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Reaction of Pyrylium Salts with Nucleophiles. Part 25.[1] Formation of Pyridine-1-oxides, 2-Isoxazolines and 1-Pyrazoline-1-oxides[+]

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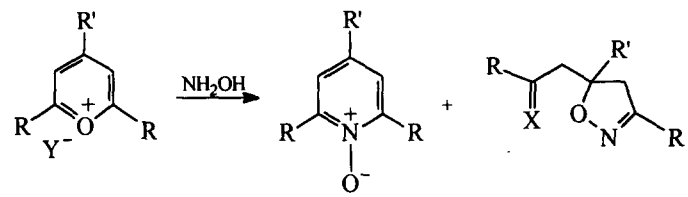
Abstract: The reaction of tri- and tetrasubstituted pyrylium salts with hydroxylamine affords acyclic keto-ketoximes (to be described in a separate paper) which cyclize yielding pyridine-1-oxides and/or 2-isoxazolines. Both these classes of compounds, with many possible applications, can thus be obtained simply and in good yield. The regioselectivity of 2-isoxazoline formation from unsymetrically substituted pyrylium salts is discussed. An unprecedented minor product formed from 2,6-di-*t*-butyl-4-methylpyrylium perchlorate and two molecules of hydroxylamine is the corresponding 1-pyrazoline-1-oxide. Mechanistic rationalization of all products are provided.

INTRODUCTION

Since its discovery in 1958,[2] the reaction between pyrylium salts **1** and hydroxylamine leading to pyridine-1-oxides **2** was of interest mainly for providing a synthetic alternative to the direct oxidation of pyridines.[3] The highly sterically hindered pyridine-1-oxides **2** (R=*t*-Bu; R'=Me, Ph or *t*-Bu) were actually prepared in moderate to good yields by the former reaction,[4] whereas the oxidative procedure was unsuccessful.[5] On the other hand, formation of pyridines rather than pyridine-1-oxides from pyrylium salts **1** with other bulky α-standing groups (R=*i*-Pr, Ph; R'=Me) was reported.[2b]



1 **2** **3** (X=O, NOH)

However, the figure of merit as preparative method for pyridine-1-oxides of this reaction is considerably lowered by the competing formation of 2-isoxazolines **3**[6] and conditions were searched for suppressing the ring-contraction reaction. It was found that the relative amount of **3** can be diminished when working under acidic rather than basic conditions: 2,4,6-triarylpyrylium salts gave only 2-isoxazolines **3** in aqueous sodium hydroxide,[7] but both **2** and **3** in comparable amounts in acetic acid buffered with sodium acetate.[8]

[+] Dedicated to the 70th anniversary of Alan Katritzky who, for 35 years, provided us with moral assistance and encouragement.

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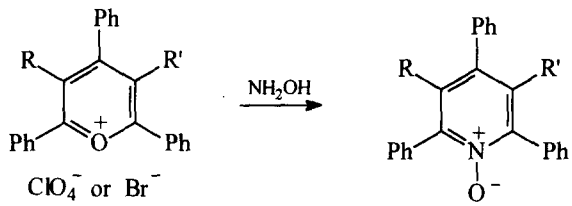
The tetrasubstituted pyrylium salts **4** (R=Me, Ph; R′=H) or the pentasubstituted pyrylium salts **4** (R=R′=Ph) with three, four or five phenyl groups were found to give in buffered acetic acid pyridine-1-oxides **5** in very high yields.[8]

Particularly striking is the formation of *t*-butyl 3,5-di-*t*-butyl-2-furyl ketone from 2,4,6-tri-*t*-butylpyrylium tetrafluoroborate and hydroxylamine hydrochloride,[9] with the latter acting presumably as O-nucleophile,[3] instead of N-nucleophile as usual.



4 **5**

In the present paper we undertook a systematic examination of the reaction between hydroxylamine and pyrylium salts **1** with various alkyls or alkyls/aryls R, R' in order to obtain a better view on the competition **2** *vs.* **3**. We report also a hitherto unprecedented ring-transformation reaction of the pyrylium cation into 1-pyrazoline-1-oxide. The regioselectivity in the reaction involving either pyrylium cations with different 2- and 6-substituents in 2,4,6-trisubstituted salts or 2,3,4,6-tetrasubstituted salts was also investigated.

RESULTS

Pyridine-1-oxide vs. 2-isoxazoline competition

We examined the pyrylium perchlorates **6a** through **6i** with identical alkyl or aryl groups R^{α} in the α-positions, the R^{γ} group in γ-position being methyl or phenyl. The substituents R^{α} were of increasing size both by the number of carbon atoms and by branching for alkyls, or by *ortho*-substitution for aryls.

The reaction was performed by heating the pyrylium salt either with equimolar amounts or a large excess (five-fold molar) of hydroxylamine hydrochloride in glacial acetic acid buffered with sodium acetate trihydrate, followed by aqueous work-up.[8] The products were separated by column chromatography on silica gel; the physical constants, elemental analysis, mass-spectra, ^{1}H-NMR and ^{13}C-NMR data of the reaction products are given in the Experimental part.

For evaluating quantitatively the composition of the reaction mixture, gas-liquid chromatography (glc) was not the appropriate method, because we noticed that the pyridine-1-oxides were partly converted into the corresponding pyridines, probably by the carrier gas (hydrogen). Therefore the molar fractions of the products were calculated from the ^{1}H-NMR spectra (at 300 MHz) of the crude reaction mixture, presenting signals with good separation for integration. The results obtained in the reactions performed with excess hydroxylamine are presented in Table 1.

Pyrylium salts **6a** and **6b** with α-methyl groups gave only pyridine-1-oxides, whereas all the other salts gave both pyridine-1-oxides and 2-isoxazolines. Unlike the above mentioned literature data,[2b] we obtained pyridine-1-oxides from pyrylium salts **6e** and **6g** with *i*-Pr or Ph in α-positions, isolating only traces of 4-methyl-2,6-diphenylpyridine starting from **6g**. The main structural proof for pyridine-1-oxides **7** was the [M-17] peak in their mass-spectra, which was also the base peak for all **7** possessing α-benzylic hydrogen(s). Heterocyclic N-oxides are known to give [M-O] and [M-OH] fragmentations, the latter prevailing when *ortho* effects operate.[10,11]

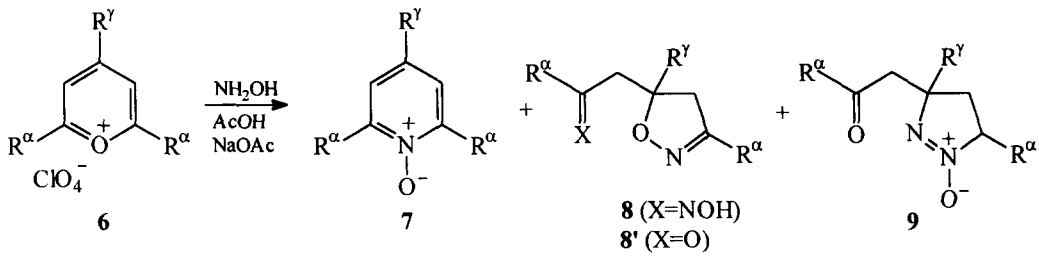
The amount of pyridine-1-oxide **7** is steadily decreasing with increasing size of R^{α} for both alkyl and aryl α-substituents. On the other hand, salts with the same R^{α} (such as **6a,b** or **6g,i**) gave the same amount of **7**, regardless of the nature of the γ-substituent (R^{γ}=Me or Ph).

The 2-isoxazolinic compounds were obtained as oximes **8** when a large excess of hydroxylamine was used, whereas with equimolar amounts the corresponding ketones **8'** were obtained, with only traces of oximes. The ketones **8'** with bulky R groups (*o*-MeC_6H_4, *t*-Bu) were not completely oximated with excess

hydroxylamine, even at long reaction times, indicating that steric hindrance lowers considerably the reaction rate.

The oximes **8** were obtained as pairs of E,Z-isomers except for **8f** and **8i** which appeared as a single E-isomer. The configurational assignment was based on ^{13}C-NMR data, comparing the E,Z-**8** pair of oximes with its ketonic counterpart **8'**. As established for a large number of alkanones,[12] the ^{13}C-NMR signals of both carbon atoms flanking the functional group in oximes are shifted upfield compared with the parent ketone, each carbon atom being in turn more shifted when in *syn* position with the hydroxy group of the oxime than when *anti*. The configurational assignment was based on this procedure (see Table 10) and was checked by Beckmann rearrangement with thionyl chloride[13] for E-**8e** and E-**8i**.

Table 1. Molar Fractions of the Products Obtained from Symmetrically Trisubstituted Pyrylium Perchlorates **6a** through **6i** and Excess Hydroxylamine Hydrochloride.



6	R^{α}	R^{γ}	7	8 (E+Z)[i, ii]	9 (*cis*+*trans*)[iii]
a	Me	Me	1.00	-	-
b	Me	Ph	1.00	-	-
c	Et	Me	≥ 0.95	≤ 0.05	-
d	*n*-Pr	Me	0.80	0.20	-
e	*i*-Pr	Me	0.60	0.40	-
f	*t*-Bu	Me	0.25[iv]	0.70[iv]	0.05
g	Ph	Me	0.35	0.65	-
h	*o*-MeC_6H_4	Me	0.18	0.82	-
i	Ph	Ph	0.35	0.65	-

(i) **8'** is formed with stoichiometric amounts of NH_2OH; **8'f** and **8'h** still present even with excess NH_2OH.
(ii) Order of R_f values and E/Z ratio: Z-**8d** > E-**8d**, 1:1; E-**8e** > Z-**8e**, 4:1; E-**8g** > Z-**8g**, 9:1; E-**8h** > Z-**8h**, 2.5:1; only E-**8f** and E-**8i**.
(iii) *cis*/*trans* ratio 1:1.
(iv) R_f order **7f** > **8f** in this case; in all other cases, the R_f order is 7 < **8**.

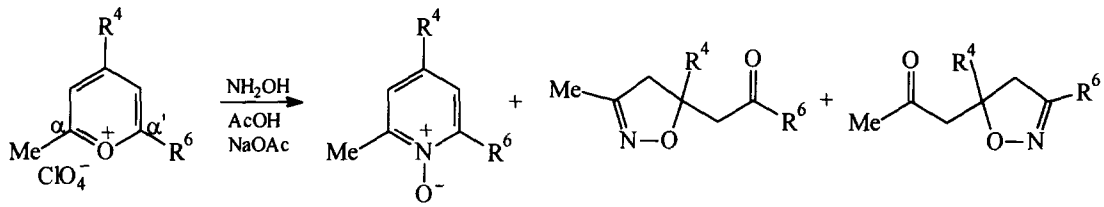
The values of the E/Z ratio displayed in Table 1 are in accordance with the general trend in oximes[12] (and in 2,4-dinitrophenylhydrazones and semicarbazones as well),[14] namely prevalence of the configuration in which the bulkier α-standing group is *anti* to the hydroxy group.

On chromatography on silica gel, using for elution mixtures of petroleum ether and ethyl ether, the 2-isoxazoline derivatives were eluted first (the order of R_f values for oximes E-**8**, Z-**8** is given in footnote (ii) of Table 1) while the more polar pyridine-1-oxides **7** were eluted later, as expected. Interestingly, this elution order was reversed for the products obtained from **6f**, the pyridine-1-oxide **7f** being eluted first. This non-trivial result might be explained by a "steric shielding" (due to the bulky α-*t*-Bu groups) of the molecular dipole in pyridine-1-oxide **7f**. This masked polarity on steric grounds agrees with the lack of nucleophilicity of the nitrogen atom in 2,6-di-*t*-butylpyridine.[15]

Regioselectivity of 2-isoxazoline formation from unsymetrically 2,4,6-trisubstituted pyrylium salts

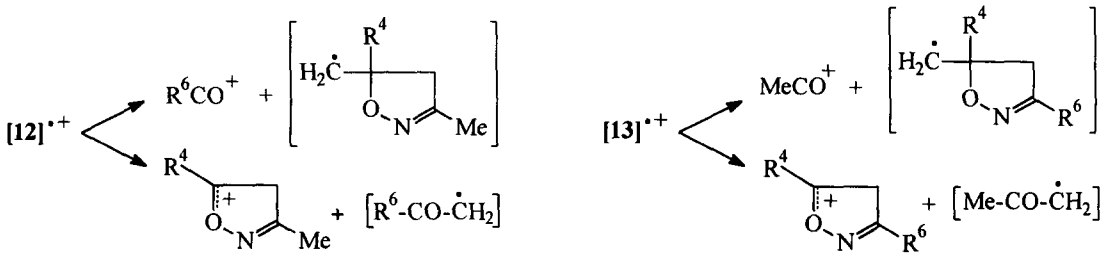
The 2,4,6-trisubstituted pyrylium perchlorates **10a** through **10f** with different groups in α-positions were chosen to examine the regioselectivity of 2-isoxazoline formation, expressed by the ratio between the isomeric

products **12** and **13**. We took a methyl group as reference in one α-position and an Et, n-Pr, *i*-Pr, Ph or *o*-MeC_6H_4 group in the other α'-position.



10 **11** **12** **13**

The reaction was performed in buffered acetic acid with equimolar amounts of pyrylium salt and hydroxylamine hydrochloride in order to obtain only keto-isoxazolines **12** and **13**, thus avoiding complicated reaction mixtures containing stereoisomeric oximes. The crude product was chromatographed on silica gel and the forerun containing **12** and **13** was analyzed by GC-MS, ^{1}H-NMR and ^{13}C-NMR. The two isomeric keto-isoxazolines **12** and **13**, separated analytically by GC-MS, were differentiated in their mass spectra by the following ions, obtained by two independent fragmentation paths of the molecular ion:



The molar fraction values of the reaction products given in Table 2 were calculated from the ^{1}H-NMR spectra (300MHz) of the crude reaction mixture.

Table 2. Molar Fractions of the Products Obtained from Equimolar Amounts of Hydroxylamine and Unsymmetrically 2,4,6-Trisubstituted Pyrylium Salts **10a** through **10f**, Having One Methyl in Position 2(α); α *vs.* α' Regioselectivity.

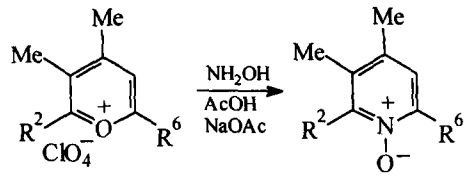
10	R^4	R^6 (α')	**11**	**12**	**13**	α *vs.* α' (%) **12/(12 + 13)**
a	Me	Et	1.00	-	-	-
b	Me	*n*-Pr	0.80	0.17	0.03	85
c	Me	*i*-Pr	0.67	0.27	0.06	82
d	Me	Ph	0.60	0.40	-	100
e	Me	*o*-MeC_6H_4	0.42	0.58	-	100
f	Ph	Ph	0.76	0.20	0.04	83

The data in Table 2 show that 2-isoxazoline formation reaction did occur even when there was only one α-substituent as bulky as *n*-Pr, *i*-Pr, Ph, or *o*-MeC_6H_4, being however less extensive than for the salts possessing two such α-groups. Product **12** prevailed always over its isomer **13** and was exclusively formed with R^6=Ph or *o*-MeC_6H_4; in other words, the initial nucleophilic attack occurred highly regioselectively at the position adjacent to the α-Me group.

These results are in agreement with previously reported data in the literature. Kinetic measurements in the hydrolysis of 2-methyl-4,6-diphenylpyrylium chloride indicated that the nucleophilic attack occurrs regioselectively at the carbon atom adjacent to α-Me.[16] In the formation of aniline derivatives from 2-ethyl-4,6-dimethylpyrylium perchlorate and primary amines, the attack at the position adjacent to α-Me is favoured over "α-Et attack" by one order of magnitude.[17]

Reaction of 2,3,4,6-tetrasubstituted pyrylium salts with hydroxylamine

In the reaction with hydroxylamine performed in buffered acetic acid, tetrasubstituted pyrylium perchlorates **14a** through **14e** gave exclusively pyridine-1-oxides **15a** through **15e**, similarly to 2,3,4,6-tetraphenylpyrylium perchlorate.[8] Therefore no regioselectivity studies could be performed.



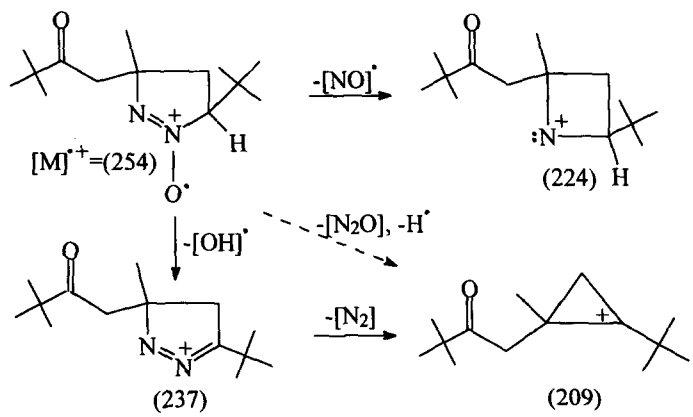
14 **15**

14, 15	R^2	R^6
a	Me	Me
b	Me	*n*-Pr
c	Me	*i*-Pr
d	*n*-Pr	*n*-Pr
e	*i*- Pr	*i*-Pr

A 1-pyrazoline-1-oxide from a pyrylium cation with bulky α-substituents

From the 2,6-di-*t*-butyl-4-methyl pyrylium perchlorate **6f** we obtained, as last-eluting chromatographic fraction, small amounts (0.05 molar fraction, Table 1) of a crystalline colorless product with formula $C_{14}H_{26}N_2O_2$ indicated by elemental analysis. According to glc, it was actually a 1:1 mixture of two compounds, namely *cis / trans* 1-pyrazoline-1-oxide **9f**, with the systematic name 4,5-dihydro-5-(1,1-dimethylethyl)-3-(3,3-dimethyl-2-oxobutyl)-3-methyl-3H-pyrazole-1-oxide. All NMR spectra were recorded with the stereoisomeric mixture because attempts of separating preparatively the two stereoisomers failed.

The mass spectra of both isomers of **9f** separated analytically by GC-MS present the same molecular ion of mass 254 and identical fragmentation patterns, but minor differences appeared in the relative intensity of the fragments, particularly for the low-mass ions. The electron impact fragmentation pattern, accounting for the structure of 1-pyrazoline-1-oxide, starts with the formation of $(M-17)^+$ and $(M-30)^+$ ions (Scheme 1). The [M-NO] fragmentation is similar to that observed for instance in 1,2,4-triazine-N-oxides[11] or pyrazoline-1,2-dioxides.[18] The [M-OH] fragmentation occurs probably through a four-membered cyclic transition state. Possibly also N_2O elimination may take place.



Scheme 1. Fragmentation modes of the molecular ion $[M]^{+}$ in the EI mass spectra of *cis*- and *trans*-**9f**; m/z values are indicated in brackets.

The IR spectrum of **9f** in carbon tetrachloride solution presents a strong absorbtion band at 1513 cm^{-1}, in agreement with values in the range 1500-1515 cm^{-1} used as structure proof for the 1-pyrazoline-1-oxides described so far.[19-21; 22,23] Figure 1 presents the ^{1}H-NMR chemical shifts (δ, ppm) and coupling constants J (Hz), along with the ^{13}C-NMR δ values (ppm) of the individual *cis*- and *trans*-isomers in the mixture **9f**. The assignment of the signals in each isomer is unambiguous, based on decoupling experiments as well as on COSY(^{1}H-^{13}C) and long-range correlations.

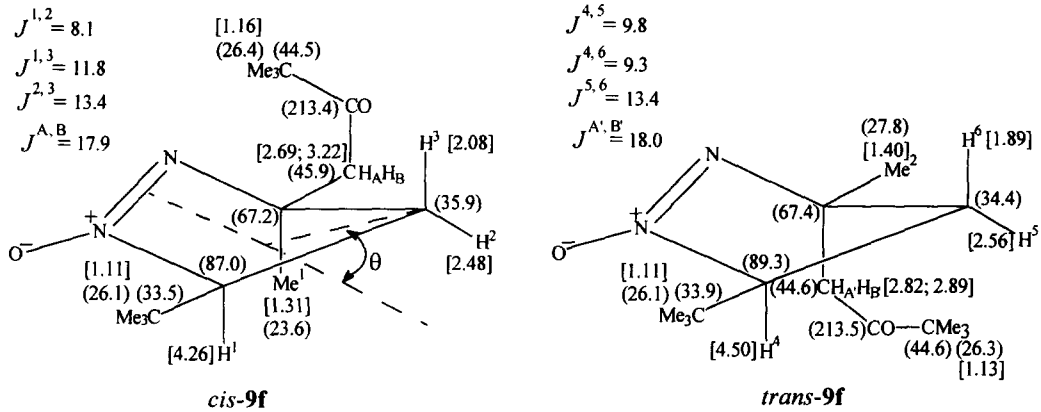


Figure 1. ^{1}H-NMR [in square brackets] and ^{13}C-NMR (in round brackets) δ values and ^{1}H/^{1}H coupling constants (J, Hz) of *cis*- and *trans*-**9f**. Protons H^1-H^3 belong to *cis*-**9f** while protons H^4-H^6 belong to *trans*-**9f**. The angle of puckering is denoted by θ.

The configurational *cis/trans* assignment presented in Fig. 1 was based on the following NOE experiments:

a) irradiation of the proton H^1 gave an increase of the signal for Me^1 protons as well as of the signal for the *cis*-vicinal H^2;
b) irradiating the proton H^4, an increase of the signals for H^5 and for $CH_{A'}H_{B'}$ group was observed. Conversely, irradiation of the proton H^6 gave an increase of the signal for Me^2 group, along with the increase of the signal for the geminal proton H^5.

The values of the coupling constants are indicative for conformation, based on previously established data for 3,5-disubstituted-1-pyrazolines.[24] The *cis*-isomer is probably locked in the conformation shown in Fig. 1, with two pseudoequatorial bulky groups, a dihedral angle close to 180° between H^1 and H^3 ($J^{1,3}$=11.8 Hz), and a large value for the angle of puckering θ (for pyrazolines held in one conformation, θ values between 22° and 31° were given).[24] Conversely, the *trans*-isomer is flexible, with both conformations indicated in Figure 2 being populated, probably with preference for the conformer with a pseudoequatorial *t*-Bu group attached to the pyrazolinic ring. This could explain the values of the coupling constants $J^{4,5}$ and $J^{4,6}$ and possibly the much smaller anisochrony in the $CH_{A'}H_{B'}$ group ($\Delta\delta$ = 2.89 - 2.82 = 0.07 ppm) than in the CH_AH_B group ($\Delta\delta$ = 3.22 - 2.69 = 0.53 ppm) due to averaging by ring-inversion.

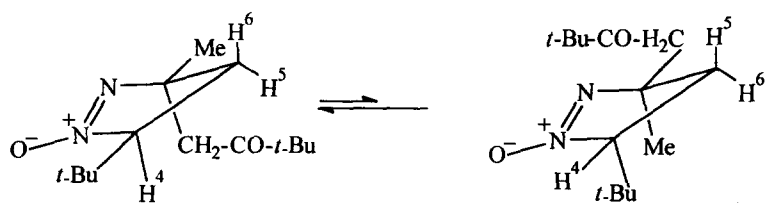
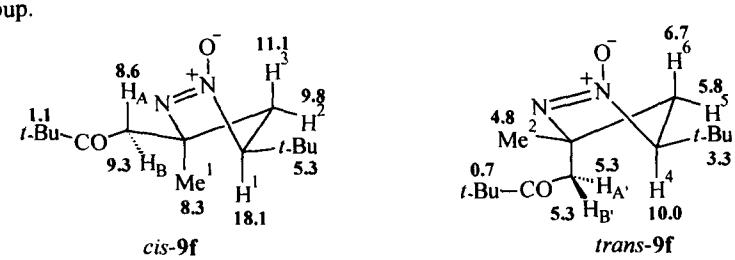


Figure 2. Conformational equilibrium of *trans*-**9f**.

This difference in ring flexibility may equally explain the molar induced shift (MIS, ppm) values in the ^{1}H-NMR spectra of *cis*- and *trans*-**9f** recorded in the presence of Eu(dpm)$_3$, as seen in Fig. 3. The protons of every group in the *cis*-isomer have definitely higher MIS values than those of the corresponding group in the *trans*-isomer, while the ordering of the MIS values over all groups is alike in both isomers. This means that the complexation site in the two isomers is the same, which is as expected, but the conformers of the *trans*-isomer are shorter lived due to ring flexibility, leading to smaller pseudocontact shift values. It seems obvious that the complexation site of the lanthanide is the N-oxide oxygen atom, as H^1 (and H^4 respectively) is closest to this atom and has the highest MIS value. The carbonyl group does not seem to compete in complexation, otherwise the MIS values for protons in CH_AH_B (CH_A·H_B·) group would have been significantly higher than that for Me^1(Me^2) group. This lack of complexation with the carbonyl group might be due to steric hindrance by the neighboring *t*-Bu group.

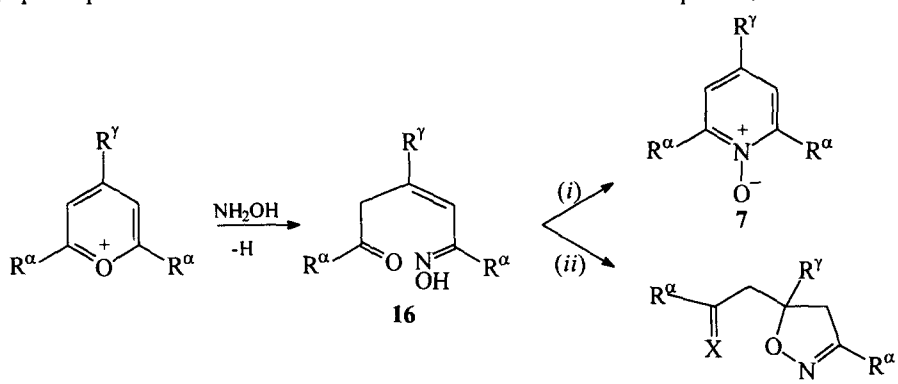


cis-**9f** *trans*-**9f**

Figure 3. Molar induced shift values (MIS, ppm, 300 MHz in $CDCl_3$) in the ^{1}H-NMR spectra of *cis*- and *trans*-**9f** in the presence of Eu(dpm)$_3$.

DISCUSSION

After the initial α-attack of the nucleophile and the ring-opening to the keto-ketoxime **16**, two competing intramolecular cyclizations can occur. The formation of an N-oxide **7** (path *i*) is acid-catalyzed, whereas the intramolecular Michael addition (path *ii*) yielding a 2-isoxazoline derivative **8'** (or **8** with another molecule of hydroxylamine) is favoured by the presence of bases.[3,8] In a separate paper we shall report on the initial ring-opened precursor **16** and discuss the influence of E/Z isomerism on products.

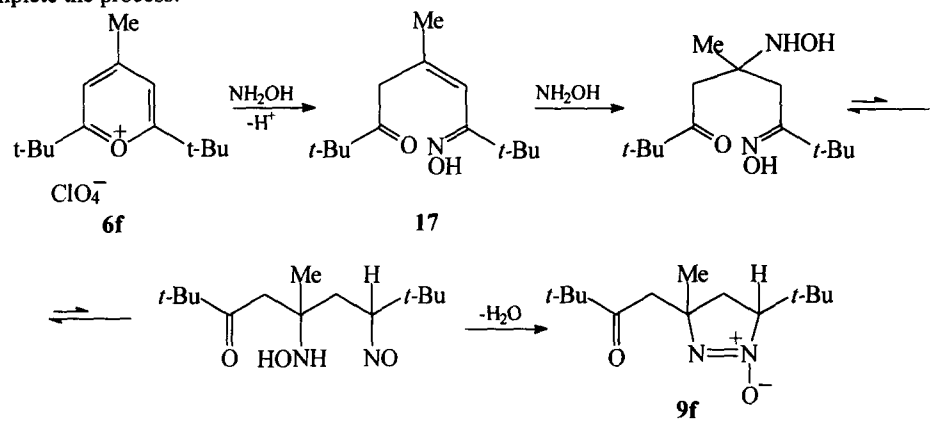


The data in this paper show that the stereoelectronic properties of substituent R^α also play a significant role in the recyclization step, influencing the relative rate of the paths (*i*) and (*ii*). Indeed, the rate of path (*i*) is much higher than the rate of path (*ii*) for small R^α group, namely methyl, either **7a** or **7b** being the sole product under acidic conditions as well as under basic conditions.[8] No influence of the nature of R^γ substituent (Me or Ph) on the **7** *vs.* **8** ratio was observed, as seen by comparing the cases **a**, **b** and **g**, **i**. Conversely, the product **8'** of path (*ii*) prevails even under acidic conditions for bulky R^α such as *t*-Bu, Ph or *o*-MeC_6H_4. The decrease in the

rate of path (*i*) may be explained by a high-energy transition state involving three bulky groups in adjacent positions, favouring thereby path (*ii*) leading to **8'**, in which no such overcrowding exists. The rates of path (*i*) and (*ii*) become comparable for medium-sized groups such as *i*-Pr.

The initial nucleophilic attack at 2,4,6-trisubstituted pyrylium cations having an α-methyl and a different α'-substituent R occurring preferentially at the carbon atom adjacent to the α-methyl group may also be explained by kinetic preference for the smaller group.

A final comment on the results presented in Table 1 regards the unprecedented formation of 1-pyrazoline-1-oxide **9f**. A plausible pathway for the formation of **9f** involves a Michael addition of hydroxylamine to the keto- ketoxime **17** initially formed from the pyrylium salt; hydrogen shift and dehydration then complete the process:



The explanation of this unprecedented reaction path may reside in the fact that the bulky substituents lower the rate of intramolecular cyclization of the keto-ketoxime **17** to **7** and **8'**, allowing thereby the competing intermolecular Michael addition of a second hydroxylamine molecule. This is the only case reported so far in which two molecules of the nucleophile reacting with the pyrylium cation become incorporated in the ANRORC[25] product.

CONCLUSION

Whereas pyrylium salts as starting materials for a simple synthesis of pyridine-1-oxides are well documented in the review literature[3,10], so far reviews on 2-isoxazolines[26] (which have considerable interest too)[27] fail to mention their formation from pyrylium salts. Our results draw attention to the potential synthetic value of pyrylium salts for 2-isoxazolines as well.

EXPERIMENTAL

Instrumentation

Melting points were determined on a Boetius hot plate and are uncorrected. The IR spectra were recorded on a Carl Zeiss UR 20 instrument. The glc analyses were performed with a Carlo Erba HRGC 5300 instrument. Mass spectra were recorded with a Carlo Erba QMD 1000 instrument, except for the mass-spectrum of compound **9f** recorded with a 70SE VG Analytical type instrument. The NMR spectra were recorded with a Varian Gemini 300BB instrument operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C.

Pyrylium perchlorates

Salts **6a**, **6c** through **6h** were prepared from *t*-butyl chloride/ acyl chloride/ anh. $AlCl_3$ ($SnCl_4$ for **6f**), then precipitation with $HClO_4$; salt **6b** was obtained similarly from α-methylstyrene, acetyl chloride/anh. $AlCl_3$ and precipitation with perchloric acid.[2b] Pyrylium perchlorate **6i** was obtained from benzaldehyde and acetophenone with conc. H_2SO_4, followed by precipitation with perchloric acid.[28] Salts **10a** through **10e** were prepared from mesityl oxide/acyl chloride/anh. $AlCl_3$, then precipitation with perchloric acid;[2b] salt **10f** was

prepared similarly from dypnone. Salts **14a**, **14d** and **14e** were obtained from 2-methyl-2-butanol/carboxylic anhydride/70% perchloric acid;[29,30] salts **14b**, **14c** were obtained from 3,4-dimethyl-3-penten-2-one/acyl chloride/anh. $AlCl_3$, then precipitation with perchloric acid.[30]

Reaction of pyrylium perchlorates with hydroxylamine. General procedure

Pyrylium perchlorate (10 mmole) and hydroxylamine hydrochloride (10 mmole or, alternatively, 50 mmole) were dissolved in 100 mL glacial acetic acid containing 170 mmole sodium acetate trihydrate and the mixture was heated under reflux for 1h. The mixture was poured into 150 mL cold water and extracted with 3x30 mL chloroform. The organic extract was washed with sodium bicarbonate solution, dried over anh. sodium sulfate and evaporated under reduced pressure; the residue, accounting for yields over 95%, was analyzed by ^{1}H-NMR (results in Tables 1 and 2). The reaction products were separated by column chromatography on silica gel (10 - 15 g SiO_2 for one gram of crude mixture). For eluting the isoxazoline derivatives, mixtures of petroleum ether with ethyl ether in ratios from 20:1 to 1:1(v/v) were used. The pyridine-1-oxides were eluted with ethyl ether, except those with aryl substituents which, being poorly soluble in this solvent, were eluted with chloroform. The products obtained from pyrylium perchlorate **6f** had a different elution order, namely 2,6-di-*t*-butyl-4-methylpyridine-1-oxide **7f** was eluted first, followed by the isoxazolinic derivatives **8'f**, E-**8f**; compound **9f** was eluted last with ethyl ether.

Glc and GC-MS analyses

The glc analyses of the crude reaction mixtures (experiments in Table 1) were performed on SE 52 fused silica capillary column (25 m/0.32 mm) under the following conditions: 200°C vaporization; 100-170°C column temperature, 5°/min heating rate. During the analysis, pyridine-1-oxides **7** were partly converted into the corresponding pyridines, identified with authentic samples.

The two isomeric keto-2-isoxazolines **12** and **13** (Table 2) were separated analytically on the same column as above, with 250° vaporization temperature. The retention times were the following: **12b** 4.72 min, **13b** 6.64 min, (column temperature 100-250°C, 10°/min heating rate); **12c** 4.31 min, **13c** 6.37 min (column temperature 100-250°C, 10°/min heating rate); **12f** 11.32 min, **13f** 13.06 min (column temperature 100-170°C, 10°/min; 170-250°C, 15°/min heating rate).

The *cis/trans* isomers of **9f** (Table 1) were separated analytically on the same column as above, 200°C vaporization, column temperature 150-240°C, 10°/min heating rate. The retention times were: *trans*-**9f** 4.30 min, *cis*-**9f** 4.44 min and the *cis/trans* ratio was 1:1.2.

The GC-MS analyses were performed on CP-Sil 5 CB fused silica capillary column (25m/0.32 mm), under electron impact (EI).

Analytical thin-layer chromatography (tlc)

Analytical tlc was performed with silica gel 60 F_{254} (Merck) on aluminum strips (10 cm length), using petroleum ether/ethyl ether mixture in 1:1 ratio (v/v) for elution. The following R_f values were obtained for compounds in Table 1:

Pyridine-1-oxides: **7a** 0.03; **7b** 0.02; **7c** 0.04; **7d** 0.06; **7e** 0.09; **7f** 0.66 (see text); **7g** 0.06; **7h** 0.06; **7i** 0.11.

Keto-isoxazolines **8'** *and E/Z oximes* **8**: **8'c** 0.43; **8'd** 0.39, E - **8d** 0.23, Z - **8d** 0.38; **8'e** 0.41, E - **8e** 0.48, Z - **8e** 0.30; **8'f** 0.57, E - **8f** 0.60; **8'g** 0.46, E - **8g** 0.40, Z - **8g** 0.25; **8'h** 0.55, E - **8h** 0.42, Z - **8h** 0.31; **8'i** 0.49, E - **8i** 0.41.

cis/trans 1-Pyrazoline-1-oxide **9f**: 0.30.

Pyridine-1-oxides

2,4,6-Trimethylpyridine-1-oxide (**7a**): m.p. 30-32° C(lit.[2a] 31°); IR(CCl_4) 1255 cm^{-1}; MS(rel. int.) 137[M^+](77), 121[M^+-O](25), 120[M^+-OH](100). *Picrate*: m.p. 170°C(lit.[2b] 170°).

2,6-Dimethyl-4-phenylpyridine-1-oxide (**7b**)[31]: m.p. 163-5°C; IR(CCl_4) 1270 cm^{-1}; MS(rel. int.) 199[M^+](100), 183[M^+-O](71), 182[M^+-OH](99.7); Anal. Calcd. For $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.03. Found: C, 78.26; H, 6.59; N, 7.43. *Picrate*: m.p. 145-6°C; Anal. Calcd. For $C_{19}H_{16}N_4O_8$: N, 13.08. Found: N, 13.12.

2,6-Diethyl-4-methylpyridine-1-oxide (**7c**): b.p. 103-113°C/1 Torr; m.p. 70-71°C; IR(CH_2Cl_2) 1230 cm^{-1}; MS(rel. int.) 165[M^+](27), 148[M^+-OH](100). *Picrate*: m.p. 126-8° C(lit.[2b] 126-7°).

2,6-Dipropyl-4-methylpyridine-1-oxide (**7d**): oil; IR(CCl_4) 1243(1275 sh) cm^{-1}; MS(rel. int.) 193[M^+](37), 176[M^+-OH](100). Anal. Calcd. For $C_{12}H_{19}NO$: N, 7.25. Found: N, 8.00. *Picrate*: m.p. 52-3°C; Anal. Calcd. For $C_{18}H_{22}N_4O_8$: N, 13.27. Found: N, 13.55.

2,6-Bis(1-methylethyl)-4-methylpyridine-1-oxide (**7e**): oil; IR(CCl_4) 1235, 1270 cm^{-1}; MS(rel. int.) 193[M^+](21), 176[M^+-OH](100). Anal. Calcd. For $C_{12}H_{19}NO$: N, 7.25. Found: N, 7.13.

2,6-Bis(1,1-dimethylethyl)-4-methylpyridine-1-oxide (**7f**): m.p. 100-102°C(lit.[4] 105-6°); IR(CCl_4) 1255 cm^{-1}; MS(rel. int.) 221[M^+](24), 204[M^+-OH](85), 137(100). *Picrate*: m.p. 164-8°C; Anal. Calcd. For $C_{20}H_{26}N_4O_8$: N, 12.44. Found: N, 12.65.

2,6-Diphenyl-4-methylpyridine-1-oxide (**7g**): m.p. 157-163°C; IR(CCl_4) 1258 cm^{-1}; MS(rel. int.) 261[M^+](36), 260[M^+-H](100), 245[M^+-O](74), 244[M^+-OH](49); Anal. Calcd. For $C_{18}H_{15}NO$: C, 82.76; H, 5.75; N, 5.36. Found: C, 82.49; H, 5.82; N, 5.48. *Picrate*: m.p. 166°C.

2,6-Bis(2-methylphenyl)-4-methylpyridine-1-oxide (**7h**): m.p. 135-145°C; IR(CCl_4) 1255, 1275cm^{-1}; MS(rel. int.) 289[M^+](26), 273[M^+-O](46), 272[M^+-OH](100); Anal. Calcd. For $C_{20}H_{19}NO$: N, 4.84. Found: N, 5.54. *Picrate*: m.p. 189°C.

2,4,6-Triphenylpyridine-1-oxide (**7i**): m.p. 181-4°C(lit.[8] 186-9°).

The ^{1}H- and ^{13}C-NMR data of compounds **7a** through **7i** are given in Tables 3 and 4, respectively.

2,4-Dimethyl-6-ethylpyridine-1-oxide (**11a**): b.p. 104°C/1 Torr; m.p. 56-7°C; IR(CCl_4) 1250 cm^{-1}; MS(rel. int.) 151[M^+](41), 134[M^+-OH](100). *Picrate*: m.p. 100-102° C. Anal. Calcd. For $C_{15}H_{16}N_4O_8$: N, 14.74. Found: N, 14.88.

2,4-Dimethyl-6-propylpyridine-1-oxide (**11b**): oil; IR(CCl_4) 1245, 1275 cm^{-1}; MS(rel. int.) 165[M^+](36), 148[M^+-OH](79), 120(100).

2,4-Dimethyl-6-(1-methylethyl)pyridine-1-oxide (**11c**): oil; IR(CCl_4) 1242, 1255 cm^{-1}; MS(rel. int.) 165[M^+](21), 148[M^+-OH](100). *Picrate*: m.p. 116-116.5°C. Anal. Calcd. For $C_{16}H_{18}N_4O_8$: N, 14.21. Found: N, 13.97.

2,4-Dimethyl-6-phenylpyridine-1-oxide (**11d**): oil; IR(CCl_4) 1240, 1260 cm^{-1}; MS(rel. int.) 199[M^+](10), 183[M^+-O](100), 182[M^+-OH](48). *Picrate*: m.p. 146-146.5°C (lit.[32] 147°).

2,4-Dimethyl-6-(2-methylphenyl)pyridine-1-oxide (**11e**): m.p. 75-7°C; IR(CCl_4) 1242, 1260 cm^{-1}; MS(rel. int.) 213[M^+](14), 196[M^+-OH](100). *Picrate*: m.p. 124-5°C. Anal. Calcd. For $C_{20}H_{18}N_4O_8$: N, 12.67. Found: N, 12.01.

2,4-Diphenyl-6-methylpyridine-1-oxide (**11f**): m.p. 183°C(lit.[2a] 180-2°); IR(CCl_4) 1270 cm^{-1}; MS(rel. int.) 261[M^+](52), 260[M^+-H](100), 245[M^+-O](45), 244[M^+-OH](24). *Picrate*: m.p. 126-7°C(lit.[2a] 125-126.5°).

The ^{1}H- and ^{13}C-NMR data of compounds **11a** through **11f** are given in Tables 5 and 6, respectively.

2,3,4,6-Tetramethylpyridine-1-oxide (**15a**): m.p. 147-8°C; IR(CCl_4) 1270 cm^{-1}; MS(rel. int.) 151[M^+](54), 134[M^+-OH](100). *Picrate*: m.p. 116-118°C. Anal. Calcd. For $C_{15}H_{16}N_4O_8$: N, 14.74. Found: N, 14.64.

6-Propyl-2,3,4-trimethylpyridine-1-oxide (**15b**): oil; IR(CCl_4) 1275 cm^{-1}; MS(rel. int.) 179[M^+](24), 162[M^+-OH](100). *Picrate*: m.p. 105-110°C. Anal. Calcd. For $C_{17}H_{20}N_4O_8$: N, 13.73. Found: N, 13.31.

Table 3. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) in ^{1}H-NMR Spectra (300 MHz, in $CDCl_3$) of Pyridine-1-oxides **7a** through **7i**.

Comp.	R^{α}	R^{γ}	2,6-R^{α}_2	4-R^{γ}	3,5-H_2
7a	Me	Me	2.51 (6H, s)	2.28 (3H, s)	6.98 (2H, s)
7b	Me	Ph	2.60 (6H, s)	7.42 (1H, t, 7.5, p-H); 7.47 (2H, t, 7.5, m-H); 7.58 (2H, d, 7.5, o-H)	7.38 (2H, s)
7c	Et	Me	1.30 (6H, t, 7.5); 2.96 (4H, q, 7.5)	2.33 (3H, s)	6.93 (2H, s)
7d	*n*-Pr	Me	1.03 (6H, t, 7.4); 1.75 (4H, sxt, 7.4); 2.89 (4H, t, 7.4)	2.30 (3H, s)	6.90 (2H, s)
7e	*i*-Pr	Me	1.28 (12 H, d, 6.9); 3.87 (2H, sep, 6.9)	2.34 (3H, s)	6.93 (2H, s)
7f	*t*-Bu	Me	1.51 (18 H, s)	2.30 (3H, s)	7.03 (2H, s)
7g	Ph	Me	7.44 (6H, m, m-H, p-H); 7.83 (4H, d, 8.0, o-H)	2.40 (3H, s)	7.21 (2H, s)
7h	o-Me-$-C_6H_4$	Me	2.27 (6H, s); 7.2-7.4 (8H, m)	2.40 (3H, s)	7.14 (2H, s)
7i	Ph	Ph	7.4-7.5 (6H, m, m-H, p-H); 7.89 (4H, d, 8.0, o-H)	7.4-7.5 (3H, m, m-H, p-H); 7.66 (2H, d, 8.0, o-H)	7.65 (2H, s)

Table 4. Chemical Shifts (δ, ppm) in ^{13}C-NMR Spectra (75 MHz, in $CDCl_3$) of Pyridine-1-oxides **7a** through **7i**.

Comp	R^{α}	R^{γ}	2,6-R^{α}_2	2,6-C_2	4-R^{γ}	4-C	3,5-$(CH)_2$
7a	Me	Me	17.8	147.7	19.8	135.7	124.4
7b	Me	Ph	18.0	148.2	136.5 (C_q); 125.9 (o-CH); 128.1 (p-CH); 128.6 (m-CH);	136.4	121.1
7c	Et	Me	10.7 (CH_3); 23.8 (CH_2)	152.5	20.4	135.8	122.1
7d	*n*-Pr	Me	13.3 (CH_3); 19.0 (CH_2); 32.2 (CH_2)	150.8	19.8	135.4	122.8
7e	*i*-Pr	Me	20.0 (2 CH_3); 27.2 (CH)	156.2	20.2	135.3	119.8
7f	*t*-Bu	Me	27.1 (CH_3); 36.0 (C_q)	157.4	20.5	133.5	121.7
7g	Ph	Me	133.3 (C_q); 127.8 (m-CH); 129.0 (p-CH); 129.4 (o-CH)	148.9	20.2	135.9	126.7
7h	o-Me-$-C_6H_4$	Me	19.6 (2'-CH_3); 133.5 (1'-C); 137.7 (2'-C); 125.6 (5'-CH); 127.4 (3'-CH);129.0 (4'-CH); 129.4 (6'-CH);	150.5	20.3	136.0 (broad)	129.7
7i	Ph	Ph	133.4 (C_q); 128.1 (m-CH); 129.4 (p-CH); 129.6 (o-CH);	149.9	136.8 (C_q); 126.5 (o-CH); 128.9 (p-CH); 129.3 (m-CH)	137.6	123.8

Table 5. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) in ^{1}H-NMR Spectra (300 MHz, in $CDCl_3$) of Pyridine-1-oxides **11a** through **11f**.

Comp.	R^4	R^6	2-Me	6-R^6	4-R^4	3-H	5-H
11a	Me	Et	2.51 (3H, s)	1.30 (3H, t, *J*=7.4); 2.95 (2H, q, *J*=7.4)	2.30 (3H, s)	6.97 (1H, s)	6.94 (1H, s)
11b	Me	*n*-Pr	2.50 (3H, s)	1.03 (3H, t, *J*=7.4); 1.76 (2H, sxt, *J*=7.4); 2.89 (2H, t, *J*=7.4)	2.29 (3H, s)	6.95 (1H, s)	6.92 (1H, s)
11c	Me	*i*-Pr	2.52 (3H, s)	1.28 (6H, d, *J*=6.9); 3.84 (1H, sep, *J*=6.9)	2.32 (3H, s)	6.97 (1H, s)	6.96 (1H, s)
11d	Me	Ph	2.54 (3H, s)	7.4-7.5 (3H, m, m-H, p-H); 7.77 (2H, d, *J*=8.0, o-H)	2.34 (3H, s)	7.07 (1H, s)	7.11 (1H, s)
11e	Me	o-Me-C_6H_4	2.54 (3H, s)	2.22 (3H, s); 7.2-7.4 (4H, m)	2.33 (3H, s)	6.99 (1H, s)	7.09 (1H, s)
11f	Ph	Ph	2.62 (3H, s)	7.45 (3H, m, m-H, p-H) 7.82 (2H, d, *J*=8.0, o-H)	7.45 (3H, m, m-H, p-H) 7.60 (2H, d, *J*=7.0, o-H)	7.44 (1H, s)	7.45 (1H, s)

Table 6. Chemical Shifts (δ, ppm) in ^{13}C-NMR Spectra (75 MHz, in $CDCl_3$) of Pyridine-1-oxides **11a** through **11f**.

Comp.	R^4	R^6	2-Me	6-R^6	2-C	6-C	4-R^4	4-C	3-CH	5-CH
11a	Me	Et	17.7	10.5 (CH_3); 23.6 (CH_2)	147.6	152.2	19.9	135.4	124.1	122.3
11b	Me	*n*-Pr	18.1	13.8 (CH_3); 19.5 (CH_2); 32.6 (CH_2)	148.0	151.3	20.1	135.7	124.4	123.5
11c	Me	*i*-Pr	18.3	20.5 (2 CH_3); 27.6 (CH)	148.2	156.8	20.4	136.2	124.3	120.9
11d	Me	Ph	18.4	133.4 (C_q); 127.9 (m-CH); 129.0 (p-CH); 129.3 (o-CH)	148.5	148.9	20.2	136.0	125.6	125.8
11e	Me	o-Me--C_6H_4	18.1	19.4 (2'-CH_3); 133.7 (1'-C); 137.4 (2'-C); 125.9 (5'-CH); 126.0 (3'-CH); 128.8 (4'-CH); 129.1 (6'-CH)	148.5	149.7	20.1	135.4	125.5	129.7
11f	Ph	Ph	18.6	133.2 (C_q); 128.0 (m-CH); 129.1 (p-CH); 129.3 (o-CH);	149.5	149.0	136.7 (C_q); 126.3 (o-CH); 128.6 (p-CH); 129.0 (m-CH);	137.1	122.6	122.6

6-(1-Methylethyl)-2,3,4-trimethylpyridine-1-oxide (**15c**): oil; IR(CCl_4) 1255, 1280 cm^{-1}; MS(rel. int.) 179[M^+](15), 162[M^+-OH](100). *Picrate*: m.p. 130°C. Anal. Calcd. For $C_{17}H_{20}N_4O_8$: N, 13.73. Found: N, 13.73.

3,4-Dimethyl-2,6-dipropylpyridine-1-oxide (**15d**): oil; IR(CCl_4) 1275 (1260 sh) cm^{-1}; MS(rel. int.) 207[M^+](26), 190[M^+-OH](100).

2,6-Bis(1-methylethyl)-3,4-dimethylpyridine-1-oxide (**15e**): m.p. 89°C; IR(CCl_4) 1275 (1260 sh) cm^{-1}; MS(rel. int.) 207[M^+](18), 190[M^+-OH](100). *Picrate*: m.p. 106-108°C. Anal. Calcd. For $C_{19}H_{24}N_4O_8$: N, 12.84. Found: N, 12.70.

The ^{1}H- and ^{13}C-NMR data of compounds **15a** through **15e** are given in Tables 7 and 8, respectively.

Table 7. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) in ^{1}H-NMR Spectra (300 MHz, in $CDCl_3$) of Pyridine-1-oxides **15a** through **15e**

Comp.	R^2	R^6	R^2	3-Me	4-Me	5-H	R^6
15a	Me	Me	2.56 (3H, s)	2.22 (3H, s)	2.24 (3H, s)	6.92 (1H, s)	2.48 (3H, s)
15b	Me	*n*-Pr	2.56 (3H, s)	2.22 (3H, s)	2.26 (3H, s)	6.88 (1H, s)	1.02 (3H, t, *J*=7.4); 1.75 (2H, sxt, *J*=7.4); 2.87 (2H, t, *J*=7.4)
15c	Me	*i*-Pr	2.57 (3H, s)	2.22 (3H, s)	2.28 (3H, s)	6.89 (1H, s)	1.27 (6H, d, *J*=6,9); 3.83 (1H, sep, *J*=6.9)
15d	*n*-Pr	*n*-Pr	1.05 (3H, t, *J*=7.5); 1.66 (2H, sxt, *J*=7.5); 3.03 (2H, t, *J*=7.5)	2.22 (3H, s)	2.24 (3H, s)	6.86 (1H, s)	1.02 (3H, t, *J*=7.5); 1.73 (2H, sxt, *J*=7.5); 2.86 (2H, t, *J*=7.5)
15e	*i*-Pr	*i*-Pr	1.48 (6H, d, *J*=6.9); (broad) 3.84 (1H, sep, *J*=6.9)	2.26 (3H, s)	2.26 (3H, s)	6.88 (1H, s)	1.25 (6H, d, *J*=6.9); 3.84 (1H, sep, *J*=6.9)

Table 8. Chemical Shifts (δ, ppm) in ^{13}C-NMR Spectra (75 MHz, in $CDCl_3$) of Pyridine-1-oxides **15a** through **15e**.

Comp.	R^2	R^6	R^2	2-C	3-Me	3-C	4-Me	4-C	5-CH	R^6	6-C
15a	Me	Me	15.4	147.1	14.1	130.2	19.3	134.5	124.0	17.8	144.9
15b	Me	*n*-Pr	15.5	147.3	14.3	130.1	19.6	134.5	123.1	13.9 (CH_3); 19.6 (CH_2); 32.7 (CH_2)	148.5
15c	Me	*i*-Pr	15.7	147.4	14.6	130.0	19.9	135.0	120.5	20.7 (2 CH_3); 27.7 (CH)	153.9
15d	*n*-Pr	*n*-Pr	14.1 (CH_3); 19.4 (CH_2); 29.6 (CH_2)	150.6	14.9	129.9	19.3	134.9	123.1	13.7 (CH_3); 19.4 (CH_2); 32.5 (CH_2)	148.4
15e	*i*-Pr	*i*-Pr	17.7 (2 CH_3); (broad) 28.2 (CH) (broad)	153.7 (broad)	15.2	129.5	19.9	135.0	120.5	20.4 (2 CH_3); 27.0 (CH)	154.2

2-Isoxazolines

3-Ethyl-5-methyl-5-(2-oxobutyl)-2-isoxazoline (**8'c**): oil; MS(rel. int.) 112[$C_6H_{10}NO^+$](100), 43[$C_2H_3O^+$](36).

5-Methyl-5-(2-oxopentyl)-3-propyl-2-isoxazoline (**8'd**): oil; MS(rel. int.) 196[M^+-CH_3](2), 126[$C_7H_{12}NO^+$] (100), 71[$C_4H_7O^+$](13), 43[$C_2H_3O^+$](30).

3-(1-Methylethyl)-5-methyl-5-(3-methyl-2-oxobutyl)-2-isoxazoline (**8'e**): oil; MS(rel. int.) 196[M^+-CH_3](2), 126[$C_7H_{12}NO^+$] (100), 71[$C_4H_7O^+$](16), 43[$C_2H_3O^+$](57).

3-(1,1-Dimethylethyl)-5-(3,3-dimethyl-2-oxobutyl)-5-methyl-2-isoxazoline (**8'f**): oil (lit.[4] b.p. 130°C/4.5 Torr); MS(rel. int.) 224[M^+-CH_3](5), 140[$C_8H_{14}NO^+$](100), 85[$C_5H_9O^+$](12), 57[$C_4H_9^+$](65).

5-Methyl-3-phenyl-5-phenacyl-2-isoxazoline (**8'g**): m.p. 55-62°C.

Oxime E - **8g**: m.p. 120-121°C. Anal. Calcd. for $C_{18}H_{18}N_2O_2$: N, 9.52. Found: N, 9.51.

5-Methyl-3-(2-methylphenyl)-5-(2-methylphenacyl)-2-isoxazoline (**8'h**): oil; IR(CCl_4) 1340, 1370, 1430, 1450, 1680 cm^{-1}. Anal. Calcd. for $C_{20}H_{21}NO_2$: N, 4.56. Found: N, 4.77.

Oxime E- **8h**: m.p. 100°C; IR(CCl_4) 1340, 1380, 1430, 1450, 3260(broad), 3585 cm^{-1}.

3,5-Diphenyl-5-phenacyl-2-isoxazoline (**8'i**): m.p. 123-4°C; (lit.[2b] 124°).

Oxime E - **8i**: m.p. 146-7°C (lit.[8] 143-5°).

The ^{1}H- and ^{13}C-NMR data of 2-isoxazolines **8'c - 8'i** and of their corresponding oximes **8d - 8i** are given in Tables 9 and 10, respectively.

3,5-Dimethyl-5-(2-oxopentyl)-2-isoxazoline (**12b**): oil; MS(rel. int.) 168[M^+-CH_3](1), 98[$C_5H_8NO^+$](100), 71[$C_4H_7O^+$](19), 43[$C_2H_3O^+$](35).

5-Methyl-5-(2-oxopropyl)-3-propyl-2-isoxazoline (**13b**): oil; MS(rel. int.) 168[M^+-CH_3](2), 126[$C_7H_{12}NO^+$] (100), 43[$C_2H_3O^+$](46); ^{1}H-NMR($CDCl_3$) 0.96(3H, t, J=7.3, CH_2-C**H$_3$**), 1.58(2H, sxt, J=7.3, C**H$_2$**-CH_3), 2.29(2H, t, J=7.3, C**H$_2$**-CH_2-CH_3), 1.40(3H, s, 5-CH_3), 2.21(3H, s, CH_3-CO), 2.82(2H, s, CO-CH_2), 2.96; 2.75(J^{gem}=17.4, 4-CH_2); ^{13}C-NMR($CDCl_3$) 13.7(**C**H_3-CH_2-), 19.6(CH_3-**C**H_2-), 25.9(5-CH_3), 29.8(-**C**H_2-CH_2-), 31.6 (**C**H_3-CO), 47.1(4-CH_2), 52.4(CO-**C**H_2), 83.5(5-C), 159.5(3-C), 207.0(CO).

3,5-Dimethyl-5-(3-methyl-2-oxobutyl)-2-isoxazoline (**12c**): oil; MS(rel. int.) 168[M^+-CH_3](2), 98[$C_5H_8NO^+$] (100), 71[$C_4H_7O^+$](15), 43[$C_2H_3O^+$] (55).

3-(1-Methylethyl)-5-methyl-5-(2-oxopropyl)-2-isoxazoline (**13c**): oil; MS(rel. int.) 168[M^+-CH_3](2), 126[$C_7H_{12}NO^+$](100), 43[$C_2H_3O^+$] (51); ^{1}H-NMR($CDCl_3$) 1.15(6H, d, J=6.9, CH(C**H$_3$**)$_2$), 2.68(1H, sep, J=6.9, C**H**(CH_3)$_2$), 1.39(3H, s, 5-CH_3), 2.21(3H, s, CH_3-CO), 2.82(2H, s, CO-CH_2), 2.97; 2.76(J^{gem}=17.2, 4-CH_2); ^{13}C-NMR($CDCl_3$) 19.7, 19.8(CH(**C**H_3)$_2$), 27.8(**C**H(CH_3)$_2$), 25.5(5-CH_3), 31.4(CH_3-CO), 44.9(4-CH_2), 52.2(CO-**C**H_2), 83.2(5-C), 164.0(3-C), 206.5(CO).

3,5-Dimethyl-5-phenacyl-2-isoxazoline (**12d**): m.p. 84-87°C; MS(rel. int.) 183(3), 147(1), 120(29), 105[$C_7H_5O^+$](98), 98[$C_5H_8NO^+$](100), 77[$C_6H_5^+$](64), 43[$C_2H_3O^+$](18).

3,5-Dimethyl-5-(2-methylphenacyl)-2-isoxazoline (**12e**): oil; MS(rel. int.) 161(1), 134(5), 119[$C_8H_7O^+$](100), 98[$C_5H_8NO^+$](88), 91[$C_7H_7^+$](48), 43[$C_2H_3O^+$](18).

3-Methyl-5-phenacyl-5-phenyl-2-isoxazoline (**12f**): oil; MS(rel. int.) 160[$C_{10}H_{10}NO^+$](76), 120(10), 105[$C_7H_5O^+$](100), 77[$C_6H_5^+$](58).

3,5-Diphenyl-5-(2-oxopropyl)-2-isoxazoline (**13f**): oil; MS(rel. int.) 222[$C_{15}H_{12}NO^+$](100), 105[$C_7H_5O^+$](80), 77[$C_6H_5^+$](43), 43[$C_2H_3O^+$](24); ^{1}H-NMR($CDCl_3$) 2.19(3H, s, CH_3-CO), 3.03;2.94(J^{gem}=17.8, 4-CH_2), 3.59(2H, s, $COCH_2$), 7.25-7.65(10H, m, H_{arom}).

The ^{1}H- and ^{13}C-NMR data of 2-isoxazolines **12b - 12f** are given in Tables 11 and 12, respectively.

1-Pyrazoline-1-oxide

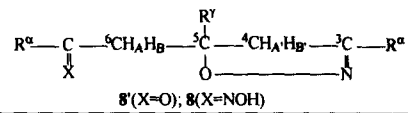
cis/trans 4,5-Dihydro-5-(1,1-dimethylethyl)-3-(3,3-dimethyl-2-oxobutyl)-3-methyl-3H-pyrazole-1-oxide (**9f**): m.p. 64-6°C; IR(CCl_4) 1340m, 1370m, 1395w, 1475m(1465sh), 1513i(1550sh), 1705i, 2870m, 2865vi cm^{-1}. Anal. Calcd. for $C_{14}H_{26}N_2O_2$: N, 11.01. Found: N, 10.60.

trans - **9f**: MS(rel. int.) 254[M^+](1.5), 237(1.4), 224(4.2), 209(2.3), 181(14), 155(16), 113(13), 99(67), 85(12), 69(24), 57(100), 41(32).

cis - **9f**: MS(rel. int.) 254[M^+](1), 237(1.4), 224(3.9), 209(2), 181(10), 155(15), 113(13), 99(42), 85(12), 69(24), 57(100), 41(29).

The ^{1}H- and ^{13}C-NMR data of *cis* - **9f** and *trans* - **9f** are given in Figure 1.

Table 9. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) in ^{1}H-NMR Spectra (300 MHz, $CDCl_3$) of Keto-2-Isoxazolines **8'c-8'i**, of E/Z-2-Isoxazoline-Oximes **8d, 8e, 8g, 8h**, and of E-2-Isoxazoline-Oximes **8f, 8i**.



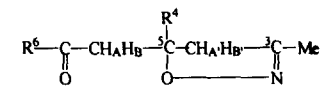
8'(X=O); 8(X=NOH)

Comp	R^α	R^γ	R^α(CX)	6-CH_AH_B	R^γ	4-$CH_{A'}H_{B'}$	3-R^α
8'c	Et	Me	1.14 (3H, t, *J*=7.5) 2.51 (2H, q, *J*=7.5)	2.81; 2.75 *J*=15.2	1.40 (3H, s)	3.02; 2.75 *J*=17.3	1.03 (3H, t, *J*=7.5) 2.32 (2H, q, *J*=7.5)
8'd	*n*-Pr	Me	0.91 (3H, t, *J*=7.4) 1.58 (2H, sxt, *J*=7,4) 2.47(2H, t, *J*=7.4)	2.81; 2.76 *J*=15.7	1.40 (3H, s)	2.99; 2.74 *J*=17.3	0.96 (3H, t, *J*=7.4) 1.58 (2H, sxt, *J*=7.4) 2.28 (2H, t, *J*=7.4)
E-8d	*n*-Pr	Me	0.95 (3H, t, *J*=7.4) 1.55 (2H, m) 2.40 (2H, m)	2.54; 2.44 *J*=14.3	1.40 (3H, s)	2.98; 2.62 *J*=17.3	0.96 (3H, t, *J*=7.4) 1.55 (2H, m) 2.27 (2H, m)
Z-8d	*n*-Pr	Me	0.91 (3H, t, *J*=7.4) 1.56 (2H, m) 2.31 (2H, m)	2.86; 2.62 *J*=13.0	1.42 (3H, s)	3.04; 2.64 *J*=17.3	0.95 (3H, t, *J*=7.4) 1.56 (2H, m, *J*=7.4) 2.27 (2H, t, *J*=7.4)
8'e	*i*-Pr	Me	1.09 (3H, d, *J*=6.9) 1.10 (3H, d, *J*=6.9) 2.68 (1H, sep, *J*=6.9)	2.90; 2.84 *J*=15.0	1.38 (3H, s)	2.97; 2.79 *J*=17.3	1.15 (3H, d, *J*=6.9) 1.16 (3H, d, *J*=6.9) 2.68 (1H,sep, *J*=6.9)
E-8e	i-Pr	Me	1.08 (3H, d, *J*=6.9) 1.11 (3H, d, *J*=6.9) 2.74 (1H, sep, *J*=6.9)	2.88; 2.63 *J*=13.2	1.43 (3H, s)	3.05; 2.64 *J*=17.3	1.14 (6H, d, *J*=6.9) 2.65 (1H, sep, *J*=6.9)
Z-8e	i-Pr	Me	1.07 (3H, d, *J*=7.1) 1.10 (3H, d, *J*=7.1) 3.37 (1H, sep, *J*=7.1)	2.53 (s)	1.41 (3H, s)	2.97; 2.67 *J*=17.6	1.15 (3H, d, *J*=6.9) 1.153 (3H, d, *J*=6.9) 2.69 (1H, sep, *J*=6.9)
8'f	*t*-Bu	Me	1.14 (9H, s)	2.94; 2.87 *J*=17.3	1.34 (3H, s)	3.08; 2.84 *J*=17.7	1.19 (9H, s)
E-8f	*t*-Bu	Me	1.16 (9H, s)	2.89; 2.80 *J*=14.0	1.36 (3H, s)	2.92; 2.69 *J*=17.3	1.17 (9H, s)
8'g	Ph	Me	7.48 (2H, t, *J*=7.0, m-H) 7.59 (1H, t, *J*=7.0, p-H) 7.97 (2H, t, *J*=7.0, o-H)	3.60; 3.45 *J*=17.0	1.60 (3H, s)	3.49; 3.33 *J*=17.2	7.39 (3H, m, m-H, p-H) 7.67 (2H, m, o-H)
E-8g	Ph	Me	7.35 (3H, m, m-H ,p-H) 7.55 (2H, m, o-H)	3.36 (2H, s)	1.46 (3H, s)	3.41; 2.96 *J*=16.8	7.35 (3H, m, m-H, p-H) 7.62 (2H, m, o-H)
Z-8g	Ph	Me	7.3-7.6 (5H, m)	3.01 (2H, s)	1.41 (3H, s)	3.26; 2.87 *J*=16.8	7.3-7.6 (5H, m)
8'h	o-Me-C_6H_4	Me	2.50 (3H, s); 7.2-7.4 (2H, m, H-3', H-5') 7.38 (1H, t, 7.4, H-4'); 7.71 (1H, d, 7.7, H-6')	3.57; 3.35 *J*=17.0	1.58 (3H, s)	3.49; 3.39 *J*=16.7	2.56 (3H, s) 7.2-7.4 (4H, m)
E-8h	o-Me-C_6H_4	Me	2.35 (3H, s) 7.1-7.3 (4H, m)	3.34; 3.27 *J*=13.0	1.39 (3H, s)	3.33; 2.93 *J*=16.7	2.47 (3H, s) 7.1-7.3 (4H, m)
Z-8h	o-Me-C_6H_4	Me	2.27 (3H, s) 7.1-7.3 (4H, m)	2.96 (2H,s)	1.47 (3H, s)	3.38; 3.00 *J*=16.8	2.50 (3H, s) 7.1-7.3 (4H, m)
8'i	Ph	Ph	7.3-7.4 (2H, m, m-H) 7.52 (1H, t, *J*=7.0, p-H) 7.88 (2H, d, *J*=7.0, o-H)	3.74 (2H, s)	7.3-7.4 (3H, m, m-H, p-H); 7.56 (2H, d, *J*=7.0, o-H)	4.12; 3.75 *J*=16.9	7.3-7.4 (3H, m, m-H, p-H); 7.66 (2H, m, o-H)
E-8i	Ph	Ph	7.3-7.6 (5H, m)	3.80; 3.42 *J*=13.9	7.3-7.6 (5H, m)	3.82; 3.46 *J*=16.9	7.3-7.6 (5H, m)

Table 10. Chemical Shifts (δ, ppm) in ^{13}C-NMR Spectra (75 MHz, in $CDCl_3$) of Keto-2-Isoxazolines **8'c** through **8'i**, of E/Z-2-Isoxazoline-Oximes **8d**, **8e**, **8g**, **8h** and of E-2-Isoxazoline-Oximes **8f**, **8i**.

Comp.	R^{α}	R^{γ}	R^{α}(CX)	C=X	6-CH_2	5-R^{γ}	5-C	4-CH_2	3-C	3-R^{α}
8' c	Et	Me	10.7 (CH_3); 37.5 (CH_2)	209.4	51.2	25.9	83.6	47.0	160.8	7.5(CH_3); 29.6 (CH_2)
8'd	*n*-Pr	Me	13.4 (CH_3); 16.8 (CH_2); 46.0 (CH_2)	208.7	51.3	25.8	83.3	47.0	159.5	13.6 (CH_3); 19.5 (CH_2); 29.7 (CH_2)
E-**8d**	*n*-Pr	Me	14.1 (CH_3); 18.9 (CH_2); 30.2 (CH_2)	159.3	43.0	26.0	84.9	46.9	159.3	13.6 (CH_3); 19.4 (CH_2); 29.7 (CH_2)
Z-**8d**	*n*-Pr	Me	13.5 (CH_3); 19.4 (CH_2); 36.8 (CH_2)	158.5	36.1	26.5	85.0	47.0	159.6	13.5 (CH_3); 19.5 (CH_2); 29.7 (CH_2)
8'e	*i*-Pr	Me	17.6 (CH_3); 17.8 (CH_3); 41.4 (CH)	212.2	45.0	25.4	83.3	49.0	164.0	19.7 (CH_3); 19.7 (CH_3); 27.8 (CH)
E-**8e**	*i*-Pr	Me	20.0 (2 CH_3); 33.6 (CH)	163.4	35.7	26.8	85.2	45.2	164.3	20.0 (CH_3); 20.6 (CH_3); 28.1 (CH)
Z-**8e**	*i*-Pr	Me	18.5 (CH_3); 18.6 (CH_3); 27.0 (CH);	162.7	39.6	25.7	84.8	45.4	164.1	20.1 (2 CH_3); 28.1 (CH)
8'f	*t*-Bu	Me	26.0 (CH_3); 44.4 (C_q)	213.6	44.7	24.8	83.9	45.5	166.8	27.8 (CH_3); 32.9 (C_q)
E-**8f**	*t*-Bu	Me	28.3 (CH_3); 37.2 (C_q)	165.1	35.1	27.0	85.2	45.4	166.8	27.9 (CH_3); 32.9 (C_q)
8g	Ph	Me	136.8 (C_q); 128.0 (o-CH); 128.5 (m-CH); 133.4 (p-CH)	197.3	47.5	25.8	85.5	45.3	157.1	129.8 (C_q); 126.5 (o-CH); 128.5 (m-CH); 129.8 (p-CH)
E-**8'g**	Ph	Me	136.1 (C_q); 126.5 (o-CH); 128.5 (m-CH); 129.4 (p-CH)	156.6	35.5	26.7	86.7	45.2	157.0	129.9 (C_q); 126.8 (o-CH); 128.5 (m-CH); 129.8 (p-CH)
Z-**8'g**	Ph	Me	133.3 (C_q); 128.0 (o-CH); 128.1 (m-CH); 129.1 (p-CH)	154.8	44.6	26.2	86.3	44.8	157.0	129.9 (C_q); 126.4 (o-CH); 128.4 (m-CH); 129.8 (p-CH)
8'h	o-Me-C_6H_4	Me	21.4 (2'-CH_3); 138.3 (1'-C); 137.7 (2'-C); 125.8 (5'-CH); 128.8 (6'-CH); 131.7 (3'-CH); 132.1 (4'-CH);	201.3	50.1	25.8	84.4	47.9	158.2	22.9 (2'-CH_3); 137.8 (2'-C); 128.9 (1'-C); 125.8 (5'-CH); 128.9 (6'-CH); 129.2 (3'-CH); 131.5 (4'-CH)
E-**8h**	o-Me-C_6H_4	Me	20.2 (2'-CH_3); 136.4 (2'-C); 135.8 (1'-C); 125.6 (5'-CH); 128.6 (6'-CH); 128.7 (3'-CH); 131.0 (4'-CH)	157.5	37.9	26.5	85.4	47.8	157.7	22.7 (2'-CH_3); 137.8 (2'-C); 128.9 (1'-C); 125.8 (5'-CH); 128.6 (6'-CH); 129.1 (3'-CH); 131.4 (4'-CH);
Z-**8h**	o-Me-C_6H_4	Me	19.8 (2'-CH_3); 137.7 (2'-C); 135.2 (1'-C); 125.6 (5'-CH); 126.7 (6'-CH); 128.8 (3'-CH); 130.2 (4'-CH)	157.6	45.1	26.0	84.9	47.5	157.6	22.8 (2'-CH_3); 137.7 (2'-C); 129.0 (1'-C); 125.7 (5'-CH); 128.6 (6'-CH); 129.1 (3'-CH); 131.4 (4'-CH)
8'i	Ph	Ph	137.2 (C_q); 128.4 (o-CH); 128.5 (m-CH); 133.3 (p-CH)	197.2	48.2	143.9 (C_q); 125.3 (o CH); 127.7 (p-CH) 128.6 (m-CH)	88.7	45.4	157.3	129.5 (C_q); 126.7 (o-CH); 128.5 (m-CH); 130.1 (p-CH)
E-**8i**	Ph	Ph	135.8 (C_q); 126.6 (o-CH); 128.4 (m-CH); 129.3 (p-CH)	156.7	37.1	145.0 (C_q); 125.0 (o-CH); 127.5 (p-CH); 128.2 (m-CH);	89.7	45.8	157.2	129.6 (C_q); 126.8 (o-CH); 128.5 (m-CH); 130.0 (p-CH)

Table 11. Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) in ^{1}H-NMR Spectra (300 MHz, in $CDCl_3$) of Keto-2-Isoxazolines **12b - 12f.**



Comp.	R^4	R^6	R^6	CH_AH_B	R^4	$CH_{A'}H_{B'}$	Me
12b	Me	*n*-Pr	0.91 (3H, t, *J*=7.4) 1.58 (2H, sxt, *J*=7.4) 2.46 (2H, t, *J*=7.4)	2.81; 2.75 *J*=16.1	1.40 (3H, s)	3.01; 2.75 *J*=17.4	1.95 (3H, s)
12c	Me	*i*-Pr	1.08 (3H, d, *J*=6.9); 1.10 (3H, d, *J*=6.9); 2.67 (1H, sep, *J*=6.9)	2.86 (2H, s)	1.39 (3H, s)	3.00; 2.78 *J*=17.4	1.96 (3H, s)
12d	Me	Ph	7.48 (2H, t, *J*=7.2, m-H) 7.59 (1H, t, *J*=7.2, p-H); 7.96 (2H, d, *J*=7.2, o-H);	3.46; 3.35 *J*=16.7	1.51 (3H, s)	3.09; 2.88 *J*=17.5	1.97 (3H, s)
12e	Me	o-MeC_6H_4	2.49 (3H, s); 7.24 (1H, d, *J*=7.5, H-3'); 7.27(1H, t, *J*=7.5, H-5'); 7.38 (1H, t, *J*=7.5, H-4'); 7.68 (1H, d, *J*=7.5, H-6')	3.37; 3.29 *J*=16.5	1.48 (3H, s)	3.12; 2.86 *J*=17.5	1.97 (3H, s)
12f	Ph	Ph	7.39 (2H, t, *J*=7.0, m-H); 7.51 (1H, t, *J*=7.0, p-H); 7.87 (2H, t, *J*=7.0, o-H)	3.54; 3.66 *J*=15.5	7.25 (1H, t, *J*=7.0, p-H); 7.33 (2H, t, *J*=7.0, m-H); 7.48 (2H, d, *J*=7.0, o-H)	3.72; 3.28 *J*=17.3	1.95 (3H, s)

Table 12. Chemical Shifts (δ, ppm) in ^{13}C-NMR Spectra (75 MHz, in $CDCl_3$) of Keto-2-Isoxazolines **12b - 12f.**

Comp.	R^4	R^6	R^6	CO	CH_AH_B	R^4	5-C	$CH_{A'}H_{B'}$	3-C	Me
12b	Me	*n*-Pr	13.4 (CH_3); 16.9 (CH_2); 46.2 (CH_2);	208.9	51.5	26.0	83.8	48.8	156.0	13.5
12c	Me	*i*-Pr	17.6 (CH_3); 17.8 (CH_3); 41.5 (CH);	212.2	49.1	25.6	83.7	48.8	155.9	13.2
12d	Me	Ph	137.0 (C_q); 128.2 (o-CH); 128.7 (m-CH); 133.4 (p-CH)	197.6	47.6	25.9	84.4	49.1	156.2	13.5
12e	Me	o-MeC_6H_4	21.3 (2'-CH_3);137.8 (2'-C); 138.1 (1'-C); 125.7 (5'-CH); 128.8 (6'-CH); 131.6 (3'-CH); 132.0 (4'-CH)	201.4	49.1	25.9	84.3	50.2	156.0	13.4
12f	Ph	Ph	137.2 (C_q); 128.3 (o-CH, m-CH); 133.2 (p-CH)	197.4	48.2	144.3 (C_q); 125.1 (o-CH); 128.3 (m-CH); 127.5 (p-CH)	87.6	48.9	156.2	13.3

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REFERENCES AND NOTES

1. Balaban A. T.; Cravey M.; Ghivirigă I. *Heterocyclic Commun.* **1994,** *1*, 17, part 24.
2. Schmitz E. *Chem. Ber.* **1958**, *91*, 1488.; b) Balaban A.T.; Nenitzescu C.D. *Liebigs Ann. Chem.* **1959**, *625*, 74.
3. Balaban A. T.; Dinculescu A.; Dorofeenko G. N.; Fischer G. W.; Koblik A.V.; Mezheritskii V. V.; Schroth W. *Pyrylium Salts. Syntheses, Reactions and Physical Properties* (*Advances in Heterocyclic Chemistry*, suppl. Vol.2; Katritzky A. R., Ed.); Academic Press: New York, 1982.
4. Weber H.; Rohn T. *Z. Naturforsch.* **1990**, *45b*, 701.
5. Evans R. F.; van Ammers M.; den Hertog H. J. *Rec. Trav. Chim. Pays-Bas* **1959**, *78*, 408.
6. Balaban A. T. *Tetrahedron* **1968**, *24*, 5059.; Balaban A. T. *Tetrahedron* **1970**, *26*, 739.
7. Kumler P. L.; Pedersen C. L.; Buchardt O. *Acta Chim. Scand.* **1968**, *22*, 2719.
8. Pedersen C. L.; Harrit N.; Buchardt O. *Acta Chem. Scand.*, **1970**, *24*, 3435.
9. Dimroth K.; Mach W. *Angew. Chem.* **1968**, *80*, 489.
10. Katritzky A. R.; Lagowski J. M. *Chemistry of the Heterocyclic N-oxides* (*Organic Chemistry*, vol. 19; Blomquist A. T., Ed.); Academic Press: London and New York, 1971.
11. Sasaki T.; Minamoto K.; Nishikawa M.; Shima T. *Tetrahedron* **1969**, *25*, 1021.
12. Hawkes G.; Herwig K.; Roberts J. D. *J. Org. Chem.* **1974**, *39*, 1017.
13. Gawley R. E. *Organic Reactions* **1988,** *35*, 287.
14. Karabatsos G. J.; Graham J. D.; Vane F. M. *J. Am. Chem. Soc.* **1962**, *84*, 753.
15. Anderson A. G.; Stang P. J. *J. Org. Chem.* **1976**, *41*, 3034; Balaban A. T. *Org. Prep. Proc. Int.* **1977**, *9*, 125.
16. Williams A. *J. Am. Chem. Soc.* **1971**, *93*, 2733.
17. Uncuţa C.; Balaban T. S.; Petride A.; Chiraleu F.; Balaban A. T. *Rev. Roumaine Chim.* **1989**, *34*, 1425.
18. Kotali A.; Papageorgiou V. P.; Tsoungas P. G. *Org. Mass Spectrom.***1986**, *21*, 435.
19. Freeman J. P; *J. Org. Chem.* **1962**, *27*, 1309.; Freeman J. P. *J. Org. Chem.* **1962**, *27*, 2881.
20. Green F. D.; Hecht S. S. *Tetrahedron Lett.* **1969**, 575.
21. Bandurco V. T; Snyder J. P. *Tetrahedron Lett.* **1969**, 4643.
22. An error is worth mentioning for compounds designated as **19** and **20** in ref. 23, which are 5H-pyrazole-1- oxides, and not 3H-pyrazole-4,5-dihydro-2-oxides as mentioned in *Chem. Abstr.* **1972**, *77*, 34062b.
23. Williams W. M.; Dolbier Jr. W. R. *J. Am. Chem. Soc.* **1972**, *94*, 3955.
24. McGreer D. E.; McKinley J. W. *Can. J. Chem.* **1971**, *49*, 105.
25. Van der Plas H. C.; *Ring Transformations of Heterocycles*, Academic Press: New York, 1973.
26. Lang Jr. S. A.; Lin Y. i. Chapter 4.16 in *Comprehensive Heterocycles Chem.* Vol 6 (Katritzky A. R.; Rees C. W. Eds.); Pergamon Press: Oxford, 1984.; Kozikowski A. P. Chapter 1.16 in the same monograph, Vol 1.
27. Kozikowski A. P. *Acc. Chem. Res.* **1984**, *17*, 410.
28. Bak T.; Rasala D.; Gawinecki R. *Org. Prep. Proc. Int.* **1994**, *26*, 101.
29. Balaban A. T.; Bota A. *Org. Prep. Proc. Int.* **1982**, *14*, 31.
30. Uncuţa C.; Balaban T. S.; Gheorghiu M. D.; Stănescu L.; Petride A.; Balaban A. T. *Tetrahedron Lett.* **1985**, *26*, 4673.
31. Prostakov N. S.; Soldatenko A. T.; Krapivko A. P.; Fomichev A. A.; Mikaya A. I.; Ustenko, A. A. *Zh. Org. Khim.* **1982**, *18*, 1106.
32. Schiess P.; Ringele P. *Tetrahedron Lett.* **1972**, 311.