable *cis* isomer **850**:[23/71]



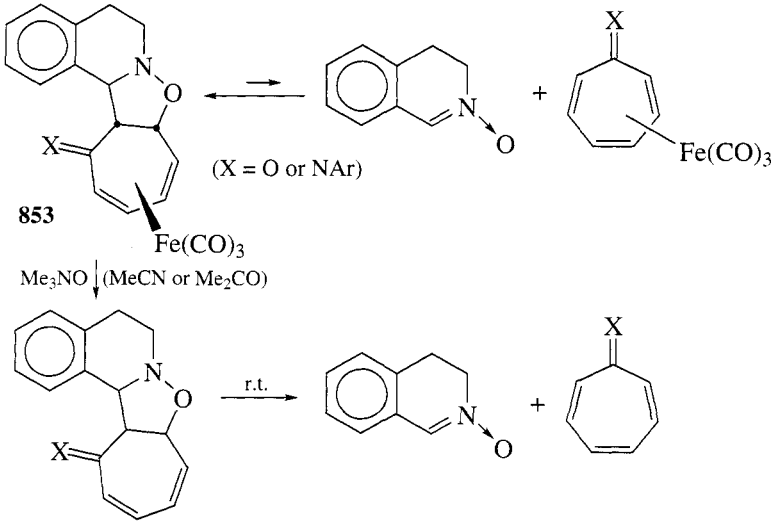
850 **851** **852**

The cycloreversion is favored by the conjugative stabilization of the incipient double bond, for instance, by the presence of a carbonyl group in the isoxazolidine 4 position. The following example illustrates this rate-enhancing effect:[32/79]

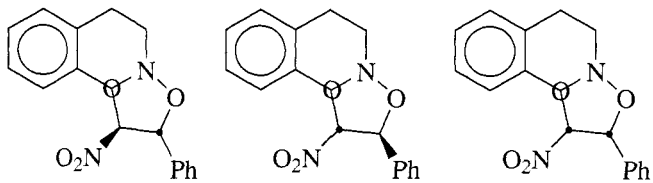


X = O: 80°C, benzene, 9 hr – 92% yield of cycloreversion
X = $(CH_2O)_2$: 110°C, toluene, 100 hr – 10% yield of cycloreversion

Tropone is known to be unreactive toward dihydroisoquinoline *N*-oxide, whereas its tricarbonyliron derivative **853**, where the conjugation of the diene moiety is partially removed by complexation, is stable at room temperature over a one-month period, and enters a very slow cycloreversion in the presence of norbornene as a reactive trapping dipolarophile for the cyclic nitrone. Moreover, the decomplexed cycloadduct undergoes a fast cycloreversion at r.t.:[32/79]



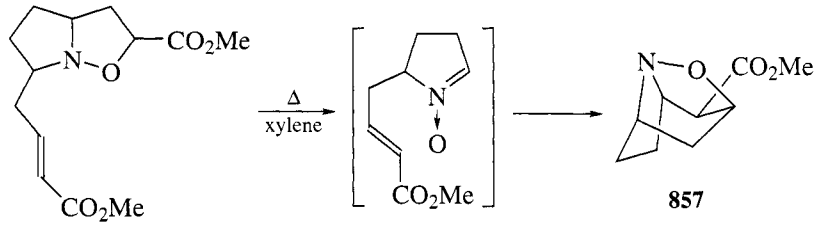
A further example of facile cycloreversion at room temperature is provided by the cycloadducts from the preceding cyclic nitrone and (*E*)- or (*Z*)-β-nitrostyrene.[21/87] In the first case both *exo*- and *endo*-cycloadducts **854** and **855**, respectively are regiospecifically obtained, whereas with the latter compound only the *exo*-stereoisomer is formed, with a noticeably higher rate. The cycloreversion, evidenced by heating in the presence of an active dipolarophile, such as cyclopentadiene or *N*-methylmaleimide, was shown to proceed through the following rate sequence: **854** > **855** > **856**; thus, isoxazolidines derived from *trans*-olefins cyclorevert faster than do isoxazolidines derived from *cis*-olefins.



854 **855** **856**

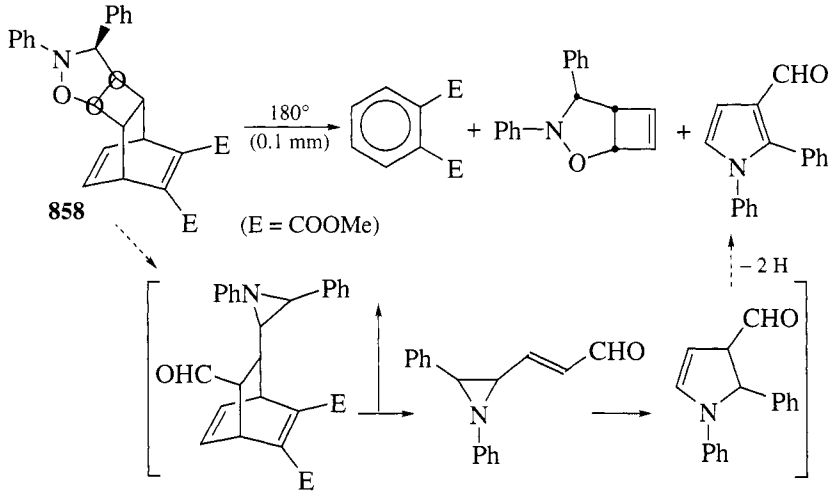
The cycloreversion rate was slightly enhanced by increasing solvent polarity. Similar results are obtained for the cycloadducts from nitrostyrene and 5,5-dimethylpyrroline-1-oxide.

An elegant use of the cycloreversion process, matched with an intramolecular cycloaddition, occurs in the synthesis of the bridged tricyclic isoxazolidine **857**, a key intermediate in the route to *dl*-cocaine:[15/78,25/79]



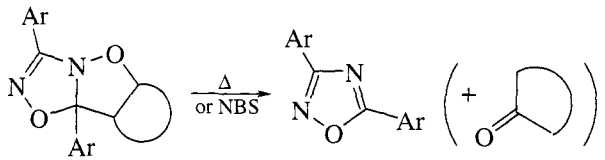
857

Thermolysis of cycloadducts (**858**) derived from dimethyl tricyclo[4.2.2.0^{2,5}] deca-3,7,9-triene-7,8-dicarboxylate affords mixtures containing the corresponding 2,3-oxazabicyclo[3.2.0]-hept-6-ene derivatives along with dimethyl phthalate and a pyrrole.[27/72]



Thermolysis, or treatment with *N*-bromosuccinimide, opens the isoxazolidine ring in compounds having general structure **859**, leading to the 3,5-diaryl-1,2,4-oxadiazole along with the corresponding cycloalkanone.[11/72]

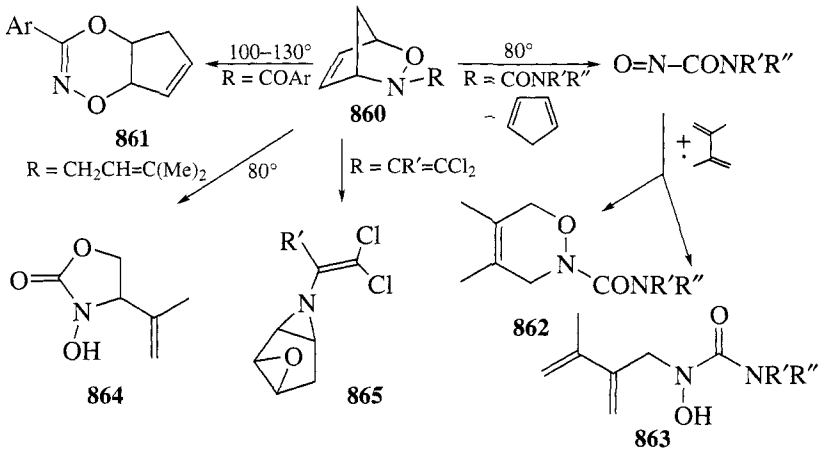
Analogous results are reported for 2,5-diphenyl-7-hydroxy-3,8-dioxa-1,3-diazabicyclo[3.3.0]oct-2-ene; the 7-methoxycarbonylamino derivative requires reflux in 50% sulfuric acid/acetic acid.[50/80]



859

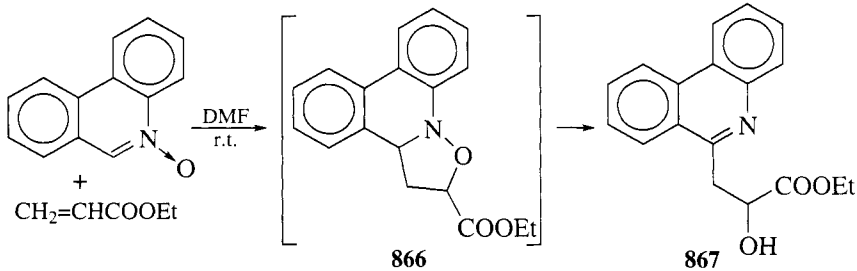
One case of thermal reductive cleavage of an adamantane-condensed isoxazolidine, leading to the aminoalcohol, is also known; both catalytic hydrogenation and reduction with Zn/AcOH are equally or better suited.[43/79,40/82]

The thermolytic behavior of the bridged 2,3-oxazabicyclo[2.2.1]hept-5-enes **860** is manifold, and the reaction outcome depends mainly on the substituent on the nitrogen atom. Cycloreversion is the predominant process for *N*-amidosubstituted derivatives, which at 80°C decompose in the presence of 2,3-dimethylbutadiene to give **862** (heterodiene synthesis) and **863** (ene reaction).[8/85] The *N*-aroyl derivatives, when heated in refluxing xylene, give a mixture of products in which **861**, derived from a [3.3]sigmatropic rearrangement, is more or less predominant.[5/79,54/81]

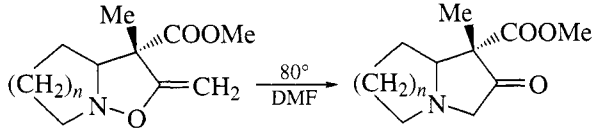


An intramolecular ene reaction, leading to **864**, has been reported for the nitrosoformate unsaturated esters, which are themselves formed by cycloreversion from the corresponding bridged isoxazolidines.[7/85] The cycloadducts, prepared from cyclopentadiene and nitrosochloroethylenes (or other similar compounds), although detected at low temperature by NMR spectroscopy, are not stable at room temperature and readily isomerize to epoxy–epimine derivatives **865**.[4/77,4/79,9/81,59/88]

Sometimes N–O bond cleavage prevails over cycloreversion processes, and in one instance, the cycloadduct **866** from phenanthridine *N*-oxide and ethyl acrylate proves to be unstable, and spontaneously opens to restore aromaticity, yielding the hydroxy ester **867**:[15/63,27/69]

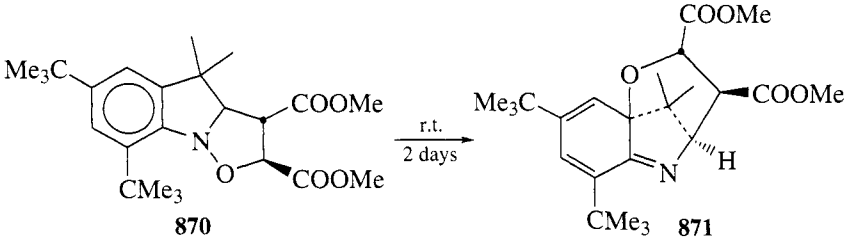


A facile thermal isomerization transforms 5-methyleneisoxazolidine **868** in fused 3-pyrrolidinone **869**:[53/87]



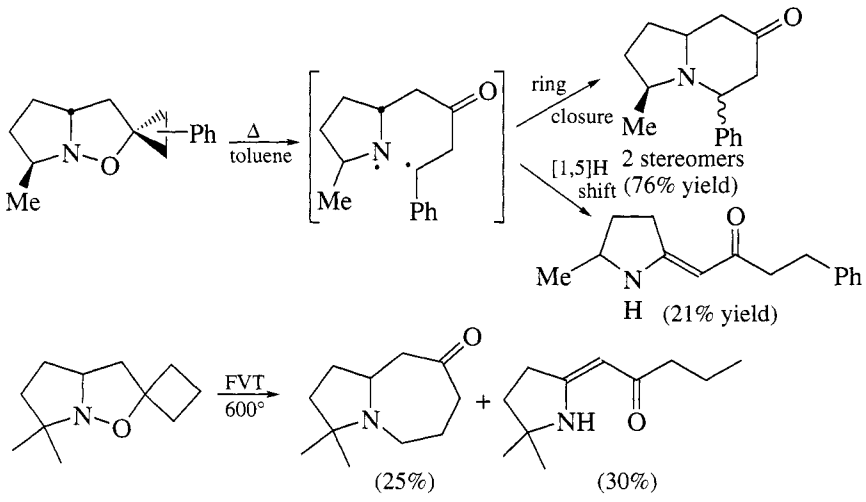
Another fused 4,5-bismethyleneisoxazolidine is relatively unstable and isomerizes to a bridged benzoperhydroazepinone.[18/83]

The remarkable isomerization of the bulky tricyclic isoxazolidine **870** at room temperature to give the bridged tricyclic oxazepine derivative **871** has been reported:[32/85]



The nonisolable cycloadduct from pyridine *N*-oxide and 7-oxabenzonorbornadiene rearranges through a [1,5]sigmatropic shift followed by aromatization, yielding a furan-condensed pyridine derivative.[21/90]

The presence of a spirocyclopropane or -cyclobutane moiety in the isoxazolidine 5 position favors the formation of indolizinones or fused azepinones, respectively, along with variable amounts of the corresponding enaminoketones.[37/86,34/88,33/90] Two examples are reported here:

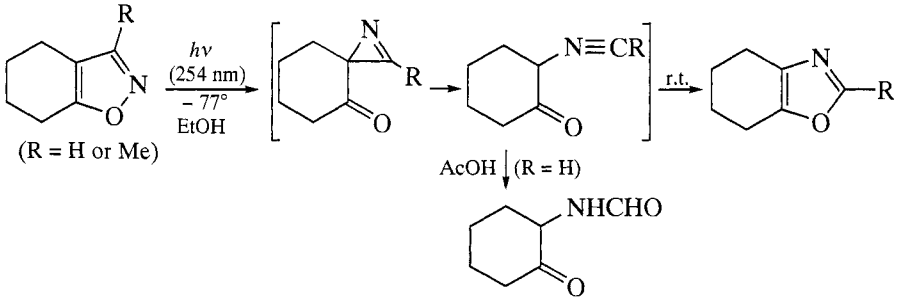


The transformations of isoxazolidines into α,β-unsaturated ketones (see Part 1, § 3.4.10.4, p. 775) should also be mentioned, as they have been applied to a 4,5-fused isoxazolidine.[70/84]

4.3.2.5. Photolysis

While the photochemical behavior of monocyclic isoxazoles is well known (see Part 1, § 1.4.5, pp. 293–298), only a limited number of papers illustrate the photolysis of fused isoxazole compounds.

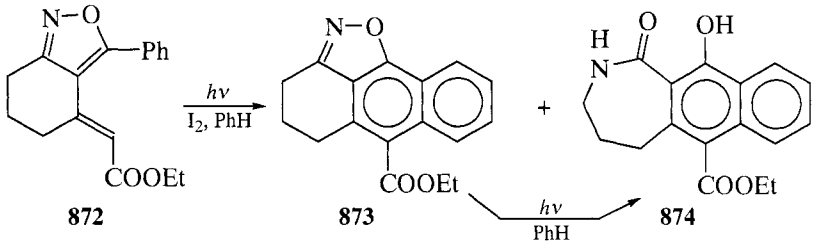
Irradiation of the tetrahydro-1,2-benzisoxazole and its 3-methylderivative causes isomerization to the corresponding oxazole derivatives; the intermediacy



of the ketoisonitrile was suggested at low temperature by spectroscopy, and by entrapment with hydrolytic agents.[33/73,1/76]

The ketospiroaziridine intermediate could be isolated by photolysis of some isoxazolophanes, although the final products are still the corresponding oxazolophanes.[3/79,6/80]

Also noteworthy is the photochemical electrocyclization of **872** in the presence of an oxidizing agent that yields the fused isoxazole **873** and, on further photolysis, the seven-membered lactam **874**:[5/81]



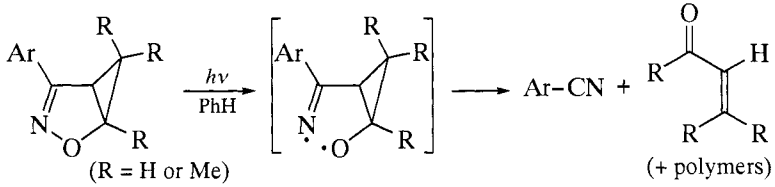
872 **873** **874**

The photorearrangement of anthraisoxazolone derivatives has also been studied.[61/86]

The photoisomerization of 2-isoxazolines to β-enaminoaldehydes and/or 3-oxazolines has been discussed (see Part 1, § 2.2.3.2a).

The photochemical behavior of 4,5-fused 2-isoxazolines has been studied in detail, and has been demonstrated to be strongly dependent on the size and structure of the fused ring. The results obtained with 3-phenyl-2-isoxazolines fused with carbocyclic rings have been summarized in a review.[35/77]

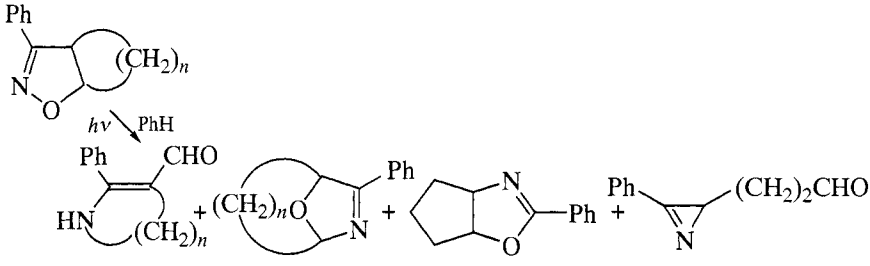
The cyclopropane ring induces a strong decomposition to benzonitrile and (in lower yields) propenal (or its substituted homologs),[39/77,62/79] according to the following general scheme:



(R = H or Me) (+ polymers)

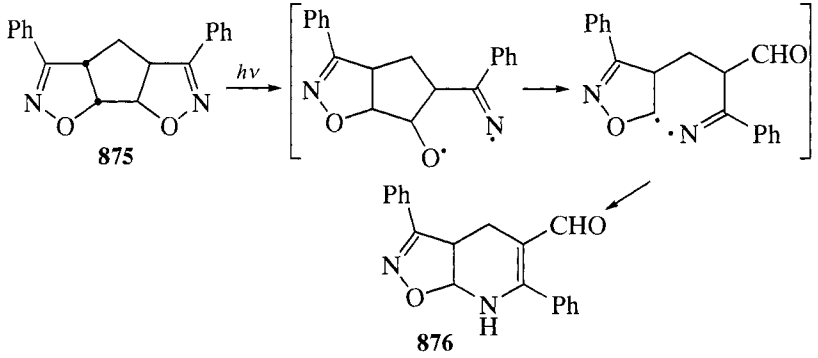
When Ar = β-naphthyl and R = Me, reclosure of the oxygen atom onto the *ortho* position of the naphthalene ring results.[62/79]

With higher (four to seven) membered cycloalkane rings the yield of benzonitrile is always under 9%, and other products (enaminoaldehydes, fused and bridged oxazole, aziridines) predominate, as tabulated below:[48/74,39/77,43/81]

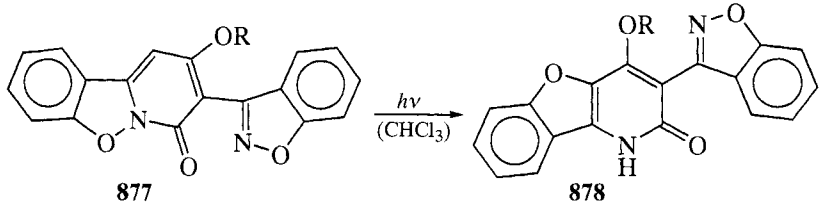


n = 2 :	26%	--	--	37%
3 :	13%	--	32%	--
4 :	9%	27%	--	--
5 :	41%	22%	--	--

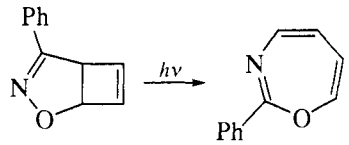
The tricyclic bisisoxazoline **875** yields **876** as sole product, through scission of both an N−O bond and a C−C bond:[41/77,42/77]



The complex benzisoxazoline derivative **877** is reported to photoisomerize to **878**:[60/82]



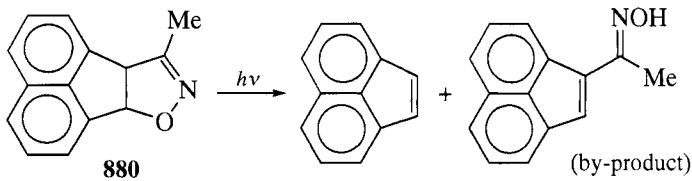
The presence of a double bond, as, for instance in **879**, diverts the reaction toward the 2-phenyl-1,3-oxazepine:[34/73,71/84]



879 (80% yield)

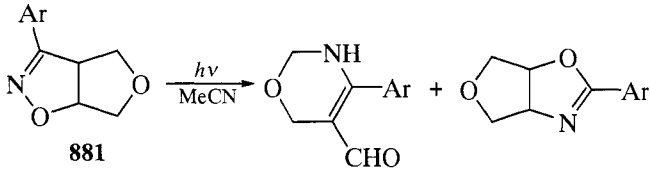
Complexation of **879** with ironpentacarbonyl to give an irontetracarbonyl complex also diverts the photodecomposition toward a mixture of 2-phenylpyridine and 2-formyl-5-phenylpyrrole.[62/86]

The tendency to aromatize provokes photoinduced cycloreversion and N–O bond cleavage in the condensed isoxazolidine **880**:[31/75]



880 (by-product)

Fusion with an oxygen-containing ring, as in furoisoxazolines **881** or other polycyclic derivatives, tends to favor photochemical formation of the enaminoaldehyde product over the oxazole.[58/83,72/84, 17/85,18/85,5/87]

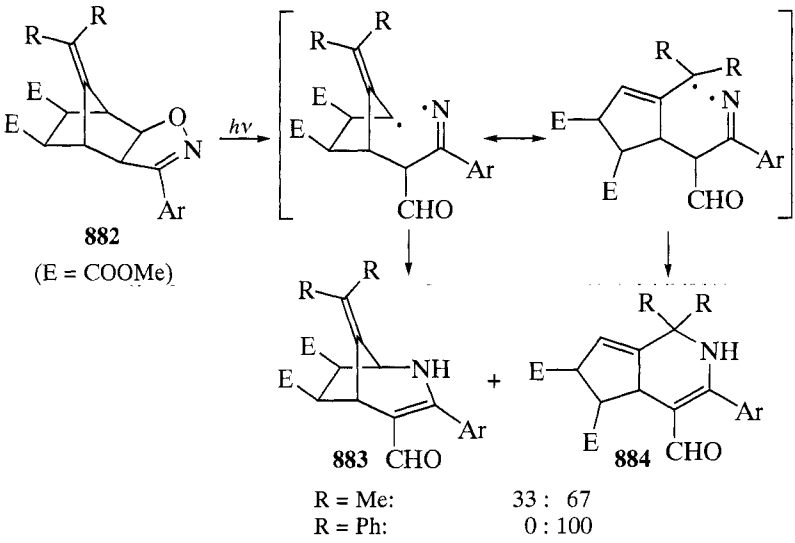


881

The nature of the substituent in the 3 position markedly influences the fate of the reaction. A 3-naphthyl group confers a high degree of photostability to fused isoxazolines,[16/86] whereas electron-attracting groups, such as cyano or ethoxycarbonyl groups, encourage exclusive formation of the enaminoaldehyde,[5/87,7/87,14/88] accompanied in the latter case by minor amounts of bicyclic lactones. The 3-benzoyl derivatives give rise to a complex product mixture,[13/88] whereas 3-pyridyl derivatives give only tarry products,[3/90] presumably because of the high degree of instability of the enaminoaldehydes. The same fate is suffered by the nitrogen analogs such as the 6-substituted 2-oxa-3,6-diazabicyclo[2.2.0]oct-3-enes.[8/87] The 3-(4′-biphenylyl) derivatives photodecompose to give biphenyl-4-carbonitrile only.[9/86]

Photoirradiation of 2-isoxazolines fused across the 4,5 positions with a 1,3-dioxepane ring invariably leads to the corresponding enaminoaldehydes, specifically, 6-substituted-7-formyl-2,4,5,8-tetrahydro-1,3-dioxa-5-azocines.[18/84, 65/85,16/86,5/87,7/87,45/90] In some cases the product instability is so high that only tarry products are reported.[19/88,3/90] Different values of quantum yields are known for *exo* versus *endo* starting materials.[28/86,29/86]

The presence of a double bond on the bridge, as in dimethyl 5-aryl-10-dimethyl- or dimethyl 5-aryl-10-diphenylmethylene-3-oxa-4-azatricyclo [5.2.1.$0^{2,6}$] dec-4-ene-8,9-dicarboxylates (**882**), stabilizes the intermediate allyl radicals and permits reclosure to occur by two possible routes, leading to enaminoaldehydes **883** and **884**, respectively.[63/86,4/90]



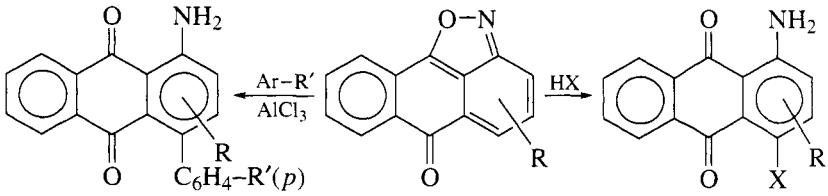
882
(E = COOMe)

The photolability of the isoxazolidine N–O is well known and, from 3,4-fused compounds, leads mainly to the isomeric fused 1,3-aziridines.[35/67,35/81]

4.3.2.6. Acid-Promoted Ring-Opening Reactions

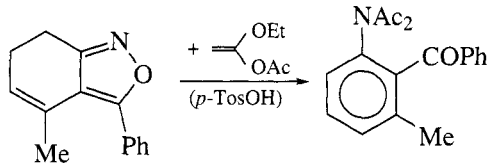
The isoxazole ring is fairly stable under acidic conditions; however, there are some exceptions in the field of fused compounds.

Anthra[1,9-*c,d*]isoxazol-6-ones are attacked by hydrochloric or hydrobromic acid to give good yields of 1-amino-4-haloanthraquinones.[55/80] Arylation with alkyl- or alkoxybenzenes in the presence of aluminum trichloride furnishes good yields of 4-aryl (or 2-aryl if position 4 is occupied) 1-aminoanthraquinones:[51/87, 62/88]



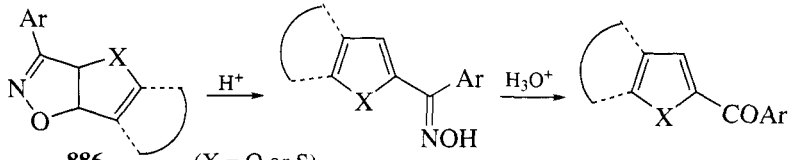
Ring cleavage is also brought about by treatment with hot concentrated sulfuric acid.[48/82]

An aromatization of the Sammler–Wolff type is reported for the dihydro-2,1-benzisoxazole **885**:[4/81]



885

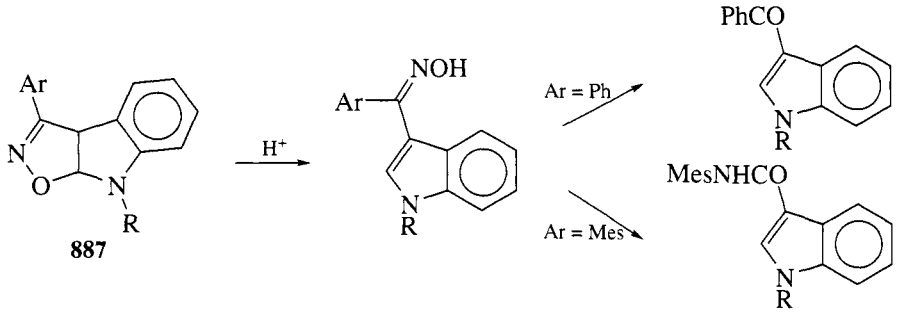
4,5-Fused 2-isoxazolines are easily cleaved by acids when a heteroatom is attached to the 5 or 4 position (isoxazoline numbering), and heteroaromatization is possible. Isomerization of cycloadducts **886** to 2-aroylfuran oximes serves to illustrate this behavior.[17/66,18/76,11/77,10/78,55/84]



886 (X = O or S)

Occasionally the isomeric amide has been obtained from the oxime through a Beckmann rearrangement.[10/78]

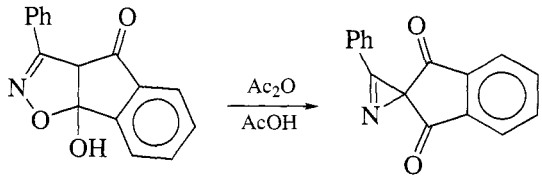
The cycloaddition of nitrile oxides to indoles is known to yield the condensed



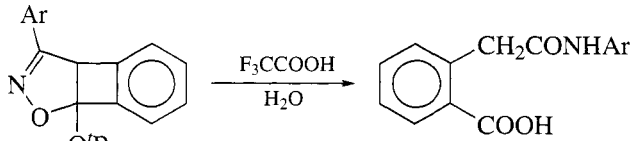
887

isoxazolines **887** with high regioselectivity; in this case ring cleavage under acidic conditions leads to 3-aroylindole oximes.[15/82,15/84]

The cyclic form of the benzoylindandione (*Z*)-oxime is reported to rearrange in the presence of acylating reagents to the spiroindandione–azirine:[41/76]



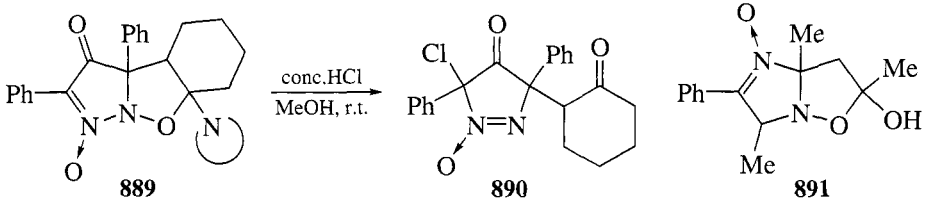
Ring cleavage of both the isoxazoline and the cyclobutene rings has been reported for the unstable compound **888**:[7/74]



888 (Ar = 4–$MeOC_6H_4$)

A strained 3-unsubstituted 4,5-fused isoxazoline is conceivably opened by heating with alcoholic hydrochloric acid, yielding the corresponding β-hydroxynitrile.[12/69,5/74]

Concentrated hydrochloric acid opens the tricyclic isoxazolidine **889** to yield the chloro-substituted compound **890**:[28/79]



889 **890** **891**

A somewhat similar ring opening is known to occur with compound **891**.[40/90]

In the field of isoxazolizidines, a double-ring cleavage with 20% sulfuric acid converts the 8-nitro derivative to 1,5-dihydroxy-3-pentanone.[23/65]

4.3.2.7. Transformations into Other Heterocyclic Systems

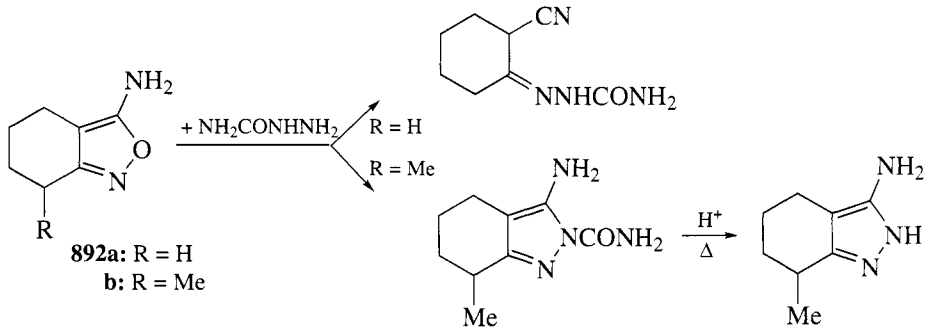
Several reactions that convert fused isoxazoles to other heterocyclic systems have been illustrated in the preceding paragraphs, and some other ones will be

mentioned in § 4.3.3. Other examples will be reported here. The field has been covered in two reviews.[32/75,55/81]

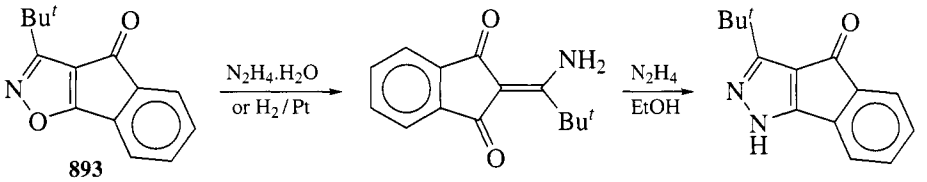
The transformation of the isoxazole into a pyrazole nucleus is well known for the monocyclic series; some cases are also reported for condensed systems.

Thus, 1-amino-3,6,6-trimethyl-4,5,6,7-indazol-4-one has been claimed to result from treatment of the corresponding isoxazole ketone with hydrazine hydrate,[36/70,35/72] although a different interpretation has been proposed.[61/79]

The 3,4-fused 5-aminoisoxazole **892a** is reported to react with semicarbazide to give 2-cyanocyclohexanone semicarbazone, whereas **892b** cyclizes further to a pyrazole derivative:[2/25]

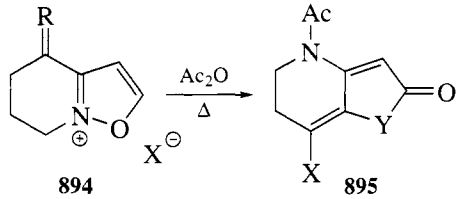


The indenoisoxazole derivative **893** reacts with hydrazine hydrate to give reductive ring opening to the enaminoketone, which, on treatment with alcoholic hydrazine, affords the indenopyrazole derivative:[2/82]



Other examples of condensed pyrazoles prepared from isoxazole derivatives seem to have limited applicability.[37/70,41/83]

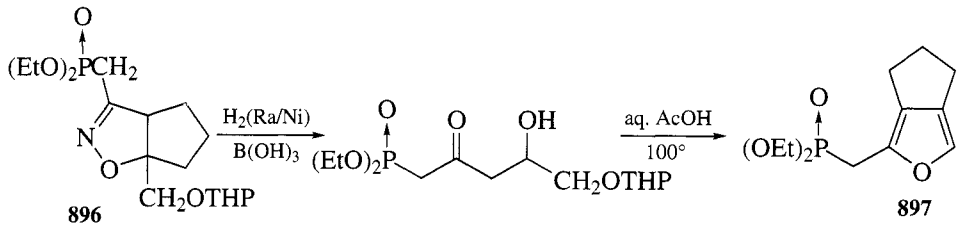
More interesting seems to be the conversion of isoxazolo[2,3-*a*]pyridinium salts of general structure **894** into pyrrolo- or furo[3,2-*b*]pyridones **895**:[36/72,45/74,41/78]



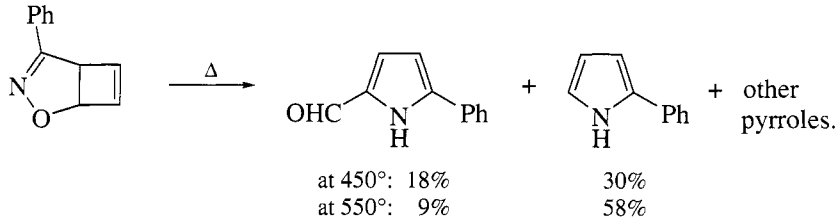
894a: R = O
b: R = NOH
c: R = NNHPh

895a: X = H; Y = O
b: X = Cl or Br; Y = NH
c: X = H; Y = NNAcPh

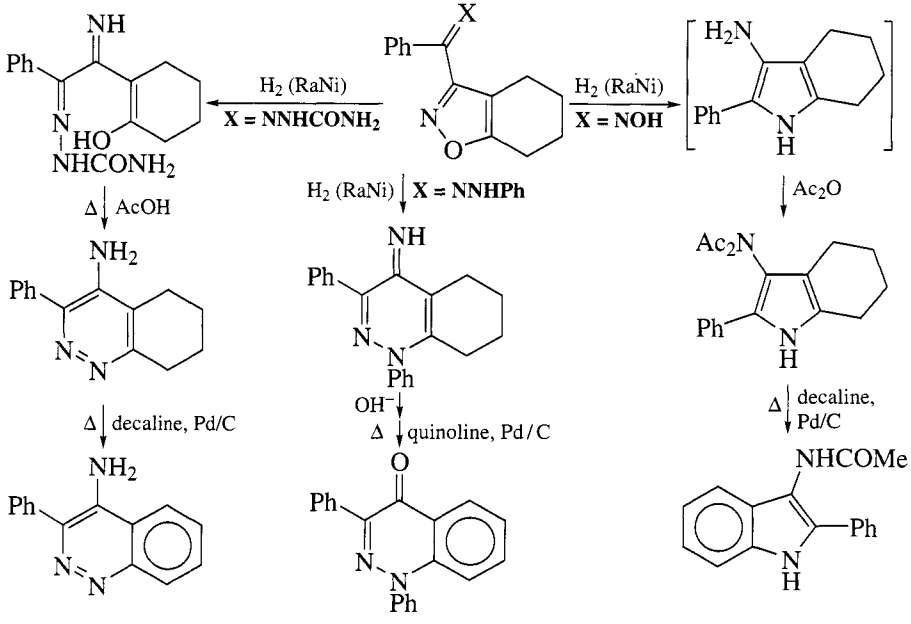
The formation of the 3,4-fused furan derivative **897** from **896** falls within a general synthetic method for the preparation of 2-(1-phosphorylalkyl)- and 2-(1-alkenyl)-furans, including a catalytic hydrogenation followed by acidic treatment:[64/88]



A thermal rearrangement to pyrroles has also been observed in the pyrolysis of 4-phenyl-2,3-oxazabicyclo[3.2.0]hepta-3,6-dienes.[49/74, 35/77]

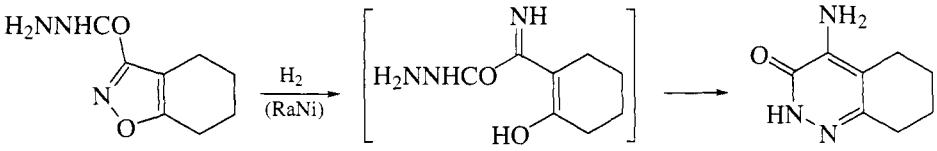


A reasonable mechanism for this transformation involves the seven-membered 1,2-oxazepine and the fused oxaziridine.

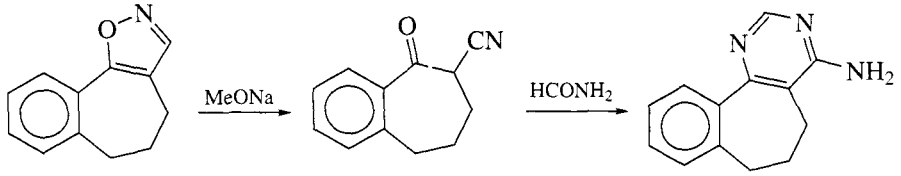


In a method of general applicability, indole and cinnoline derivatives have been synthesized from 4,5-fused isoxazole derivatives containing an acyl group at the 3 position.[13/71,29/71]

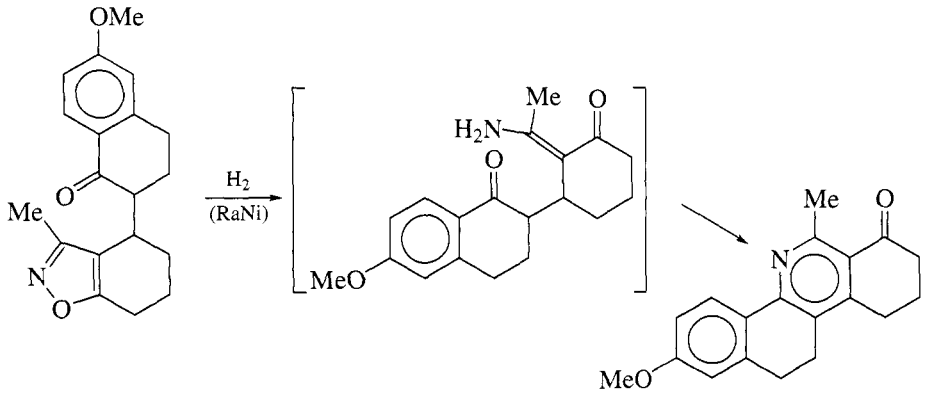
An analogous transformation makes use of the 3-hydrazido derivative:[28/71]



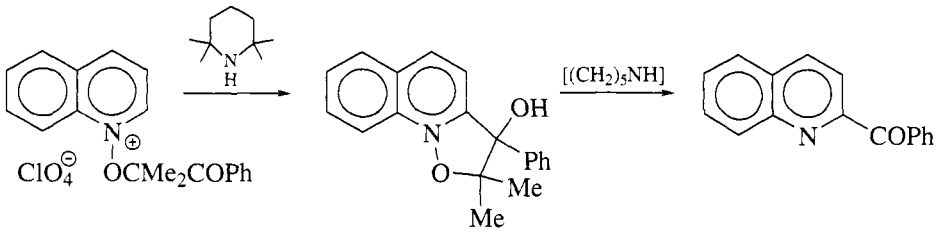
A 1,3-diazine-containing polycyclic system can be prepared utilizing the base-promoted ring opening of 3-unsubstituted isoxazoles.[6/86]



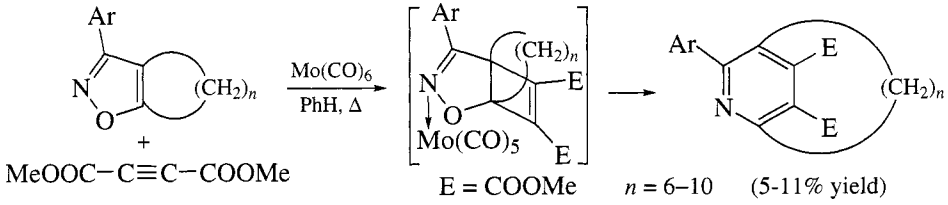
The presence of a carbonyl group in the isoxazole 4γ-position facilitates formation of a pyridine nucleus, as shown in the following example:[64/90]



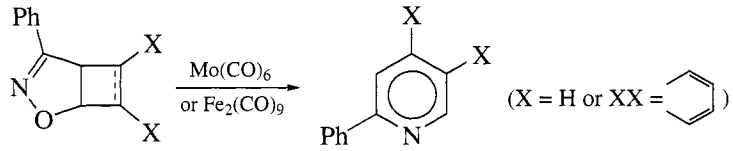
A synthesis of 2-benzoylquinoline or 1-benzoylisoquinoline, involving a condensed isoxazoline, starts from the *N*-alkoxyquinolinium or *N*-alkoxyisoquinolinium salt.[69/86,29/87,36/87]



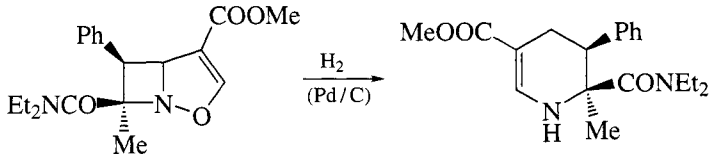
The condensation of monocyclic isoxazoles with acetylenic esters, induced by hexacarbonyl–molybdenum, is known to furnish moderate yields of pyridines (see Part 1, § 1.4.10.6, p. 365). An extension to isoxazoles 4,5-fused with 8–12-membered cycloalkane rings gives even lower yields of the corresponding [*n*](2.5)pyridinophane system:[12/84,56/85]



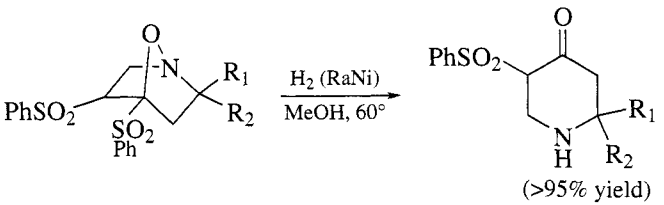
Better yields of pyridines are achieved in the metal-carbonyl-promoted rearrangement of 2-isoxazolines fused with a four-membered ring, as in the following scheme:[59/83,51/85,66/85]



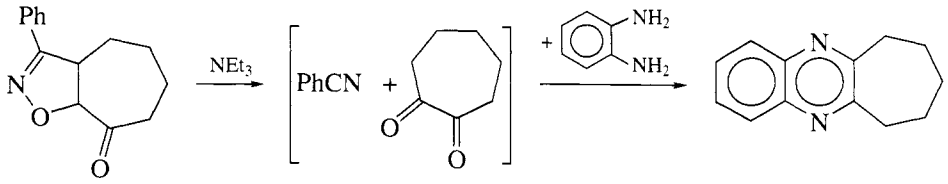
Functionalized tetrahydropyridines are produced by hydrogenolysis of 4-isoxazolines fused at the 2,3 positions with a four-membered ring, as in the following example:[34/82]



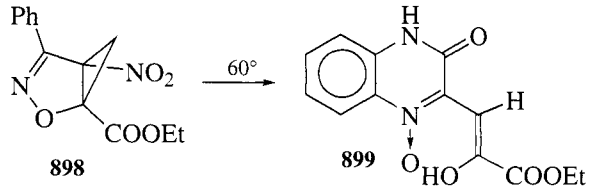
4-Piperidones have been obtained by hydrogenolysis of 7-oxa-1-azabicyclo [2.2.1]heptanes; analogous treatment of the quaternary salts thereof gives *N*-methylpiperidones:[40/91]



Condensed quinoxalines can be prepared by base-promoted ring fragmentation of 5-acyl-2-isoxazolines in the presence of *o*-phenylenediamine.[15/73]

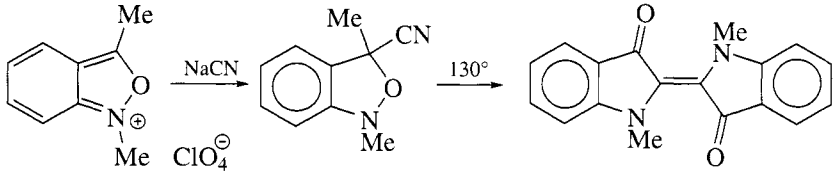


The quinoxaline *N*-oxide derivative **899** has unexpectedly been obtained by thermal isomerization of the cyclopropane–condensed isoxazoline **898**:[68/90]



Dibenzo-1,4-oxazepines are formed by isomerization of the unstable benzazete[1,2-*b*]benzisoxazole system.[24/75]

N,N'-Dimethylindigo is produced, along with *N*-methylindoxyl, by thermolysis of the 3,4-benzisoxazoline, obtained, in turn, by reaction of sodium cyanide with 3-methyl-2,1-benzisoxazolium perchlorate:[42/78]



4.3.3. Use of Fused or Bridged Isoxazole Derivatives as Key Intermediates in Synthetic Design

The value of isoxazole and its derivatives, principally 2-isoxazolines and isoxazolidines, as intermediates in the synthesis of complex molecules and natural products, has already been illustrated in Part 1, § 1.4.12 (isoxazoles), § 2.2.3.3 (2-isoxazolines), and § 3.4.10 (isoxazolidines). Since the appearance of the first installment in this series in 1984, the utilization of the isoxazole nucleus in synthesis has increased steadily, in large part due to some obvious advantages of this approach, which are summarized below:

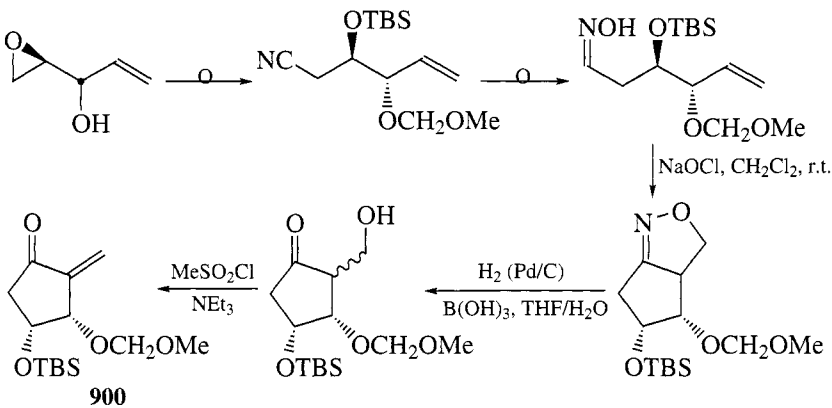
1. The isoxazole ring is prepared under mild conditions from easily available starting materials, such as aldehydes, ketones, or nitroalkanes.
2. The most commonly used method of preparation, the 1,3-dipolar cycloaddition of nitrile oxides and nitrones, adheres to well-defined rules of regio- and stereoselectivity and often affords products with predictable levels of diastereomeric or enantiomeric purity.
3. The isoxazole nucleus is remarkably stable under various conditions, thereby permitting an extensive array of functional-group manipulations to be performed on appended side chains or fused rings.
4. Ring cleavage can be accomplished with a high degree of stereocontrol under appropriate conditions, as already illustrated in the preceding paragraphs.

Since the treatment of this topic in Part 1 was not limited to monocyclic isoxazole derivatives but also included fused and bridged compounds, the current discussion will focus on relevant literature that has appeared during the period from 1984 to 1991. Pertinent details of material already covered in Part 1 will be briefly mentioned.

4.3.3.1. Syntheses of Alicyclic Compounds

Highly functionalized or fused-ring derivatives of cyclopentane can be prepared by intramolecular cycloaddition of nitrile oxides or nitrones and subsequent reductive ring opening.

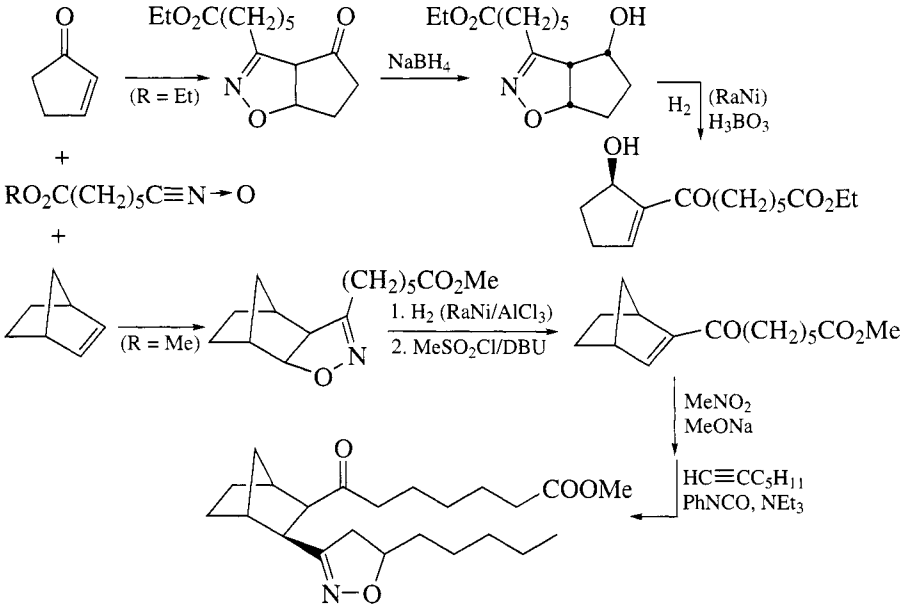
This approach has been employed in the synthesis of a variety of prostanoids, among them prostaglandin $PGF_{2\alpha}$[20/84], whose preparation has been reported in Part 1 (p. 592; Scheme 2.36, p. 595). Enone **900**, a useful intermediate for the synthesis of chiral prostaglandins, has been prepared as illustrated in Scheme 4.6.[68/88]



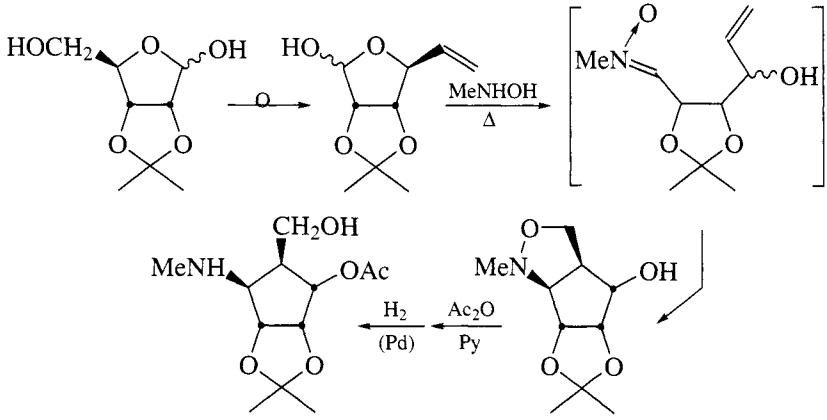
Scheme 4.6

The key step involves a regioselective intramolecular nitrile oxide cycloadddition and a subsequent reductive ring cleavage to ultimately afford an α,β-unsaturated ketone.

The further utility of this method is illustrated in a simple approach to 7-keto-prostanoids,[31/88] and in the synthesis of analogs of PGH_1 endoperoxide:[4/89]



A different approach to prostanoid synthesis is based on the intramolecular cycloaddition of appropriately substituted *C*-3-butenyl nitrones (see §4.2.2.7),[44/86,56/87,39/89] or of *C*-4-pentenyl nitrones obtained from α-glucose derivatives.[34/81]

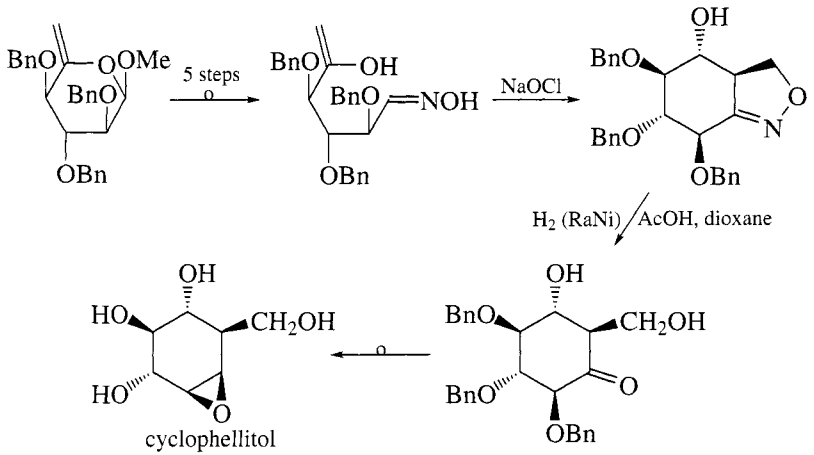


Scheme 4.7

Intramolecular nitrone cycloaddition of carbohydrates offers a rapid entry into polyhydroxylated aminocarbocycles (Scheme 4.7).[40/89]

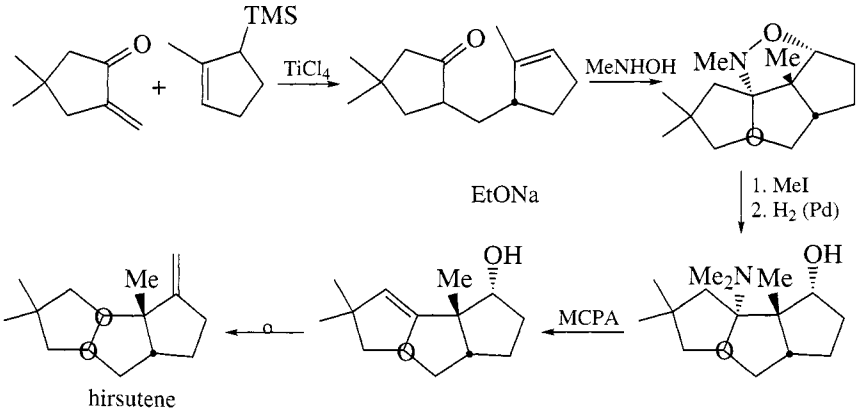
A stereoisomeric methyl(2,3,4-trihydroxy-5-hydroxymethyl)cyclopentylamine, that functions as a potent α-mannosidase inhibitor, has been similarly prepared.[58/90]

An enantiospecific total synthesis of cyclophellitol, starting from L-glucose relies on the presumed chair-like transition state of an INOC reaction to control relative stereochemistry and represents a general entry into highly oxygenated cyclohexanes (pseudosugars, Scheme 4.8).[13/90]



Scheme 4.8

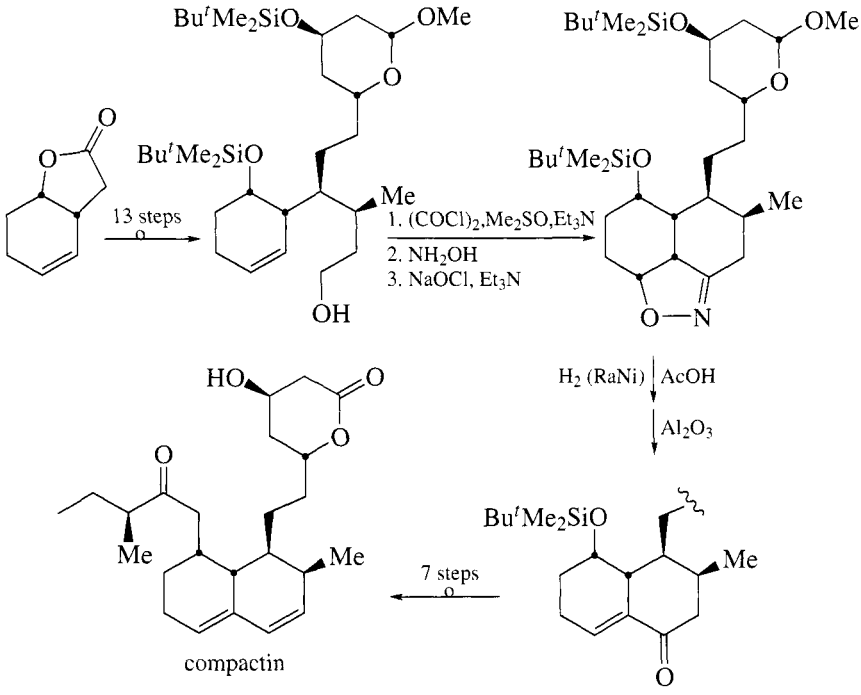
Similarly, a convenient stereocontrolled synthesis of the linearly fused tricyclopentane hirsutene takes advantage of an intramolecular nitrone cycloaddition as a key step (Scheme 4.9).[63/84,67/85]



Scheme 4.9

In this example, the formation of an alkenyl nitrone having an *anti*-configuration is dictated by steric constraints and leads to stereoselective creation of the central third ring.

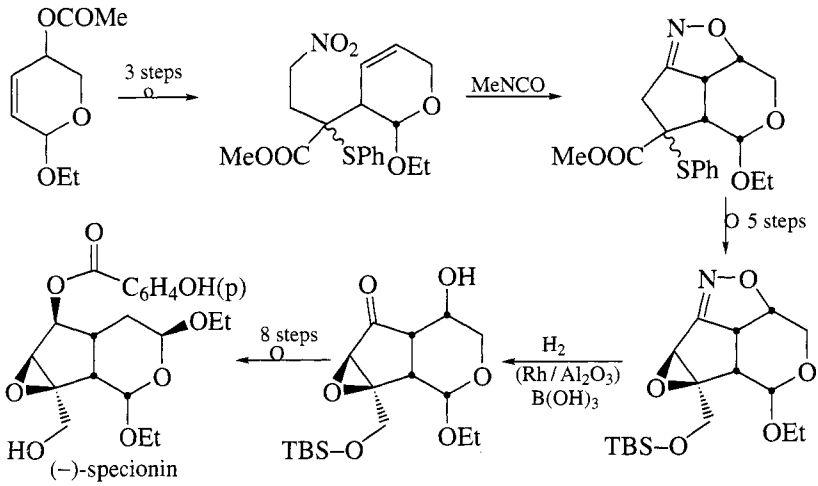
The INOC reaction was successfully applied during construction of the hexahydronaphthalene nucleus during a total synthesis of the hypocholesterolemic agent compactin (Scheme 4.10).[41/87]



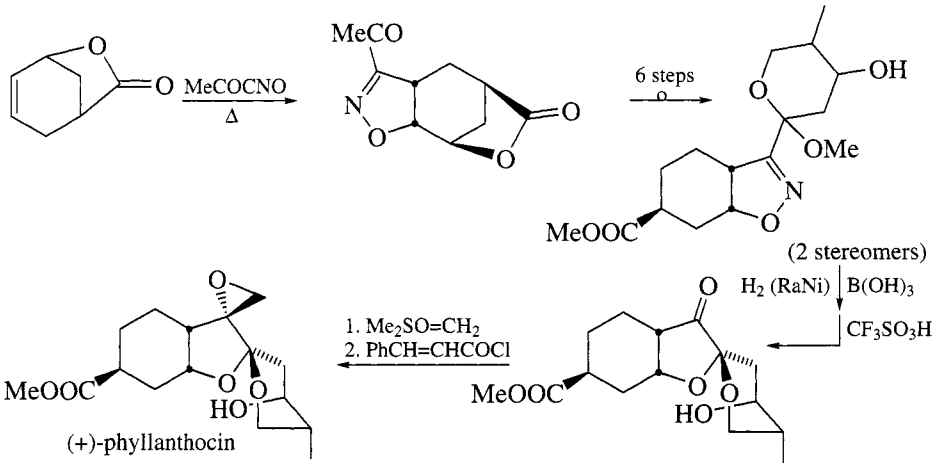
Scheme 4.10

The stereoselective total synthesis of (−)-specionin, summarized in Scheme 4.11, exemplifies a general entry into a broad class of iridoid aglycones and relies on a combination Claisen rearrangement/nitrile oxide cycloaddition.[42/87,28/88]

(+)-Phyllanthocin, the aglycon of the antitumor agent phyllanthoside, has been synthesized by a route that commences with 1,3-dipolar cycloaddition of pyruvonitrile oxide to (1*R*,5*S*)-7-oxabicyclo[3.2.1]oct-2-en-6-one. A tricyclic 2-isoxazoline having the correct regio- and stereochemistry is obtained as the main cycloadduct, along with minor amounts of a regioisomer and a stereoisomer. Opening of the lactone ring and elaboration of the 3-acetyl group, followed by hydrogenolytic ring scission and a series of suitable manipulations, led ultimately to the target molecule (Scheme 4.12).[8/89]



Scheme 4.11



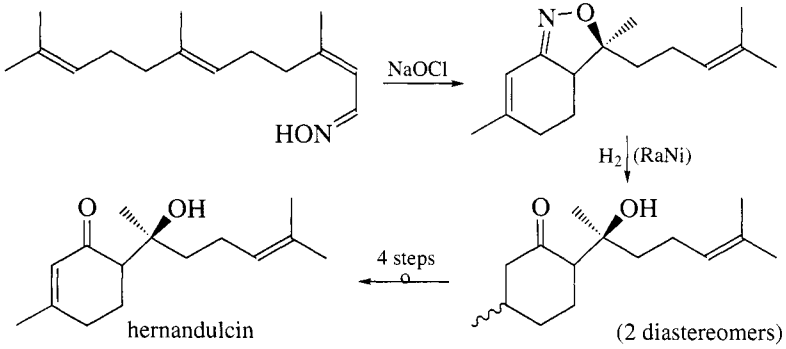
Scheme 4.12

Also reported in Part 1 are the syntheses of sarkomycin[21/82] (p. 591 and Scheme 2.35, p. 594) and the general approach to glutarimide antibiotics[14/76,13/79] (p. 407 and Scheme 1.56, p. 408). In a recent synthesis of the glutarimide derivative sesbanimide, a 3-ethylcyclopentano-2-isoxazoline is employed as a precursor in the construction of the 3-methylenetetrahydrofuran ring.[83/90]

4.3.3.2. Terpenoids

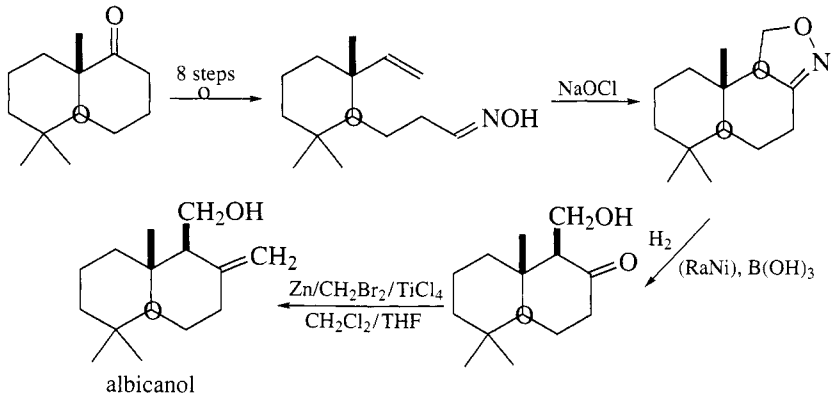
Several sesquiterpenes have been synthesized by routes that proceed through intramolecular 1,3-dipolar cycloadditions. The syntheses of α-bisabolols[44/79,41/79] and α-terpineol[40/79] utilize the nitrone approach, and have been reported in Part 1 (pp. 775–776).

A facile preparation of hernandulcin involves oxidation of (2*Z*,6*E*)-farnesal oxime to generate the corresponding nitrile oxide *in situ* which then cyclizes to the bicyclic isoxazoline. Subsequent reduction to the aldol and dehydrogenation afford the desired target (Scheme (4.13).[19/89,48/90]



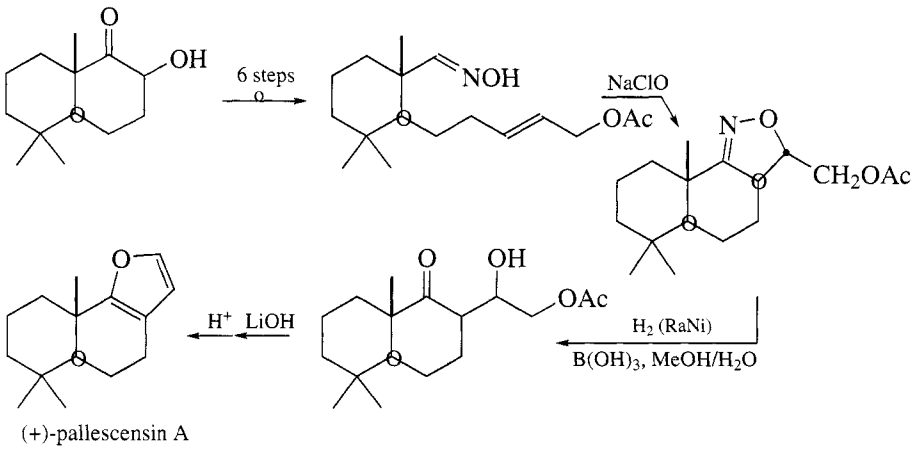
Scheme 4.13

A high degree of diastereoselectivity is observed in the INOC reaction utilized during an efficient total synthesis of (+)-albicanol from the easily available (−)*trans*-5,5,8a-trimethyloctahydronaphthalen-1(2*H*)-one, as outlined in Scheme 4.14.[16/89,47/90]



Scheme 4.14

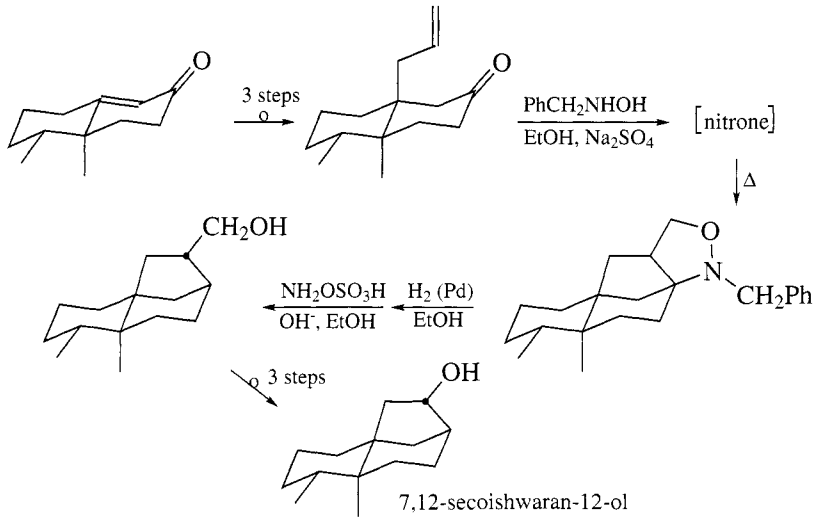
In a variation of this approach, the total synthesis of the marine furanosesquiterpene (+)-pallescensin A was accomplished (Scheme 4.15).[15/90]



Scheme 4.15

The total synsthesis of the sesquiterpenoid (±)-bisabolangelone starts with a regioselective cycloaddition of acetonitrile oxide to 5-methylcyclohex-2-en-1-one.[9/89]

Intramolecular cycloaddition of nitrones to *endo*- or *exo*-cyclic double bonds has been utilized for the total synthesis of tricyclic sesquiterpenes (±)-7,12-secoishwaran-15-ol, (±)-coriolin, and (±)-hirsutene.[67/85] The sequence leading to the former compound is reported in Scheme 4.16.



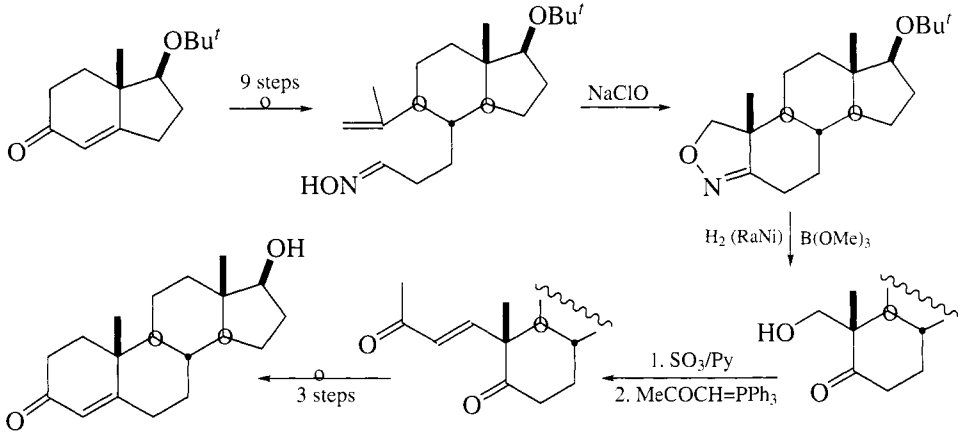
Scheme 4.16

An intramolecular nitrone–olefin cycloaddition is also the key step in the syntheses of (±)-α- and (±)-β-eudesmol from methyl farnesate.[39/85]

Forskolin is a highly oxygenated diterpene, whose skeleton consists of a decaline ring fused with a γ-pyranone ring. The construction of an oxygenated decaline-fused isoxazoline, suitable as intermediate for the synthesis of forskolin, is based on a stereoselective Diels–Alder cycloaddition and an INOC reaction as key steps.[27/88] A more advanced approach, starting from α-damascone, leads through a Michael addition, INOC reaction, reduction of the fused isoxazoline to the aldol, epimerization, and further manipulations to a model tricyclic system, incorporating the complete array of oxygenated functions of the AB portion of forskolin.[30/86,20/89]

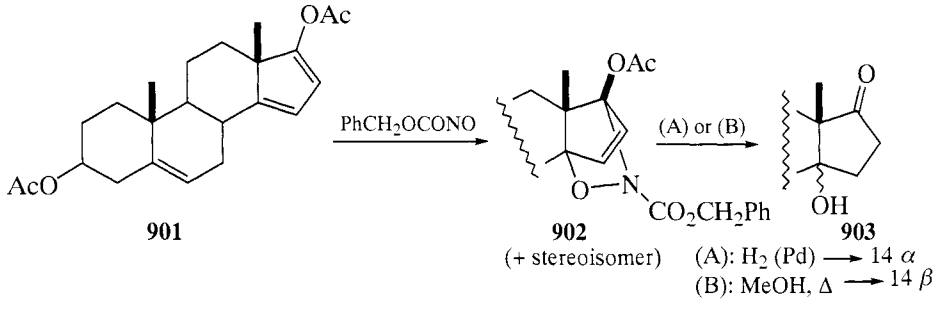
4.3.3.3. Steroids

The construction of the A/B ring system of steroids can be accomplished by an INOC reaction, followed by an incorporation of a three-carbon unit, as the following total synthesis of (+)-testosterone shows (Scheme 4.17):[14/90,15/91]



Scheme 4.17

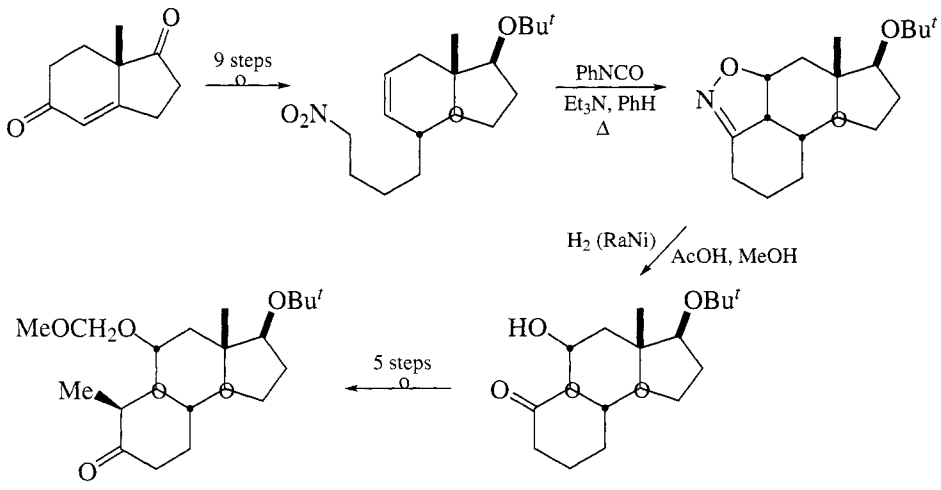
The stereocontrolled conversion of steroidal 14,16-dien-17-ol acetate **901** to either the 14β- or 14α-hydroxysteroids **903** utilizes the formation of isomeric



901 **902** (+ stereoisomer) **903**

isoxazolidines **902** by the [4+2] cycloaddition of benzyl nitrosoformate to the diene moiety:[53/89]

The stereoselective assembly of the steroidal BCD ring system, starting from a chiral indanone has been reported as summarized in Scheme 4.18, and may be regarded as an interesting general approach to 11α-oxygenated steroids.[57/87]



Scheme 4.18

4.3.3.4. Macrocycles

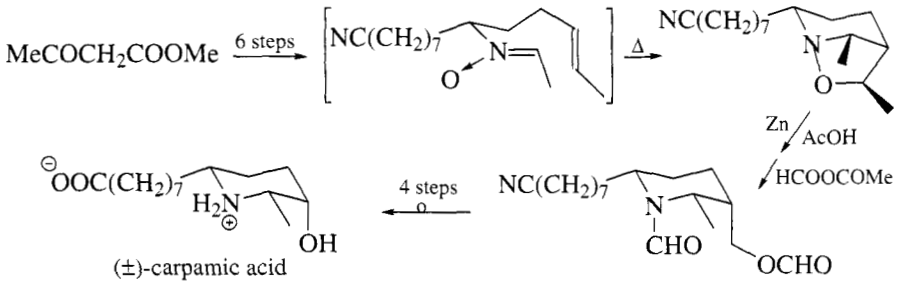
The syntheses of macrocycles maytansine,[19/84] pyrenophorin,[22/81] and antibiotic (±)-A26771B[20/82] illustrate the utility of 3,5-fused 2-isoxazolines as key intermediates, and have been reported in Part 1 (p. 588, Scheme 2.29; p. 593, Scheme 2.37; p. 595, Scheme 2.39).

A four-step synthesis of (±)-muscone was based on the intramolecular cyclization of the unsaturated nitrile oxide produced by Mukaiyama's method from ω-nitropentadec-1-ene.[21/85]

A short stereoselective synthesis of (±)-carpamic acid, the precursor of macrocyclic dilactone carpaine, utilizes an intramolecular nitrone cycloaddition, as summarized in Scheme 4.19.[51/86]

More recently, an advanced intermediate for crassin acetate has been synthesized starting from farnesyl acetate. Hydrogenolytic cleavage of a fused 2-isoxazoline intermediate furnishes the correct stereochemistry for the acetyl and the δ-lactone moieties.[17/91]

The oxahydrindene moiety of the milbemycin and avemectin families of macrolide antibiotics, suitably functionalized for further elaboration, has been constructed by two slightly different sequences, both showing an INOC reaction as key passage.[22/85,23/85]

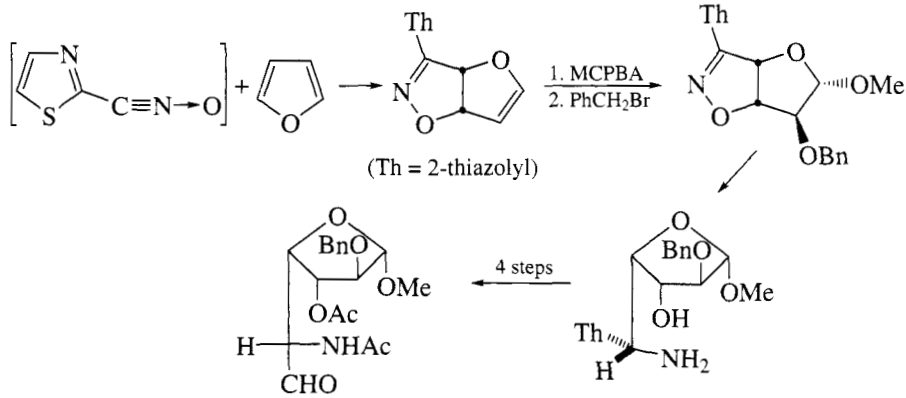


Scheme 4.19

4.3.3.5. Aminosugars

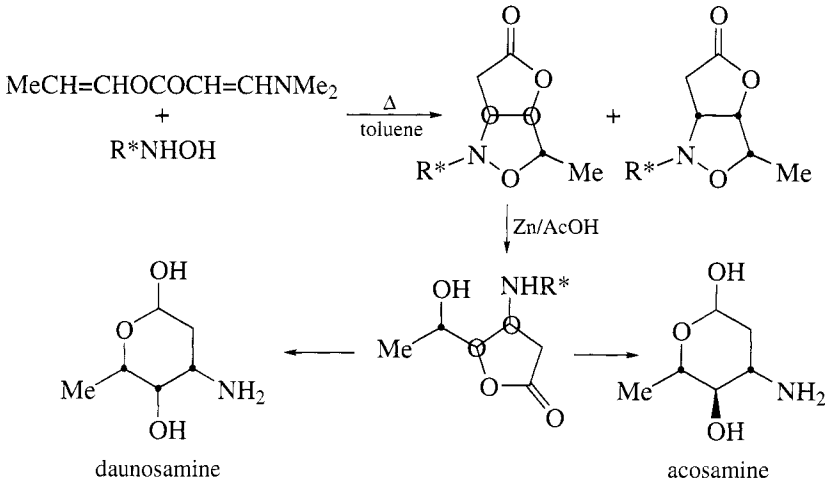
One of the most promising approaches to a vast variety of aminosugars is the cycloaddition of suitably substituted nitrile oxides or nitrones to furan or 2-methylfuran. The dihydrofuran component of the resulting cycloadduct can be stereoselectively functionalized, and the subsequent reduction of the isoxazoline or isoxazolidine N–O bond furnishes the expected aminosugars. Several examples of this synthetic route have already been reported in Part 1, such as the synthesis of 5-amino-5-deoxyidose,[13/82,16/85] 4-amino-4-deoxyarabinose, and 2-amino-2-deoxyxylose[55/85].

Another interesting variation utilizes the 2-thiazolyl group as masked formyl group equivalent. Indeed, 2-thiazolylcarbonitrile oxide enters regiospecific cycloaddition to furan to give the expected cycloadduct. After functionalization of the double bond, reductive ring cleavage, and liberation of the formyl group from the thiazole ring, the protected 5-amino-5-deoxydialdofuranose was obtained with fair overall yield (Scheme 4.20).[38/88]



Scheme 4.20

An intermolecular nitrone–furan cycloaddition is the starting point for a total synthesis of nojirimycin[30/82] (Part 1, p. 771, Scheme 3.25). The intramolecular version, involving a chiral nitrone, allows the total synthesis of 1-daunosamine and 1-acosamine to proceed along the sequence summarized in Scheme 4.21.[37/81,45/85]



Scheme 4.21

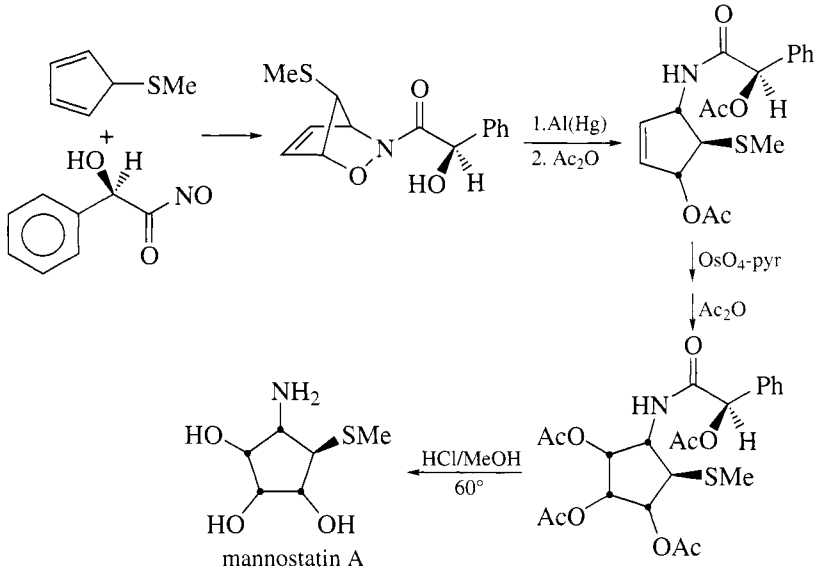
A simple synthesis of protected 3-*epi*-gentosamine starts from a chiral *N*-methylnitrone and vinylene carbonate; the cycloaddition exhibits no diastereofacial selectivity, but the isomeric cycloadducts are easily separable.[75/84]

Stereoisomerically pure polyhydroxylated aminocyclopentane derivatives are formed from nitrones derived from unsaturated monosaccharides (Part 1, p. 769).[37/79,38/79,39/79]

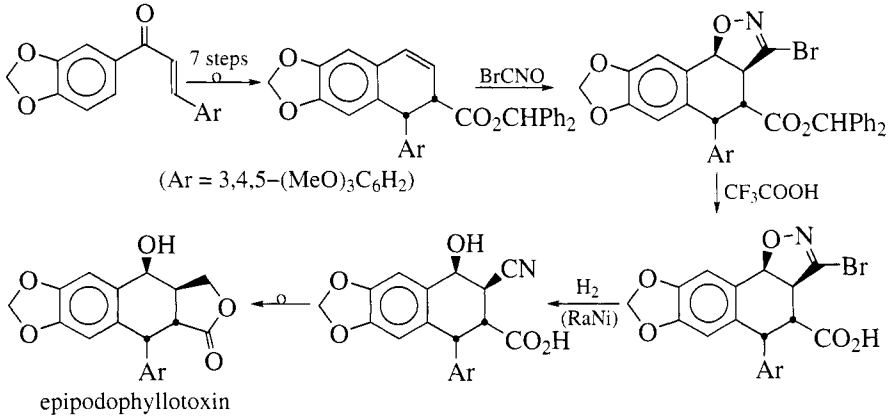
A short synthesis of the enantiomerically pure mannostatin A, an unusual sulfur-containing glucosidase inhibitor, is based on an asymmetrical nitrosocycloaddition. The resulting unsaturated bridged isoxazolidine is subjected to reductive ring opening, stereoselective osmylation, and hydrolysis along the sequence outlined in Scheme 4.22.[1/91]

4.3.3.6. Aromatic derivatives

A total synthesis of the naturally occuring lignan (±)-epipodophyllotoxin makes use of the regiospecific cycloaddition of bromoformonitrile oxide to a dihydronaphthalene derivative in order to establish the desired stereochemistry of the substituents in ring B of the target molecule, as summarized in Scheme 4.23.[21/86]



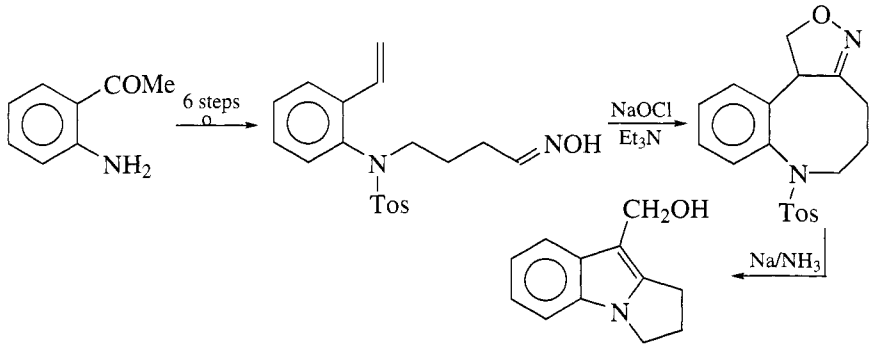
Scheme 4.22



Scheme 4.23

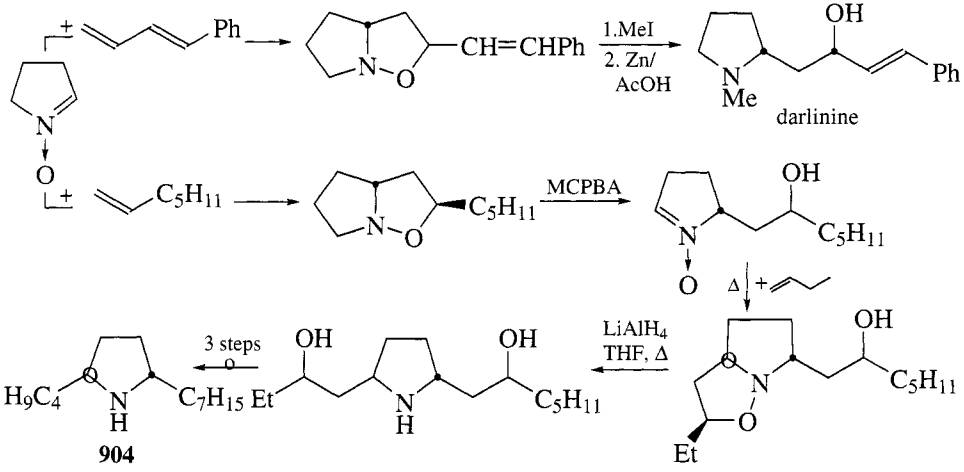
A possible approach to the important class of mitomycins is illustrated by the synthesis of a model pyrrolo[1,2-*a*]indole derivative along the sequence at p. 728.[21/88]

The choice of reagents for ring opening of the key intermediate condensed isoxazoline is crucial; hydrogenation furnishes the useless α,β-unsaturated cyclanone, whereas treatment with sodium and ammonia promotes both *N*-detosylation and N–O cleavage, thus allowing the transannular ring closure to occur.



4.3.3.7. *Alkaloids*

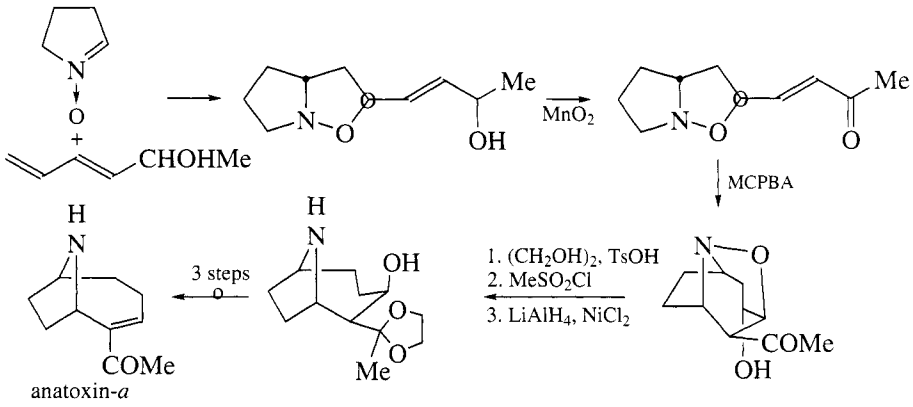
Mono- and disubstituted *pyrrolidine alkaloids* can be obtained starting from pyrroline *N*-oxide. Regiospecific cycloadditions with 1-phenylbutadiene or with 1-heptene and subsequent elaboration, as reported in Scheme 4.24, are features of the syntheses of darlinine and related alkaloids.[35/86] In the synthesis of 2,5-dialkylpyrrolidine alkaloids, such as **904**, the initial isoxazolidine product is converted into a substituted pyrroline *N*-oxide, which undergoes a second cycloaddition en route to the product.[34/86]



Scheme 4.24

The synthesis of anatoxin-*a*, the so-called "very fast death factor," a marine algae toxin having a bridged pyrrolidine structure, starts with an analogous sequence of inter- and intramolecular 1-pyrroline *N*-oxide cycloadditions,

followed by reductive ring cleavage of the bridged isoxazolidine (Scheme 4.25).[58/84,28/85]

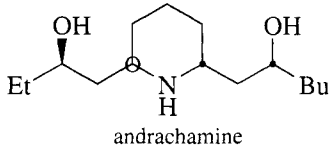


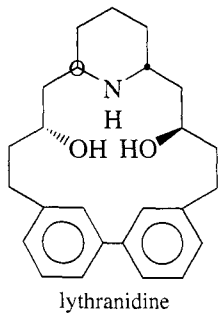
Scheme 4.25

The short syntheses of the *piperidine alkaloids*, sedridine, allosedamine, and sedamine have been discussed in Part 1 (p. 754).[19/78] More recently, a variation of the synthesis of (±)-allosedamine has been reported that utilizes lithium iodide instead of LAH for the ring cleavage of the isoxazolidine quaternary salt.[31/89]

Similarly, three minor alkaloids, belonging to the sedamine class, but hydroxylated at the piperidine ring, have been synthesized by the nitrone-based route.[58/87]

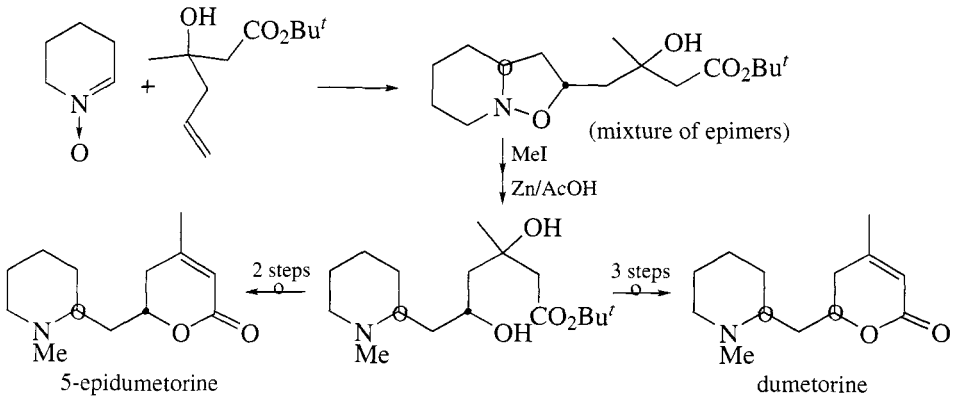
Tetrahydropyridine *N*-oxide has been used in a manner similar to that of its lower homolog (1-pyrroline-*N*-oxide) in the synthesis of (±)-andrachamine.[53/90] The low yield has been attributed to the lower regioselectivity, relative to their lower homologs, observed during peroxyacid oxidation of the 9-oxa-1-azabicyclo[4.3.0]nonane intermediate (see also § 4.3.2.2).





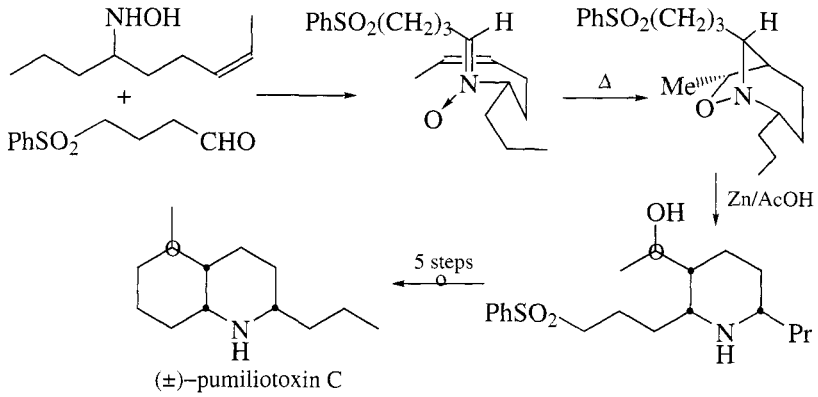
Better results with the same strategy have been obtained in the formation of the more symmetrical *trans*-2,6-dialkylpiperidine portion of the cyclophane alkaloid (±)-lythranidine.[30/91]

A short and stereospecific approach to dumetorine (and its epimer) starts from a stereocontrolled and regiospecific nitrone cycloaddition; reduction is carried out on the quaternary salt, as summarized in Scheme 4.26.[59/87]



Scheme 4.26

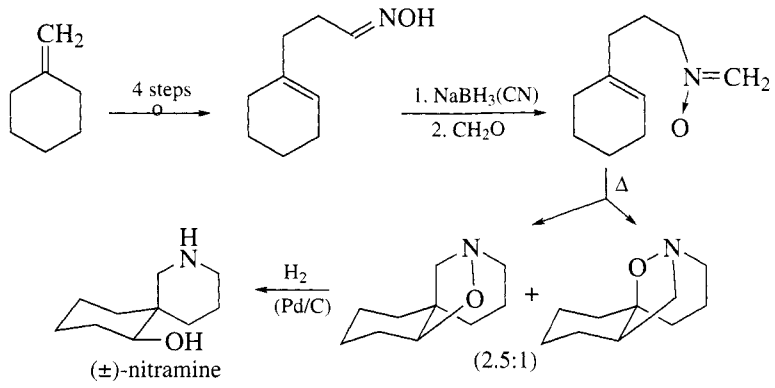
The level of stereocontrol attainable in the formation of the stereogenic centers is the great advantage offered by the intramolecular nitrone–olefin cycloaddition. This power is well illustrated by the short and efficient synthesis of the bicyclic alkaloid (±)-pumiliotoxin C (Scheme 4.27).[46/89]



Scheme 4.27

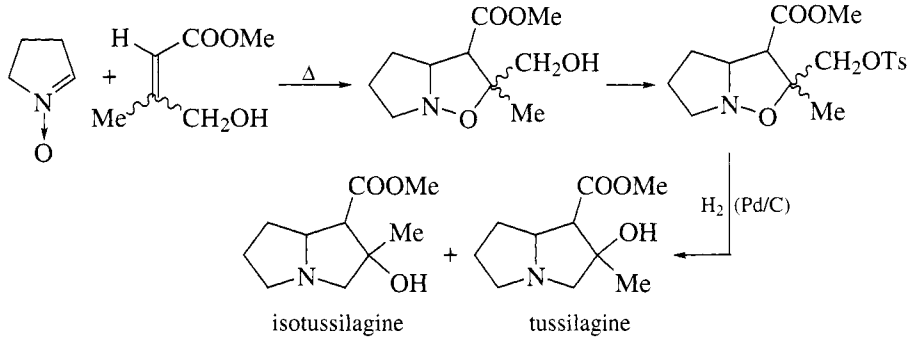
The spiropiperidine alkaloid (±)-nitramine has been synthesized in seven steps (Scheme 4.28) from methylenecyclohexane in 33% overall yield.[40/84]

Synthetic efforts toward the structurally related class of histrionicotoxins have been reported in Part 1 (p. 763, Scheme 3.18).[20/75,46/82,61/82]

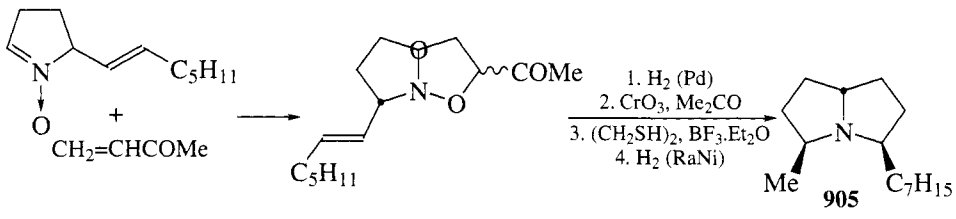


Scheme 4.28

An electrophilic carbon atom in the 2 position of the hexahydropyrrolo[1,2-*b*]isoxazole ring is required for formation of the new pyrrolidine nucleus after reductive cleavage of the isoxazole ring. In the stereoselective synthesis of tussilagine and isotussilagine,[67/84] illustrated in Scheme 4.29, this role is satisfied by a primary tosylate, while in the synthesis of **905**,[64/86] a component of a *Solenopsis* ant's venom, an acetyl group serves the purpose, as illustrated in Scheme 4.30.

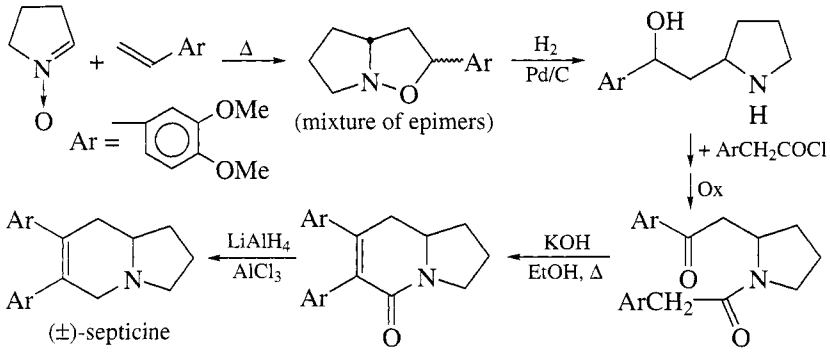


Scheme 4.29



Scheme 4.30

An alternate strategy has been employed in the synthesis of (±)-septicine and the related (±)-tylophorine, which relies on the approach already utilized in the synthesis of the higher homologs of the quinolizidine series.[30/81] As illustrated in Scheme 4.31, the aminoalcohols obtained by hydrogenolysis of the fused isoxazolidines are arylacetylated site-specifically on the nitrogen atom; after oxidation of the alcoholic function, an aldol recyclization and the subsequent reduction yield the target molecules.[31/84]



Scheme 4.31

A general entry into functionalized pyrrolizidines, indolizidines, and quinolizidines, utilizing the intramolecular thermal oxime–olefin cycloaddition, introduces three stereogenic centers in one step, and might therefore be very useful in natural products synthesis.[48/89]

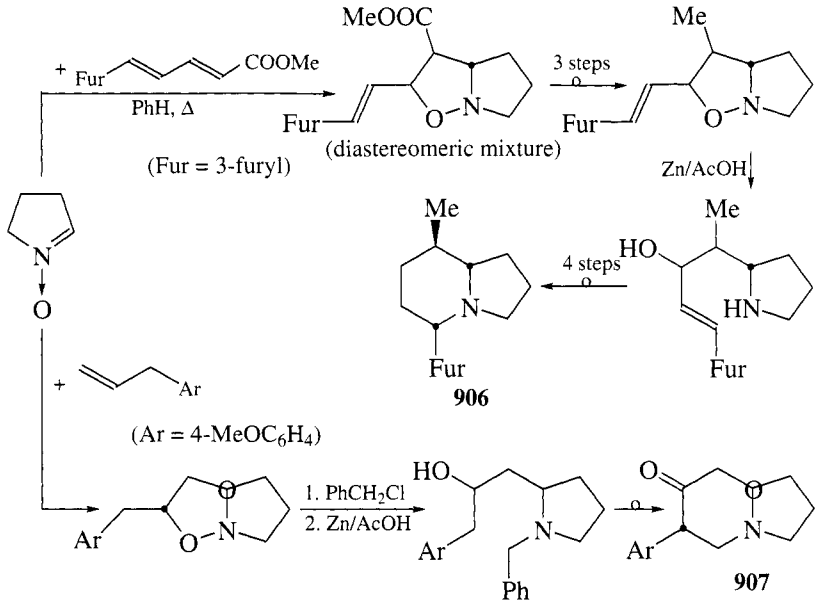
Some *pyrrolizidine alkaloids*, prepared by the nitrone cycloaddition route, such as (±)supinidine,[20/71,14/75] *dl*-retrocenine,[27/80] *dl*-croalbinecine, and *dl*-isoretronecanol,[60/79, 62/82] have already been reported (Part 1 p. 755).

The synthesis of several *quinolizidine alkaloids* that begin with tetrahydropyridine *N*-oxide have been reported in Part 1: lupinine (pp. 756–757),[39/76,62/82] (+)-decaline and (±)-vertaline,[60/83,61/85] (±)-abresoline[51/82] and analogous arylquinolizidinols[47/81] (p. 757), lasubine I, epilasubine II, subcosine and its epimer[28/83,33/84] (p. 757), porantheridine and porantherilidine[29/80,30/80,56/80] (p. 757), and julandine and cryptopleurine[30/81,31/84] (p. 758). Two somewhat different stereoselective approaches to the synthesis of lasubine II have also been proposed.[65/86]

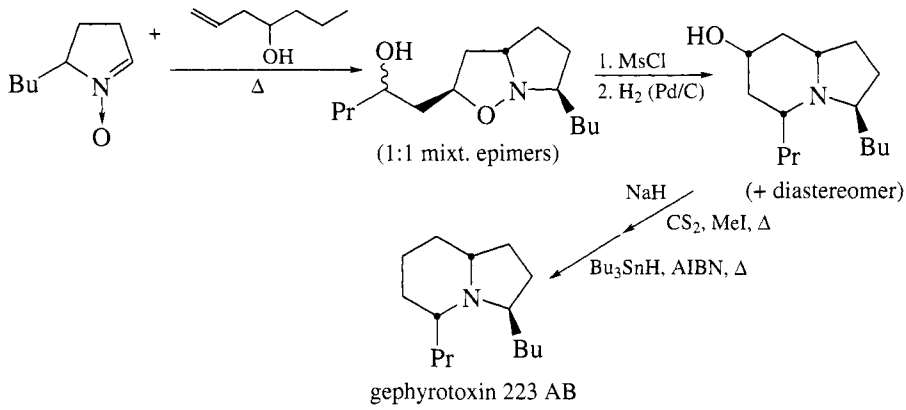
An elegant synthesis of α-isosparteine, starting from tetrahydropyridine *N*-oxide and 4*H*-pyran, has been summarized in Part 1 (p. 757);[29/83,54/90] a more recent attempt employs cyclopentadiene as the dipolarophile. However, the initial cycloaddition is only regioselective, and the major product is the wrong isomer.[54/90]

Both inter- and intramolecular nitrone–olefin cycloadditions have been widely utilized for the synthesis of *indolizidine alkaloids*. Examples of the former approach include the syntheses of the *Nuphar* alkaloid **906** (Scheme 4.32,

upper row),[22/87] of the bicyclic ketone **907**, a key intermediate in the total synthesis of ipalbidine (Scheme 4.32, lower row),[29/85] and a short synthesis of (±)-gephyrotoxin 223AB (Scheme 4.33).[28/89]



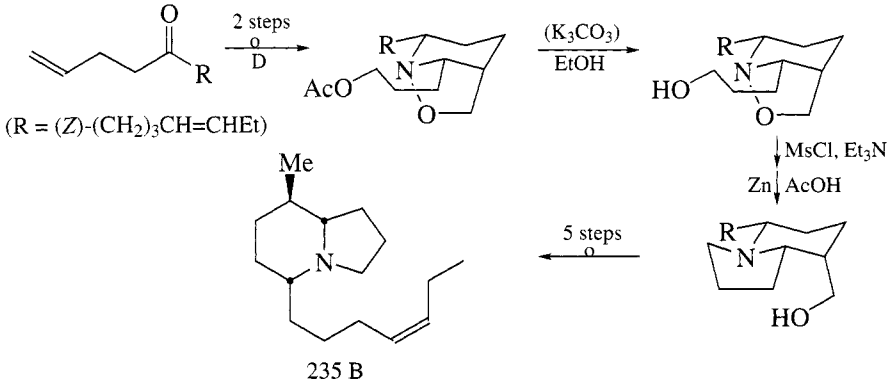
Scheme 4.32



Scheme 4.33

Highly stereoselective intramolecular cycloadditions of (*Z*)-*N*-alkenylnitrones, have been applied to the synthesis of (−)-indolizidine 209B and of other

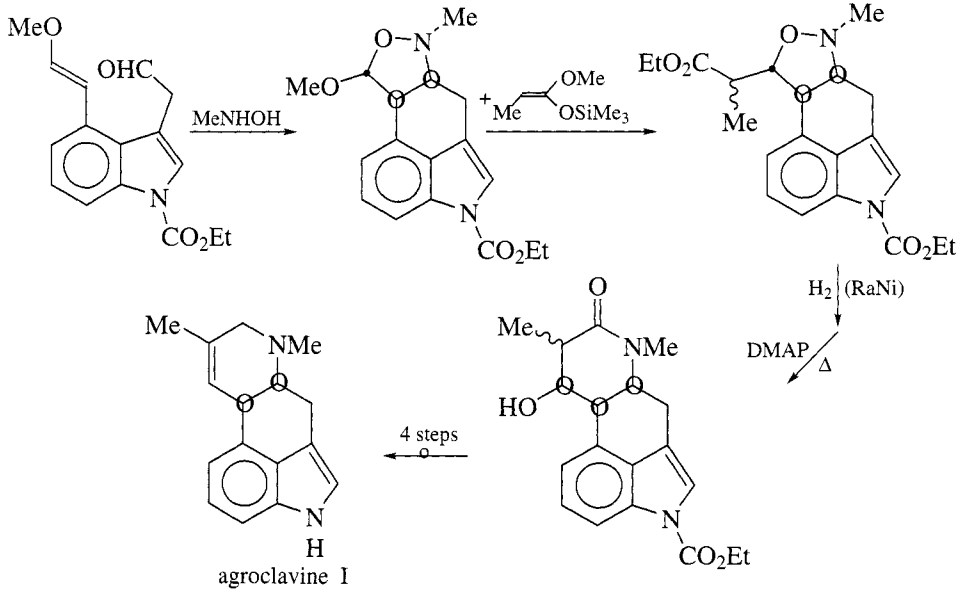
(±)-indolizidines, respectively.[54/88,42/91,43/91] As an example, the total synthesis of indolizidine 235B has been summarized in Scheme 4.34.



Scheme 4.34

Several other indolizidine alkaloids have been mentioned in Part 1: elaeokanine-A and -C[24/79] and isoelaeocarpicine (p. 759, Scheme 3.15),[26/79] elaeocarpine and isoelaeocarpine,[26/79] ipalbine (p. 759),[25/83] and septicine (pp. 759–760, Scheme 3.16).[26/80,24/83]

In the field of *indole alkaloids*, two routes for the total synthesis of chanoclavine I utilize the INOC reaction[44/80] and the intramolecular nitrone–olefin

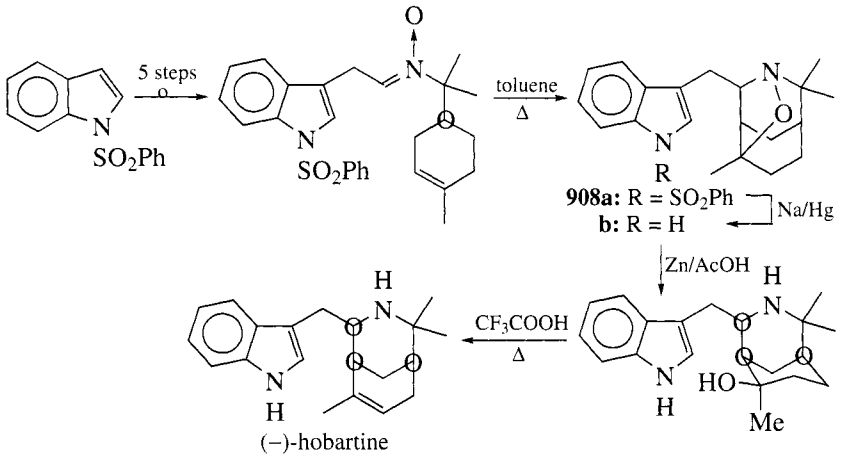


Scheme 4.35

cycloaddition,[33/80] respectively, and have been illustrated in Part 1 (p. 580, Scheme 2.23 and p. 764, Scheme 3.20, respectively). Closely related are the syntheses of paliclavine and epipaliclavine (see Part 1, p. 580, Scheme 2.24)[23/81,21/84] and of catharanthine (ibid. p. 765).[57/80]

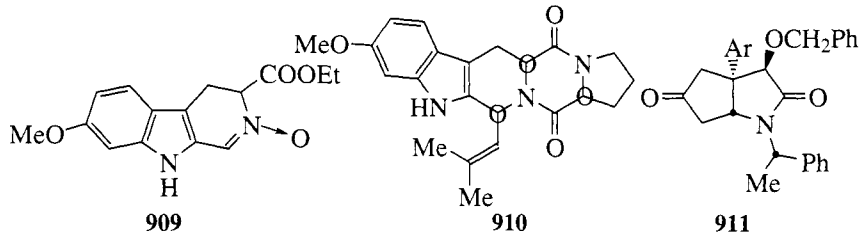
The ergot alkaloid agroclavine I has been similarly prepared (Scheme 4.35)[40/85] and is noteworthy for replacement of the 5-methoxy group in the isoxazolidine intermediate with a 5-*C* substituent by reaction with the ketene silyl acetal of methyl propionate in the presence of Zn triflate.

Another synthesis based on a stereocontrolled intramolecular nitrone cycloaddition involves the *Aristotelia* alkaloids (−)-hobartine and, as minor products under suitable conditions, (+)-aristoteline and (+)-makomaleine.[48/85] The reduction of the fused isoxazolidine **908b** was cleanly accomplished with zinc and aqueous acetic acid, while other reductants (even $LiAlH_4$) failed completely (Scheme 4.36).



Scheme 4.36

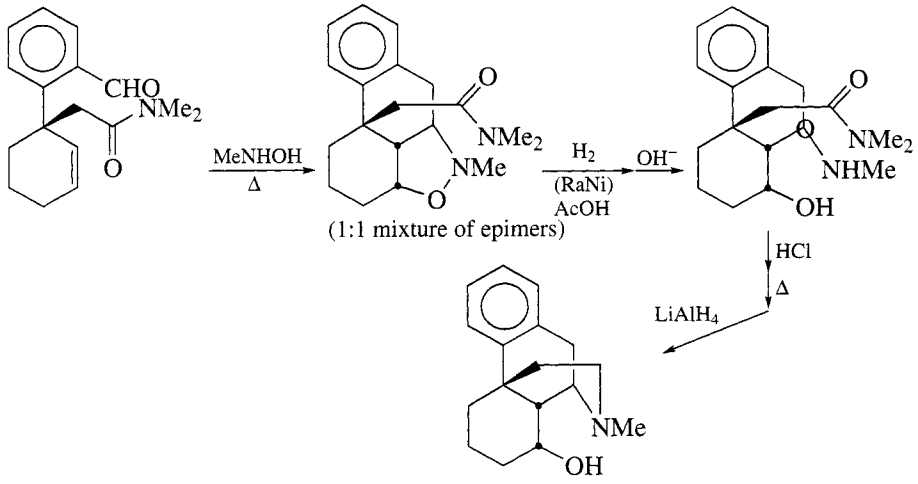
Nitrone **909**, which is easily attainable from 6-methoxy-*N*-hydroxytryptofan, offers an interesting entry into the class of fumitremorgins, a group of tremorgenic mycotoxins. Regio- and stereocontrolled intermolecular cycloaddition of **909** to isobutene, followed by reductive ring cleavage and further suitable elaborations, led to the first total synthesis of (−)-fumitremorgin C (**910**).[54/87,39/88]



909 **910** **911**

In the course of studies directed toward the synthesis of optically active pretazettine, the bicyclic system **911** has been prepared as a model compound through a highly stereoselective INOC reaction.[36/91]

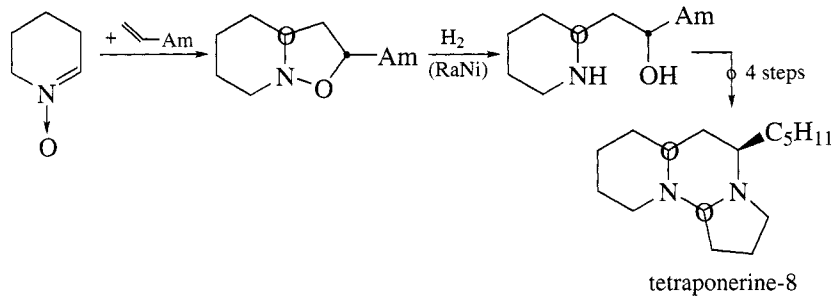
A general entry into the morphinans that utilizes an intramolecular nitrone–olefin cycloaddition has been proposed (Scheme 4.37).[39/84]



Scheme 4.37

Reference is made to Part 1 for the outstanding achievements in the total syntheses of pseudotropine (p, 761),[27/73,25/79] *dl*-cocaine (p. 761, Scheme 3.17),[15/78,28/78,25/79] adaline (p. 762),[36/80] and *dl*-luciduline (p. 763, Scheme 3.19)[26/76] and its pure (+)-enantiomer.[43/78]

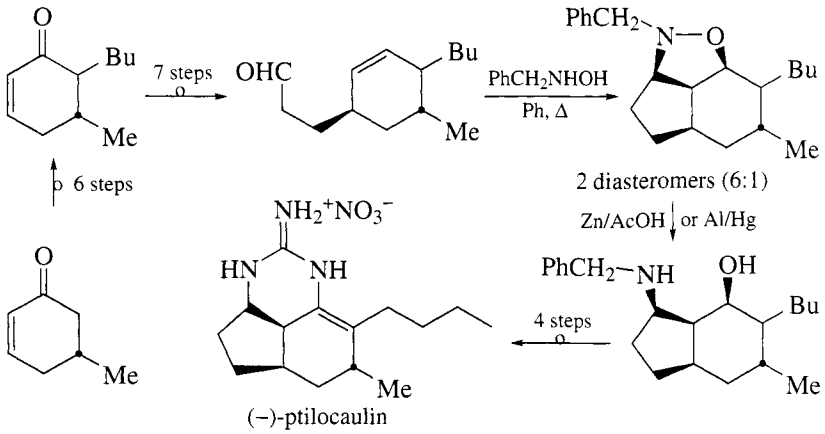
A simple stereocontrolled total synthesis of the tricyclic alkaloid (±)-tetraponerine-8 was accomplished through the following sequence:[73/88,29/91]



tetraponerine-8

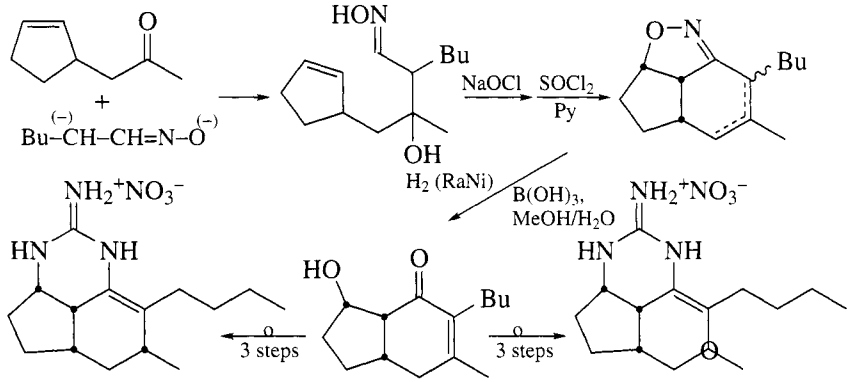
4.3.3.8. Other Nitrogen-Containing Natural Compounds

An efficient total synthesis of enantiomerically pure (−)-ptilocaulin, an interesting guanidine containing natural product isolated from marine sponges, is illustrated in Scheme 4.38.[38/84,42/85]



Scheme 4.38

A different, shorter approach, which utilizes an INOC reaction for building the six-membered ring, led both to ptilocaulin and to 7-epiptilocaulin (as nitrates), as summarized in Scheme 4.39.[66/86]

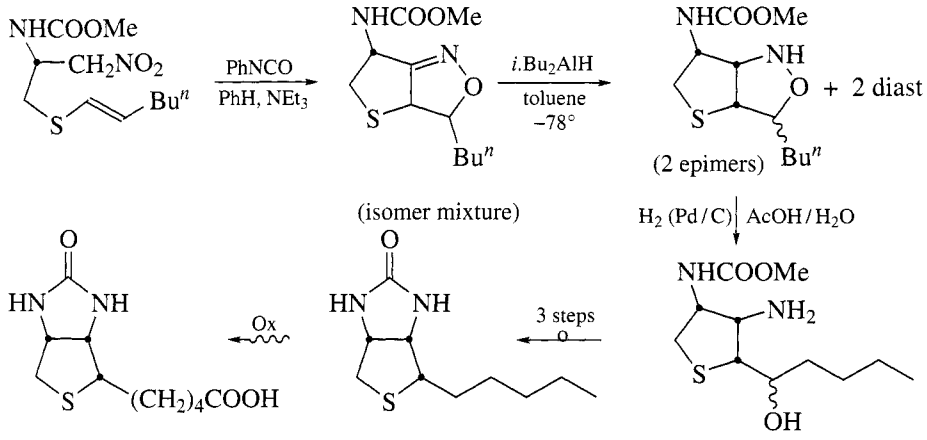


Scheme 4.39

Biotin can be synthesized by a route that relies on an intramolecular 1,3-dipolar cycloaddition as a key step. The approach to the racemic compound, starting from cycloheptene and involving a nitrile oxide or a nitrone cycloaddition to the endocyclic double bond, has already been illustrated in Part 1 (p. 579, Scheme 2.22 and p. 767, respectively).[12/78,20/80,35/80] An intramolecular nitrone cycloaddition is also crucial in the stereocontrolled synthesis of *d*-biotin starting from L-cisteine dimethyl ester, reported in Part 1 (p. 767, Scheme 2.23).[41/82,42/82]

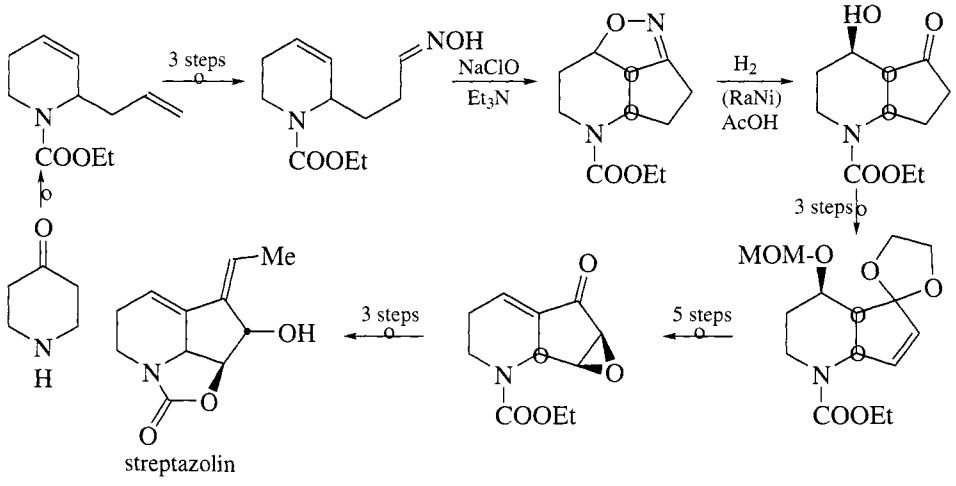
An interesting variation[24/81,17/87] of the latter approach involves an initial intramolecular cycloaddition, followed by reduction of the isoxazoline to the isoxazolidine ring (Scheme 4.40). The four stereoisomeric bicyclic isoxazolidines thus obtained in approximately equal amounts are easily separable; two

of the isomers are transformed to deoxybiotin, which is known to convert readily to *d*-biotin by microbiological oxidation.



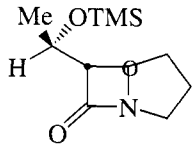
Scheme 4.40

The total synthesis of streptazolin, a fungal metabolite, makes use of an INOC reaction as key step that is followed by hydrogenolysis of the fused isoxazoline and multistep elaboration of the resulting β-hydroxyketone.[26/85,16/90] The sequence is summarized in Scheme 4.41.

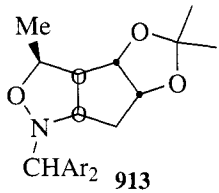


Scheme 4.41

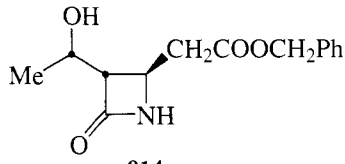
A synthesis of β-lactams based on the regio- and stereoselective cycloaddition of pyrroline *N*-oxide to methyl *trans*-crotonate has been reported in Part 1 (p. 766)[27/79] (where formula **328** should be corrected in **912**). A more recently proposed formal stereocontrolled synthesis of (+)-thienamycin utilizes an intramolecular nitrone cycloaddition to prepare **913**. Ring cleavage and further elaboration furnish the key intermediate **914**.[46/91]



912



913



914

The γ-lactam analogs of carbapenicillanic acid have been prepared starting from 5-methoxycarbonyl-1-pyrroline *N*-oxide and methyl acrylate.[26/83,59/84]

4.4. PHYSICOCHEMICAL PROPERTIES

No new IR or UV spectroscopic or dipole-moment data have been produced for fused 2-isoxazoline and isoxazolidine derivatives, which might add something relevant to what is known for the monocyclic systems. (see Part 1).

^{1}H- and ^{13}C-NMR spectra are routinely used to elucidate the structures of fused isoxazolines and isoxazolidines. Thus, in almost every paper dealing with structural assignments of these compounds, there is a wealth of NMR data (chemical shifts and coupling constants). A disappointing feature, that often characterizes these data, is that assignments of signals to protons or carbons are missing so that they are almost useless for a reviewer and, even more, for a general reader. Anyway, in Part 1 a number of ^{1}H- and ^{13}C-NMR chemical shifts as well as proton–proton coupling constants for monocyclic isoxazolines and isoxazolidines have been reported, that serve to illustrate the spectroscopic behavior of nuclei in these heterocycles. Thus, we will try to avoid as far as possible duplication of data and emphasize only the aspects of NMR spectra that are peculiar to fused derivatives.

The multiplicities of signals for hydrogen and carbon nuclei are not reported.

Numbering refers, as a rule, to the isoxazoline or isoxazolidine moieties.

As for X-ray structural data, those relevant (i.e., torsion angles) for discussion of conformational aspects of isoxazolidines will be quoted together with the related NMR data in the NMR section, while a collection of bond lengths and bond angles can be found in the X-ray section.

4.4.1. NMR Data of Fused 2-Isoxazolines

4.4.1.1. Chemical Shifts and Regiochemistry of 4,5-Fused 2-Isoxazolines

It is well established that the "natural" chemical-shift order of the proton and carbon atoms at positions 4 and 5 of 2-isoxazoline derivatives, in particular for monocyclic derivatives as shown in Part 1, features lower field absorptions for H5 and C5 compared to those of H4 and C4, respectively. The data in Table 4.12

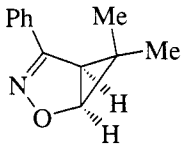
TABLE 4.12. ^{1}H- AND ^{13}C-NMR DATA [$\delta(CDCl_3)$, J (Hz)] OF 4,5-FUSED 2-ISOXAZOLINES **915–929**

Compound	H4	H5	$J_{4,5}$	$J_{4,a}$	$J_{5,b}$	C3	C4	C5	References
915[a]	2.60	4.52	6.0	—	—	—	—	—	2/90
916a	4.23	5.25	7.3	—	—	160.1	49.6	79.5	57/91
916b	4.03	5.22	8.7	—	—	158.3	51.8	87.5	57/91
916c	3.72	4.88	10.7	—	—	160.0	51.3	84.7	57/91
916d	3.43	4.50	9.2	—	—	162.2	50.0	85.4	57/91
917	4.55	5.55	4.0	1.6	3.0	159.7	57.1	82.2	57/91
918a	3.76	4.76	4.0	1.5	2.8	157.0	54.6	84.2	4/83
918b	4.25	5.09	4.0	2.0	4.0	154.0	58.2	86.2	57/91
919	5.27	6.10	4.5	—	—	—	—	—	7/74
920a[b]	4.34	4.54	6.9	2.2	2.1	—	—	—	6/77
920b[c]	4.93	5.09	8.1	6.8	5.6	—	—	—	6/77
921a[d]	3.73	4.98	8.3	—	—	—	—	—	12/73
921b	3.83	5.27	10.0	—	—	—	—	—	10/74
922[e]	6.05	6.05	—	—	—	143.9	88.4	88.4	51/79
923a[f,g]	5.15	6.39	8.6	—	—	155.0	62.3	87.6	57/91
923b[f,h]	6.07	6.98	8.7	—	—	166.2	62.8	88.2	57/91
924a	3.40	4.70	—	—	—	—	—	—	60/80
924b[i]	4.40	5.25	8.0	—	—	—	—	—	30/73
925[a]	3.38	4.62	8.7	—	2.0	—	—	—	17/70
926	4.19	5.50	9.6	1.3	3.9	155.1	59.5	89.4	10/77
927a	3.27	4.58	10.0	—	—	—	—	—	17/76
927b	3.30	4.50	12.0	—	—	—	—	—	17/76
928a	3.57	4.36	13.0	9.6	9.6 3.7	—	—	—	13/83
928b	4.10	4.75	—	5.7	—	—	—	—	13/83
929a	3.50	4.63	12.0	—	7.5	—	—	—	13/83
929b	3.85	4.67	12.8	—	7.5	—	—	—	13/83

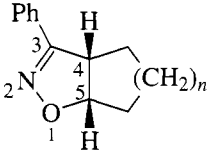
[a] CCl_4.
[b] $J_{4,b} = -1.4$ Hz and $J_{5,a} = 0$ Hz.
[c] DMSO-d_6, $J_{4,b} = 3.3$ Hz and $J_{5,a} = 2.3$ Hz.
[d] $\delta_{H3} = 6.95$ (d, $J_{3,4} = 1.5$ Hz).
[e] $\delta_{H3} = 7.38$ (s).
[f] Acetone-d_6.
[g] $\delta_{Me} = 2.08$ (d, $J = 1.1$ Hz).
[h] $\delta_{CMe} = 2.85$ (dq, $J = 1.0$ and 1.0 Hz); $\delta_{NMe} = 3.93$ (dq, $J = 1.0$ and 1.8 Hz).
[i] DMSO-d_6, $\delta_{Me} = 3.95$ (t, $J = 1.5$ Hz).

clearly indicate that this generalization also holds for isoxazolines fused, at positions 4 and 5, to carbocyclic rings. In fact, the chemical-shift difference between C4 and C5 is higher than 25 ppm, whereas that between H4 and H5 is of the order of 1 ppm.

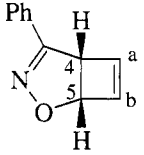
The simplest carbocyclic *cis*-4,5-fused 2-isoxazolines (i.e., **916a–d**) exhibit the C3 signal at δ 158–162, the C4 signal at about δ 50, and the C5 signal at a chemical shift higher than δ 79. For isoxazolines fused to a saturated carbocyclic ring (see Table 4.12, entries **916a–d**, **921**, **927**, **928a** and **929a**), the characteristic absorptions of H4 span (in $CDCl_3$) the range δ 3.20–4.20, whereas those of H5 span from δ 4.40 to δ 5.30. The only exception, not unexpectedly, is represented by H4 of **915** (with a fused three-membered ring), which absorbs at δ 2.60. As far as the influence of the size of the fused carbocyclic ring on chemical shifts is concerned, there is an increase in the chemical shift of both H4 and H5 on going from the three-membered ring (i.e., **915**) to the four-membered ring (i.e., **916a**), but then a progressive slight decrease in the chemical shift of both H4 and H5 is observed along the four-, five-, six- and eight-membered ring series (i.e., **916a–d**).



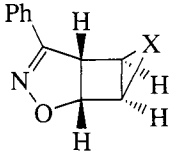
915



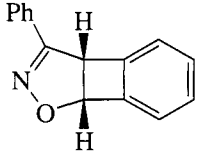
916
a: $n = 0$; **b:** $n = 1$;
c: $n = 2$; **d:** $n = 4$



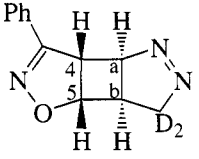
917



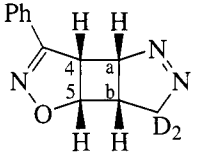
918
a: X = CH_2;
b: X = O



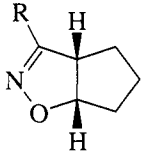
919



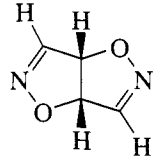
920a



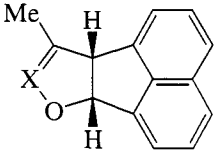
920b



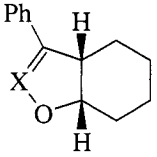
921
a: R = H;
b: R = CO_2Et



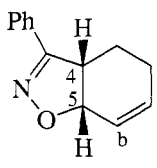
922



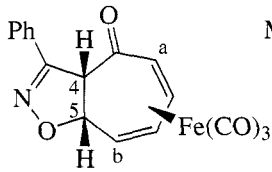
923
a: X = N; **b:** X = $NMe^+BF_4^-$



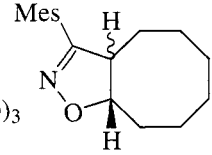
924
a: X = N→O;
b: X = $NMe^+ClO_4^-$



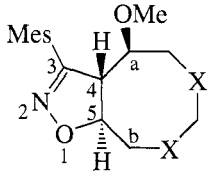
925



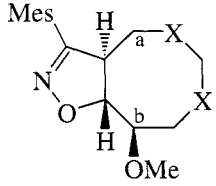
926



927 a: *cis*; **b:** *trans*



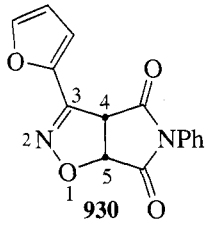
928 a: X = CH_2; **b:** X = O



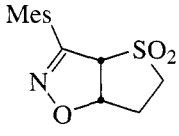
929 a: X = CH_2; **b:** X = O

Table 4.12 shows that there is no appreciable change in the chemical shifts of H4 and H5 on going from *cis*-fused to *trans*-fused derivatives (e.g., from **927a** to **927b**), whereas transformation of an isoxazoline derivative into an isoxazolinium salt (i.e., from **923a** to **923b**) brings about, as expected, a deshielding of H4 and H5 as well of C4, C5 and, to a larger extent, of C3. The presence of sites of unsaturation in the fused ring (e.g., **917** and **919**) gives rise to the expected downfield shift of isoxazoline protons.

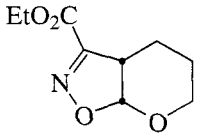
Table 4.13 provides additional ^{13}C-NMR data for 2-isoxazolines 4,5-fused to five-, six- and seven-membered rings (i.e., **930–934**), which confirm the trends already evident in Table 4.12.



930



931



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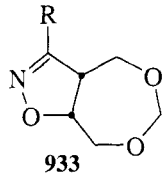
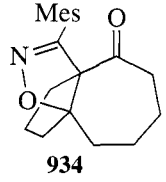


933

a: R = Me;
b: R = Ph;
c: R = Mes



934

The significantly lower chemical shift of H4 and C4 as compared to that of H5 and C5, respectively, certainly provides the most useful diagnostic feature to establish the regiochemistry of 2-isoxazoline derivatives.

TABLE 4.13. ^{13}C-NMR DATA [δ($CDCl_3$)] OF 4,5-FUSED 2-ISOXAZOLINES **930**,[8/91] **931**,[64/83] **932**,[7/87] **933a**,[12/87] **933b**,[18/84] **933c**,[45/90] AND **934**[19/86]

Compound	C3	C4	C5	Compound	C3	C4	C5
930[a]	145.8	56.5	81.9	**933b**[b]	158.3	52.9	84.4
931	151.4	70.4	82.4	**933c**	157.9	49.6	81.5
932	154.3	42.2	104.1	**934**	—	79.1	98.7
933a	154.9	54.4	80.8				

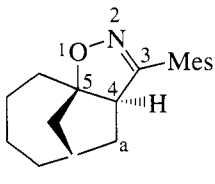
[a] DMSO-d_6.
[b] CD_3CN.

TABLE 4.14. ^{1}H- AND ^{13}C-NMR DATA [δ($CDCl_3$)] OF 4,5-FUSED 2-ISOXAZOLINES **935–938**[8/79]

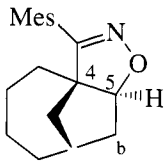
Compound	H4	H5	C4	C5	Compound	H4	H5	C4	C5
935[a]	3.60	—	61.8	96.9	**937b**[d]	2.67	—	66.6	92.9
936[b]	—	4.91	68.1	97.6	**938a**[e]	3.42	—	61.4	94.9
937a[c]	3.10	4.42	61.3	86.7	**938b**[f]	3.39	—	56.6	88.9

[a] $J_{4,a}$ = 10 and 6 Hz.
[b] $J_{5,b}$ = 8 and 4 Hz.
[c] $J_{4,a}$ and $J_{5,b}$ = <1 Hz, $J_{4,5}$ = 8 Hz.
[d] $J_{4,a}$ = 1.5 Hz.
[e] $J_{4,a}$ = 7 and 4 Hz.
[f] $J_{4,a}$ = 8 and 6 Hz.

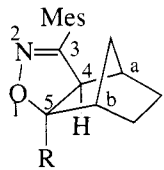
Thus, for example, the assignment of regiochemistry to compounds **935–938** (Table 4.14) on the basis of the chemical shift of the only isoxazoline proton present in these systems, is straightforward even when we are dealing with only one regioisomer as in the case of **937b** and **938a,b**. Chemical shifts significantly lower than 4.0 ppm tell us that we are in the presence of H4, while chemical shifts higher than 4.0 ppm represent reliable evidence of the presence of H5. Even more informative are the ^{13}C chemical shifts, which make regiochemistry of structures **935–938** a "beyond doubt" assignment. In fact, the signal at higher fields (between those of C4 and C5, specifically, that of C4) will appear as a doublet in the ^{13}C off-resonance spectrum [or as a positive peak in the APT (attached proton test) experiment] of **935**, **937a,b**, and **938a,b** and as a singlet (negative peak) in that of **936**. Notice that both the C4 and C5 signals in



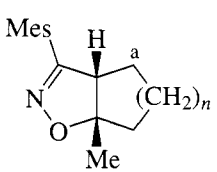
935



936



937
a: R = H;
b: R = Me



938
a: n = 1;
b: n = 4

compounds **935–938** are shifted to lower fields, with respect to the signals of the corresponding nuclei in compounds (bearing carbon substituents at position 4 and 5) of Table 4.12 and 4.13, but also that they maintain a difference of >25 ppm.

The large "natural" chemical-shift difference between C4 and C5 makes assignments of signals to these nuclei very reliable. Consequently, distinction between H4 and H5 (taking into account, as discussed below, that inversion in the order of proton chemical shifts is more frequently observed than that in the order of carbon chemical shifts) can be easily ascertained by ^{1}H–^{13}C heterocorrelated spectra.

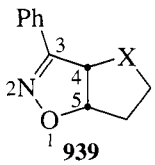
It is quite obvious that the presence of substituents with a strong deshielding effect (in particular with a strong electron-attracting effect) at only one end, that one attached to position 4 of the isoxazoline moiety, of the fused ring heavily reduces the chemical-shift difference between H4 and H5 and even can give rise to reversal of their relative chemical shifts.

This latter possibility is not frequently borne out as shown by the data of compounds **939–944** as well as by those of compounds **945** and **946** (Table 4.15). Regardless, compounds **939e**, **941e**, and **947a,b** provide examples in which H4 absorbs downfield relative to H5 as a result of the deshielding effect of an oxygen atom or an SO_2 group. The effect of the latter seems to be exalted when

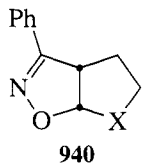
TABLE 4.15. ^{1}H-NMR DATA [$\delta(CDCl_3)$, J (Hz)] OF 4,5-FUSED 2-ISOXAZOLINES **939–944**[16/73,18/76,9/78,10/78,14/82,15/82,16/84,57/91] AND **945–946**[15/73]

	X	H4	H5	$J_{4,5}$	H4	H5	$J_{4,5}$	
Compound			**939**			**940**		
b	S	5.01	5.49	8.2	4.97	6.45	8.2	
d	SO_2	4.73	5.55	8.8	4.78	5.42	9.3	
e	O	5.78	5.18	6.3	4.10	6.32	6.7	
Compound			**941**			**942**		
a	CH_2	4.22	5.72	9.3	4.66	5.42	8.2	
b	S	5.56	6.18	10.6	—	—	—	
d	SO_2	5.11	6.05	9.9	—	—	—	
e	O	6.17	5.93	8.5	4.81	6.70	7.8	
Compound			**943**			**944**		
a	CH_2	4.56	6.23	9.5	5.14	5.54	8.0	
b	S	5.62	6.39	9.6	5.52	6.68	9.2	
c	NCO_2Et	6.28	6.45	8.7	5.25	6.85	9.0	
d	SO_2	5.36	6.40	9.7	5.73	5.88	9.1	
e	O	6.21	6.30	8.7	5.35	7.03	7.4	
n	Compound	H4	H5	$J_{4,5}$	Compound	H4	H5	$J_{4,5}$
1	**945a**	4.08	5.49	8.8	**946a**	4.43	4.82	10.0
2	**945b**	4.23	5.12	9.6	**946b**	4.20	4.68	9.4
3	**945c**	4.41	5.00	12.0	**946c**	3.95	5.12	11.3

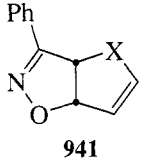
it is embedded in a four-membered ring (as in **947a,b**), since the SO_2 group in **939d** (where it is part of a five-membered ring) is far from succeeding in bringing about such a reversal.



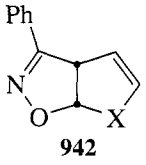
939



940



941



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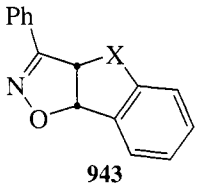
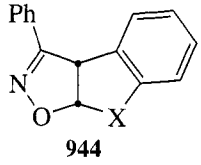
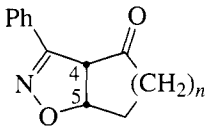


943

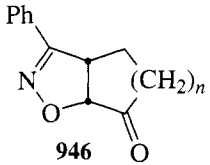


944

a: X = CH_2; **b:** X = S; **c:** X = NCO_2Me; **d:** X = SO_2; **e:** X = O



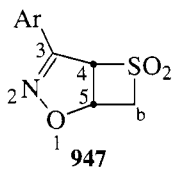
945



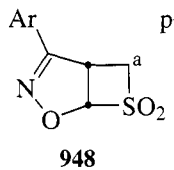
946

The observation that H4 can resonate at lower fields than H5 suggests that caution is warranted when using chemical shifts as diagnostic tools for the solution of regiochemical problems involving isoxazolines with electron-attracting substituents when only one regioisomer is formed.

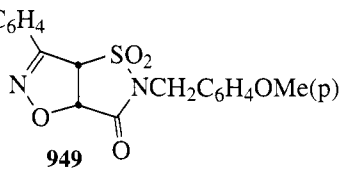
For example, the reaction of benzonitrile oxide with thiete-1,1-dioxide afforded only the regioisomer **947a** (Ar = Ph). It would not have been reasonable to assign structure **947a** solely on the basis of proton chemical shifts, since these are also fully consistent (or apparently even more consistent) with structure **948a**. However, when both the regioisomers are present [as in the case of **947b/948b** (Ar = Mes), **939e/940e**, and **941e/942e**], one can make a safe choice on the basis of the absolute value of the chemical-shift difference between H5 and H4. In fact, $|\Delta\delta_{5,4}\ (H)| = |\delta(H5) - \delta(H4)|$ is always much larger in the



947



948



949

a: Ar = Ph; **b**: Ar = Mes

TABLE 4.16. ^{1}H-NMR AND ^{13}C-NMR [δ($CDCl_3$), J (Hz)] OF ISOXAZOLINES **947–949**

Compound[a]	H4	H5	$J_{4,5}$	C3	C4	C5	Ca or Cb	References
947a[b]	6.14	5.44	8.5	151.7	91.4	66.6	78.3	57/91
947b[c]	6.12	5.39	8.4	151.3	93.8	66.6	77.8	57/91
948b[d]	4.68	6.87	6.8	157.7	54.5	115.7	59.4	57/91
949[e]	6.50	6.05	10.0	—	—	—	—	66/89

[a] δ($CDCl_3$), J (Hz).
[b] δ_{Hb} = 4.62 and $\delta_{Hb'}$ = 4.78, $J_{4,b}$ = 1.3 Hz, $J_{4,b'}$ = 3.1 Hz, $J_{5,b}$ = 3.5 Hz, $J_{5,b'}$ = 7.0 Hz, $J_{b,b'}$ = 14.8 Hz.
[c] δ_{Hb} = 4.58 and $\delta_{Hb'}$ = 4.68, $J_{4,b}$ = 1.2 Hz, $J_{4,b'}$ = 3.6 Hz, $J_{5,b}$ = 3.6 Hz, $J_{5,b'}$ = 6.6 Hz, $J_{b,b'}$ = 14.5 Hz.
[d] δ_{Ha} = 3.10 and $\delta_{Ha'}$ = 3.24, $J_{4,a}$ = 1.0 Hz, $J_{4,a'}$ = 6.8 Hz, $J_{5,a}$ = $J_{5,a'}$ = 0 Hz, $J_{a,a'}$ = 13.5 Hz.
[e] DMSO-d_6.

isoxazoline derivative that bears the stronger deshielding group at position 5 (e.g., $|\Delta\delta_{5,4}$ (H)| = 2.19 ppm in **948b**) than that in its regioisomeric counterpart (e.g., $|\Delta\delta_{5,4}$ (H)| = 0.73 ppm in **947b**).

In compounds **947**, with a 4,5-fused four-membered ring, the electron attracting SO_2 group at position 4 also causes C4 to resonate at lower fields than C5 (by ≈ 26 ppm; Table 4.16). The signal of the former nucleus actually is in the range (although on the higher side) of characteristic C5 chemical shifts, while the chemical shift of the latter, quite surprisingly, is half way between typical C4 and C5 chemical shift values. However, here again, the absolute value of the chemical-shift difference between C5 and C4 [$|\Delta\delta_{5,4}$ (C)| = 61 ppm in **948b** and 27 ppm in **947b**] unambiguously supports the regiochemical assignment.

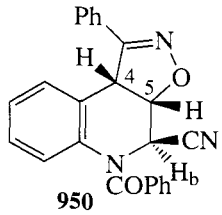
The SO_2 group in **931**, with a 4,5-fused five-membered ring, surprisingly does not succeed in giving rise to such a reversal. In fact, it has been claimed that the signal of C5 in **931** is downfield of that of C4 by 12 ppm (Table 4.13).

Reported data suggest that, in some cases, reversal of H4 and H5 chemical shifts is not accompanied by reversal of C4 and C5 chemical shifts. This might well be reasonable in the presence of groups (e.g., aryl groups) whose effect may be relatively higher on proton chemical shifts than on carbon chemical shifts. For example, it has been reported that in **950** H4 is less shielded than H5 by 1.2 ppm while C4 resonates upfield relative to C5 by 23 ppm (Table 4.17). However,

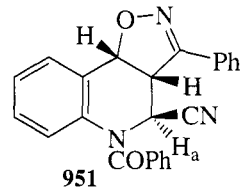
TABLE 4.17. ^{1}H- AND ^{13}C-NMR DATA [δ($CDCl_3$), J (Hz)] OF 4,5-FUSED ISOXAZOLINES **950–951**,[47/89] **952a–953a**,[13/76] and **952b–953b**[21/81]

Compound	H4	H5	$J_{4,5}$	Compound	H4	H5	$J_{4,5}$
950[a]	5.90	4.70	10.0	**952a**	4.73	5.18	10.6
951[b]	5.40	5.90	10.0	**953a**	3.69	5.61	9.3
	C4	C5		**952b**[c]	4.67	5.27	11.0
950	56.1	79.5		**953b**	≈4.0	5.60	8.0
951[b]	54.9	79.5					

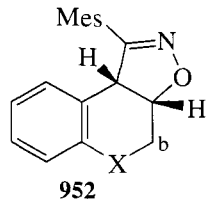
[a] $J_{5,b}$ = 0 Hz.
[b] $J_{4,a}$ = 0 Hz.
[c] $J_{5,b}$ = $J_{5,b'}$ = 4 Hz.



950



951



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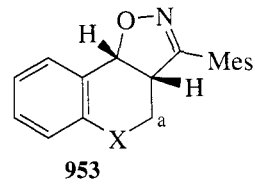


953

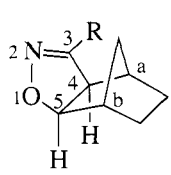
a: X = CH_2; **b**: X = O

it should be stressed that ^{1}H-NMR data for **950** and **951** are not convincing [$|\Delta\delta_{5,4}$ (H)| is too small in **951** (0.5 ppm) and too large in **950** (1.2 ppm)], and the claimed proton chemical-shift reversal is not confirmed by the data of the strictly related compounds **952** and **953**.

At this point we can state that, even if in some cases proton chemical shifts do not help in the regiochemical choice (e.g., between **945** and **946**), a combined use of proton and carbon chemical shifts (and taking into account the shielding and deshielding effects of substituents) allows, as a rule, one to satisfactorily determine regiochemistry of 4,5-fused 2-isoxazolines.

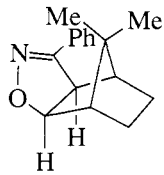
^{1}H-NMR data of compounds **954–964**, 2-isoxazolines 4,5-fused to polycyclic compounds, are gathered in Table 4.18. Chemical shifts ($\delta_{H4} \approx 3.20$–4.20 and $\delta_{H5} \approx 4.40$–5.40) are in the range of "natural" chemical shifts of 2-isoxazolines fused to saturated carbocyclic systems (see Table 4.12).

The problem of assigning regiochemistry to adducts **958–961** has been elegantly solved by the use of NOE (nuclear Overhauser effect) techniques. For example, irradiation of the signals of Ha and, respectively, Hb of **958–961** leads to a substantial intensity enhancement of the signals of the higher-field (i.e., H4) and, respectively, lower-field (i.e., H5) isoxazoline protons.

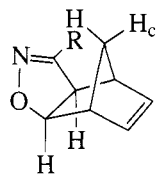


954

a: R = H; **b:** R = Ph;
c: R = $PhSO_2$

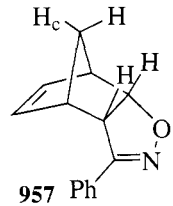


955



956

a: R = H;
b: R = Ph;



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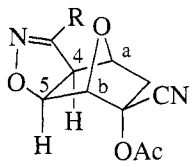
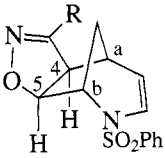
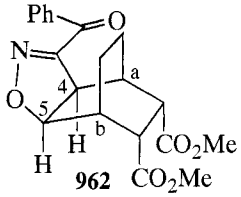


958 **a:** R = Me; **b:** R = Ph **959**

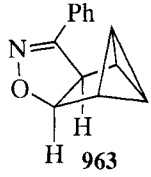


960 **a:** R = Ph; **b:** R = PhCO **961**

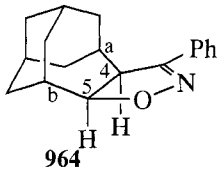


962

$\delta_{Me}(CDCl_3)$ = 3.63 and 3.67



963



964

TABLE 4.18. ^{1}H-NMR DATA [$\delta(CDCl_3)$, J (Hz)] OF 4,5-FUSED 2-ISOXAZOLINES **954–964**

Compound	H4	H5	$J_{4,5}$	References	Composition	H4	H5	$J_{4,5}$	References
954a[a]	3.15	4.39	8.3	12/73	**959a**[f]	3.61	4.70	8.0	41/90
954b	3.45	4.56	8.2	37/67	**959b**[f]	4.12	4.91	8.2	6/89
954c	3.50	4.70	10.0	5/84	**960a**[f]	4.21	4.91	8.5	3/78
955[b]	3.33	4.58	10.2	17/73	**960b**[f]	4.20	4.92	8.5	3/78
956a[c]	3.44	4.72	8.2	12/73	**961a**[f]	4.10	5.12	8.5	3/78
956b[d]	3.78	4.97	8.5	11/68	**961b**[f]	3.77	5.00	8.5	3/78
957[e]	4.12	5.39	9.2	11/68	**962**[g]	3.88	5.27	12.0	45/78
958a[f]	3.48	4.97	8.0	41/90	**963**[b,h]	3.79	4.98	7.9	59/86
958b[f]	4.02	5.12	8.2	6/89	**964**[i]	4.00	5.10	14.0	8/78

[a] δ_{H3} = 6.92 (d, $J_{3,4}$ = 1.5 Hz).
[b] CCl_4.
[c] δ_{H3} = 6.90 (d, $J_{3,4}$ = 1.5 Hz).
[d] $J_{4,a}$ = 2.9 Hz, $J_{5,b}$ =3.2 Hz, $J_{5,c}$ = 1.5 Hz and $J_{4,c}$ = 0.8 Hz.
[e] $J_{4,a}$ = 3.9 Hz and $J_{5,b}$ = 4.0 Hz.
[f] $J_{4,a} = J_{5,b} \approx 0$ Hz.
[g] $J_{4,a} = J_{5,b}$ = 3.5 Hz.
[h] ^{13}C NMR $\delta(CDCl_3)$ = 56.1 (C4), 88.7 (C5), and 156.1 (C3).
[i] $J_{4,a}$ = 3.7 Hz and $J_{5,b}$ = 5.3 Hz.

4.4.1.2. Coupling Constants and cis/trans-4,5 Relationship in 4,5-Fused 2-Isoxazolines

Coupling constants between H4 and H5 in *cis*-4,5-fused 2-isoxazolines are, as a rule, in the range 8.0–11.0 Hz (Tables 4.12–4.18). The highest $J_{4,5}$ so far reported for *cis* coupling is of 14.0 Hz in compound **964** (Table 4.14), while the coupling constants of isoxazolines fused to the bicyclo[2.2.2]octane skeleton [e.g., **962** (Table 4.18); see also **980–983**, Table 4.21] are also on the high side. The lowest values ($\approx$ 4.0 Hz) have been observed for isoxazolines *cis*-4,5-fused to a planar four-membered ring as in compounds **917–919** (Table 4.12). Given that the H4C4C5H5 torsion angle in **917–919** is certainly very close to 0°, the observed decrease in $J_{4,5}$ can be attributed, at least in part, to the increase in H5C5C4 and H4C4C5 bond angles [which are close to 120° in **917–919** and $\approx$ 7° wider than those of compounds of the type **962** and **980–983** (AM1 and PM3 geometries)].[57/91]

These observations make it evident that a *cis* relationship between H4 and H5 does not necessarily gives rise to a high coupling constant. Moreover, *trans* coupling constants between these protons, notwithstanding the very few data reported to date (i.e., the last five entries of Table 4.12), seem to be on the higher side of fused isoxazoline vicinal coupling constant values and even to exhibit slightly higher figures than those of their *cis* counterparts [e.g., *trans* coupling in **927b** ($J_{4,5}$ = 12 Hz) is higher than *cis* coupling in **927a** ($J_{4,5}$ = 10 Hz)].

In *trans*-4,5-fused 2-isoxazolines protons H4 and H5 are forced toward an antiperiplanar relationship (i.e., with a torsion angle >140°), thus easily explaining—on the basis of the Karplus relationship—the experimental finding. Whatever the underlying reason for the high figures for the *trans* coupling constants, the widespread statement that a high $J_{4,5}$ in fused isoxazolines not only is consistent but also supports a *cis* against a *trans* relationship between H4 and H5 is wrong and certainly is grounded more on the ^{1}H-NMR data of monocyclic isoxazolines than on those of fused isoxazolines. In fact, it is true that $J_{4,5}$ is, as a rule, higher in *cis* monocyclic 2-isoxazolines than in their *trans* counterparts, but this rule does not hold for 4,5-fused 2-isoxazolines.

4.4.1.3. 3,4-Fused 2-Isoxazolines: Chemical Shifts and Coupling Constants

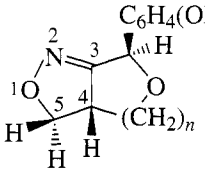
4,5-Fused 2-isoxazolines are so widespread because they can easily be prepared by intermolecular 1,3-dipolar cycloaddition of nitrile oxides to cyclic olefins. Likewise, intramolecular 1,3-dipolar cycloadditions can easily produce not only 2-isoxazolines 3,4-fused to carbocyclic and heterocyclic rings of various sizes (e.g., **965–971**) but also 2-isoxazolines with ring fusion at both 3,4 and 4,5 positions (e.g., **972–976**).

TABLE 4.19. ^{1}H- AND ^{13}C NMR DATA [δ($CDCl_3$), J (Hz)] OF 3,4-FUSED 2-ISOXAZOLINES **965**,[13/91] **966**,[11/90] **967**,[20/84] **968–969**,[18/89] **970**,[67/89] AND **971**[39/87]

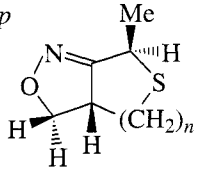
Compound	H4	H5	H5′	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	C3	C4	C5
965a	4.25	4.03[a]	4.56[a]	12.0	9.0	8.0	170.5	54.7	73.5
965b	3.38	3.82	4.64	12.0	10.0	8.0	156.8	43.8	73.7
966a	4.25	4.03	4.53	10.0	10.0	8.0	169.9	54.7	74.4
966b	—	—	—	—	—	—	157.6	45.3	73.6
967[b]	3.28	3.79	4.50	12.9	9.1	8.1	—	—	—
968	3.69	—	5.20	—	11.6	—	174.2	61.2	89.3
969a[c]	3.32	—	5.64	—	11.0	—	162.0	53.0	83.3
969b[d]	3.00	5.03	—	9.5	—	—	162.4	57.5	87.7
970[e]	3.16	—	5.14	—	12.7	—	161.2	55.7	89.6
971a	3.38	4.21	4.35	7.5	11.5	9.5	—	57.2	68.7
971b	3.53	4.14	4.35	6.0	11.0	9.0	—	61.0	70.5

[a] Of the two protons at position 5, H5 indicates the higher-field proton and H5′ the lower-field one.
[b] $J_{4,a}$ = 10.5 Hz.
[c] $J_{4,a}$ = 6.0 and 6.0 Hz.
[d] $J_{4,a}$ = 6.3 Hz and 10.6 Hz.
[e] $J_{4,a}$ = 5.9 and 12.8 Hz.

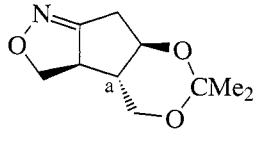
Compounds **965–971** (Table 4.19) provide some examples of 2-isoxazolines 3,4-fused to five- and six-membered rings. Inspection of Table 4.19 shows that in **965a** and **966a** one of the two protons at position 5 (H5) resonates at higher fields than does H4, whereas in all of the other compounds of Table 4.19 the "natural" chemical-shift order holds; that is the signals of both protons at position 5 are downfield of the signal of the proton at position 4.



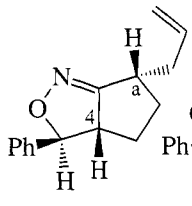
965
a: n = 1; **b:** n = 2



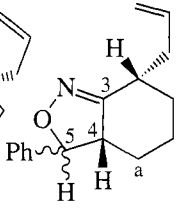
966
a: n = 1; **b:** n = 2



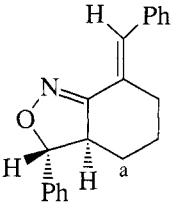
967



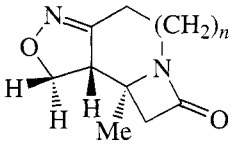
968



969
a: 4,5-*cis*;
b: 4,5-*trans*



970



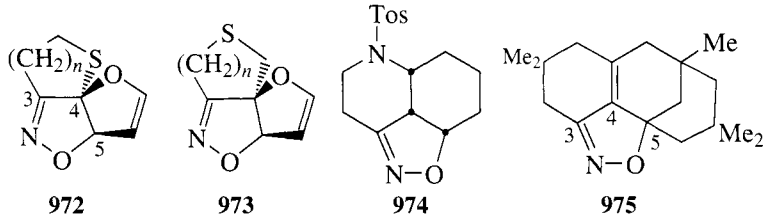
971
a: n = 1; **b:** n = 2

As for the coupling constants between H4 and the two protons at position 5, J_{cis} in **969a** ($J_{4,5}$ = 11.0 Hz) is only slightly larger than J_{trans} in **969b** ($J_{4,5'}$ = 9.5 Hz), J_{cis} exhibits exactly the same value as J_{trans} in **966a** ($J_{4,5} = J_{4,5'}$ = 9.5 Hz), while in **968** and **970** J_{trans} ($J_{4,5'}$) is as high as 11.6 and 12.7 Hz, respectively. All this is underlined in order to emphasize that in 3,4-fused 2-isoxazolines, when two protons are present at position 5, assignment of the larger $J_{4,5}$ to a *cis* relationship between the involved protons must be considered only tentative and requires further confirmation by other techniques such as NOE experiments.

The C4 and C5 signals in compounds of Table 4.19 are well separated with C5 absorbing at lower fields than C4 by ≈ 10–30 ppm.

A noteworthy aspect of C3 and C4 chemical shifts in bicyclic 3,4-fused derivatives is that they are influenced by the size of the fused ring. In fact, in the presence of a 3,4-fused five-membered ring (e.g., **965a**, **966a**, and **968**), C3 and C4 give rise to a significantly lower-field signal (by at least 12 and 4 ppm, respectively) as compared to the corresponding nuclei in derivatives 3,4-fused to a six-membered ring (e.g., **965b**, **966b**, and **969b**, respectively).

This very same characteristic emerges also, although somewhat attenuated for C3 and enhanced for C4, in the tricyclic (with ring fusion at both positions 3,4 and 4,5) isoxazolines **972a** and **973a** with respect to **972b** and **973b**, respectively. In fact, in the former derivatives (with a 3,4-fused five-membered ring) the C3 and C4 chemical shifts are higher by ≈ 7 and ≈ 11 ppm, respectively, than those in the latter derivatives (with a 3,4-fused six-membered ring) (Table 4.20).



972 **973** **974** **975**

a: n = 1; **b:** n = 2

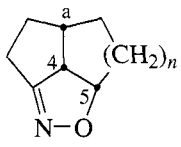
In compounds **972** and **973**, as a result of the presence of two substituents with a strong deshielding effect at position 4, we can observe a clearcut reversal of C4 and C5 chemical shifts, with C4 resonating at lower fields than C5 by 9–19

TABLE 4.20. ^{13}C-NMR DATA [δ($CDCl_3$)] OF 3,4-FUSED 2-ISOXAZOLINES **972–973**,[18/91] **974**,[10/90] **975**,[78/90] and **976b**[19/80]

Compound	C3	C4	C5	Compound	C3	C4	C5
972a	161.0	110.8	91.5	**974**	155.0	53.1	78.5
972b	153.2	99.6	90.4	**975**	154.8	135.3	82.7
973a	160.3	106.2	89.5	**976b**	171.7	57.1	78.2
973b	153.7	95.3	86.6				

ppm. Notice also how a disubstitution at position 5, with two alkyl substituents, does not result in a particular downfield shift of the C5 signal (compare the data of **974** and **975**).

With regard to the ^{1}H-NMR data of tricyclic isoxazolines, an interesting feature of compounds **976** is that an increase in size of the 4,5-fused ring is roughly paralleled by an increase in both $J_{4,5}$ and $J_{4,a}$ (the latter is the coupling constant between H4 and its next outside proton).



976

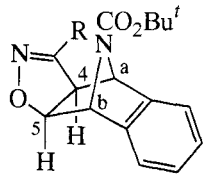
	H4	H5	$J_{4,5}$	$J_{4,a}$
a: $n = 1$	3.95	4.85	7	7
b: $n = 2$	3.65	4.69	8.5	4
c: $n = 3$	3.71	4.66	11.0	6
d: $n = 4$	3.23	4.45	10.0	10.0

Ref. 19/80; $\delta(CDCl_3)$; J(Hz)

4.4.1.4. NMR Data as Tools for Choice between Two Diastereoisomers

The addition, either intermolecular or intramolecular, of a nitrile oxide to the diastereotopic faces of a double bond produces a mixture of diastereoismers. ^{1}H-NMR spectroscopy, needless to say, has systematically been used to assign stereochemistry to these isomers. One can easily guess that in the future NOE experiments will increasingly become the method of choice to solve this problem, but in the 1970s and in the 1980s coupling constants and chemical shifts were routinely used as diagnostic tools to assign stereochemistry to facial stereoisomers.

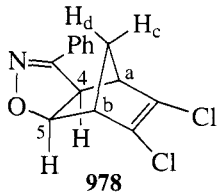
For example, starting with 4,5-fused 2-isoxazolines, the *syn/anti* (relative to the methano bridge) stereochemistry of adducts of nitrile oxides to norbornene and norbornadiene derivatives can safely be established on the basis of coupling constants between the isoxazoline protons and the bridgehead protons of the norbornene skeleton (i.e., $J_{4,a}$ and $J_{5,b}$). A figure close to 0 (i.e., less than 2 Hz) for these couplings unambiguously supports *syn* structures (as for **954–956**, **958–961**, **977**, and **978**), whereas a $J \geq 3.0$ Hz provides a reliable proof for the *anti* structures (e.g., **957** and **979**).



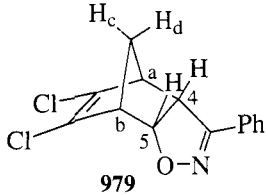
977

	H4	H5	$J_{4,5}$	$J_{4,a}$	$J_{5,b}$
a: R = Ph	3.94	5.03	7.6	0	0
b: R = PhCO	3.96	4.98	7.5	0	0

Ref. 11/80; $\delta(CDCl_3)$; J(Hz)



978



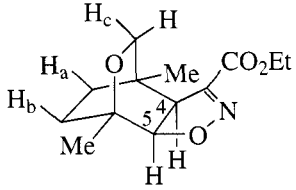
979

Compound	H4	H5	Hc	Hd	$J_{4,5}$	$J_{4,a}$	$J_{5,b}$	$J_{5,c}$
978	4.01	5.10	1.66	1.91	8.0	1.0	1.5	1.5
979	4.20	5.46	1.51	2.01	9.0	3.5	4.0	0

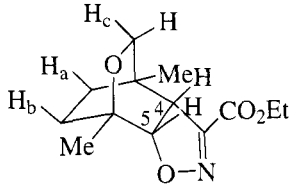
Reference 14/80; $\delta(CDCl_3)$, J(Hz).

Moreover, the presence (in *syn* isomers, e.g., **956b** and **978**) or the absence (in *anti* isomers, e.g., **957** and **979**) of long-range (^4J) W coupling constants between one proton (i.e., Hc) of the methano bridge and the isoxazoline protons can be profitably used to confirm stereochemical assignments.

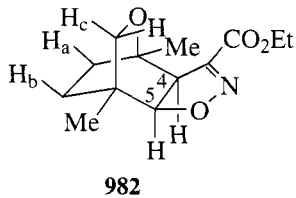
Likewise, a significant ^4J (of the order of 2.0 Hz, owing to the presence of a W coupling pathway) between H4 and Hc in **980** as well as between H5 and Hc in **982** leaves no doubt about the *anti* (with respect to the heterosubstituted bridge) stereochemistry of these adducts, and also the regiochemistry, as an additional bonus, is definitely established (i.e., **980** and **982** feature the oxygen atom of the former nitrile oxide as proximal and distal, respectively, with respect to the oxygen atom of the bicyclooctane moiety).



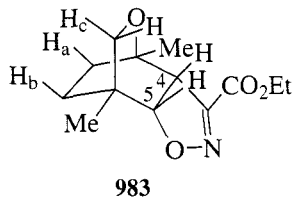
980



981



982



983

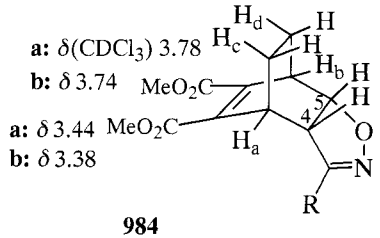
These conclusions are corroborated by the absence of these couplings in **981** and **983** (Table 4.21) as well as by the presence in the latter compounds of ^4J involving H4 (H5) and Ha (Hb), which is missing in **980** and **982**.

TABLE 4.21. ^{1}H-NMR DATA [$\delta(CDCl_3)$, J(Hz)][a] OF 2-ISOXAZOLINES 4,5-FUSED TO BICYCLO[2.2.2]OCTANE SKELETONS **980–984**

Compound	H4	H5	$J_{4,5}$	$J_{4,a}$	$J_{4,c}$	$J_{5,b}$	$J_{5,c}$	References
980	3.49	4.60	12.3	0	2.5	0	0	42/90
981	3.53	4.63	11.8	2.0	0	1.9	0	42/90
982	3.47	4.62	11.9	0	0	0	1.9	42/90
983	3.67	4.71	11.8	2.4	0	2.1	0	42/90
984a	3.95	4.98	10.0	4.0	0	4.0	0	45/78
984b	3.88	4.93	10.0	3.0	0	4.0	0	45/78

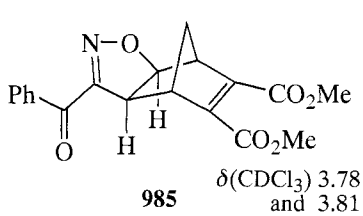
[a] In **980–983** the methyl group proximal to the oxygen atom resonates at $\delta \approx 1.2$ and the other at $\delta \approx 0.9$.

In the case of adducts **984**, owing to the symmetry of the bicyclo[2.2.2]octane skeleton, vicinal couplings between the isoxazoline protons and the bridgehead protons (i.e., $J_{4,a}$ and $J_{5,b}$) are of no help in assigning stereochemistry; that is, owing to the symmetry of the rigid bicyclooctane skeleton, also the diastereomers of **984** (i.e., the *anti* ones) should exhibit $J_{4,a}$ and $J_{5,b}$ of the order of 3–4 Hz. However, the absence of a long-range W coupling between H4 and Hc as well as between H5 and Hd is consistent only with the *syn* (with respect to the etheno bridge) structure **984**. This structure is also strongly supported by the substantial chemical-shift difference ($\Delta\delta_{OMe} \approx 0.3$ ppm) between the two methoxy groups attributable to the shielding effect by the aryl group on one of them, specifically, that one proximal.[45/78]

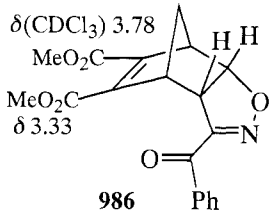


984

a: R = PhCO; **b:** R = Ph



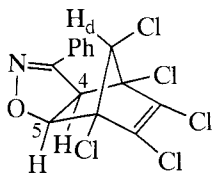
985 $\delta(CDCl_3)$ 3.78 and 3.81



986

This latter observation can be used as a general criterion and, for example, allows structure attribution to **985** (no difference in the chemical shifts of the methoxy groups) and **986** ($\Delta\delta_{OMe} \approx 0.45$ ppm).[8/77,45/78]

Finally the absence of aromatic solvent-induced shift for the sterically shielded Hd in **987** on going from $CDCl_3$ to C_6D_6 [$\delta(CDCl_3) - \delta(C_6D_6) = 0.1$ ppm] clearly establishes the *syn* (to the methano bridge) stereochemistry of the isoxazoline moiety in that compound. The *syn* heterocyclic ring efficiently prevents solvation of Hd. Consistently, in the *anti* adduct **988** this proton suffers a strong shift [$\delta(CDCl_3) - \delta(C_6D_6) = 1.2$ ppm; actually, also higher than those of H4 and H5] to higher fields on passing from deuterochloroform to deuterobenzene.[14/80]



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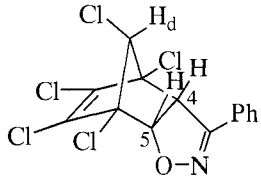
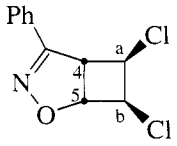


988

	987			988		
	H4	H5	Hd	H4	H5	Hd
$\delta(CDCl_3)$	4.46	5.18	4.60	4.58	5.33	4.48
$\delta(C_6D_6)$	3.45	4.50	4.50	3.58	4.66	3.26

A reliable choice between *anti* (e.g., **989**) and *syn* adducts (e.g., **991**) of nitrile oxides to *cis*-3,4-disubstituted cyclobutenes is made possible by the following facts: (1) *syn* adducts exhibit a significantly lower Rf (retardation factor) on TLC than do *anti* adducts as a result of the higher dipole moment of the former with respect to the latter; (2) vicinal couplings between the isoxazoline protons (H4 and H5) and the vicinal cyclobutane protons (Ha and Hb, respectively) are always higher for *cis* than for the corresponding *trans* relationships; (3) *cis* relationships between H4 (H5) and Ha (Hb) always give rise to vicinal couplings higher than 5.5 Hz; and (4) the absolute value of long-range four-bond cross-coupling constants (i.e., $^4J_{4,b}$ and $^4J_{5,a}$) is, as a rule, slightly larger for *cis* than for *trans* relationships between the involved protons. However, an elegant NMR



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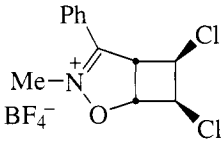

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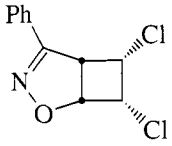

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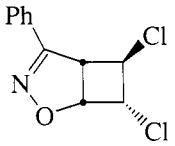

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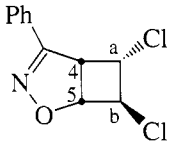


993

TABLE 4.22. ^{1}H-NMR DATA [δ(ACETONE-d_6), J(Hz)] OF 2-ISOXAZOLINES 4,5-FUSED TO FOUR-MEMBERED RINGS, **989-993**[30/71,37/73,57/91]

Compound	H4	H5	Ha	Hb	$J_{4,5}$	$J_{a,b}$	$J_{4,a}$	$J_{5,b}$	$J_{4,b}$	$J_{5,a}$
989	4.68	5.40	5.02	5.01	8.7	6.9	2.7	4.4	−1.8	−0.6
990[a]	5.64	6.01	5.55	5.80	9.0	7.5	3.4	4.0	−1.8	−0.5
991	5.38	5.24	5.03	5.40	7.6	6.8	7.1	5.1	2.1	3.0
992	4.57	5.58	4.50	5.00	7.6	5.7	4.4	5.9	2.2	−0.8
993	5.13	5.21	4.89	4.43	7.6	6.9	8.2	3.6	−1.4	1.3

[a] $J_{4,Me}$ = 1.5 Hz.

study[30/71,37/73] convincingly showed that a beyond doubt diagnostic tool to assign relative stereochemistry of protons in cyclobutane fused 2-isoxazolines is provided by the sign (evaluated through selective decoupling and tickling experiments) of $^4J_{4,b}$ and $^4J_{5,a}$: a negative sign means *trans* coupling and positive sign *cis* coupling (Table 4.22).

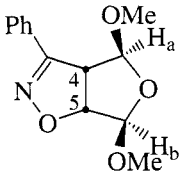
Vicinal coupling constants have also been used for structure attribution to 2-isoxazolines fused at position 4,5 to a five-membered ring, in particular a tetrahydrofuran ring as in **994** and **995** or a lactone ring as in **996**. In fact, no coupling is observed between H4 and Ha or H5 and Hb ($J_{4,a}$ and $J_{4,b}$ = 0) in these compounds when these protons are *trans* to each other, while the coupling constant ($J_{4,a'}$) is as high as 9 Hz in the case of a *cis* relationship (Table 4.23). The absence of coupling between *trans* protons can be easily explained on the basis of a dominant envelope conformation of the fused ring with the flap of the envelope pointing toward [i.e., "inward," (i)-**999**] the almost planar 2-isoxazoline residue. In this conformation the torsion angles between the isoxazoline protons (H4 and H5, respectively), and the *trans* vicinal protons (Ha and Hb, respectively) are not far from 90°, while those involving the isoxazoline protons and the *cis* vicinal protons (Ha′ and Hb′, respectively) are of the order of 30°. These geometrical arrays should give rise, on the basis of the Karplus equation ($^3J = 7.76\cos^2\theta - 1.1\cos\theta + 1.4$),[61/80] to a coupling of ≈ 0 and > 6.0 Hz, respectively. However, it should be remembered that an envelope conformation with

TABLE 4.23. ^{1}H- AND ^{13}C- NMR DATA [$\delta(CDCl_3)$, J(Hz)] OF 2-ISOXAZOLINES 4,5-FUSED TO FIVE-MEMBERED RINGS, **994–998**

Compound	H4	H5	$J_{4,5}$	$J_{4,a}J_{4,a'}$	$J_{5,b}$	C3	C4	C5	References
994[a]	4.38	5.23	9.0	0	0	151.2	59.7	89.5	9/87
995[b]	4.30	5.40	6.0	9.0	0	155.7	57.1	90.3	9/87
996	4.83	5.47	9.1	—	0	152.2	54.2	86.6	9/91
997[c]	4.26	5.85	7.8	7.8	—	—	—	—	37/76
998[d]	4.15	5.35	8.2	6.0	—	—	—	—	37/76

[a] δ_{OMe} = 3.46 and 3.47.
[b] δ_{OMe} = 3.35 and 3.46.
[c] $\delta_{Ha'}$ = 3.64, δ_{NMe} = 2.25 and 2.85.
[d] δ_{Ha} = 3.46, δ_{NMe} = 2.20 and 2.80.

the flap pointing away from the isoxazoline ring [i.e., "outward", (o)-**999**] is energetically easily accessible and that in this conformation both the *trans* protons (H4/Ha and H5/Hb, torsion angle ≈ 150°) and *cis* protons (H4/Ha′ and H5/Hb′, torsion angle ≈ 30°) should exhibit similar coupling constants [> 6.0 Hz, as in **997** ($J_{4,a'}$ = 7.8 Hz) and **998** ($J_{4,a}$ = 6.0 Hz)]. This remark and the well-known conformational mobility of saturated (carbocyclic and heterocyclic) five-membered rings indicate that stereochemical assignments based on coupling constants (in particular in the presence of only one diastereoisomer with $J_{4,a}$ ($J_{5,b}$) > 6.0 Hz) must be considered, in these systems, tentative.



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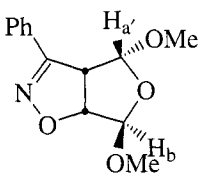

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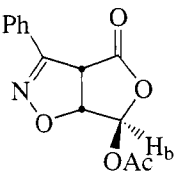

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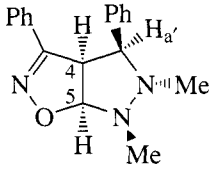

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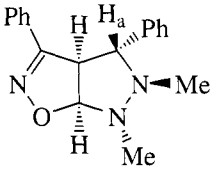

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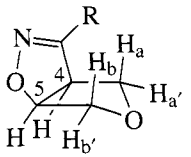
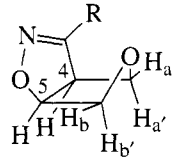
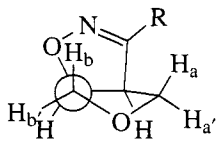


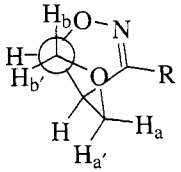
(o)-**999**



(i)-**999**



Newman view
along C_b–C_5



Newman view
along C_b–C_5

The coupling constants between the isoxazoline protons and their vicinal protons ($J_{4,a}$ and $J_{5,b}$; Table 4.24) of the fused six-membered ring in compounds **1000–1004** can easily be explained on the basis of a chair-like conformation of the cyclohexane or tetrahydropyran moiety with the OCO or CH_2O moiety in axial positions. Thus, for example, in **1000** the coupling constants between H5

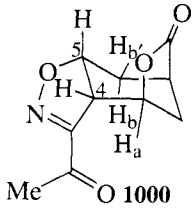
TABLE 4.24. ^{1}H-NMR DATA [δ($CDCl_3$), J(Hz)] OF 2-ISOXAZOLINES 4,5-FUSED TO SIX-MEMBERED RINGS, **1000–1016**[a]

Compound	H4	H5	$J_{4,5}$	$J_{4,a}$	$J_{4,a'}$	$J_{5,b}$	$J_{5,b'}$	References
1000[b]	3.86	5.04	10.3	<1	—	8.0	3.2	8/89
1001[c]	3.51	4.82	9.3	—	2.5	0	6.3	8/89
1002[d]	3.66	4.78	10.0	10.0	8.1	3.7	—	8/89
1003	4.49	4.82	10.0	—	—	1.2	—	16/88
			(6.9)[j]			(2.1)		2/92
1004	4.56	5.49	—	—	—	—	6.0	16/88
1005[e]	3.95	5.03	10.0	0.8	—	7.0	—	19/85
			(7.2)[j]	(1.4)		(9.1)		18/82
1006[f]	3.19	4.20	8.0	10.0	—	0	—	19/85
1007a[g]	4.76	5.29	10.0	2.0	—	3.0	—	17/84
1007b[g]	4.24	4.90	8.5	2.0	—	—	—	17/84
1008[g]	≈3.98	5.20	8.0	9.5	—	4.0	—	17/84
1009[h]	3.97	4.83	8.0	8.0	8.0	3.0	3.0	75/85
1010[h]	3.48	4.74	8.0	8.0	7.0	4.0	4.0	75/85
1011	3.72	5.62	10.5	6.6	1.9	—	—	11/87
1012[i]	3.43	4.78	8.1	5.8	—	3.6	3.6	46/88
			(6.2)[j]	(9.7)		(0.5)	(5.6)	46/88
1013[k]	3.68	4.27	8.0	9.4	7.6	0.6	—	46/88
1014[l]	3.63	4.60	8.5	—	6.1	3.1	3.1	46/88
1015	4.46	4.70	11.5	—	—	7.5	—	20/85
1016	4.68	4.93	11.0	—	—	—	3.0	20/85

[a] Ha (Hb) and Ha′ (Hb′) indicate the *trans* and the *cis*, respectively, outside vicinal protons relative to H4 (H5). Thus, $J_{4,a}$ ($J_{5,b}$) is a *trans* coupling constant and $J_{4,a'}$ ($J_{5,b'}$) a *cis* coupling constant.
[b] $\delta_{Ha} = 5.09$.
[c] $\delta_{Ha'} = 4.86$.
[d] $\delta_{Hb} = 5.01$, $J_{5,c} = 1.2$ Hz.
[e] $\delta_{Ha} = 5.16$ and $\delta_{Hb} = 4.97$.
[f] In C_6D_6, $\delta_{Ha} = 5.22$ and $\delta_{Hb} = 5.12$.
[g] DMSO-d_6 at 50–60°C.
[h] $CDCl_3 + D_2O$.
[i] $\delta_{Ha} = 4.41$, $\delta_{Hb} = 2.03$ and $\delta_{Hb'} = 2.16$.
[j] Calculated according to the following equation: $^3J = 7.76 \cos^2\phi - 1.1 \cos\phi + 1.4$.[61/80] For example, the angles (°) used in the case of **1012** were the following: H4CCH5 = 31, H4CCHa = −164, H5CCHb = −84, H5CCHb′ = −36; in the case of **1005**, the following: H4CCH5 = −20, H4CCHa = −91, H5CCHb = 158.
[k] $\delta_{Ha} = 1.61$, $\delta_{Ha'} = 1.98$, and $\delta_{Hb} = 4.96$.
[l] $\delta_{Ha} = 4.89$, $\delta_{Hb} = \delta_{H\text{-}b'} \approx 2.15$.

and its next outside protons [Hb′ (*cis*) and Hb (*trans*)] are consistent with the axial-like position of H5 $J_{5,b(ax,ax)} = 8.0$ Hz and $J_{5,b'(ax,eq)} = 3.0$ Hz]. Likewise, the axial position of H4 in **1002** can be held responsible for the high values found for both $J_{4,a'}$ (8.1 Hz, $J_{ax,eq}$) and $J_{4,a}$ (10.0 Hz, $J_{ax,ax}$) and the equatorial position of H5 in **1001** for the small values of $J_{5,b'}$ (6.3 Hz, $J_{eq,ax}$) and of $J_{5,b}$ (0 Hz, $J_{eq,eq}$). This latter value also shows that the torsion angle between H5 and Hb in **1001** is distorted from the natural value of 60° to a value that approaches, to some extent, 90°. A similar distortion is experienced by the torsion angle involving the equatorial protons H5 and Hb in **1003** as clearly shown by $J_{5,b} = 1.2$ Hz but not

by that involving the axial H5 and the equatorial Hb′ in **1004** ($J_{5,b'}$ = 6.0 Hz, $J_{ax,eq}$). Anyway, structures **1000** (actually of a compound derived from **1000**)[8/89] and **1003** were secured beyond doubt by X-ray analysis.[16/88,2/92]



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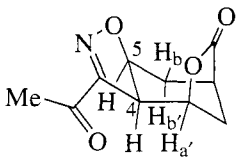

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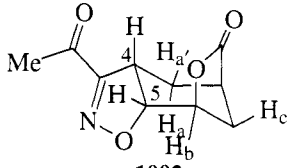

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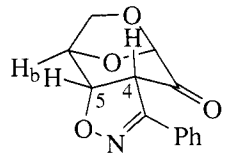

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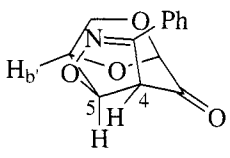

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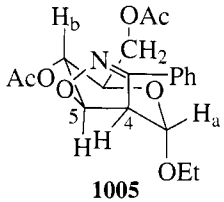

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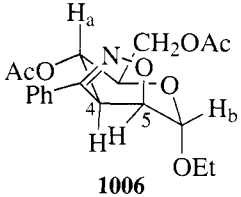
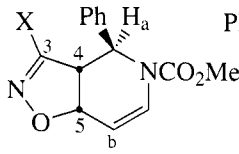
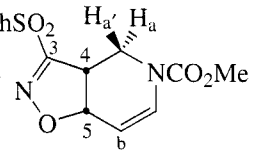


1006



1007

a: X = SO_2Ph; **b:** X = OMe



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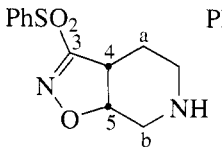
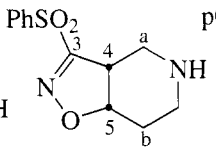
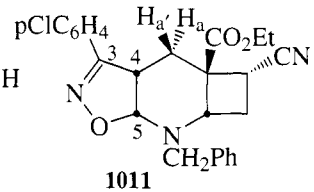


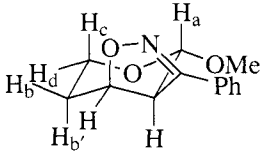
1009



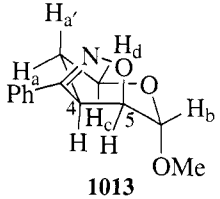
1010



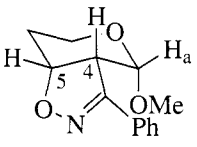
1011



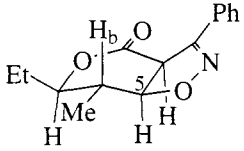
1012



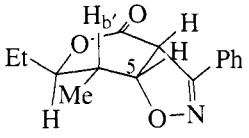
1013



1014



1015



1016

The chair conformation of the tetrahydropyran ring of **1005** and **1006** is reflected in the high axial–axial *trans* coupling between H5 and Hb in **1005** and between H4 and Ha in **1006** as well as in the very low (once again close to 0) equatorial–equatorial *trans* coupling between H4 and Ha in **1005** and between H5 and Hb in **1006**. These reasonings are definitely confirmed by the crystal structure of **1005** even if calculated J values (in parentheses in Table 4.24; evaluated on the basis of Karplus' equation[61/80] and using torsion angles from the X-ray data) are only in loose accord with the experimental values.[18/82]

X-Ray diffraction studies of **1007a**[17/84] show that H4 and Ha bear a *trans* diequatorial relationship in agreement with their small (2.0 Hz) coupling constant. The replacement of the phenyl group (at position a) of **1007a** by a hydrogen atom, as in **1008**, is, most probably, accompanied by a conformational change of the half-chair six-membered ring that moves H4 from equatorial to axial position with Ha axial and Ha′ equatorial. This observation is based on the fact that $J_{4,a}$ (9.5 Hz) in **1008** requires an axial–axial relationship between the involved protons.

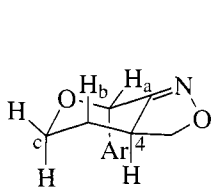
The fact that the presence of a *cis*-fused isoxazoline imposes some distortion on the chair conformation of a saturated six-membered ring is further confirmed by the coupling constants in compounds **1009** and **1010** (Table 4.24). One can tentatively assign H4 and H5 to an axial position and to an equatorial position, respectively (both in **1009** and in **1010**). However, the fact that H4 in **1009** and in **1010** exhibits the same (and relatively high) coupling to both the vicinal a and a′ protons and H5, exactly the same (and small) coupling to vicinal b and b′ protons certainly suggests that the six-membered ring suffers some flattening. It should also be remembered that the reported coupling constants actually, as a rule, are splitting values that may well be different (and even strongly different) from "true" coupling constants as a results of second-order effects, which are highly probable in the presence of multispin systems, in particular when low-field spectrometers are used.

Paton et al.[46/88] concluded, on the basis of NMR data (some are reported in Table 4.24), that in compounds **1012**–**1014** the tetrahydropyran moiety adopts a chair-like arrangement, albeit somewhat distorted, to accommodate the *cis*-fused isoxazoline ring, with the oxygen from the former nitrile oxide occupying an axial-like position. Particularly informative was considered the high coupling constant ($J \approx 11.0$ Hz) between Hb′ and Hc in **1012** and that between Ha′ and Hc in **1013**, indicating a *trans* diaxial relationship between these protons. Structure **1012**, and in particular the chair-like geometry of the tetrahydropyran moiety, was eventually established by X-ray crystallography.[46/88] Then, the Authors tried to reproduce the experimental coupling constants by calculating them with Karplus' equation and using the solid state torsion angles. But, once again, the agreement between experimental and calculated (in parentheses in Table 4.24) values is poor. This might well suggest that the solution conformation of **1012** is somewhat different from its solid-state conformation.

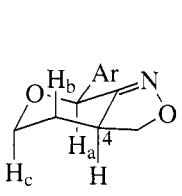
Only a boat conformation of the six-membered lactone moiety allows H5 and Hb of **1015** to attain an antiperiplanar arrangement, which nicely explains why

$J_{5,b}$ (7.5 Hz) in this compound is larger than the related coupling constant ($J_{5,b'}$ = 3.0 Hz) of its facial isomer **1016**.[20/85]

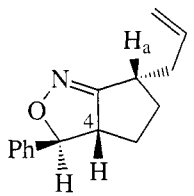
Passing to 3,4-fused 2-isoxazolines, conformation and configuration of **965b** (the *trans* derivative) and **965b′** (the *cis* derivative) were assigned on the basis of NOE experiments as well as chemical shifts and coupling constants.[13/91] In fact irradiation of the benzylic proton Ha in **965b′** caused an enhancement of 6% of Hc [$\delta(CDCl_3)$ 3.73] and of 2.5% of H4 (δ3.50) in accord with chair conformation of the tetrahydropyran ring and the "above-plane" orientation of the aryl group. In **965b** the "below-plane" orientation of the aryl group gave rise to an upfield shift of both C4 [$\delta(CDCl_3)$ 43.8 vs. 46.6 in **965b′**)] and Cc [$\delta(CDCl_3)$ 59.6 vs. 66.5 in **965b′**)], also suggesting a chair conformation for the six-membered ring of this compound. The suggested conformations of **965b** and **965b′** are further supported by the diaxial coupling constant ($J \approx 13$ Hz) between H4 and Hb.[13/91]



965b



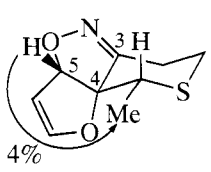
965b′



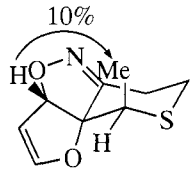
968

A long-range COSY (Correlated Spectroscopy) spectrum revealed the presence of a coupling between H4 and Ha in **968**, thus establishing the relative stereochemistry of these protons as *cis*.[18/89]

Irradiation of H5 of **1018** brought about a 10% increase in intensity of the methyl signal, whereas only a 4% NOE effect on the methyl group was observed on irradiation of H5 of **1017**, thus allowing an easy choice between these two diastereoisomers.



1017



1018

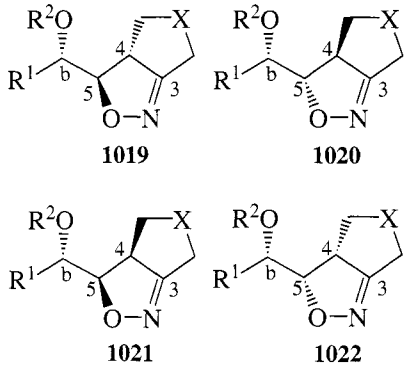
	H5	C3	C4	C5
1017	5.43	154.4	98.4	87.0
1018	5.50	152.8	99.4	85.9

Ref. 18/91; δ(DMSO-d_6)

TABLE 4.25. ^{1}H-and ^{13}C-NMR DATA [δ($CDCl_3$), J(Hz)] OF 3,4-FUSED 2-ISOXAZOLINES **1019–1022**[16/87,68/87]

Compound	H5	Hb	$J_{4,5}$	$J_{5,b}$	C4	C5	Cb
1019a	4.29	3.82	9.7	5.0	57.4	90.9	74.0
1020a	4.44	3.81	10.0	5.5	57.5	89.7	74.0
1021a	4.43	3.68	11.2	8.5	57.9	84.8	73.0
1022a	4.56	3.65	10.5	5.6	57.3	85.5	73.7
1019b	4.20	4.06	9.3	4.2	56.7	91.6	67.7
1020b	4.29	4.07	9.5	5.4	56.4	90.1	67.7
1021b	4.33	4.04	11.0	5.3	57.1	85.9	68.2
1022b	4.40	3.93	10.5	6.0	57.0	85.8	67.9
1019c	4.16	3.88	11.3	4.5	55.8	91.4	73.7
1020c	4.26	3.82	11.9	6.9	56.8	91.1	74.9
1021c	4.36	3.60	11.0	8.0	57.5	83.9	73.3
1022c	4.45	3.56	10.7	6.6	56.7	84.9	73.8
1019d	4.02	3.77	8.7	4.8	49.6	89.1	74.9
1020d	4.16	3.74	9.1	6.0	49.5	88.1	74.8
1021d	4.34	3.70	10.8	8.4	50.6	83.5	73.6
1022d	4.40	3.67	10.3	6.0	50.1	84.7	73.9

To establish the relative configuration of a stereogenic center in a chain just outside the polycyclic skeleton of fused 2-isoxazolines is certainly a hard task. For example, in compounds **1019–1022** one cannot rely on the vicinal coupling constants between H5 and Hb, since the rule that $J_{5,b}$ is higher in *syn* (Masamune's nomenclature)[2/94] than in *anti* isomers is misleading. In fact, inspection of Table 4.25 shows that on passing from *anti* (relative configuration of positions 5 and b) **1019** to *syn* **1020** (which are obtained from the same precursor) there is always (for all the four derivatives, i.e., **a–d**) an increase in $J_{5,b}$. However, on going from *anti* **1021** to *syn* **1022** in only one case (i.e., the **b** derivative) the rule that "*anti* derivatives exhibit a lower $J_{5,b}$ than their *syn*



1019 **1020**

1021 **1022**

a: R^1 = Me, X = S, R^2 = CH_2Ph

b: R^1 = Me, X = S, R^2 = $SiMe_2But^t$

c: R^1 = Me, X = CH_2, R^2 = CH_2Ph

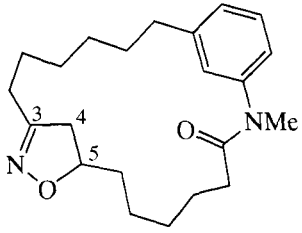
d: R^1 = Me, X = $(CH_2)_2$, R^2 = CH_2Ph

counterparts" is confirmed, while the other three cases are "exceptions." As a consequence, the use of this coupling constant can lead to an incorrect assignment.

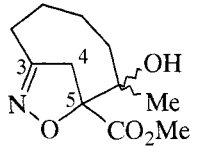
The only general and reliable NMR diagnostic feature is the relative chemical shift of H5; this proton always resonates at slightly lower fields in *syn* (i.e., **1020** and **1022**) than in the corresponding *anti* diastereoisomers, (i.e., **1019** and **1021**). Notwithstanding the small difference ($\leq$ 0.2 ppm) observed, this criterion seems to be without exceptions. A noteworthy feature of NMR data of compounds **1019–1022** is that there is no strong difference between the couplings involving H4 and H5 ($J_{4,5}$) related to whether they are in a *trans* or *cis* relationship.

4.4.1.5. Miscellaneous Data

Compounds **1023**[19/84] and **1024**[77/84] have a bridge between positions 3 and 5. Owing to the very large size of this bridge in **1023**, its ^{1}H NMR spectrum exhibits a pattern, as far as the isoxazoline protons are concerned, very similar to that of a monocyclic 3,5-disubstituted-2-isoxazoline.

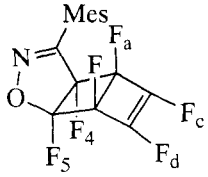


1023
$\delta(CDCl_3)$: 2.54 (H4, $J_{4,4'}$ = 17.0 Hz, $J_{4,5}$ = 6.0 Hz), 2.84 (H4', $J_{4',5}$ = 10.0 Hz), 4.60 (H5)



1024
$\delta(CDCl_3)$: 149.3 (C3), 34.6 (C4), 100.1 (C5).

Finally compound **1025**[10/73] provides chemical shifts of fluorine nuclei at positions 4 and 5 of the isoxazoline ring.



1025

F4	F5	Fa or Fb[a]	Fc or Fd[a]
82.7	40.0	104.9, 110.6	40.0, 43.4

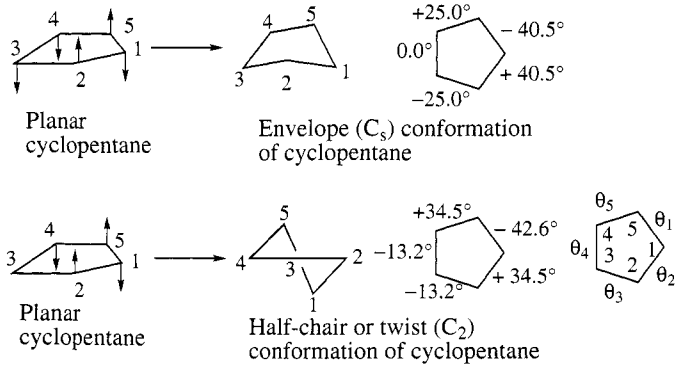
Ref. 10/73; δ(in ppm to high field of external trifluoroacetic acid; acetone)
[a]Not individually assigned

4.4.2. NMR Data and Conformational Behavior of Fused Isoxazolidines

4.4.2.1. Introduction

Going from 2-isoxazolines to isoxazolidines, the problem of assigning stereochemistry to the heterocyclic ring on the basis of NMR data becomes more complicated owing to the presence of a pyramidal nitrogen atom, which can undergo inversion at a rate that is dependent on substituents on nitrogen, and of a further possible stereogenic center at position 3 in addition to those at positions 4 and 5.

Moreover, in the case of isoxazolidines, we are dealing with a saturated five-membered ring, that is, with a system for which there is no highly favored ("natural") conformation.[1/94] The two most stable conformations of cyclopentane [envelope (E, which exhibits point-group symmetry C_s) and half-chair or twist (T, which belongs to the point group C_2), with the envelope conformation slightly more stable (by 0.5 kcal/mol)][4/59] are sketched in Scheme 4.42, where the ring torsion angles [MM2 Molecular Mechanics & calculations] are also reported. In the envelope conformation C2, C3, C4 and C5 lie in the same plane with C1 as the out-of-plane atom (E_{C1}), while in the twist conformation C2, C3, C4 and the binary axis define a plane which bisects the C1–C5 bond ($^{C5}T_{C1}$). Actually, there are 10 mutually indistinguishable envelope forms (five with one of the carbon atoms in turn pointing up and five with one of the carbon atoms pointing down) and 10 half-chair forms (5 mutually indistinguishable with the 5 pairs of adjacent atoms located at the site of maximum pucker of the half-chair and 5 that are the enantiomeric counterpart of the former five forms since the half chair form is chiral). The barriers between the E and T forms are very low, and cyclopentane is characterized by a rapid conformational flux among the 10 C_2 and 10 C_s conformations, which alternate with each other in the so-called pseudorotation circuit. Pseudorotation is the "apparent" rotation of the out-of-



Scheme 4.42

plane atom around the ring even if each atom actually moves perpendicularly to the ring. Along this circuit the molecule never passes through the high-energy planar form, but the intermediate conformations between C_2 and C_s have no symmetry ($C1$).[36/75] Pseudorotation has also been defined as the passage of a ring possessing a symmetry plane through an atom into one with an axis of symmetry bisecting the bond adjacent to that atom and vice versa.[39/67]

Scheme 4.42 shows the displacements parallel to the fivefold axis which lead from a planar regular pentagon to the two distinct kinds of ring puckering of the E and T forms. The quantitative specification of puckering in a regular five-membered ring can involve either the five torsion angles θ_j about the ring bonds[38/67] or the displacements (z_i), of the five atoms, perpendicular to a mean plane ($z = 0$), which corresponds to the reference planar form.[36/75]

Thus, the torsion angles of any of the infinity of forms, which a regular cyclopentane can assume in the pseudorotation course, are given by equation (4.1).[38/67] In (4.1) θ_{max} is the maximum value that a torsion angle can adopt

$$\theta_j = \theta_{max} \cos[\psi + 4\pi(j\text{-}1)/5] \quad \text{with } j = 1, 2, 3, 4, 5 \tag{4.1}$$

(i.e., $\theta_{max} = 42.6°$ in the twist form, Scheme 4.42) and ψ is a phase angle along the pseudorotation circuit, describing various kinds of puckering. If ψ is set to 0°, we have a half-chair form (actually the half-chair form of Scheme 4.42 if one uses $\theta_{max} = -42.6°$) and equation (4.1) gives the simultaneous variation of the torsion angles θ_1–θ_5. As ψ goes from 0° to 360°, the structure goes through the 10 T forms (ψ = 0°, 36°, 72°,...,324°) and the 10 E forms (ψ = 18°, 54°, 90°,...,342°), with the two forms alternating at 18° intervals passing through intermediate conformations of no symmetry.

Likewise, the puckering of a regular cyclopentane can be described, according to equation (4.2),[36/75] with a set of out-of-plane displacements z_i (parallel to each other and perpendicular to the reference plane $z = 0$) of atoms i, related to two puckering parameters, that is, an overall puckering amplitude q and a pseudorotation phase angle φ. Thus, the angle φ describes the movement of puckering around the five-membered ring (starting at an arbitrarily defined origin), and q tells us how far (0.43 Å in the case of cyclopentane) an atom can move above and below the average plane of the ring.[1/94] A factor for normalization [$(2/5)^{1/2}$] is included, so equation (4.3) also holds. In the case of a five-membered ring the lowercase q also gives the "total puckering amplitude" Q.[36/75] Using equation (4.2), the E forms (in which atoms 1, 2, 3, etc. progressively play the role of the out-of-plane atom) correspond to φ = 0°, 36°, 72°, and so on, while the T forms correspond to φ = 18°, 54°, 90°, and so forth:

$$z_i = (2/5)^{1/2}\, q \cos[\varphi + 4\pi(i-1)/5] \quad \text{with } i = 1, 2, 3, 4, 5 \tag{4.2}$$

$$\Sigma_i z_i = 0 \quad \text{and} \quad \Sigma_i z_i^2 = q^2 = Q^2 \tag{4.3}$$

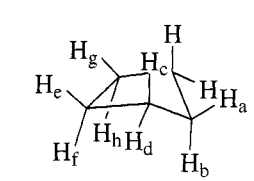
Although the preceding discussion has been in terms of a regular pentagon, given any puckered ring of five nonequivalent atoms (e.g., isoxazolidines) a

reference plane $z = 0$ can be chosen so that displacements perpendicular to this plane are given by equation (4.2) for some q,φ pairs.[36/75]

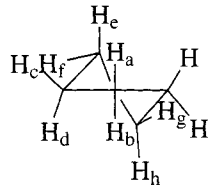
To underline a difference between a regular cyclopentane and a five-membered ring with unequal bond lengths and angles, such as isoxazolidines, it should be noted that for $\varphi = 0$ we have in both cases an envelope conformation with apex at atom 1, and this leads to $z_2 = z_5$ and $z_3 = z_4$. However , this condition implies coplanarity of atoms 2–3–4–5 in the regular cyclopentane but not in a general five-membered ring.[36/75]

What is most interesting to us is that in substituted isoxazolidines there could be a large number of conformational minima [in addition to the 20 conformational cyclopentane minima (10 half-chairs and 10 envelopes) other minima (in principle infinite) can be exhibited by a general substituted heterocyclopentane)] of slightly different energy on the pseudorotation circuit that can convert into each other in fast processes. In other words, the conformational "softness" of five-membered rings gives rise, as a rule, to shallow potential-energy wells so that ring conformations are seldom well defined. As a consequence, the preferred conformation of any one isoxazolidine is likely to be different from that of any others, and we can only loosely speak of distorted envelope and distorted half-chair conformations. Moreover, in the case of fused isoxazolidines the fused rings tend to impose their own conformation so that the actual structure is a compromise that minimizes angle and torsion strains as well as interactions between substituents in all of the rings. For sake of simplicity, it may be useful to assume that the isoxazolidine ring adopts an envelope or a twist conformation, but we must be aware that actually it adopts a conformation somewhere in between these two structures.

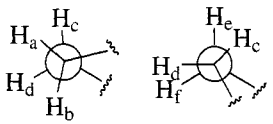
As far as torsion angles between vicinal protons in five-membered rings are concerned, Table 4.26 reports their absolute values for E and T forms of the parent cyclopentane. It is quite evident that torsion angles between *cis* protons span a relatively small range (i.e., from 16° to 48° in the T form and from 0° to 46° in the E form), whereas torsion angles between *trans* protons cover a much larger range (i.e., from 74° to 169° in the T form and from 75° to 167° in the E



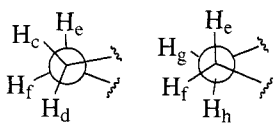
Envelope (E) conformation



Twist (T) conformation



Newman projections of the E conformation



Newman projections of the T conformation

TABLE 4.26. EXOCYCLIC TORSION ANGLES [H_xCCH_y, (°), ABSOLUTE VALUES (MM2 CALCULATIONS)] IN THE ENVELOPE AND TWIST CYCLOPENTANE FORMS[a]

Protons involved	Envelope H_xCCH_y	Twist H_xCCH_y	Protons involved	Envelope H_xCCH_y	Twist H_xCCH_y
H_aCCH_c	45.0	15.8	H_dCCH_e	90.1	160.3
H_aCCH_d	75.3	136.0	H_dCCH_f	29.0	38.9
H_bCCH_c	166.7	103.6	H_eCCH_g	0.0	47.6
H_bCCH_d	46.3	16.7	H_eCCH_h	119.8	168.8
H_cCCH_e	30.7	40.8	H_fCCH_g	119.8	73.6
H_cCCH_f	149.8	80.6	H_fCCH_h	0.0	47.6

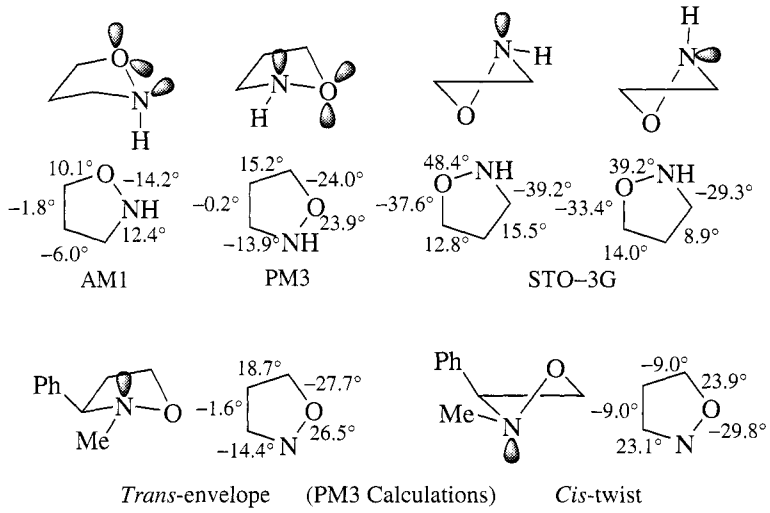
[a]The E and T forms depicted above are not meant to represent two consecutive forms on the pseudorotation circuit but only two general E and T forms.

form). What is more important, is that in the latter range we can find values (in particular 90° for H_dCCH_e in the E form and 81° for H_cCCH_f in the T form) that, according to the Karplus relationship,[61/80] should lead to small coupling constants as well as values (i.e., 167° for H_bCCH_c in the E form and 169° for H_eCCH_h in the T form) for which coupling constants even larger than *cis* coupling constants are to be expected. The obvious conclusion of these observations is that there is not any room left to use vicinal coupling constants as a general and reliable diagnostic feature to definitely assign a *cis/trans* relationship between protons in both monocyclic and fused polycyclic isoxazolidines. As a corollary, coupling constants can certainly help in conformational analysis of these systems but cannot give a definitive answer to this problem.

The problem of assigning *cis/trans* stereochemistry to vicinal position of isoxazolidines can at present satisfactorily solved by NOE experiments, given that vicinal *cis* protons give rise to significant (≥ 3–6%) NOE effects, which, in contrast, are, as a rule, almost negligible when the vicinal protons involved are *trans* to each other.

At this point it should be stressed that the routinely used molecular mechanics and semiempirical MO calculations do not provide, for the time being, a satisfactory answer to isoxazolidine conformational problem as these methods are not properly parameterized to deal with isoxazolidine derivatives and high level ab initio methods, in particular for the large systems that are of interest to experimentalists, are (or, better, were) out of reach of most researchers.

Anyway, the only minimum on the potential energy surface of the parent isoxazolidine found by AM1 calculations is a rather flat envelope (Scheme 4.43) conformation with nitrogen as the out-of-plane atom (E_N) and N–H in a pseudoaxial position, while an envelope conformation with oxygen as the out-of-plane atom (E_O) and N–H in a pseudoequatorial position is the minimum for PM3 calculations (Scheme 4.43)[57/91]. The minimal basis-set (STO-3G) (Slater-type orbitals, 3-Gaussian) ab initio method gives two minima of similar energy corresponding to pseudoaxial NH and pseudoequatorial NH (the former is more stable by 0.8 kcal/mol) derivatives of a distorted (^NT_O) half-chair form with the two heteroatoms in the most puckered region of the ring.[57/91] These data,

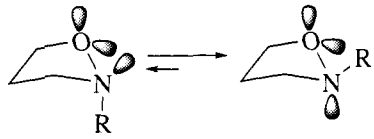


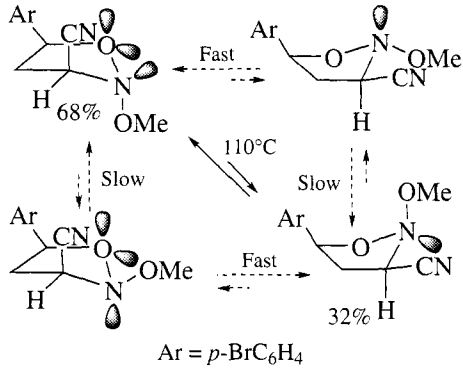
Scheme 4.43

while confirming the very high conformational flexibility of the isoxazolidine ring, allow one to assume that there is a slight intrinsic tendency of the heteroatoms, in particular the nitrogen atom, to be located in the most puckered region of the ring in both half-chair and envelope conformations of isoxazolidines. This observation can be interpreted as a result of an attempt by the system to induce staggering between lone pairs in order to minimize lone-pair/lone-pair repulsions of the 1,2-oxaza moiety (we have used the "rabbit ear" model to depict the oxygen lone pairs).[70/87]

The global minimum of *N*-methylisoxazolidine in AM1 and PM3 calculations, respectively, exhibits the same conformation (and with similar puckering) of the parent isoxazolidine. As for 2,3-disubstituted isoxazolidines, PM3 calculations show that the most stable conformation of 2-methyl-3-phenylisoxazolidine is a *trans*-envelope conformation with oxygen as the out-of-plane atom and methyl group in pseudoequatorial position (see *trans* envelope in Scheme 4.43). However, this conformation is only slightly more stable (0.3 kcal/mol) than a twist conformation with substituents *cis* to each other (*cis*-twist in Scheme 4.43). In the case of the 2,3-diphenyl derivative, PM3 calculations suggest that the conformational choice of the heterocyclic ring also depends on the conformational choice of the *N*-phenyl substituent.[57/91]

On the experimental side, PES (photoelectron spectroscopic) data of *N*-methyl and *N-tert*-butylisoxazolidine were interpreted as indicating the presence of a mixture of pseudoequatorial and pseudoaxial (the former is dominant, 10:1 for *t*-Bu and 4:1 for Me at 20°C, Scheme 4.44) isomers of the same envelope conformation (with N as the out-of-plane atom).[46/78] In general, one can assume that alkyl and aryl substituents on the nitrogen atom feel more comfortable, other things being equal, in the pseudoequatorial position with the lone pair in the pseudoaxial position.





Scheme 4.44

X-Ray analysis of monocyclic *N*-methoxyisoxazolidines (see Part 1) indicates that these compounds adopt an envelope conformation with the nitrogen atom as the out-of-plane atom and that the methoxy group always occupies a pseudoaxial position (Scheme 4.44). This structure is favored by the "anomeric" antiperiplanar stabilizing interaction between the pseudoaxial oxygen lone pair and the N–OMe bond. The alkoxy group on the nitrogen atom, as a result of its relatively strong stereoelectronic effect, is probably the only substituent capable of imposing a well-defined conformational choice to the isoxazolidine derivatives. In fact, the steric congestion due to other substituents can be easily alleviated by adjustment of the isoxazolidine ring conformation with a low energy cost so that even very bulky groups can be accommodated in both pseudoaxial and pseudoequatorial positions.

Another important point to take into account in addressing configurational and conformational analysis of monocyclic and polycyclic isoxazolidines is that the presence, in these derivatives, of an oxygen atom attached to a nitrogen atom leads to a marked increase in the inversion barrier of the latter, making the inversion process much slower than the pseudorotation process. In fact, it is well known that nitrogen inversion in monoaza five-membered ring (typically barriers are in the range 8–15 kcal/mol) is already significantly slower than pseudorotation (barriers to this process are of the order of 0–4 kcal/mol),[1/92] and the difference in rate between the two processes must increase on going to isoxazolidines. This is to say that in all isoxazolidine derivatives, either (1) nitrogen

inversion and conformational change occur in the same step or (2) the slow nitrogen inversion is followed by a very fast conformational flipping [see the equilibrium of 2-methoxy-3-cyano-5-(p-bromophenyl)isoxazolidine in Scheme 4.44].[22/76,46/76]. The effect of the oxygen of the ring can be reinforced by the effect of the oxygen of a *N*-substituent (see Part 1) as demonstrated by *N*-methoxyisoxazolidines (Scheme 4.44) whose invertomers are stable at room temperature and can be isolated in a pure state.

As for NMR spectra of isoxazolidines, one can safely assume that the slow processes that reveal themselves through pronounced line broadening involve nitrogen inversion. Poorly resolved room-temperature NMR spectra are actually everyday experience for researchers in the isoxazolidine field. In fact, even when one invertomer is highly dominant, the presence of small amounts of the other invertomer should lead to significant broadening in the presence of a relatively slow equilibration process and of a substantial frequency difference (favored by the use of high-field NMR spectrometers) between the absorptions of the nuclei of the two invertomers. This intricacy may be easily remedied by recording spectra at low and high temperature in order to attain both fast and slow exchange limits ($\leq -60°C$ and $\geq 60°C$ usually suffice for a 300-MHz spectrometer).

4.4.2.2. 4,5-Fused Isoxazolidines

4,5-Fused isoxazolidines are usually prepared by cycloaddition of a cyclic nitrones to cyclic olefins. Table 4.27 gathers the ^{1}H-NMR and ^{13}C-NMR data for

TABLE 4.27. ^{1}H- and ^{13}C-NMR DATA [$\delta(CDCl_3)$, J(Hz)] OF ISOXAZOLIDINES **1026–1030**,[12/74,57/91] **1031–1032**,[15/71] **1033–1034**,[17/88] AND **1035–1036**[17/82]

Compound	NMe	H3	H4	H5	*J*3,4	*J*4,5	C3	C4	C5	NMe
1026	2.72	3.49	3.39	4.72	6.6	6.5	74.1	51.2	76.5	43.3
1027a	2.60	3.69	3.11	4.75	7.3	5.8	76.3	53.2	82.8	43.9
1028a	2.50	2.89	2.95	4.70	8.3	6.8	81.0	58.0	83.0	42.5
1027b	2.82	4.10	2.41	4.59	5.2	3.5	76.5	48.0	75.1	46.0
1028b	2.72	3.41	2.49	4.28	7.5	6.7	77.6	50.8	75.7	44.7
1027c[a]	2.71	4.02	2.78	4.42	7.5	7.0	76.2	48.4	81.0	45.0
1028c	2.48	2.87	2.41	4.26	9.5	8.8	81.7	55.8	81.2	42.8
1029a	—	4.93	3.23	4.81	8.8	6.2	73.5	53.6	85.0	—
1030a	—	3.78	3.02	4.88	6.7	6.7	77.6	59.0	82.8	—
1031[b]	2.60	3.65	—	4.05	9.5	—				
1032[b]	2.55	3.15	—	4.25	9.5	—				
1033	3.30 4.20	6.15	3.60	5.10	8.8	9.0				
1034	3.40 3.63	5.30	3.90	5.20	12.7	9.3				
1035[c,d]	—	3.92	5.60	5.20	6.5	6.5	73.1	90.9	61.9	—
1036[c,d]	—	4.42	5.32	5.12	4.0	6.0	71.2	92.1	62.8	—

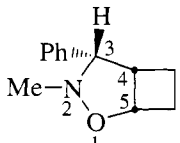
[a] At −50°C.

[b] Which is which between **1031** and **1032** has not been established.

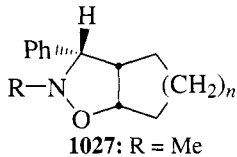
[c] DMSO-d_6.

[d] Coupling constants from the spectrum in benzene-d_6.

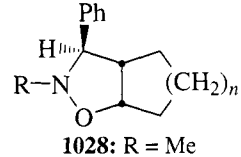
isoxazolidines of this type, namely, **1026–1036**. Along the series **1026**→ **1027a–c** there is a progressive increase in size of the fused carbocyclic ring.



1026

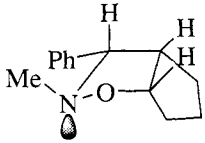


1027: R = Me
1029: R = Ph

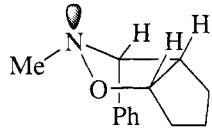


1028: R = Me
1030: R = Ph

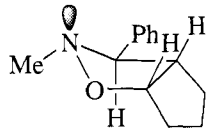
a: n = 1; **b:** n = 2; **c:** n = 4



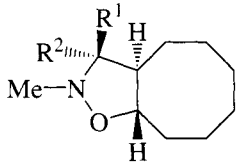
(i)-**1027a**



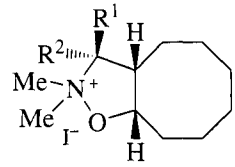
(o)-**1027a**



(o)-**1028a**

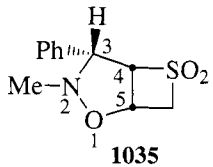


1031: R^1 = Ph, R^2 = H
1032: R^1 = H, R^2 = Ph

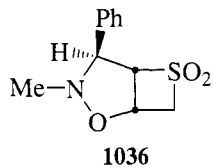


1033: R^1 = H, R^2 = Ph
1034: R^1 = Ph, R^2 = H

The expected "natural" order of the chemical shifts of the three carbon atoms of the heterocyclic ring is C4 << C3 ≈ C5. This expectation is borne out by the data of Table 4.27, which, however, also demonstrate that the presence of strong electron attracting groups at position 4 (e.g., **1035** and **1036**) leads to a complete reversal of absorptions (C4 >> C3 > C5).



1035

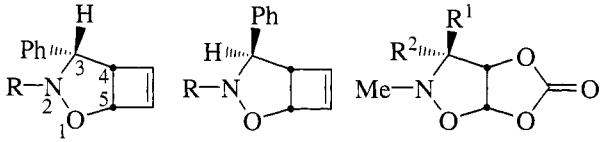


1036

Likewise the "natural" order of proton chemical shifts in isoxazolidines is H4 << H3 < H5. Also in the case of protons, the presence of a strong electron attracting group (e.g., SO_2 group in **1035** and **1036**) at position 4 causes H4 to absorb at lower fields than both H3 and H5, while reversal of chemical shift

between H3 and H5 is a much more frequent observation as it may happen even in the absence of a strong electron-withdrawing group at position 3. In the isoxazolidinium salt **1033** H3 is downfield of H5 by ≈ 1 ppm.

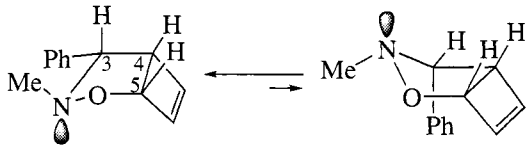
An interesting feature disclosed by Table 4.27 is that isoxazolidines fused to a carbocyclic ring and with a *cis* relationship between H3 and H4 (i.e., compounds **1027** and **1029**) exhibit higher chemical shifts for H3 than do their *trans* counterparts (i.e., compounds **1028** and **1030**). This observation [which, however, stands in contrast to the data for other *cis*/*trans* pairs as , e.g., **1035/1036** (Table 4.27), **1037/1038**, **1039/1040**, and **1043a/1044a** (Table 4.28)] reasonably should be traced back to the different shielding (or deshielding) of H3 in the two isomers by the nitrogen lone pair. Carrié [46/76] has observed that in *N*-methoxyisoxazolidines H3 *cis* to the nitrogen lone pair (in one invertomer) resonates slightly upfield relative to H3 *trans* to the nitrogen lone pair (in the other invertomer). However, in both invertomers the lone pair occupies a pseudoequatorial position (e.g., see Scheme 4.44 and **1041**), so that this finding is probably useless for discussing structures of *N*-alkyl and *N*-arylisoxazolidines in which the nitrogen lone pair can occupy both pseudoaxial and pseudoequatorial positions. In the case of the latter derivatives, a more important effect should result from an antiperiplanar *trans* relationship between a pseudoaxial lone pair and pseudoaxial H3, which, as a result of hyperconjugative effects, gives rise to shielding of this proton.[37/66] If the latter effect is dominant, H3 in the *trans* derivatives **1028** and **1030** (where it experiences a higher shielding) must be antiperiplanar to the



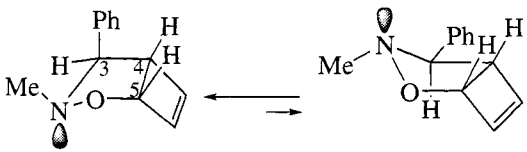
1037
a: R = Me;
b: R = Ph

1038
a: R = Me;
b: R = Ph;
c: picrate of **a**

1039: R^1 = H, R^2 = Ph
1040: R^1 = Ph, R^2 = H



(i)-**1037a** (o)-**1037a**



(i)-**1038a** (o)-**1038a**

nitrogen lone pair, as it is in the conformer (o)-**1028a**. This conclusion is supported by the high value of $J_{3,4}$ ($\geq$ 6.7 Hz) found in compounds **1028a–c** and **1030a**, which demonstrates (Karplus relationship) that the torsion angle between H3 and H4 is > 140° just as in structures of type (o)-**1028a**. As a necessary corollary of this explanation, the *cis* derivatives should prefer a conformation, such as (o)-**1027a**, in which H3 is not antiperiplanar to the nitrogen lone pair. Disappointingly, in sharp contrast to this latter statement, both MM2 and PM3 calculations indicate as more stable (by $\approx$1–3 kcal/mol) (i)-**1027a** (with H3 antiperiplanar to the nitrogen lone pair) than (o)-**1027a**.[57/91]

As far as coupling constants in 4,5-fused isoxazolidines are concerned, and starting with coupling constants involving H4 and H5, the vast majority of $J_{4,5}$ in *cis*-fused derivatives is in the range 5–9 Hz. However, they can be as small as $\approx$ 3 Hz when the fused ring is a cyclobutene ring (see compounds **1037** and **1038**, Table 4.28). Here again a widening of the H4C4C5 and H5C5C4 bond angles can be held responsible of this observation while the low value in **1039** and **1040** ($J_{4,5}$ = 4.0 Hz) can be attributed to the presence of two electron-withdrawing groups. Data for *trans*-4,5 coupling constants are missing.

It should be emphasized that *cis*-4,5 relationship for known 4,5-fused isoxazolidines is based on chemical reasoning, that is on the very reasonable assumption that 1,3-dipolar cycloaddition to *cis* double bonds of cyclic olefins takes place with retention of stereochemistry as a result of a concerted mechanism, more than on NMR data. Observed 4,5 coupling constants can be considered consistent with a *cis* relationship between the involved protons but in no way they prove it.

TABLE 4.28. ^{1}H NMR DATA [δ($CDCl_3$), J(Hz)] OF ISOXAZOLIDINES **1037–1044**

Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$	References
1037a	3.19	3.88	5.04	6.1	3.3	27/72, 57/91
1037b[a]	4.01	4.01	5.15	6.6	3.3	27/72, 57/91
1038a[a]	3.91	3.84	5.18	1.1	3.3	27/72, 57/91
1038b	4.90	3.89	5.35	<0.5	3.1	27/72, 57/91
1038c	5.15	4.20	5.73	<0.5	3.3	27/72, 57/91
1039	3.58	5.20	6.20	4.0	5.0	29/82
1040	4.34	5.31	6.19	<0.5	5.5	29/82
(i)-**1041**[b]	4.51	4.09	5.13	8.3	7.3	22/76
(o)-**1041**[b]	4.61	4.27	5.20	8.9	7.5	22/76
(i)-**1042**[b]	4.63	4.21	5.18	0.6	7.6	22/76
1043a	3.95	3.83	5.02	8.8	7.8	57/91
1043b	4.92	4.04	5.27	9.0	7.8	57/91
1044a[c]	4.22	3.84	5.05	3.8	7.5	57/91
(i)-**1044a**[d]	4.65	3.98	5.18	<0.5	7.5	57/91
(o)-**1044a**[d]	3.82	3.94	5.21	7.8	7.8	57/91
1044b	5.75	4.00	5.09	0.6	7.5	57/91

[a] Coupling constants from the spectrum in benzene-d_6.
[b] In acetone-d_6.
[c] At 50°C, δ_{Me} = 2.54.
[d] At −50°C, δ_{Me} = 2.38 and 2.76, respectively, for (i)-**1044a** and (o)-**1044a**.

It is also very interesting to compare *cis* and *trans* coupling involving H3 and H4 ($J_{3,4}$) of compounds **1026–1036** (Table 4.27). Thus, $J_{3,4\text{-}cis}$ is smaller than $J_{3,4\text{-}trans}$ in the **1027a/1028a**, **1027b/1028b**, and **1027c/1028c** pairs, $J_{3,4\text{-}cis}$ has the same value as $J_{3,4\text{-}trans}$ in the **1031/1032** pair, and $J_{3,4\text{-}cis}$ is larger than $J_{3,4\text{-}trans}$ in the **1029a/1030a**, **1033/1034**, and **1035/1036** pairs. It is quite evident that neither is the expectation of a higher value for *cis*-3,4 as compared to *trans*-3,4 coupling constants fulfilled by these data nor do they leave room for the possibility of using relative values of $J_{3,4}$ as general rule to reliably establish relative configuration of two epimers at position 3.

Actually the relative configurations of stereogenic centers at positions 3 and 4 of the *N*-methyl derivatives **1027**, **1028**, **1035**, and **1036** were firmly proved by chemical methods,[12/74] while in the case of the *N*-phenyl derivatives **1029a** and **1030a**, structure assignment is based on the significant (≈5%) intensity enhancement of H4 signal in the former compound in comparison to the very small effect on the same proton observed in the latter compound, on irradiation of H3.[57/91] NOE experiments also secured attribution of structures to *N,N*-dimethylisoxazolidinium salts **1033** and **1034**. This latter, a *trans*-3,4 derivative, seems to hold the record of the *trans*-3,4 coupling constants ($J_{3,4}$ = 12.7 Hz).

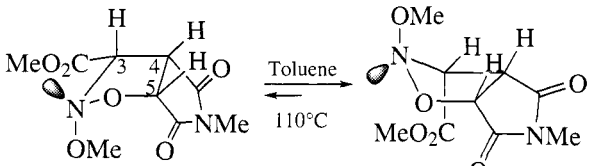
Are we left with the disappointing conclusion that vicinal coupling constants, in particular $J_{3,4}$, are completely useless for determining *cis/trans* relationships in 4,5-fused isoxazolidines?

Actually, a value of $J_{3,4}$ close to 0 in 4,5-fused isoxazolidines can reliably be taken as proof of *trans* relationship between H3 and H4 as well as of the presence of a highly dominant conformation, that is, an "inward"* envelope-like conformation [e.g., (i)-**1038a**]. In this conformation the torsion angle between H3 and H4 is very close to 90°, thus giving rise to a very small value for the related *J*. A very small $J_{3,4}$ also eliminates (in the fast exchange limit) the presence, in equilibrium with the *trans*-3,4-(i) conformation, of substantial amounts of the *trans*-3,4 "outward"* conformation [e.g., (o)-**1038a**] in which the antiperiplanar relationship between H3 and H4 should result in a high *J* (> 6.0 Hz).

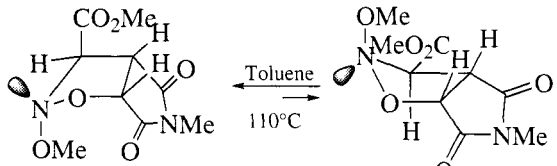
On the other hand, a $J_{3,4}$ close to 0 cannot be consistent with a *cis* relationship between these two protons. Torsion angles between *cis* protons [e.g., H3 and H4 in both "inward" and "outward" conformations, (i)-**1037a** and (o)-**1037a**] in five-membered rings (even in distorted rings) are certainly far from 90° [they should be less than 50°; see Table (4.26)] and, consequently, should give rise to significant coupling even in the presence of electron-attracting substituents (which tend to decrease vicinal coupling constants). In fact, $J_{3,4}$ for 4,5-fused isoxazolidines, with a bona fide *cis*-3,4 relationship, are, as a rule, higher than 5–6 Hz (the lowest reported value is that of **1039**, 4.0 Hz; see Table 4.28).

*Throughout we have used the (i) and (o) descriptors for the envelope conformations of five-membered rings fused to other rings. The (i) descriptor indicates the envelope conformation whose flap points "inward," whereas the (o) descriptor is used when the flap of the envelope points "outward" (i.e., the atom of the five-membered ring at the apex is *syn* and, respectively, *anti* with respect to the fused ring).

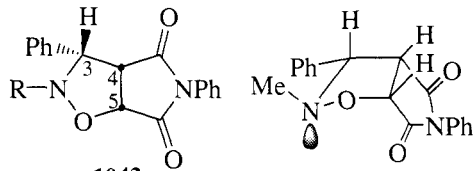
Compounds **1037–1044** provide examples in which the presence of fused planar rigid four or five-membered rings locks the C3–C4 and O–C5 bonds of the isoxazolidine moiety in the same (or almost the same) plane, thus forcing it to adopt an envelope-like (i.e., with C3C4C5O torsion angle $< 5°$ and nitrogen as the out-of-plane atom) conformation and reducing the conformational choice to that between (i) and (o) conformations. Consistently, $J_{3,4} \leq 1$ Hz in *trans* derivatives also indicates that they strongly prefer (i) over (o) conformation, as in the case of **1038a–c**, **1040**, **1042**, and **1044b** (R^1 = Ph).



(i)-**1041** 30% (o)-**1041** 70%

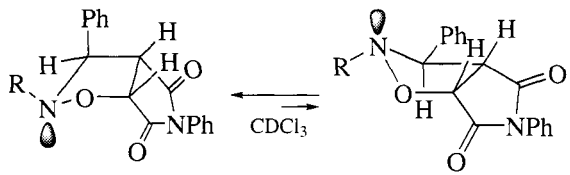


(i)-**1042** >95% (o)-**1042** < 5%



1043
a: R = Me;
b: R = Ph

(i)-**1043a**



(i) (o)

1044a: R = Me 72% 28% (at – 50°C)
1044b: R = Ph >95% < 5%

In the case of *trans*-**1044a** (R = Me), a strong broadening of the methyl signal and the presence of a very broad and flat signal attributable to H3 (at first sight H3 seems to be missing) in the room-temperature ^{1}H-NMR spectrum (at 300

MHz) discloses the presence of equilibrating isomers with an exchange rate in the coalescence region. At −50°C ($CDCl_3$) the isomer (i)-**1044a** (72%, $J_{3,4} \leq 0.5$ Hz) is prevalent over (o)-**1044a** (28%, $J_{3,4} = 7.8$ Hz), but population of two isomers is almost the same at +50°C as supported by the observation that at this temperature $J_{3,4}$ (3.8 Hz) is almost the average of $J_{3,4}$ in (i)-**1044a** and (o)-**1044a** (at −50°C).[57/91]

By contrast, the ^{1}H-NMR spectrum of the epimer of **1044a**, that is the 3,4-*cis* derivative **1043a**, did not appreciably change on passing from −50°C to +50°C,[57/91] in agreement with the presence of only one invertomer, most probably (see below) (i)-**1043a**.

Only one invertomer [with (i) envelope conformation, $J_{3,4} = 0.6$] was detected in the case of the *trans*-3,4 derivative **1042**, while two stable (at room temperature) isomers were isolated in the case of the *cis* derivative **1041**, specifically, (i)-**1041** and (o)-**1041**. As expected, both the latter invertomers exhibit high 3,4-coupling constants ($J_{3,4} \approx 8.5$ Hz) and convert into each other at 110°C. If one assumes, by analogy with the X-ray structure of *N*-alkoxy monocyclic and polycyclic isoxazolidines, that the methoxy group in **1041** and **1042** strongly prefers the pseudoaxial position (favored by anomeric stabilization), all configurational and conformational details of these structures are completely defined (as shown in the structural formulas). In particular, going from (i)-**1041** to (o)-**1041** inversion at the nitrogen atom is accompanied by flipping of the envelope.

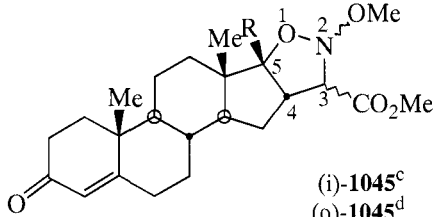
The position, whether pseudoaxial or pseudoequatorial, of the *N*-substituent in *N*-alkyl or *N*-aryl derivatives (such as **1037**, **1038**, **1043**, and **1044**) cannot be assigned on the basis of well-established conformational preferences for alkyl and aryl substituents. That depicted in structural formulas is consistent with the results of MM2 and semiempirical calculations. Actually these calculations can give at least a clue to this problem. Thus, they suggest that the *N*-methyl-*cis*-3,4 derivatives (e.g., **1037a** and **1043a**) should prefer the (i) conformation with both the methyl and phenyl group in pseudoequatorial position over the (o) conformation with methyl still in pseudoequatorial position while phenyl is now in pseudoaxial position. In the case of the *N*-methyl-3,4-*trans* derivatives (e.g., **1038a** and **1044a**), calculations predict that the (i) conformation with phenyl in pseudoaxial and methyl in pseudoequatorial position should be more stable than the (o) conformation with methyl and phenyl in a *trans* diequatorial disposition.

Notice how the H3 chemical shift (δ = 3.95) in *cis*-3,4 (i)-**1043a** is very similar to that (δ = 3.82) of the same proton in *trans*-3,4 (o)-**1044a** (in both compounds H3 is antiperiplanar to the nitrogen lone pair) and significantly lower than that (δ = 4.65) of H3 in *trans*-3,4 (i)-**1044a** (H3 is synclinal to the lone pair). Thus for these compounds (at variance with what found in the case of **1027–1030**) there is full agreement between structures required for rationalization (based on the "antiperiplanar shielding effect" by the nitrogen lone pair) of the proton chemical shifts and the structures predicted as most stable by calculations. We may conclude that when H3 in the *trans*-3,4-isomer resonates downfield relative H3 in the corresponding *cis*-3,4-isomer, this is simply the

consequence of the fact that both the *cis* and *trans* isomers tend to adopt (i) conformations that, however, differ from each other by the relative orientation of H3 and the lone pair (antiperiplanar in the *cis* derivative).

The statement that the conformational flexibility of isoxazolidines make conformations deduced from NMR data tentative is nicely illustrated by conformational studies on **1045** and **1046**.[17/77,63/79]

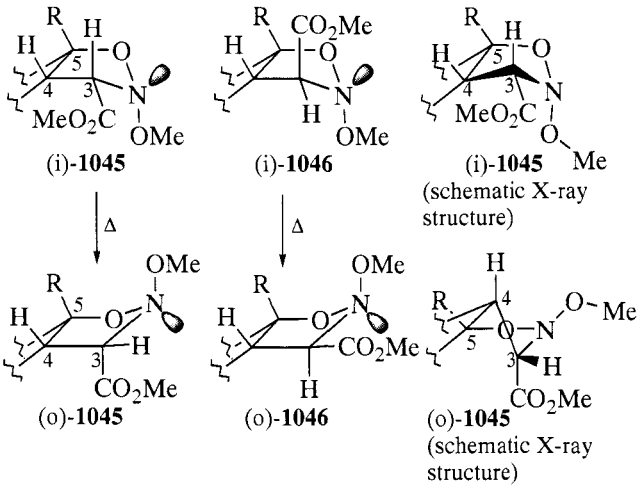
Steroidal isoxazolidines **1045** (a *cis*-3,4 derivative) and **1046** (a *trans*-3,4 derivative) (Schemes 4.45 and 4.46) were obtained from cycloaddition of (*E*)- and (*Z*)-*N*-methoxy-*C*-methoxycarbonylnitrone with 16-dehydroprogesterone at 20–30°C under high pressure (14,000 atm). In the reaction of (*Z*)-nitrone a 3:4 mixture of (i)-**1045** and (o)-**1046** is formed, deriving from *endo* (with respect to the polycyclic moiety of the dipolarophile) and *exo* transition states, respectively, with attack *anti* relative to the methyl group of the dipolarophile. Likewise (i)-**1046** and (o)-**1045** (2:1) are formed from the (*E*)-nitrone once again in a 100% facial selective attack. In both reactions only isoxazolidines in



1045 and **1046**
R = COMe

	H3[a]	$J_{3,4}$[b]	$^2J_{15N,H3}$
(i)-**1045**[c]	3.95	6.6	6.2
(o)-**1045**[d]	4.40	9.8	<0.1
(i)-**1046**[d]	3.60	2.0	–
(o)-**1046**[d]	3.61	7.6	5.4

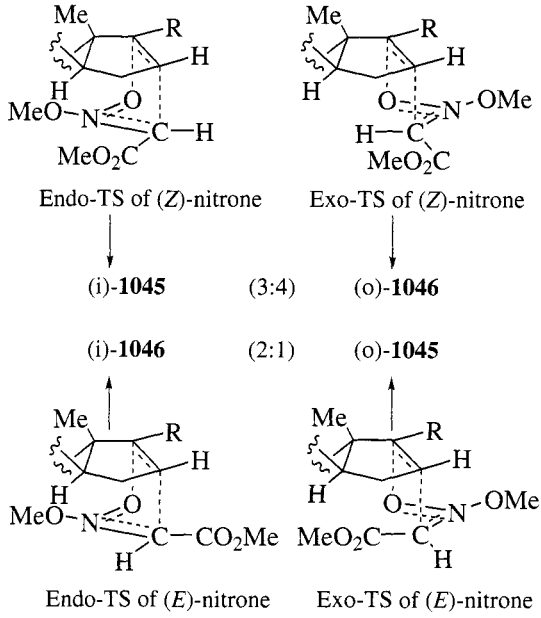
[a] δ; [b] Hz; [c] $CDCl_3$; [d] C_6D_6



(i)-**1045**
(i)-**1046**
(i)-**1045** (schematic X-ray structure)
(o)-**1045**
(o)-**1046**
(o)-**1045** (schematic X-ray structure)

Scheme 4.45

which the lone pair on the nitrogen develops on the nitrone face opposite to the one that interacts with the dipolarophile are produced (i.e., notice how in the schematic transition states the N-methoxy group is slightly shifted upward with respect to the nitrone plane, in Scheme 4.46).



Scheme 4.46

All the isomers were separated and characterized by ^{1}H-NMR and ^{15}N-NMR methods. The invertomers (conformers) (o)-**1045** and, respectively, (o)-**1046** are more stable than their counterparts (i)-**1045** and, respectively, (i)-**1046** and on standing, or melting, or refluxing in benzene the latter are easily transformed into the formers (Scheme 4.45).

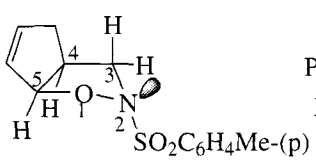
^{1}H- and ^{15}N-NMR data were considered fully consistent with envelope conformations, for the isoxazolidine moiety, in which the nitrogen atom occupies the out-of-plane position and the *N*-methoxy group a pseudoaxial position (Scheme 4.45).[17/77] A single-crystal X-ray structure of (i)-**1045** and (o)-**1045**[63/79] confirmed the configuration of the C3 stereogenic center as well as the pseudoaxial position of the methoxy group in both compounds. The solid-state torsion angle between H3 and H4 is smaller in (o)-**1045** (27°, $J_{3,4}$ = 9.8 Hz) than in (i)-**1045** (46°, $J_{3,4}$ = 6.6 Hz) in accord with the larger coupling constant found in the former compound. However, solid state conformation of (o)-**1045** is a slightly distorted twist-like conformation [isoxazolidine ring torsion angles (°) (about NO bond, NC3 bond, C3–C4 bond, etc.): O–N–C3–C4–C5–O = 10.0, −30.0, 40.2, −34.0, and 13.7], with the C5, O, and

N atoms in the least puckered region of the heterocyclic ring. Moreover, solid-state conformation of (i)-**1045** is a distorted conformation half way between an envelope and a half-chair conformation [isoxazolidine ring torsion angles (°): O–N–C3–C4–C5–O = −16.3, 35.0, −40.0, 28.0, and −7.7] with C3 as the out-of-plane atom as shown in Scheme 4.45. Even if it is well known that solid-state conformations may be different from solution conformations, it is quite evident that the solid-state distorted twist conformations are as compatible with solution NMR data as the proposed envelope conformations.

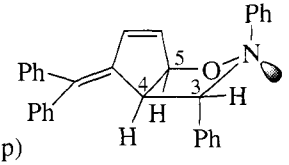
Crystal structures of others 4,5-fused isoxazolidines seem to indicate that (1) there is a tendency of the nitrogen atom to be located in the most puckered part of the isoxazolidine ring, and (2) the distorted envelope and half-chair structures of these fused isoxazolidines are slightly more flat than are related cyclopentane conformations.

For example, the rather flat conformation of **1047** (solid state)[65/83] features the nitrogen atom as *anti* with respect to the cyclopentene moiety, and it is difficult to classify this structure [isoxazolidine ring torsion angles (°): O–N–C3–C4–C5–O = 28.2, −32.3, 23.4, −6.5, and −13.3] as either envelope or half-chair. The nitrogen substituent adopts a pseudoaxial position and torsion angles H3C3C4H4 (26°) as well as H3′C3C4H4 (147°) are consistent with the finding that $J_{3,4} = J_{3',4} = 9.5$ Hz (Table 4.28), thus suggesting that the geometry of **1047** does not heavily change on passing from solid-state to chloroform solution.

The isoxazolidine ring of compound **1048** [torsion angles (°): O–N–C3–C4–C5–O = 33.6, −38.1, 28.0, −8.1, and −15.1] is somewhat more puckered than that of compound **1047**, the nitrogen atom is *syn* to the fused carbocyclic ring, and both phenyl substituents occupy a pseudoaxial position.[22/89] The torsion angle H3C3C4H4 (85°) nicely explains the absence of coupling between H3 and H4.



1047

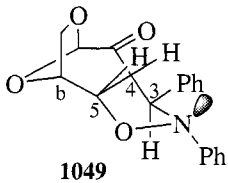


1048

The coupling between H3 and H4 ($J_{3,4}$ = 4.5 Hz) in **1049** suggests a *trans* relationship between these protons that is confirmed by the absence of NOE effects on H3 on irradiation of H4 and by X-ray analysis.[16/88,2/92] Crystal structure disclosed a distorted half-chair conformation [isoxazolidine ring torsion angles (°): O–N–C3–C4–C5–O = −48.3, 35.8, −12.0, −16.5, and 39.5] with the nitrogen atom *anti* to the fused bicyclic system, the two phenyl groups *trans* to each other and both in pseudoequatorial positions and the torsion angle between H3 and H4 of 129°. This angle on the basis of Karplus equation ($^3J = 7.76 \cos^2\theta$

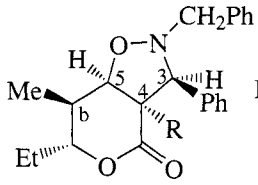
$-1.1\cos\theta + 1.4)^{61/80}$ should give rise to $J_{3,4} = 5.1$ Hz not far from the experimental value (4.5 Hz). Likewise, also calculated $J_{4,5}$ (7.1 Hz, H4C4C5H5 = 13.9°) and $J_{5,b}$ (1.8 Hz, H5C5CbHb = 72.1°) are in good agreement with the observed J values (6.8 and 1.3 Hz, respectively). Moreover, in **1049** the oxygen and nitrogen atoms are situated below and above (a $^{N}T_{O}$ conformation), respectively, the plane through C3, C4, and C5 by 0.389 and 0.303 Å. Paton et al. also realized that the puckering of the isoxazolidine ring is well described by equation (4.2) (see § 4.4.2.1) with $q = 0.431$ Å and $\varphi = 15.9°$ (oxygen is atom 1, nitrogen atom 2, etc.).[2/92]

The $J_{3,4}$ value in *cis*-**1050a** is exactly the same as $J_{3,4}$ in *trans*-**1051a** (8.5 Hz; Table 4.29) and cannot be used to choose between them. However, structures **1050a** and **1051a** unambiguously follow from those of the corresponding methyl derivatives **1050b** and **1051b**, respectively, on the basis of NOE experiments and X-ray diffraction studies.[20/85] On irradiation of Me at position 4, intensity enhancements of 0% and 12% for H3 and H5, respectively, were observed in **1051b**, whereas in **1050b**, NOE effects were similar for both H3 and H5 (13% and 15%, respectively). Then, crystal structure of *cis*-**1050b** (R = Me) demonstrated that this compound adopts an "inward" envelope conformation [i.e., (i)-**1050b**, torsion angles (°): O–N–C_3–C_4–C_5–O = 46.9, −45.2, 27.1, 0.7, and −28.6] characterized by strong puckering and with nitrogen as the out-of-plane atom. However, an "inward" envelope conformation is certainly not adopted by

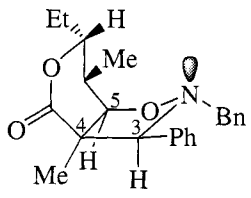


1049

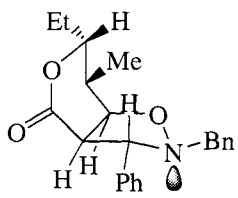
O–N–C_3–C_4–C_5–O
−48.3° 35.8° −12.0° −16.4° 39.5°



1050 **a:** R = H **1051**
b: R = Me



(i)-**1050b**



(o)-**1051a**

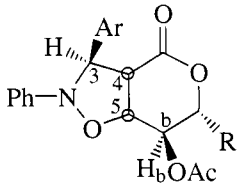
TABLE 4.29. ^{1}H NMR DATA [$\delta(CDCl_3)$, J(Hz)] OF ISOXAZOLIDINES **1047–1055**

Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$	$J_{5,b}$	References
1047[a,b]	2.90	3.15	5.48	9.5	7.8[c]	—	65/83
	4.38			9.4			
1048[d]	4.96	4.24	5.45	0	7.0	—	22/89
1049[e]	4.86	3.34	4.64	4.5	6.8	1.3	16/88
							2/92
1050a	4.34	3.95	4.51	8.5	8.5	3.5	20/85
1051a	3.73	3.47	4.46	8.5	8.5	3.0	20/85
1052	5.29	4.00	4.95	8.3	9.1	4.0	60/85
1053	4.63	3.52	4.93	5.4	6.8	3.0	60/85
1054	5.22	3.81	4.85	8.0	9.3	8.8	60/85
1055	4.88	3.57	4.83	5.1	9.1	6.1	60/85

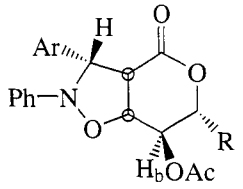
[a] $J_{3,3e} = 11.9$ Hz
[b] $\delta_{C3} = 55.1$, $\delta_{C4} = 43.3$ and $\delta_{C5} = 93.0$.
[c] H4C4C5H5 = 8°.
[d] $\delta_{C3} = 71.2$, $\delta_{C4} = 58.1$, and $\delta_{C5} = 87.1$.
[e] $\delta_{C3} = 70.7$ (or 72.9), $\delta_{C4} = 58.5$, and $\delta_{C5} = 77.8$.

trans-**1051a**, at least in $CDCl_3$ solution, as it would require $J_{3,4} \approx 0$ Hz in contrast to the high value (8.5 Hz) found. Conformation (o)-**1051a**, that is, an "outward" envelope conformation (or something like that), nicely rationalizes this J.

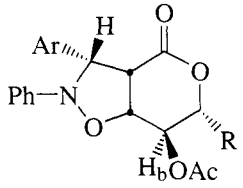
The larger values of $J_{3,4}$ in **1052** and **1054** as compared to those in **1053** and **1055** testify, according to the authors, to *trans*-3,4 configuration for the latter compounds and *cis*-3,4 configuration for the former compounds. This is certainly reasonable although not completely cogent. Similarly, the higher coupling constants between H5 and Hb ($J_{5,b}$) in **1054** and **1055**, relative to those in **1052**



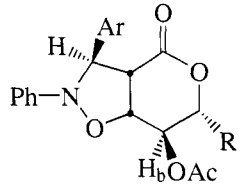
1052



1053



1054



1055

R = CH_2OAc, Ar = p-$MeOC_6H_4$

TABLE 4.30. ^{1}H- and ^{13}C-NMR DATA [δ($CDCl_3$), J(Hz)] OF ISOXAZOLIDINES **1055–1063**

Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$	C3	C4	C5	References
1056a	4.00	4.57	6.03	7.8	6.7	77.1	58.5	83.2	57/91
1056b[a]	3.38	4.51	6.09	8.2	6.8	79.6	63.1	83.8	57/91
1057[b]	5.43	4.13	5.65	2.0	5.0	69.5	71.9	80.0	20/81
1058[c]	5.39	4.41	6.09	4.0	6.0	70.4	75.0	78.2	64/83
									29/84
1059	5.68	5.91	5.57	<0.5	7.0				24/80
1060a	4.94	3.95	5.92	7.7	5.5	72.9	51.0	105.1	28/82
1061a	5.03	3.75	6.01	2.0	5.5	73.6	50.1	108.7	28/82
1060b	5.04	4.25	6.02	8.4	6.5				21/83
1061b	4.67	3.87	6.25	5.2	6.6				21/83
1062	5.14	—	5.03	8.2	—	74.0	52.9	83.3	28/82
1063	4.77	3.61	5.02	4.3	6.0	75.3	53.7	83.5	28/82

[a] At −30°C.
[b] $J_{5,b}$ = 0.7 Hz.
[c] H3C3C4H4 = 123.3° and H4C4C5H5 = 18.5° in the solid state.

and **1053**, suggest that the involved protons tend, in the former compounds, to adopt an antiperiplanar disposition. This array is attainable only if they are *trans* to each other, thus demonstrating the relative configuration of the stereogenic center at position b, next to position 5 of the isoxazolidine ring.

Further ^{1}H-NMR and ^{13}C-NMR data for isoxazolidine 4,5-fused to five-membered ring (i.e., **1056–1063**) are reported in Table 4.30, while ^{1}H-NMR data for isoxazolidines 4,5-fused to norbornane and bicyclo[2.2.2]octane skeletons are gathered in Table 4.31.

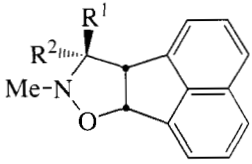
The value of $J_{3,4\text{-}cis}$ (≈ 8.0 Hz) does not change appreciably in compounds of Table 4.30, while $J_{3,4\text{-}trans}$ spans the range ≈ 0–8.2 Hz. Nothing can be said, on the basis of these data, about conformational choice of *cis* derivatives, while in the case of *trans* derivatives, conformational changes and related variations in

TABLE 4.31. ^{1}H-NMR DATA [δ($CDCl_3$), J(Hz)] OF ISOXAZOLIDINES **1064–1070**, **1073**, AND **1074**

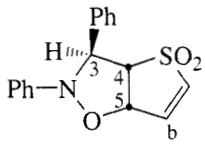
Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$	References
1064[a]	4.84	—	4.25	9.3	6.5	17/68
1065[a]	3.60	—	4.22	7.0	6.7	17/68
1066	3.74	2.71	4.35	6.8	6.5	11/80
1067	4.90	3.27	4.57	9.0	7.0	65/88
1068	4.08	3.14	4.56	7.3	7.3	65/88
1069	4.66	3.05	4.80	9.0	7.0	65/88
1070	4.00	2.98	4.83	7.3	7.3	65/88
1073[b]	3.89	3.37	4.69	8.6	8.3	57/91
1074[c]	3.19	2.88	4.61	9.1	8.3	57/91

[a] In CCl_4.
[b] δ_{OMe} = 3.46 and 3.84, δ_{NMe} = 2.62, $J_{4,a}$ = 3.3 Hz, and $J_{5,b}$ = 3.5 Hz.
[c] δ_{OMe} = 3.82 and 3.89, δ_{NMe} = 2.44, $J_{4,a}$ = 3.1 Hz, and $J_{5,b}$ = 3.3 Hz.

H3C3C4H4 torsion angles, which take place in order to lessen ring strains and steric interactions between substituents, are more clearly reflected in coupling constants. Here again a $J_{3,4\text{-}trans} \approx 0$ indicates the presence of a dominant "inward" envelope conformation [e.g., (i)-**1059**], $J_{3,4\text{-}trans} \approx 8$ Hz, an "outward" envelope conformation and $J_{3,4\text{-}trans} \approx 2$–5 Hz, either a flat conformation or a fast equilibrating (i)–(o) conformation mixture.



1056a: R^1 = H, R^2 = Ph
1056b: R^1 = Ph, R^2 = H



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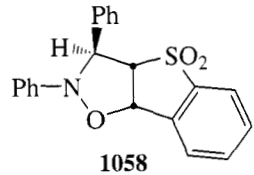

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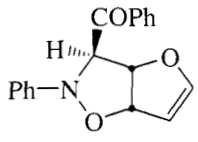

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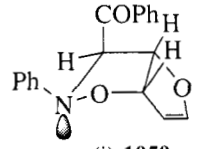
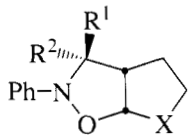
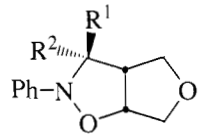


(i)-**1059**



1060: R^1 = H, R^2 = COPh
1061: R^1 = COPh, R^2 = H
a: X = O; **b**: X = S

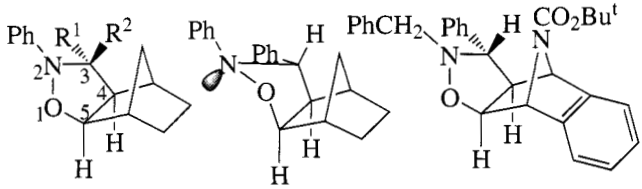


1062: R^1 = H, R^2 = COPh
1063: R^1 = COPh, R^2 = H

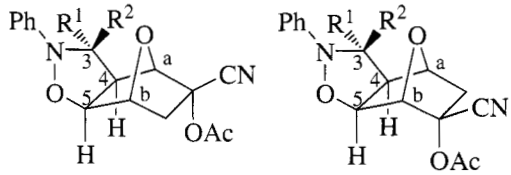
In the adducts of acyclic nitrones to norbornene derivatives (only *syn* adducts, relative to the methano bridge, are observed), coupling constants between H3 and H4 are, as a rule, always high and remarkably constant; *cis* coupling ($J_{3,4}$ = 9.0 Hz) is larger than *trans* coupling ($J_{3,4}$ = 7.0 Hz) by ≈ 2.0 Hz. In spite of this small difference, one can use this observation not only to choose which is which when pairs of epimers are formed but also to attribute configuration to the stereogenic center at position 3 of the isoxazolidine ring, even when only one epimer is produced. But caution is in order as this rule, which works well for isoxazolidines fused to a norbornane skeleton, does not hold for other systems as documented by **1073** and **1074**, in which the isoxazolidine ring is fused to a bicyclo[2.2.2]octane skeleton: $J_{3,4\text{-}trans}$ in the latter compound is slightly larger than $J_{3,4\text{-}cis}$ in the former compound.[57/91]

As for conformational details of adducts **1064–1074**, it is quite obvious that the rigid polycyclic skeleton imposes an envelope-like conformation on the

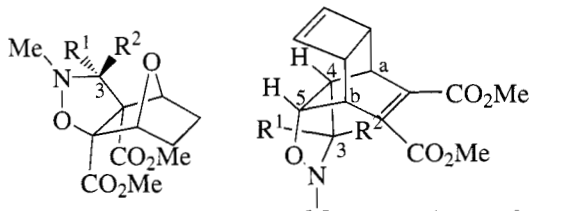
isoxazolidine ring with nitrogen as the out-of-plane atom. The relatively high value of $J_{3,4\text{-}trans}$ demonstrates that the nitrogen atom at the flap points outside [e.g., (o)-**1065**] in the case of *trans*-3,4 derivatives, while MM2 and PM3 calculations suggest that in the *cis*-3,4 derivatives the flap points inside [(i) conformation] with both the substituents at positions 2 and 3 in pseudoequatorial positions.



1064: R^1 = H, R^2 = Ph (o)-**1065** **1066**
1065: R^1 = Ph, R^2 = H



1067: R^1 = H, R^2 = Ph **1069:** R^1 = H, R^2 = Ph
1068: R^1 = Ph, R^2 = H **1070:** R^1 = Ph, R^2 = H



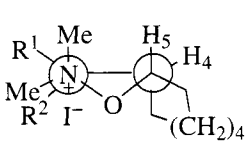
1071: R^1 = H, R^2 = Ph **1073:** R^1 = H, R^2 = Ph
1072: R^1 = Ph, R^2 = H **1074:** R^1 = Ph, R^2 = H

Relative configuration at C3 in **1071–1074** , not attributable on the basis of coupling constants, can safely be inferred from the substantial chemical-shift difference (≈ 0.4 ppm, owing to the shielding of one methoxy group by the 3-phenyl substituent) between the two methoxy groups in **1072** [δ($CDCl_3$) 3.15 and 3.84][14/81] and **1073** [δ($CDCl_3$) 3.46 and 3.84][57/91] as compared to almost the same chemical shift observed for these groups in **1071** [δ($CDCl_3$) 3.76 and 3.83][14/81] and **1074** [δ($CDCl_3$) 3.82 and 3.89].[57/91]

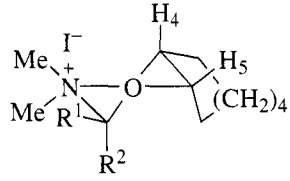
The *syn* stereochemisty of nitrone adducts to norbornene derivatives is obviously based on the absence of significant coupling between the isoxazolidine protons (at positions 4 and 5) and the bridgehead protons of the norbornane skeleton. In general, problems dealing with establishment of structure of diastereoisomers, resulting from attack of nitrones to the two diastereotopic

faces of plane nonsymmetric double bonds, are almost exactly the same as those discussed for the adducts from nitrile oxide cycloadditions, so there is not any need to discuss them again.

In the 1990s measurements of NOE effects for structural assignments have become a routine technique. The NOEDS study of isoxazolidinium salts **1033** and **1034** provides an example of the use of this technique in the isoxazolidine field (Table 4.32). The data of Table 4.32 unambiguously establish the relative configuration of the three stereogenic centers of the isoxazolidinium ring. Vicinal NOE between *trans* protons is significantly lower, as expected, than that between *cis* protons (e.g., NOE effects involving H3 and H4). The authors also suggest an envelope conformation, with oxygen as the out-of-plane atom, as consistent with the observed effects both for the *trans* and the *cis* derivative. However, the large coupling constant between H3 and H4 (J = 12.7 Hz) in the *trans* derivative, suggesting that they are involved in an almost exact antiperipla-



1033: R^1 = H3, R^2 = Ph
1034: R^1 = Ph, R^2 = H3



Twist-**1034**

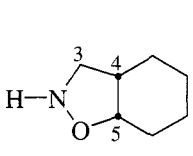
TABLE 4.32. NUCLEAR OVERHAUSER DIFFERENCE SPECTRA (NOEDS, η OBSERVED VALUES AS % OF η_{max})[a] OF ISOXAZOLIDINES **1033–1034**[17/88]

			1033			
	{H-*o*}[b]	{H3}	{H4}	{H5}	{NMe_{df}}	{NMe_{uf}}
H-o	—	12				9
H3	13		9	4	9	2
H4		8		9	5	
H5		4	8		8	
NMe_{df}[c]	2	8	6	8		8
NMe_{uf}[c]	6				6	
			1034			
	{H-*o*}[b]	{H3}[d]	{H4}	{H5}[d]	{NMe_{df}}	{NMe_{uf}}
H-o		5	9	4		5
H3	8		3		5	2
H4	10	6		7		2
H5	3		8			3
NMe_{df}[c]		6				2
NMe_{uf}[c]	4	3		3	2	

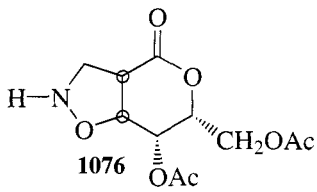
[a] Chemical shifts and coupling constants of **1033** and **1034** are reported in Table 4.27.
[b] Ortho protons of the phenyl substituent.
[c] df = downfield, uf = upfield.
[d] Irradiation affects both H3 (δ = 5.30) and H-5 (δ = 5.20), which are partly overlapped.

nar array, seems to be more convincingly explained by a half-chair conformation with oxygen and nitrogen atoms in the mean plane of the heterocyclic ring (i.e., T-**1034**).

To conclude this section, **1075**[15/77] and **1076**[25/89] represent examples of 2,3,3-unsubstituted-4,5-fused isoxazolidines, while **1077** represents that of a bisisoxazolidine.[41/69] Notice how in this latter compound the strong through-space deshielding effect of the two *cis* methoxycarbonyl groups causes H4 to resonate downfield relative to H3.



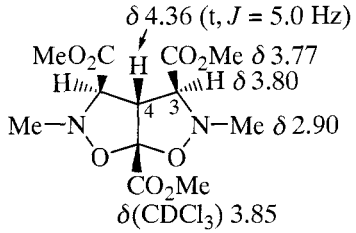
1075



1076

Compound	NH	H3	H3′	H4	H5	$J_{3,3'}$	$J_{3,4}$	$J_{3',4}$	$J_{4,5}$
1075	5.45	2.90	3.30	2.38	3.86	10.0	3.0	6.5	4.5
1076	—	3.23	3.58	3.69	4.45	10.0	6.3	8.5	8.1

References 15/77 and 25/89; $\delta(CDCl_3)$, J (Hz).

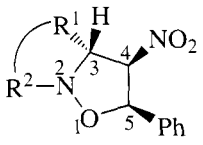


1077

4.4.2.3. 2,3-Fused Isoxazolidines

NMR data of several 2,3-fused isoxazolidines are reported in Tables 4.33–4.36 and Scheme 4.47. These data do not need detailed comments as they do not exhibit features that are strikingly different from those of monocyclic and 4,5-fused isoxazolidines. The trend in proton and carbon chemical shifts (in $CDCl_3$) of 2,3-fused isoxazolidines is as follows: H4 << H3 ≤ H5 and C4 < C5 ≤ C3. These orders can obviously be altered by the presence of electron-attracting substituents. For example, in **1078–1080** (Table 4.33) the signal of C4 is always at lower fields than those of both C3 and C5, while the signal of H4 is, in several cases, downfield that of H3. However, if proper attention is paid to the shielding

effects of substituents, the natural orders of carbon and proton chemical shifts can confidently be used to assign regiochemistry as, for example, in the case of compounds **1096–1109**.



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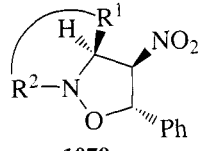

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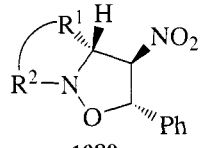
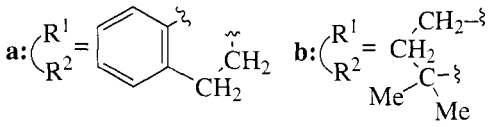
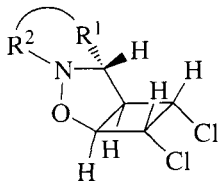
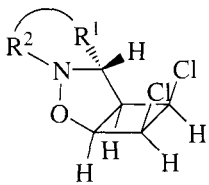


1080





1081



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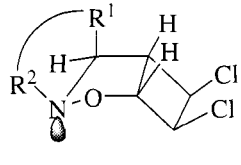
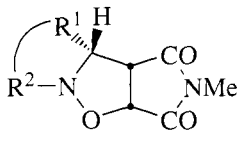


(i)-**1081**



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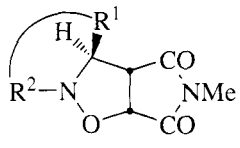

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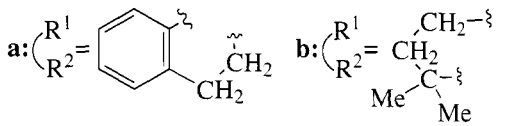
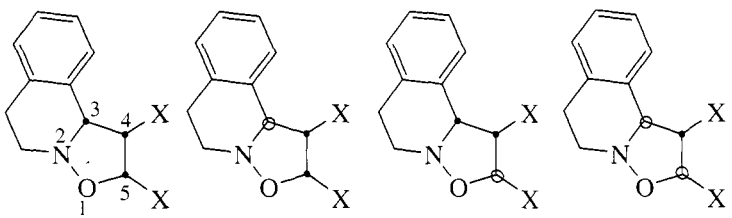
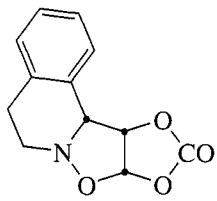




1085 **1086** **1087** **1088**

a: X = CO_2Me; **b:** X = CN; **c:** X = COPh; **d:** X = SO_2Ph; **e:** X = Ph



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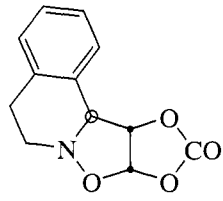

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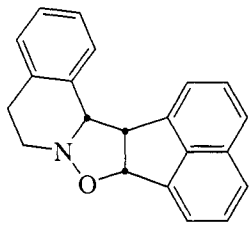

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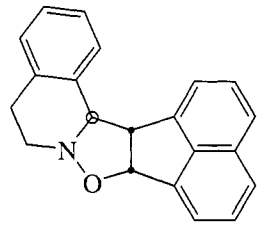
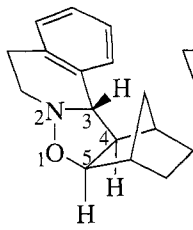


1092



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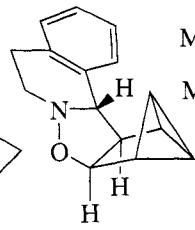

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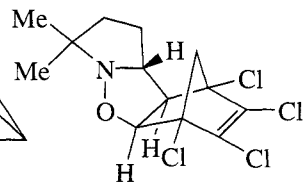
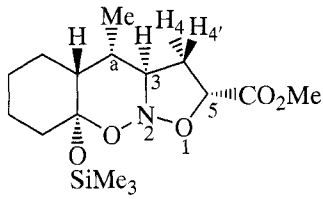


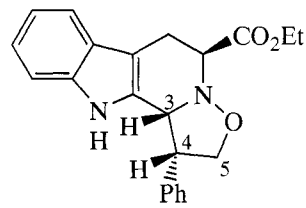
1095



1096

H3	H4	H4′	H5	$J_{3,4}$
3.54	2.22	2.64	4.99	7.5
$J_{3,4'}$	$J_{4,5}$	$J_{4',5}$	$J_{4,4'}$	$J_{3,a}$
11.7	3.4	10.4	11.8	1.2

Ref. 19/87; $\delta(CDCl_3)$, J(Hz)



1097

H3	H3	H5	H5′
4.10	4.10	4.62	4.70
$J_{3,4}$	$J_{3,4}$	$J_{4,5'}$	$J_{5,5'}$
8.1	4.5	3.6	8.5

Ref. 39/86; $\delta(CDCl_3)$, J(Hz)

Scheme 4.47

As for coupling constants some typical features are as follows: (1) $J_{4,4'}$ is always larger than $J_{5,5'}$ because this latter is decreased by the electron-attracting effect of the oxygen atom; (2) *cis* coupling between H4 and H5 is, as a rule,

TABLE 4.33. ^{1}H-NMR [$\delta(C_6D_6)$, J (Hz)] AND ^{13}C-NMR DATA [$\delta(CDCl_3)$] OF ISOXAZOLIDINES **1078–1080**[21/87]

Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$	C3	C4	C5
1078a	5.55	4.92	5.32	7.0	8.5	68.0	98.5	81.4
1079a[a]	4.80	5.15	5.95	9.0	6.0	68.1	100.7	84.3
1080a[a]	5.15	4.90	5.60	3.5	6.0	67.2	100.7	83.6
1078b	4.20	4.94	5.11	1.0	7.0	68.7	98.8	82.5
1079b	3.84	5.12	5.64	7.0	6.0	67.3	96.5	78.4
1080b	4.23	4.45	5.35	2.0	6.0	69.9	99.2	83.2

[a] In the case of **1079a** and **1080a**, ^{13}C-NMR spectra were recorded in C_6D_6 solution.

TABLE 4.34. ^{1}H-NMR DATA [δ, J (Hz)] OF ISOXAZOLIDINES **1081–1082**,[15/75] **1083–1084**,[21/87] **1085–1092**,[15/75] **1093**,[17/68] **1094**,[35/73], and **1095**[17/79]

Compound	Solvent	H3	H4	H5	$J_{3,4}$	$J_{4,5}$
1081a	$CDCl_3$	4.44	3.75	4.85	—	—
	C_6D_6	3.77	3.40	4.55	<0.5	—
1082a	$CDCl_3$	5.03	3.76	4.55	—	—
	C_6D_6	4.78	3.09	4.05	2.5	—
1081b	$CDCl_3$	3.71	3.40	4.70	—	—
	C_6D_6	3.02	3.02	4.51	<0.5	—
1082b	$CDCl_3$	3.96	3.58	4.73	—	—
	C_6D_6	3.77	2.73	4.13	<0.5	—
1083a	$CDCl_3$	4.30[a]	3.98	4.97	7.0	7.0
1084a	$CDCl_3$	4.83	3.75	4.83	2.0	7.0
1083b	C_6D_6	3.55[a]	3.10	4.22	8.0	7.5
1084b	$CDCl_3$	3.96	3.49	4.79	<0.5	7.5
1085a	C_6D_6	4.68	3.88	4.78	9.5	9.5
1086a	C_6D_6	5.33	3.43	4.83	8.5	9.5
1087a	C_6D_6	5.02	4.15	5.52	10.0	7.0
1088a	C_6D_6	5.02	3.90	5.15	8.5	7.8
1085b	$CDCl_3$	4.82	4.32	5.27	8.0	9.0
1086b	$CDCl_3$	4.93	3.72	5.24	7.0	8.5
1087b	$CDCl_3$	5.05	4.18	5.25	8.2	3.8
1088b	$CDCl_3$	4.83	3.90	5.10	9.0	7.0
1085c	C_6D_6	5.10	5.10	5.45	—	—
1086c	C_6D_6	5.83	4.24	5.46	7.0	8.5
1087c	C_6D_6	5.10	5.70	6.07	10.0	7.0
1088c	C_6D_6	5.60	5.60	5.60	—	—
1086d	$CDCl_3$	5.52	4.50	5.05	5.0	7.0
1087d	$CDCl_3$	—	5.08	5.85	8.0	3.0
1088d	$CDCl_3$	5.20	4.50	5.32	3.0	5.0
1086e	C_6D_6	4.98	3.82	5.47	8.0	9.0
1088e	C_6D_6	4.95	3.51	5.37	8.0	9.0
1089	$CDCl_3$	4.15[a]	5.61	6.30	5.0	5.0
1090	$CDCl_3$	4.76	5.45	6.05	0.5	5.0
1091	$CDCl_3$	5.24	4.96	6.25	8.0	7.0
1092	$CDCl_3$	4.52	4.68	6.23	6.0	6.5
1093	$CDCl_3$	3.83	—	4.13	7.5	6.5
1094	$CDCl_3$	4.35	—	5.05	6.3	7.6
1095	$CDCl_3$	3.80	2.95	4.28	<0.5	6.0
	C_6D_6	3.75	2.57	3.88		

[a] Very broad signal.

TABLE 4.35. ^{1}H-NMR DATA [δ(CD_3COCD_3), J (Hz)] OF ISOXAZOLIDINES **1098–1102**[17/72]

Compound	H4	H4′	H5	$J_{4,5}$	$J_{4',5}$	$J_{4,4'}$
1098	2.69	3.12				
1099	2.62	3.53	5.15	10.5	5.5	−14.0
1100	3.09	3.19	5.68	5.5	9.5	−13.5
1101	3.43	3.35	5.92	6.2	11.0	−13.5
1102	3.05	3.30	6.02	6.3	9.7	−13.0
	2.84[a]	3.60	5.18	10.3[b]	5.7	−14.0

[a] These data refer to protons of the left isoxazolidine ring.
[b] *cis* coupling constant.

TABLE 4.36. ^{1}H- AND ^{13}C-NMR DATA [δ ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1103–1106**,[29/89] **1107**,[64/86,33/89] AND **1108–1109**[20/88]

Compound	H4	H4′	H5	$J_{4,5}$	$J_{4',5}$	$J_{4,4'}$	C3	C4	C5
1103	2.52	2.65	4.83	3.4	8.3	12.8	72.2	48.7	64.1
1104	2.57	2.62	4.71	6.7	8.2	13.5	74.0	47.5	64.2
1107	2.17	2.46	4.44	8.0	7.0	12.6			
Compound	H4	H5	H5′	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	C3	C4	C5
1105	—	3.94	4.28	7.2	8.0	9.0	72.8	44.3	68.0
1106	—	4.08	4.14	6.3	7.9	8.8	—	43.8	68.3
Compound	H3	H4	H4′	$J_{3,4}$	$J_{3,4'}$	$J_{4,4'}$	C3	C4	C5
1108	4.08	≈2.0	2.60	—	8.0	11.0	65.0	43.0	61.3
Compound	H3	H5	H5′			$J_{5,5'}$	C3	C4	C5
1109	3.32	3.65	3.85			7.0	71.0	31.5	73.1

higher than *trans* coupling between the same protons, and even if this difference is often of the orders of only 1–2 Hz, no examples of clearcut reversal have been reported; and (3) *cis* coupling between H3 and H4 is usually higher than *trans* coupling between these protons, but examples of reversal of this difference are known (e.g., entries **1087b** and **1088b** of Table 4.34).

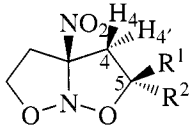
Also in the case of 2,3-fused isoxazolidines, the value of $J_{3,4}$ provides unambiguous information about stereochemistry only when it is lower of ≈ 3 Hz, indicating a *trans* relationship between H3 and H4. Here again, the presence of an additional rigid 4,5-fused ring forces the isoxazolidine ring to adopt an envelope conformation. Consequently, $J_{3,4} < 1.0$ Hz (as in **1081a**, **1081b**, **1082b**, **1084b**, **1090** and **1095**) can confidently considered as proof that in these compounds the flap of the isoxazolidine envelope points inside [(i) conformation, e.g., (i)-**1081**] while $J_{3,4} > 6.0$ Hz (as in **1092–1094**) demonstrates a dominance of the (o) conformation.

In addition to coupling constants, some other tools (solvent effects, NOE experiments, and dipole-moment values) have been used to establish the relative configuration of the stereogenic center at position 3.

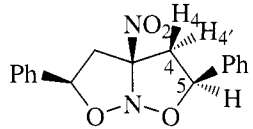
Thus, the small aromatic solvent–induced shift (ASIS) to high fields experienced by H3, on going from $CDCl_3$ to C_6D_6 solution, in **1082**[15/75] and

1095,[17/79] unambiguously proves the inside position of this proton, thus preventing its efficient solvation.

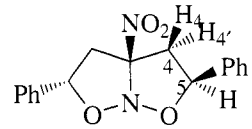
The *cis*-diphenyl derivative **1101** exhibits a higher dipole moment (5.21 D, at 25°C in C_6D_6) than that of the unsubstituted compound **1098** (5.03 D) as a result of the fact that the dipole moment of the C–Ph bond in **1101** is directed toward the phenyl group, thus reinforcing the dipole-moment vector of **1098** (which is directed toward the nitro group). In the *trans*-diphenyl derivative **1102** the two C–Ph groups counteract each other with a resultant slight decrease of the dipole moment of the molecule (4.92 D).[17/72] Coupling constants, with $J_{4,5\text{-}cis}$ higher than $J_{4,5\text{-}trans}$ (Table 4.35), are in agreement with the stereochemistry assigned on the basis of dipole moments.



1098: $R^1 = R^2 = H$
1099: $R^1 = H$, $R^2 = Ph$
1100: $R^1 = Ph$, $R^2 = H$

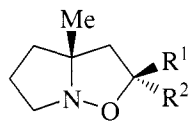


1101

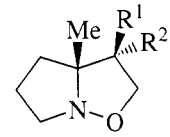


1102

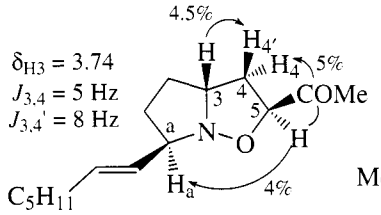
NOE experiments convincingly succeeded in determining the relative configuration of C5 and Ca stereogenic centers with respect to that of C3 in **1107**. In fact, irradiation of H5 brought about 5% and 4%, respectively, enhancements in signal intensity of H4 and Ha, while irradiation of H3 induced a 4.5% enhancement of H4′, thus proving that H3 is located on the opposite face with respect to H5 and Ha.[64/86]



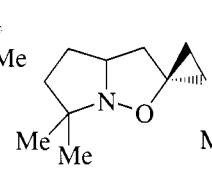
1103: $R^1 = CN$, $R^2 = H$
1104: $R^1 = H$, $R^2 = CN$



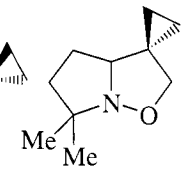
1105: $R^1 = CN$, $R^2 = H$
1106: $R^1 = H$, $R^2 = CN$



1107



1108



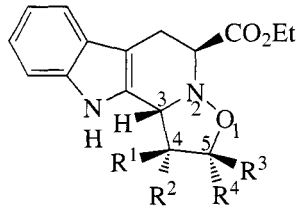
1109

TABLE 4.37 TORSION ANGLES (°) OF THE ISOXAZOLIDINE RING AND TORSION ANGLES (°, ABSOLUTE VALUES)[a] BETWEEN THE ISOXAZOLIDINE PROTONS IN COMPOUNDS **1110**,[72/86,73/86] **1111**,[66/83] AND **1112**[50/80]

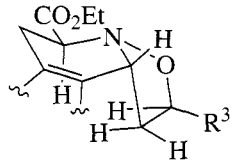
Torsion angles	**1110a**	**1110b**	**1110c**	**1110d**	**1110e**	**1111**	**1112**
C5ONC3	38.7	38.2	40.3	40.0	14.3	38.1	16.4
ONC3C4	−34.5	−35.5	−36.8	−36.1	−31.3	−48.8	5.7
NC3C4C5	18.3	20.3	20.4	20.1	35.9	41.5	−25.0
C3C4C5O	4.7	2.6	3.6	3.6	−26.6	−18.6	34.8
C4C5ON	−27.2	−25.6	−27.4	−27.2	8.2	−11.5	−32.2
H3C3C4H4(*cis*)	16	18	18	—	37		
H3C3C4H4(*trans*)	139	141	—	139	160		
H4C4C5H5(*cis*)	4	1	3	3	29		
H4C4C5H5(*trans*)	126	124	124	119	94		

[a] Evaluated on the basis of the heavy-atom structure.

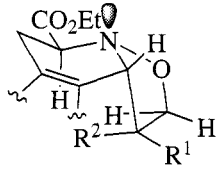
As for the stereochemistry of the ring junction at positions 2 and 3 (whether *cis* or *trans*, i.e., with the substituent at position 3 *cis* or *trans* relative to the nitrogen lone pair), no safe conclusions can be inferred from the NMR data of compounds **1078–1109**. A solution to this problem has been given for several derivatives by X-ray diffraction studies. In particular, the results of a noteworthy systematic study of compounds **1110a–e** are gathered in Table 4.37 (torsion



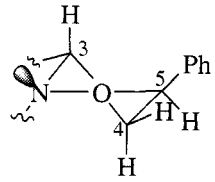
1110



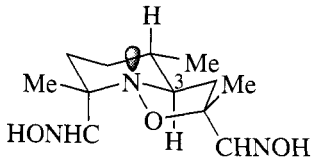
1110a: $R^3 = CH_2CO_2H$
1110b: $R^3 = CO_2Me$



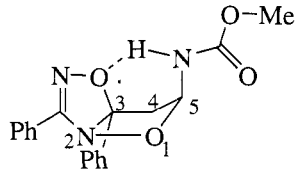
1110c: $R^1 = H$, $R^2 = CO_2Me$
1110d: $R^1 = CO_2Me$, $R^2 = H$



1110e



1111



1112

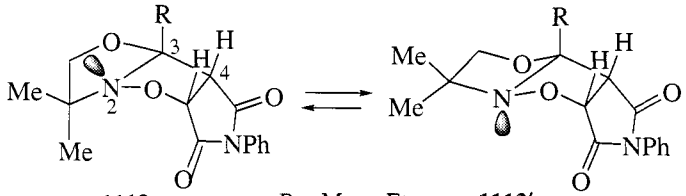
angles of the isoxazolidine ring as well as those involving vicinal protons on this ring). In all five derivatives the 2,3-fused cyclohexene moiety adopts a half-chair conformation with the N–O bond equatorial and the nitrogen lone-pair axial. The 2,3 ring junction always features a *cis* structure (H *cis* to the lone pair). Interesting is the observation that the isoxazolidine ring exhibits almost exactly the same structure, an envelope-like conformation with nitrogen as the out-of-plane atom, in both the *endo*-4-**1110c** ($J_{3,4}$ = 9.2 Hz)[39/86] and *exo*-4-methoxycarbonyl **1110d** ($J_{3,4}$ = 9.0 Hz)[39/86] diastereomers. That is, the higher steric congestion present in the *endo* derivative **1110c** does not give rise to any relevant conformational change with respect to **1110d**. Also the envelope conformation of the *exo*-5-substituted derivatives **1110a** and **1110b** bears a close resemblance to those of **1110c–d**. Thus, it is surprising that the *exo*-5-phenyl derivative **1110e** ($R^1 = R^2 = R^4 = H$, R^3 = Ph) prefers a quite different (see torsion angles) twist-like conformation with C3 and C4 as atoms above and below the plane of the N,O and C5 atoms ($^{C3}T_{C4}$). The surprise comes from the observation that the phenyl group points away from the polycyclic part of the molecule, that is, it does not increase steric congestion, and there is no other apparent reason that can explain its particular effect on the conformational choice of the isoxazolidine moiety. Unfortunately, reported NMR data do not help to decide whether this anomalous behavior is present in solution, too.

In the case of **1111**, in which the saturated six-membered ring adopts a chair conformation, we have an example of *trans* 2,3-fusion with H3 and the lone pair in axial positions and the N–O and C3–C4 bonds in equatorial positions. The C3 and N atoms are in the region of maximum puckering of the isoxazolidine twist conformation.

The single crystal X-ray structure of isoxazolidine **1112**, in which the isoxazolidine moiety is 2,3-fused to a five-membered ring, certifies that these systems prefer a *cis* junction (see also refs. 17/78 and 32/85 for further examples) in accord with the well known higher stability of *cis*-bicyclo[3.3.0]octane isomer relative to its *trans* counterpart. The distorted envelope conformation of **1112** (Table 4.37), with the out-of-plane atom (C5) pointing inside, is certainly driven by hydrogen bonding as shown in **1112**.

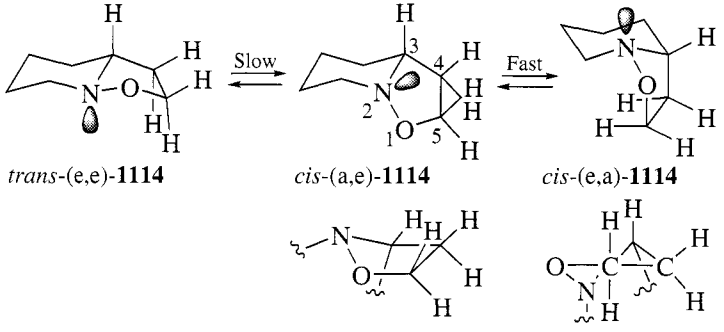
But what about NMR evidence on ring junction structure in 2,3-fused isoxazolidines as well as on their interconversion processes involving conformation flipping and nitrogen inversion? Strong broadening of the H3 signal in the ^{1}H-NMR spectrum (at room temperature) of *endo* adducts of 3,4-dihydroisoquinoline-*N*-oxide and 5,5-dimethyl-1-pyrroline-1-oxide to maleimides (i.e., **1083a** and **1083b**) is indicative of the presence of relatively fast, on the NMR timescale, equilibrating processes more than of nitrogen nuclear quadrupole relaxation effects as previously suggested.[11/86] The reaction of 2-*R*-4,4-dimethyloxazoline-*N*-oxides with *N*-phenylmaleimide[23/89] led to cycloadducts that were homogeneous by ^{1}H-NMR at 27°C ($CDCl_3$) and whose structure was established as *endo* on the basis of significant NOE effects between H4 and R (for R = Et). At −40°C two isomeric forms were clearly disclosed by the ^{1}H-NMR spectrum, and the authors suggested the two invertomers **1113** (with *cis*-junction between

the oxazolidine and isoxazolidine rings, i.e., with the lone pair *cis* to R) and **1113′** (*trans* junction, lone pair *trans* to R) (R = Me, ratio **1113/1113′**≈ 2:3) as reasonable structures for them. Apparently, the two isomers crystallized separately, affording two kinds of crystals with slightly different melting points and depression of mixed melting point.



1113 R = Me or Et **1113′**

The problem of conformational isomerism has been more extensively studied and documented by NMR techniques in the case of adducts deriving from cycloaddition of 3,4,5,6-tetrahydropyridine-1-oxide and its derivatives to double bonds. The presence of conformationally mobile tertiary nitrogen atom in these compounds, as shown for the parent perhydroisoxazolo[2,3-*a*]pyridine system **1114**, permits the establishment in solution of an equilibrium between a *trans*-fused conformer [*trans*-(e,e)] and two *cis*-fused conformers [*cis*-(a,e) and *cis*-(e,a)] (where e = equatorial, a = axial). The *cis* pair is in rapid equilibrium through chair inversion, while one of the *cis* conformers [*cis*-(a,e)] is transformed into the *trans* conformer by the relatively slow (at least much slower than chair inversion) nitrogen inversion process. It is evident that in order to use NMR data for structural assignments, it is mandatory to record NMR spectra at temperatures low enough to freeze at least the nitrogen inversion process so that to observe the signals of the *trans* derivative plus the averaged signals of the still fast interconverting *cis* pair.



trans-(e,e)-**1114** *cis*-(a,e)-**1114** *cis*-(e,a)-**1114**

As far as the geometry of these isomers is concerned, PM3 optimizations shows that the isoxazolidine ring in the *trans*-(e,e) isomer as well as in the

cis-(a,e) isomer [the former of the two descriptors in parentheses refers to the position of the N–O bond; thus (a,e) indicates that N–O is axial and C3–C4 equatorial] has an envelope-like form with nitrogen as the out-of-plane atom [*trans*-(e,e)-**1114**, ring torsion angles (°): O–N–C3–C4–C5–O = −38.8, 41.0, −27.5, 4.5 and 20.5; *cis*-(a,e)-**1114** is less puckered, ring torsion angles (°): O–N–C3–C4–C5–O = 32.0, −30.5, 18.5, 0.9, and −19.7] whereas *cis*-(e,a) has a flat half-chair-like form with the nitrogen and C3 atoms below and above, respectively, with respect to the C4–C5–O plane [*cis*-(e,a)-**1114**, ring torsion angles (°): O–N–C3–C4–C5–O = −21.9, 26.2, −21.1, 7.9, and 8.4].[57/91] The cyclohexane ring has a chair conformation with some flattening at the pyramidal nitrogen atom in order to reduce ring fusion strain. According to PM3 calculations the *cis*-(a,e) conformer is more stable (lower ΔH_{f°) than both *cis*-(e,a) (by 2.8 kcal/mol) and *trans*-(e,e) (by 5.1 kcal/mol) conformers, while by the AM1 method the *cis*-(a,e) form is predicted only slightly more stable than the *cis*-(e,a) form but much more stable (by ≈ 7.0 kcal/mol) than the *trans*-(e,e) form. These semiempirical methods probably overestimate the relative stability of the *cis* isomers as compared to the *trans* isomer, for they also indicate as more stable *cis*-hydrindane than *trans*-hydrindane (PM3, ΔH_{f° (*cis*) − ΔH_{f° (*trans*) = −1.3 kcal/mol) in contrast to the experimental higher heat of combustion of the former (by 1.1 kcal/mol).[1/94] The relative stability of *cis* and *trans*-hydrindane is well reproduced, needless to say, by MM2 calculations [$E_{steric}(cis) - E_{steric}(trans)$ = 1.2 kcal/mol] which predict that *cis*-(e,a)-**1114** form should be less stable by 2.7 kcal/mol than both the other two isomers (which have the same steric energy). In the MM2 geometries of the three conformers the isoxazolidine ring exhibits conformations similar to those of the semiempirical geometries but with a more pronounced puckering [e.g., *trans*-(e,e)-**1114**, ring torsion angles (°): −48.9, 49.1, −29.0, 2.1, 27.6].[57/91]

It is important to notice that the *cis* (*trans*) torsion angles between H4 and H5 in the three conformers (PM3 structures) are in the range 0–12° (110–130°) and that the *cis* (*trans*) torsion angle between H3 and H4 is 31° (149°) in both the *cis*-(e,a) and *trans*-(e,e) derivatives but definitely smaller—11° (107°; this value decreases to 98° in the MM2 structure)—in the *cis*-(a,e) isomer. Thus, one can anticipate that (1) $J_{4,5\text{-}cis}$ should be slightly larger than $J_{4,5\text{-}trans}$; (2) $J_{3,4\text{-}trans}$ can exhibit high values comparable to $J_{3,4\text{-}cis}$, thus leaving undetermined the relative configuration of positions 3 and 4; and (3) a $J_{3,4} < 3.0$ Hz value can confidently be considered a sure proof of *trans* relationship between the involved protons. It also certifies the dominance of the *cis*-(a,e) form.

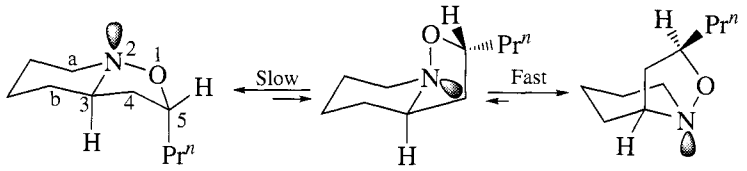
The problem of conformational isomerism of adducts of tetrahydropyridine-1-oxide to alkenes was addressed in an elegant paper by Eda Gössinger.[29/81] By using 4-*t*-butyltetrahydropyridine-1-oxide, she could freeze the perhydroisoxazolopyridine system of its *exo* adduct to 1-pentene (i.e., **1116**) in the *cis*-(e,a) conformation in order to obtain bona fide values for carbon and proton absorptions of this conformer. With these values in hand, she could reach, for example, reliable conclusions about the structure of the conformers of the *exo* adduct of tetrahydropyridine-1-oxide to 1-pentene, i.e. **1115**. In fact, nitrogen inversion in

TABLE 4.38. ^{1}H- AND ^{13}C-NMR SPECTRA ($CDCl_3$, 35°C) OF **1115** AND **1116** AND ^{1}H-NMR SPECTRUM of **1115** AT 120°C (C_4Cl_6)[29/81]

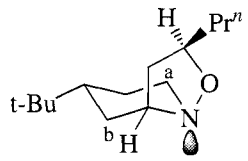
Compound	H3	H4 (H4′)	H5	Ha_{ax}	Ha_{eq}
(e,e)-**1115**[a]	≈2.5	—	4.04	2.42	3.41
(e,a)-**1115**[b]	3.60	—	4.30	2.70	3.00
1115 (at 120°C)	2.40	1.94 (1.60)	3.98	2.48	3.21
(e,a)-**1116**	3.61	2.38 (<2.0)	4.40	2.66	3.10
Compound	C3	C4	C5	Ca	Cb
(e,e)-**1115**[a]	66.3	40.2	75.8	55.1	35.5
(e,a)-**1115**[b]	59.5	39.0	76.5	49.8	35.8
(e,a)-**1116**	60.1	38.0	76.9	50.2	35.6

[a] Major isomer.
[b] Minor isomer.

1115 is slow on the NMR timescale even at 35°C, and both the ^{1}H-NMR and ^{13}C-NMR spectra display two series of signals (Table 4.38) attributable to two invertomers [intensity ratio: 75:25 in $CS_2/CDCl_3$ (85/15) and 70:30 in MeOD]. Chemical shifts of the carbon and proton signals of the minor invertomer bear a close resemblance to those of **1116**, thus demonstrating that this invertomer adopts the *cis*-(e,a) conformation [i.e., *cis*-(e,a)-**1115**] with, at most, very small amounts of the *cis*-(a,e)-**1115** conformation in fast equilibrium with it. Consequently, the major invertomer must have the *trans*-(e,e) structure. Moreover, she interpreted the shift to higher fields of H3 in the major isomer, as compared to the minor one, as an indication that this proton is antiperiplanar (in the major isomer) to the nitrogen lone pair (viz., they both occupy an axial position, on the assumption that this relationship gives rise to upfield shift as compared to *cis* axial–equatorial relationship between a proton and a lone pair). Since this is possible only in the *trans*-(e,e) conformation, the latter reasoning further supports that the major isomer chooses this conformation.

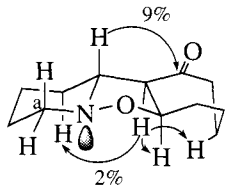


trans-(e,e)-**1115** *cis*-(a,e)-**1115** *cis*-(e,a)-**1115**



cis-(e,a)-**1116**

Catalan researchers carefully studied the conformational problem for isoxazolidines fused at both 2,3 and 4,5 positions.[32/89,55/90] They convincingly demonstrated, by using $^1H\{^1H\}$ and $^{13}C\{^1H\}$ techniques along with MM2 calculations, that the *trans*-(e,e) conformation of adduct **1117** is highly dominant over the *cis*-(e,a) conformation (93:7 at room temperature in $CDCl_3$).[55/90]

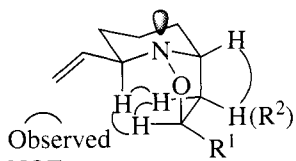


1117

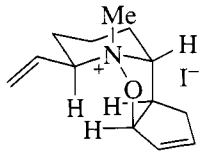
H3	H4	H5	Ha,ax	Ha,eq
2.68	3.29	4.16	2.51	3.46
$J_{3,4}$	$J_{4,5}$			
9.6	9.6			
C3	C4	C5	Ca	
68.7	54.9	73.1	54.6	

Ref. 55/90; $\delta(CDCl_3)$, J(Hz)

Gallagher et al. used COSY and NOE experiments to establish structures of compounds **1118**.[30/85,33/89] Although they did not explicitly discuss the problem of conformational isomerism and focused their interest mostly on the configurational problem, structures **1118a–c**, which they advanced to rationalize spectroscopic observations, also detail the conformation of the perhydroisoxazolopyridine moiety as *cis*-(e,a).



(e,a)-**1118**



(e,a)-**1119**

a: $R^1 = CO_2Me$(NOE at −50 °C; $J_{3,4} = 10.0$ Hz and $J_{3,4'} = 7.0$ Hz at r.t.)

b: R^1–R^2 = –CH=CHCH$_2$– (NOE at r.t.)

c: R^1–R^2 = –CH=CHCH$_2$CH$_2$–

However, NOE effects proved inconclusive and even deceptive in the case of **1118c**. Thus, an unambiguous stereochemical assignment was eventually obtained by a single-crystal X-ray analysis of the *N*-methyl derivatives of **1118b** (i.e., **1119**) and **1118c**.[33/89] In the solid state the *N*-methyl derivatives adopt the *cis*-(e,a) array with the isoxazolidine ring in an envelope-like conformation [nitrogen is the out-of-plane atom; isoxazolidine ring torsion angles (°): O–N–C3–C4–C5–O = −37.7, 40.3, −27.0, 5.2, and 20.5] that exactly reproduces that suggested by Gallagher et al. for compounds **1118** and can reasonably be accepted as the prevalent conformation of these compounds also in solution.

The two invertomers of the *exo* adduct of tetrahydropyridine-1-oxide to cyclopentadiene[54/90] and to styrene[47/87] interconvert slowly at room temperature.

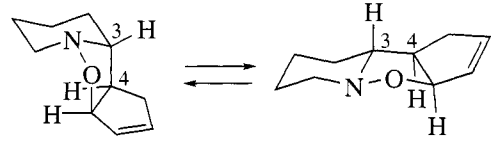
TABLE 4.39. ^{1}H-NMR DATA [δ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1121–1123**,[37/88] AND **1124**[31/89]

Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$
1121	3.62	3.26	5.45	8.5	5.5
1122	3.58	3.18	5.32	10.5	6.3
1123	3.55	3.41	4.74	10.0	10.0
1124	5.03	2.96 3.23	6.05	—	—

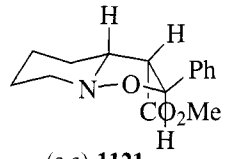
For example, the NMR spectrum of **1120** showed two doublets for H3 (δ 4.82 and 5.21 in DMSO-d_6, each with J = 8.0 Hz), which coalesced to one doublet (δ 5.14, J = 8.0 Hz) at 100°C.[54/90] An equilibrium between (e,a)-**1120** and (e,e)-**1120** very satisfactorily accounts for this finding. According to PM3 calculations, H3C3C4H4 is practically the same (≈151°) in both conformations and the (e,a) form is more stable than the (e,e) form by 1.8 kcal/mol.[57/91]

X-Ray analysis showed that the major adduct of the same nitrone to methyl cynnamate, namely, **1121**,[37/88] has the *trans*-(e,e) conformation in the solid state.[77/90] The high value of $J_{3,4}$ in *trans*-3,4 **1122** and **1123**[37/88] definitely eliminates the *cis*-(a,e) conformation, but the other two conformations are both consistent with this observation. (See Table 4.39.)

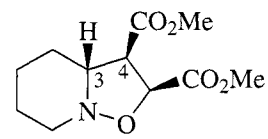
A *cis*-(e,a) conformation is certainly very reasonable for the isoxazolidinium salt **1124** and is supported by NOE effects (8%), which prove that Ha and H5 are close to each other.[31/89]



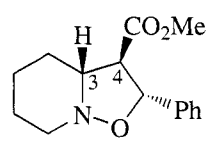
(e,a)-**1120** (e,e)-**1120**



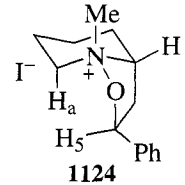
(e,e)-**1121**



1122

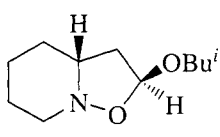


1123

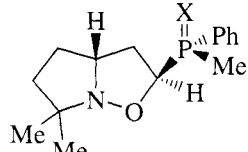


1124

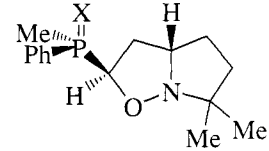
Slow nitrogen inversion shows up also in the adducts of tetrahydropyridine-1-oxide to isobutylvinylether, namely, **1125**. At −10°C the ^{1}H-NMR spectrum displays the signals of two distinct forms. The two invertomers were found to convert into each other at a rate of ≈ 10 s^{-1} at 30°C.[70/88]



1125



1126



1127

The observation that slow conformational equilibria emerge more frequently in the case 2,3-fused isoxazolidines than for other isoxazolidines can be attributed to the fact that the pyramidal nitrogen atom in the 2,3-fused derivatives is located at the ring fusion and, as a consequence, its inversion process necessarily must bring about a deep-seated rearrangement of the molecule, which necessarily involves both rings, thus becoming energetically more expensive.

To conclude this section on 2,3-fused isoxazolidines, only a few further quotations will be mentioned. Shift reagents were used either simply to cause signals of two diastereoisomers to separate in order to easily determine their ratio [53/74,47/76] or, in a much more sophisticated approach, to define configuration and conformation of isoxazolidines 2,3-fused to a seven-membered ring.[38/82]

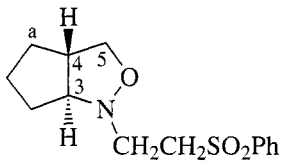
A quick and easy choice between the two diastereoisomers from the reaction of 5,5-dimethyl-1-pyrroline-1-oxide with chiral vinylposphinoxides, sulfides, selenides, and imines (e.g., **1126** and **1127**; X = O, S, Se, and NPh) is made possible by the observation that ^{31}P of the dominant adduct, namely, **1126**, resonates at lower fields than ^{31}P of its diastereoisomer, namely, **1127**, by 0.1–1.9 ppm.[25/91] The origin of this effect has not been established, and the difference is far from being dramatic, but it seems to work very well.

4.4.2.4. 3,4-Fused Isoxazolidines

4.4.2.4a. 3-Oxa-2-azabicyclo[3.3.0]octane Derivatives

Isoxazolidines 3,4-fused to a carbocyclic five-membered ring feature 3-oxa-2-azabicyclo[3.3.0]octane structures. It is well known that *trans* fusion is not easily accommodated by a bicyclo[3.3.0]octane system. In fact, the maximum ring torsion angle in cyclopentane (<50°) is too far from the the exocyclic *trans* torsion angle (>90°) in cyclopentane, so that considerable ring distortion must result in the case of *trans* fusion between two cyclopentane rings. Whereas *trans*-fused monoheterobicyclo[3.3.0]octane derivatives are easily prepared,[1/94] *trans*-3,4-fused isoxazolidines (3-oxa-2-azabicyclo[3.3.0]octanes) are, indeed, uncommon. A possible example of *trans*-fused derivative is provided by **1128**,

whose structure is based on the absence of NOE enhancement of the signal of H4 (while a 6% enhancement is observed for NCH_2) on irradiation of H3 whereas saturation of H4 gives rise to a significant intensity increase in the signals of cis-H5 (5%) and *cis*-Ha (6%).[38/91]

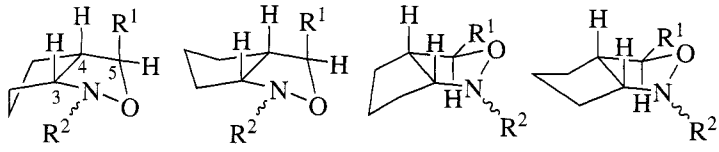


1128

H3	H4	H5	H5′
2.65	2.38	2.85	3.60
$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
6.5	6.2	8.4	8.4

Ref. 38/91; $\delta(C_6D_6)$, J(Hz)

However, as a rule, reported 3-oxa-2-azabicyclo[3.3.0]octanes are characterized by *cis* ring junction. Not surprisingly, the conformational flexibility of this array is very high. Even assuming absence of puckering at the ring junction, there are at least four envelope conformations [(i,i)-, (i,o)-, (o,i)- and (o,o)-**1129**] with the oxygen atom as the out-of-plane atom, each one with two possible invertomers at the nitrogen atom. Puckering at the ring fusion allows the system to accommodate a large number of combinations of distorted half-chair-like and envelope-like conformations of the two rings, thus making conformational analysis very difficult. Anyway, a very low value for $J_{4,5}$ can be interpreted as indicative both of a *trans* relationship between these two protons and of an envelope conformation [i.e., the H4C4C5H5 torsion angle is close to 90° in the (i,i) or (i,o) conformations]. However, while configurational choice (*trans*) is safe, one must realize that the H4C4C5H5 torsion angle is not far from 90° also in other conformations, thus making the conformational choice only tentative.



(i,i)-**1129** (i,o)-**1129** (o,i)-**1129** (o,o)-**1129**

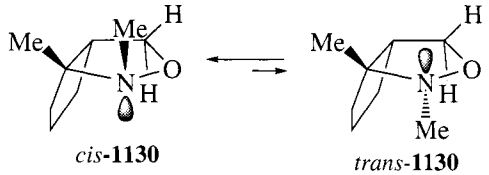
Nitrogen inversion in these systems appears to have been studied by NMR, for the first time, in the case of the dimethyl derivative **1130**.[26/70] Its ^{1}H-NMR spectrum, recorded at −50°C in toluene-d_8, displayed the signals of two isomers, which collapsed into the signals of only one (apparently) compound in the averaged room-temperature spectrum. The first-order rate constant and the related barrier of the conformational interchange ($\Delta G^{\neq} \approx 13$–$14$ kcal/mol; see Table 4.40) was evaluated in different solvents both by complete lineshape analysis and by the approximate expression $k_c = 2.22\ \Delta\nu$, and both gave the same result. An increase in the barrier of ≈ 0.7 kcal/mol was found on passing from non

TABLE 4.40. EQUILIBRIUM CONSTANTS (K), RATE CONSTANTS (k_c), AND ACTIVATION FREE ENERGY OF INTERCONVERSION BETWEEN (o,o)-**1130** AND (i,o)-**1130**[26/70]

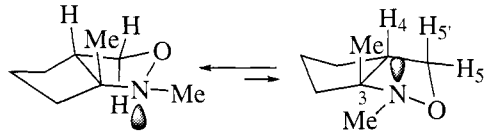
Solvent	T_c (°C)[a]	K [(i,o)/(o,o)][b]	k_c (s^{-1})[b]	$\Delta G^{\neq}$ (kcal/mol)[b,c]
Toluene-d_8	−24	0.4	9.5	13.4
$CDCl_3$	−21	0.5	4.5	13.9
CD_3COCD_3	−28	0.4	4.6	13.5
CD_3OD/D_2O (4:1)	−18	1.0	2.5	14.4
$CD_3CO_2D/(CD_3)_2CO$ (1:1)	−5	1.4	10	14.4

[a] Coalescence temperature.
[b] At the coalescence temperature.
[c] From lineshape analysis.

hydroxylic solvents to hydroxylic solvents. Le Bel[26/70] et al. assigned structure *cis*-**1130**, considered sterically less congested than *trans*-**1130**, to the major isomer, whose *Me*C resonates slightly upfield relative to that of the minor isomer. The authors also depicted the equilibrium between *cis*- and *trans*-**1130** as characterized only by inversion at the nitrogen atom and did not comment about possible ring flipping.



cis-**1130** *trans*-**1130**

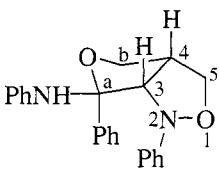


(o,o)-**1130** (i,o)-**1130**

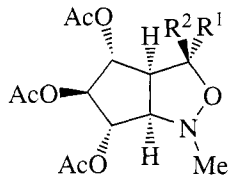
Actually, from the published spectra, it is deduced that nitrogen inversion is accompanied by a change in ring conformation. H5 (at $\delta \approx 3.30$) and H5′ (at $\delta \approx 3.80$) of the prevalent invertomer appear as triplets in the low-temperature spectrum, while at room temperature (where they are averaged with the corresponding protons of the minor isomer) the lower-field signal (H5′) continues to be a triplet while the other becomes a double doublet with well-differentiated J values. In other words, the coupling constant between H4 and H5 in the minor isomer must be very small, implying a change (with respect to the major isomer) in the torsion angle involving these protons. This observation can be explained only on the basis of nitrogen inversion with concomitant ring flipping. Thus, an equilibrium between (o,o)-**1130** (dominant) and (i,o)-**1130**, with the

N-methyl groups of both isomers in pseudoequatorial position, seems to better account for the experimental observations and for minimization of steric interactions. Certainly, the measured activation free energy (>13.1 kcal/mol) no doubt reflects the energy required to surmount the barrier to nitrogen inversion. In fact as quoted in Section 4.4.2.1, ring conformation readjustement processes (such pseudoratation or ring flipping) should require a much lower (<5.0 kcal/mol) free activation energy. This conclusion is supported also by the rate decrease observed in hydroxylic solvents; the involvement of the lone pair in hydrogen bonding makes the inversion process slower in these solvents.

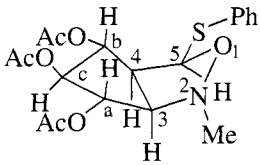
Isoxazolidines **1131–1136** exhibit *cis*-3,4 ring fusion to a cyclopentane or tetrahydrofuran ring. In all these compounds (Tables 4.41 and 4.42) the coupling constant between the two protons at ring fusion, specifically, $J_{3,4}$, is large ($\approx$ 9.0 Hz) and remarkably constant. This finding can be read as an indication that H3 and H4 are nearly eclipsed and, consequently, that the ring junction is located in the least puckered region of the molecule. But one is not allowed to conclude



1131

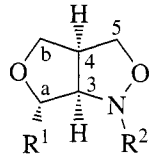


1132

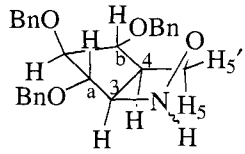


1132b

a: $R^1 = R^2 = H$
b: $R^1 = H$, $R^2 = SPh$
c: $R^1 = SPh$, $R^2 = H$

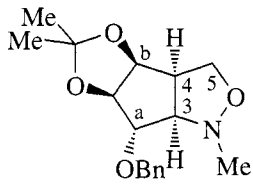


1133

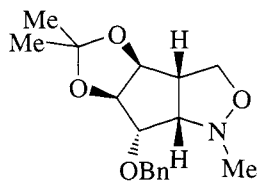


1134

a: R^1 = Me, R^2 = 4-*t*-BuC_6H4
b: R^1 = Ph, R^2 = 4-*t*-BuC_6H4
c: $R^1 = R^2$ = Me



1135



1136

TABLE 4.41. ^{1}H- NMR DATA [δ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1131**,[54/85] **1132**,[36/83] **1133**,[39/91] **1134**,[37/79] **1135**,[39/79] AND **1136**[39/79]

Compound	H3	H4	H5	H5′	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{3,a}$	$J_{4,b}$[a]	$J_{4,b'}$[a]	$J_{5,5'}$
1131	4.23	3.49	3.94	3.96	9.2	4.7	4.9	—	8.4	8.4	—
1132a	3.47	3.05	4.05	4.06	9.7	6.6	4.2	5.8	6.5	—	—
1132b	3.25	3.55	5.53	—	9.1	6.9	—	3.8	7.4	—	—
1132c	3.56	3.07	—	5.38	9.2	—	3.4	4.3	5.5	—	—
1133a	3.94	3.25	3.60	4.24	8.8	7.8	8.4	6.1	1.6	6.2	8.8
1133b	4.26	3.35	3.77	4.47	8.8	8.2	8.5	6.7	1.3	6.0	8.7
1133c	3.10	3.30	3.50	4.15	8.4	6.6	8.3	6.1	2.5	6.9	9.1
1134[b]	3.25	2.48	2.75	3.55	9.0	7.0	0	—	6.0		9.0
1135[c]	3.50	3.29	3.95	4.20	8.5	8.5	3.8	5.5	—	8.5	8.5
1136[d]	3.1–3.3		3.70	4.20	—	4.5	8.5	—	6.0	—	8.5

[a] $J_{4,b}$ is a J *trans* while $J_{4,b'}$ is a *J cis*
[b] In C_6D_6, δ_{NH} = 4.2-4.5.
[c] δ_{NMe} = 2.58.
[d] δ_{NMe} = 2.77.

TABLE 4.42. ^{13}C-NMR DATA [δ($CDCl_3$)] OF ISOXAZOLIDINES **1131**,[54/85] **1132**,[36/83] **1133**,[39/91] **1134**[37/79]

Compound	C3	C4	C5	Compound	C3	C4	C5
1131	83.2	49.8	70.2	**1133a**	78.3	49.7	72.5
1132a	73.1	50.6	71.0	**1133b**	79.8	49.8	73.2
1132b	73.4	53.3	86.9	**1133c**	79.2	48.7	72.6
1132c	71.8	57.6	89.6	**1134**	66.1	49.5	75.7

that both the two fused five-membered rings will adopt an envelope conformation. For example, the X-ray crystal structure of **1132b** demonstrates that in the solid state both rings have a slightly distorted half-chair conformation (ring torsion angles (°): O–N–C3–C4–C5–O = −32.6, 10.3, 13.6, −32.9, 41.5 and C4–C3–Ca–Cc–Cb–C4 = 14.9, 15.7, −40.3, 50.2, −39.8).[36/83] The cyclopentane ring is more puckered than the isoxazolidine ring, and the largest puckering in this latter is at the C5–O part while in the former at the Cb–Cc moiety.

In the case of **1131**, a highly puckered envelope conformation of the tetrahydrofuran ring and a rather flat structure of the isoxazolidine ring, both of which conformations are (o) (i.e., the oxygen atom points outward with respect to the bicyclic array of the molecule), appear to be consistent with the observed coupling constants involving H4 and the vicinal protons at 5 and b positions.[54/85] (Table 4.41.)

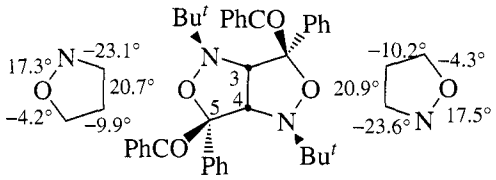
Passing to compounds **1133**, the very similar values for $J_{4,5}$ and $J_{4,5'}$ as well as the significantly different figures for $J_{4,b\text{-}trans}$ (< 2.5 Hz) and $J_{3,a\text{-}trans}$ (> 6.0 Hz) (Table 4.41)[39/91] can be explained by the presence of an envelope conformation in both rings; C5 and C4 play the role of the out-of-plane atom in the envelope conformation of the isoxazolidine and, respectively, the tetrahydrofuran ring. In

particular, this conformation forces *trans*-H5 in an almost antiperiplanar orientation with respect to H4.

The "missing" $J_{4,5'}$ in **1134** is convincingly rationalized by an (i) envelope conformation of the isoxazolidine moiety.

However, it should be stressed that in the absence of variable temperature studies the exercise of explaining ^{1}H-NMR data on the basis of a presumed "highly" dominant conformation, as done in the last paragraph, is acceptable only if it is clearly understood that this leads to nothing more that very tentative structures and, in particular, that the presence of several conformations in rapid equilibrium may give rise to deceptive NMR spectra.

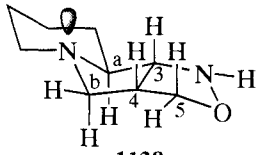
Obviously, no doubt about conformational choice in the solid state is left by X-ray analysis, as in the case for 3,4-fused bisisoxazolidine **1137** whose rings have flat structures [left ring torsion angles (°): O–N–C3–C4–C5–O = 17.3, −23.1, 20.7, −9.9, −4.2] with the *t*-Bu groups in pseudoaxial positions.[59/89]



1137

It is hoped that a proper parameterization of molecular mechanic methods will in the near future provide organic chemists with a fast, easy, and reliable method to tackle the subtle conformational problems of five-membered heterocyclic rings with two heteroatoms. Anyway, some molecular mechanic calculations have already been performed with the existing methods. For example, full MM2 calculations, using the Still–Steliou Model 2.94 program, were performed by Padwa et al. on compound **1138**.[41/91] According to these calculations, there are seven conformers (seven local minima) within 3 kcal/mol of the lowest-energy conformer (global minimum). However, the Amber force field (as implemented in Model) predicts only five conformers and the lowest energy conformer has a geometry different from that of Model's MM2 force field. Evaluation of vicinal coupling constants according to Karplus' equation leads (after weighting by the Boltzmann populations of the conformers, on the basis of steric energies at 25°C) to values in acceptable agreement with experimental data if Amber geometries are used [e.g., $J_{3,a}$ = 7.5 Hz (calc.) vs. 8.5 Hz (exp.)] but to wrong results if MM2 geometries are used [e.g., $J_{3,a}$ = 5.05 Hz (calc.) vs. 8.5 Hz (exp.)]. The experimental *J* values of this compound are also qualitatively well rationalized by the naive and rough "one conformation" approach; in other words, they are consistent with the conformation detailed for **1138**: (1) a chair and an envelope-like conformation of the six-membered and

five-membered, respectively, rings of the *trans*-indolizidine moiety; and (2) an "inward" envelope conformation of the isoxazolidine ring.



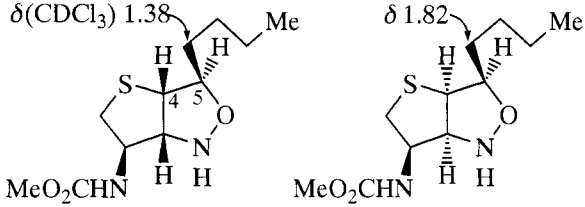
1138

H3	H4	H5	H5′	
3.62	3.09	3.42	3.94	
$J_{3,4}$	$J_{3,a}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
8.5	8.5	6.5	1.0	9.0

$J_{4,b} = J_{4,b'} = 8.5$; $J_{3,NH} = 4.5$

Ref. 41/91; $\delta(CDCl_3)$, J(Hz)

Chemical-shift values were used to attribute relative configurations to C4 and C5 stereocenters of isoxazolidines **1139** and **1140**.[17/87] The ^{1}H-NMR spectrum of **1140**, which has the *n*-butyl side chain and the thiophane system *cis* to each other, displays the α-methylene protons of the side chain as a multiplet at δ 1.82 downfield (as a result of deshielding by the sulfur atom) of the multiplet at δ 1.33 of the other methylene protons. Consistently, in **1139** all protons of the three side-chain methylene groups resonate upfield at δ 1.38. These assignments were definitely substantiated by X-ray investigations.[17/87]



1139 **1140**

Coupling constants proved unreliable in elucidating stereochemistry of adducts **1141–1142** derived from intramolecular cycloadditions of *cis*/*trans* mixtures of unsaturated nitrones.[62/90] Nevertheless, trends in proton and carbon chemical shifts (Table 4.43) and NOE experiments as well as analogy with pre-

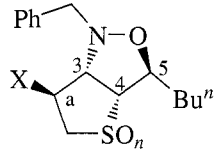
TABLE 4.43. ^{1}H- AND ^{13}C-NMR DATA [$\delta(CDCl_3)$, J (Hz)] OF ISOXAZOLIDINES **1141–1142**[62/90]

Compound[a,b]	H3	H4	H5	Ha	C3	C4	C5	Ca
1141a	3.13	3.55	3.84	2.12	82.2	58.0	87.2	41.4
1142a	3.38	4.21	4.32	2.24	79.5	56.2	80.8	43.8
1141b	3.38	3.48	4.42	2.21	76.2	70.7	79.5	31.6
1142b	3.51	3.97	4.58	2.46	74.9	67.9	80.5	35.5
1141c	3.43	3.57	3.78	3.90	81.6	56.9	86.1	76.2
1142c	3.71	4.17	4.31	4.20	78.3	56.1	79.4	79.1

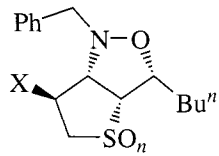
[a] *Anti* isomers, **1141**: $J_{3,4}$ = 7.8–8.0 Hz; $J_{3,a}$ = 1.0–2.3 Hz; $J_{4,5}$ = 6.5–7.6 Hz.

[b] *Syn* isomers, **1142**: $J_{3,4}$ = 6.0–7.0 Hz; $J_{3,a}$ = 2.9–5.3 Hz; $J_{4,5}$ = 4.3–6.0 Hz.

vious attributions for similar systems allowed the authors to satisfactorily solve this problem. Thus, in one diastereomer Ha, H3, H4, H5 and Ca resonate upfield and C3, C4, and C5 downfield, as a rule, relative to the corresponding nuclei in the other diastereomer, and this makes it possible to group all adducts in two series (i.e., **1141** and **1142**). The *syn* (Masamune's nomenclature)[2/94] configuration at C3/C4 in both series is supported by the 7–10% enhancement observed for H4 signal on irradiation of H3. Likewise, the *anti* configuration at C3/Ca in both series is certified by the 6% enhancement of H3 on irradiation of the methyl group (in **1141a** and **1142a**) and by the 5% intensity increase of the signal of the methyl group at position a on saturation of H3 (in **1141b** and **1142b**). This leads to the conclusion that the two series differ in configuration at C5. The assignment of the last stereochemical detail, specifically, the C4/C5 *anti* configuration to compounds **1141** and hence the *syn* one to compounds **1142** (left open by the fact that the dipolarophilic double bond is a *cis*/*trans* mixture), is consistent with (1) the lower chemical shifts of C4 and C5 in the latter derivatives as compared to those of the corresponding nuclei in the former ones, (2) NOE experiments, and (3) attributions for similar systems.[62/90]



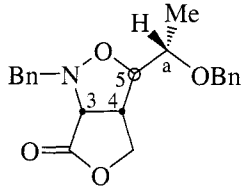
1141



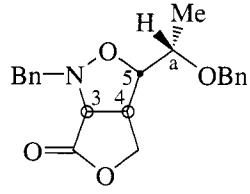
1142

a: n = 0, X = Me; **b:** n = 2, X = Me; **c:** n = 0, X = OH

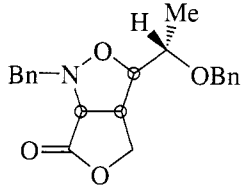
Very similar diagnostic tools can be used successfully to establish stereochemistry of four diastereoisomers as in the case of **1143–1146**.[28/90] In these



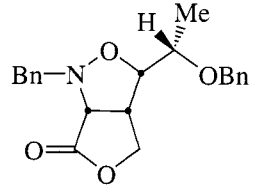
1143



1144



1145



1146

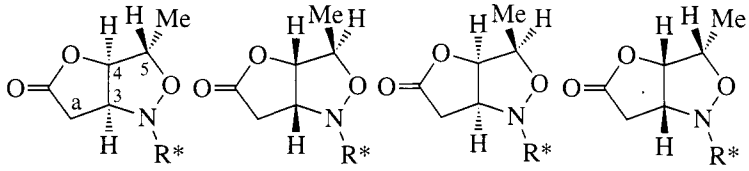
Bn = $PhCH_2$

TABLE 4.44. ^{1}H- AND ^{13}C-NMR DATA [δ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1143–1146**[28/90]

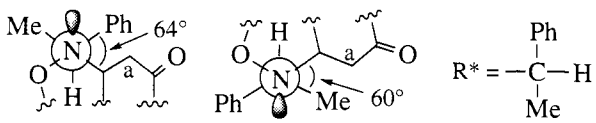
Compound	H3	H4	H5	Ha	$J_{3,4}$	$J_{4,5}$	$J_{5,a}$	C3	C4	C5	Ca
1143	3.77	3.44	3.84	3.65	9.0	5.5	6.0	66.8	46.5	88.2	74.7
1144	3.75	3.35	4.04	3.69	8.0	5.6	6.0	66.7	45.4	86.8	73.2
1145	4.01	3.57	4.19	3.68	7.8	7.8	9.0	67.1	44.2	81.7	60.1
1146	3.96	3.52	4.37	3.74	8.5	5.5	8.0	66.5	45.3	83.7	60.8

compounds the relative stereochemistry at C4/C5 (*anti* in **1143–1144** and *syn* in **1145–1146**) is secured by the starting alkene configuration and further supported by NOE effects (6–8% enhancements) observed for H4 on irradiation of H5 in **1145** and **1146**. The C3/C4 *syn* stereochemistry in all four isomers is demonstrated by 7–11% intensity increase of H3 on irradiation of H4. Configuration at C5/Ca rests firmly on the chemical shifts of H5 and Ha (Table 4.44; $J_{5,a}$ does not lend itself to reliably discriminate between *syn* and *anti* derivatives), which always increase on passing from isomers with *anti* stereochemistry, (i.e., **1143** and **1145**) to the corresponding *syn* isomers, i.e., (**1144** and **1146**). The effect is small, but apparently it is very reliable even if no explanation has been offered for this behavior. Finally, NOE experiments provide a clue also to side-chain conformation of **1143–1146**. In fact, saturation of H5 in **1144** and **1146** brings about 5–10% enhancements of Ha, while no effect is observed when the same experiment is carried out with **1143** and **1145**, thus suggesting that the highly dominant conformation is the one depicted in the formulas.

The pairs of diastereoisomers **1147/1148** and **1149/1150** were obtained by intramolecular 1,3-dipolar cycloaddition of chiral *trans*- and, respectively, *cis*-δ, ε-unsaturated nitrones bearing a stereogenic center (NCHMePh) directly attached to the nitrogen.[45/85] The well-established stereospecificity of 1,3-dipolar cycloadditions leaves no doubt about the *trans*-H4/H5 and *cis*-H4/H5



1147 **1148** **1149** **1150**



1147′ **1148′**

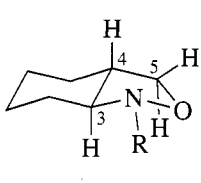
TABLE 4.45. ^{1}H- AND ^{13}C-NMR DATA [δ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1147–1150**[45/85]

Compound	H3	H4	H5	Ha	Ha′	$J_{3,4}$	$J_{4,5}$	$J_{3,a}$	$J_{3,a'}$
1147	3.44	4.52	4.02	1.69	1.98	8.0	5.0	2.0	8.0
1148	3.52	4.56	3.99	2.60		7.0	4.0	6.0	6.0
1149	3.95	5.10	4.28	2.58	2.62	7.0	4.0	8.0	5.5
1150	4.05	5.05	4.12	2.48	2.90	7.0	4.0	9.0	4.0

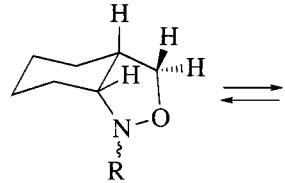
relationship, respectively, in the former and latter pair. Thus, the very similar values of $J_{4,5}$ (Table 4.45) in all these compounds once more confirm that there is not, as a rule, a diagnostic relationship between vicinal coupling constants and relative configuration of vicinal stereocenters in isoxazolidines 3,4-fused to five-membered rings (see also $J_{4,5}$ in **1141** and **1142** and footnotes in Table 4.43). In **1147** and **1148** the relative configuration of the bicyclic array with respect to the stereocenter attached to the nitrogen atom, as well as conformation of this stereocenter, was deduced from the rather large (≈ 1 ppm) upfield shift (attributed to the shielding effect by the phenyl group; see **1147′**) of the methylene protons α to carbonyl (i.e., Ha and Ha′) in the former compound relative to the latter (see also **1148′**) and, more unambiguously, from crystallographic analysis.

4.4.2.4b 8-Oxa-7-azabicyclo[4.3.0]nonanes

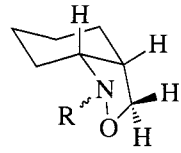
Another system, whose NMR behavior is well documented, is that of isoxazolidines 3,4-fused to six-membered rings, such as **1151–1154**. In these 8-oxa-7-azabicyclo[4.3.0]nonane derivatives the six-membered ring adopts (owing to its higher rigidity) its preferred conformation, while which conformation is chosen by the flexible diheterocyclopentane moiety also depends strongly on substituents. Both *trans*-fused and *cis*-fused derivatives have been reported.



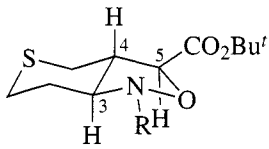
trans-(e,e)-**1151**



cis-(a,e)-**1151**

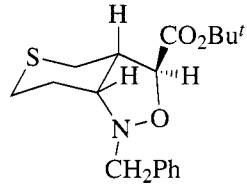


cis-(e,a)-**1151**

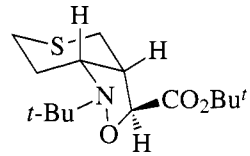


trans-(e,e)-**1152**

a: R = Me; **b:** = $PhCH_2$



cis-(a,e)-**1153**



cis-(e,a)-**1154**

TABLE 4.46. ^{1}H- AND ^{13}C-NMR DATA [δ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1152–1153**[23/90]

Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$	C3	C4	C5
1152a	1.92	2.46	4.02	9.8	9.3	72.5	53.2	77.9
1152b[a]	2.27	2.55	3.95	10.5	9.3	70.0	53.1	78.0
1153	3.15	2.95	4.32	5.0	4.3	61.6	45.9	79.8
1154	3.31	2.81	4.47	7.0	9.6	57.4	45.7	77.7

[a] In $C_2D_2Cl_4$ at 100°C.

In the case of *trans* fusion, both the C3–N and C4–C5 bonds of the isoxazolidine ring must occupy equatorial positions [e.g., *trans*-(e,e)-**1151**; the first descriptor in parentheses refers to the conformational position of the C3–N bond and the second one to that of C4–C5 bond], and conformation of this ring is forced either toward an envelope conformation with the flap in the region of ring fusion or toward a twist conformation with the maximum pucker at C3–C4. For example, the high values of $J_{3,4}$ in *trans*-**1152a–b** (Table 4.46) demonstrate that both H3 and H4 occupy axial positions as their strong coupling requires that they bear an exact antiperiplanar relationship. Likewise, $J_{4,5}$ = 9.3 value in these two compounds suggests that an almost antiperiplanar disposition should involve H4 and H5 as confirmed also by PM3 geometries (H4C4C5H5 = >170°). Line broadening is present in the r.t. ^{1}H-NMR spectrum of **1152b**. However, it is not the result of an equilibrium between nitrogen invertomers (with concomitant ring flipping as *trans* fusion highly reduces the conformational mobility of the isoxazolidine moiety) but can be attributed to equilibrating rotamers of the benzyl residue.[23/90]

A fast equilibrium between two conformers with the C–N bond in equatorial position [i.e., *cis*-(e,a)-**1151**, *N*-equatorial] and, respectively, in axial position [i.e., *cis*-(a,e)-**1151**, *N*-axial] is a priori possible for *cis*-fused derivatives. This equilibrium, obviously, may well lie completely on either side. For example, in the case of **1154** the equilibrium is strongly shifted to the side of the *N*-equatorial conformation, whereas for **1153** the *N*-axial conformation is strongly preferred. In fact, the *trans*-H4C4C5H5 torsion angle in *cis*-(e,a) structures is close to 150° (giving rise to $J_{4,5}$ = 9.6 Hz in **1154**), whereas in *cis*-(a,e) structures it should be close, on the higher side, to 100°, in keeping with $J_{4,5}$ = 4.3 Hz in **1153**. The $J_{3,4}$ value in **1153** and **1154** reflects the axial–equatorial relationship between H3 and H4 and is consistently smaller than $J_{3,4}$ in *trans* derivatives where these two protons feature an axial–axial antiperiplanar array. As for ^{13}C resonances (Table 4.46), notice how, on going from *trans*-fused to *cis*-fused derivatives, the signals of C3 and C4 shift upfield while the chemical shift of C5 remains substantially unaltered.

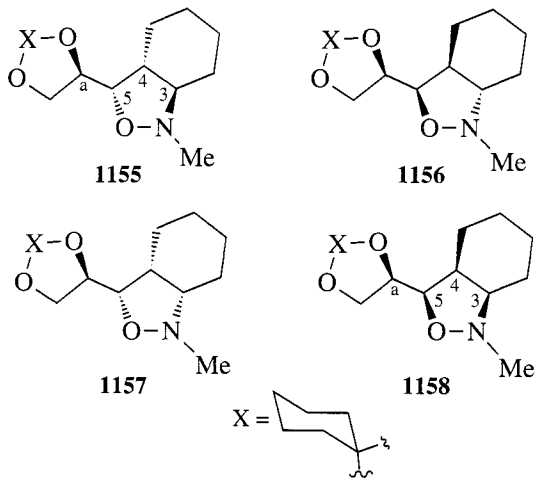
The relative configuration of all stereocenters in **1155–1158** has been established on the basis of ^{1}H and ^{13}C-NMR data and chemical reasoning (Table 4.47). Here again (see compounds **1143–1146**), the relative configuration at C5/Ca relies on the different chemical-shift values of H5 and Ha. The signals of

TABLE 4.47. ^{1}H- AND ^{13}C-NMR DATA [δ($CDCl_3$)][a] OF ISOXAZOLIDINES **1155–1158**[26/87]

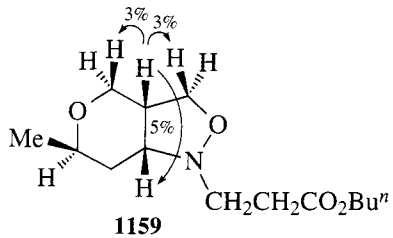
Compound	H3	H4	H5	Ha	C3	C4	C5	Ca
1155	1.98	2.16	3.87	3.86	70.3	50.6	79.0	74.9
1156	2.16	2.30	3.96	3.96	70.1	50.5	77.7	75.7
1157	2.85	2.43	4.03	4.06	67.2	45.3	80.4	73.0
1158	2.85	2.23	4.10	4.20	67.3	45.3	81.5	75.5

[a] $J_{5,a}$ are in the range 6–9 Hz and do not allow for discrimination between **1155** and **1156** as well as between **1157** and **1158**.

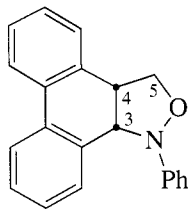
these protons in the *syn* isomers, specifically **1156** and **1158**, are downfield of those of the corresponding *anti* products, specifically **1155** and **1157**, respectively. Likewise, the chemical-shift values of C3 and C4 are diagnostic for the relative configuration of these stereocenters. In the case of the *syn* isomers, now **1157** and **1158**, the resonances are at higher fields than those of their *anti* counterparts: **1155** and **1156**. Finally, the *syn* relationship at C4/C5 in all of four compounds is the result of the *cis* stereochemistry of the starting dipolarophilic double bond.



NOE experiments on **1159** provide clear evidence that *cis* protons experience a significant (3–5%) effect that, in contrast, is negligible for *trans* protons.[38/91]



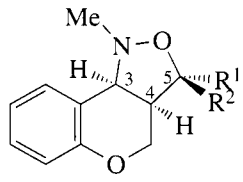
Examples of 3,4-fused isoxazolidines in which the fused six-membered ring is part of a polycyclic system are provided by compounds **1160**,[23/78] **1161**,[29/70] and **1162–1164**.[37/83] In the case of *cis*-fused **1161d**, X-ray diffraction studies show that it has a *cis*-(a,e) (C–N bond in axial position) structure in which the isoxazolidine ring exhibits a distorted and strongly puckered half-chair conformation [ring torsion angles (°): O–N–C3–C4–C5–O = 45, −51, 38, −12 and −20].[29/70] The nitrogen atom is located in the most puckered region of the ring, while the N–Me adopts a pseudoequatorial position with the C3–N–Me angle widened (115°) to remove steric congestion.



1160

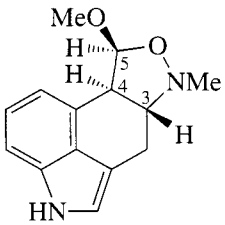
H3	H4	H5	H5′
5.20	3.37	3.68	4.28
$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
5.5	7.0	6.0	9.0

Ref. 23/78; $\delta(CDCl_3)$, in the presence of $Eu(fod)_3$; J(Hz)



1161

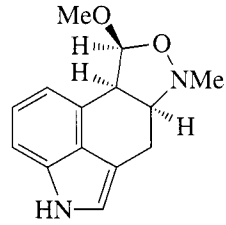
Comp.	**a**	**b**	**c**	**d**
R^1	H	Me	H	CH_2Cl
R^2	H	H	Me	H
$J_{3,4}$	7	7	6	5.5
$J_{4,5cis}$	8		6.5	
$J_{4,5trans}$	4	4.5		3.5



1162

$J_{3,4}$ = 11 Hz

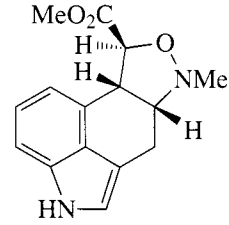
$J_{4,5}$ = 4.5 Hz



1163

$J_{3,4}$ = 5 Hz

$J_{4,5}$ = 5 Hz



1164

$J_{3,4}$ = 7 Hz

$J_{4,5}$ = 7 Hz

Noteworthy, *trans*-3,4 coupling in **1162** is significantly higher than *cis*-3,4 coupling in **1160**, **1161**, **1163**, and **1164**.

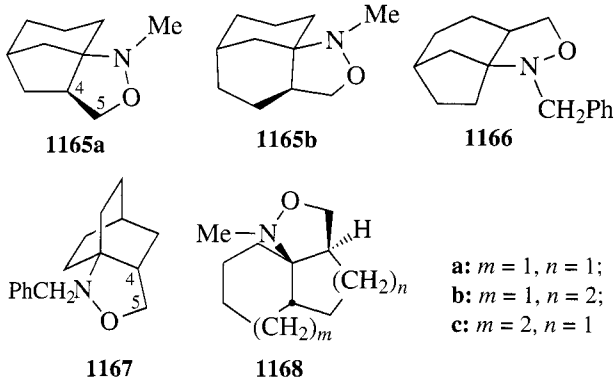
Intramolecular cycloadditions open an easy way to complex molecules such as **1165–1168** in which the isoxazolidine ring is 3,4-fused to a bicyclic system and the C–N bond occupies a bridgehead position. As for NMR data, notice how

TABLE 4.48. ^{1}H-NMR DATA [δ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1165–1167**[67/85] AND **1168**[35/81]

Compound	Me or CH_2	H5	H5′	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
1165a	2.53	3.42	4.05	4.2	8.4	8.1
1165b	2.53	3.45	3.99	6.8	7.5	7.5
1166	3.80	3.42	4.05	10.5	7.5	6.0
1167	3.85	3.61	4.18	10.0	9.2	7.0
1168a	2.63	3.48	4.10	3.5	8.0	8.0
1168b[a]	2.43	3.47	3.98	9.0	10.0	7.0
1168c	2.52	3.23	3.82	4.5	8.0	8.0

[a] In C_6D_6.

the 5,5′ geminal coupling constant can exhibit a value as low as 6.0 Hz (Table 4.48).



1165a **1165b** **1166**

1167 **1168**

4.4.2.5. Isoxazolidines with Multiple Ring Fusion and with Bridged Fusion

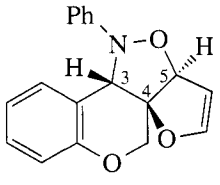
The presence of multiple ring fusion strongly reduces and often practically eliminates the conformational mobility of the isoxazolidine moiety in these derivatives. Examples of isoxazolidines ring-fused at 3,4/4,5 and at 2,3/3,4 positions are provided by compounds **1169–1173** and, respectively, **1174–1175**. Related NMR data are given in Table 4.49, and there is no need for a detailed comment on these data. Nevertheless, the ^{13}C-NMR values of these compounds demonstrate once more that (1) C5 is less shielded than C3 when there are substituents at both positions 5 and 3, (2) the opposite is true (i.e., $\delta_{C3} > \delta_{C5}$) for 5-unsubstituted derivatives, and (3) the presence of a heteroatom at C4 can shift the signal of this carbon to lower fields than both those of C3 and C5.

Molecular models reveal that in the case of **1170a,b** the high value of $J_{4,a}$ is the result of a dihedral angle close to 0° imposed on the *cis* protons H4 and Ha

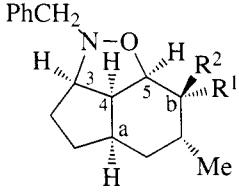
TABLE 4.49. ^{1}H- AND ^{13}C-NMR DATA [δ($CDCl_3$), J (Hz)] OF ISOXAZOLIDINES **1169–1171** AND **1173–1175**

Compound	H3	H4	H5	$J_{3,4}$	$J_{4,5}$	C3	C4	C5	References
1169	5.24	—	5.24	—	—	67.8	94.5	87.8	23/84
1170a[a]	3.61	2.77	4.39	6.0	6.0	72.1[b]	61.8	78.3[b]	42/85
1170b[c]	3.60	2.77	4.35	5.5	5.5	71.8[b]	61.4	75.1[b]	42/85
1171	—	—	—	—	—	65.6	48.4	74.9	51/81
1173a	4.35	2.96	4.88	6.0	7.5	—	—	—	40/82
1173b	3.3–3.6		4.85	—	9.0	56.2	47.4	86.9	40/82
1174[d]	—	2.63	3.44	—	4.5	75.1	50.6	72.2	20/75
			4.26		9.5				
1175a	—	2.96	4.90	—	8.7	80.8	56.4	84.0	26/90
1175b	—	2.68	4.82	—	6.7	80.5	59.3	86.3	26/90

[a] $J_{4,a}$ = 7.9 Hz and $J_{5,b}$ = 2.7 Hz.
[b] Not individually assigned.
[c] $J_{4,a}$ = 9.0 Hz and $J_{5,b}$ = 1.9 Hz.
[d] $J_{5,5'}$ = 9.5 Hz.

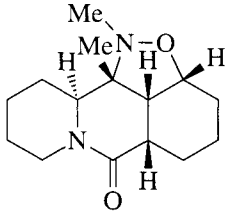


1169

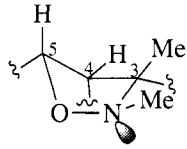


1170a: R^1 = H, R^2 = n-C_4H_9

1170b: R^1 = n-C_4H_9, R^2 = H

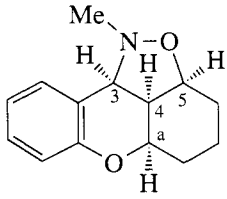


1171



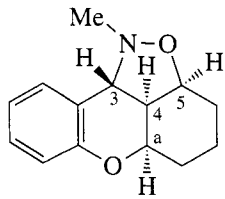
O—N—C_3—C_4—C_5—O

–28.0° 1.9° 22.9° –40.1° 43.1°



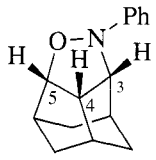
1172a

$J_{3,4}$ = 9 Hz
$J_{4,5}$ = 7 (or 5) Hz
$J_{4,a}$ = 7 (or 9) Hz

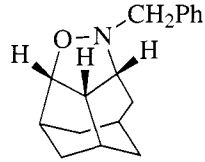


1172b

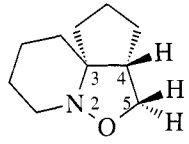
$J_{3,4}$ = 12 Hz
$J_{4,5}$ = 7 Hz
$J_{4,a}$ = 7 Hz



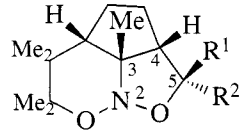
1173a



1173b



1174

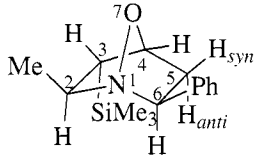


1175a: R^1 = H, R^2 = CO_2Me
1175b: R^1 = CO_2Et, R^2 = H

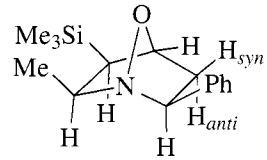
by the rigid tricyclic ring system.[42/85] An antiperiplanar relationship between H3 and H4 in the *trans* derivative **1172b** explains why $J_{3,4\text{-}trans}$ in this compound is higher than $J_{3,4\text{-}cis}$ in **1172a**.[28/70]

Passing to conformational aspects, crystal structure shows that the isoxazolidine ring of **1171** has a slightly distorted envelope conformation with C5 as the out-of-plane atom (isoxazolidine ring torsion angles (°): O–N–C3–C4–C5–O = −28.0, 1.9, 22.9, −40.1, 43.1). Nonbonded interactions between the nearly eclipsed methyl groups are accommodated by a combination of bond lengthening (C–N = 1.509 Å) and bond angle widening (C3–N–CH3 = 115.9°).[51/81]

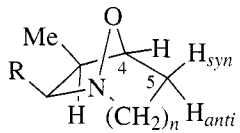
In compounds **1176–1188** the isoxazolidine ring is embedded in a rigid bicyclo[*n*.2.1] skeleton. In some derivatives the oxygen atom is located at the monoatomic bridge with the nitrogen atom at a bridgehead position (**1176a,b**[52/88] **1177**,[46/85] **1183–1185**,[25/79] **1186**,[36/80] and **1188**[40/84]), whereas in other derivatives the oxygen is part of the diatomic bridge with the nitrogen atom either at a bridgehead position (**1178**[46/85] and **1187**[40/84]) or in the diatomic bridge (**1179**,[38/79] **1180**,[51/88] **1181**,[42/89] and **1182**[76/85]).



1176a



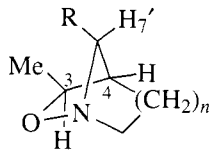
1176b



1177

	H4	$J_{4,5syn}$	$J_{4,5anti}$
a: n = 1, R = H	4.4	6	0
b: n = 3, R = H	4.1	8	0
c: n = 1, R = p-$NO_2C_6H_4$	4.5	5	0

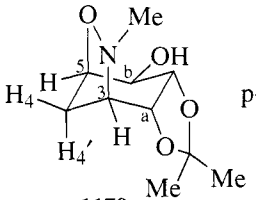
Ref. 46/85; $\delta(CDCl_3)$, J(Hz)



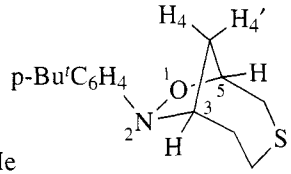
	H3	$J_{3,4}$	$J_{4,7'}$
a: n = 2, R = H	4.35	0	–
b: n = 3, R = H	4.10	1.8	–
c: n = 2, R = p-$NO_2C_6H_4$	4.35	0	0

1178

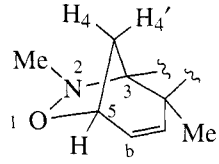
Ref. 46/85; $\delta(CDCl_3)$, J(Hz)



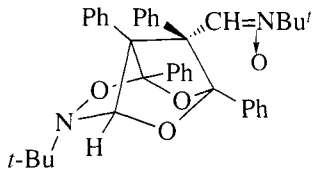
1179



1180



1181



1182

When the isoxazolidine ring is part of a bicyclo[2.2.1] system, stereochemical informations can confidently be inferred from vicinal coupling constants profiting from what is very well established for related norbornane derivatives, in particular, that (1) vicinal *cis* coupling constants between protons of the diatomic bridges are higher by 2–3 Hz than the corresponding *trans* coupling constants; and (2) coupling constants between bridgehead protons and vicinal *anti* (with respect to the monoatomic bridge) protons of the diatomic bridges are close to 0, significantly smaller than those involving *syn* protons and vicinal bridgehead protons. The latter characteristic should be magnified in 7-oxa-1-azanorbornane derivatives (e.g., **1176a** and **1176b**) with respect to the parent norbornane system. In fact, the O–N and O–C bonds of the monoatomic bridge of 7-oxa-1-azanorbornane are shorter than the corresponding C–C bonds in norbornane. As a result, there is widening of the $H_{bridgehead}CCH_{anti}$ and a narrowing of the $H_{bridgehead}CCH_{syn}$ torsion angles by $\approx 10°$ with the former angle that in the heteroderivative more closely approaches 90° (78° in norbornane) while the latter angle reaches 35° (42° in norbornane). These structural changes are clearly reflected in the data of compounds **1176** (Table 4.50), **1177–1178** and **1183–1186** (Table 4.52) with $J_{bridgehead,anti} \approx 0$ Hz and $J_{bridgehead,syn} \geq 4$ Hz. The observation that in 7-oxa-1-aza derivatives, as in norbornane derivatives, *syn* protons of the two diatomic bridges connected by a W path give rise to significant ^4J (e.g., $J_{3\text{-syn},5\text{-syn}}$ = 2.4 Hz in **1176a**) while the corresponding coupling

TABLE 4.50. ^{1}H-NMR DATA [δ ($CDCl_3$), J(Hz)] OF ISOXAZOLIDINES **1176a** AND **1176b**[52/88]

	1176a	**1176b**		**1176a**	**1176b**
H2	2.93	3.37	$J_{2,3}$	6.2	9.5
H3	1.12	1.19	$J_{3,4}$	4.9	0
H4	4.90	4.84	$J_{3,5\text{-}syn}$	2.4	0
$H5_{anti}$	2.22	2.02	$J_{4,5\text{-}anti}$	0	0
$H5_{syn}$	1.90	2.18	$J_{4,5\text{-}syn}$	4.9	4.3
H6	3.74	3.92	$J_{5\text{-}syn,5\text{-}anti}$	11.9	11.2
			$J_{5\text{-}anti,6}$	8.2	8.3
			$J_{5\text{-}syn,6}$	5.2	5.6

between *syn* and *anti* protons falls down to 0 (e.g., $J_{3\text{-anti},5\text{-syn}}$ = 0 Hz in **1176b**) is very useful for stereochemical assignments.

In compounds **1178–1181** the coupling constants between the protons of the monoatomic bridge (i.e., H-7′ in **1178** and H-4 and H4′ in **1179–1181**; see Table 4.51) and the bridgehead protons are noteworthy. The J value involving the proton *syn* to the diatomic bridge is larger ($J_{4,\text{bridgehead}} \geq 5$ Hz) than that involving the *anti* proton ($J_{7',\text{bridgehead}}$ and $J_{4',\text{bridgehead}} \leq 1$ Hz) and this observation provides a very reliable diagnostic tool for determining the stereochemistry of a stereogenic center at the monoatomic bridge in these derivatives.

TABLE 4.51. ^{1}H-NMR DATA [δ, J (Hz)] OF ISOXAZOLIDINES **1179** (C_6D_6), **1180** ($CDCl_3$), AND **1181** ($CDCl_3$)

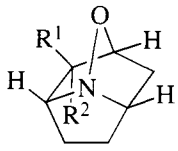
Compound	H3	H4	H4′	H5	$J_{3,4}$	$J_{3,4'}$	$J_{4,4'}$	$J_{4,5}$	$J_{4',5}$	References
1179[a]	2.97	1.63	1.87	4.07	5.0	0	12.0	6.0	0	38/79
1180[b]	4.06	2.20	2.63	5.08	7.6	0	12.3	9.4	<1.0	51/88
1181[c]	—	1.70	2.55	4.38	—	—	11.0	5.5	0	42/89

[a] δ_{NMe} = 2.28, $J_{3,a} \approx J_{5,b}$ = 2.0 Hz, δ_{C3} ($CDCl_3$) = 64.2, δ_{C4} = 27.8, δ_{C5} = 75.3, δ_{NMe} = 46.8.
[b] δ_{C3} = 66.2, δ_{C5} = 78.8.
[c] $J_{5,b}$ = 5.5 Hz , δ_{C3} = 69.1, δ_{C4} = 37.2, δ_{C5} = 70.7.

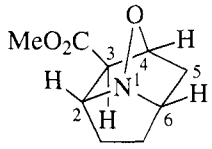
TABLE 4.52. ^{1}H-NMR DATA [δ($CDCl_3$), J(Hz)] OF ISOXAZOLIDINES **1183–1185**[25/79] AND **1186**[36/80]

Compound	H2	H4	H6	$J_{3,4}$	$J_{4,5\text{-}syn}$	$J_{5\text{-}anti,6}$	$J_{5\text{-}syn,6}$
1183a[a]	3.18	4.84	3.67	4.5	4.5	—	—
1183b[b]	3.69	5.03	3.86	0	5.0	—	—
1184	3.53	4.95	3.86	0	5.5	—	—
1185[c]	4.42	5.58	4.76	0	5.5	—	—
1186	—	4.47	3.60	5.0	5.0	5.0	10.5

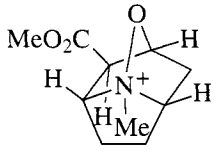
[a] δ_{H3} = 3.67(m).
[b] δ_{H3} = 2.44 (d, $J_{2,3}$ = 3.0 Hz).
[c] MeOD.



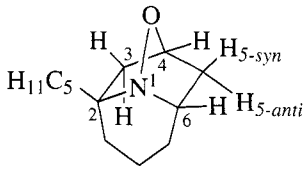
1183a: R^1 = H, R^2 = CN
1183b: R^1 = CN, R^2 = H



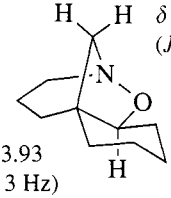
1184



1185



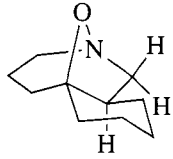
1186



δ 2.57 and 3.38 (J = 11.0 Hz)

$\delta(CDCl_3)$ 3.93 (J = 6 and 3 Hz)
Ref. 40/84

1187

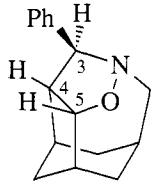


$\delta(CDCl_3)$ 3.27 (d, J = 11.5 Hz)

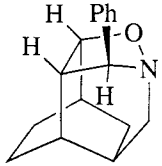
δ 2.94 (dd, J = 11.5 and 4.0 Hz)
Ref. 40/84

1188

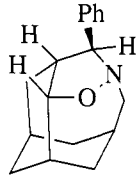
Some further NMR data of polycyclic isoxazolidines, specifically those of compounds **1189–1192** (see Table 4.53), simply confirm the trends and characteristics that have repeatedly been emphasized above.



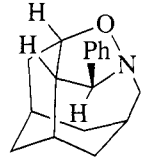
1189



1190



1191



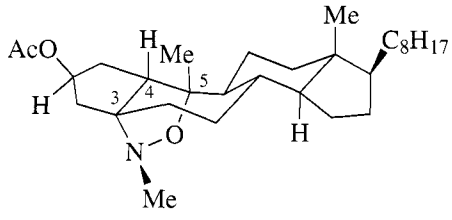
1192

TABLE 4.53. ^{1}H- AND ^{13}C-NMR DATA [$\delta(CDCl_3)$, J (Hz)] OF ISOXAZOLIDINES **1189–1192**

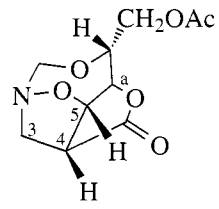
Compound	H3	H5	$J_{3,4}$	$J_{4,5}$	C3	C4	C5	References
1189	4.20	4.90	0	9.0	68.1	61.2	89.1	47/85
1190	4.02	4.15	0	6.0	—	—	—	47/85
1191	4.06	4.74	3.0	10.0	79.5[a]	48.6	81.0[a]	55/88
1192[b]	4.77	4.06	0	7.1	69.8[a]	50.4	74.4[a]	55/88

[a] Not individually assigned.
[b] δ_{H4} = 2.83.

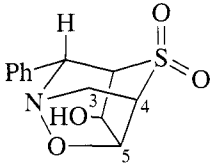
To conclude with a comment on conformations adopted by the isoxazolidine ring in polycyclic derivatives, it is quite evident that in the rigid bicyclo[*n*.2.1] frameworks of compounds **1179–1188**, the isoxazolidine ring is frozen in an envelope conformation as confirmed by the crystal structure of **1182** (ring torsion angles (°): O–N–C3–C4–C5–O = −0.7, 28.8, −42.5, 42.3, −28.0).[76/85] Also the isoxazolidine ring of **1195** (torsion angles (°): O–N–C3–C4–C5–O = −51.5, 49.3, −30.1, −0.4, 32.0) has an envelope conformation with the nitrogen atom as the out-of-plane atom.[10/86] By contrast, compounds **1193** and **1194** provide examples of half-chair conformations. Thus, the isoxazolidine moiety in **1193** adopts a twist conformation with the C3 and nitrogen atom, in the region of maximum pucker, above and below ($^{C3}T_N$) the plane of C4, C5, and O atoms (torsion angles (°): O–N–C3–C4–C5–O = −42.2, 51.8, −43.4, 19.3,13.0) and with the methyl group in pseudoequatorial position.[58/88] A slightly distorted and flattened half-chair conformation (ring torsion angles (°): O–N–C3–C4–C5–O = 34.2, −26.0, 9.1, 11.4, −28.7) is exhibited by the isoxazolidine ring in **1194**, while its lactone moiety has a flat envelope conformation with the carbon atom (a) next to the oxygen as the out-of-plane atom.[68/89]



1193



1194



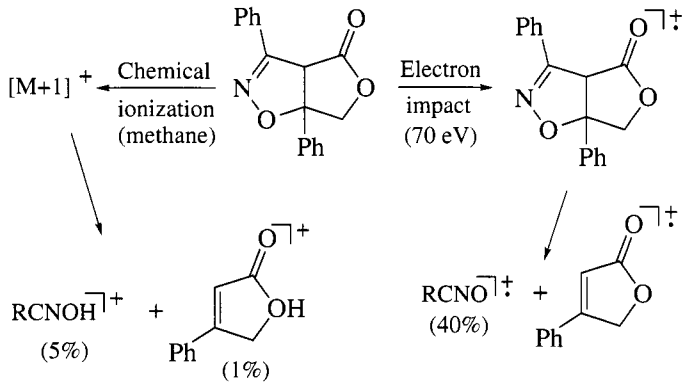
1195

4.4.3. Mass Spectra

Even if mass spectrometry has frequently been used as an analytical tool to characterize fused 2-isoxazolines and fused isoxazolidines, the examples, whose mass fragmentation has been thoroughly discussed, are very scanty.

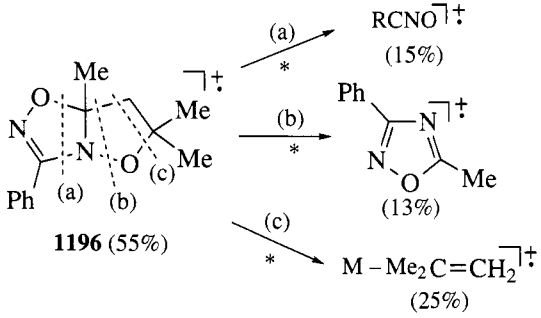
A typical fragmentation observed in mass spectra of 2-isoxazolines and isoxazolidines is the 1,3-dipolar cycloreversion process. For example, in the case of the adduct of benzonitrile oxide to 3-phenylbutenolide, 1,3-dipolar cycloreversion is the only unambiguously interpretable electron-impact-induced

fragmentation (Scheme 4.48). This process gives rise to an intense RCNO radical ion peak and a weak butenolide radical ion peak. Under chemical ionization conditions there is formation of the $[M+1]^+$ ion, which to a small extent suffers decomposition in a "quasi-cycloreversion process" to give the protonated nitrile oxide (prevalent) and phenylbutenolide.[52/74]



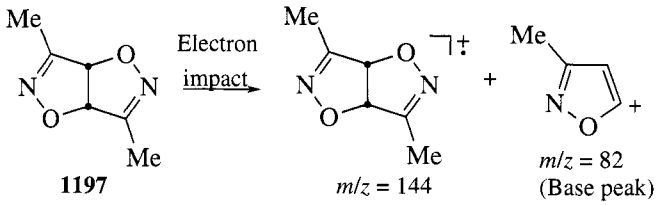
Scheme 4.48

Two out of the three fragmentation pathways inferred from the mass spectrum of the precursor of the molecular ion **1196** can be considered cycloreversions involving fragmentation of the oxadiazoline moiety [pathway (a)] and of the isoxazolidine ring [pathway (c)]. The three pathways are secured by the presence of the corresponding metastable peaks.[56/79]



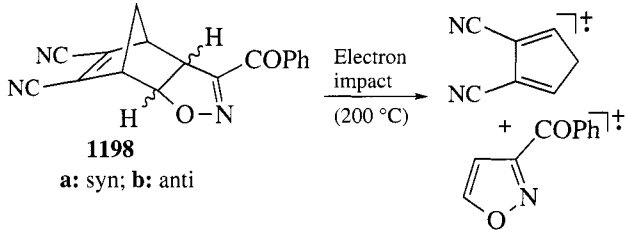
Intense peaks corresponding to fragment ions derived from 1,3-dipolar cycloreversions have also been observed in the mass spectra of bisadducts of nitrile oxides to thiophene (the nitrile oxide radical ion is the more intense of the two peaks)[11/77] and to tetrasubstituted cyclopentadienones (no molecular ion observed)[10/79] as well as in the adducts of nitrile oxides to 2,5-dimethoxy-2,5-dihydrofuran.[9/87]

The molecular ion of **1197** fragments with loss of acetonitrile oxide and hydrogen radical to give the 3-methylisoxazole ion as the most abundant ion.[51/79]



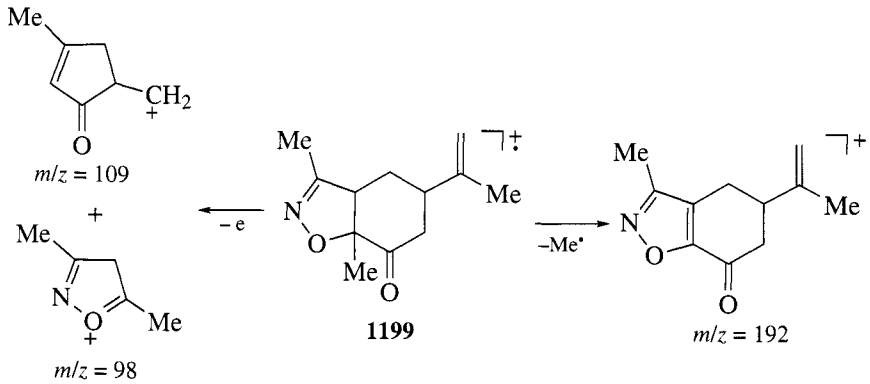
1197

No molecular ion is present in the mass spectra of *syn* and *anti* adducts **1198a** and **1198b** but only peaks derived from a formal electron-impact induced Diels–Alder cycloreversion. However, the high temperature of injection (200°C) might well induce a thermal retro-Diels–Alder reaction (facilitated by formation of the aromatic isoxazole) as a primary process followed by ionization of the resulting fragments.[8/77]

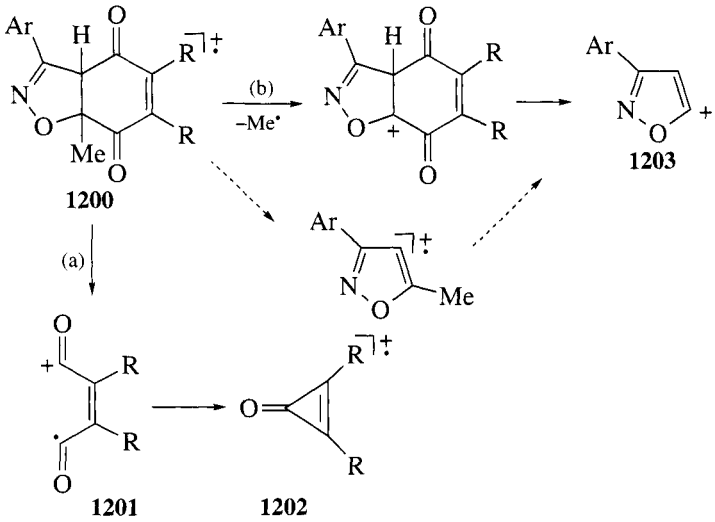


1198
a: syn; **b:** anti

However, the presence of cycloreversion processes as important fragmentation pathways is not the rule, as shown by the following few examples. Thus, the radical ion **1199** undergoes both fragmentation of the six-membered ring, with formation of the protonated dimethyl isoxazole (*m/z* = 98), and aromatization with loss of the angular methyl group.[16/76]

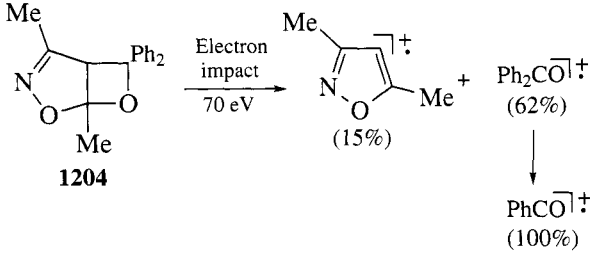


In the mass spectra of the adducts of nitrile oxides to double bonds of substituted *p*-benzoquinones, the peak of the molecular ion, namely, **1200**, is generally very weak, while in most cases the most intense signals are due either to **1201** or **1202** resulting from pathway (a). The other important fragmentation of **1200** [pathway (b)] starts with the loss of the angular methyl and terminates with formation of the isoxazole ion **1203**.[11/83]

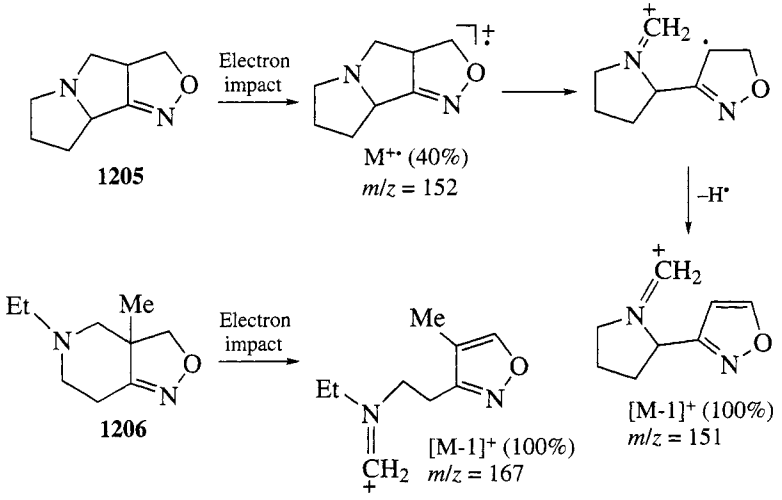


Ar = 2,6-$Cl_2C_6H_3$, 2,4,6-$Me_3C_6H_2$ R = H, Me etc.
2,3,5,6-Me_4-C_6H

As expected, the highly prevalent decomposition of **1204** under electron bombardment affords the radical ions of 3,5-dimethylisoxazole and of benzophenone.[60/81]



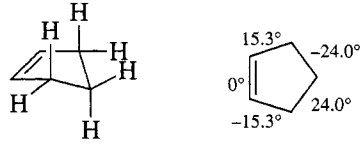
Finally, the mass spectrometric data of the 3,4-fused isoxazolines of type **1205** and **1206** show that the aromatization of these compounds into isoxazole derivatives is the most important reaction that occurs in the mass spectrometer. The aromatization occurs after cleavage, facilitated by the presence of the amine function, followed by loss of an H• radical and formation of a $[M-1]^+$ ion, a very stable even-electron cation.[58/91]



4.4.4. Structural Data from X-Ray Analysis

4.4.4.1. Fused 2-Isoxazolines

The conformational behavior of cyclopentene is much simpler than that of cyclopentane. In fact, cyclopentene, with its torsion angles imposed by the double bond, can adopt only the envelope conformation, which is significantly less puckered than that of cyclopentane.



Ring torsion angles in the envelope conformation of cyclopentene

Likewise, the conformational behavior of isoxazolines does not present all the problems illustrated for isoxazolidines. The C=N moiety tends to impose an envelope conformation with O, N, C3 and C4 in the same plane and C5 as the out-of-plane atom (E_{C5}). Moreover, in the planar conformation of the parent 2-isoxazoline, with respect to cyclopentene, there is a lower number of synperiplanar destabilizing C–H/C–H interactions, with resultant reduction of the unfavorable torsional strain. As a consequence, 2-isoxazolines tend to be more planar than cyclopentenes. For example, MM2 and semiempirical calculations give a planar structure as the global minimum for the parent 2-isoxazoline.

TABLE 4.54. BOND LENGTHS (Å) OF 2-ISOXAZOLINE RINGS

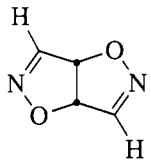
Compound	N–O	C3–N	C3–C4	C4–C5	C5–O	References
922	1.418	1.257	1.480	1.493	1.452	51/79
963	1.412	1.276	1.502	1.529	1.452	59/86
1003	1.425	1.282	1.502	1.533	1.442	2/92
1005	1.427	1.287	1.509	1.534	1.436	18/82
1012	1.424	1.282	1.496	1.517	1.454	46/88
1207	1.426	1.260	1.501	1.495	1.436	8/90
1208	1.405	1.286	1.506	1.527	1.452	56/89
1209	1.412	1.280	1.496	1.544	1.446	5/90
1210	1.443	1.267	1.483	1.511	1.452	59/91
1211	1.400	1.281	1.505	1.528	1.491	69/89
1212	1.423	1.295	1.537	1.573	1.462	48/78
1213	1.417	1.280	1.536	1.567	1.480	64/79
1214	1.396	1.279	1.508	1.518	1.474	68/87

TABLE 4.55. BOND ANGLES [DEGREES (°)] OF 2-ISOXAZOLINE RINGS

Compound	O–N–C3	N–C3–C4	C3–C4–C5	C4–C5–O	C5–O–N
922	109.2	115.1	101.3	105.9	108.3
963	109.8	114.5	100.4	105.8	109.3
1003	108.6	113.4	99.7	103.4	108.2
1005	108.6	113.7	98.2	104.4	107.3
1012	108.2	113.2	98.5	102.5	106.5
1207	109.0	114.2	99.5	105.8	107.4
1208	109.6	113.0	99.3	104.1	108.0
1209	110.2	113.7	101.4	104.7	109.9
1210	106.7	116.8	100.2	105.1	108.9
1211	110.0	113.9	101.7	103.6	109.7
1212	110.7	114.0	97.8	105.2	107.8
1213	109.5	115.3	100.0	104.5	110.8
1214	110.9	112.6	102.0	104.1	109.4

Compounds **922**, **963**, **1003**, **1005**, **1012**, and **1207–1214** provide examples of fused 2-isoxazolines whose structure has been determined by single crystal X-ray analysis. The torsion angles of the isoxazoline ring are reported below the formulas, while bond lengths and bond angles are gathered in Table 4.54 and Table 4.55, respectively.

Some of the reported examples have an almost planar 2-isoxazoline ring (i.e., **922**, **963**, **1209**, and **1213**), and in others (i.e., **1210**, **1211**, and **1214**) the heterocyclic ring is slightly puckered. When a substantial puckering is present, the 2-isoxazoline ring adopts, in agrement with predictions, a slightly distorted E_{C5} conformation (envelope with C5 at the apex). The displacements of the isoxazoline atoms with respect to the reference plane (the least-square plane) can be described by the Cremer and Pople puckering parameters q and φ (see Section 4.4.2.1).[36/75] For example, in the case of **1003**, **1211**, and **1214**, the q (Å)/φ(°) pairs were found to be the following: 0.249/323 (oxygen as atom 1, nitrogen as atom 2, etc.),[2/92] 0.102/140,[69/89] and 0.10/316,[68/87] respectively.



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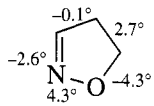

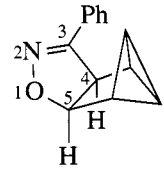

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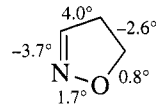

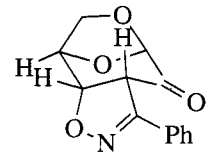

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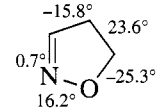

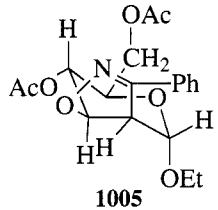

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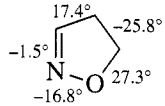

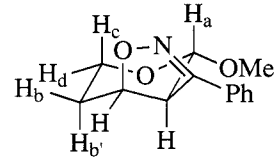

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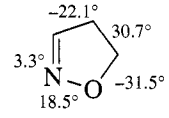

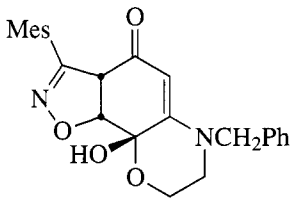

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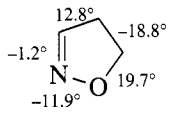

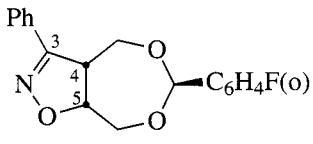

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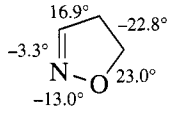

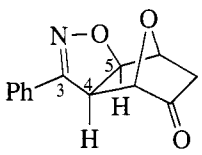

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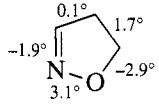

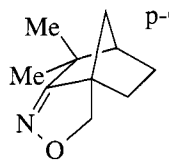

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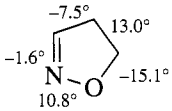
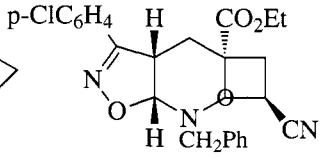
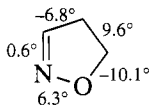
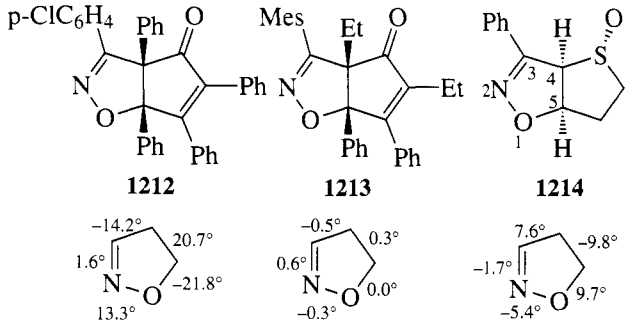




1211





It is clear that the amount of puckering of the 2-isoxazoline moiety is dictated by the fused ring and by substituents. In this context it is surprising, at first sight, that compounds **1212** and **1213**, which look so similar, actually exhibit a strongly different puckering of the isoxazoline ring. However, the two structures differ in other important details. For example, the aromatic ring at position 3 is almost coplanar with the isoxazoline ring in **1212** (dihedral angle between the two least-square planes = 7°) while the two planes are almost perpendicular to each other (dihedral angle = 85°) in **1213**. Moreover, the dihedral angle between the least-square planes of the two five-membered rings in **1212** (107°) is 6° smaller than that in **1213** (113°).

As for this latter angle, in **1214** it has a value that is the average of those in **1212** and **1213**.

More interesting is the remark on the conformational behavior of the aryl substituent at position 3, which actually is general; as expected, aromatic rings at position 3 tend to be coplanar with the C=N bond to take advantage of conjugation [reported values for dihedral angles between the two planes range from 23° [47/78] (e.g., 20° in **1003**)[2/92] to 4° (in **1214**, 4.6° in **1012**)], but the presence of two *ortho* substituents leads to a perpendicular arrangement (as in **1213**) in order to lessen as far as possible steric interactions.

As for bond angles, O–N–C3 and C5–O–N have similar values (≈109°), which are about 5° larger than those of C4–C5–O. The highest figures are, as expected, those of N–C3–C4 (≈114°), and the lowest are those of C3–C4–C5 (≈100°).

The data of Table 4.54 demonstrate that bond lengths do not change significantly (variations ≤ 0.08 Å) even when the 2-isoxazoline moiety is embedded in very different structures.

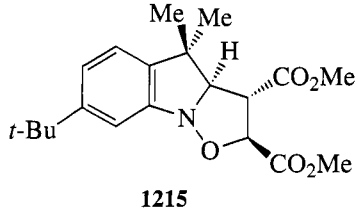
In **1211** the six-membered ring has a boat-like conformation.

4.4.4.2. Fused Isoxazolidines

The conformational behavior of isoxazolidines has been discussed in Section 4.4.2. Compound **1218** represents a further example of a strongly puckered

isoxazolidine ring with an intermediate E/T structure, while the conformation of the isoxazolidine ring of **1219** can be classified as twist.

Variation of isoxazolidine bond lengths, although slightly larger than that of 2-isoxazolines, is less than 0.09 Å, while that of bond angles ranges from 4° for C4–C5–O to 9° for O–N–C3 (Tables 4.56 and 4.57).



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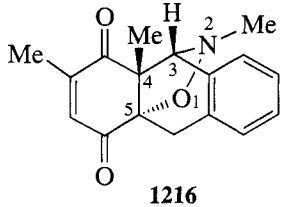
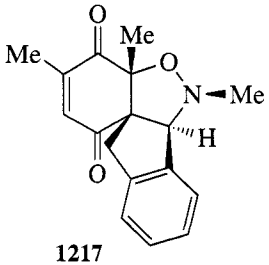


1216



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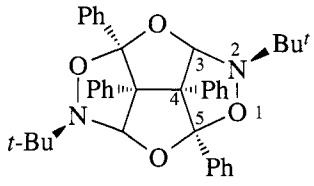
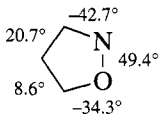
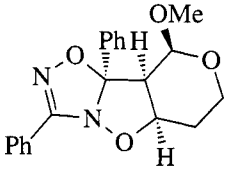


1218





1219

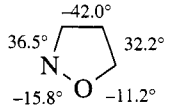


TABLE 4.56. BOND LENGTHS (Å) OF ISOXAZOLIDINE RINGS

Compound	N–O	C3–N	C3–C4	C4–C5	C5–O	References
(i)-**1045**	1.458	1.507	1.508	1.534	1.460	63/79
(o)-**1045**	1.426	1.487	1.529	1.538	1.451	63/79
1047	1.429	1.473	1.531	1.528	1.482	65/83
1048	1.442	1.469	1.550	1.534	1.471	22/89
1049	1.463	1.494	1.560	1.553	1.421	2/92
1050b	1.457	1.458	1.560	1.548	1.438	20/85
1110a	1.436	1.476	1.532	1.510	1.464	72/86
1110b	1.446	1.486	1.529	1.528	1.449	72/86
1110c	1.437	1.473	1.566	1.519	1.453	72/86
1110d	1.444	1.475	1.556	1.528	1.433	72/86
1110e	1.460	1.489	1.516	1.526	1.447	72/86
1111	1.461	1.471	1.520	1.517	1.478	66/83
1112	1.471	1.485	1.546	1.506	1.473	50/80
1119	1.432	1.524	1.519	1.538	1.475	33/89
1132b	1.459	1.475	1.541	1.521	1.432	36/83

TABLE 4.56. (*continued*)

Compound	N–O	C3–N	C3–C4	C4–C5	C5–O	References
1137	1.439	1.463	1.531	1.538	1.455	59/89
1161d	1.47	1.48	1.53	1.53	1.45	29/70
1171	1.446	1.509	1.545	1.517	1.438	51/81
1182	1.476	1.425	1.557	1.569	1.411	76/85
1193	1.461	1.479	1.539	1.528	1.471	58/88
1194	1.450	1.469	1.528	1.512	1.432	68/89
1195	1.458	1.477	1.547	1.547	1.458	10/86
1215	1.439	1.495	1.547	1.535	1.449	32/85
1216	1.492	1.480	1.531	1.545	1.443	43/87
1217	1.483	1.494	1.571	1.530	1.425	43/87
1218	1.465	1.437	1.538	1.586	1.432	43/84
1219	1.473	1.473	1.519	1.517	1.450	46/88

TABLE 4.57. BOND ANGLES [DEGREES (°)] OF ISOXAZOLIDINE RINGS

Compound	O–N–C3	N–C3–C4	C3–C4–C5	C4–C5–O	C5–O–N
(i)-**1045**	100.0	106.9	99.9	104.5	112.9
(o)-**1045**	103.1	106.3	103.5	104.3	107.7
1047	104.8	106.7	102.4	107.1	108.5
1048	104.7	103.9	102.9	106.4	107.9
1049	103.5	102.6	103.5	104.8	103.8
1050b	102.0	102.7	101.3	106.4	104.8
1110a	102.2	105.9	103.2	106.1	108.0
1110b	102.6	105.9	103.6	105.8	107.6
1110c	102.3	105.5	102.0	106.6	107.6
1110d	102.4	105.2	102.5	106.4	108.1
1110e	103.5	105.4	101.7	105.4	111.2
1111	101.6	100.4	102.8	104.4	106.9
1112	107.8	105.1	103.6	103.8	107.4
1119	103.3	103.2	103.7	106.4	107.0
1132b	104.7	107.2	101.9	103.4	106.7
1137	107.0	106.9	103.4	103.3	107.0
1161d	100	100	102	105	105
1171	106.7	104.5	101.4	103.1	105.6
1182	105.7	104.9	94.6	105.3	108.8
1193	102.1	96.9	103.4	103.6	106.1
1194	104.0	107.0	103.8	106.5	107.9
1195	98.4	103.3	101.6	104.4	105.1
1215	106.1	103.2	104.8	106.6	107.9
1218	103.2	103.9	101.8	104.5	103.5
1219	106.9	105.7	100.2	103.4	105.9

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