Pergamon

Tetrahedron, Vol. 52, No. 18, pp. 6421-6436, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00276-1

Cycloaddition of Benzonitrile Oxide to Pyridazine, Pyrimidine and Pyrazine.(*)

Antonino Corsaro, Giancarlo Perrini, Venerando Pistarà

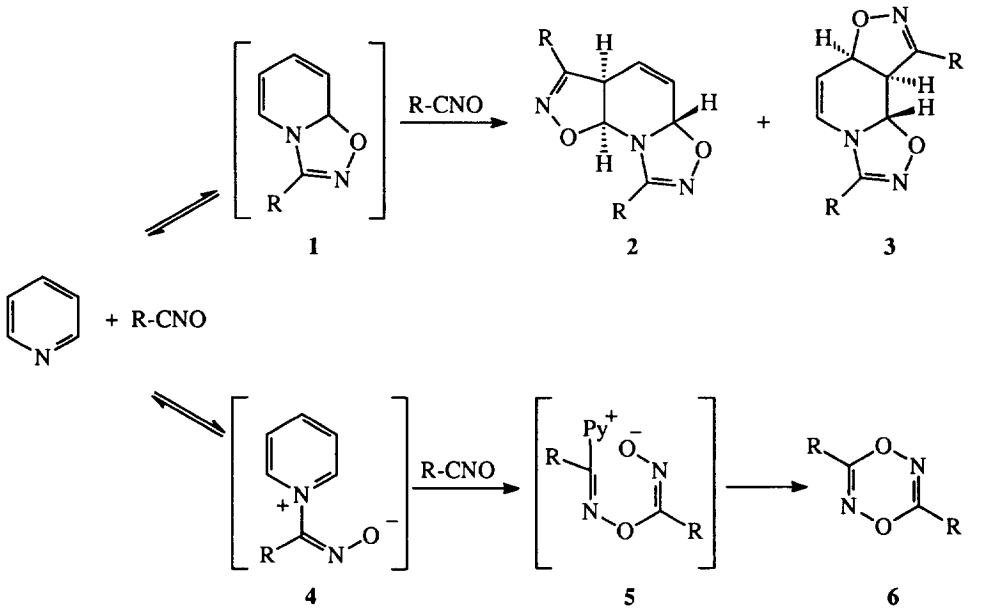
Dipartimento di Scienze Chimiche, Università di Catania; Viale A. Doria, 8 I-95125 Catania

Paolo Quadrelli, Anna Gamba Invernizzi, and Pierluigi Caramella

Dipartimento di Chimica Organica, Università degli Studi di Pavia; Viale Taramelli, 10 I-27100 Pavia

Abstract: Cycloaddition of benzonitrile oxide to pyridazine affords an isolable mono-cycloadduct. In cycloadditions to pyrimidine and pyrazine the primary mono-cycloadducts are labile intermediates which undergo further cycloaddition affording isolable bis- and tris-cycloadducts.

In previous papers we dealt with the reaction of nitrile oxides with pyridine and some of its derivatives.[1-5] In apolar solvents benzonitrile oxide (BNO) and pyridine afford the isolable bis-cycloadduct **2** in fair yields along with minor amounts of the site-isomeric bis-cycloadducts **3** (Scheme 1). The mono-cycloadduct **1** is a labile intermediate in equilibrium with the reactants and unstable towards cycloreversion. On the other hand in polar solvents the labile intermediate is the zwitterion **4** which, by addition of BNO and cyclization of the extended zwitterion **5**, affords the dioxadiazine **6** quantitatively.[6]



1 **2** **3** **4** **5** **6**

Scheme 1

(*). Dedicated to Prof. Giovanni Purrello on the occasion of his 72nd birthday and the leave of teaching duties.

In a search of evidence for the competing mechanisms and the proposed labile intermediates, we explored appropriate modification of the reactants in order to increase the stability of the intermediates. By reducing the loss of aromaticity in the cycloaddition step the mono-cycloadducts can be stabilized towards cycloreversion. In cycloaddition to quinoline and isoquinoline we obtained indeed stable mono-cycloadducts, which cyclorevert only upon heating. On the other hand the zwitterionic intermediates can be stabilized by providing convenient charge delocalization. A yellow dipolar adduct was indeed obtained by exposing benzoylcarbonitrile oxide to pyridine.[2]

The following is an extension of this line of research. We have investigated the reaction of BNO with the three aromatic diazines in order to study the effect of an aza-substitution in the pyridine nucleus on the reaction. The aza-substitution in the pyridine nucleus is known to cause a drastic fall in the basicity of the diazines and, in the case of pyridazine, significantly reduces the aromaticity of the ring.[7]

A few cycloaddition reactions of the diazines have been reported. A bis-adduct of pivalonitrile bis-(trifluoromethyl)-methylid to pyrazine[8] and cycloadducts of C-methoxycarbonyl N-phenyl and diaryl nitrile imines to the diazines [9,10] have been described. A recent report[11] deals with the reaction of BNO to the diazines. Because of the unfortunate experimental conditions chosen for the reactions (boiling benzene), however, the authors missed most of the fragile adducts.

Several Diels-Alder reactions of the diazines as heterocyclic azadienes have been reported and reviewed.[12] The unsubstituted diazines react with donor substituted dienophiles in an inverse-demand Diels-Alder reaction.

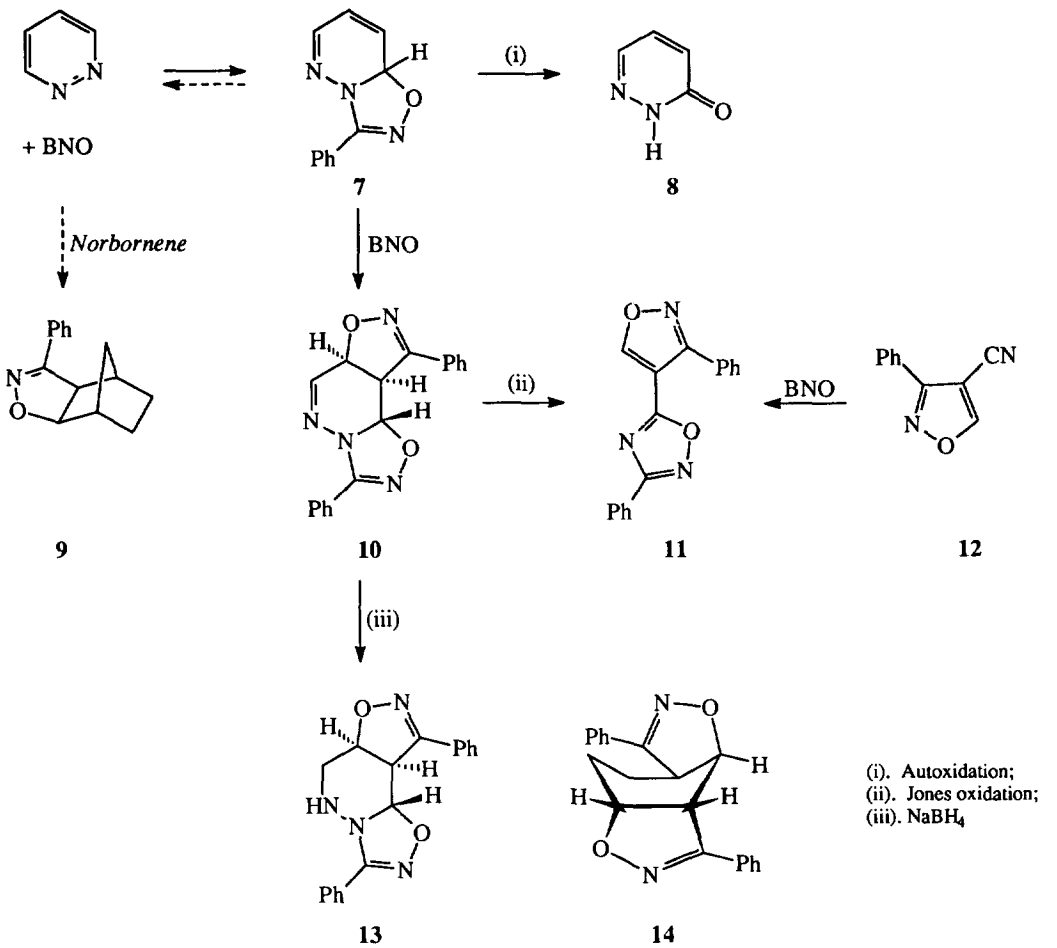
RESULTS

Pyridazine

Pyridazine shows a surprisingly high dipolarophilic activity towards BNO. Generation of BNO *in situ* in diethyl ether at 0 °C in the presence of 3 equivs. of pyridazine affords in a 72% yield the stable mono-cycloadduct **7**, colorless crystals mp 90-1 °C. The structure of **7** relies upon analytical and spectroscopic data as well as on the transformations reported in Scheme 2. The nmr spectrum shows (Table 1) the azomethine H at 7.11 δ (dd, J=3.6, 1.3 Hz) coupled with the vicinal and distal olefinic Hs, which appear at 6.24 and 6.37 δ. The latter olefinic H is coupled with an allylic H at 5.80 δ (d, J=2.7 Hz), in the usual range reported for 5-oxadiazolinic protons.[13]

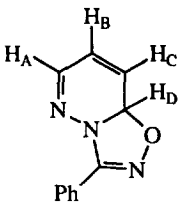
The mono-cycloadduct **7** is fairly stable in solution at r.t.. Upon standing in solvents in the presence of air, however, it undergoes a slow autoxidation (r.t., 1-2 weeks) affording the known pyridazinone **8**. This fragmentation is related to the easy abstraction of the 5-oxadiazolinic proton and was already reported for similar adducts of BNO to quinoline and isoquinoline.[1] The mono-cycloadduct **7** is thermally unstable and cycloreverts to the addends upon heating. By refluxing a solution of **7** in benzene in the presence of excess norbornene (10 equivs.) cycloreversion is complete in 5 hrs and affords pyridazine and the BNO adduct to norbornene **9** in almost quantitative yields.

The mono-cycloadduct **7** is still reactive towards BNO and its exposure to excess BNO (2 equivs.) affords mainly the bis-cycloadduct **10**, colorless crystals mp 162-3 °C, in a 41% yield. Bis-adduct **10** was also isolated from the cycloaddition mixture of BNO to pyridazine in a low yield (3%) and variable amounts of **10** could be detected in the solution of the mono-cycloadduct **7** after keeping at r.t. for some weeks or by refluxing a few hours.

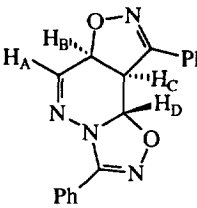

+ BNO
Norbornene
BNO
(i)
(ii)
(iii)
BNO
7
8
9
10
11
12
13
14
(i). Autoxidation;
(ii). Jones oxidation;
(iii). NaBH4

Scheme 2

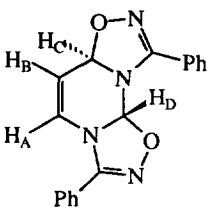
Table 1 - Chemical shifts[a] and coupling constants[b] of cycloadducts and their fragmentation products.



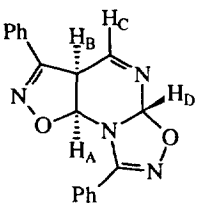
7



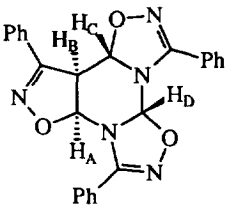
10



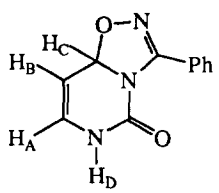
18



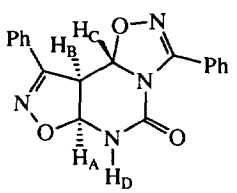
19



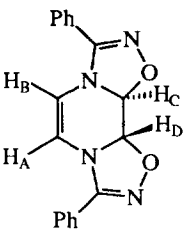
20



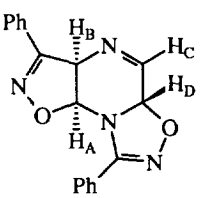
22



24



30



31

Compd.	H_A	H_B	H_C	H_D
7	7.11 (dd) $J_{A,B}$=3.6;$J_{A,C}$=1.3	6.24 (dd) $J_{B,C}$=10.0	6.37 (dd) $J_{C,D}$=2.7	5.80 (d)
10	6.85 (d) $J_{A,B}$=2.9	4.78 (dd) $J_{B,C}$=9.1	3.76 (t) $J_{C,D}$=9.1	5.07 (d)
18	6.68 (dd) $J_{A,B}$=7.9;$J_{A,C}$=1.4	5.66 (dd) $J_{B,C}$=3.0	5.57 (dd)	6.31 (s)
19	6.10 (d) $J_{A,B}$=9.0	4.68 (dd) $J_{B,C}$=4.2	8.28 (dd) $J_{C,D}$=2.0	6.61 (d)
20	6.17 (d) $J_{A,B}$=8.8	4.40 (dd)= $J_{B,C}$=3.7	5.98 (d)	6.63 (s)
22	6.18 (dd) $J_{A,B}$=8.0;$J_{A,D}$=5.1[c]	5.28 (ddd) $J_{B,C}$=2.2;$J_{B,D}$=1.1[c]	5.87 (d)	7.20 (b)[c]
24	5.82 (dd) $J_{A,B}$=7.0;$J_{A,D}$=4.0[c]	3.75 (t) $J_{B,C}$=7.2	5.76 (d)	6.17 (b)[c]
30	6.10 (s)		5.38 (s)	
31	5.82 (d) $J_{A,B}$=8.5	5.53 (dd) $J_{B,C}$=2.0	8.26 (d)	5.69 (s)

(a). Chemical Shifts in ppm (δ) in $CDCl_3$ from internal TMS. Multiplicity: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; b, broad signal (NH). (b). Coupling Constants in Hz. (c). Disappearing upon deuterium exchange.

The structure of bis-adduct **10** relies upon the nmr spectrum, which shows the 4- and 5-isoxazolinic protons in the usual range[14] at 3.76 and 4.78 δ and coupled with the azomethine H at 6.85 δ (d, J=2.9 Hz) and with the 5-oxadiazolinic H at 5.07 δ (d, J=9.1 Hz), resp.. The *anti* stereochemistry of the bis-adduct, as depicted in Scheme 2, follows from the large vicinal coupling constant (9.1 Hz) along the bond connecting the two heterocyclic five-membered rings. Bis-adduct **10** corresponds to the minor bis-cycloadduct **3** obtained in the cycloaddition to pyridine. The aza-substitution in the dienaminic system of mono-cycloadduct **1** reduces the reactivity of the α,β double bond (i.e. the NN=C bond in **7**) in accord with the reduced dipolarophilic activity of hydrazones and oximes.[15] From the cycloaddition to pyridazine in boiling benzene, Grassi *et al.*[11] could only isolate bis-adduct **10** and confirmed the structure with an X-ray crystallographic analysis.

Further structural proof for the bis-adduct **10** was provided by Jones oxidation. The six-membered ring is cleaved affording the 4-(1,2,4-oxadiazol-5-yl) isoxazole **11**, which was independently obtained by cycloaddition of BNO to the CN triple bond of 4-cyano-3-phenylisoxazole **12**. The $NaBH_4$ reduction of **10** afforded instead the hexahydropyridazine **13**. The nmr spectrum of **13** is fully consistent with the structure but shows an unexpected low coupling constant (1.6 Hz) between the vicinal protons along the bond connecting the two five-membered heterocyclic rings. A similar low coupling constant is reported[16] for the bis-adduct of BNO to cyclohexadiene, **14**, whose *anti* stereochemistry was recently proved with an X-ray crystallographic analysis.[17] In the boat conformation of the six-membered ring shown in **14** the dihedral angle between the relevant CH bonds approaches 90°.

Since pyridazine showed an unexpectedly high dipolarophilic activity and the mono-cycloadduct **7** is stable enough for controlled handling, we have determinated the relative reactivity of pyridazine and 1-hexene by performing competition experiments in a few solvents and determining the ratio of the cycloadducts by hplc. Table 2 shows the solvent dependence on the relative reactivity. In diethyl ether or benzene the reactivity of pyridazine is about a half of that of 1-hexene while in the polar CH_3CN or DMF the reactivities become almost identical. In alcoholic solvents the reactivity of pyridazine increases slightly more and surpasses that of 1-hexene but the total change on going from apolar to alcoholic solvents remains behind a factor 3.

Table 2 - Solvent effect on the competitive cycloaddition of BNO to pyridazine and 1-hexene.[a]

Solvent	Adduct yield (%)[b]		Relative rates
	Pyridazine adduct **7**	1-hexene adduct	$K_{pyridazine}/K_{1\text{-hexene}}$
Diethylether	37.6	60.8	0.62
Benzene	34.2	63.4	0.54
Dichloromethane	35.3	63.4	0.55
Acetonitrile	46.4	52.8	0.88
DMF	48.2	50.2	0.96
Methanol	63.8	36.1	1.76
Ethanol	61.4	36.8	1.67

(a). BNO was generated *in situ* from benzhydroximoyl chloride and triethylamine in a solution of the appropriate solvent containing 5 equivs. of pyridazine and 1-hexene. The mixtures were kept for two days at room temperature under nitrogen and then diluted to know volume with chloroform (hplc grade) which dissolved any precipitate. (b). Determined by hplc analysis of diluted reaction mixtures to which a weighted amount of 4-methoxy-benzonitrile was added as internal standard. The maximum deviation from the average of duplicate runs was ±2.

Pyrimidine

Pyrimidine behaves much like pyridine. In the cycloaddition of BNO to 3 equivs. pyrimidine the main products are the bis-cycloadduct **18** (11%) and tris-cycloadduct **20** (14%) along with a substantial amount of the usual dimer of BNO diphenylfuroxane **17** (43%) (Scheme 3). The fragile tris-adduct **20**, which does not survive a normal chromatographic separation, crystallized out from the reaction mixture in colorless crystals mp 121-2 °C, while column chromatography afforded the more stable bis-adduct **18**, colorless crystals mp 117-8 °C. The two adducts are not related since bis-adduct **18** remains unchanged after exposure to excess BNO (2 equivs).

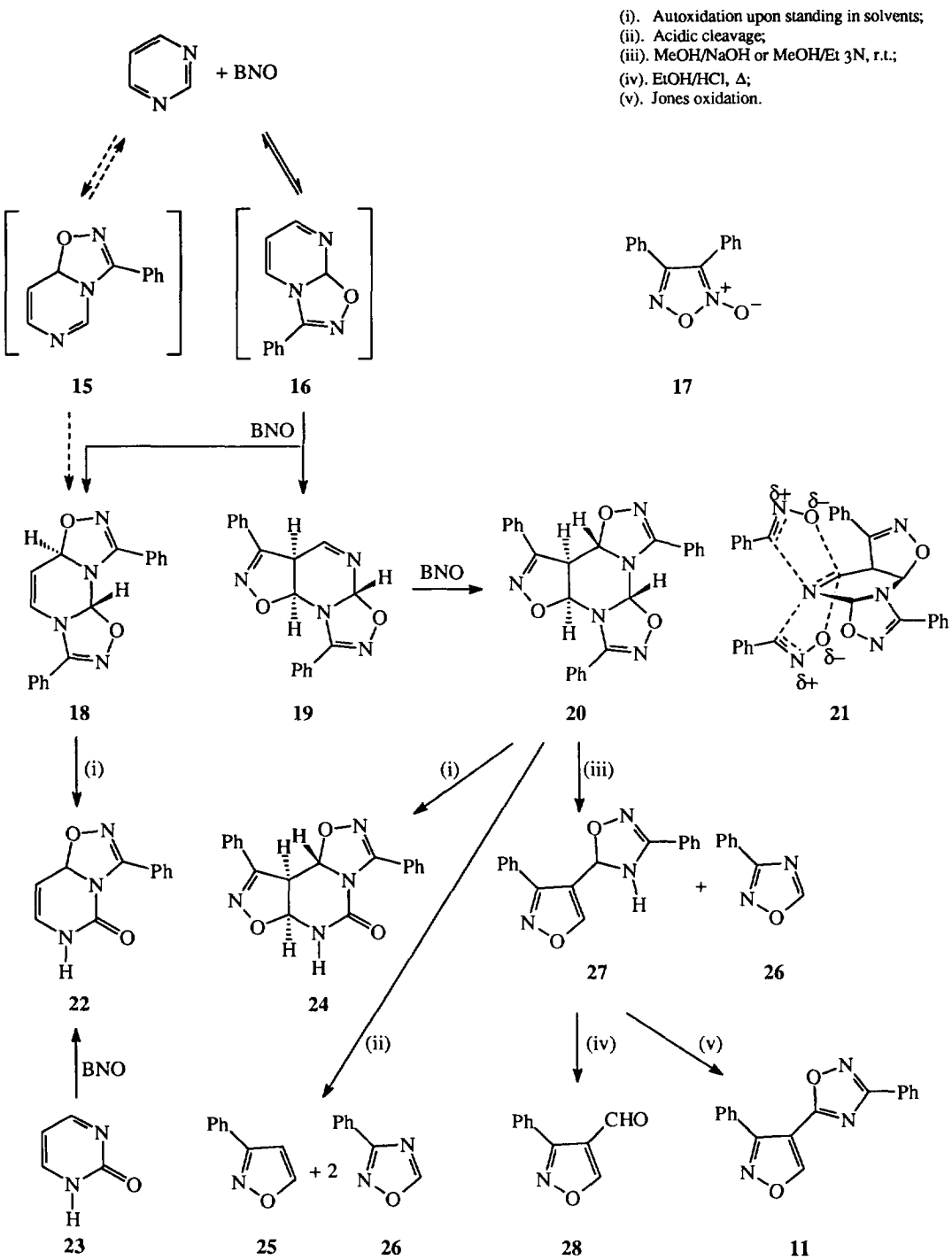
Monitoring the cycloaddition of BNO to pyrimidine in $CDCl_3$ by nmr spectroscopy shows in the first hour the initial formation of bis-adduct **18** and signals attributable to bis-adduct **19** in a ca. 1:1 ratio, along with minor amounts of the tris-adduct **20**. Subsequently a neat reversal of the ratio **19/20** takes place and after 4-5 hrs the signals of bis-adduct **18** and tris-adduct **20** are present in a ca. 1:1 ratio along with minor amounts of bis-adduct **19**, which almost disappears after 1-2 days. Conceivably tris-adduct **20** derives from bis-adduct **19** which adds easily BNO on the iminic C=N bond. Simple imines display a high dipolarophilic activity.[15,18] Accordingly the aza-substitution in the dienaminic system of mono-cycloadduct **1** in the δ position increases the reactivity of the γδ double bond (the C=N bond in **16**).

The structure of adducts **18-20** relies upon nmr data. Bis-adduct **18** shows the α and β enaminic protons as double doublets at 6.68 and 5.66 δ, in the same range of the analogous protons of the pyridine adduct **3** and coupled with the allylic (oxadiazolinic) H at 5.57 δ. The transient bis-adduct **19** shows the 4- and 5-isoxazolinic Hs at 4.68 (dd) and 6.10 (d) δ, in the range typical for similar condensed isoxazolines, e.g. **2**. The azomethine H appears at 8.28 δ (dd) and is coupled with the vicinal 4-isoxazolinic H and the allylic 5-oxadiazolinic H, which appears at 6.61 δ (d, J=2 Hz). In tris-adduct **20** the isoxazolinic Hs remain in the same range of **19**, 4.40 (dd) and 6.17 (d) δ, and the two oxadiazolinic Hs appear at 5.98 (d, J=3 Hz) and 6.63 (s) δ.

The *anti* stereochemistry of bis-adduct **18** and **19** could not be deduced from the spectra and is proposed by analogy to the pyridine adduct **2** and **3**, whose stereochemistry relies upon an X-ray crystallographic analysis[4] as well as on nmr data.[1] Under the assumption of an *anti* stereochemistry for bis-adducts **19**, the stereochemistry of **20**, depicted in Scheme 3 with the two oxadiazolinic rings *anti* to the isoxazoline, is inferred from the stereochemistry of one of the degradation product of **20**, namely **24**, discussed below. The addition of BNO to bis-adduct **19** then takes place selectively on the face *syn* to the oxadiazolinic ring (and *anti* to the isoxazoline). Cycloadditions are remarkably affected by the steric effect of α-substituents[15] and model examinations show that the addition *syn* to the oxadiazolinic ring, sketched in **21** (attack from below), is less hindered than the *anti* addition, since BNO meets the lesser steric bulk of the oxadiazolinic oxygen with respect to the isoxazolinic PhC in the attack from above.

Bis-adduct **18** undergoes autoxidation upon standing in solvents affording the fragmentation product **22**, which was independently obtained from cycloaddition of BNO to 2-pyrimidone **23**, while tris-adduct **20** fragments to the *anti* tetrahydro pyrimidone **24**. The *anti* stereochemistry of **24** relies upon the large (J=7.2 Hz) vicinal coupling constant along the bond connecting the two heterocyclic five-membered rings. The lower coupling constant between the corresponding Hs in tris-adduct **20** may be due to the adoption of a boat conformation of the satured six-membered ring, as in the cases of the cyclohexadiene bis-adduct **14** and

Scheme 3

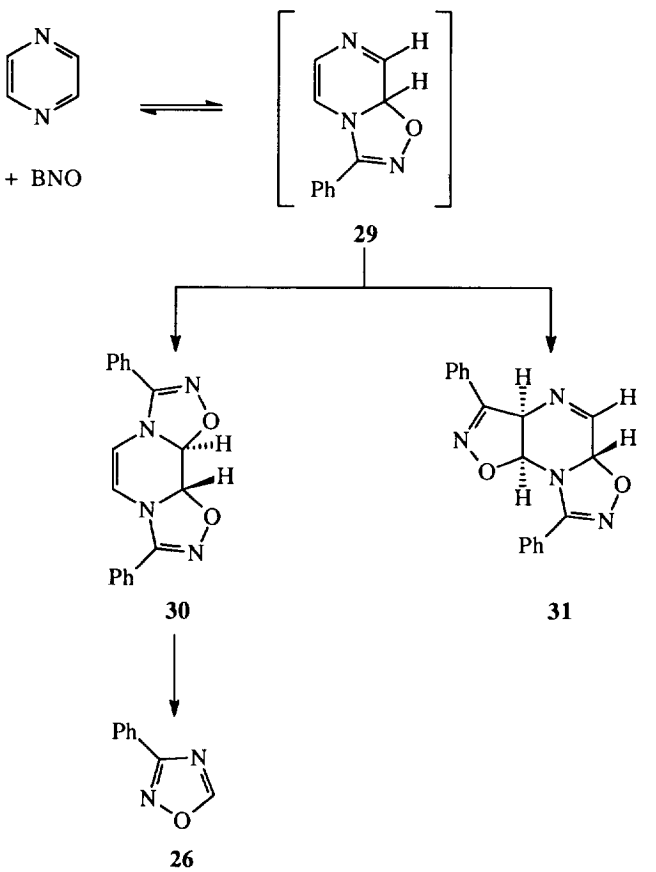

(i). Autoxidation upon standing in solvents;
(ii). Acidic cleavage;
(iii). MeOH/NaOH or MeOH/Et 3N, r.t.;
(iv). EtOH/HCl, Δ;
(v). Jones oxidation.
+ BNO
15
16
17
BNO
18
19
BNO
20
21
(i)
(i)
(iii)
22
24
27
26
BNO
(ii)
(iv)
(v)
23
25
26
28
11

the hexahydro pyridazine **13**. From the cycloaddition to pyrimidine in boiling benzene Grassi *et al.*[11] could only isolate the degradation products **22** and **24**.

In the presence of acids or bases tris-adduct **20** affords different products. In the presence of acids a [2+2+2] cycloreversion takes place affording 3-phenylisoxazole **25** and 3-phenyl-1,2,4-oxadiazole **26**. Adduct **20** is immediately cleaved when dissolved in ordinary (acidic) $CDCl_3$ while is stable in $CDCl_3$ dried on Na_2CO_3 or in the presence of triethylamine. In methanol and in the presence of bases (MeOH/NaOH or MeOH/Et_3N, r.t.) abstraction of the 4-isoxazolinic proton and elimination of the oxadiazole **26** affords the oxadiazoline **27**. A similar degradation takes place with the pyridine adduct **2**.[4]Acidic hydrolysis of **27** yields the known aldehyde **28** while Jones oxidation affords the oxadiazole **11**.

Pyrazine

Pyrazine behaves like pyridine and pyrimidine. The mono-cycloadduct **29** is a labile intermediate and only the bis-cycloadduct **30** (15%), colorless crystals mp 172-3 °C and **31** (7%), colorless crystals mp 132-6 °C, could be isolated from the cycloaddition mixture along with substantial amounts of diphenylfuroxane **17** (68%) (Scheme 4).



Scheme 4

The symmetrical structure of bis-adduct **30** is immediately apparent from the nmr spectrum, which shows two singlets at 6.10 (2H, =CH) and 5.38 δ (2H, 5-oxadiazolinic H). Adduct **30** was also isolated by Grassi *et al.*,[11] who established the *anti* stereochemistry with an X-ray crystallographic analysis. The structure of the minor bis-adduct **31** relies upon the nmr spectrum, which shows an azomethine proton at 8.26 δ (d, J=2 Hz) coupled with the 4-isoxazolinic H at 5.53 δ (dd, J= 8.5 and 2.0 Hz). The 5-isoxazolinic and 5-oxadiazolinic Hs appear at 5.82 δ (d, J=8.5 Hz) and 5.69 δ (s), resp..We suggest an *anti* stereochemistry for **31** by analogy to the pyridine cycloadduct **2**. As in the case of pyrimidine, the aza-substitution in the dienaminic system of mono-cycloadduct **1** in the γ position increases the reactivity of the γδ double bond (the N=C bond in **29**) and reverses the regiochemistry of the γδ attack, too.

Attemps to epoxidize bis-adduct **30** with *m*.chloro-perbenzoic acid resulted in fragmentation of the six-membered ring affording 3-phenyl-1,2,4-oxadiazole **26**

DISCUSSION

The three diazines enter cycloaddition reactions with BNO with different ease. Pyridazine has a high dipolarophilic activity, like quinoline and isoquinoline, and a stable mono-cycloadduct could be easily isolated. On the other hand pyrimidine and pyrazine behave like pyridine and only stable bis- and tris-cycloadducts could be obtained. The behaviour nicely reflects the changes in resonance energies (*RE*)[19,20] of the heteroaromatic dipolarophiles. The *RE*s are gathered in Table 3 along with the pK_a,[21] the electron affinities (EA)[22] and the ionization potentials (IP)[23] of the diazines and pyridine. In the case of pyridine, pyrimidine and pyrazine, which have similar high resonance energies, the loss of aromaticity in the cycloaddition makes these reactions reversible while in the case of pyridazine, which is significantly less aromatic, and in the case of quinoline and isoquinoline as well, the mono-cycloadducts become stable towards cycloreversion and are isolable.

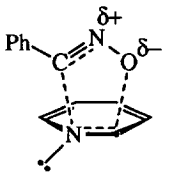
Table 3 - Resonance energies, pK_a, electron affinities and the first (n) and second (π) ionization potentials of pyridine and diazines.

	Pyridine	Pyridazine	Pyrimidine	Pyrazine
RE (Kcal/mol)	34	26	33	32
pK_a	5.2	2.1	1.1	0.4
EA (eV)	-0.62	0.25	0	0.40
$IP_{(n)}$ (eV)	9.59	9.31	9.73	9.63
$IP_{(\pi)}$ (eV)	9.73	10.61	10.41	10.18

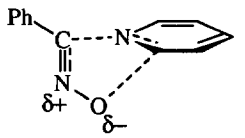
The aza-substitution in pyridine reduces significantly the basicity of the three diazines by 3 to 5 power of ten. This decrease in basicity leads to a destabilization of the zwitterion intermediates analogous to **4** and in the reaction of diazines the competing formation of the dioxadiazine **6** observed in the reaction with pyridine is entirely suppressed. The minute solvent effect observed in cycloaddition with pyridazine is also incompatible with the involvement of zwitterionic intermediates in these reactions.

The cycloadditions of BNO to the diazines can then be regarded as concerted processes. The diazines are however highly aromatic, and the *RE*s are close to the familiar *RE* of benzene, which is totally unreactive

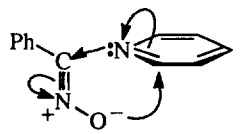
towards nitrile oxides. Our previous studies on the cycloadditions of BNO to five-membered heteroaromatic compounds have disclosed the importance of aromaticity in slowing down these reactions.[15] In cycloadditions of BNO to furan[24] and thiophene[25] about 1/4 of the aromaticity is lost in the transition state (*TS*) of the cycloadditions causing a rate decrease of three and four powers of ten, resp..



32



33



34

To account for the unexpected reactivity of pyridine the classical $[\pi_S^4+\pi_S^2]$ *TS* **32** appeared to us then unlikely and we proposed[1] the pseudopericyclic *TS* **33**. This *TS* implies the attack of the pyridine on the nitrile oxide carbon while the oxygen interacts with the electrophilic π system of pyridine as shown in **34**. The 8 electrons involved are not cyclically delocalized, since the *n* and π orbitals at the pyridine nitrogen are orthogonal. This addition mode, which belong to the pseudopericyclic variety,[26] is neither allowed nor forbidden and is stabilized by an acyclic delocalization of the allylic type, as in the isoconjugate heptatrienate anion. More interestingly this addition mode makes use of the best frontier orbital (*FO*) interactions.

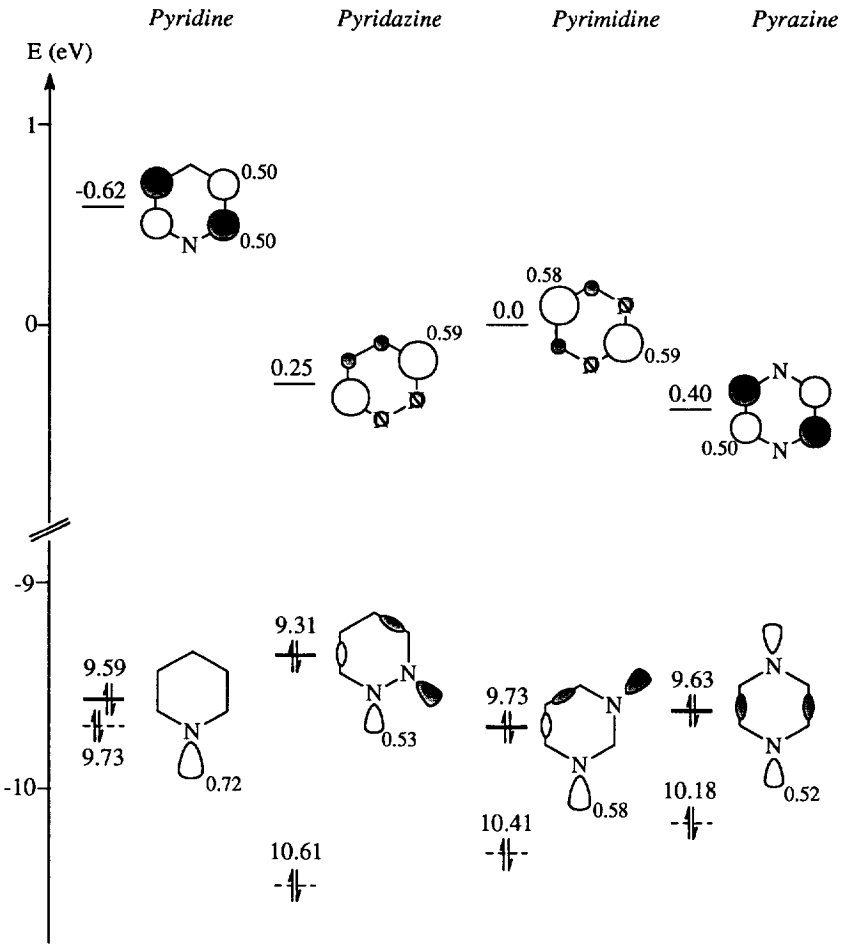
The energies and the shapes [27] of the *FO*s of pyiridine and of the diazines are displayed in the Figure. The *HOMO*s are always the lone pairs (*n*) while the *LUMO*s are the π^* orbitals, which have the highest coefficients α to nitrogen. On going from pyiridine to the diazines the *LUMO*s drop remarkably in accord with the increased reactivity of the diazines towards nucleophiles.[7] The energy of the *HOMO*s changes less in the series while the *n* coefficients decrease sizeably owing to the delocalization.

The reversibility of the first cycloaddition step in the reaction of BNO to pyridine, pyrimidine and pyrazine does not yet allow a fair comparison of the relative rates. The similar behaviour observed in this work suggests, however, that their reactivities are not very different and the pseudopericyclic addition mode is admirably suited in accounting for similar reactivities. On going to the diazines the $HOMO_{(pyridine)}$ - $LUMO_{(BNO)}$ interaction decreases owing to the decrease of the *n* coefficients while the $HOMO_{(BNO)}$ - $LUMO_{(pyridine)}$ interaction increases because of the reduced energy gap. In the case of pyrimidine the shape of the *LUMO*, which has the highest coefficient on C-2, supports the preferred formation of mono-cycloadduct **16**.

CONCLUSIONS

The diazines add BNO in a concerted pseudopericyclic cycloaddition. Pyridazine affords a stable mono-cycloadduct while in the cycloadditions of pyrimidine and pyrazine the mono-cycloadducts are labile intermediates, which are unstable towards cycloreversion and add further BNO affording isolable bis- and tris-cycloadducts.

Figure - Frontier orbitals of pyridine and diazines.[a,b]



(a). The *FO*s are ordered according to the experimental IPs and EAs which are given near the levels. Dashed levels indicate the lower lying *HOMO*s of π symmetry. (b). Shapes from AM1 calculations[27] for AM1 optimized geometries. Numbers near the lobes represent the p_z AO coefficients. Numbers near the lone pairs are the square roots of the sum of the squares of the s, p_x and p_y AO coefficients at nitrogen.

EXPERIMENTAL

All mps are uncorrected. Elemental analyses were done on a C. Erba 1106 elemental analyzer. ^{1}H-nmr spectra were recordered on a Bruker AC 300 spectrometer in $CDCl_3$ solutions. Chemical shifts are expressed in ppm from internal tetramethylsilane (δ) and coupling constants are in hertz (Hz). Ir spectra (nujol mulls) were recordered on a Perkin-Elmer 197 spectrophotometer. Hplc analyses were carried out by means of a Varian LC 5000 instrument equipped with Whatmann Partisil 10 column and a Jasco Uvidec 100-III UV detector; and a mixture of n-hexane/ethyl acetate (from 5 to 100% in acetate) was used as eluent. In quantitative analyses weighted amounts of suitable compounds were used as internal standard. Column chromatography

and tlc: silicagel H 60 and GF_{254} (Merck) respectively, eluant cyclohexane/ethyl acetate 9:1 to 7:3. The identification of samples from different experiments was secured by mixed mps and superimposable ir spectra.

Starting and reference materials. Benzhydroximoyl chloride was obtained by treatment of benzaldoxime with sodium hypochlorite.[28] Samples of the BNO adducts to 1-hexene[29] and to norbornene **9**,[30] 3-phenylisoxazole **25**,[31] 3-phenyl-1,2,4-oxadiazole **26**[32] and 3-phenyl-isoxazole-4-carbaldehyde **28**[33] were prepared following literature procedures. A sample of 3-phenyl-isoxazole-4-carbonitrile **12**, colourless crystals mp 56-8 °C,[34] was prepared by cycloaddition of BNO to *trans*-3-dimethylaminoacrylonitrile (Aldrich) with the same procedure[33] used for aldehyde **28**. Column chromatography afforded **12** in a 55% yield.

General procedure for the cycloadditions of BNO to the diazines. To a stirred, ice cooled, solution of benzhydroximoyl chloride (5 g, 32 mmol) and diazines (3 equivs.) in anhydrous diethyl ether (100 ml), 1.1 equivs. of triethylamine in the same solvent (20 ml) were added over a 0.5 hrs period. After keeping the reaction mixture two days at room temperature, triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure leaving a residue, which was crystallized or separated by column chromatography.

Cycloaddition of BNO to pyridazine.

Crystallization of the residue from cyclohexane/ethyl acetate afforded the mono-cycloadduct **7** (3.8 g, 60%), colourless crystals, mp 90-1 °C (found: C, 66.50; H, 4.48; N, 20.98%; $C_{11}H_9N_3O$ requires: C, 66.32; H, 4.55; N, 21.10%). Column cromatography separation of the mother liquors gave 3,5-diphenylfuroxane **17** (5%), bis-adduct **10** (0.16 g, 3%), colourless crystals from cyclohexane/ethyl acetate, mp 162-3 °C (found: C, 67.63; H, 4.45; N, 17.91%; $C_{18}H_{14}N_4O_2$ requires: C, 67.91; H, 4.43; N, 17.60%), and 0.76 g of mono-cycloadduct **7** (total yield 72%).

The mono-cycloadduct **7** is indefinitely stable when stored in the solid state in a refrigerator. When kept in benzene solution under nitrogen and in the dark for 2-3 weeks at r.t., it was recovered largely unchanged (nmr) while, in the presence of air and light, it was converted to pyridazinone **8** (90%), colourless crystals from ethyl acetate, mp 102-4 °C, ir: ν_{NH} 3240, $\nu_{C=O}$ 1680 cm^{-1}, identical with a sample prepared according to the literature.[35]

By refluxing a benzene solution of **7** (200 mg, 1 mmol) in the presence of excess norbornene (10 equivs) cycloreversion is complete in 5 hrs (tlc). Evaporation of the reaction mixture and crystallization from cyclohexane afforded the BNO adduct to norbornene **9** (86%), colourless crystals, mp 99-100 °C, identical with an authentic sample.[30]

Addition of BNO to mono-adduct 7. To a solution of **7** (0.20 g, 1 mmol) and benzhydroximoyl chloride (0.31 g, 2 mmol) in diethyl ether at 0 °C triethylamine (2 mmol) was added. After keeping 2 days at r.t., triethylamine hydrochloride was filtered off. The filtrate was evaporated and the residue was separated by column cromatography affording, besides 3,5-diphenylfuroxane **17**, bis-adduct **10** (0.13g, 41%) and unreacted **7** (0.07 g, 35%).

*Cleavage of **10** with Jones reagent.* To a solution of **10** (0.14 g, 0.5 mmol) in acetone (5 ml) an excess of Jones reagent[36] (0.5 ml, 4 equivs) was added at r.t.. The mixture was stirred 1 hr and then diluted with water and extracted with chloroform. The extracts were dried on Na_2SO_4 and evaporated. Column cromatography afforded 187 mg (65%) of 3-phenyl-5-(3-phenylisoxazol-4-yl)-1,2,4-oxadiazole **11**, colourless crystals from cyclohexane, mp 109 °C (found: C, 70.71; H, 3.81; N, 14.18%; $C_{17}H_{11}N_3O_2$ requires: C, 70.58; H, 3.83; N,

14.53%), nmr: 7.47-7.56 (m, 6H, Ph-*H*), 7.68-7.92 (m, 2H, Ph-*H*), 8.05-8.08 (m, 2H, Ph-*H*), 9.29 (s, 1H, 5-isoxazole-*H*).

Compound **11** was indipendently obtained in a modest yield by cycloaddition of excess BNO to 3-phenyl-4-cyanoisoxazole **12**. To a stirred, ice-cooled, solution of 3-phenyl-4-cyanoisoxazole (350 mg, 2 mmol) containing benzhydroximoyl chloride (610 mg, 4 mmol) in anhydrous diethyl ether (50 ml) a solution of triethylamine (0.6 ml, 4.3 mmol) in the same solvent (10 ml) was added dropwise. After keeping two days at r.t., triethylamine hydrochloride was filtered off and the filtrate was evaporated under reduced pressure. Column cromatography of the residue afforded, besides 3,5-diphenylfuroxane **17**, adduct **11** (50 mg, 17%) and unreacted nitrile **12** (0.26 g, 74%).

Reduction of bis-adduct 10 with $NaBH_4$. To a solution of adduct **10** (0.1 g) in MeOH (20 ml) an excess of $NaBH_4$ (0.1 g) was added. After stirring 2 hrs at r.t., the reaction mixture was diluted with water and extracted with diethyl ether. After drying on Na_2SO_4, evaporation of the solvent gave the hexahydropyridazine **13** (86 mg, 86%), colourless crystals from cyclohexane/ethyl acetate, mp 147-9 °C (found: C, 67.38; H, 5.07; N, 17.51%. $C_{18}H_{16}N_4O_2$ requires: C, 67.48; H, 5.03; N, 17.49%), ir: ν_{NH} 3300 cm^{-1}, nmr: 3.10 (m, 2H, CH_2), 3.97 (dd, J=10.0 and 5.5, *NH*), 4.51 (dd, J=10.9 and 1.6, 4-isoxazolinic *H*), 4.92 (dt, J=10.9 and 1.5, 5-isoxazolinic *H*), 5.40 (d, J=1.6, 5-oxadiazolinic *H*), 7.5 (m, 6H, aromatic *H*s), 7.8 (m, 4H, aromatic *H*s).

Cycloaddition of BNO to pyrimidine.

Column cromatography of the residue obtained following the general procedure afforded, besides 3,5-diphenylfuroxane **17** (43%), bisadduct **18** (0.55 g, 11%), colourless crystals from cyclohexane/ethyl acetate 9:1, mp 117-8 °C (found: C, 68.02; H, 4.36; N, 17.89%; $C_{18}H_{14}N_4O_2$ requires: C, 67.91; H, 4.43; N, 17.60%), and the tetrahydropyrimidone derivative **24** (0.80 g, 15%), colourless crystals from ethyl acetate, mp 226-8 °C (found: C, 65.05; H, 4.20; N, 16.67%; $C_{18}H_{14}N_4O_3$ requires: C, 64.66; H, 4.22; N, 16.76%), ir: ν_{NH} 3280, $\nu_{C=O}$ 1710 cm^{-1}.

The fragile tris-adduct **20** could be isolated by adding to a cooled solution of BNO (6 mmol) in diethyl ether (40 ml), prepared from benzhydroximoyl chloride and NaOH 14%,[37] 3 equivs. of pyrimidine and keeping 4 days at 0 °C. Tris-adduct **20** (120 mg, 14%) crystallized out, colourless crystals from diethyl ether or ethanol, mp 120-1 °C (found: C, 68.35; H, 4.46; N, 15.91%; $C_{25}H_{19}N_5O_3$ requires: C, 68.64; H, 4.38; N, 16.01%). The mother liquors afforded by column chromatography diphenylfuroxane **17** and bis-adduct **18** in yields similar to those reported above.

Degradation of bis-adduct 18. Stored in the solid state in a refrigerator, bis-adduct **18** is indefinitely stable, but in solution in the presence of air and light it decomposes within a few days. A benzene solution of **18** kept for two weeks at r.t. afforded almost quantitatively the tetrahydropyrimidone derivative **22**, colourless crystals from benzene, mp 139-140 °C (found: C, 61.20; H, 4.28; N, 19.61%; $C_{11}H_9N_3O_2$ requires: C, 61.39; H, 4.22; N, 19.53%), ir: ν_{NH} 3240 and $\nu_{C=O}$ 1714 cm^{-1}.

Compound **22** was indipendently obtained by exposure of 2-pyrimidone **23** to excess BNO (2 equivs.). To a stirred solution of 2-pyrimidone (133 mg, 1.5 mmol) and benzhydroximoyl chloride (470 mg, 3 mmol) in dichloromethane (20 ml) a stoichiometric amount of triethylamine in the same solvent (5 ml) was added over a 10 minutes period at r.t.. After keeping two days at r.t., the reaction mixture was evaporated under reduced pressure and the residue was taken up with ethyl acetate. Triethylamine hydrochloride separated out and the filtrate was evaporated under reduced pressure. The residue was separated by column chromatography affording, besides 3,5-diphenylfuroxane **17** and unreacted 2-pyrimidone, adduct **22** (70%).

Degradation of tris-adduct 20. Tris-adduct **20** proved to be rather unstable even in the solid state. The crystals of **20**, stored a few weeks in a refrigerator, were found throughly decomposed into a complex mixture of products containing mainly tetrahydropyrimidone **24** (nmr).

Tris-adduct **20** dissolves unchanged in acetone-d_6 or in $CDCl_3$, dried on Na_2CO_3 or in $CDCl_3$ containing a trace of triethylamine. When dissolved in ordinary $CDCl_3$ it fragments immediately in a 1:2 mixture of 3-phenylisoxazole **25** and 3-phenyl-1,2,4-oxadiazole **26**. Samples of the two oily fragmentation product **25** and **26** could be obtained by column chromatography, benzene serving as the eluent, and identified by comparison of their ir and nmr spectra with those of authentic specimens.

Tris-adduct **20** is cleaved in MeOH in the presence of bases. To a stirred suspension of tris-adduct **20** (0.1 g) in MeOH (10 ml) 0.2 ml of triethylamine (or a drop of NaOH 5%) were added. After stirring 3 hrs at r.t. the clear solution was evaporated leaving a 1:1 mixture (nmr) of 3-phenyloxadiazole **26** and oxadiazoline **27**. A sample of the oily 3-phenyloxadiazole **26**, bp 80-90 °C (bath)/1 Torr, was obtained by kugelrohr distillation. The residue was crystallized from $EtOH/H_2O$ yielding 40 mg (60%) of 3-phenyl-5-(3-phenylisoxazol-4-yl)-1,2,4-oxadiazoline **27**, colourless crystals, mp 102-3 °C (found: C, 69.87; H, 4.58; N, 14.18%. $C_{17}H_{13}N_3O_2$ requires: C, 70.09; H, 4.50; N, 14.43%), ir: ν_{NH} 3180 cm^{-1}, nmr: 4.95 (broad, 1H, *NH*), 6.67 (d, 1H, J=5, 5-oxadiazolinic *H*), 7.4-7.8 (m, 10H, aromatic *H*), 7.73 (s, 1H, 5-isoxazolinic *H*). Upon exchanging with D_2O the signal at 4.95 δ disappears and the doublet at 6.67 δ collides into a singlet.

The oxadiazoline **27** (29 mg) was hydrolized by refluxing its solution in EtOH (10 ml) and conc. HCl (1 drop) for 0.5 hrs. The solution was then concentrated, diluted with water and extracted with ether. The extracts were dried on Na_2SO_4 and evaporated, leaving the isoxazole-4-carbaldehyde **28** (15 mg), mp 44°C, identical with an authentic specimen.[33]

Oxidation of the oxadiazoline **27** (29 mg) with Jones reagent (0.1 ml) in acetone (10 ml) at r.t. afforded a sample of the 4-isoxazolyl-oxadiazole **11** (20 mg), mp 109 °C, identical with the product obtained in the cleavage of **10** with Jones reagent.

Cycloaddition of BNO to pyrazine.

A portion (250 mg) of the crystalline bis-adduct **30** separated out along with triethylamine hydrochloride, which was removed by treatment with water. Column chromatography of the reaction residue gave 3,5-diphenylfuroxane **17** (68%), bis-adduct **30** (510 mg, total yield 15%), colourless crystals from cyclohexane/ethyl acetate 7:3, mp 172-3 °C (found: C, 67.69; H, 4.28; N, 17.37%; $C_{18}H_{14}N_4O_2$ requires: C, 67.91; H, 4.43; N, 17.60%) and bis-adduct **31** (350 mg, 7%), colourless crystals from benzene/cyclohexane, mp 132-6 °C (found: C, 67.97; H, 4.50; N, 17.50%; $C_{18}H_{14}N_4O_2$ requires: C, 67.91; H, 4.43; N, 17.60%).

A solution of bis-adduct **30** (70 mg) and *m*.chloroperbenzoic acid (100 mg) in $CHCl_3$ (30 ml) was stirred 24 hrs at r.t.. The mixture was diluted with $CHCl_3$, washed with $NaHCO_3$ 5%, dried on Na_2CO_3 and evaporated. Column chromatography of the residue afforded the oily 3-phenyl-1,2,4-oxadiazole **26** (30 mg, 41%), identical with an authentic specimen.

Acknowledgements: Financial support by CNR and MURST is gratefully acknowledged.

REFERENCES AND NOTES

1. Corsaro, A.; Perrini, G.; Caramella, P.; Marinone Albini, F.; Bandiera, T. *Tetrahedron Lett.* **1986**, *27*, 1517.
2. Caramella, P.; Bandiera, T.; Marinone Albini, F.; Gamba Invernizzi, A.; Corsaro, A.; Perrini, G. *Tetrahedron* **1988**, *44*, 4917.
3. Caramella, P.; Bertolasi, V.; Forte, S.; De Franco, R.; Bandiera, T.; Marinone Albini, F. *J. Chem. Res.* **1989**, (S), 308; (M), 2364.
4. Marinone Albini, F.; De Franco, R.; Bandiera, T.; Caramella, P. Corsaro, A.; Perrini, G. *J. Heterocyclic Chem.* **1989**, *26*, 757.
5. Marinone Albini, F.; De Franco, R.; Bandiera, T.; Grünanger, P.; Caramella, P. *Gazz. Chim. Ital.*,**1990**, *120*, 1.
6. De Sarlo, F; Guarna, A. *J. C. S. Perkin Trans. II*, **1976**, 626.
7. Boulton, A. J.; McKillop, A. *Comprehensive Heterocyclic Chemistry*, Boulton, A. J.; McKillop, A. Eds.; Pergamon Press: Oxford, 1984; Vol. 2, p. 1; p. 29.
8. Burger, K.; Roth, W. D. *Synthesis* **1975**, 731.
9. Dalla Croce, P. *J. Heterocyclic Chem.* **1975**, *12*, 1133.
10. Grubert, L.; Pätzel, M.; Jugelt, W.; Riemer, B.; Liebscher, J. *Liebigs Ann. Chem:* **1994**, 1005.
11. Grassi, G.; Risitano, F.; Foti, F. *Tetrahedron* **1995**, *51*, 11855.
12. Boger, D. L. *Chem. Rev.* **1986**, 781.
13. Srivastava, R. M:; Brinn, I. M. *J. Org. Chem.*, **1977**, *42*, 1555.
14. Sustmann, R.; Huisgen, R.; Huber, H. *Chem. Ber.*, **1967**, *100*, 1802.
15. Caramella, P.; Grünanger, P. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Eds.; John Wiley and Sons, Inc.: New York, 1984; p. 291.
16. Bettinetti, G.; Gamba, A. *Gazz. Chim. Ital.*, **1970**, *100*, 1144.
17. Bettinetti, G.; Bovio, B. unpublished results.
18. Bast, K; Christl, M.; Huisgen, R.; Mack, W. *Chem. Ber.* **1973**, *106*, 3312.
19. Wiberg, K. B.; Nakaji, D.; Breneman C. M. *J. Am Chem. Soc.* **1989**, *111*, 4178.
20. Cook, M. J.; Katritzky, A. R.; Linda, P. *Adv. Heterocyclic Chem.* **1974**, *17*, 255.
21. Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: New York, 1985.
22. Nenner, I.; Schulz, G. J. *J. Chem. Phys.* **1975**, *62*, 1747.
23. Gleiter, R.; Heilbronner, E.; Hornung, V. *Helv. Chim. Acta* **1972**, *55*, 255.
24. Caramella, P.; Cellerino, G.; Corsico Coda, A.; Gamba Invernizzi, A.; Grünanger, P.; Houk, K. N.; Marinone Albini, F. *J. Org. Chem.* **1976**, *41*, 3349.
25. Caramella, P.; Cellerino, G.; Grünanger, P.; Marinone Albini, F.; Re Cellerino, M. R. *Tetrahedron* **1978**, *34*, 3545.
26. Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325; Dewar, M. J. S.; McKee, M. L. *ibidem* **1978**, *100*, 7499.
27. Dewar, M. J. S.; Zoebish, E. G.; Healy E. F.; Stewart J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
28. Corsico Coda, A.; Tacconi, G. *Gazz. Chim. Ital.* **1984**, *114*, 131.
29. Bianchi, G.; Grünanger, P. *Tetrahedron* **1965**, *21*, 817.

30. Fliege, W.; Huisgen, R. *Liebigs Ann. Chem.* **1973**, 2038.
31. Bast, K.; Christl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3258.
32. Arbasino, M.; Grünanger, P. *Chim. Ind. (Milan)* **1963**, *45*, 1238.
33. Caramella, P.; Cereda, E. *Synthesis*, **1971**, 433.
34. Bautz, S. B.; Blom, N. F.; Boeyens, J. C. A.; Michael J. P. *S. Afr. J. Chem.* **1982**, *35*, 166.
35. Schimdt, P.; Druey, J. *Helv. Chim. Acta* **1954**, *37*, 134.
36. Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. *J. Chem. Soc.* **1953**, 2548.
37. Quilico, A.; Speroni, G. *Gazz. Chim. Ital.* **1946**, *76*, 148.

(*Received in UK* 9 *February* 1996; *revised* 1 *March* 1996; *accepted* 7 *March* 1996)