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Advances in Nitrile Oxides Chemistry*

by ADOLFO QUILICO

Nitrile oxides represent a class of substances isomeric with isocyanates, endowed with a remarkable chemical activity.

Although the fundamental member of the series, fulminic acid, was known as early as the beginning of the last century, the idea that it could be considered as the oxide of formonitrile struck the attention of chemists only relatively recently, when the extensive study of nitrile oxides showed the close similarity existing between the chemical behaviour of fulminic acid and these substances.

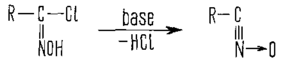
Until 1940 the only member of the series which was known practically was benzonitrile oxide, discovered in 1894 by WERNER and BUSS[1] who obtained it by treatment of benzohydroxamic chloride with cold aqueous solution of alkalies, a method which, when suitably modified, is still the procedure employed practically for the preparation of most nitrile oxides.

Strange as it may appear, nitrile oxides chemistry was neglected during the half century following the discovery of benzonitrile oxide. The interest of chemists was averted from the study of these substances partly by the singular statement contained in WIELAND's paper of 1907[2] that benzonitrile oxide is a product comparatively inert, incapable of giving addition reactions and in every respect far less active than the corresponding nitrile. The investigations which my collaborators and I had initiated in 1938, have shown that, on the contrary, nitrile oxides are endoved with an enhanced reactivity which can be compared to that of aliphatic diazocompounds and azides[3] to which they are linked by striking structural similarities. To the discovery of the addition reaction on acetylenic triple bonds[3] which gives isoxazoles followed that on ethylenic double bonds which yield 2-isoxazolines[4]. Both reactions have been extended to a large variety of unsaturated compounds containing C=C and C≡C bonds, and still represent the most general and valuable method for the synthesis of isoxazoles and isoxazolines. In a more recent period we are indebted to HUISGEN[5] and his school for the generalization of the concept of 1,3-dipoles, a class of compounds to which nitrile oxides as well as diazoparaffins and azides belong, for the study and theoretical interpretation of the mechanism of the 1,3-dipolar-cycloadditions, and the discovery of new addition reactions of nitrile oxides.

Among the researchers who have contributed to the development of the modern nitrile oxides chemistry, I want to mention GRUNDMANN et al.[6], who have prepared a number of new members of the series and investigated their chemical behaviour. The scientific production dealing with nitrile oxides can presently be estimated at about 250 papers. Besides the synthetic uses in heterocyclic chemistry, practical applications of stable nitrile oxides have been suggested starting from 1964 as pesticides[7] and for the preparation of cross-linked copolymers with monomers containing carbon-carbon double and triple bonds[8].

Methods of preparation

A) The original method of WERNER and BUSS[1] consisting of treatment with bases of hydroxamic chlorides is still the most used:



$$R-\underset{\Vert\atop NOH}{C}-Cl \xrightarrow[-HCl]{base} R-\underset{\Vert\!|\atop N\rightarrow O}{C}$$

Na_2CO_3 and dilute NaOH at low temperature, but also alkoxides and organic bases like pyridin, can be employed. Most convenient for the generation in situ

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* 12. Paul-Karrer-Vorlesung in der Aula der Universität Zürich am 24. Juni 1970.

[1] A. WERNER and H. BUSS, Ber. *27*, 2193 (1894).

[2] H. WIELAND, Chem. Ber. *40*, 1667 (1907).

[3] A. QUILICO and G. SPERONI, Gazz. chim. ital. *76*, 150 (1946).

[4] A. QUILICO, G. STAGNO D'ALCONTRES and P. GRÜNANGER, Nature, Lond. *166*, 226 (1950).

[5] R. HUISGEN, Proc. chem. Soc. *1961*, 357; Angew. Chem. *75*, 604, 742 (1963).

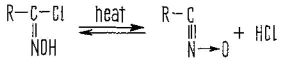
[6] C. GRUNDMANN, Angew. Chem. *75*, 450 (1963). – C. GRUNDMANN and J. M. DEAN, Angew. Chem. *76*, 682 (1964); J. org. Chem. *30*, 2809 (1965). – C. GRUNDMANN and R. RICHTER, J. org. Chem. *33*, 476 (1968). See also the excellent Monograph published in *Houben-Weyl, Methoden der organischen Chemie*, vol. 10/3, 837 (1965), G. Thieme Verlag, Stuttgart, and the review in *Fortschritte der chemischen Forschung*, Band 7, 1966/67, p. 62., Springer Verlag, Berlin, New York.

[7] J. T. HACKMANN, P. A. HARTHOORN and J. KIDD, Shell Research Ltd, Brit. 949372, C.A. *1964*, 13199 *a*.

[8] E. J. FREZZA, US 3213068, Chem. Abstr. *1966*, 2189 *f*; Hercules Inc., Neth. Appl. 6604936, Chem. Abstr. *1967*, 66468 *c*.

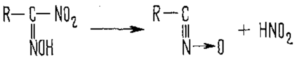
of nitrile oxides is the procedure suggested by Huisgen[9], consisting of treatment of the hydroxamic chloride with Et_3N. The same procedure can be applied also to aliphatic chloroximes, now readily available in high yield by chlorination at —60°C in ether solution of aliphatic oximes[10], a procedure more advantageous than the original method based on the use of nitrosyl chloride[11].

Since hydroxamic chlorides on heating in an inert solvent eliminate HCl giving nitrile oxides[12]:



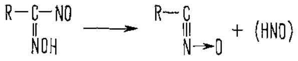
many addition reactions can be carried out simply by heating the solution of the chloroxime with the unsaturated compound.

B) The thermal or spontaneous decomposition of nitrolic acids first reported by Wieland and Semper[13] has been used for the preparation in situ of particular members[14]:

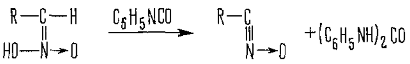


The intervention of nitrolic acids as a source of fulminic acid and nitrile oxides plays an essential role in the formation of isoxazoles in the reactions between HNO_3, acetylene and other unsaturated compounds[14].

Of limited importance is the formation of nitrile oxides from nitrosolic acids, reported by Wieland and Hess[15]:



C) As we had anticipated in 1946, primary nitroparaffins can represent a potential source of nitrile oxides through dehydration, and actually in 1960 Mukaiyama and Hoshino[16] succeeded in accomplishing this reaction by the use of isocyanates:

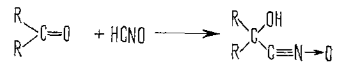


This procedure has found application for the generation in situ of aliphatic and heterocyclic nitrile oxides[17].

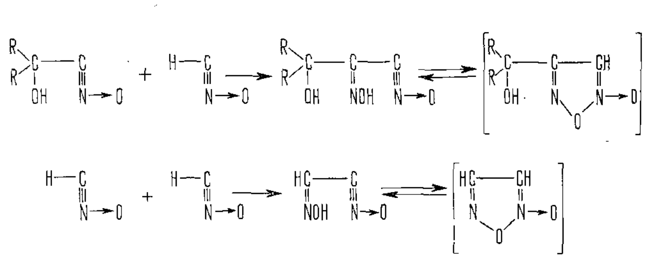
D) While all attempt to prepare nitrile oxides by oxidation of nitriles with reagents such as H_2O_2 and peracids have proved unsuccessful, dehydrogenation of aldoximes to nitrile oxides has been achieved by the use of different oxidants:

Most convenient among them is NaOBr[18]. This procedure is useful when chlorination of aromatic aldoximes to hydroxamic chlorides is accompanied by unwanted chlorination in the benzene ring. N-bromosuccinimide in the presence of Et_3N or CH_3ONa has also been used[19]. Lead tetraacetate oxidation of syn-aldoximes also gives nitrile oxides; with hindered aldoximes satisfactory yields have been obtained[20].

E) A mode of formation which is peculiar to nitrile oxides of α-hydroxyacids consists in the nucleophilic addition of fulminic acid on the carbonyl group of ketones, a reaction that in every aspect corresponds to the addition of HCN to give cyanohydrines[21]:



These investigations have also revealed the capacity of fulminic acid to react with the nitrile oxide function of the product first formed to give new nitrile oxides, as shown in formula:



The dimeric fulminic acid can be considered as the open form of the fundamental member still unknown of the furoxans series, and it is most probable that monosubstituted furoxans actually possess a nitrile oxide structure.

Known members of the series

About 50 nitrile oxides have been isolated in more or less pure form. As shown in Table I most of them are aromatic, but the list includes some representatives of the aliphatic series such as acetonitrile oxide and trimethylacetic nitrile oxide, a terpenic member (*O*-methyl-podocarpic nitrile oxide), and a few heterocyclic members. Terms containing 2 and 3 CNO functions like oxalo-, isophtalic-, terephtalic- and trimesic-nitrile oxides have also been prepared.

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[9] R. Huisgen and W. Mack, Tetrahedron Lett. *1961*, 583. – R. Huisgen, W. Mack and E. Anneser, Tetrahedron Lett. *1961*, 587; Angew. Chem. *73*, 656 (1961).

[10] G. Casnati and A. Ricca, Tetrahedron Lett. *1967*, 327.

[11] O. Piloty and H. Steinbock, Chem. Ber. *35*, 3113 (1902). G. Zinner and M. Gunther, Angew. Chem., Int. Edn. *3*, 383 (1964).

[12] R. Lenaers and F. Elroy, Helv. chim. Acta *46*, 1076 (1963).

[13] H. Wieland and L. Semper, Chem. Ber. *39*, 2522 (1906).

[14] A. Quilico and M. Simonetta, Gazz. chim. ital. *76*, 200 (1946); *77*, 586 (1947).

[15] H. Wieland and H. Hess, Chem. Ber. *42*, 4175 (1909).

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[17] R. Paul and S. Tchelitcheff, Bull. Soc. chim. France *1962*, 2215.

[18] C. Grundmann and J. M. Dean, J. org. Chem. *30*, 2809 (1965).

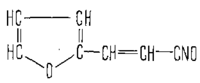
[19] C. Grundmann and R. Richter, J. org. Chem. *33*, 476 (1968).

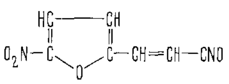
[20] G. Just and K. Dahl, Tetrahedron Lett. *1966*, 2441. – G. Just and W. Zehetner, Tetrahedron Lett. *1967*, 3389.

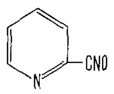
[21] A. Quilico and G. Stagno d'Alcontres, Gazz. chim. ital. *79*, 654, 703 (1949).

Many others have been prepared in situ and employed without isolating them, such as:

$Cl—CNO$ $Br—CNO$ $O_2N—CNO$ $C_2H_5—CNO$ $CH_3CO—CNO$ $C_2H_5OCO—CNO$ $C_6H_5—CH{=}CH—CNO$







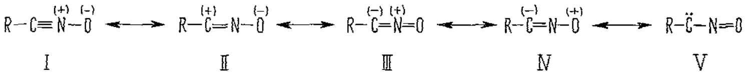
etc.

Elementorganic nitrile oxides such as $(C_6H_5)_3Si\text{-}CNO$ and $C_6H_5Hg\text{-}CNO$[41] have also been reported.

The stability toward dimerization to furoxans is very variable and depends essentially on steric factors. Aromatic *ortho*-disubstituted nitrile oxides are very stable and some of them do not dimerize but rearrange to isocyanates on heating. Nevertheless, they give the usual reactions of 1,3-dipolar cycloaddition and nucleophilic addition.

Structure of nitrile oxides

The structure of nitrile oxides has been argued in a number of investigations. WERNER and BUSS[1], taking into account its ready dimerization to diphenylfuroxan, assigned to benzonitrile oxide the open chain structure presently accepted in its modern description of 1,3-dipole. Researches on dipole moments and IR-spectra by SPERONI et al.[42] (1957/58) and WILEY[25] (1958), have led to the conclusion that the molecule of nitrile oxides is linear; in aromatic members the CNO group lies in the plane of the benzene ring and is directed radially. The molecule can be considered a resonance hybrid with the participation of structures (I–V):



$$\underset{\text{I}}{R-C\equiv\overset{(+)}{N}-\overset{(-)}{O}} \longleftrightarrow \underset{\text{II}}{R-\overset{(+)}{C}=N-\overset{(-)}{O}} \longleftrightarrow \underset{\text{III}}{R-\overset{(-)}{C}=\overset{(+)}{N}=O} \longleftrightarrow \underset{\text{IV}}{R-\overset{(-)}{C}=N-\overset{(+)}{O}} \longleftrightarrow \underset{\text{V}}{R-\ddot{C}-N=O}$$

Limit forms (I) and (III) are octet formulas, forms (II), (IV) and (V) are sextet formulas. Structure (II) which, because of the strong separation of the charges should give only a limited contribution to the resonance hybrid, is frequently used for a schematic representation of the 1,3-dipolar cycloaddition reactions discussed in another section. The participation of structure (III) would result from the study of IR-spectra, which would indicate for the N–O bond a partial character of double bond, and from theoretical calculations of the resonance energy which would show in the aromatic members, in comparison with the corresponding nitriles a weaker coupling with the benzene ring. The bathochromic shift of the N–O band noticeable in the IR-spectrum of trimethylacetic nitrile oxide (in which the pronounced +I effect of the tertiary butyl group enhances structure III), is also in favour of the participation in some extent of (III) to the hybrid. The intervention of the nitroso carbenic form (V) has been maintained in order to explain the dimerization to furoxans[43] and the addition on the NO group of aromatic nitrosoderivatives[44].

Dipole moments of some aromatic nitrile oxides have been determined in pyridin solution and compared with those of the corresponding nitriles[42]. The values of μ are practically the same for the 2 classes of substances, in contrast with the strong difference existing between tert. amines and their N-oxides. The low dipole moment of benzonitrile oxide (4,0 D) in respect to the value (8,9 D) calculated with the MO method, has been attributed to a redistribution of the electrons in the CNO function which suppresses the expected increase of polarity. IR-spectra of nitrile oxides exhibit an absorption band in the 2280–2310 cm^{-1} region which is assigned to the CN stretching. An appreciable hypsochromic effect is evident in comparison with the cor-

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[22] G. SPERONI, unpublished data, reported by A. QUILICO in the Monograph on Isoxazoles and Related Compounds of the collection *The Chemistry of Heterocyclic Compounds* (Ed. A. WEISSBERGER; Interscience Publishers, New York, London 1962), vol. 17, p. 21.

[23] T. KUBOTA, K. EZUMI, M. YAMAKAWA and Y. MATSUI, J. molec. Spectrosc. *24*, 378 (1967).

[24] C. GRUNDMANN and J. M. DEAN, Angew. Chem. *76*, 682 (1964).

[25] R. H. WILEY and B. J. WAKEFIELD, J. org. Chem. *25*, 546 (1960).

[26] P. BELTRAME, C. VEGLIO and M. SIMONETTA, J. chem. Soc. *1967*, 867.

[27] P. GRÜNANGER, Atti Accad. naz. Lincei *16*, 726 (1954).

[28] F. ELOY and R. LENAERS, Bull. Soc. chim. Belg. *74*, 129 (1965).

[29] A. DONDONI, Tetrahedron Lett. *1967*, 2397.

[30] C. GRUNDMANN, in *Fortschritte der chemischen Forschung* (Springer Verlag, Berlin, New York 1966/67), vol. 7, p. 81.

[31] C. GRUNDMANN and J. M. DEAN, Angew. Chem. *77*, 966 (1965).

[32] Y. IWAKURA, M. AKIYAMA and S. SHIRAISHI, Bull. chem. Soc. Japan *38*, 335 (1965).

[33] Y. IWAKURA, M. AKIYAMA and K. NAKABUKO, Bull. chem. Soc. Japan *37*, 767 (1964).

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[35] P. VITA-FINZI and P. GRÜNANGER, Chimica Ind. *46*, 516 (1965).

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[37] C. GRUNDMANN, Angew. Chem. *75*, 450 (1963).

[38] C. GRUNDMANN, V. MINI, J. M. DEAN and H. FROMMELD, Justus Liebigs Annln Chem. *687*, 191 (1965).

[39] G. PONZIO, Gazz. chim. ital. *66*, 119, 127 (1936).

[40] G. PONZIO, Gazz. chim. ital. *71*, 693 (1941).

[41] W. BECK, Angew. Chem. *75*, 872 (1963).

[42] S. CALIFANO, R. MOCCIA, R. SCARPATI and G. SPERONI, J. chem. Physics *26*, 1777 (1957). – G. DEL RE, Atti Accad. naz. Lincei *22*, 491 (1957). – S. CALIFANO, R. SCARPATI and G. SPERONI, Atti Accad. naz. Lincei *23*, 263 (1958).

[43] R. HUISGEN, Angew. Chem. *75*, 751 (1963). – C. GRUNDMANN, H. D. FROMMELD, K. FLORY and S. K. DATTA, J. org. Chem. *33*, 1464 (1968).

[44] F. MINISCI, R. GALLI and A. QUILICO, Tetrahedron Lett. *1963*, 785.

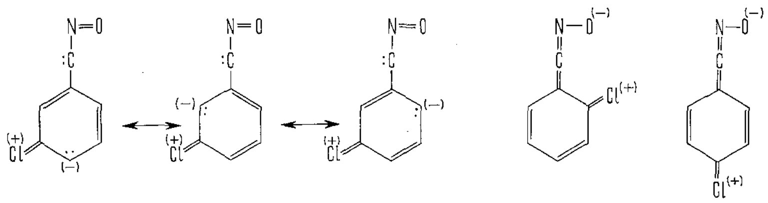
responding nitriles in which the CN band is located at 2220–2240 cm^{-1}. To the stretching of the NO group is attributed the strong band at 1350–1370 cm^{-1} that is ranged between the NO band of tert. amine-N-oxides (at 947–970 cm^{-1}) and that of the same group of nitroso derivatives (at 1488–1621 cm^{-1})[45].

Chemical behaviour of nitrile oxides

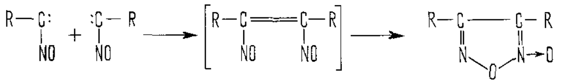
Nitrile oxides show a remarkable reactivity, as shown by the number of addition reactions presently known. They react far more easily than azides and show an enhanced electrophilic character of which azides are practically devoid.

1. *Dimerization and polymerization.* Several products of dimerization and polymerization are known. The easy dimerization to furoxan of benzonitrile oxide had been observed by WERNER and BUSS[1]. For the different members of the series the rate of this reaction is strongly influenced by the nature of R. Thus there are nitrile oxides such as R–CNO with R = COOAlkyl, COR′, Cl, Br etc. which cannot be isolated even in solution; others, such as most of the aromatic members, which are fairly stable, and others which are very stable and do not dimerize.

Table II[46] gives the approximate time required for complete dimerization to furoxan of some nitrile oxides in benzene solution at 18°C. Steric influences are evident. Electronic effects are visible in the case of the 3 isomeric chlorobenzonitrile oxides:



Ortho and *para* isomers are significantly more stable than the *meta* isomer, apparently because the Cl in *meta* position does not affect the charge distribution of the CNO group, whereas the same substituent in *o*- and *p*-position can promote a strong contribution to the hybrid of forms that prevent a high participation of the nitrosocarbenic form which is believed to be involved in the dimerization to furoxan. As already mentioned, stable aromatic nitrile oxides rearrange on heating to isocyanates, but recently GRUNDMANN et al.[47] have succeeded in dimerizing strongly hindered nitrile oxides such as mesityl nitrile oxide which, on prolonged heating at 60°C in petrolether affords in 12% yield the corresponding furoxan. This fact, as well as the enhanced reactivity of *m*-chlorobenzonitrile oxide, would support the mechanism first suggested by HUISGEN[43] involving the intervention of the nitrosocarbonic form:



rather than that of a 1,3-dipolar cycloaddition:

Table I. Known (isolated) nitrile oxides

A) Aromatic members
Benzonitrile oxide[1,3]
4-Methyl-benzonitrile oxide[22]
2,6-Dimethyl-benzonitrile oxide[23]
2,4,6-Trimethyl-benzonitrile oxide[18,24]
2,3,5,6-Tetramethyl-benzonitrile oxide[18,24]
2-Chloro-benzonitrile oxide[22]
3-Chloro-benzonitrile oxide[22]
4-Chloro-benzonitrile oxide[9,22]
2,4-Dichloro-benzonitrile oxide[25]
2,6-Dichloro-benzonitrile oxide[7,18]
3,5-Dichloro-benzonitrile oxide[25]
3,5-Dichloro-2,4,6-trimethyl-benzonitrile oxide[26]
2,3,6-Trichloro-benzonitrile oxide[7]
4-Bromo-benzonitrile oxide[22,27]
2-Chloro-6-bromo-benzonitrile oxide[7]
2-Nitro-benzonitrile oxide[22]
3-Nitro-benzonitrile oxide[9,22]
4-Nitro-benzonitrile oxide[22,28]
4-Methoxy-benzonitrile oxide[29]
4-Methoxy-2,6-dimethyl-benzonitrile oxide[30]
2,4,6-Trimethoxy-benzonitrile oxide[18,24]
2-Methoxy-6-chloro-benzonitrile oxide[25]
4-Dimethylamino-2,6-dimethyl-benzonitrile oxide[30,31]
Isophtalic-*bis*-nitrile oxide[32]
2,4,6-Trimethyl-isophtalic-*bis*-nitrile oxide[19]
2-Chloro-isophtalic-*bis*-nitrile oxide[8]
4-Dimethylamino-2,6-dimethyl-isophtalic-*bis*-nitrile oxide[30]
Terephtalic-*bis*-nitrile oxide[8,33]
2-Methyl-terephtalic-*bis*-nitrile oxide[8]
2,3,5,6-Tetramethyl-terephtalic-*bis*-benzonitrile oxide[18,24]
Trimesic-*tris*-nitrile oxide[8]
1-Methoxy-naphtalene-2-nitrile oxide[19]
Anthracene-8-nitrile oxide[18]

B) Aliphatic and Hydroaromatic members
Acetonitrile oxide[34,35]
Trimethyl-acetonitrile oxide[22,34]
Diethyl-acetonitrile oxide[34]
Triphenyl-acetonitrile oxide[36]
Oxalo-*bis*-nitrile oxide[37,38]
Oximino-phenyl-acetonitrile oxide[39]
Oximino-*p*-tolyl-acetonitrile oxide[40]
Hexahydro-terephtalic-*bis*-nitrile oxide[8]
O-Methyl-podocarpionitrile oxide[20]

C) Heterocyclic members
3-Phenyl-5-methyl-isoxazole-4-nitrile oxide[3,22]
2,4,6-Trimethoxy-pyrimidino-5-nitrile oxide[30]
4,6-Dimethyl-2-dimethylamino-pyrimidino-5-nitrile oxide[30]

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[45] About the spectral properties of nitrile oxides see also: M. YAMAKAWA, T. KUBOTA and H. AKAZAWA, Bull. chem. Soc. Japan *40*, 1600 (1967). – T. KUBOTA, K. EZUMI, M. YAMAKAWA and Y. MATSUI, J. molec. Spectrosc. *24*, 378 (1967). – M. YAMAKAWA, T. KUBOTA, H. AKAZAWA and I. TANAKI, Bull. chem. Soc. Japan *41*, 1046 (1968).

[46] From the Monograph on Isoxazoles of the collection *The Chemistry of Heterocyclic Compounds* (Interscience Publishers, New York, London 1962), p. 21.

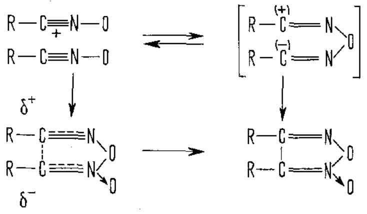
[47] C. GRUNDMANN, H. D. FROMMELD, K. FLORY and S. K. DATTA, J. org. Chem. *33*, 1464 (1968).

Table II. Stability of some nitrile oxides R–C≡N–O toward dimerization to furoxan

R	mp/°C	Approximative time for complete dimerization (at 18 °C)	mp of furoxan/°C	References
Phenyl	14–15	30–60 min	114–115	22
p-Tolyl	55–56	5–7 days	143–144	22
o-Chlorophenyl	27–28	3–6 days	130–131	22
m-Chlorophenyl	42–43	50–60 min	96–97	22
p-Chlorophenyl	82–83	10 days	144–145	22
p-Bromophenyl	83–84	not determined	164–165	22
2,6-Dichlorophenyl	86–87	30–35 days	199–200	22
o-Nitrophenyl	76–77 dec.	1–2 days	199–200	22
m-Nitrophenyl	82–83	20–25 days	183–186	22
p-Nitrophenyl	95	very slow	205–206	22
2,4,6-Trimethylphenyl	114	very stable	–	18,24
2,3,5,6-Tetramethylphenyl	120	very stable	–	18,24
Methyl	−5	< 1 min	106–107	34
tert-Butyl	13–16	2–3 days	67	22
Oxalo-*bis*-nitrile oxide	exploses	5–6 h	–	37,38
4-(3-Phenyl-5-methylisoxazolyl)	83	very stable	230	3,22

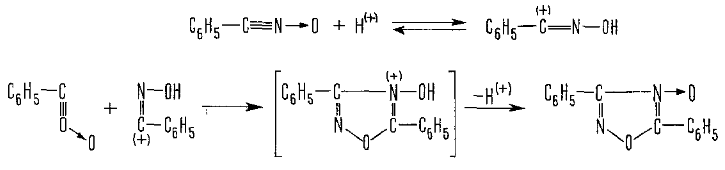
which would not respect the principle of the maximum gain in σ-bond energy.

However, recent measurement by DONDONI et al.[48] of the rates of dimerization to furoxan of *p*-methoxy- and *p*-chlorobenzonitrile oxide would lead to a reconsideration of the one step concerted mechanism as a possible alternative to the nitrosocarbenic mechanism or to that involving the formation of a zwitterionic intermediate:

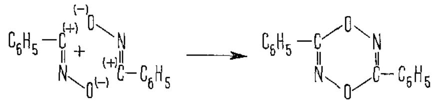


In acidic milieu benzonitrile oxide gives a second dimer, 3,5-diphenyl-1,2,4-oxadiazole-4-oxide, that WIELAND[49] had obtained by thermic decomposition of benzohydroxamic chloride, and that SPERONI[50] prepared by treatment of the nitrile oxide with dry HCl in benzene solution.

For this reaction experiments performed last year by RICCA et al.[51] would indicate as most probable a mechanism involving the addition of benzonitrile oxide to the C=N bond of the protonated nitrile oxide followed by elimination of H^+ from the intermediate product, as shown by formula:

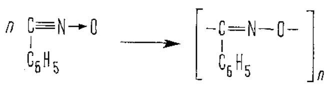


A third dimer, 3,5-diphenyl-2,5-dioxodiazine, was obtained by SPERONI[52] on heating the pyridin solution of benzonitrile oxide:



At low temperature in strongly basic milieu (15% NaOH), benzonitrile oxide yields a product which is insoluble in all solvents. The same substance had been obtained on treatment of benzonitrolic acid with cold soda solution by WIELAND[53] who assigned to the product the trimeric structure of triphenyltriazine-*tris*-N-oxide.

Actually it is a polymer of the possible structure indicate below:



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[48] G. BARBARO, A. BATTAGLIA and A. DONDONI, J. chem. Soc. (B), *1970*, 588.

[49] H. WIELAND, Chem. Ber. *40*, 1667 (1907).

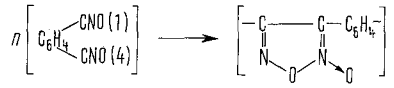
[50] Unpublished data.

[51] S. MORROCCHI, A. RICCA, A. SELVA and A. ZANAROTTI, Gazz. chim. ital. *99*, 165 (1969).

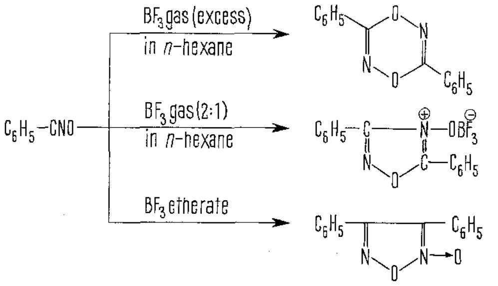
[52] Reported by G. SPERONI at the 14th Int. Congress of Chemistry, Zurich 1955 (Birkhäuser Verlag, Basel), Nr. 52, p. 30.

[53] H. WIELAND, Chem. Ber. *42*, 803, 806 (1909).

Dinitrile *bis*-oxides such as oxalic and terephtalic nitrile oxides yield on polymerization at low temperature substances which can be considered as polyfuroxans[54]:



Quite recently (1969) RICCA et al.[51] have found that boron trifluoride catalyzes nitrile oxides dimerization through the intermediate formation of complexes of type $R-\overset{(+)}{C}=N-O\overset{(-)}{B}F_3$. Depending on the conditions, one or other of the 3 dimers is formed, as shown in formmula[1].



Scheme 1. BF_3 catalyzed dimerization of nitrile oxides.

The first is formed by reaction of 2 moles of the complex, the second by addition of a molecule of the complex to one of the free nitrile oxide; when ether is the solvent, the strong complexing power of ether toward BF_3 prevents the formation of the complex nitrile oxide-BF_3 and furoxan is obtained. With mesityl nitrile oxide, which is very stable to dimerization to furoxan, only (I) and (II) are formed.

2. *Nucleophilic additions of nitrile oxides.* Nitrile oxides possess a typical electrophilic reactivity that manifests itself in a variety of additions to nucleophilic reagents. In some instances these reactions are competitive with the 1,3-dipolar cycloaddition as discussed later. The products thus obtained are shown in Table III. For all these reactions the probable mechanism is a nucleophilic attack of the reagent on the carbon atom of the nitrile oxide function.

3. *Addition reactions of nitrile oxides to the double and triple bonds of unsaturated systems.* These are the most important and characteristic reactions of nitrile oxides. From the practical point of view they provide valuable general methods for the synthesis of a number of five-membered heterocycles containing the –C=N–O– goupment. Under the theoretical aspect, the interpretation of their mechanism, notwithstanding the far-reaching researches of HUISGEN[66] and his school on 1,3-dipolar cycloadditions, still offers material for further speculation and investigation.

Table III. Nucleophilic additions of nitrile oxides

RCNO	OH^-	$R-\underset{\underset{NOH}{\|}}{C}-OH$	Hydroxamic acids[55]
	X^- X=Cl, Br, I	$R-\underset{\underset{NOH}{\|}}{C}-X$	Hydroxamic halides[18,55,56]
	CN^-	$R-\underset{\underset{NOH}{\|}}{C}-CN$	Hydroxamic cyanides[55]
	$AlkO^-$, ArO^-	$R-\underset{\underset{NOH}{\|}}{C}-OAlk(Ar)$	Hydroxamic *O*-esters[55,57]
	HS^-	$R-\underset{\underset{NOH}{\|}}{C}-SH$	Thiohydroxamic acids[55]
	NH_3	$R-\underset{\underset{NOH}{\|}}{C}-NH_2$	Amidoximes[55]
	$R'NH_2$	$R-\underset{\underset{NOH}{\|}}{C}-NHR'$	Amidoximes[18,39,55]
	$R'R''NH$	$R-\underset{\underset{NOH}{\|}}{C}-NR'R''$	Amidoximes[55,57,34]
	$'ArNHNH_2$	$R-\underset{\underset{NOH}{\|}}{C}-NHNHAr$	Hydrazidoximes[55]
	$R'MgX$	$R-\underset{\underset{NOH}{\|}}{C}-R'$	Ketoximes[2]
	$R'SH$	$R-\underset{\underset{NOH}{\|}}{C}-SR'$	Thiohydroxamic S-esters[34,55,58]
	$R'COOH$	$R-\underset{\underset{NOCOR'}{\|}}{C}-OH$	Acylhydroxamic acids[55,59–61]
	$R'COCl$	$R-\underset{\underset{NOCOR'}{\|}}{C}-Cl$	Acylchloroximes[62]
	$R'SO_2Cl$	$R-\underset{\underset{NOSO_2R'}{\|}}{C}-Cl$	Chloroxime sulphonic esters[62–64]

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[54] C. GRUNDMANN, in *Houben-Weyl, Methoden der organischen Chemie* (G. Thieme Verlag, Stuttgart 1965), vol. 10/3, p. 857.

[55] C. GRUNDMANN and H. D. FROMMELD, J. org. Chem. *31*, 157 (1966).

[56] P. SOUCHAY and J. ARMAND, C. r. Acad. Sci., Paris *265*, 4907 (1963).

[57] N. E. ALEXANDROU and D. N. NIKOLAIDES, Hem. Hron. *30*, 49 (1965); Chem. Abstr. *1965*, 13126 *d*.

[58] M. H. BENN, Can. J. Chem. *42*, 2393 (1964).

[59] N. E. ALEXANDROU and D. N. NIKOLAIDES, Tetrahedron Lett. *1966*, 2947.

[60] A. QUILICO and P. GRÜNANGER, Gazz. chim. ital. *85*, 1451 (1955).

[61] A. QUILICO, D. GRÜNANGER and C. GANDINI, Rc. Ist. lomb. Sci. Lett. *93*, 467 (1959).

[62] P. RAJAGOPALAN and C. N. TALATY, Tetrahedron Lett. *1966*, 2101.

[63] J. F. KING and T. DURST, Can. J. Chem. *44*, 409 (1966).

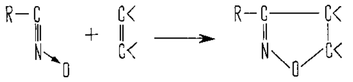
[64] F. ELOY and A. VAN OVERSTRAETEN, Bull. Soc. chim. Belges *76*, 63 (1967).

[65] A. QUILICO, G. STAGNO D'ALCONTRES and P. GRÜNANGER, Gazz. chim. ital. *80*, 480 (1950). – A. QUILICO and P. GRÜNANGER, Gazz. chim. ital. *82*, 140 (1952). – A. QUILICO, P. GRÜNANGER and R. MAZZINI, Gazz. chim. ital. *82*, 349 (1952). – A. QUILICO and P. GRÜNANGER, Gazz. chim. ital. *85*, 1250, 1449 (1955). – N. BARBULESCU and A. QUILICO, Gazz. chim. ital. *91*, 326 (1961). – N. BARBULESCU, P. GRÜNANGER, M. R. LANGELLA and A. QUILICO, Tetrahedron Lett. *1961*, 89.

[66] R. HUISGEN, Angew. Chem. *75*, 613 (1963).

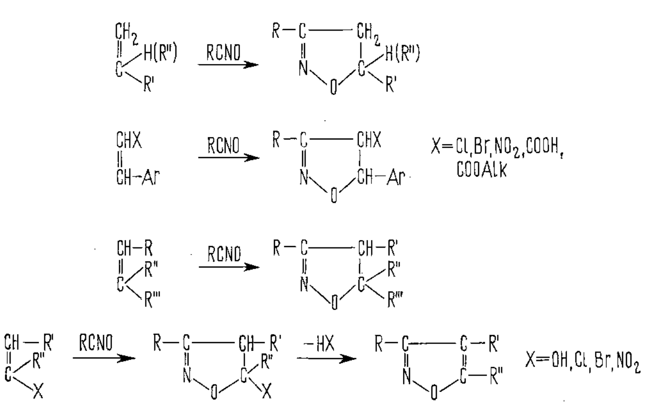
A) *Addition to the ethylenic double bonds and to the enolic forms of β-dicarbonylic compounds*

In 1950, starting from the structural similarity with aliphatic diazocompounds and azides, we found that nitrile oxides add easily to the carbon-carbon double bonds giving 2-isoxazolines[4]:



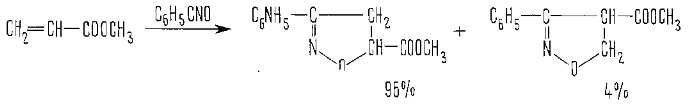
This reaction has a general character and more than 300 compounds containing the C=C double bond have been tested with positive results[65]. Usually it is sufficient to leave at room temperature the ether solution of the nitrile oxide and ethylenic derivative to get the isoxazoline in yields which are generally good. As expected, the reactivity of the double bond changes considerably with the nature of the substituents, which affects the double bond character of the C=C linkage, and is sensitive to steric factors. Less marked is the effect of the substituents of the nitrile oxide. In the case of poorly reactive double bonds, because of the competitive dimerization reaction to furoxan of the nitrile oxides, the result can be negative. This difficulty can be overcome, as suggested by Huisgen[66], by keeping low the concentration of the nitrile oxide generated in situ by adding gradually the Et_3N to the solution of the hydroxamic chloride and the alkene. Also the use of stable nitrile oxides is advisable in these cases[67]. With these expedients adducts have been obtained with olefins such as cyclohexene, cyclooctatetraene, tetramethylethylene[67], furane[68] etc. formerly given as inactive.

About the orientation of the addition, for unsymmetrical substituted olefins generally only 1 of the 2 possible adducts is formed. The rules experimentally derived from a large number of cases, are summarized in formula:



Thus for α-olefins derivatives, $CH_2{=}CH{-}R'$ and $CH_2{=}CR'R''$ the 5-substituted isoxazoline is always formed. For olefins of type $R'CH{=}CH{-}R''$, the formation of one or the other of the 2 possible isomers depends on the nature of R′ and R″. As a rule, the most electronegative group enters the 4-position. Thus $Ar{-}CH{=}CH{-}X$ with X = Cl, Br, NO_2, COOH, $COOC_2H_5$ give exclusively isoxazolines containing X in position 4. For *tris*-substituted ethylenic derivatives, the addition direction is that shown above; when R″ is Cl, Br, NO or OH, as in the enolic form of β-dicarbonylic compounds, instead of the expected isoxazolines the corresponding isoxazoles are formed, owing the elimination of R″H. The experimental results would indicate a strong prevalence of steric factors on electronic effects.

Recent experiments reported by Huisgen[69] (1968) have shown that the rule of the unique direction of the addition is not always respected. Thus the addition of benzonitrile oxide to methyl acrylate gives, besides the strongly prevalent 3-phenyl-5-carbomethoxy-2-isoxazoline, a small amount of the 4-carbomethoxy isomer:



The relative kinetic constants of the 2 reactions are 27 and 1,1, respectively.

The interpretation of the experimental results concerning the orientation in the addition of nitrile oxides to ethylenic dipolarophiles, poses a problem that is far from being solved, as confirmed by the recent discussion (1968) between Huisgen[69] and Firestone[70], who opposes Huisgen's theory of the concerted 1,3-dipolar cyclotoaddition, a mechanism involving a spin paired diradical intermediate. The fact that benzonitrile oxide combines with all monosubstituted ethylens in the same direction whether the substituent be alkyl or aryl, electronrelasing or electronattracting is not easy to explain, unless by admitting the intervention of the form $C_6H_5{-}\overset{(+)}{C}{=}N{-}\overset{(-)}{O}{}^-$ in one case, of form $C_6H_5{-}\overset{(+)}{C}{=}N{-}\overset{(-)}{O}$ in the other.

Huisgen contests this argument as meaningless to assign an electrophilic and a nucleophilic end to a 1,3-dipole, while is significant to attribute a certain electron density to the incipient σ-bonds in the transition state. According to Huisgen a predominant influence in determining the direction of the addition have steric factors. On this point it is worth mentioning that, in the case of cinnamic esters, the orientation of the addition with benzonitrile oxide is influenced by the configuration of the ester. While the *trans* ester

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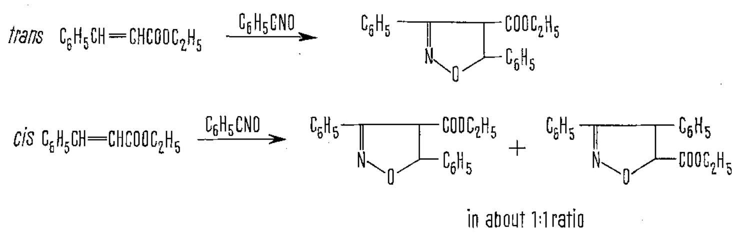
[67] C. Grundmann, Monograph in *Houben-Weyl, Methoden der organischen Chemie* (G. Thieme Verlag, Stuttgart 1965), vol. 10/3, p. 861.

[68] A. Corsico Coda, P. Grünanger and G. Veronesi, Tetrahedron Lett. *1966*, 2911.

[69] R. Huisgen, J. org. Chem. *33*, 2291 (1968).

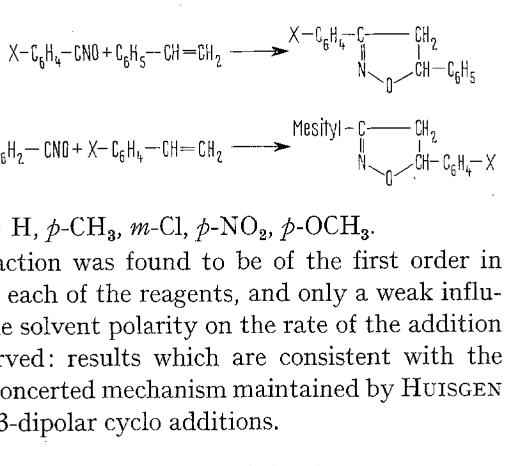
[70] R. A. Firestone, J. org. Chem. *33*, 2285 (1968).

gives the isoxazoline containing the carbothoxy group in position 4, the *cis* ester yields a mixture about 1:1 of the 4 and 5-carbothoxy derivatives[71], as shown in the Formula.



An important feature of the addition of nitrile oxides on ethylenic double bonds is its stereospecificity. As we found as early as 1950, *cis* and *trans* isomers give 2 different isoxazolines which are diastereoisomers. Thus maleic and fumaric esters yield 2 different 3-phenylisoxazoline-4,5-dicarboxylic esters[72] and in the same way behave citraconic and mesaconic esters[73], *cis* and *trans* cinnamic esters[61], *cis* and *trans* stilbenes[61]. There is no doubt that this characteristic of the reaction is perhaps the strongest argument in favour of the one step concerted cycloaddition theory.

Before closing this section, I want to mention that a kinetics study was performed 2 years ago of the reaction of aromatic nitrile oxides with styrenes[74]. The cases examined are reported below:

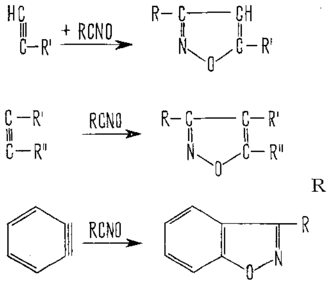


with X = H, p-CH_3, m-Cl, p-NO_2, p-OCH_3.

The reaction was found to be of the first order in respect of each of the reagents, and only a weak influence of the solvent polarity on the rate of the addition was observed: results which are consistent with the one step concerted mechanism maintained by HUISGEN for the 1,3-dipolar cyclo additions.

B) *Addition to the acetylenic triple bond*

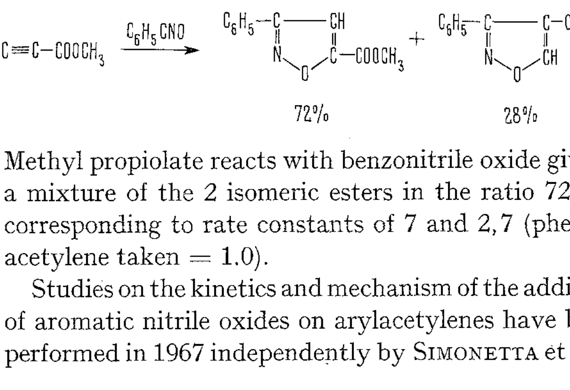
This reaction, first reported by us in 1939 for fulminic acid[75] and in 1946 for benzonitrile oxide[3], leads to isoxazoles:



R′, R″ = H, Alkyl, Ar, CH_2OH CH_3 al, CH_2NH_2, COOH, COOAlk, C=CH, C=CAlk OAlk etc.

Fulminic acid in the proper conditions reacts with acetylene giving the fundamental member of the series[76]. Among the acetylene derivatives, monosubstituted acetylenes react in a general way and the addition yields preferentially 5-substituted isoxazoles. For disubstituted acetylenes addition occurs only when at least one of R′, R″ is electron-attracting, such as COOH or COOAlk. Thus butynediol, tolan, methylphenylacetylene do not react. However, benzyne readily adds benzonitrile oxide giving 3-phenylbenzoisoxazole[77]. As anticipated for the reaction with ethylenic compounds, the result can be negative for poorly reactive triple bonds and unstable nitrile oxides because the competitive dimerization of the latter to furoxans can prevent the formation of the adduct. According to our early experiments, the reaction is strongly catalyzed by alkaline hydroxydes[3].

As to the orientation mentioned above, the substituents are found in the 5-position independently from its character of electron-attracting or electron-releasing group. However, examples are known in which both the isomers are formed[78]:



Methyl propiolate reacts with benzonitrile oxide giving a mixture of the 2 isomeric esters in the ratio 72:28, corresponding to rate constants of 7 and 2,7 (phenylacetylene taken = 1.0).

Studies on the kinetics and mechanism of the addition of aromatic nitrile oxides on arylacetylenes have been performed in 1967 independently by SIMONETTA et al.[26]

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[71] M. ARBASINO and P. VITA-FINZI, Ricerca scient. *36*, 1339 (1966); Chem. Abstr. *1967*, 100041 *r*.

[72] A. QUILICO, G. STAGNO D'ALCONTRES and P. GRÜNANGER, Gazz. chim. ital. *80*, 479 (1950). – A. QUILICO and P. GRÜNANGER, Gazz. chim. ital. *85*, 1250, 1449 (1955).

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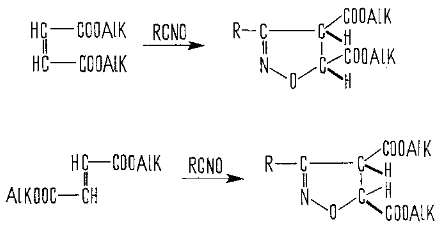
[75] A. QUILICO and G. SPERONI, Gazz. chim. ital. *69*, 508 (1939).

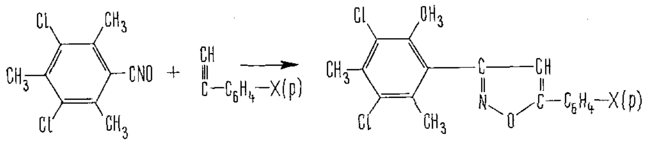
[76] A. QUILICO and G. STAGNO D'ALCONTRES, Gazz. chim. ital. *79*, 703 (1949).

[77] F. MINISCI and A. QUILICO, Chimica Ind. *46*, 428 (1964).

[78] R. SUSTMANN, reported by HUISGEN in J. org. Chem. *33*, 2296 (1968).

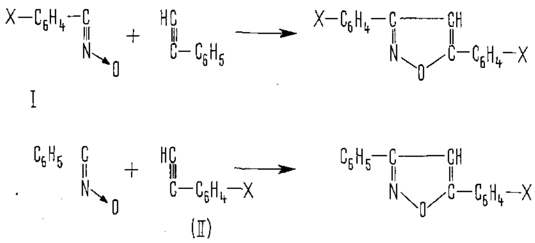
and DONDONI[29]. The formers used a strongly hindered nitrile oxide (3,5-dichloro-2,4,6-trimethylbenzonitrile oxide) and a number of *p*-substituted phenylacetylenes:




$X = H, Cl, Br, NO_2, CH_3, OCH_3, N(CH_3)_2$

The reaction was carried out in $CHCl_3$ or CCl_4 at temperatures ranging between 25° and 45 °C, and its progress was followed by IR-analysis on the basis of the 3300 cm^{-1} and 2294 cm^{-1} bands typical for $C{\equiv}CH$ and $C{\equiv}N \rightarrow O$. Rate constants were found to be correlated by a V-shaped Hammett plot, and only a small dependence of the rates from the nature of the solvent was observed. Moreover it was shown by model studies that the diarylisoxazoles produced in the reaction would be sterically hindered if they were 3,4-instead of 3,5-derivatives, a further confirmation of the predominance of steric influences on the orientation of the addition.

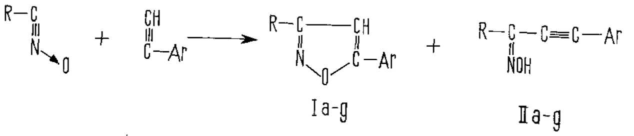
DONDONI studied in a similar way the reactions:


$X = H, m\text{-}Cl, p\text{-}Cl, p\text{-}CH_3, p\text{-}OCH_3$

$X = H, p\text{-}Cl, p\text{-}CH_3, p\text{-}NO_2, p\text{-}OCH_3$

Kinetics studies carried on at 25° in CCl_4 indicated that the reaction follows a kinetics of the second order. Rates are influenced by the nature of X in (I) in the order *m*-Cl > *p*-Cl > H > *p*-CH_3 > *p*-OCH_3 whereas for (II) the order is: *p*-NO_2 > *p*-Cl > H < *p*-CH_3 < *p*-OCH_3. The V-effect of the substituents in (II) and the low activation energies are in agreement with a mechanism of concerted 1,3-dipolar cycloaddition: however the positive value of the Hammett constant for the substituents of (I) suggests a predominant electrophilic character for the nitrile oxide.

New experimental facts resulting from a more accurate study of the products formed in this reaction, require a re-examination of the whole problem. It has been found that in all the cases reported in Formula 4, beside the expected isoxazoles (I), the isomeric acetylenic oximes (II) were present in the reaction product[79]:

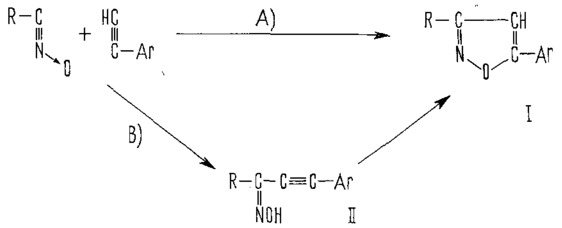


a)	R	CH_3	Ar	C_6H_5
b)	R	C_2H_5	Ar	C_6H_5
c)	R	C_6H_5	Ar	C_6H_5
d)	R	Mesityl		C_6H_5
e)	R	C_6H_5	Ar	α-Naphtyl
f)	R	$pBrC_6H_4$	Ar	α-Naphtyl
g)	R	C_6H_5	Ar	Mesityl

Oximes II always found; yields in isolated (II) g) 24%, e) 18%, f) 13%

All the oximes II a–g have been isolated, some of them in consistent yield, that for II g reaches 24% and is of 18% and 13% respectively for II e and II f. The study of the configuration of one of them (II e) has shown the configuration to be *syn* in respect to the triple bond.

Taking into account the easy cyclization to isoxazoles of acetylenic oximes, the question arises whether isoxazoles are formed directly by a concerted 1,3-dipolar cycloaddition, or through a 2 steps mechanism involving the acetylenic oximes as intermediates:



In order to ascertain the role of the acetylenic oximes in the isoxazole synthesis from nitrile oxides and acetylenes, BATTAGLIA and DONDONI[80] re-examined the reaction *p*-chlorobenzonitrile oxide + phenylacetilene (in tenfold excess). Beside the isoxazole (80% yield) the oxime was found in 16% yield. Kinetics measurements showed that during the progress of the reaction the molar ratio I_s/O_x is fairly constant and that, at least in neutral medium, the isomerization of the acetylenic oxime to isoxazole is consistently slower than the formation of both isomers (I) and (II). The conclusion is that 2 competitive processes take place but that in the specific case examined, the formation of the isoxazole via oxime is negligeable in comparison with the direct formation. In any case, the authors admit that their results cannot be generalized.

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[79] S. MORROCCHI, A. RICCA, A. ZANAROTTI, G. BIANCHI, R. GANDOLFI and P. GRÜNANGER, Tetrahedron Lett. *1969*, 3329.

[80] A. BATTAGLIA and A. DONDONI, Tetrahedron Lett. *1970*, 1221.

A different approach to the study of this reaction has been tested this year by RICCA et al.[81]. By the use of the isotopic exchange with deuterium of the oximic hydrogen, they have determined, for a number of nitrile oxides and acetylenic derivatives, the extent of the two competitive processes which lead to isoxazoles and acetylenic oximes. For this purpose, nitrile oxides and acetylenes (mol. ratio 1:2) were allowed to react at ordinary temperature in tetrahydrofurane solution in the presence of D_2O till the complete disappearance of the nitrile oxide. NaDO was then added to complete the cyclization of the oxime, and the ratio 4-D-isoxazole/4-H-isoxazole in the mixture was estimated by M.S.

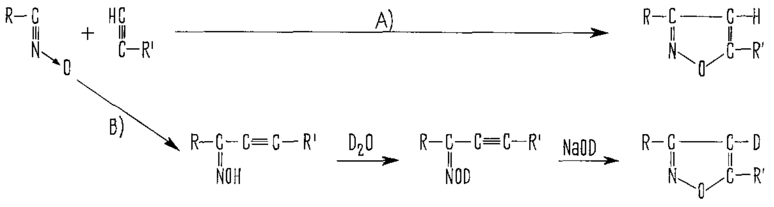
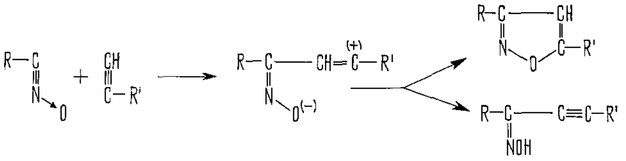


Table IV. % of 4-deuteroisoxazole in the mixture (I) + (II)

R	CH_3		C_2H_5		$(CH_3)_3C$		C_6H_5	
R'	CH_2Br	0	CH_2Br	0	C_6H_5	9	$COOCH_3$	0
	n-C_4H_9	5	n-C_4H_9	4			p-ClC_6H_4	7
	C_6H_5	23	C_6H_5	36			C_6H_5	12
	p-$(CH_3)_2NC_6H_4$	83					α-Naphtyl	19
R	p-$NO_2C_6H_4$		Mesityl		2,4,6-Trimethyl-3,5-dichlorophenyl		2,4,6-Trimethoxyphenyl	
R'	C_6H_5	18	n-C_4H_9	0	p-$(CH_3)_2NC_6H_4$	67	p-ClC_6H_4	2
	p-$(CH_3)_2NC_6H_4$	74	p-ClC_6H_4	4			C_6H_5	3,5
			C_6H_5	6				
			p-$(CH_3)_2NC_6H_4$	45				

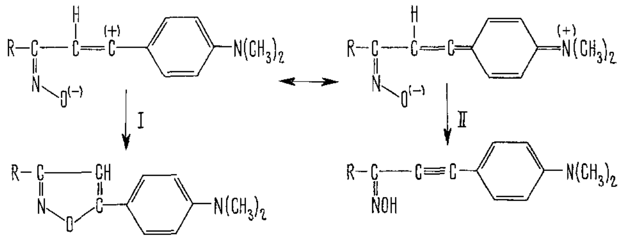
From Table IV it appears that in most cases both processes take place to an extent which is strongly influenced by the nature of R and R'. Whereas in some cases direct cycloaddition is complete or prevalent, in other cases this reaction plays a secondary role, and the main reaction is the formation of the oxime.

Further investigations will be necessary for a complete understanding of this reaction (for instance, a study of the kinetics of the cyclization to isoxazoles of the different acetylenic oximes at different pH and the interpretation of the role of alkaline catalysis), but it is certain that nitrile oxides and acetylenes can react also following a mechanism which is different from that of the concerted 1,3-dipolar cyclo addition postulated by HUISGEN, in agreement with the enhanced electrophilic character that nitrile oxides exhibit in a number of reactions. The new experimental facts now reported would prompt the reconsideration, as an alternative to the one step mechanism, of a two steps mechanism involving the intervention of a zwitterionic intermediate from which both the isoxazole and the acetylenic oxime could be formed:



Obviously, for disubstituted acetylenes, only the isoxazole is obtained.

This scheme would account for the strong influence of the substituent R' in the acetylenic derivative on the ratio isoxazole/oxime in the reaction product. Thus, in the case of p-dimethylaminophenylacetylene, which always gives the oxime in high yield, the strong contribution of form (II) to the resonance hybrid of the zwitterionic intermediate should favorize the formation of the oxime rather than that of the isoxazole[82]:



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[81] S. MORROCCHI, A. RICCA, A. SELVA and A. ZANAROTTI, Atti. Accad naz. Lincei (1970), in print.

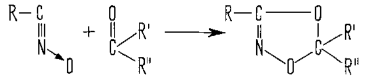
[82] A. RICCA, private communication.

The constancy of the molar ratio isoxazole/oxime during the progress of the addition observed for the reaction p-chlorobenzonitrile oxide + phenylacetylene[80] would also support the zwitterionic mechanism.

Researches in progress have demonstrated that the same is true also for the addition to acetylenes of other 1,3-dipoles closely similar to nitrile oxides. Thus, in the case of nitrilimines $R-\overset{(+)}{C}=N-\overset{(-)}{N}-R'$, acetylenic hydrazones are formed beside pyrazoles[83]. In this kind of researches particular care has to be taken in the treatment used for the isolation of the reaction products, because cyclization of open chain isomers may occur.

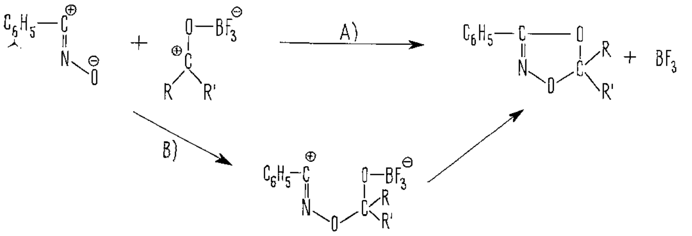
C) *Other cycloaddition reactions of nitrile oxides*

A number of addition reactions of nitrile oxides to multiple bonds such as C=O, C=S, C=N and C≡N are known, all giving five membered heterocycles. Huisgen et al. found in 1961[84] that carbonylic compounds such as aldehydes, ketones, α-diketones, α-ketoesters, sum up nitrile oxides yielding 1,3,4-dioxazoles:



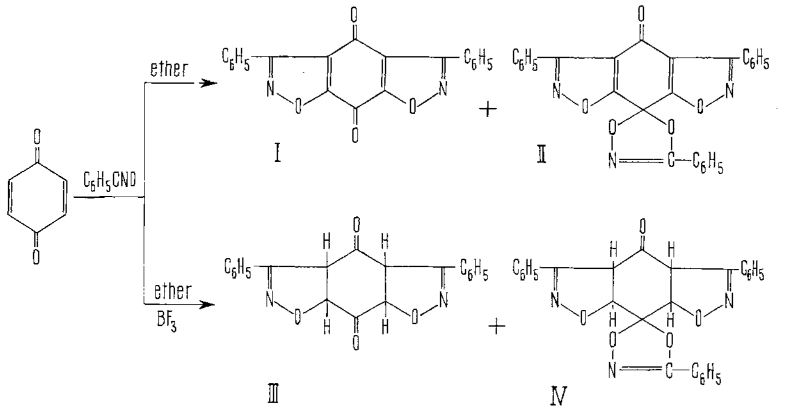
Reaction occurs only when the carbonyl group is activated: thus aliphatic aldehydes and ketones, and arylalkylketones such as acetophenone do not react. Recently Ricca et al.[85] succeeded in enlarging the range of application of this reaction by increasing the dipolarophilic character of carbonylic compounds through complexation with BF_3. As shown in Table V, at —50 °C, in the presence of BF_3, the reaction can be carried out with aliphatic aldehydes, acetone and other alkylketones, acetophenone and cyclohexanone:

The mechanism could be either a concerted 1,3-dipolar cycloaddition or a nucleophilic attack on the carbon atom of the complexated carbonyl:

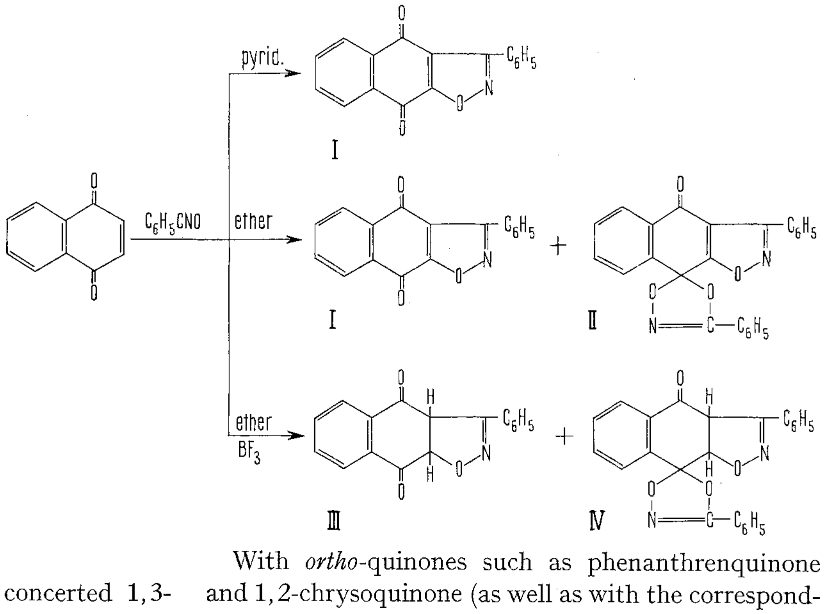


The addition to β-dicarbonylic componds reported in 1946 by Quilico and Speroni[3], concerns the double bond of the enolic form and leads to isoxazoles by elimination of water from the 5-hydroxyisoxazoline first formed.

Among carbonylic compounds, quinones deserve particular mention. Benzoquinone adds benzonitrile oxide on the C=C and C=O bonds giving diisoxazolo-benzoquinone (I) and the diisoxazolo-spiro-dioxazole (II) formed by spontaneous oxidation of the corresponding isoxazolinic adducts (III) and (IV)[86,87]. These last can be isolated in substantial yield when the reaction is carried out in the presence of boron trifluoride:



Similar results were obtained with α-naphtoquinone which gives adducts with 1 and 2 molecules of benzonitrile oxide, as shown in schema:



With *ortho*-quinones such as phenanthrenquinone and 1,2-chrysoquinone (as well as with the corresponding quinone-monoimines) the addition takes place on one of the carbonyls (or on the C=NH of the imine) giving spiro-dioxazoles (respectively spiro-oxadiazo-

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[83] S. Morrocchi, A. Ricca and A. Zanarotti, Tetrahedron Lett., in print.

[84] R. Huisgen and W. Mack, Tetrahedron Lett. *1961*, 583; Angew. Chem. *75*, 614 (1963).

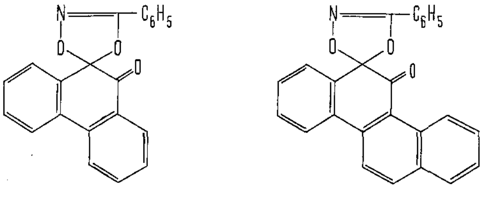
[85] S. Morrocchi, A. Ricca and L. Velo, Tetrahedron Lett. *1967*, 331.

[86] A. Quilico and G. Stagno d'Alcontres, Gazz. chim. ital. *80*, 140 (1950).

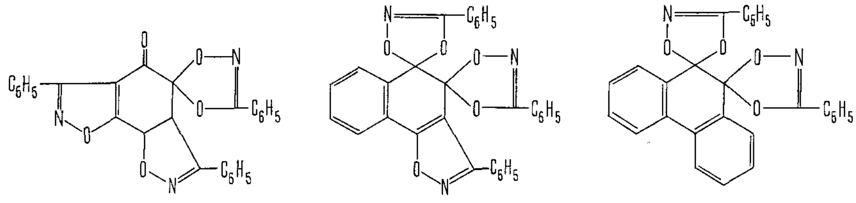
[87] S. Morrocchi, A. Quilico, A. Ricca and A. Selva, Gazz. chim. ital. *98*, 891 (1968).

les)[88]. *Ortho*-benzoquinone gives an adduct with 3 molecules of benzonitrile oxide, *o*-naphtoquinone and phenanthrenquinone in the proper conditions yield adducts respectively with 3 and 2 molecules of nitrile oxide, in which all the available C=C and C=O bonds have reacted[89]:

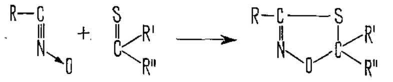
Adducts with phenanthrenquinone and 1,2-chrysoquinone



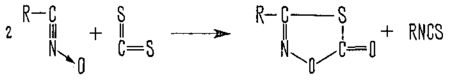
Adducts with *o*-benzoquinone, *o*-naphtoquinone and phenanthrenquinone



Cycloadditions on the C=S bond of thioketones, thiocarboxylic esters, thio, dithio- and trithiocarbonic esters leading to 1,4,2-oxathiazoles have been reported by HUISGEN[90]:

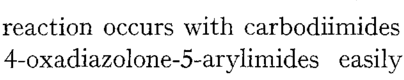


Carbon disulphide also reacts with stable nitrile oxides giving 1,4,2-oxathiazolin-5-ones[91]:

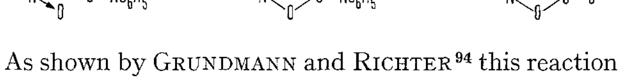


Addition to double and triple carbon-nitrogen bonds

The double bond of Schiff's bases reacts with nitrile oxides giving 4,5-dihydro-1,2,4-oxadiazolines[92,93,84]:



The same reaction occurs with carbodiimides[93] which yield 1,2,4-oxadiazolone-5-arylimides easily hydrolyzed by acids to 1,2,4-oxadiazolones-5:



As shown by GRUNDMANN and RICHTER[94] this reaction when catalyzed by BF_3 leads to spiro-oxadiazoles by addition of 2 molecules of nitrile oxide.

Conjugated aldoimines such as the Schiff's bases of cinnamic aldehyde react in the C=N double bond instead with –CH=CH– giving 4,5-dihydro-1,2,4-oxadiazolines[95]. A wider interest is offered by the cycloaddition of nitrile oxides to the carbon-nitrogen triple bond of nitriles. This reaction, first reported in 1957 by LEANDRI[96] for aromatic nitriles, gives 1,2,4-oxadiazoles:

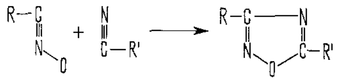
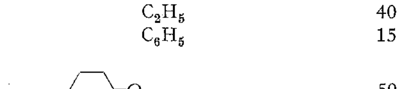
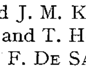


Table V. BF_3 catalyzed addition on carbonylic compounds



R	R′	Yield in 1,3,4-dioxazole
CH_3	H	40
n-C_3H_7	H	25
CH_3	CH_3	49
CH_2Cl	CH_2Cl	28
CH_3	C_2H_5	40
CH_3	C_6H_5	15
		50

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[88] W. I. AWAD, J. M. ABDEL, R. OMRAN and M. SOBHY, J. org. Chem. *31*, 331 (1966).

[89] S. MORROCCHI, A. RICCA, A. SELVA and A. ZANAROTTI, Gazz. chim. ital. *99*, 565 (1969).

[90] R. HUISGEN, W. MACK and E. ANNESER, Angew. Chem. *73*, 656 (1961).

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[92] T. MUKAIYAMA and T. HOSHINO, Am. chem. Soc. *82*, 5339 (1960).

[93] L. FABRINI and F. DE SARLO, Chimica Ind. *45*, 242 (1963).

[94] C. GRUNDMANN and R. RICHTER, Tetrahedron Lett. *1968*, 963.

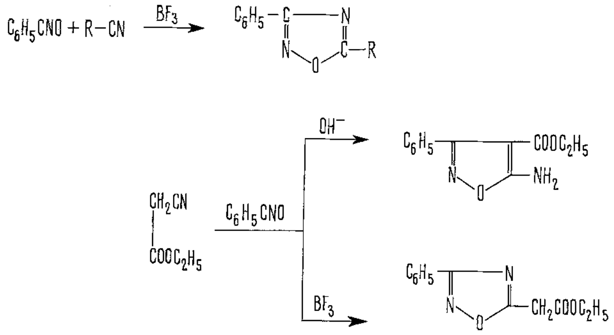
[95] N. SINGH, J. S. SANDHU and S. MOHAN, Tetrahedron Lett. *1968*, 4453.

[96] G. LEANDRI and M. PALOTTI, Annuar. Chim. scient. ind. *47*, 376 (1957).

Successively HUISGEN et al.[97] found that aliphatic nitriles react only when activated by electronattracting substituents, as confirmed in a number of cases by FLOY[98] who employed aliphatic nitrile oxides (mostly CH_3CNO) generated in situ from RCH_2NO_2 and isocyanates. This reaction is given also by the CN group of α-ketonitriles[99] and tosylcyanides[100].

RICCA et al.[85] reported in 1967 that in the presence of BF_3 react also unsubstituted aliphatic nitriles such as aceto-, propio- and butyronitrile, which afford in 35–40% yield the expected 1,2,4-oxadiazoles, as shown in Table VI.

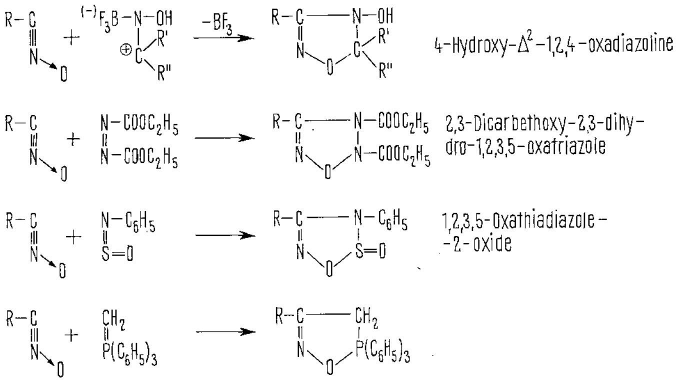
Table VI. BF_3 catalyzed addition to aliphatic nitriles



R	Yield % 1-2-4-oxadiazole
CH_3	35
C_2H_5	40
n-C_3H_7	40
$CH_2COOC_2H_5$	14

Cyanacetic ester which in alkaline milieu gives 3-phenyl-carbethoxy-5-aminoisoxazole[3], in the presence of BF_3 reacts in the CN group. This reaction has been extended to the CN group of cyanoguanidine of the type R′R″N–C(NH)–NHCN[101].

A group of cycloadditions in which are involved other types of double bonds are summarized in the following scheme:

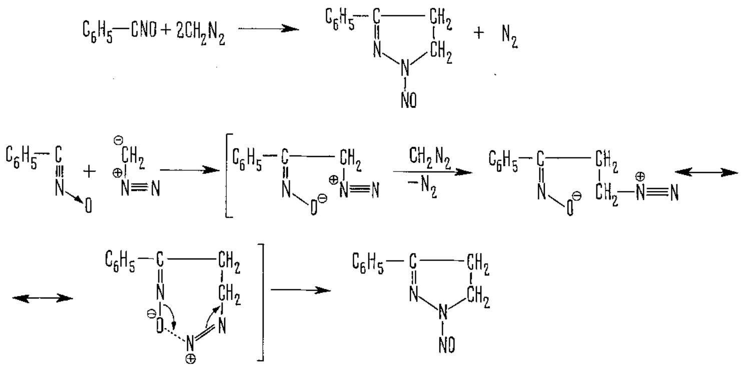


By using BF_3, it was possible to react the scantily reactive carbon-nitrogen double bond of the oximes, with formation of 4-hydroxy-1,2,4-oxadiazolines[102]. Most likely the reaction involves the intervention of an activate oxime-BF_3 complex, as shown above. The hydroxyoxadiazolines derived from aldehydes are easily dehydrated to the corresponding 1,2,4-oxadiazoles. As an example of cycloaddition on nitrogen-nitrogen double bonds we can mention the addition of benzonitrile oxide on azodicarboxylic ester, which leads to 2,3-dicarbethoxy-2,3-dihydro-1,2,3,5-oxatriazoles[103]. Thionylamines Ar–N=SO also react with benzonitrile oxide giving 1,2,3,5-oxathiadiazole-2-oxides[104]. A cycloaddition reaction that affords a phosphorus-containing ring has been reported by HUISGEN and WULFF[105].

Reaction of nitrile oxides with diazomethane and ylides

Among the nucleophilic additions, which lead to the formation of heterocyclic systems through more sophisticated mechanisms, we must mention the reactions of nitrile oxides with diazomethane and the ylides of sulfur and arsenic.

Diazomethane and benzonitrile oxide react in ether at room temperature with nitrogen evolution, giving 1-nitroso-3-phenyl-2-pyrazoline[106]. In the process two molecules of diazoalkane are involved. A possible mechanism is shown in scheme:



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[97] R. HUISGEN, W. MACK and E. ANNESER, Tetrahedron Lett. *1961*, 587.

[98] F. FLOY, Bull. Soc. chim. Belge *73*, 793 (1964).

[99] P. GRÜNANGER and P. VITA-FINZI, Atti. Accad. naz. Lincei *31*, 277 (1961).

[100] A. M. VAN LENSEN and J. C. JAGT, Tetrahedron Lett. *1970*, 971.

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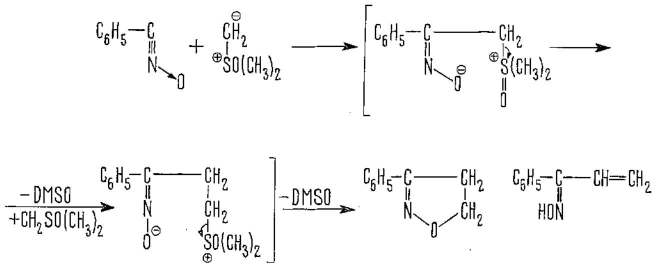
[104] P. RAJAGOPALAN and H. U. DAENIKER, Angew. Chem. *75*, 91 (1963). – P. RAJAGOPALAN and B. G. ADVANI, J. org. Chem. *30*, 3369 (1965).

[105] R. HUISGEN and J. WULFF, Tetrahedron Lett. *1967*, 917, 921. – H. J. BESTMANN and R. KUNSTMANN, Angew. Chem. Int. Ed. *5*, 1039 (1966).

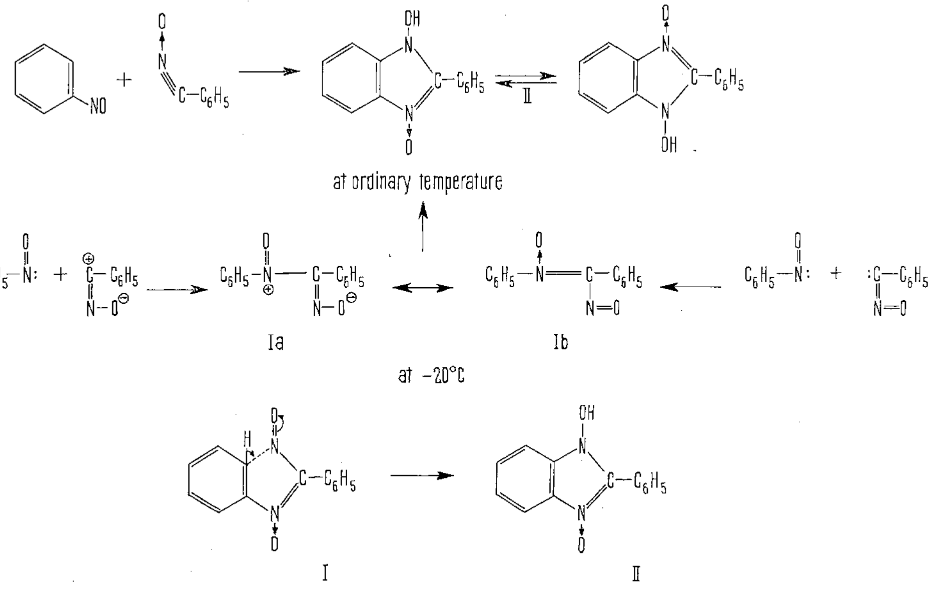
[106] G. LO VECCHIO, M. CRISAFULLI and M. C. AVERSA, Tetrahedron Lett. *1966*, 1909.

A behaviour similar in some respects is exibited by dimethyloxosulphonium methylide, a reagent of well known nucleophilic activity. On treatment with benzonitrile oxide in dimethylsulfoxide solution it gives in low yield (10%) 3-phenyl-2-isoxazoline besides other products of which the most abundant (30%) is phenylvinylketone syn-oxime[107]. As in the case of diazomethane, 2 molecules of ylide take part to the reaction:



A still more complicated course is shown by the reaction of benzonitrile oxide with triphenylarsonium methylide[108]. A mixture of several products is formed, among them the syn- and anti-oximes of 3-phenyl-4-benzoyl-2-isoxazoline, whose formation can be explained by admitting an alternate attack by the nitrile oxide and the ylide on the intermediate formed by addition of 1 molecule of nitrile oxide to 1 of ylide.

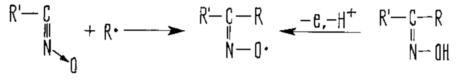
A peculiar character is seen in the reaction of benzonitrile oxide with aromatic nitrosocompounds which gives benzimidazole derivatives[44]. Benzonitrile oxide and nitrosobenzene in ether solution at —20 °C yield a yellow crystalline adduct possessing structure (I) which at room temperature rearranges to 1-hydroxy-2-phenylbenzimidazole-3-oxide. As shown in scheme, the intermediate (Ia, Ib) could be formed either by nucleophilic attack of benzonitrile oxide by the nitrosoderivative, or through the intervention of the nitrosocarbenic form of the nitrile oxide by a process quite similar to the dimerization of nitrosoderivatives and to the dimerization to furoxans of nitrile oxides:



In any case, the intermediate (I) isolated at low temperature rearranges at room temperature to the imidazole (II) by a mechanism which is probably that indicated in the formula.

Before closing this review which does not pretend to be complete, in which I have endeavoured to present synthetic a picture of the actual state of nitrile oxides chemistry and to outline some of the problems that still have to be solved, I want to mention a line of research in this field that is only at its beginning, that is the study of the reactivity of nitrile oxides toward free radicals.

That free radicals should react with nitrile oxides was considered probable by the fact that the reaction would produce particularly stable radicals, which are the same as obtained by monoelectronic transfer oxidation of oximes[109]:



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[107] A. Umani-Ronchi, P. Bravo and G. Gaudiano, Tetrahedron Lett. *1966*, 3477. – G. Gaudiano, A. Umani-Ronchi, P. Bravo and M. Acampora, Tetrahedron Lett. *1967*, 107. – P. Bravo, G. Gaudiano and A. Umani-Ronchi, Gazz. chim. ital. *97*, 1664 (1967). – G. Gaudiano, P. P. Ponti and A. Umani-Ronchi, Gazz. chim. ital. *98*, 48 (1968).

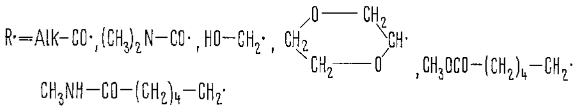
[108] G. Gaudiano, C. Ticozzi, A. Umani-Ronchi and A. Selva, Chimica Ind. *49*, 1343 (1967).

[109] R. O. C. Norman and B. C. Gilbert, *Advances in Physical Organic Chemistry* (Ed. V. Gold; Academic Press, New York 1967), vol. 5, p. 83.

Because of the well-known influence of the polar characteristics of free radicals on their reactivity, it might be expected that a more enhanced reactivity would occur of nucleophilic radicals on the carbon atom of the nitrile oxide which possess a clear electrophilic character. It is known that the electrophilic or nucleophilic character of a free radical can be correlated with the oxido-reductive potentials of the equilibria:

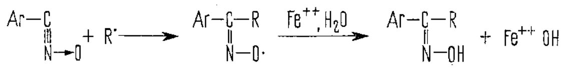
$$R\cdot + e \rightleftharpoons R^-$$
$$R\cdot - e \rightleftharpoons R^+$$

In a preliminary work[110] we allowed to react with aromatic nitrile oxides the following radicals of proved nucleophilic character:



generated in the presence of the nitrile oxide by suitable redox systems from aldehydes, dimethylformamide, methanol, dioxan, cyclohexanone etc.

In all the cases experimented reaction did occur according to the general scheme:



The products thus obtained are the oximes of α-diketones, α-ketols, α-ketoacids dimethylamides, aryldioxanylketones, ω-ketoesters and methylamides.

In its final result this reaction would consist in the 1,3-addition to nitrile oxides of aldehydes, formylamines, alcohols, ethers, esters and amides of monocarboxylic acids, and has therefore interest also for its possible synthetic applications.

Riassunto. Dopo una breve introduzione storica, viene dato un quadro delle attuali conoscenze sulla chimica degli ossidi di nitrili con particolare riguardo ai suoi più recenti sviluppi. L'applicazione di metodi già noti e l'introduzione di nuovi metodi di preparazione hanno portato alla cinquantina il numero dei nitrilossidi isolati, oltre a quelli numerosi preparati in situ e utilizzati in reazioni di addizione senza isolarli. Vengono esaminate le reazioni di dimerizzazione e polimerizzazione, le numerose reazioni di addizione nucleofila che mettono in evidenza lo spiccato carattere elettrofilo dei nitrilossidi e, in particolare le addizioni sopra i legami etilenici e acetilenici che portano a isossazoline e isossazoli. Nuove acquisizioni sperimentali, come l'isolamento in rese sostanziali e talvolta preponderanti di ossime acetileniche accanto agli isossazoli, rimettono sul tappeto la questione della via battuta da quest'ultima reazione, suggerendo come possibile alternativa al meccanismo generalmente ammesso di cicloaddizione 1,3-dipolare concertata quello che passa attraverso uno «zwitterione» intermedio, dal quale tanto l'isossazolo che l'ossima possono prendere origine. Viene illustrato l'effetto catalitico del BF_3 su alcune reazioni di addizione dei nitrilossidi, che consente l'ampliamento del campo di applicazione di queste reazioni. Vengono infine riportati i primi risultati dello studio della reattività dei nitrilossidi verso i radicali liberi al carbonio, studio che appare suscettibile di interessanti sviluppi.

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[110] T. Caronna, F. Minisci and A. Quilico, Tetrahedron Lett., *1970*, 3633.

SPECIALIA

A Correlation of the Ionization Energies of Water and Ethers with the Polar and Inductive Substituent Constants

A wide variety of structure and reactivity data have successfully been correlated by the Hammett and Taft equations[1].

The ionization potentials of alkyl free radicals, $R\cdot$, have been correlated[2] with Taft's polar substituent constants, σ^*.

We now demonstrate that the ionization energies of ethers, R_2O, are also a linear function of both σ^* and σ_I. The gas-phase expulsion of an electron from the nonbonding lone pair on the oxygen atom of an ether molecule is in accord with the equation:

$$R\text{-}\underset{\cdot\cdot}{\ddot{O}}\text{-}R \xrightarrow{E_I} R\text{-}\underset{\cdot\cdot}{\overset{\cdot +}{O}}\text{-}R + \bar{e}.$$

and the ionization potential, E_I, of course, corresponds approximately to the energy of the highest occupied