Chemistry of Heterocyclic Compounds, Vol. 34, No. 4, 1998

2,3,4,5-TETRAHYDROPYRIDINE 1-OXIDES. SYNTHESIS AND PROPERTIES (REVIEW)

M.-G. A. Shvekhgeimer

Published data on the synthesis and transformations of 2,3,4,5-tetrahydropyridine 1-oxides are summarized for the first time, classified, and analyzed.

INTRODUCTION

Among other cyclic nitrones, the 1-oxides of 2,3,4,5-tetrahydropyridine (Δ^1-piperideine) and its derivatives are extremely reactive 1,3-dipoles that enter readily into [3+2]-cycloaddition with alkenes and alkynes and also undergo a series of other transformations. The chemistry of these oxides has developed particularly strongly in the last 10-15 years, when it was found that many of the products from 1,3-cycloaddition with these compounds were useful starting materials for the synthesis of a series of alkaloids.

There are now a large number of papers in the literature on the synthesis of the nitrones and their reactions and also on the transformations of the products from their 1,3-cycloaddition to unsaturated compounds. In 1975 a comprehensive review of the papers containing data on 1,3-cycloaddition with various nitrones was published [1]. However, it did not contain information on methods for the synthesis of 2,3,4,5-tetrahydropyridine 1-oxides; data on their reactions are scarce and lost among the mass of other material. Limited information on the chemistry of the N-oxides of 2,3,4,5-tetrahydropyridines are given in the monograph [2], where there are a small number of examples of the synthesis of alkaloids based on cyclic nitrones.

It was felt that a summary of published data on the chemistry of 2,3,4,5-tetrahydropyridine 1-oxides would be interesting and useful to investigators working in the region of nitrogen-containing heterocyclic compounds.

1. SYNTHESIS OF THE 1-OXIDES OF 2,3,4,5-TETRAHYDROPYRIDINE AND ITS DERIVATIVES

Four main methods have been developed for the production of the 1-oxides of 2,3,4,5-tetrahydropyridine and its derivatives: The oxidation of 1-hydroxypiperidine and its derivatives; the oxidation of piperidine and its derivatives; the oxidative cleavage of derivatives of perhydroisoxazolo[2,3-*a*]pyridine; the cyclization of unsaturated oximes or the corresponding hydroxylamine derivatives.

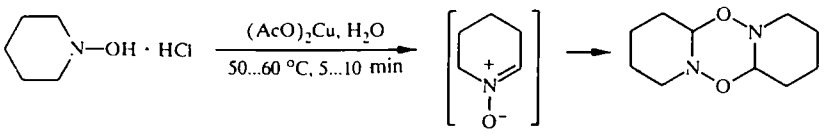
1.1. Oxidation of 1-Hydroxypiperidine and Its Derivatives

2,3,4,5-Tetrahydropyridine 1-oxide (I) was synthesized by German scientists by the action of copper acetate on 1-hydroxypiperidine hydrochloride briefly heated in an aqueous medium. Here the nitrone (I) was isolated in the form of the dimer (II), the yield of which depended on the treatment of the reaction mixture [3].

Thus, in the case of treatment with sodium bicarbonate solution at 20°C for 12 h the yield of the product (II) amounted to 32%; it was possible to increase the yield to 46% by washing the reaction mixture with cold water and to 50% by boiling it with petroleum ether [3].

A. N. Kosygin Moscow State Textile Academy, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 435-481, April, 1998. Original article submitted April 1, 1996.

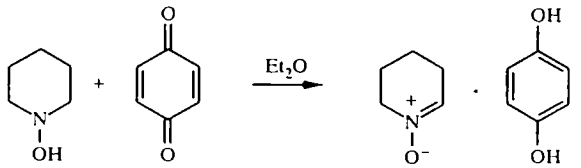
0009-3122/98/3404-0387$20.00



I II

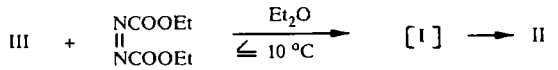
The dimer (II) was also obtained from 1-hydroxypiperidine (III) by the action of mercuric acetate in chloroform at 20°C [4].

The reaction of the hydroxy derivative (III) with quinone in ether gave a 35% yield of the complex of the nitrone (I) with hydroquinone (IV) [5].

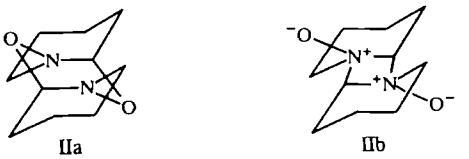


III IV

The same paper described the production of the nitrone (I), isolated in the form of the dimer (II), by the reaction of the hydroxy derivative (III) with azodicarboxylic ester EtOOCN=NCOOEt at low temperature.

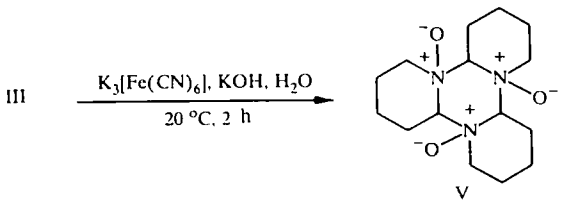


After oxidizing compound (III) by the familiar method [3] the authors in [6] extracted the reaction mixture with ether and obtained the dimer (II) in the pure form. According to their data, the dimer represented a mixture of the valence isomers (IIa) (mostly in the solid state) and (IIb) (mostly in the form of a hydrate).



IIa IIb

Oxidation of the hydroxy derivative (III) with potassium hexacyanoferrate in the presence of potassium hydroxide gave a 41% yield of the trimer (V) of the nitrone (I) [7].

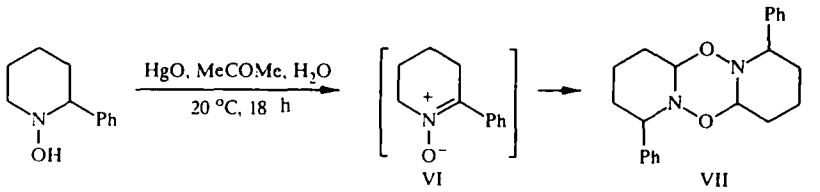


V

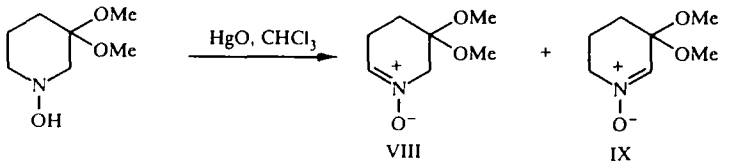
Compound (V) is formed with a quantitative yield by the treatment of the dimer (II) with 2 N hydrochloric acid and then with an aqueous solution of potassium hydroxide at 20°C [7].

The method most widely used for the production of six-membered cyclic nitrones from the respective 1-hydroxy derivatives is the oxidation of the latter with yellow mercuric oxide. Such transformation of compound (III) into the nitrone (I) was conducted in chloroform [8-12] or in dichloromethane [13-17] at temperatures below 0°C [13-15], at 0°C [11, 15, 17], and at 20°C [8-12, 16].

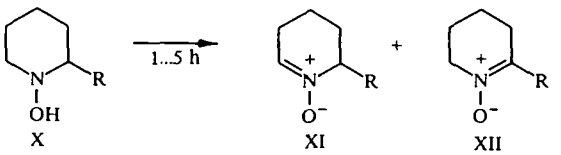
2-Phenyl-2,3,4,5-tetrahydropyridine 1-oxide (VI), isolated with a yield of 29% in the form of the dimer (VII), was synthesized by the oxidation of 1-hydroxy-2-phenylpiperidine (VI) with yellow mercuric oxide [7].



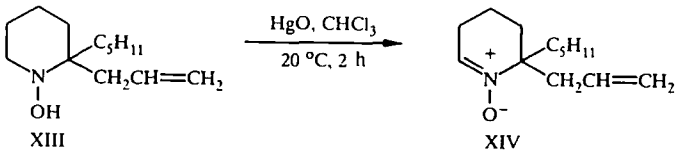
The oxidation of 1-hydroxy-3,3-dimethoxypiperidine with mercuric oxide resulted in the formation of a mixture of 3,3-dimethoxy-2,3,4,5-tetrahydropyridine 1-oxide (VIII) and 5,5-dimethoxy-2,3,4,5-tetrahydropyridine 1-oxide (IX). The ratio of (VIII) to (IX) was 3:1 if the reaction was conducted at $-10°C$ or 1:1 at 0°C [18].



A series of derivatives (X) of 1-hydroxypiperidine (III) containing various substituents at position 2 were oxidized with mercuric oxide in chloroform [4, 8, 19, 20] or in dichloromethane [21] and also with quinone in dichloromethane [21]. As a result the corresponding derivatives of 2,3,4,5-tetrahydropyridine were obtained in the form of mixtures of the aldonitrones (XI) and ketonitrones (XII) (Table 1). It was established that the ratio of (XI) to (XII) varied according to the oxidizing agent [21].



One product (XIV) was isolated as a result of the oxidation of the hydroxy derivative (XIII) containing two substituents at position 2 [20].



It is interesting that the oxidation of the diastereomers of 1-hydroxy-2-pentyl-6-allylpiperidine (XV, XVI) with mercuric oxide under identical conditions led to different products. Thus, the nitrone (XVII) was obtained from the *cis* isomer (XV) and the nitrone (XVIII) from the *trans* isomer (XVI) [20].

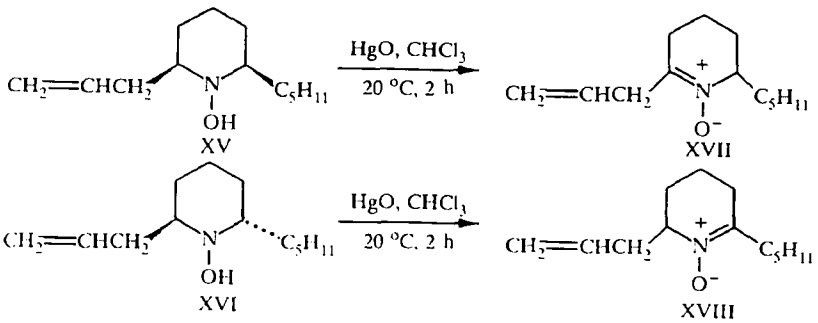
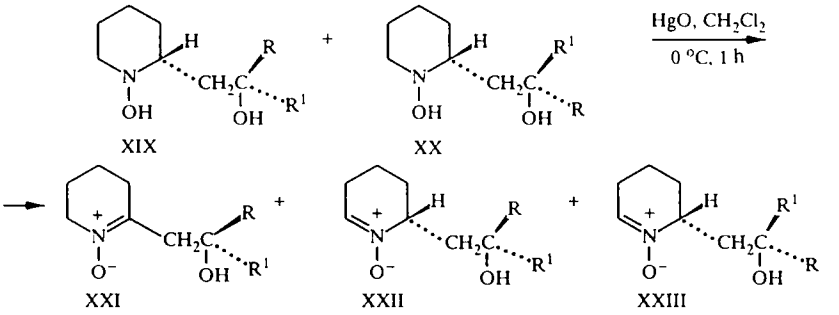


TABLE 1. Conditions for the Oxidation of Compounds (X) and the Ratios of the Isomers (XI) and (XII) Formed

R	Oxidizing agent	Temperature, °C	Reaction time, h	(XI): (XII) ratio	Reference
t-BuMe$_2$SiOCH(Me)(CH$_2$)$_3$	HgO	45	5	25 : 75	8, 19
C_5H_9	HgO	20	1	—	4
C_5H_{11}	HgO	20	3	—	20
Me	HgO	0	1	25 : 75	21
Me	Quinone	0		18 : 82	21
PhCH$_2$	HgO	0	1	25 : 75	21
PhCH$_2$	Quinone	0		20 : 80	21

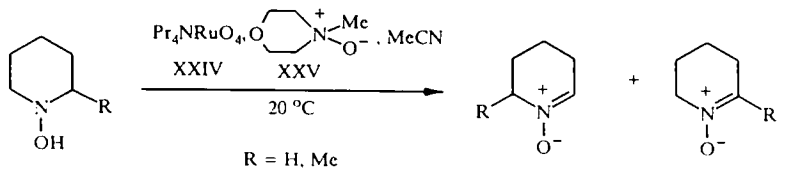
The joint oxidation of the diastereomers (XIX, XX) with mercuric oxide under analogous conditions gives the ketonitrone (XXI) and a mixture of the two diastereomeric aldonitrones (XXII, XXIII). The overall amount of the latter products increases for compounds with a tertiary hydroxyl group in the side chain [21].



XIX XX XXI XXII XXIII

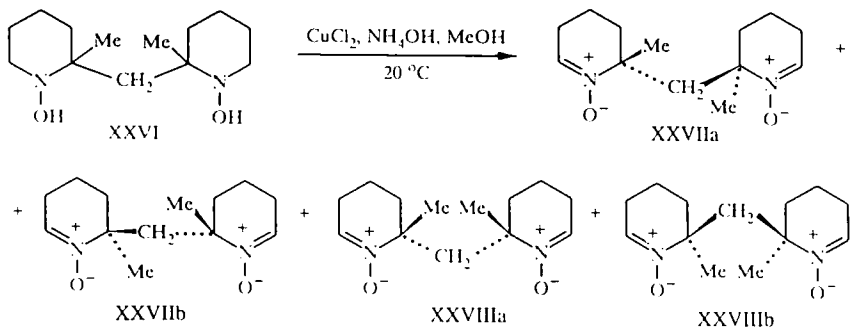
R, R^1, ratio XXI : (XXII + XXIII): CH$_2$OH, H, 35 : 65; Ph, H, 30 : 70; CH$_2$OH, CH$_2$OH, 40 : 60; Me, Ph, 7 : 93; Me, CH$_2$OH, 10 : 90; Me, CH$_2$OSiMe$_2$Bu-*t*, 5 : 95; Me, CH$_2$CH$_2$OH, 5 : 95; CH$_2$CH$_2$OH, CH$_2$OH, 10 : 90

Recently, the system consisting of tetrapropylammonium perruthenate (XXIV) and 1-methylmorpholine 1-oxide (XXV) was used for the conversion of the 1-hydroxy derivatives of piperidine into the respective nitrones [22].



The total yield of the products amounted to 79% for R = H and 100% for R = Me; in the absence of Pr_4NRuO_4 it was less than 10% even after prolonged treatment of the reagents (3 days).

As a result of the oxidation of compound (XXVI) in the presence of copper chloride a mixture of the aldonitrones (XXVIIa, b) and (XXVIIIa, b) was obtained with an overall yield of 31%. The ratio of (XXVII) to (XXVIII) was 1.5:1 [23].



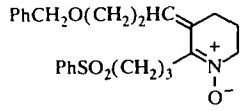
XXVI XXVIIa XXVIIb XXVIIIa XXVIIIb

TABLE 2. Conditions and Results of the Oxidative Cleavage of Compounds (XXXII)

XXXIII (eq.)	Solvent	Temperature, °C	(XXXIV): (XXXV) ratio	Yield of (XXXIV) + (XXXV)
1	CH_2Cl_2	-78	1,22 : 1	93
1	CH_2Cl_2	20	1,4 : 1	98
1	CH_2Cl_2	40	1,3 : 1	99
1	MeOH	20	2,38 : 1	80
1,5	MeOH	20	5,46 : 1	70
2	MeOH	20	Only XXXIV	14
1,5	MeOH	-78...20	5,9 : 1	74
1,3	MeOH	45	2,7 : 1	82

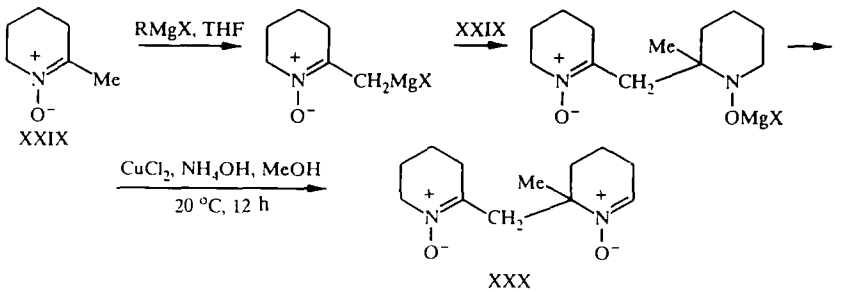
TABLE 3. Conditions for the Oxidative Cleavage of Compounds (XLIX) and the Yields of the Nitrones (L) and (LI)

Oxidizing agent	Solvent	Temperature, °C	Reaction time	Yield, %	
				L	LI
XXXIII (60%)	CH_2Cl_2	-78	5 min	21	56
XXXIII (75%)	CH_2Cl_2	20	5 min	46	23
XXXIII (80%)	CH_2Cl_2	20	5 min	21	56
XXXIII (75%)	CH_2Cl_2	40	55 min	18	—
K-Monoperoxyphthalate (90%)	MeOH	-78...20	20 min	—	62
K-Monoperoxyphthalate (90%)	MeOH	20	20 min	—	68
$KHSO_5$ (2 eq.)	MeOH	65	2 h	—	15*
CF_3COOOH	CH_2Cl_2 †	20	5 min	14	43
t-BuOOH (2 eq.)	CH_2Cl_2	0...20	24 h	—	—
XXXI (R = H)	CH_2Cl_2	20	16 h	38	28

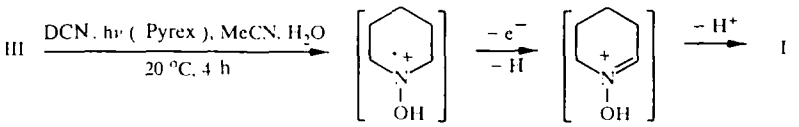
*The product  is also formed with a 32% yield.

†The reaction was carried out in an atmosphere of argon.

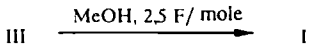
In the same paper the bisnitrone (XXX) was obtained with a yield of 12% from 6-methyl-2,3,4,5-tetrahydropyridine 1-oxide (XXIX).



During exposure to a 450-W medium-pressure mercury lamp in the presence of an electron acceptor (1,4-dicyanonaphthalene, DCN) at room temperature in aqueous acetonitrile the hydroxy derivative (III) is converted into the nitrone (I) (yield 90%) [24].

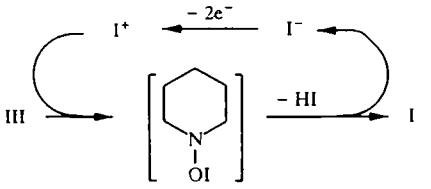


The electrochemical oxidation of the hydroxy derivative (III) to the nitrone (I) was also realized. The reaction was carried out by passing current through a solution of the electrolyte in methanol [25].

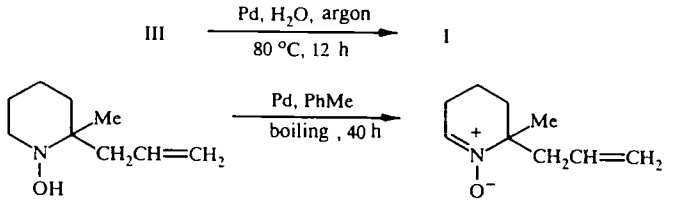


Electrolyte, amount (eq), yield (%): NaI, 0,2, 92; NaI, 0,5, 90; NaI 1, 89; KI, 0,2, 83; $Et_4N^+I^-$, 0,2, 80; NaBr, 0,2, 54; NaCl, 0,2, 16

In the same work the nitrone (XXIX) was obtained during the analogous oxidation of 1-hydroxy-2-methylpiperidine (2.2 F, KI, MeOH) (yield 68%). The authors propose the following scheme for the oxidation of I^- to active I^+ at the anode and the regeneration of I^-:

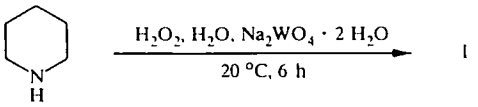


Palladium black was used to convert the 1-hydroxy derivative (III) or 1-hydroxy-2-allyl-2-methylpiperidine into the corresponding nitrones [26].



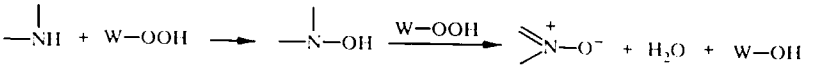
1.2. Oxidation of Compounds of the Piperidine Series

For the oxidation of compounds of the piperidine series to nitrones it is possible to use the hydrogen peroxide–$Na_2WO_4 \cdot 2H_2O$ system [27-30]. Thus, treatment of piperidine with a 30% aqueous solution of hydrogen peroxide in the presence of $Na_2WO_4 \cdot 2H_2O$ gave the nitrone (I) (yield 40%). Under analogous conditions (reaction time 3 h) 2-methylpiperidine gave the nitrone (XXIX) (yield 76%) [27].



The latter was obtained with a 68% yield as a result of the treatment of 2-methylpiperidine with the same oxidizing agent at 0°C in an atmosphere of argon [30].

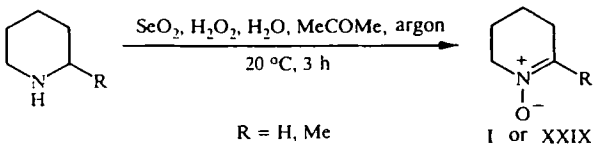
The following scheme was proposed for the oxidation of secondary amines to nitrones by tungsten peracids [30]:



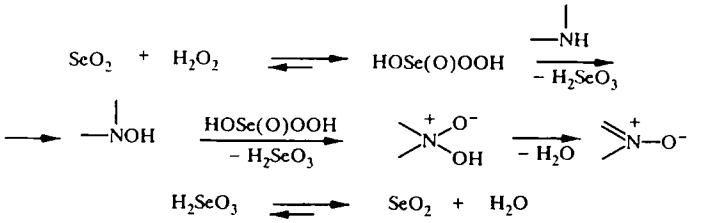
W—OOH (W = WO_5^-, WO_4^-, WO_6^-)

The transformation of piperidine into the nitrone (I) by the action of hydrogen peroxide and selenium oxide was described in the Japanese patent [31].

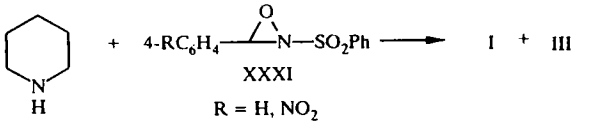
The products (I) and (XXIX) were obtained with yields of 88 or 79% respectively as a result of the treatment of piperidine or 2-methylpiperidine with 30% hydrogen peroxide and SeO_2 in an atmosphere of argon [32].



In the opinion of the authors of this paper the mechanism of the transformation of secondary amines into nitrones by the action of the $H_2O_2-SeO_2$ system can be represented by the following scheme:

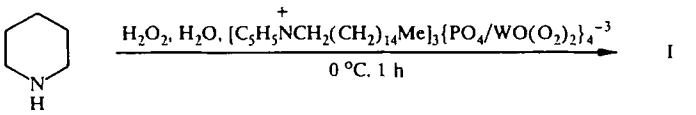


The oxidation of piperidine by oxazidirine derivatives (XXXI) was also studied [33]. The formation of the nitrone (I) and the hydroxy derivative (III) was detected by PMR.



It was shown that the product (III) is mainly formed if one equivalent of the oxidizing agent is used, while the use of two equivalents leads mainly to the product (I).

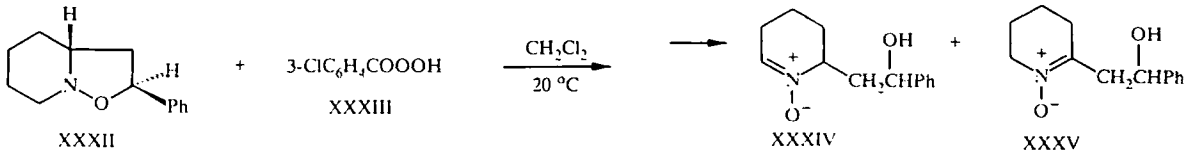
The nitrone (I) was synthesized with a 55% yield as a result of the treatment of piperidine with 35% hydrogen peroxide in the presence of tris(cetylpyridinium) tetrakis(diperoxotungsto)phosphate [34].



1.3. Oxidative Cleavage of Perhydroisoxazolo[2,3-*a*]pyridine Derivatives

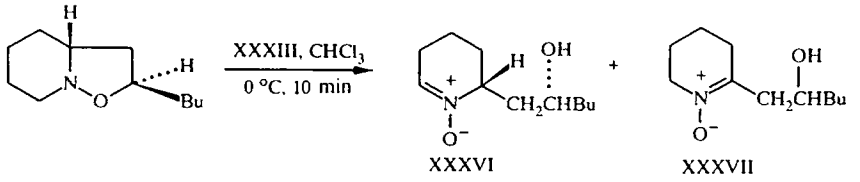
This method, developed in the last decade, usually involves the action of oxidizing agents on the products from the 1,3-dipolar cycloaddition of six-membered cyclic nitrones to alkenes. It results in the formation of nitrones with more complex structures than those used in cycloaddition.

The exo isomer of 8-phenyl-9-oxa-1-azabicyclo[4.3.0]nonane (XXXII) is converted during oxidation with 3-chloroperbenzoic acid (XXXIII) into a mixture of the aldonitrone (XXXIV) and the ketonitrone (XXXV), which the authors were unable to separate [35, 36].



In the same work the oxaziridine derivative (XXXI) (R = H) was also used as oxidizing agent in methylene chloride at 20°C. The overall yield of the nitrones (XXXIV) and (XXXV) here amounted to 88%, and the ratio of (XXXIV) to (XXXV) was 1.55:1.

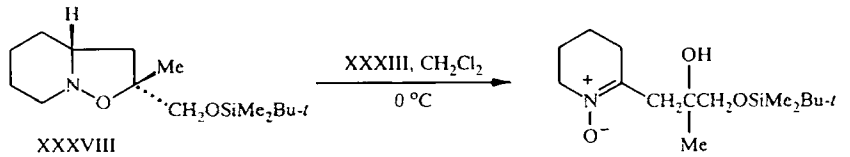
The oxidation of the exo isomer of 8-butyl-9-oxa-1-azabicyclo[4.3.0]nonane by the peracid (XXXIII) leads to the formation of the isomeric 1-oxides of 2-(2-hydroxyhexyl)-2,3,4,5-tetrahydropyridine (XXXVI) and 6-(2-hydroxyhexyl)-2,3,4,5-tetrahydropyridine (XXXVII) [36].



XXXVI XXXVII

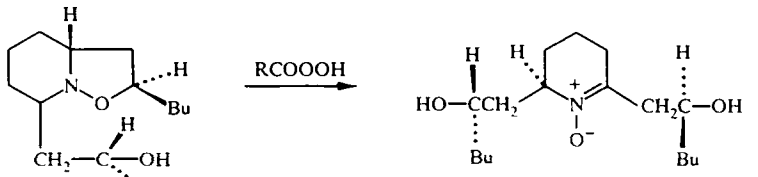
The reaction was studied in detail in [37] under various conditions. The overall yields of the products (XXXIV) and (XXXV) and also their ratios were determined (Table 2).

However, only the ketonitrone (XXXIX) is formed in the case of compound (XXXVIII), containing two substituents at position 9 [21].



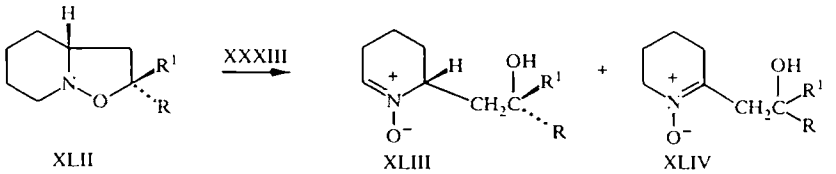
XXXVIII XXXIX

It was shown that the oxidative cleavage of the 9-oxa-1-azabicyclo[4.3.0]nonane derivative (XL) takes place stereoselectively with the formation of the product (XLI) [38].



XL XLI

Depending on the nature of the substituents at position 8, either a mixture of the ketonitrone and the aldonitrone or only the aldonitrone is formed from derivatives of 9-oxa-1-azabicyclo[4.3.0]nonane (XLII) during oxidative cleavage. The treatment of compounds (XLII) with the peracid (XXXIII) led to mixtures of the respective aldonitrone (XLIII) and the ketonitrone (XLIV) in various ratios, and only in the case of R = CH_2OH and R^1 = H was the aldonitrone formed alone [39].

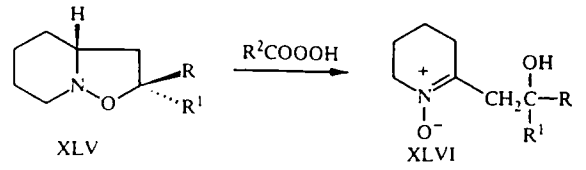


XLII XLIII XLIV

R, R^1, ratio XLIII : XLIV: H, Ph, 35 : 65; COOMe, Me, 15 : 85; H, CH_2OH, 30 : 70; H, CH_2OAc, 20 : 80; CH_2OH, H, 100 : 0

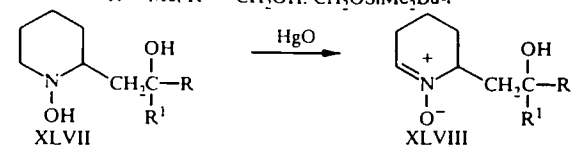
In the same work a mixture (82:18) of the products (XLIII) and (XLIV) (R = H, R^1 = Ph) was obtained during the treatment of 1-hydroxy-2-(2-hydroxy-2-phenylethyl)piperidine with yellow mercuric oxide in dichloromethane.

It was shown that only the ketonitrone (XLVI) was formed during the oxidative cleavage of derivatives of 9-oxa-1-azabicyclo[4.3.0]nonane (XLV) by the action of peracids, and only the aldonitrone (XLVIII) was formed as a result of the oxidation of the dihydroxy derivatives (XLVII) with yellow mercuric oxide [40].



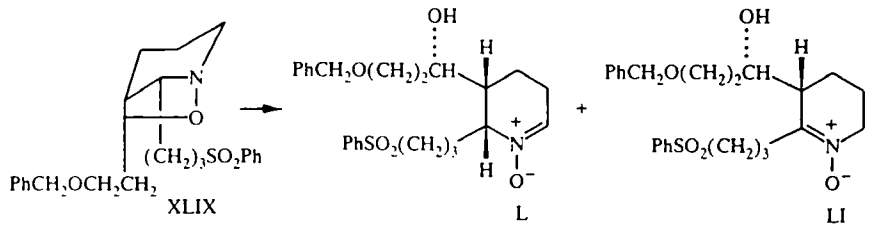
XLV XLVI

R = CH_2OH, CH_2OAc, Ph, R^1 = H; R = H, R^1 = CH_2OH, CH_2OAc; R = Me, R^1 = CH_2OH, CH_2OSiMe_2Bu-t



XLVII XLVIII

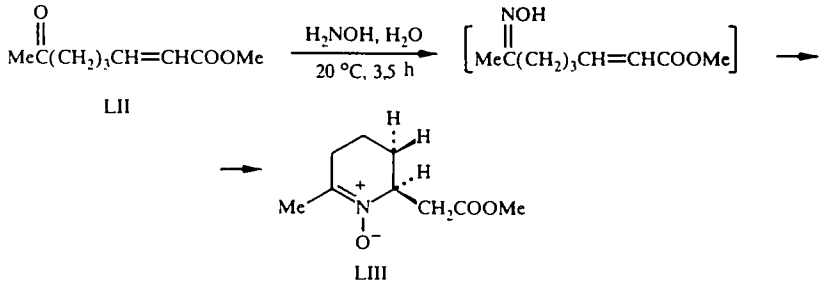
The oxidative cleavage of the bicyclic compound (XLIX) was investigated under various conditions, leading to the aldonitrone (L) and/or the ketonitrone (LI) [37, 41] (Table 3).



XLIX L LI

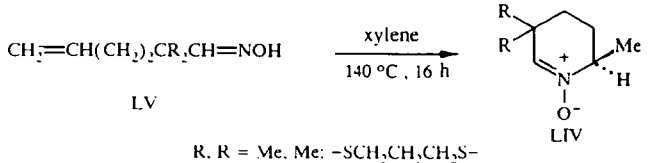
1.4. Cyclization of Unsaturated Oximes or the Corresponding Derivatives of Hydroxylamine

The oxime formed during the reaction of methyl 7-keto-2-octenoate (LII) with hydroxylamine undergoes cyclization under the reaction conditions with the formation of the nitrone (LIII) [42].



LII LIII

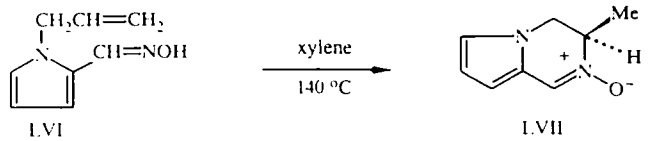
In [43, 44] the nitrones (LIV), brought into 1,3-dipolar cycloaddition *in situ* (see section 2.3), were obtained by heating the oximes (LV) in xylene.



LV LIV

R, R = Me, Me; $-SCH_2CH_2CH_2S-$

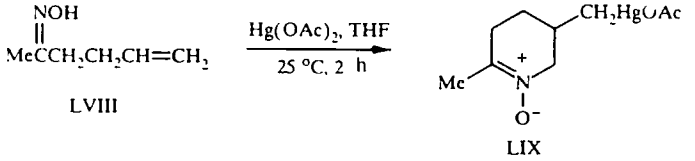
Under the same conditions the oxime (LVI) is converted into the nitrone (LVII) [43].



LVI LVII

The authors of the indicated papers [43, 44] propose the following scheme for the cyclization of the unsaturated oximes:

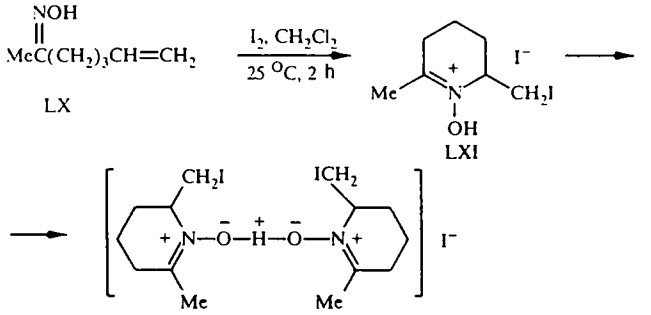
When treated with mercury acetate in tetrahydrofuran, the oxime (LVIII) undergoes cyclization with the formation of the product (LIX), containing the substituent $-CH_2HgOAc$ [45].



LVIII

LIX

In reaction with iodine in dichloromethane the oxime (LX) undergoes more complex transformations; the salt of the nitrone (LXI) is formed initially and is then transformed into the dimeric salt (LXII) (quantitative yield) [46].

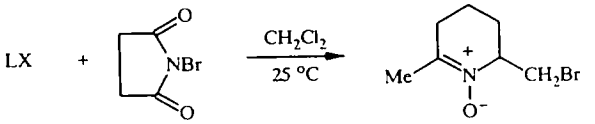


LX

LXI

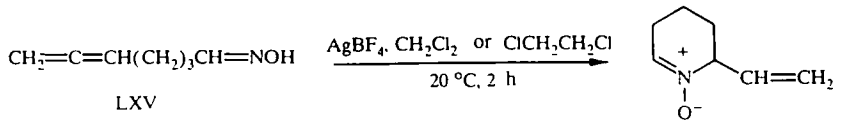
LXII

The nitrone (LXIII) was obtained by the reaction of the oxime (LX) with N-bromosuccinimide [46].



LXIII

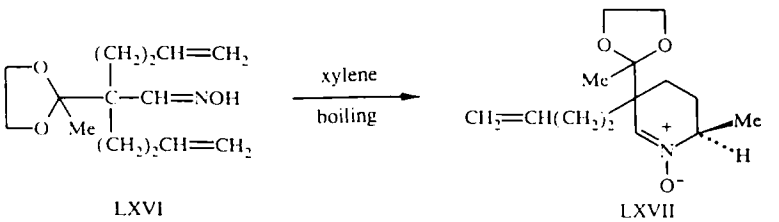
2-Vinyl-2,3,4,5-tetrahydropyridine 1-oxide (LXIV) was synthesized by the action of silver tetrafluoroborate on a mixture of the (*E*) and (*Z*) isomers of hepta-5,6-dienal oxime (LXV) [47, 48].



LXV

LXIV

The transformation of oximes containing two terminal $-CH{=}CHR$ groups at an identical distance from the hydroxyimino group was studied in a series of papers. Thus, when boiled in xylene the oxime (LXVI) is transformed into the aldonitrone (LXVII) [43].



LXVI

LXVII

TABLE 4. Conditions of the Reactions, the Yields, and the Ratios of the Adducts (CLXIVa):(CLXIVb):(CLXVa):(CLXVb)

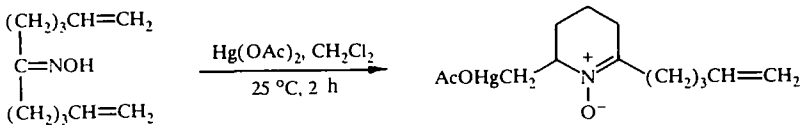
R	Solvent	Temperature, °C	Reaction time, h	CLXIVa : CLXIVb : CLXVa : CLXVb	Total yield, %	Reference
Me	PhMe	110	4	100 : 0:0 : 0	53	15, 79
OEt*	EtOH	40	12	93 : 7 : 0 : 0	67	15, 17, 80
CH_2OH	PhMe	80	5	83 : 17 : 0 : 0	84	15, 80
Ph	PhMe	110	5	95 : 5 : 0 : 0	92	80
COOMe	CH_2Cl_2	0	0,2	69 : 15 : 10 : 6	96	15, 80
COOMe	PhMe	100...110	12	CLXIV : CLXV = = 84 : 16	73	79
CN	CH_2Cl_2	25	0,2	61 : 20 : 13 : 6	92	15, 80
CHO	CH_2Cl_2	25	0,2	3 : 5 : 24 : 68	96	15, 80

*6% of the dimer (II) was also isolated from the reaction mixture [17].

TABLE 5. Conditions and Results of the Reaction of the Nitrone (I) with 1,1-Disubstituted Alkenes (CLXXXV)

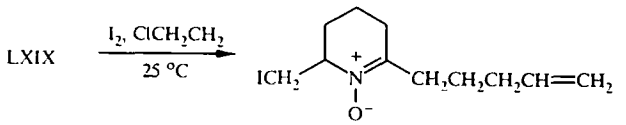
R	Temperature, °C	Reaction time, h	Solvent	(CLXXXIVa): (CLXXXIVb) ratio	Yield, %	Reference
CHO	25	0,4	CH_2Cl_2	100 : 0	94	15, 80
COOMe	25	1,5	CH_2Cl_2	96 : 4	86	15, 80
CH_2OH	95	5	PhMe	85 : 15	77	15, 80
CH_2OAc	95	2	PhMe	83 : 17	66	15, 80
CH_2OSiMe_2Bu-*t*	95	1,5	PhMe	70 : 30	55	15, 80
CH_2O-Tetrahydro-2-pyranyl	95	1,5	PhMe	67 : 33	58	15
Ph	105	1	PhMe	58 : 42	71	15

The nitrone (LXVIII) is formed from the ketoxime (LXIX) in the presence of mercury acetate even at 25°C [45].



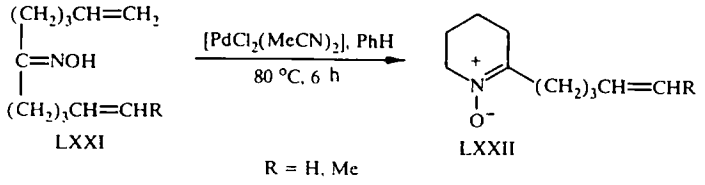
LXIX LXVIII

The ketoxime (LXIX) is converted into the nitrone (LXX) as a result of treatment with iodine in dichloroethane [46].

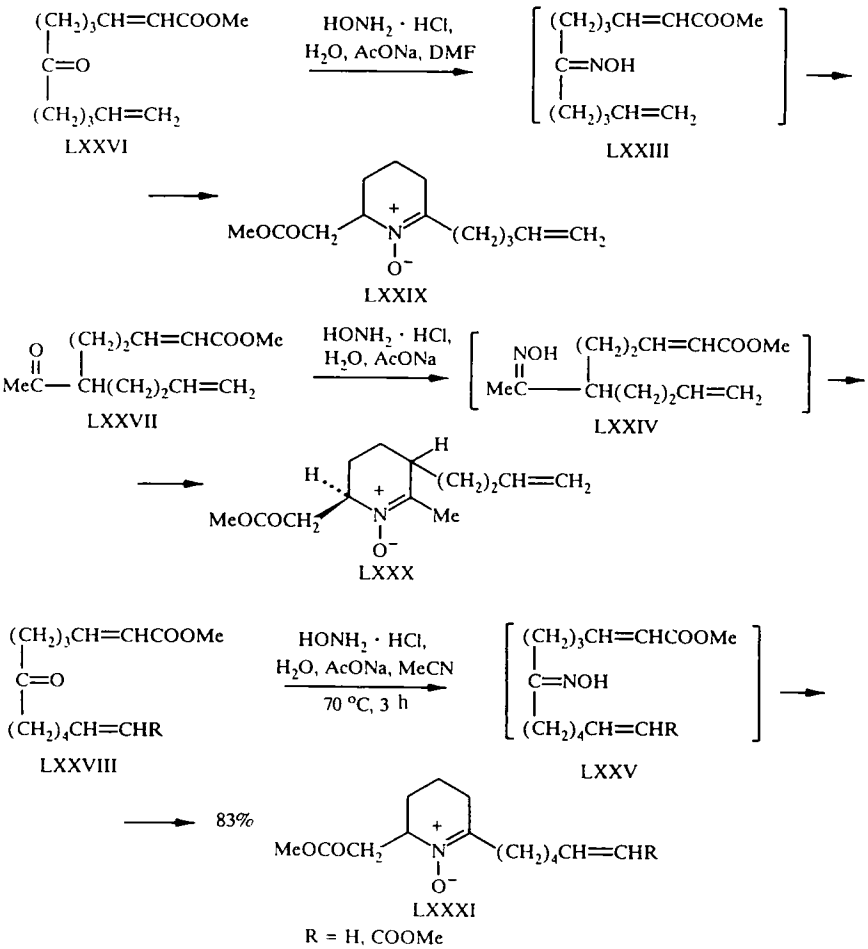


LXX

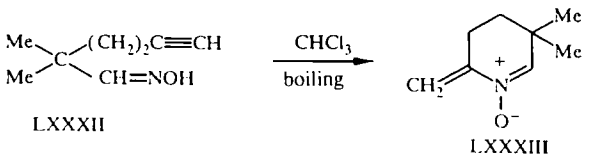
If there are terminal $-CH{=}CH_2$ and $-CH{=}CHR$ groups in the oxime, one of them takes part in cyclization, depending on the nature of the substituent R. When the latter is an electron donor, as in the case of the oxime (LXXI) (R = H, Me), the unsubstituted vinyl group takes part in cyclization, and the products (LXXII) are formed [49].



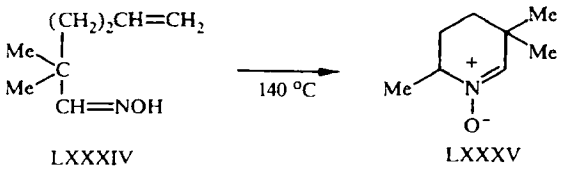
If, however, R is an electron acceptor, cyclization takes place at the substituted vinyl group. Thus, the series of ketoximes (LXXIII-LXXV), formed from the ketones (LXXVI-LXXVIII) and hydroxylamine, are converted into the nitrones (LXXIX-LXXXI) [50].



Aldoximes containing a terminal ethynyl group $-C\equiv CH$ in the molecule have also been used for the synthesis of nitrones. Thus, the product (LXXXIII) was obtained when 2,2-dimethyl-5-hexynal oxime (LXXXII) was boiled in chloroform [51].

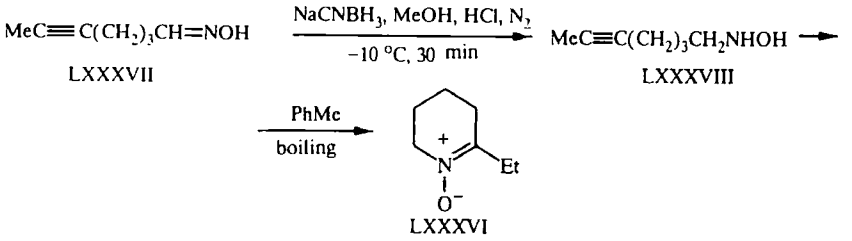


However, the oxime of unsubstituted 5-hexynal does not form the corresponding nitrone under the same conditions [51]. The ethylene analog of compound (LXXXII), i.e., 2,2-dimethyl-5-hexenal oxime (LXXXIV), is not transformed into 2,5,5-trimethyl-2,3,4,5-tetrahydropyridine 1-oxide (LXXXV) even when boiled in chloroform for 48 h. To obtain the nitrone (LXXXV) from the oxime (LXXXIV) it is necessary to conduct the reaction at 140°C [51].



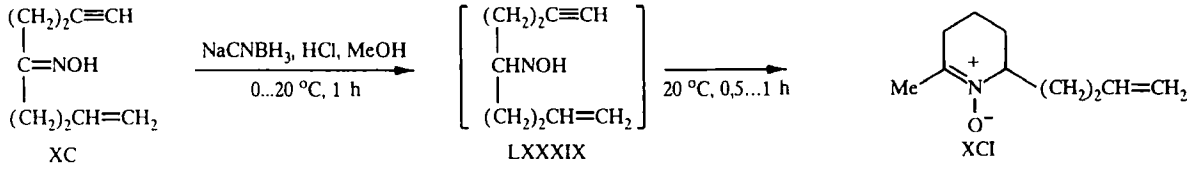
LXXXIV LXXXV

6-Ethyl-2,3,4,5-tetrahydropyridine 1-oxide (LXXXVI) was synthesized with a 94% yield by the reduction of 5-heptynal oxime (LXXXVII) with sodium cyanoborohydride in the presence of hydrogen chloride in an atmosphere of nitrogen and subsequent boiling of the obtained hydroxylamine derivative (LXXXVIII) in toluene [52].



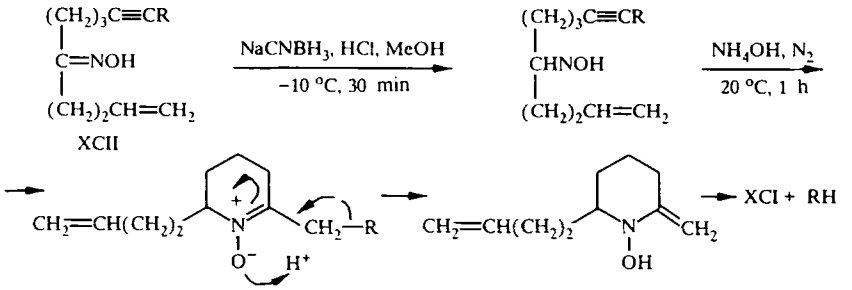
LXXXVII LXXXVIII LXXXVI

If there are ethylene and acetylene bonds in the hydroxylamine derivatives (formed during the reduction of the respective ketoximes), cyclization to the nitrones takes place through the triple bond. For instance, the hydroxylamine derivative (LXXXIX), produced by the action of $NaCNBH_3$ and hydrogen chloride on the ketoxime (XC) in aqueous methanol, is converted with 67-79% yields into 2-(3-butenyl)-6-methyl-2,3,4,5-tetrahydropyridine (XCI) [52, 53].



XC LXXXIX XCI

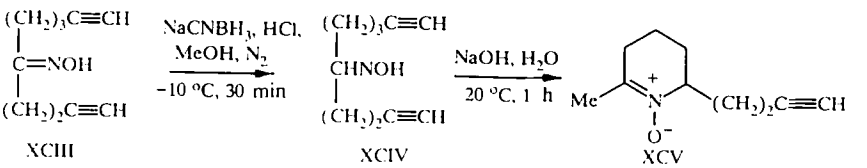
The nitrone (XCI) is formed from the ketoximes (XCII) according to the following scheme [52].



XCII

R, yield (%): $SiMe_3$, 69; $SiMe_2Bu$-t, 62

The oxime (XCIII), containing two terminal ethynyl groups, was reduced by the action of $NaCNBH_3$ and hydrogen chloride in methanol to the hydroxylamine derivative (XCIV), which was converted to the nitrone with a yield of 92% when treated with sodium hydroxide [52].

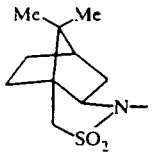
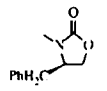


XCIII XCIV XCV

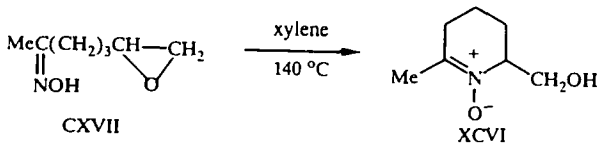
TABLE 6. Conditions and Results of the Reaction of the Nitrone (I) with Alkenes (CXCI)

R	R^1	Reaction temperature, °C	Reaction time, h	(CXCIIa): (CXCIIb) ratio	Yield, %	Reference
Ph	COOMe	55 (in PhMe)	2	87 : 13	79	15, 86
Me	CHO	25	2	100 : 0	87	15
Me	COOMe	40	1	90 : 10	94	15, 86
COOMe	COOMe	25	2	60 : 40	89	15, 86
Ph	CHO	35	8	100 : 0	82	15
CH_2OH	COOMe	25	24	77 : 23	88	86

TABLE 7. Effect of Zinc Iodide on the Yields and Stereoselectivity of the Reaction of the Nitrone (I) with Amides (CXCVIII)

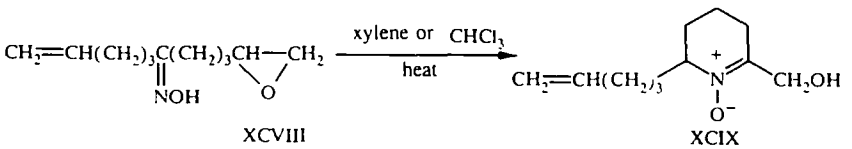
R	Catalyst	Reaction time, h	(CXCVIIa): (CXCVIIb) ratio	Total yield, %
	—	24	2 : 1	99
	ZnI_2	96	19 : 1	30
	ZnI_2 Pressure 10 kbar	24	4 : 1	74
	—	24	1 : 1,4	99
	ZnI_2	48	29 : 1	82

Oximes containing an epoxide group at the γ position undergo cyclization to nitrones when heated. Thus, 2-(hydroxymethyl)-6-methyl-2,3,4,5-tetrahydropyridine 1-oxide (XCVI) was synthesized by boiling the epoxide (XCVII), containing a ketoxime group, in xylene [54].



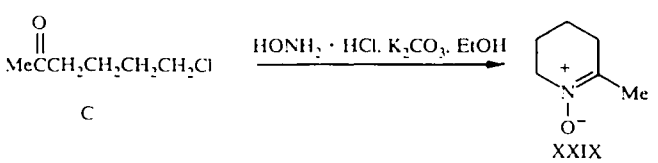
CXVII XCVI

The cyclization of the oxime (XCVIII), containing a vinyl and an epoxide group, to the nitrone (XCIX) takes place through the epoxide group [54].



XCVIII XCIX

6-Methyl-2,3,4,5-tetrahydropyridine 1-oxide (XXIX) was synthesized by the reaction of the chloro ketone (C) with hydroxylamine in alcohol [55].



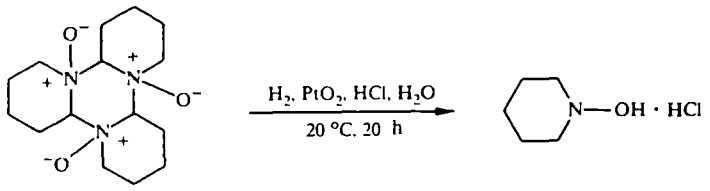
C XXIX

For quantitative determination the nitrones are reacted with trifluoroacetic anhydride and sodium iodide in acetone, and the amount of iodine released is determined by titration with sodium thiosulfate or by spectrophotometry [56].

2. CHEMICAL TRANSFORMATIONS OF 2,3,4,5-TETRAHYDRO-PYRIDINE 1-OXIDES

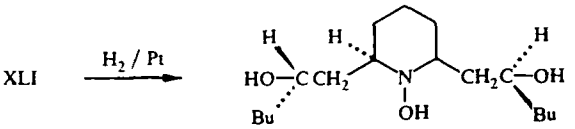
2.1. Reduction

During the catalytic hydrogenation of the trimer (V) in the presence of platinum oxide in hydrochloric acid 1-hydroxypiperidine hydrochloride was obtained with a yield of 98.5% [7].



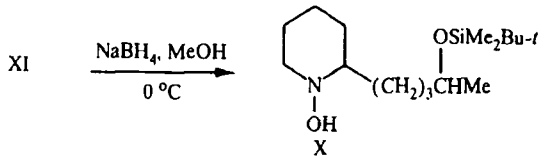
V

The catalytic hydrogenation of the nitrone (XLI) over platinum takes place stereoselectively with the formation of compound (CI) [38].



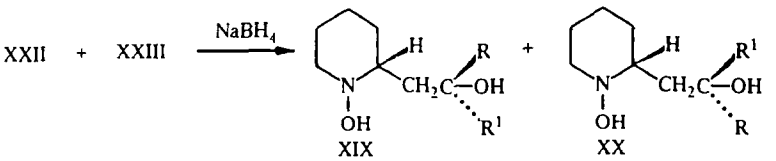
CI

During reduction with sodium borohydride in methanol the ketonitrone (XI) [R = $(CH_2)_3CH(Me)OSiMe_2Bu$-*t*] is transformed with a yield of 84% into 1-hydroxy-2-[4-(*tert*-butyldimethylsilyloxy)pentyl]-2,3,4,5-tetrahydropyridine (X) [R = $(CH_2)_3CH(Me)OSiMe_2Bu$-*t*] [8, 19].



X

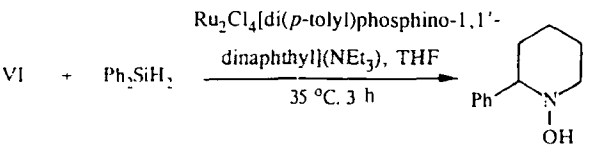
The reduction of the mixture of diastereomers of the ketonitrones (XXII, XXIII) with sodium borohydride takes place stereoselectively, and the corresponding diastereomers of the 1-hydroxy derivative (XIX, XX) are formed [21, 39].



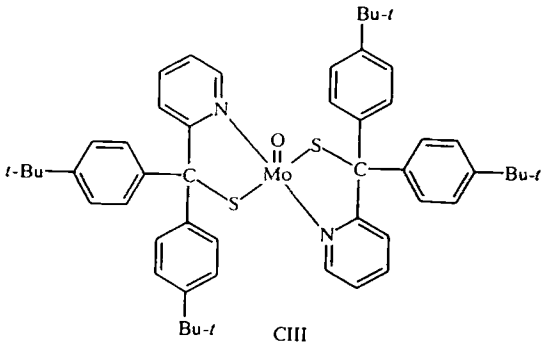
XIX XX

R, R^1 = CH_2OH, H; Ph, H; Me, CH_2OH; Me, Ph; CH_2OH, CH_2OH; Me, CH_2OSiMe_2Bu-*t*; Me, CH_2CH_2OH; CH_2CH_2OH, CH_2OH

6-Phenyl-2,3,4,5-tetrahydropyridine 1-oxide (VI) was converted into 1-hydroxy-2-phenylpyridine (yield 77%) by reaction with diphenylsilane in the presence of the complex ruthenium catalyst (CII) in tetrahydrofuran [57].



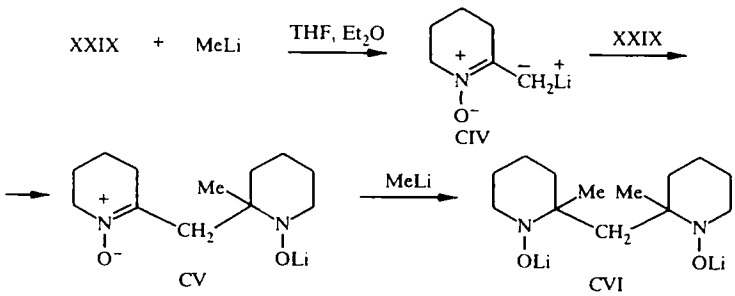
6-Methyl-2,3,4,5-tetrahydropyridine is formed with a 96% yield from the nitrone (XXIX) in reaction with compound (CIII), in which the molybdenum changes from hexavalent to octavalent [58].



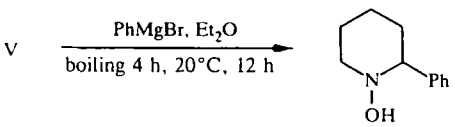
CIII

2.2. Reactions with Heteroorganic Compounds

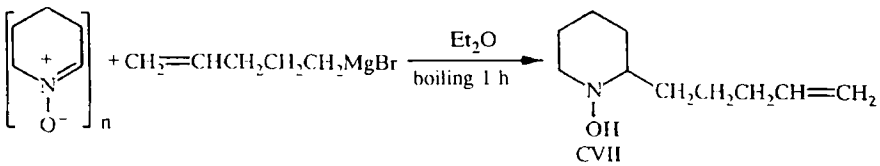
In reaction with methyllithium the ketonitrone (XXIX) is converted into the anion (CIV), which reacts with another molecule of the nitrone (XXIX) to form the product (CV). The latter enters into reaction with the methyllithium to give the bisalcoholate (CVI) [23].



In the reaction of the trimer (V) with phenylmagnesium bromide in ether followed by treatment of the reaction mixture with an aqueous solution of ammonium chloride 1-hydroxy-2-phenylpiperidine was obtained with a yield of 46% [7].

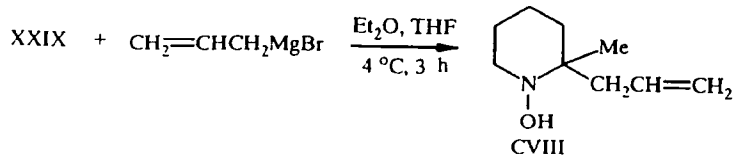


1-Hydroxy-2-(4-pentenyl)piperidine (CVII) (yield 52%) was obtained by boiling the oligomer of the nitrone (I) with 4-pentenylmagnesium bromide in ether [4].



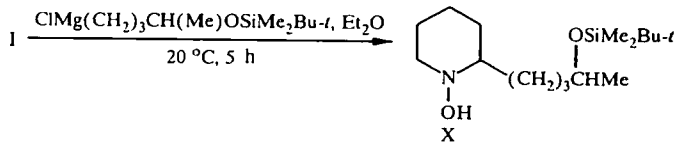
CVII

As a result of the reaction of the nitrone (XXIX) with allylmagnesium bromide in a mixture of ether and tetrahydrofuran followed by heating with an aqueous solution of ammonium chloride 1-hydroxy-2-methyl-2-allylpiperidine (CVIII) was obtained with a 46% yield [27].

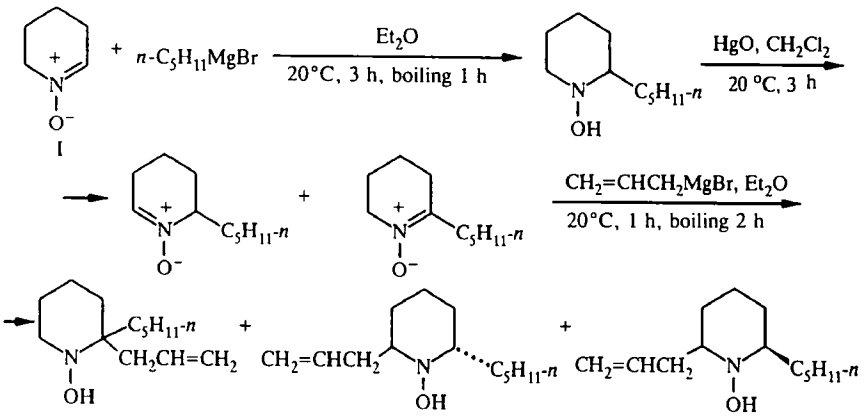


In another paper [28], without citing the reaction conditions, the authors report that they obtained compound (CVIII) with a yield of 86%.

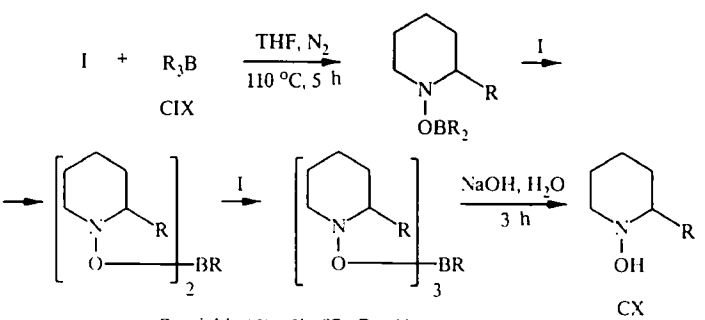
The piperidine derivative (X) [R = $(CH_2)_3CH(Me)OSiMe_2Bu$-*t*] was synthesized with a 77% yield by the reaction of the nitrone (I) with the Grignard reagent $ClMg(CH_2)_3CH(Me)OSiMe_2Bu$-*t* followed by decomposition of the reaction mixture with an aqueous solution of ammonium sulfate [8, 19].



The reaction of the nitrone (I) with pentylmagnesium bromide followed by treatment of the reaction mixture with an aqueous solution of ammonium chloride gave 1-hydroxy-2-pentylpiperidine (yield 70.5%), which was converted by oxidation with yellow mercuric oxide into a mixture of 6-pentyl- and 2-pentyl-2,3,4,5-tetrahydropyridine 1-oxides. From this mixture by the action of allylmagnesium bromide and then an aqueous solution of ammonium chloride 1-hydroxy-2-pentyl-2-allylpiperidine and the diastereomers of 1-hydroxy-2-allyl-2-pentylpiperidine were synthesized [20].



When a 2:1 mixture of the nitrone (I) with trialkylboranes (CIX) was kept in an atmosphere of nitrogen in a sealed tube at 110°C, followed by treatment of the reaction mixture with aqueous sodium hydroxide, the corresponding 2-alkyl-substituted 1-hydroxypiperidines (CX) were obtained [59].



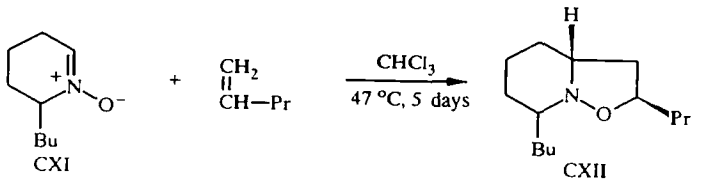
R, yield (%): Et, 97; Bu, 99; *sec*-Bu, 63

TABLE 8. Conditions and Results of the Reaction of the Nitrone (I) with Unsaturated Lactones (CCXIX)

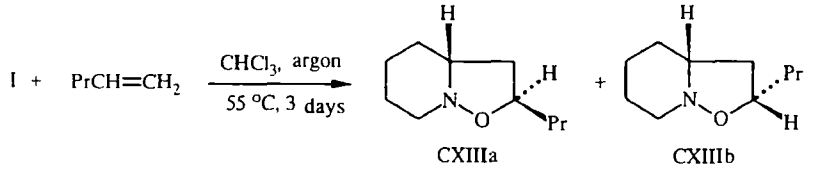
R	Reaction temperature, °C	Reaction time, h	*exo/endo*	*exo-anti/exo-syn*	Total yield, %
H	4	3 days	31	—	90
H	110	15 h	6	—	79
Me	40	17 h	21	8	73
Me	110	15 h	7	2	84
$CH_2CH_2OCH_2Ph$	25	18 days	Traces of *endo*	10	70
$CH_2CH_2OCH_2Ph$	110	15 h	14	6	78

2.3. Intermolecular [3+2]-Cycloaddition Reactions

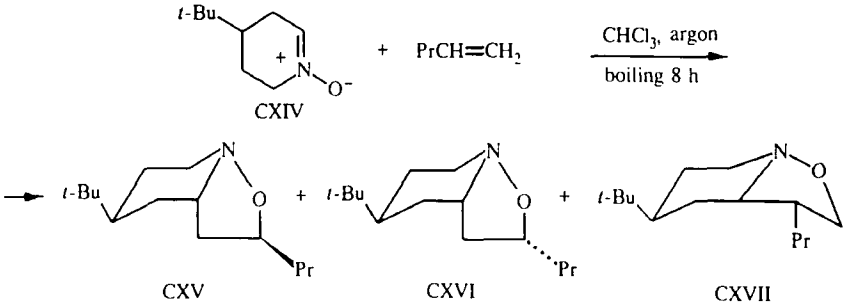
2.3.1. Reactions with Alkenes. In [60] the 1,3-dipolar cycloaddition of 1-pentene to various nitrones was investigated. Thus, in the case of the nitrone (CXI) one adduct (CXII) was obtained with a yield of 27%.



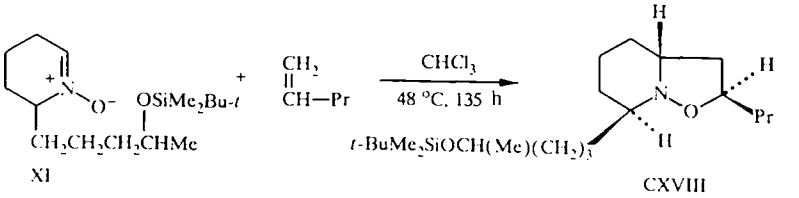
As a result of the regioselective reaction of the nitrone (I) with 1-pentene two diastereomers (CXIIIa, CXIIIb) were obtained with an overall yield of 67%. The content of the second isomer in the mixture amounted to only 2.2%.



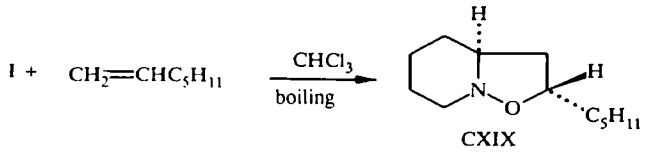
A more complicated picture was observed for the nitrone (CXIV); two diastereomers (CXV, CXVI) and also a regioisomer (CXVII) were isolated from the reaction products.



The reaction of the pentene with the nitrone (XI) [R = $(CH_2)_3CH(Me)OSiMe_2Bu$-*t*] resulted in the formation of the [3+2]-cycloaddition product (CXVIII) with a yield of 57% [8, 19].

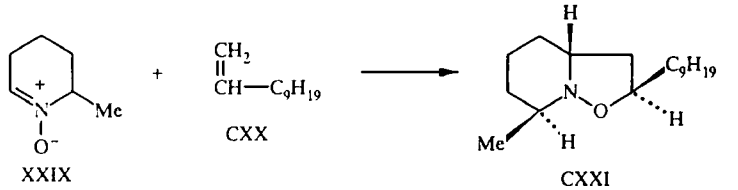


When the nitrone (I) was boiled with 1-heptene in chloroform, a high yield (94%) of the adduct (CXIX) was obtained [9].



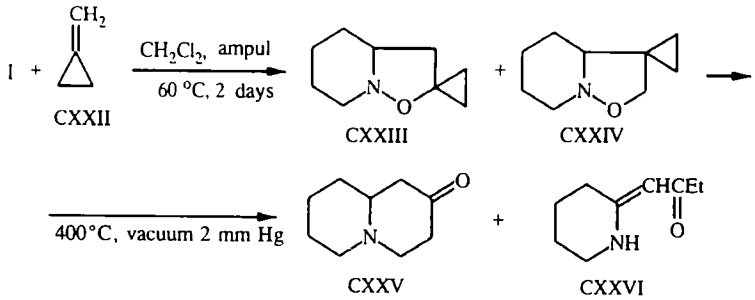
CXIX

The temperature regime for the cycloaddition of 2-methyl-2,3,4,5-tetrahydropyridine 1-oxide (XXIX) with 1-undecene (CXX) has a significant effect on the yield of the obtained adduct (CXXI). In the reaction in chloroform at 50°C the yield amounted to 47% [61], and when the reagents were kept at 150°C it increased to 87% [62].



XXIX CXX CXXI

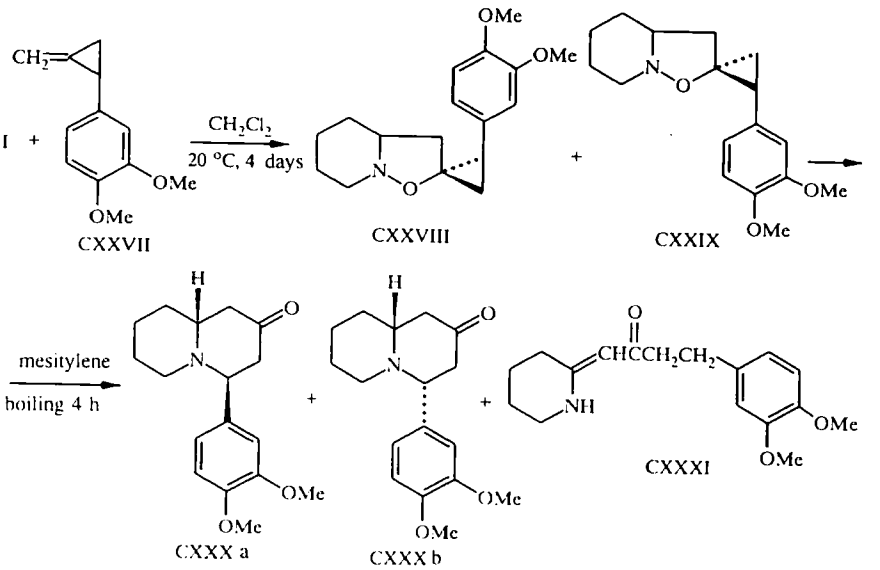
The reaction of the nitrone (I) with methylenecyclopropane (CXXII) at 60°C is nonregioselective, and a mixture (9:1) of two products (CXXIII, CXXIV) is formed with an overall yield of 69%. When heated under vacuum they are converted into compounds (CXXV) (yield 32%) and (CXXVI) (yield 19%) [63, 64].



CXXII CXXIII CXXIV CXXV CXXVI

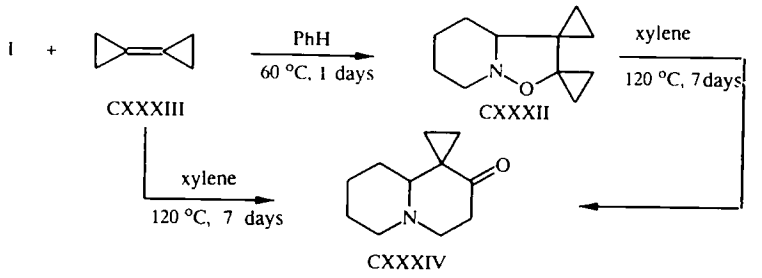
The last two compounds can also be obtained without isolating the adducts (CXXIII, CXXIV) by heating the initial compounds (I) and (CXXII) in a sealed tube at 100°C for 24 h [63].

The nitrone (I) reacts with the methylenecyclopropane derivative (CXXVII) at room temperature with the formation of two regioisomers (CXXVIII, CXXIX) (yields 44 and 36% respectively). When heated in mesitylene the adduct (CXXVIII) is converted into two stereomers (CXXXa) (yield 26%) and (CXXXb) (yield 38%), while the adduct (CXXIX) is converted into the ketone (CXXXI) (yield 14%) [64].

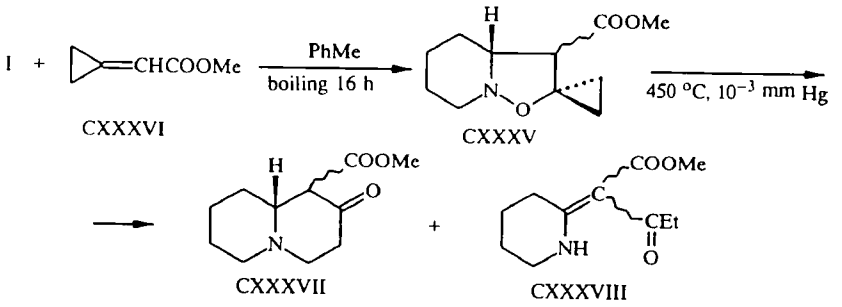


CXXVII CXXVIII CXXIX CXXXI CXXX a CXXX b

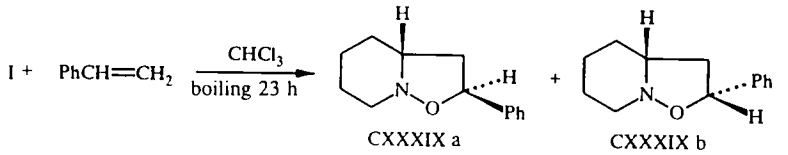
The product from 1,3-dipolar cycloaddition (CXXXII) was obtained with a 60% yield by heating the nitrone (I) with biscyclopropylidene (CXXXIII) in benzene and was converted into the quinolizine derivative (CXXXIV) (yield 68%) by heating in xylene for 7 days. Under the latter conditions compound (CXXXIV) was also obtained directly from the indicated reagents (I) and (CXXXIII) with a 50% yield [65].



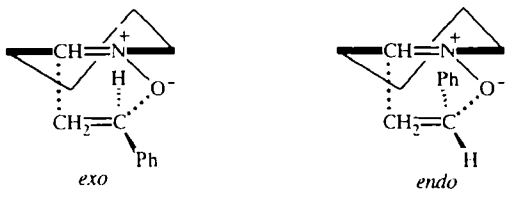
The only product (CXXXV), formed with a yield of 78% as a result of the reaction of the nitrone (I) with methoxycarbonylmethylenecyclopropane (CXXXVI), is converted by thermolysis into two compounds, i.e., the ester (CXXXVII) (yield 46%) and the keto ester (CXXXVIII) (yield 20%) [66].



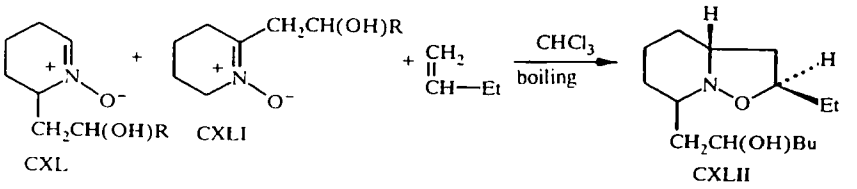
The nitrone (I) enters into cycloaddition with styrene when boiled in chloroform with the formation of a 97:3 mixture of diastereomers (CXXXIXa, b) (total yield 58%) [11, 36].



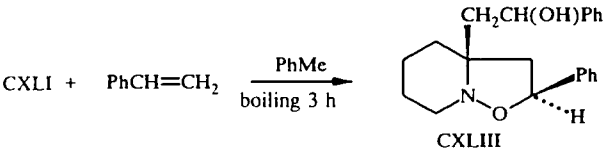
When this reaction was carried out in boiling toluene, the total yield of the isomers (CXXXIXa, CXXXIXb) amounted to 91%, and the ratio of the *a* and *b* isomers was 78:22 [67]. The diastereomer (CXXXIXa) is formed with the *exo* orientation of the addends in the transition state, and the isomer (CXXXIXb) is formed with the *endo* orientation [67].



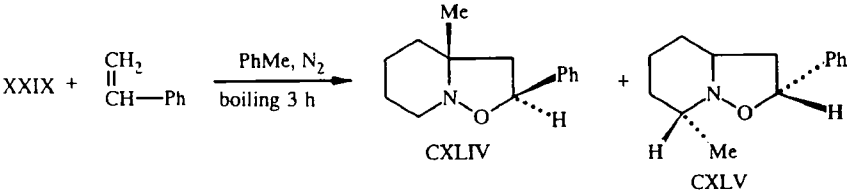
The authors in [35, 36] established that aldonitrones and ketonitrones containing substituents $-CH_2CH(OH)R$ (R = Bu, Ph) at the α position differ greatly in reactivity in 1,3-dipolar cycloaddition with alkenes. Thus, when a mixture of the aldonitrone (CXL) (R = Bu) and the ketonitrone (CXLI) (R = Bu) is boiled with 1-butene in chloroform only the aldonitrone enters into cycloaddition with the formation of the adduct (CXLII) (R = Bu) (yield 13%). The yield of compound (CXLII) with R = Ph under the same conditions was not indicated.



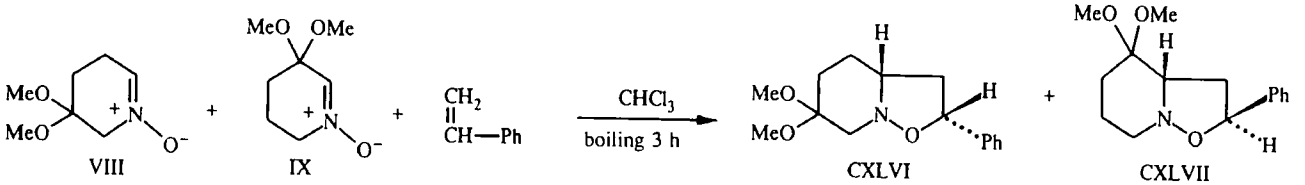
It was possible to obtain the product (CXLIII) from styrene and the ketonitrone (CXLI) (R = Ph) with a yield of 32% by conducting the reaction in boiling toluene [35, 36].



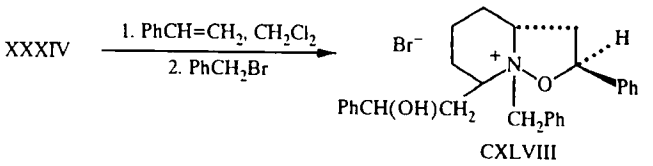
Under the indicated conditions two compounds (CXLIV) (yield 35%) and (CXLV) (yield 2.4%) are formed from 6-methyl-2,3,4,5-tetrahydropyridine 1-oxide [36].



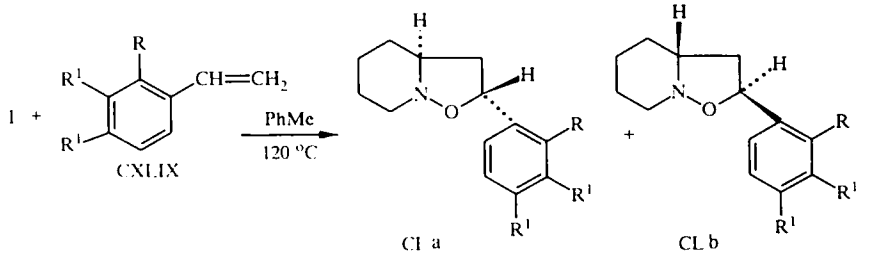
A mixture of equimolar amounts of the nitrones (VIII) and (IX) reacts with styrene in boiling chloroform, giving a 90% yield of compounds (CXLVI) and (CXLVII) in a ratio of 1:1 [18].



The reaction of the nitrone (XXXIV) with styrene and benzyl bromide gave an 80% yield of the salt (CXLVIII) [68].

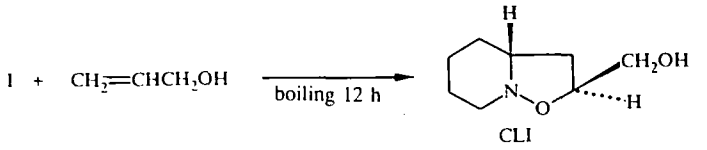


The substituted styrenes (CXLIX) enter stereoselectively into cycloaddition with the nitrone (I) in boiling toluene, giving in each case two diastereomers (CLa, b) in a ratio of 20:1 [69-71].



R, R^1, reaction time, total yield (%): OH, H, 5 days, 73 [69]; H, OMe, 5 h, 93 [70, 71]

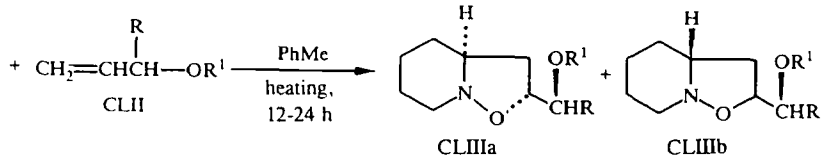
The cycloaddition of nitrones to allyl alcohol and its derivatives has been studied in a series of papers. When compound (I) was boiled with allyl alcohol, the adduct (CLI) was obtained with a 17% yield [29].



CLI

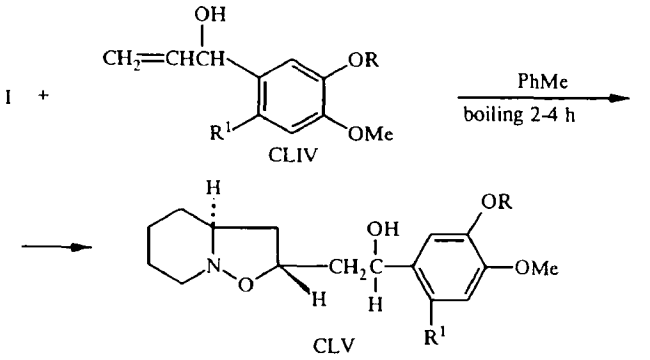
The latter was obtained with a 91% yield when the reaction was carried out in chloroform [67].

The 1,3-dipolar cycloaddition of the nitrone (I) to derivatives of allyl alcohol (CLII) takes place regio- and stereoselectively with the formation of the diastereomers (CLIIIa, b). The isomers (CLIIIa) are formed preferentially. The degree of stereoselectivity depends of the size of the alkyl substituent at the chiral allylic center [72].



R, R^1, total yield (%), (CLIIIa):(CLIIIb) ratio: Me, CH_2Ph, 68, 67 : 33; Me, $SiPh_2Bu$-*t*, 66, 60 : 40; *i*-Pr, CH_2Ph, 79, 91 : 9; *i*-Pr, $SiPh_2Bu$-*t*, 85, 93 : 7; Bu, CH_2Ph, 66, 79 : 21; Bu, $SiMe_2Bu$-*t*, 67, 71 : 29; Bu, $SiPh_2Bu$-*t*, 80, 75 : 25; Bu-*t*, CH_2Ph, 75, 95 : 5; R + R^1 = $CH_2OC(CH_2)_5$, 74, 80 : 20

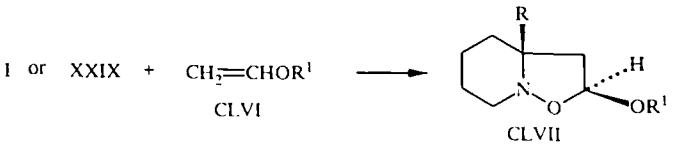
Compounds (CLV) were synthesized with almost quantitative yields by boiling the nitrone (I) with the allyl alcohol derivatives (CLIV) in toluene. The authors [13, 14, 73-75] were unable to separate them into individual diastereomers.



CLV

R, R^1 = OMe, $—OC_6H_4CH_2CH_2COOMe$-4 [13, 14]; CH_2Ph, H [73, 75]; CH_2CH_2OMe, H [74, 75]

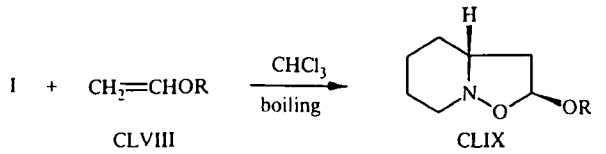
The [3+2]-cycloaddition of 2,3,4,5-tetrahydropyridine 1-oxide (I) or 6-methyl-2,3,4,5-tetrahydropyridine 1-oxide (XXIX) to vinyl ethers (CLVI) gave derivatives of 9-oxa-1-azabicyclo[4.3.0]nonane (CLVII) [26, 27, 29, 30, 32].



CLVII

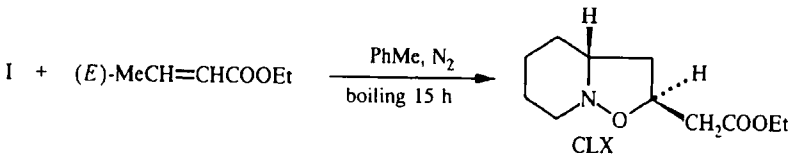
R, R^1, temperature, °C, reaction time (h), yield (%): Me, Bu, 90, 1, 54 [27]; H, Bu, 20, 3, 69 [32]; H, Bu, 0, 3 (argon), 54 [30]; H, Bu-*i*, 20, 24, 30 [29]; H, Bu, 100, 12, 64; H, CH_2O-tetrahydro-2-pyranyl , 110, 12, 66 [26]

For the reaction of the nitrone (I) with vinyl ethers (CLVIII) a high degree of stereoselectivity during the formation of the 9-oxa-1-azabicyclo[4.3.0]nonane derivatives (CLIX) is observed [76].

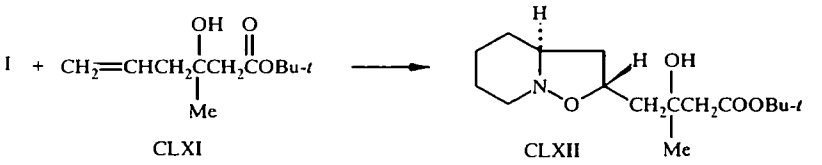


R, yield (%): (−)-menthyl, 52; 8-phenylmenthyl 36; isopinocamphenyl, 59; (S)-CHMePh, 50; (S)-CHPhPr-*i*, 62; (R)-CHPhBu-*t*, 89

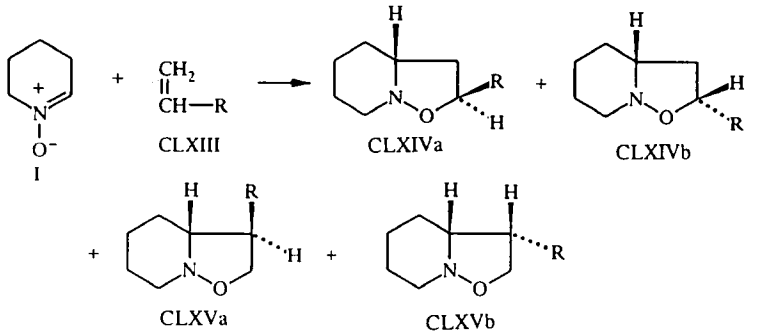
When the nitrone (I) was boiled with ethyl crotonate in toluene in an inert atmosphere, only one isomer of 8-methoxycarbonyl-9-oxa-1-azabicyclo[4.3.0]nonane (CLX) was obtained with a yield of 87% [77].



The cycloaddition of the nitrone (I) to compound (CLXI) takes place regio- and stereoselectively with the formation of the adduct (CLXII) (yield 72%) [78].

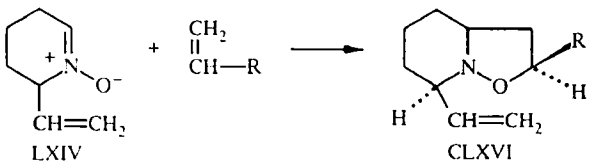


Ali and coworkers [15, 17, 79, 80] investigated the 1,3-dipolar cycloaddition of the nitrone (I) with monosubstituted alkenes RCH=CH$_2$ (CLXIII) in detail under various conditions (Table 4). It was established that in the case of R = Me one isomer (CLXIVa) was formed, but with R = OEt, CH$_2$OH, or Ph the reaction products were pairs of diastereomers (CLXIVa) and (CLXIVb). Four compounds each, i.e., the diastereomers (CLXIVa) and (CLXIVb) and the diastereomers of their regioisomers (CLXVa) and (CLXVb) were obtained in the reaction of the nitrone (I) with alkenes, in which R represents the electron-withdrawing groups COOMe, CN, and CHO.



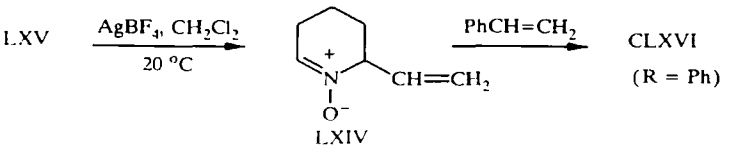
In [26], however, it was reported that only the isomer (CLXVa) (R = COOEt, yield 73%) was isolated in the reaction of the nitrone (I) with ethyl acrylate at 100-110°C for 12 h.

Derivatives of 9-oxa-1-azabicyclo[4.3.0]nonane (CLXVI) containing a vinyl group at position 2 were synthesized by the reaction of 2-vinyl-2,3,4,5-tetrahydropyridine 1-oxide (LXIV) with styrene or methyl acrylate [47].

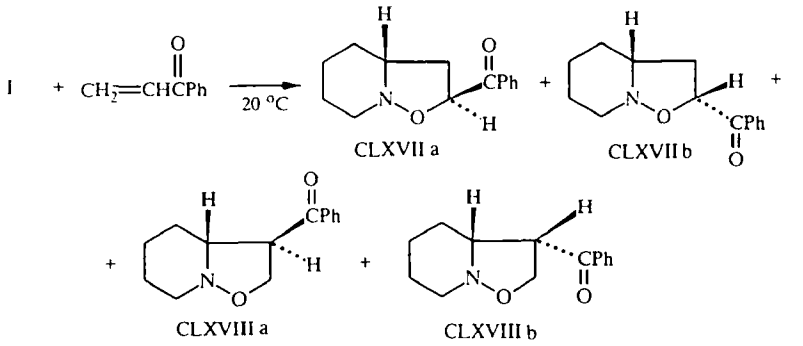


R, yield (%): Ph, 42; COOMe, 25

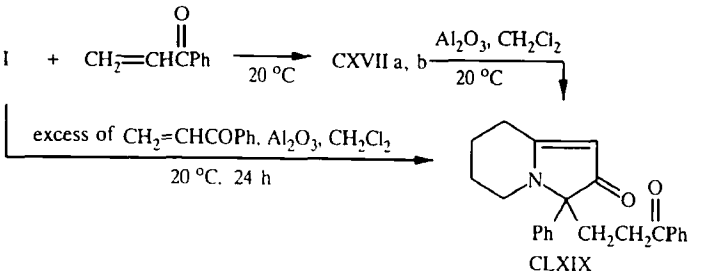
The nitrone (LXIV), formed from the (*E*) or (*Z*) isomer of the hydroxy derivative (LXV), was brought into reaction with styrene. As a result the adduct (CLXVI) was obtained with yields of 83 and 27% respectively [on the initial (LXV)] [47].



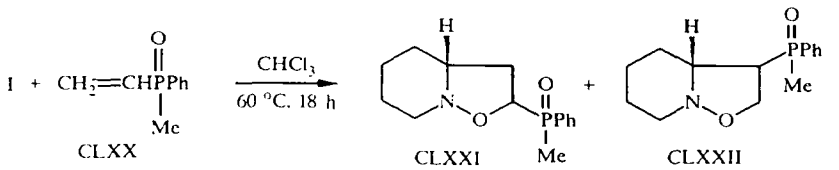
The reaction of the nitrone (I) with phenyl vinyl ketone resulted in the formation of two regioisomers, and each was a mixture of the diastereomers (CLXVIIa) and (CLXVIIb) (a:b = 2.5:1) and also (CLXVIIIa) and (CLXVIIIb) (a:b = 5:1) [81].



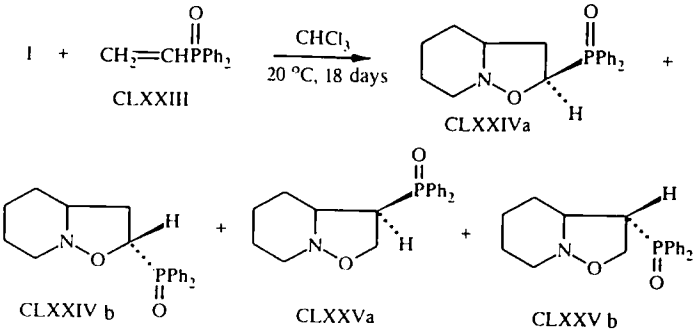
The products (CLXVIIa, b) are unstable compounds and are converted in the presence of aluminum oxide into 9-phenyl-9-(3-phenyl-3-oxopropyl)-1-azabicyclo[4.3.0]non-6-en-8-one (CLXIX) with a yield of 50%. The latter is formed directly from the nitrone (I) and an excess of phenyl vinyl ketone in the presence of aluminum oxide [81].



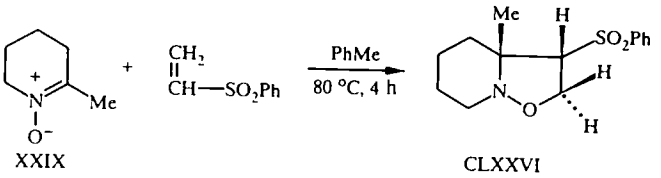
From the nitrone (I) and methylphenylvinylphosphine oxide (CLXX) a 95:5 mixture of the regioisomers (CLXXI) and (CLXXII) was obtained with a yield of 91% [12].



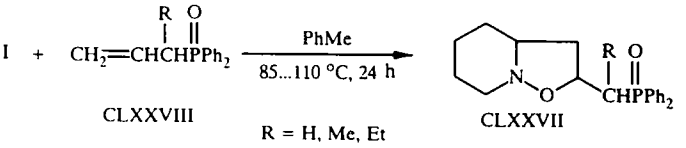
With vinyldiphenylphosphine oxide (CLXXIII) the same nitrone (I) gives a 93% yield of a 76:24 mixture of the regioisomers (CLXXIV) and also (CLXXV), each of which in turn consists of two diastereomers (CLXXIVa, b) (a:b = 1.5:1) and (CLXXVa, b) (a:b = 1:1).



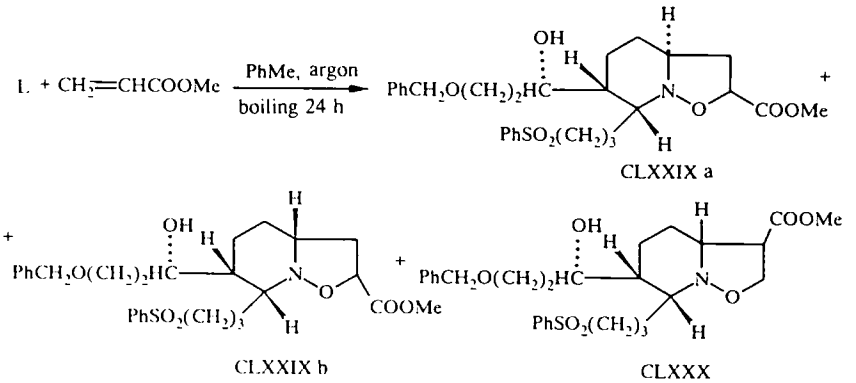
At 110°C the reaction takes 24 h, and the ratio of the diastereomers (CLXXIV):(CLXXV) becomes equal to 60:40, while the ratios of the diastereomers (CLXXIVa):(CLXXIVb) and (CLXXVa):(CLXXVb) are 1.2:1 and 1.4:1 respectively [82]. From the products of the reaction of the nitrone (XXIX) with vinyl phenyl sulfone only one compound (CLXXVI) was isolated with a yield of 45% [83].



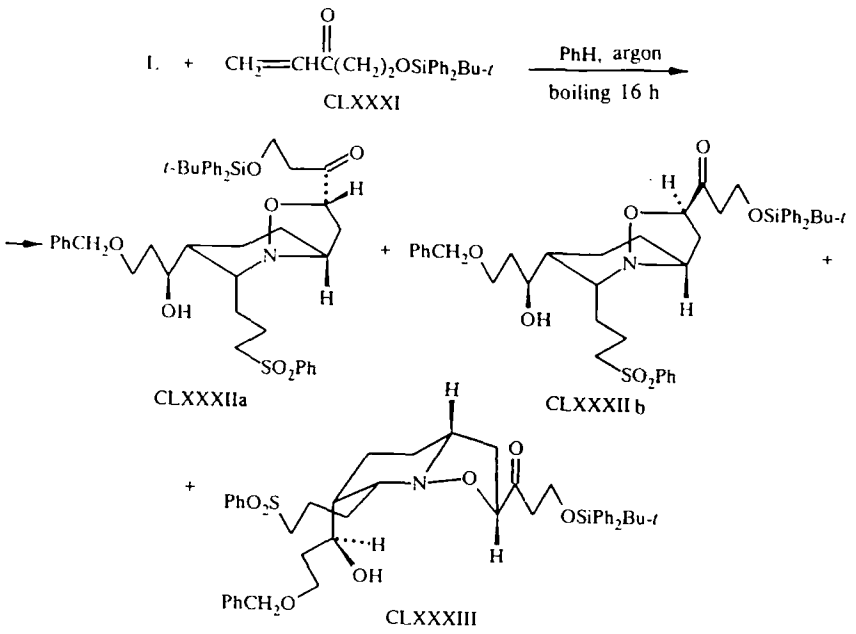
The authors in [84] mention that the adducts (CLXXVII) are formed from the nitrone (I) and the unsaturated compounds (CLXXVIII) through an *exo* transition state. They established that with R = H the reaction is fully selective, and the *trans* isomer is formed, but with R = Me, Et mixtures of *anti,trans* and *syn,trans* isomers are formed. (Their ratio was 57:43 for R = Me and was not determined for R = Et.)



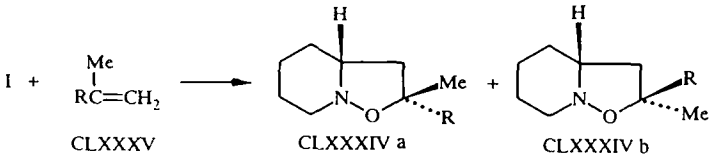
In the reaction of methyl acrylate with the nitrone (L) there is no strict regioselectivity in the process, and two diastereomers (CLXXIXa, b) (yields 49 and 42%) and also the regioisomer (CLXXX) (yield 3%) were found in the reaction products [41].



At the same time the reaction of the nitrone (L) with the vinyl ketone (CLXXXI) takes place regioselectively with the formation of a 1:1:1 mixture of three isomers (CLXXXIIa, b) and (CLXXXIII) with an overall yield of 80% [41].

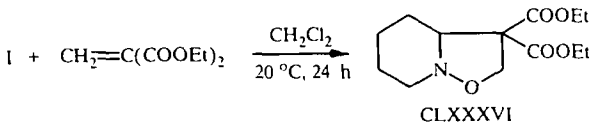


The ratio and the yield of the diastereomers (CLXXXIVa, b) formed as a result of the [3+2]-cycloaddition of the nitrone (I) to 1,1-disubstituted alkenes (CLXXXV) are determined by the nature of the substituent R in the alkene (Table 5) [15].

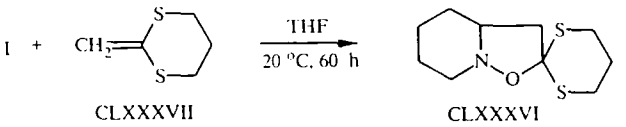


As seen from the data presented in Table 5, the reaction of the nitrone (I) with 1,1-disubstituted alkenes results mainly in the formation of adducts containing substituents at the α position to the oxygen atom. The tendency to form the diastereomers (CLXXXIVa) increases with increase in the electron affinity of the radical R.

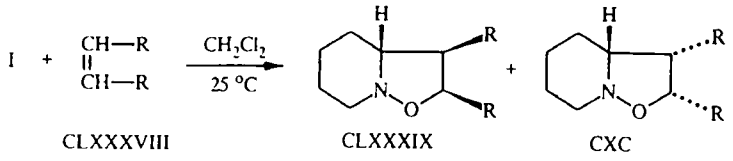
The regioselectivity of the [3+2]-cycloaddition process is completely reversed if a dipolarophile having a high ionization potential is used. Thus, in the reaction of the nitrone (I) with diethyl methylenemalonate 7,7-di(ethoxycarbonyl)-9-oxa-1-azabicyclo[4.3.0]nonane (CLXXXVI) was obtained with a yield of 90% [79, 80].



The spiro compound (CLXXXVI) was synthesized with a yield of 88% by the reaction of the nitrone (I) with 2-methylene-1,3-dithiane (CLXXXVII) [85].



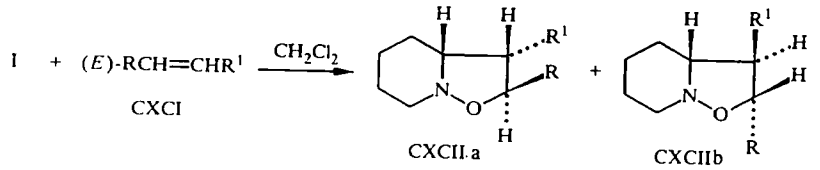
The *cis*-1,2-disubstituted alkenes (CLXXXVIII) react with the nitrone (I) at 25°C with the formation of the isomers (CLXXXIX) and (CXC) in a ratio of 4:1 respectively [15, 86].



CLXXXVIII CLXXXIX CXC

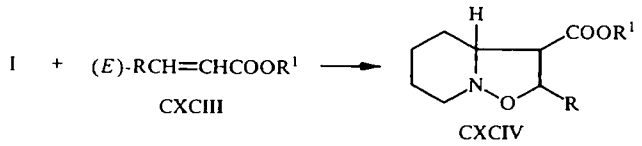
R, reaction time (h), yield (%),
CXXXIII : CXXXIX: COOMe, 2,0, 93, 84 : 16; $(CO)_2O$, 0,1, 98, 81 : 19

In the reaction of the nitrone (I) with *trans*-1,2-substituted alkenes (CXCI) the diastereomers (CXCIIa, b) are formed in various ratios. When R = Me or Ph and R^1 = CHO, only the (CXCIIa) isomers are obtained (Table 6) [15, 86].



CXCI CXCII a CXCII b

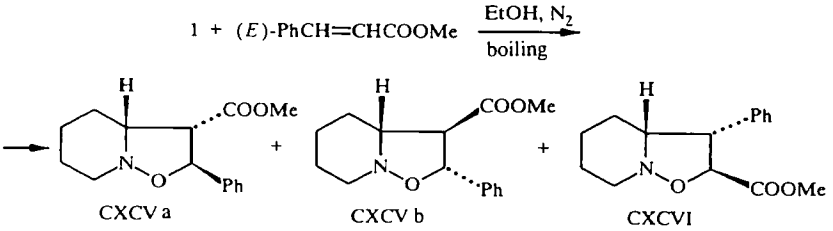
Derivatives of 9-oxa-1-azabicyclo[4.3.0]nonane (CXCIV), containing an ester group at position 7, were described as the only products from the reaction of the nitrone (I) with the esters of *trans*-α,β-unsaturated acids (CXCIII) [26, 87].



CXCIII CXCIV

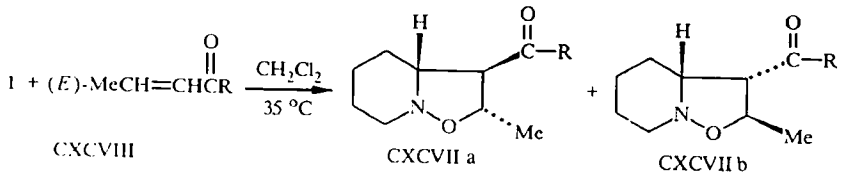
R = Me, R^1 = Et [26]; R = Me, Ph, R^1 = Me, Pr—*i*, Bu-*t* [87]

Other authors [88] have reported that three adducts, i.e., the two diastereomers (CXCVa, b) and the regioisomer (CXCVI) (in ratios of 83:12:5 respectively), were isolated from the products of the reaction of the nitrone (I) with methyl *trans*-cinnamate. The formation of mainly the diastereomer (CXCVa) is explained by the fact that the COOMe group has superiority over the Ph group in the manifestation of secondary orbital interaction in the transition state.



CXCV a CXCV b CXCVI

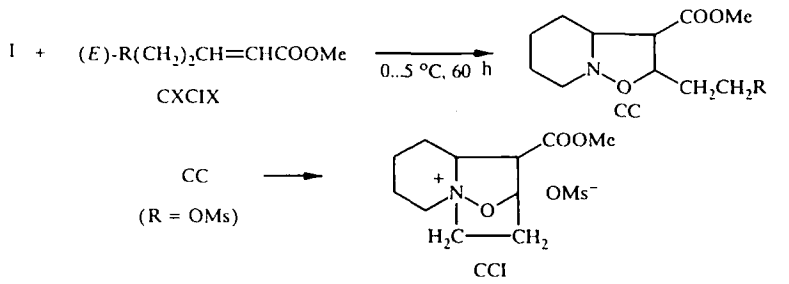
The effect of zinc iodide on the yields and ratios of the products (CXCVIIa, b) formed during the reaction of the nitrone (I) with amides (CXCVIII) was studied (Table 7) [89].



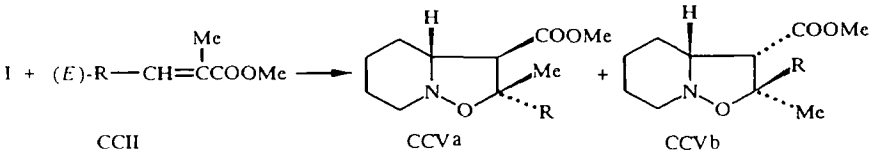
CXCVIII CXCVII a CXCVII b

It follows from the data in Table 7 that the addition of zinc iodide reduces the yield of the products and increases the duration of the process but improves its diastereoselectivity.

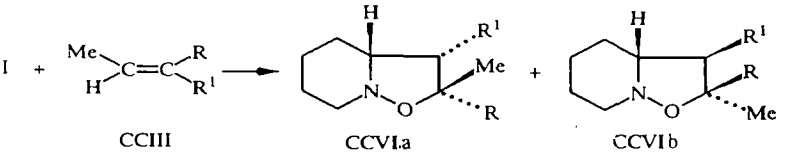
In the reaction of the nitrone (I) with the esters of unsaturated acids (CXCIX) products (CC) containing an ester group at the β position of the isoxazolidine ring are formed. Compound (CC) (R = OMs) undergoes intramolecular N-acylation under the reaction conditions and is converted into the salt (CCI) [90, 91].



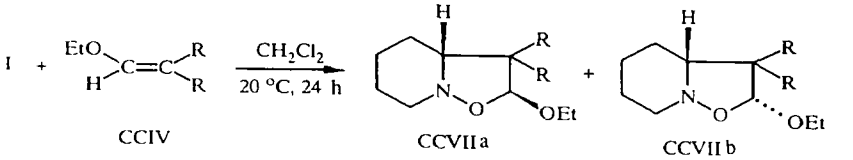
The stereoselectivity and regioselectivity of the reactions of the oxide (I) with the trisubstituted derivatives of ethylene (CCII, CCIII, CCIV) are determined by the nature and position of the substituents, and pairs of diastereomers (CCVa, b), (CCVIa, b), or (CCVIIa, b) are formed in each case [92].



R, solvent, temperature, °C, reaction time (h), yield (%), CCVa : CCVb: COOMe, CH_2Cl_2, 20, 24, 93, 100 : 0; Me, PhMe, 80, 5, 81, 57 : 43



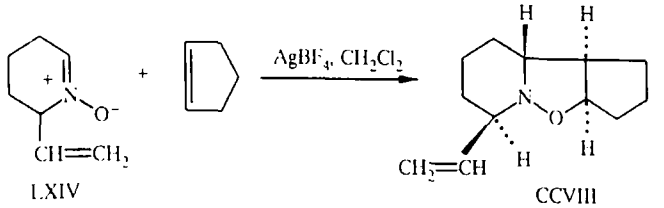
R, R^1, solvent, temperature, °C, reaction time (h), CCVIa : CCVIb: COOMe, COOMe, PhMe, 65, 2, 66, 4 : 33, 6; $(CO)_2O$, CH_2Cl_2, 20, 6, 75 : 25



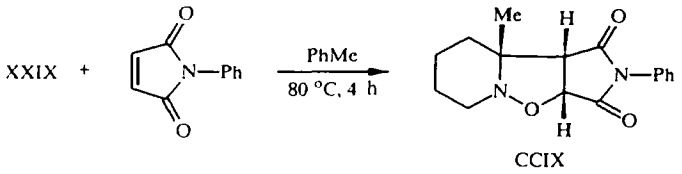
R, yield (%), CCVIIa : CCVIIb: COOEt, 92, 70 : 30; COOMe, 86, 75 : 25; $(CO)_2O$, 84, 78 : 22

During investigation of the kinetics of the [3+2]-cycloaddition of the nitrone (I) to alkenes it was established that this reaction had second order. The rate constants $k_2 \cdot 10^5$ $mole^{-1} \cdot sec^{-1}$ for the reaction of the nitrone (I) in deuterochloroform are 27,400 with maleic anhydride, 340 with dimethyl fumarate, 209 with methyl acrylate, 105 with dimethyl maleate, 22.6 with methyl methacrylate, 1.82 with methyl crotonate, 1.82 with allyl alcohol, 7.56 with styrene, and 8.1 with ethyl vinyl ether [93, 94].

The reaction of the nitrone (LXIV) with cyclopentene in the presence of silver tetrafluoroborate resulted in the formation of the tricyclic compound (CCVIII) with a yield of 29% [47].

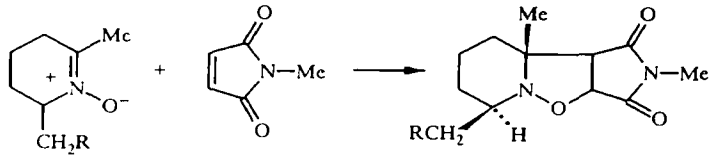


Only one isomer (CCIV) was isolated from the products of the reaction of the nitrone (XXIX) with N-phenylmaleimide (yield 56%) [83].



CCIX

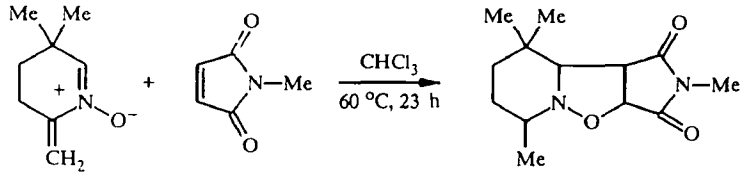
The reaction of N-methylmaleimide with the nitrones (CCX) (R = OH, Br, COOMe) [42, 46, 54] leads to the products (CCXI) (R = OH, Br, COOMe) with yields of 80, 33, and 100% respectively, and each of them is formed as two diastereomers (*endo* and *exo*).



CCX CCXI

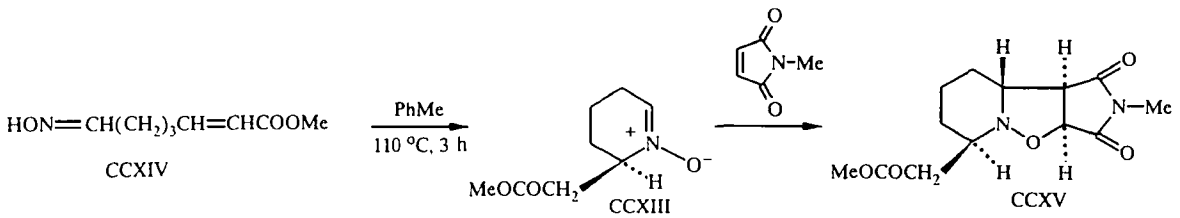
R, solvent, temperature, °C, reaction time (h), *endo*:*exo*: OH, xylene, 140, 8.1:6; Br, xylene, 140, 8, 2, 3 : 1; COOMe, $CHCl_3$, 20, —, 1 : 3

The reaction of the same imide with the nitrone (LXXXIII) also gives a mixture (1:1) of the *endo* and *exo* isomers of compound (CCXII) (yield 84%) [51].



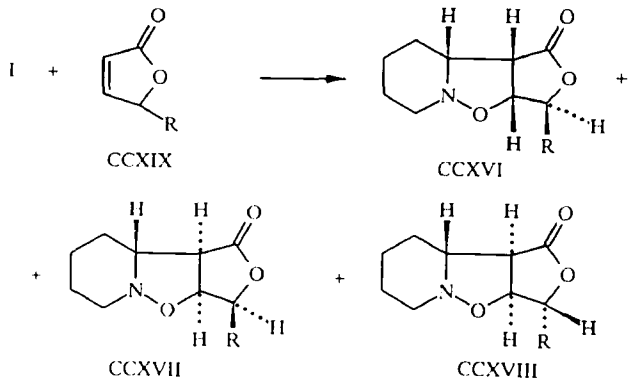
LXXXIII CCXII

On the other hand, the *exo* isomer of compound (CCXV) was synthesized with a 90% yield from 2-(methoxycarbonylmethyl)-2,3,4,5-tetrahydropyridine 1-oxide (CCXIII), which was obtained by heating the unsaturated oxime (CCXIV) in toluene and was brought *in situ* into 1,3-dipolar cycloaddition with N-methylmaleimide [42].



CCXIV CCXIII CCXV

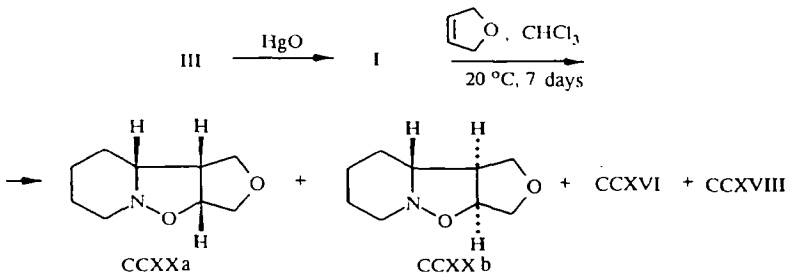
Three adducts each [*endo* (CCXVI), *exo-syn* (CCXVII), and *exo-anti* (CCXVIII)] are formed in various ratios in the reaction of the nitrone (I) with the unsaturated lactones (CLXIX) under various conditions (Table 8) [10, 95, 96].



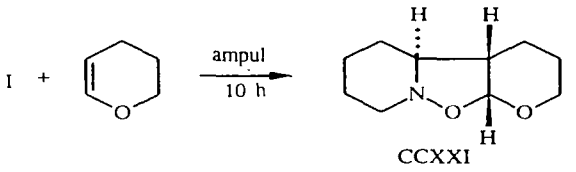
CCXIX CCXVI

CCXVII CCXVIII

During the production of the nitrone from 1-hydroxypiperidine (III) by the action of mercuric oxide in the presence of 2,5-dihydrofuran compounds (CCXVI) (R = H, yield 2%) and (CCXVIII) (R = H, yield 13%) were unexpectedly obtained in addition to the expected diastereomeric adducts (CLXXa, b) (yields 2 and 44% respectively). The formation of these two compounds is explained by oxidation of the dihydrofuran by mercuric oxide to the unsaturated lactone (CCXIX) (R = H), which then reacts with the nitrone (I) [10].

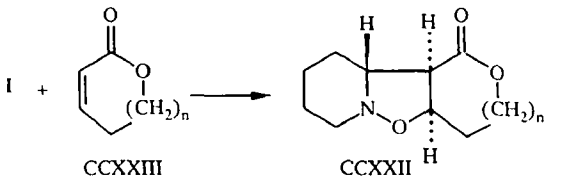


The yield of the product (CCXXI), formed from the nitrone (I) and 2,3-dihydropyran, depends substantially on the temperature and on the solvent [97].



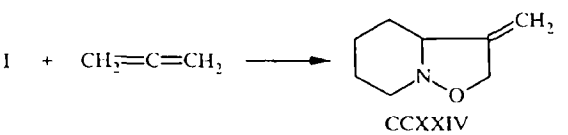
Solvent, temperature, °C, yield (%): PhH, 110, 12; PhH, 140, 10; PhH, 190, 3; EtOH, 80, 32; DMSO —, 22; C_5H_5N, —, 19

The effects of the nature of the solvent, the temperature, and the length of the process on the yields of the adducts (CCXXII), obtained as a result of the reaction of the nitrone (I) with the unsaturated lactones (CCXXIII), were investigated [10, 98].

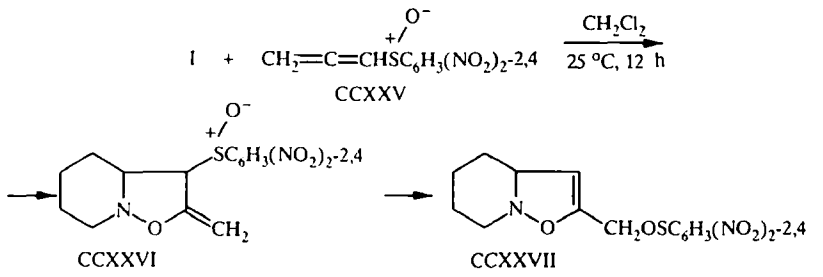


n, solvent, temperature, °C, reaction time (h), yield (%):
1, CH_2Cl_2, 20, 312, 86; PhMe, 110, 15, 85; 2, CH_2Cl_2, 20, 24, 31; 2, $CHCl_3$, 60, 38, 49; 2, PhMe, 100, 9, 59

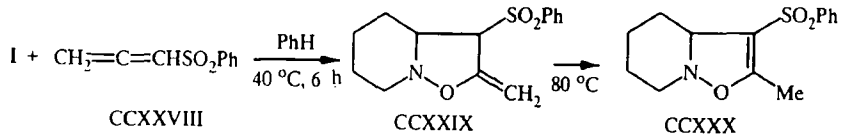
2.3.2. Reactions with Dienes. Allene reacts with the nitrone (I) regioselectively in such a way that the adduct (CCXXIV), containing a methylene group at the β position of the isoxazolidine ring, is formed [79].



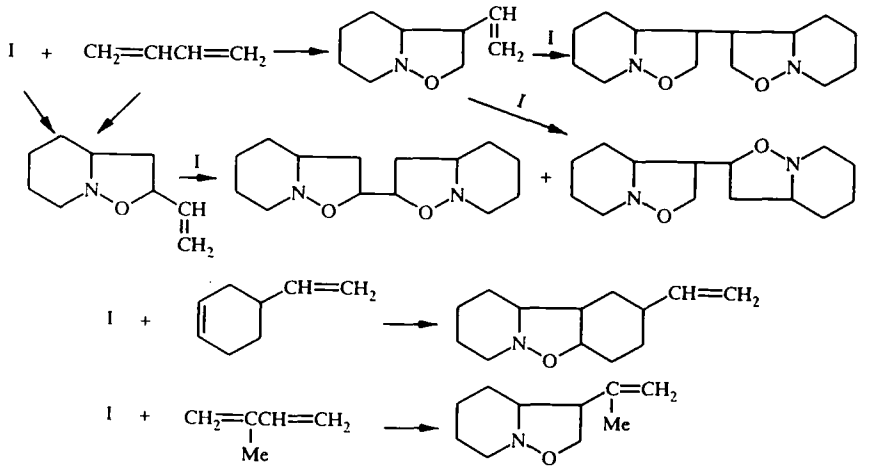
In the reaction of allene sulfoxide (CCXXV) with the same nitrone the double bond closest to the substituent enters into [3+2]-cycloaddition, and the adduct (CCXXVI) is formed. It is converted as a result of [2,3]-sigmatropic rearrangement into 8-[(2,4-dinitrophenyl)sulfinyloxymethyl]-9-oxa-1-azabicyclo[4.3.0]non-7-ene (CCXXVII) with a yield of 95% [16, 99].



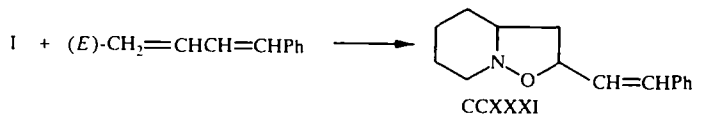
The cycloaddition of the nitrone (I) to allenyl phenyl sulfone (CCXXVIII) is also strictly regioselective and leads to compound (CCXXIX), which is converted at 80 °C into 7-phenylsulfonyl-8-methyl-9-oxa-1-azabicyclo[4.3.0]non-7-ene (CCXXX) [100].



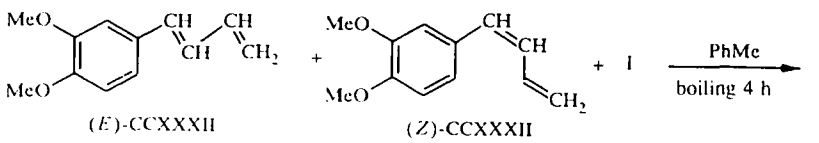
The authors of [101] describe the adducts that can be obtained as a result of the [3+2]-cycloaddition of the nitrone (I) to 1,3-butadiene, 4-(vinyl)cyclohexene (1,3-butadiene dimer), or isoprene.

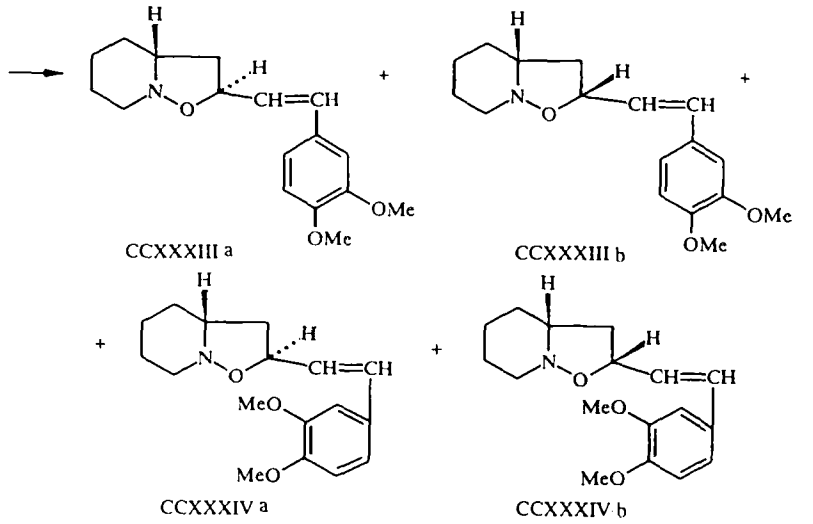


trans-1-Phenyl-1,3-butadiene reacts with the nitrone (I) through the unsubstituted vinyl group, and 8-(2-phenylvinyl)-9-oxa-1-azabicyclo[4.3.0]nonane (CCXXXI) is formed with a yield of 94% [102].

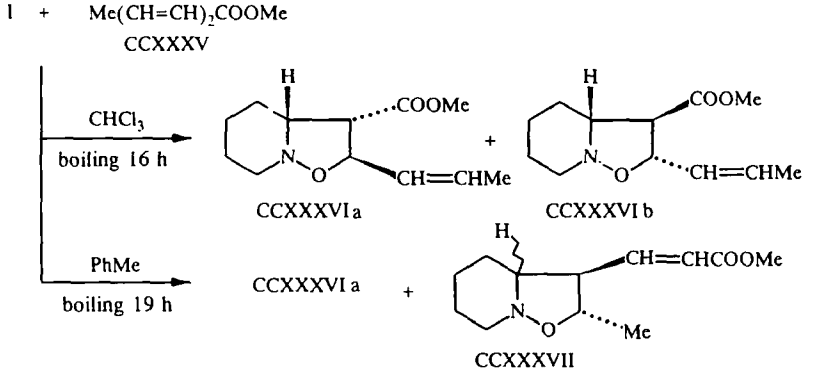


The reaction of the nitrone (I) with a mixture (9:5) of the (*E*) and (*Z*) isomers of 1-(3,4-dimethoxyphenyl)-1,3-butadiene (CCXXXII) was carried out by boiling in toluene. The diastereomers (CCXXXIIIa, b) (yield 49%, a:b = 10:3) and (CCXXXIVa, b) (yield 22%, a:b = 5:1) respectively were obtained [103, 104].

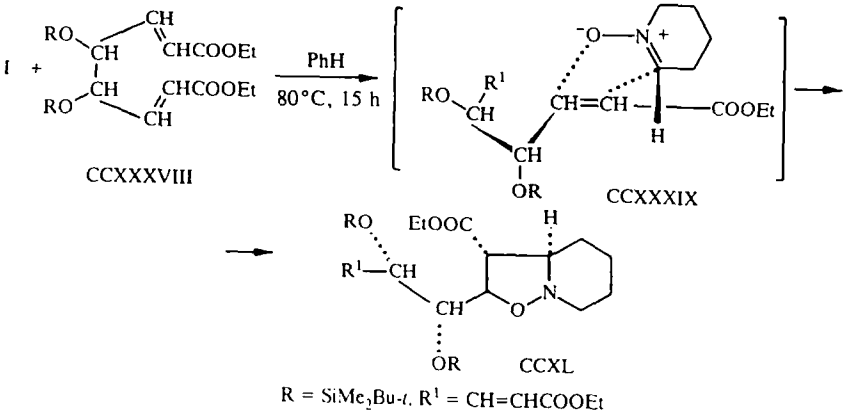




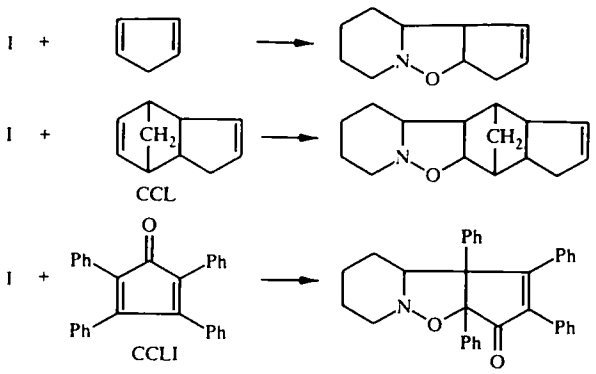
When the nitrone (I) was boiled with methyl (2*E*),(4*E*)-2,4-hexadienoate (CCXXXV) in chloroform, the diastereomers (CCXXXVIa, b) (yields 4.4 and 14% respectively) and also their mixture (yield 14%) were obtained. When boiled in toluene the same reagents gave the isomer (CCXXXVIa) (yield 5%) and also compound (CCXXXVII) (yield 10%) [95].



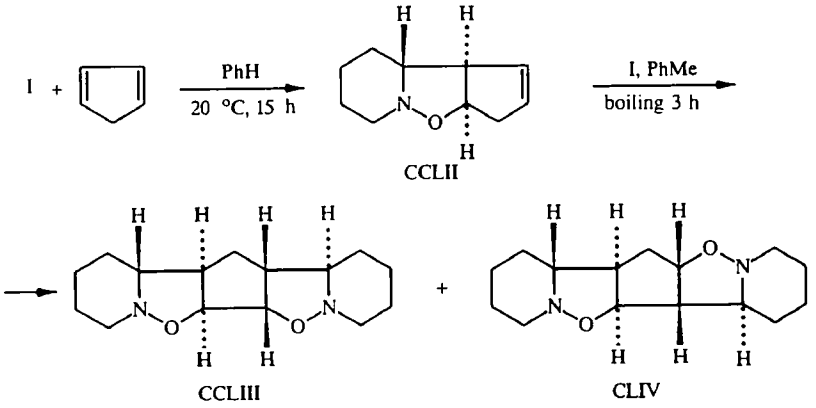
The [3+2]-cycloaddition of the nitrone (I) to the diene (CCXXXVIII) takes place through the *endo* transition state (CCXXXIX) and leads to a mixture (16:1) of the diastereomers of compound (CCXL) (yield 77%) [105].



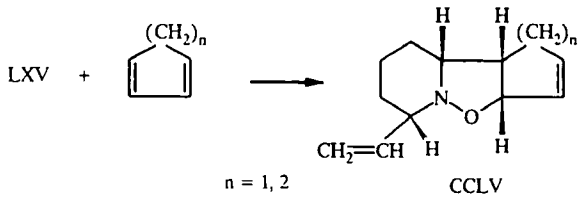
In 1960 a paper appeared on the products from the reaction of the nitrone (I) with cyclopentadiene, its dimer (CCL), and 2,3,4,5-tetraphenylcyclopentadiene (CCLI) [101].



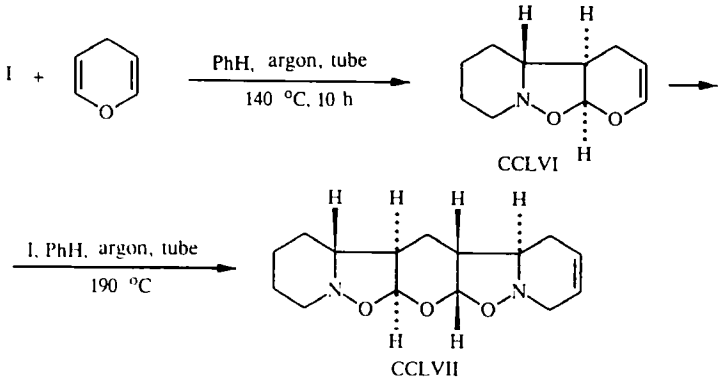
More recently the reaction of the nitrone (I) with cyclopentadienes was studied in greater detail. It was found that in benzene at 20°C they give a 65% yield of the 1:1 adduct (CCLII). In boiling toluene this reacts with another molecule of the nitrone (I) and is converted into a 1:2 mixture of the regioisomers (CCLIII) and (CCLIV) [106].



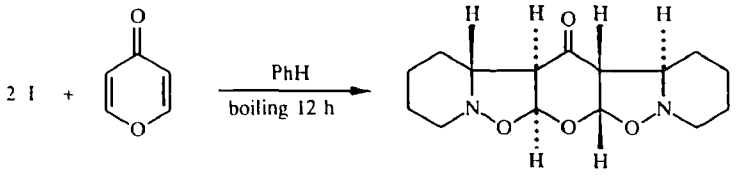
Compounds (CCLV) were synthesized from the nitrone (LXV) and cyclopentadiene or cyclohexane by 1,3-dipolar cycloaddition with yields of 43 and 35% respectively [47].



The reaction of the nitrone (I) with pyran in benzene in a tube at 140°C takes place regioselectively and stereoselectively with the formation of the 1:1 adduct (CCLVI) (yield 70%). The latter reacts with the nitrone under the same conditions, giving a 32% yield of the *exo,exo-trans* bisadduct (CCLVII) [106, 107].

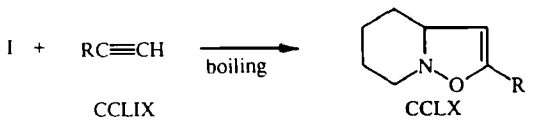


When boiled in benzene γ-pyrone reacts with two molecules of the nitrone (I), and compound (CCLVIII) is formed with a yield of 40-65% [106, 107].



CCLVIII

2.3.3. Reactions with Alkynes. There are only two papers on the reactions of the nitrone (I) with compounds containing a triple carbon–carbon bond. Thus, in the case of compound (CCLIX) with a terminal ethynyl group the cycloaddition process is strictly regioselective, and as a result only the 8-substituted derivatives of 9-oxa-1-azabicyclo[4.3.0]non-7-ene (CCLX) are formed [108].



CCLIX CCLX

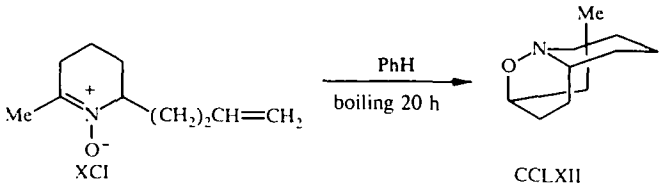
R, solvent, yield (%): Ph, $CHCl_3$, 81; C_5H_{11}-*n*, $MeCCl_3$, 70; CH_2Cl, $CHCl_3$, 85; CH=CHPh, $CHCl_3$, 65

It is necessary to mention the specific regioselectivity of the [3+2]-cycloaddition of the nitrones to alkenes or alkynes. If unsaturated compounds containing an electron-donating substituent at the double bond on one side and an electron-withdrawing substituent on the other take part in the reaction, derivatives of 9-oxa-1-azabicyclo[4.3.0]nonane containing an electron-withdrawing substituent at position 7 are mostly formed. This is illustrated by a series of the examples in section 2.3.1. Similarly, the reaction of the nitrone (I) with methyl(phenylsulfonyl)acetylene gave 7-phenylsulfonyl-8-methyl-9-oxa-1-azabicyclo[4.3.0]non-7-ene (CCLXI) [100].

CCLXI

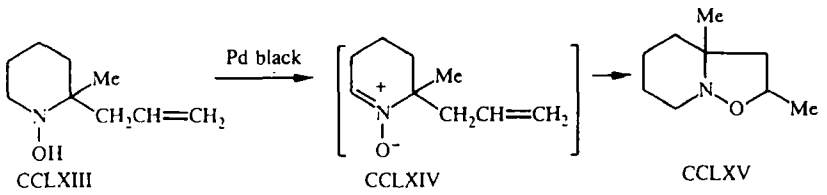
2.4. Intramolecular [3+2]-Cycloaddition Reactions

When boiled in benzene, 2-(3-butenyl)-6-methyl-2,3,4,5-tetrahydropyridine 1-oxide (XCI) enters into intramolecular 1,3-dipolar cycloaddition with the formation of (3R*,6R*,10S*)-10-methyl-2-oxa-1-azatricyclo[4.4.0.$1^{3,10}$]undecane (CCLXII) (yield 74%) [53].



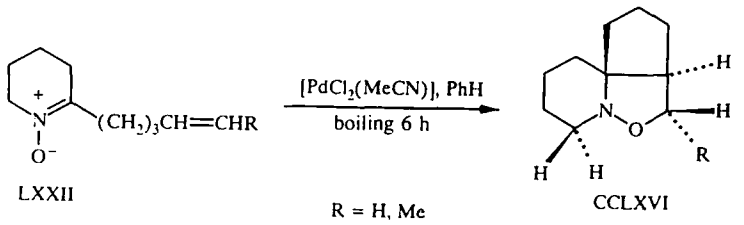
XCI CCLXII

In the presence of palladium black 1-hydroxy-2-methyl-2-allylpiperidine (CCLXIII) is converted into 2-methyl-2-allyl-2,3,4,5-tetrahydropyridine (CCLXIV). The latter undergoes intramolecular cycloaddition and is converted into 6,8-dimethyl-9-oxa-1-azabicyclo[4.3.0]nonane (CCLXV) [30].



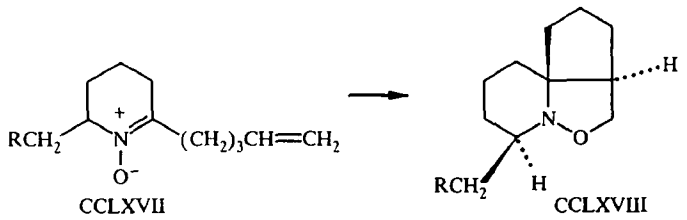
CCLXIII CCLXIV CCLXV

When boiled in benzene in the presence of a palladium-containing catalyst, the nitrone (LXXII) undergoes cyclization to the tricyclic compound (CCLXVI) with a yield of 82-85% [49].



LXXII R = H, Me CCLXVI

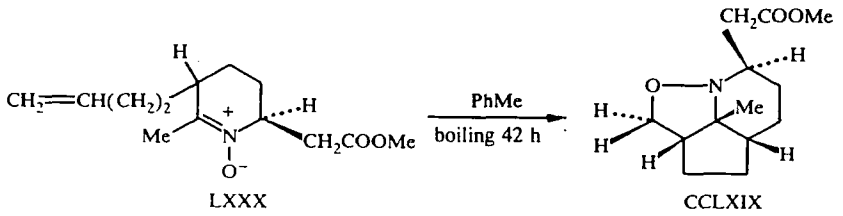
The stereoselective intramolecular cyclization of the nitrones (CCLXVII) leads to single products (CCLXVIII) [45, 46, 50].



CCLXVII CCLXVIII

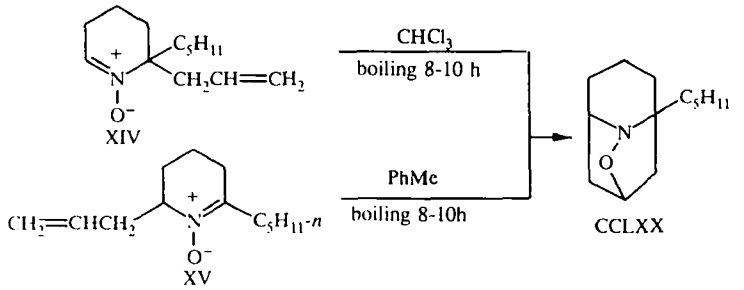
R, solvent, temperature, °C, reaction time (h), yield (%): HgOAc, MeCN, 80, 6, 65
[45]: I, PhH, 80, 5, 53 [46]; COOMe, DMF, 100-105, 1, 70 [50]

A tricyclic compound (CCLXIX) with a different structure is formed with a 70% yield during the prolonged heating of the nitrone (LXXX) in toluene [50].



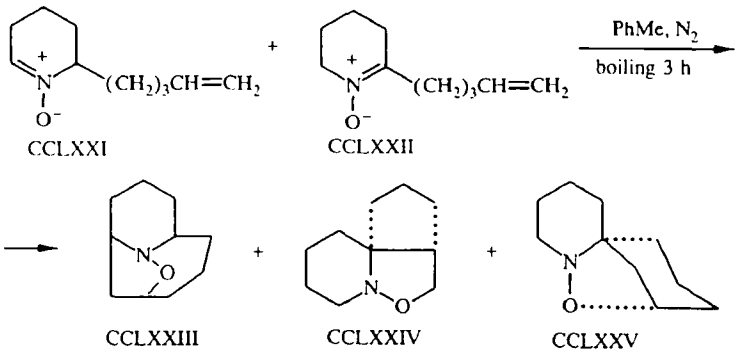
LXXX CCLXIX

When 2-allyl-2-pentyl-2,3,4,5-tetrahydropyridine 1-oxide (XIV) was boiled in chloroform or 2-allyl-6-pentyl-2,3,4,5-tetrahydropyridine 1-oxide (XV) was boiled in toluene, one and the same compound (CCLXX) was obtained [20].



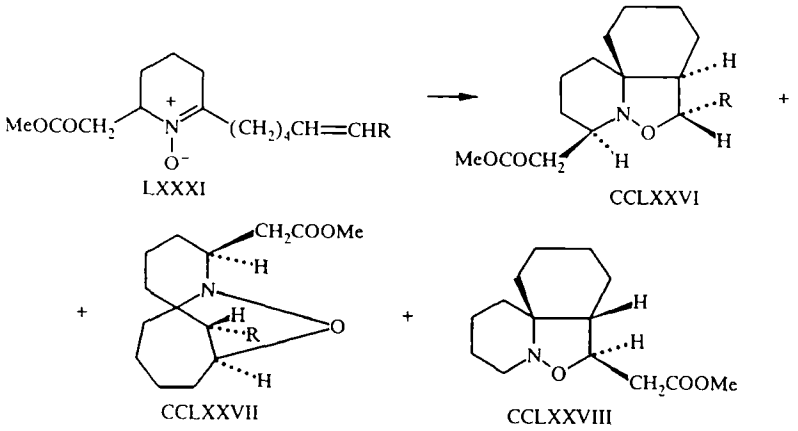
CCLXX

By boiling the nitrones (CCLXXI) and (CCLXXII) together in toluene the authors of [4] synthesized compound (CCLXXIII) (yield 7%) from the oxide (CCLXXI) and compounds (CCLXXIV) (yield 64%) and (CCLXXV) (yield 14%) from the oxide (CCLXXII).



CCLXXI CCLXXII CCLXXIII CCLXXIV CCLXXV

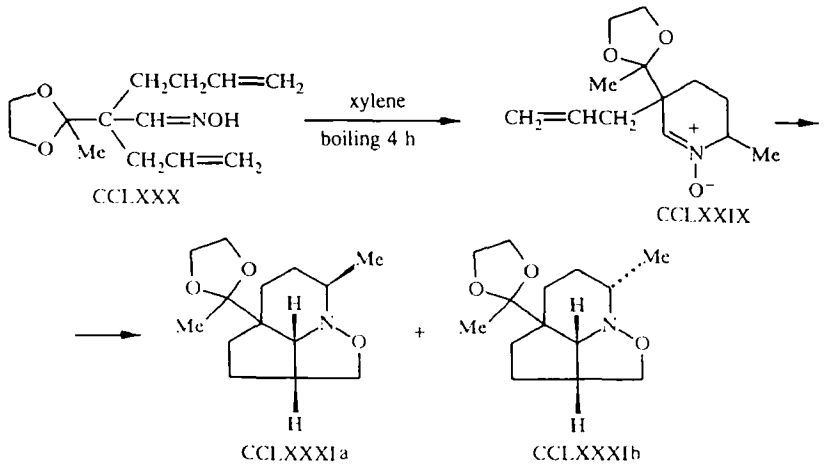
The nature of the substituent R in the nitrones (LXXXI) determines the composition of the products from the intramolecular [3+2]-cycloaddition of these compounds; with R = H two adducts (CCLXXVI) and (CCLXXVII) are formed, and with R = COOMe the adduct (CCLXXVIII) is obtained as well [50].



LXXXI CCLXXVI CCLXXVII CCLXXVIII

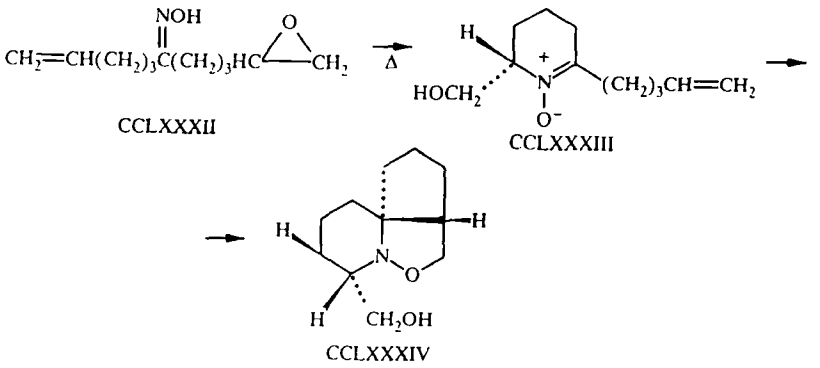
R, solvent, temperature, °C, reaction time (h), ratios CCLXXVI : CCLXXVII : CCLXXVIII, total yield (%): H, DMF, 110, 2 days, 1 : 1 : ~60; COOMe, MeCN, 80, 16 h, 10 : 2 : 1.72

The nitrone (CCLXXIX), formed from the oxime (CCLXXX) after boiling in xylene, undergoes intramolecular [3+2]-cycloaddition, as a result of which the diastereomers (CCLXXXIa, b) are obtained. The overall yield, according to PMR, is ~100%; the yield of the isolated mixture (CCLXXXIa, b) is 58% with the ratio a:b = 1:1.2 [50].



CCLXXX CCLXXIX CCLXXXIa CCLXXXIb

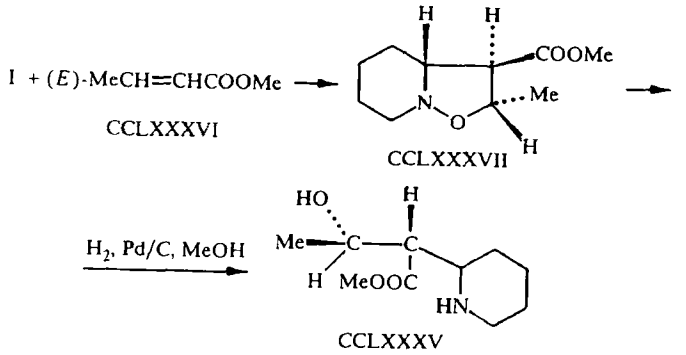
When heated, the oxime (CCLXXXII) undergoes cyclization, being converted into 2-hydroxymethyl-6-(4-pentenyl)-2,3,4,5-tetrahydropyridine (CCLXXXIII), which undergoes cyclization *in situ* with the formation of the tricyclic compound (CCLXXXIV) (yield 90%) [54].



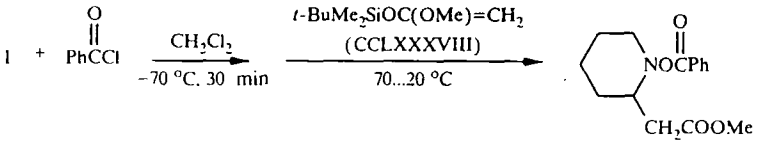
Solvent, temperature, °C, reaction time (h): xylene, 140, 6; $CHCl_3$, 60, 24

2.5. Other Reactions

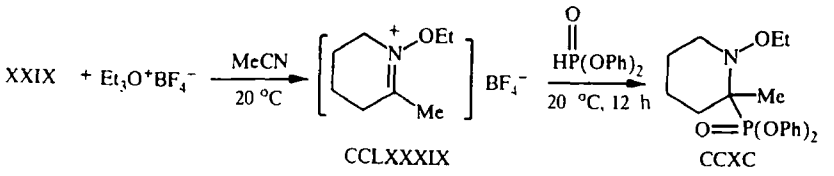
The oxidation of the nitrone (I) and 1-hydroxypiperidine (III) by $FeCl_3$ was investigated by spectrophotometry. The obtained hydroxamic acid was characterized in the form of a 1:1 complex with Fe^{3+} with an absorption maximum at 500-508 nm [109]. The kinetics and mechanism of oxidation were studied [110]. Compound (CCLXXXV) was synthesized with a 70% yield from the nitrone (I) and the ester (CCLXXXVI) followed by hydrogenolysis of the obtained adduct (CCLXXXVII) [111].



1-Benzoyloxy-2-(methoxycarbonylmethyl)piperidine (yield 68%) was obtained by treating the reaction mass from the reaction of the nitrone and benzoyl chloride in the presence of a molecular sieve (4 Å) with compound (CCLXXXVIII) [112].

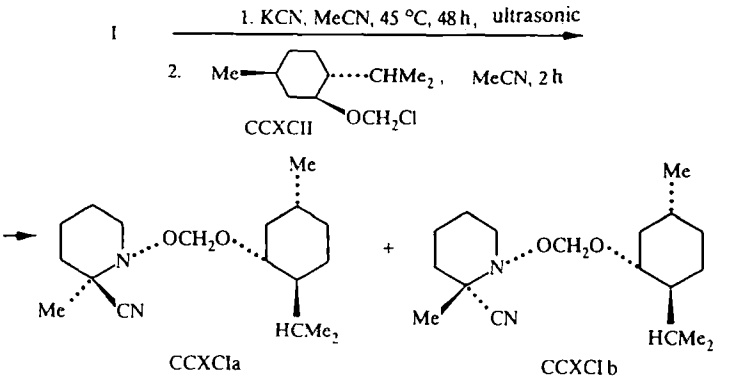


With triethyloxonium tetrafluoroborate 6-methyl-2,3,4,5-tetrahydropyridine 1-oxide (XXIX) forms the salt (CCLXXXIX). The latter is converted by reaction with diphenyl phosphite, followed by treatment with a solution of sodium carbonate, into diphenyl 1-ethoxy-2-methyl-2-piperidinylphosphonate (CCXC) with a yield of 78% [113].



CCLXXXIX CCXC

The diastereomeric nitriles of (1^1R,2R,2^1R,5^1R)- and (1^1R,2S,2^1S,5^1R)-1-[(2-isopropyl-5-methylcyclohexyl)-oxymethoxy]-2-methyl-2-pyridinecarboxylic acid (CCXCIa, b) were synthesized by the reaction of the nitrone (I) with potassium cyanide and (−)-menthyl ether (CCXCII) by ultrasonic treatment (yields 33 and 36% respectively) [114].



CCXCII CCXCIa CCXCIb

REFERENCES

1. D. St. Black, R. F. Crozier, and V. Ch. Davis, Synthesis, No. 4, 205 (1975).
2. K. Torssell, in: Nitrile Oxides and Nitronates in Organic Synthesis, H. Feuer (ed.), VCH Publishers (1988).
3. J. Thesing and H. Mayer, Chem. Ber., **89**, 2159 (1956).
4. E. Gössinger, R. Imhoff, and H. Wehrli, Helv. Chim. Acta, **58**, 96 (1975).
5. M. Colonna and U. De Martino, Gazz. Chim. Ital., **93**, 1183 (1963).
6. E. J. Alford, J. A. Hall, and M. A. Th. Rogers, J. Chem. Soc. (C), No. 12, 1103 (1966).
7. J. Thesing and H. Mayer, Liebigs Ann. Chem., **609**, 46 (1957).
8. E. Gössinger, Monatsh. Chem., **111**, 143 (1980).
9. P. Merlin, J. C. Braekman, and D. Daloze, Tetrahedron Lett., **29**, 1691 (1988).
10. P. Cid, P. March, M. Figueredo, J. Font, S. Milan, A. Soria, and A. Virgili, Tetrahedron, **49**, 3857 (1993).
11. C. Hootele, W. Ibebeke-Bomangwa, F. Driessens, and S. Sabil, Bull. Soc. Chim. Belg., **96**, 57 (1987).
12. A. Brandi, P. Cannavo, K. M. Pietrusiewicz, and M. Zablocka, J. Org. Chem., **54**, 3073 (1989).
13. K. Shishido, K. Tanaka, K. Fukumoto, and T. Kametani, Tetrahedron Lett., **24**, 2783 (1983).
14. K. Shishido, K. Tanaka, K. Fukumoto, and T. Kametani, Chem. Pharm. Bull., **33**, 532 (1985).
15. Sk. A. Ali and M. J. M. Wazeer, J. Chem. Soc. Perkin Trans. I, No. 3, 597 (1988).
16. A. Padwa, W. H. Bullock, B. H. Norman, and J. Perumattam, J. Org. Chem., **56**, 4252 (1991).
17. Sk. A. Ali and M. J. M. Wazeer, J. Chem. Soc. Perkin Trans. II, No. 11, 1789 (1986).
18. W. Ibebeke-Bomangwa and C. Hootele, Tetrahedron, **43**, 935 (1987).
19. E. Gössinger, Tetrahedron Lett., No. 23, 2229 (1980).
20. E. Gössinger and B. Witkop, Monatsh. Chem., **111**, 803 (1980).
21. Sk. A. Ali, Tetrahedron Lett., **34**, 5325 (1993).
22. A. Goti, F. De Sarlo, and M. Romani, Tetrahedron Lett., **35**, 6571 (1994).
23. Yo. Zhang and G.-Zh. Xu, J. Chem. Res. Synop., No. 2, 42 (1991).
24. G. Pandey, G. Kumaraswamy, and A. Krishna, Tetrahedron Lett., **28**, 2649 (1987).
25. T. Shono, Yo. Matsumura, and K. Inoue, J. Org. Chem., **51**, 549 (1986).
26. Sh.-I. Murahashi, H. Mitsui, T. Watanabe, and S. Zenki, Tetrahedron Lett., **24**, 1049 (1983).

27. Sh.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, and Sh. Watanabe, J. Org. Chem., **55**, 1736 (1990).
28. Sh. Murahashi and M. Hitoshi, German Pat. No. 3406805; Chem. Abs., **102**, 78863 (1985).
29. W. Carruthers and R. C. Moses, J. Chem. Soc. Perkin Trans. I, No. 8, 2251 (1988).
30. H. Mitsui, S.-I. Zenki, T. Shiota, and Sh. I. Murahashi, J. Chem. Soc. Chem. Commun., No. 13, 874 (1984).
31. M. Shunichi and Sh. Tatsuki, Jpn. Pat. No. 8863651; Chem. Abs., **109**, 92271 (1988).
32. Sh.-I. Murahashi and T. Shioda, Tetrahedron Lett., **28**, 2383 (1987).
33. W. W. Zajac, Th. R. Walters, and G. M. Darcy, J. Org. Chem., **53**, 5856 (1988).
34. F. P. Ballisteri, U. Chiachio, A. Rescifina, G. A. Tomaselli, and R. M. Toscano, Tetrahedron, **48**, 8677 (1992).
35. W. Carruthers, P. Coggins, and J. B. Weston, J. Chem. Soc. Chem. Commun., No. 1, 91 (1990).
36. W. Carruthers, P. Coggins, and J. B. Weston, J. Chem. Soc. Perkin Trans. I, No. 8, 2323 (1990).
37. A. B. Holmes, A. B. Hughes, and A. L. Smith, Synlett, No. 1, 47 (1991).
38. Sk. A. Ali, J. Chem. Res. Synop., No. 1, 32 (1994).
39. Sk. A. Ali and M. I. Wazeer, Tetrahedron Lett., **33**, 3219 (1992).
40. Sk. A. Ali, J. Chem. Res. Synop., No. 2, 54 (1994).
41. A. B. Holmes, A. B. Hughes, and A. L. Smith, J. Chem. Soc. Perkin Trans. I, No. 5, 633 (1993).
42. W. J. Armstrong, J. Chem. Soc. Chem. Commun., No. 17, 1327 (1987).
43. R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar, and W. J. Warnock, Tetrahedron Lett., **31**, 559 (1990).
44. R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, M. Thornton-Pett, and W. J. Warnock, Tetrahedron, **47**, 4007 (1991).
45. R. Grigg, M. Hadjisoteriu, P. Kennewell, J. Markandu, and M. Thornton-Pett, J. Chem. Soc. Chem. Commun., No. 19, 1388 (1992).
46. R. Grigg, M. Hadjisoteriu, P. Kennewell, J. Markandu, and M. Thornton-Pett, J. Chem. Soc. Chem. Commun., No. 17, 1340 (1993).
47. D. Lathbury and T. Gallagher, Tetrahedron Lett., **26**, 6249 (1985).
48. D. Lathbury and T. Gallagher, J. Chem. Soc. Chem. Commun., No. 13, 1017 (1986).
49. M. Frederickson, R. Grigg, J. Markandu, and J. Redpath, J. Chem. Soc. Chem. Commun., No. 19, 2225 (1994).
50. R. Grigg, J. Markandu, S. Sivagnanasundram, M. Thornton-Pett, and W. J. Warnock, Tetrahedron, **48**, 10399 (1992).
51. R. Grigg, T. R. Perrior, G. J. Sexton, S. Surendrakumar, and T. Suzuki, J. Chem. Soc. Chem. Commun., No. 4, 372 (1993).
52. M. E. Fox, A. B. Holmes, I. T. Forbes, and M. Thompson, J. Chem. Soc. Chem. Perkin Trans. I, No 23, 3379 (1994).
53. A. B. Holmes, A. L. Smith, S. F. Williams, L. R. Hughes, Z. Lidert, and C. Swithenbank, J. Org. Chem., **56**, 1393 (1991).
54. R. Grigg and J. Markandu, Tetrahedron Lett., **30**, 5489 (1989).
55. Sh. Shatzmiller and E. Shalom, Liebigs Ann. Chem., No. 6, 897 (1983).
56. W. Ciesielski, Z. H. Kudzin, M. Tasz, and J. Drabowicz, Can. J. Chem., **68**, 679 (1990).
57. Sh. Murahashi and H. Otake, Jpn. Pat. No. 05255220; Chem. Abs., **119**, 249856 (1993).
58. B. E. Schultz, S. F. Gheller, M. C. Muetterties, M. Scott, and R. H. Holm, J. Am. Chem. Soc., **115**, 2714 (1993).
59. W. G. Hollis, Ph. L. Smith, D. K. Hood, and S. M. Cook, J. Org. Chem., **59**, 3485 (1994).
60. E. Gössinger, Monatsh. Chem., **112**, 1017 (1981).
61. W. Carruthers and M. J. Williams, J. Chem. Soc. Chem. Commun., No. 16, 1287 (1986).
62. D. R. Adams, W. Carruthers, and M. J. Williams, J. Chem. Soc. Perkin Trans. I, No. 8, 1507 (1989).
63. A. Brandi, A. Guarna, A. Goti, and F. De Sarlo, Tetrahedron Lett., **27**, 1727 (1986).
64. A. Brandi, S. Garro, A. Guarna, A. Goti, F. Cordero, and F. De Sarlo, J. Org. Chem., **53**, 2430 (1988).
65. A. Brandi, A. Goti, S. Kozushov, and A. Meijere, J. Chem. Soc. Chem. Commun., No. 18, 2185 (1994).
66. F. M. Cordero, B. Anichini, A. Goti, and A. Brandi, Tetrahedron, **49**, 9867 (1993).
67. J. J. Tufariello and Sk. A. Ali, Tetrahedron Lett., **47**, 4647 (1978).
68. J. J. Tufariello and J. M. Puglis, Tetrahedron Lett., **27**, 1489 (1986).
69. U. Chiaccho, F. Casuscelli, A. Corsaro, A. Rescifina, G. Romeo, and N. Uccella, Tetrahedron, **50**, 6671 (1994).
70. H. Iida and Ch. Kibayashi, Tetrahedron Lett., **22**, 1913 (1981).
71. H. Iida, Yo. Watanabe, M. Tanaka, and Ch. Kibayashi, J. Org. Chem., **49**, 2412 (1984).
72. M. Ito, M. Maeda, and Ch. Kibayashi, Tetrahedron Lett., **33**, 3765 (1992).

73. S. Takano and K. Shishido, J. Chem. Soc. Chem. Commun., No. 18, 940 (1981).
74. S. Takano and K. Shishido, Heterocycles, **19**, 1439 (1982).
75. S. Takano and K. Shishido, Chem. Pharm. Bull., **32**, 3892 (1984).
76. W. Carruthers, P. Coggins, and J. B. Weston, J. Chem. Soc. Chem. Commun., No. 2, 117 (1991).
77. N. Takatsu, Sh. Ohmiya, and H. Otomasu, Chem. Pharm. Bull., **35**, 891 (1987).
78. A. S. Amarasekara and A. Hassner, Tetrahedron Lett., **28**, 3151 (1987).
79. Sk. A. Ali, P. A. Senaratne, C. R. Illig, H. Meckler, and J. J. Tufariello, Tetrahedron Lett., No. 43, 4167 (1979).
80. Sk. A. Ali, J. H. Kham, and M. J. M. Wazeer, Tetrahedron, **44**, 5911 (1988).
81. F. M. Cordero, A. Brandi, F. De Sarlo, and G. Viti, J. Chem. Soc. Chem. Commun., No. 9, 1047 (1994).
82. A. Brandi, S. Cicchi, A. Goti, K. M. Pietrusiewicz, and W. Wishniewski, Tetrahedron, **46**, 7093 (1990).
83. T. Hisano, K. Harano, T. Matsuoka, S. Watanabe, and T. Matsuzaki, Chem. Pharm. Bull., **37**, 907 (1989).
84. S. K. Armstrong, E. W. Collington, J. Stonehouse, and S. Warren, J. Chem. Soc. Perkin Trans. I, No. 19, 2825 (1994).
85. M. Yamamoto, T. Suenaga, K. Suzuki, K. Naruchi, and K. Yamada, Heterocycles, **26**, 755 (1987).
86. Sk. A. Ali, J. H. Khan, M. J. M. Wazeer, and H. P. Perzanowski, Tetrahedron, **45**, 5979 (1989).
87. Sk. A. Ali, J. Chem. Res. Synop., No. 5, 146 (1992).
88. Sk. A. Ali, M. I. M. Wazeer, and M. Ul-Hague, Tetrahedron, **46**, 7207 (1990).
89. Sh.-I. Murahashi, Ya. Imada, M. Kohno, and T. Kawakami, Synlett, No. 6, 395 (1993).
90. J. J. Tufariello and J. J. Fegeler, Tetrahedron Lett., No. 45, 4037 (1976).
91. J. J. Tufariello and A. D. Dyszlewski, J. Chem. Soc. Chem. Commun., No. 15, 1138 (1987).
92. Sk. A. Ali and M. I. M. Wazeer, J. Chem. Soc. Perkin Trans. II, No. 6, 1035 (1990).
93. Sk. A. Ali and M. I. M. Wazeer, J. Chem. Res. Synop., No. 2, 62 (1992).
94. Sk. A. Ali and M. I. M. Wazeer, Tetrahedron, **44**, 187 (1988).
95. M. Figueredo, J. Font, and P. March, Chem. Ber., **122**, 1701 (1989).
96. P. Cid, P. March, M. Figueredo, J. Font, and S. Milan, Tetrahedron Lett., **33**, 667 (1992).
97. T. Iwashita, T. Kusumi, and H. Kakisawa, J. Org. Chem., **47**, 230 (1982).
98. P. Cid, M. Figuredo, J. Font, C. Jaime, P. March, and A. Virgili, Magn. Reson. Chem., **28**, 947 (1990).
99. A. Padwa, B. H. Norman, and J. Perumattam, Tetrahedron Lett., **30**, 663 (1989).
100. A. Padwa, S. P. Carter, U. Chiacchio, and D. N. Kline, Tetrahedron Lett., **27**, 2683 (1986).
101. C. W. Brown, K. Marsden, M. A. Th. Rogers, C. M. B. Tylor, and R. Wright, Proc. Chem. Soc., 254 (1960).
102. J. J. Tufariello and R. C. Gatrone, Tetrahedron Lett., No. 31, 27 (1978).
103. H. Iida, M. Tanaka, and Ch. Kibayashi, J. Chem. Soc. Chem. Commun., No. 20, 1143 (1983).
104. H. Iida, M. Tanaka, and Ch. Kibayashi, J. Org. Chem., **49**, 1909 (1984).
105. S. Saito, T. Ishikawa, and T. Moriwake, Synlett, No. 4, 279 (1994).
106. H. Oinuma, Sh. Dan, and H. Kakisawa, J. Chem. Soc. Perkin Trans. I, No. 9, 2593 (1990).
107. H. Oinuma, Sh. Dan, and H. Kakisawa, J. Chem. Soc. Chem. Commun., No. 12, 654 (1983).
108. V. Mancuso and C. Hootele, Tetrahedron Lett., **29**, 5917 (1988).
109. J. F. Elsworth and M. Lamchen, J. S. Afr. Chem. Inst., **24**, 196 (1971).
110. J. F. Elsworth and M. Lamchen, J. S. Afr. Chem. Inst., **25**, 1, (1972).
111. J. J. Tufariello, G. E. Lee, P. A. Senaratne, and M. Al-Nuri, Tetrahedron Lett., **45**, 4359 (1979).
112. Sh. Murahashi and H. Ootake, Jpn. Pat. No. 05148208; Chem. Abs., **119**, 249856 (1993).
113. Sh. Shatzmiller, B. Z. Dolithzky, R. Meirovich, R. Neidlein, and Ch. Weik, Liebigs Ann. Chem., No. 2, 161 (1991).
114. Sh. Shatzmiller, B. Z. Dolithzky, and E. Bahar, Liebigs Ann. Chem., No. 4, 375 (1991).