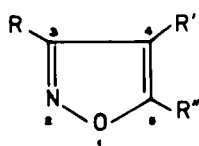# Isoxazoles from Nitrile Oxides and Acetylenes.
Substituent Effect on the PMR Spectra of Disubstituted Isoxazoles

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Isoxazoles (I) and (II) may be prepared by several methods (2,3), and among these, one of the most useful and general is that from nitrile oxides and acetylenic derivatives.

(I)   R' = H
(II) R' = H or other groups

Extensive investigations (2,3,4) of the reaction of nitrile oxides with monosubstituted acetylenes have shown that the orientation of the cycloaddition affords mainly 3,5-disubstituted isoxazoles (I). Moreover this reaction leads to 3,5-diarylsubstituted isoxazoles where the position of the substituents is unambigously defined. This is not the case in other syntheses (2,3) where both 3,5-derivatives with the substituents interchanged can be obtained. For instance unsymmetrical 1,3-diketones and hydroxylamine yielded two isomeric 3,5-disubstituted isoxazoles (5), the structures of which were difficult to determine and in

TABLE I

Chemical Shifts in τ Units for H-4 in 3,5-Diarylisoxazoles (I)

Compound	R	R"	H-4 (τ)
(Ia)	p-OCH$_3$C$_6$H$_4$	C$_6$H$_5$	3.23
(Ib)	C$_6$H$_5$	C$_6$H$_5$	3.23
(Ic)	p-ClC$_6$H$_4$	C$_6$H$_5$	3.26
(Id)	p-CH$_3$C$_6$H$_4$	C$_6$H$_5$	3.26
(Ie)	m-ClC$_6$H$_4$	C$_6$H$_5$	3.27
(If)	C$_6$H$_5$	p-NO$_2$C$_6$H$_4$	2.96
(Ig)	C$_6$H$_5$	p-OCH$_3$C$_6$H$_4$	3.29
(Ih)	C$_6$H$_5$	m-NO$_2$C$_6$H$_4$	2.96
(Ii)	C$_6$H$_5$	p-ClC$_6$H$_4$	3.16
(Ij)	C$_6$H$_5$	p-CH$_3$C$_6$H$_4$	3.23
(Ik)	C$_6$H$_5$	m-BrC$_6$H$_4$	3.16

most cases an independent synthesis of the products by another route was carried out.

The results of PMR spectra of several 3,5-disubstituted isoxazoles show that it is possible to overcome this difficulty. The compounds reported here were synthetized in connection with our studies (6) on the mechanism of cycloaddition reactions of nitrile oxides to carbon-carbon unsaturated centers and were identified by PMR spectra. The chemical shifts of the H-4 protons in 3,5-diarylisoxazoles (I) are reported in Table I; the other resonances are omitted since they do not contribute to the present discussion.

Table I shows that the chemical shifts of the H-4 protons are essentially unaffected by the presence of *para* or *meta* substituted phenyl groups at position 3. The chemical shift is in fact 3.23 τ for the unsubstituted compound (Ib) and it changes only a few hundreths of a ppm when *meta* or *para*-substituted phenyl groups are present at this position.

However, some appreciable variation of chemical shift of proton H-4 is observed when the substituted phenyl group is at position 5. This fact can be used as an analytical tool for determining the site of substitution in 3,5-diarylisoxazoles. Furthermore, the shift produced by a substituted phenyl group at position 5 can be predicted quantitatively. In fact a diagram of the correlation of the shift of the H-4 protons as a function of Hammett σ-constants of the substituents for 3,5-diarylisoxazoles (If-k) and (Ib) is shown in Figure 1, (relation a). Although the experimental points are not linear, a linear correlation can be obtained by a least square treatment of the data. The equation is given by

$$\tau\,(\text{H-4}) = -0.30\,\sigma + 3.21$$

The mean average deviation $\bar{\Delta}$ between experimental and calculated chemical shifts is equal to ±0.03 ppm which is considered the limit of reproducibility of the predicted chemical shifts for different substituents. Changes in chemical shift for the H-4 protons in 5-phenyl substituted isoxazoles and a rough linear correlation between τ values and Hammett's σ of the substituents were also observed when the 3,5-dichloro-2,4,6-trimethylphenyl group was present at position 3 (7). In this particular case the 5-

unsubstituted phenyl derivative shows a chemical shift (τ = 3.56) larger than the corresponding compound (Ib) (τ = 3.23) due to the presence of the 3,5-dichloro-2,4,6-trimethylphenyl group at position 3. It seems, therefore, that only *para* and *meta* substituents in the phenyl ring at position 3 are ineffective on the chemical shift of the H-4 proton, which is, on the contrary, largely affected by *ortho* substitution in the same phenyl ring. In fact the H-4 proton in 3-mesityl-5-phenylisoxazole (IIe) (Table II) shows a chemical shift of 3.49 τ very close to that reported in Ref. 7. Moreover, the effect of the mesityl group is nearly the same when present at position 5 or 3 as indicated by the chemical shift of 3.46 τ of the isoxazole IIa (Table II).

The data relative to H-4 in isoxazoles reported in Ref. 7 show a linear correlation with Hammett's σ, and this is reported in Figure 1 (correlation b). The corresponding equation

$$\tau\,(\text{H-4}) = -0.27\,\sigma + 3.59 \qquad \bar{\Delta} = \pm 0.02$$

indicates a sensitivity of the chemical shift of H-4 very near to that found in our compounds.

Table II also reports isoxazoles in which the *n*-butyl and carbethoxy groups are directly bonded to the isoxazole ring. These substituents at position 5 exert a large effect on the chemical shift of the 4-H proton which is shifted to higher and lower field, respectively, in the case of *n*-butyl and carbethoxy groups, with respect to the unsubstituted compound (3-phenylisoxazole, τ (H-4) = 3.50 (7)). These results are qualitatively in line with the substituent effect previously discussed and with previous data for similar compounds (7,8).

The reaction of *p*-chlorobenzonitrile *N*-oxide and ethyl propriolate affords in addition to the "normal" isoxazole (IIc), the isomer (IId). A similar result was recently reported (8). The PMR spectrum of (IId) shows that the chemical shift of the H-5 proton is at 1.05 τ. It is known that in 3-phenylisoxazole (7) the H-4 and H-5 protons lie respectively at 3.50 and 1.75 τ; in 4-carbomethoxyisox-

azole (8) the H-5 proton lies at 0.85 τ while in the 5-carbomethoxy derivative (8) the H-4 proton lies at 2.93 τ.

It may be concluded that the carbethoxy group when directly bonded to the isoxazole ring either at position 4 or 5 quantitatively affects the vicinal proton to the same extent (low field shift 0.7 ppm).
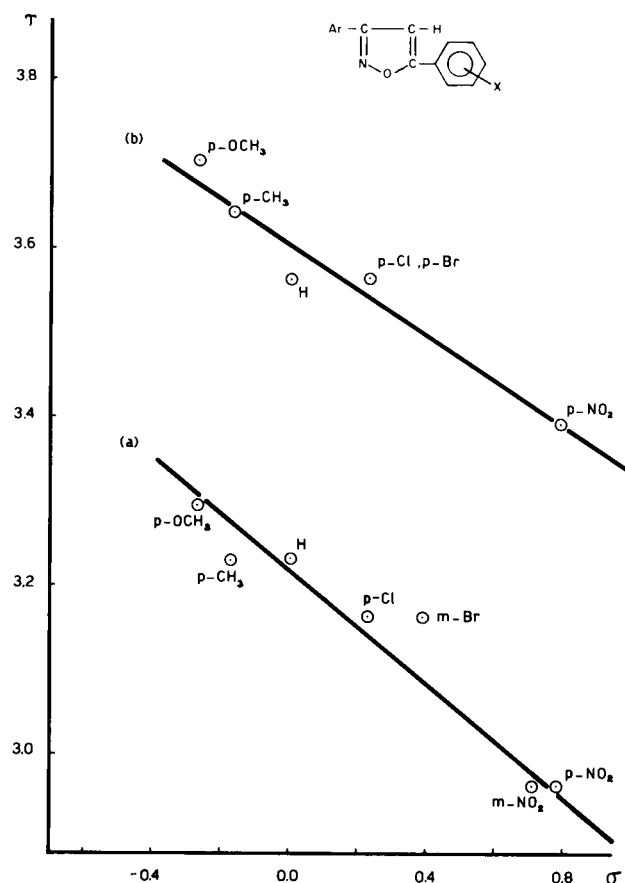

Figure 1. Plots of chemical shifts in τ units of H-4 against Hammett's σ for isoxazoles (If-k) (relation a) and for isoxazoles reported in Ref. 7 (relation b).

TABLE II

Chemical Shifts in τ Units for Isoxazole Derivatives

Compound	R	R'	R"	H-4 (τ)	H-5 (τ)
(IIa)	p-ClC$_6$H$_4$	H	Mesityl	3.46	---
(IIb)	p-ClC$_6$H$_4$	H	n-C$_4$H$_9$	3.73	---
(IIc)	p-ClC$_6$H$_4$	H	COOC$_2$H$_5$	2.77	---
(IId)	p-ClC$_6$H$_4$	COOC$_2$H$_5$	H	---	1.05
(IIe)	Mesityl	H	C$_6$H$_5$	3.49	---

EXPERIMENTAL

Melting points are uncorrected. The 60 MHz spectra were determined in deuteriochloroform on a JEOL JNM-C-60 HL instrument at 26°, tetramethylsilane being used as internal standard.

Materials and Products.

Isoxazoles (I) and (II) were obtained by allowing benzonitrile N-oxides to react with excess acetylenes (molar ratio 1:20) for twenty-four hours in carbon tetrachloride solution at room temperature. Unstable nitrile oxides were prepared before use and isolated as pure materials as previously described (9). In some cases variable amounts of diarylfuroxans, dimers of nitrile oxides, (2,10,11) were obtained as side products.

Infrared spectra of isoxazoles (I) and (II) (carbon tetrachloride/-carbon disulfide) included major bands in the region 3100-2800 cm^{-1}, at ca. 1600 cm^{-1} and in the range 980-800 cm^{-1}.

3-Aryl-5-phenylisoxazoles (Ia-e).

These compounds were prepared from the corresponding benzonitrile N-oxides (2,9,10) and phenylacetylene (12). The solvent was distilled in vacuo and the crude material recrystallized from ethanol: 3-(p-methoxyphenyl)-5-phenylisoxazole (Ia), 71%, m.p. 120-121° (lit. (13) m.p. 119°); 3,5-diphenylisoxazole (Ib), 72%, m.p. 144° (lit. (14) m.p. 141°); 3-(p-chlorophenyl)-5-phenylisoxazole (Ic), 80%, m.p. 174-175° (lit. (15) m.p. 175°); 3-(p-tolyl)-5-phenylisoxazole (Id), 86%, m.p. 130-131° (lit. (16) m.p. 125°); 3-(m-chlorophenyl)-5-phenylisoxazole (Ie), 76%, m.p. 126-127°.

Anal. Calcd. for $C_{15}H_{10}ClNO$: C, 70.5; H, 3.94; Cl, 13.9; N, 5.47. Found: C, 70.3; H, 3.89; Cl, 14.2; N, 5.48.

3-Phenyl-5-arylisoxazoles (If-k).

Following the above procedure these products were obtained from benzonitrile N-oxide and arylacetylenes (12,17). Yields and m.p.'s are: 3-phenyl-5-(p-nitrophenyl)isoxazole (If), 95%, m.p. 225-226° (from ethyl acetate) (lit. (18) m.p. 226-227°); 3-phenyl-5-(p-methoxyphenyl)isoxazole (Ig), 91%, m.p. 128-129° (from ethanol) (lit. (19) m.p. 128°); 3-phenyl-5-(m-nitrophenyl)isoxazole (Ih), 70%, m.p. 180-181° (from ethyl acetate) (lit. (18) m.p. 180.5-181.5°); 3-phenyl-5-(p-chlorophenyl)isoxazole (Ii), 87%, m.p. 178-179° (from ethanol) (lit. (14) m.p. 177°); 3-phenyl-5-(p-tolyl)isoxazole (Ij), 90%, m.p. 138-139° (from ethanol) (lit. (16) m.p. 136-137°); 3-phenyl-5-(m-bromophenyl)isoxazole (Ik), 87%, m.p. 133-134° (from ethanol).

Anal. Calcd. for $C_{15}H_{10}BrNO$: C, 60.0; H, 3.36; N, 4.65. Found: C, 59.8; H, 3.27; N, 4.53.

3-(p-Chlorophenyl)-5-mesitylisoxazole (IIa).

p-Chlorobenzonitrile N-oxide (1.2 g., 0.0078 mole) was allowed to react for twenty-four hours with 3.65 g. (0.025 mole) of mesitylacetylene (12,17) in 120 ml. of carbon tetrachloride at room temperature. After distillation of the solvent in vacuo the residue was chromatographed over silica (benzene/light petroleum 2:1) to yield 1.05 g. (50%) (20) of isoxazole (IIa), m.p. 67-68° (from ligroine).

Anal. Calcd. for $C_{18}H_{16}ClNO$: C, 72.6; H, 5.42; N, 4.71. Found: C, 72.6; H, 5.22; N, 4.84.

3-(p-Chlorophenyl)-5-n-butylisoxazole (IIb).

p-Chlorobenzonitrile N-oxide (0.8 g., 0.0052 mole) and 1-hexyne (12) (5.3 g., 0.065 mole) under the standard conditions outlined above afforded an oily material from which 0.9 g. (73%) of (IIb) was isolated by distillation, b.p. 143-144° (0.5 mm), m.p.

32-33°.

Anal. Calcd. for $C_{13}H_{14}ClNO$: C, 66.2; H, 5.98; N, 5.94. Found: C, 66.4; H, 5.95; N, 6.04.

3-(p-Chlorophenyl)-5-carbethoxy- (IIc) and 3-(p-Chlorophenyl)-4-carbethoxyisoxazole (IId).

A mixture of p-chlorobenzonitrile N-oxide (1.5 g., 0.0098 mole) and ethyl propiolate (21) (5.1 g., 0.05 mole) in 250 ml. of carbon tetrachloride was allowed to react for fifteen hours at 25°; the solvent was distilled in vacuo and the residue chromatographed over silica (benzene/light petroleum 2:1) to yield 1.32 g. (62%) of (IIc), m.p. 141-142° (from ethanol).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.3; H, 4.00; N, 5.57. Found: C, 57.7; H, 4.07; N, 5.59.

Subsequent elution gave 0.76 g. (28%) of (IId), m.p. 49-50° (from light petroleum).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.3; H, 4.00; N, 5.57. Found: C, 57.6; H, 3.95; N, 5.65.

Both (IIc) and (IId) show the infrared features of the other isoxazoles. The peak at 1.05 τ of (IId) (see Table II) does not disappear by addition of deuterium oxide as we observed (20) for the broad signal around 0.6-1.4 τ in the case of acetylenic oximes.

3-Mesityl-5-phenylisoxazole (IIc).

This product was prepared following the procedure as described by Gründmann (22) in 85% yield, m.p. 90-91° (from methanol) (lit. (22) m.p. 94°).

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