1,3-CYCLOADDITION OF BENZONITRILE OXIDES TO DIAZEPINES. III. 1*H*-1,2-BENZODIAZEPINE

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Abstract - Arylnitrile oxide (**1**) and 1*H*-1,2-benzodiazepine (**2**) undergo 1,3-cycloaddition reactions to give derivatives of 1,2,4-oxadiazole (**3**) and isoxazole (**4**). Although usually stable, the nitrile oxide partly dimerizes giving a 1,2,4-oxadiazole (**7**). Secondary products were also identified: for one of them (**6**) the structure was unambiguously determined by X-ray diffraction. Overall kinetics and product distribution were measured at 40-70°C, in mixtures of 1,1,2,2-tetrachloroethane and DMF: a set of parallel reactions was evidenced.

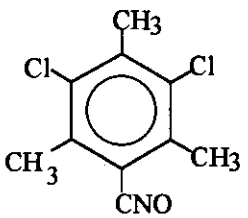
After some works on the reaction of benzonitrile oxides with 1,2-diazepines, which evidenced [3+2] cycloaddition both at C=N and C=C bonds, besides secondary products,[1-4] the reactivity of a benzodiazepine has been taken into consideration. The stable 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (**1**) and 1*H*-1,2-benzodiazepine (**2**) were the reactants. Several products were separated, identified and determined, and kinetic measurements were effected, operating at temperatures in the range 40-70 °C and

in different solvents, mainly mixtures of 1,1,2,2-tetrachloroethane (TCE) and *N*,*N*-dimethylformamide (DMF).

RESULTS

Preparation and separation of products

An excess amount of benzodiazepine (**2**) was treated with nitrile oxide (**1**) in a TCE+DMF mixed solvent at 70 °C.



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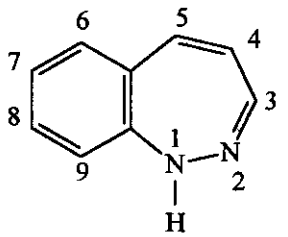

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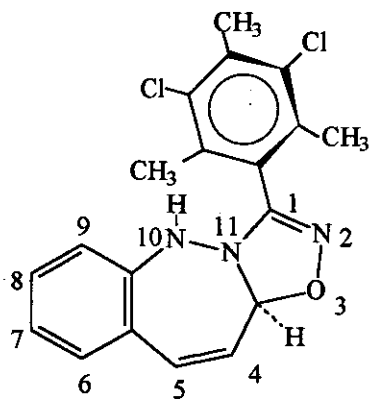
Chromatographic separation, followed by elemental, spectral, and in one case, diffractometric analysis, evidenced the following products:



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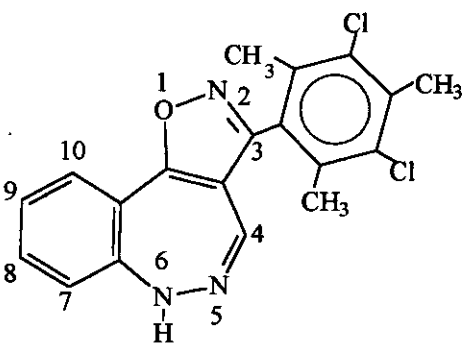

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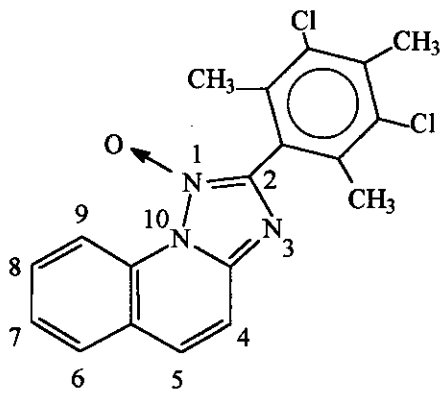
1- (3,5-dichloro-2,4,6-trimethylphenyl)- 3a*H*- 10*H*-[1,2,4] oxadiazolo[4,5-*b*][1,2]benzo-diazepine (**3**); 3-(3,5-dichloro-2,4,6-trimethylphenyl)- 6*H*- isoxazolo [4,5-*d*][1,2]benzo-

diazepine (**4**); 2-(3,5-dichloro-2,4,6-trimethylphenyl)-[1,2,4]triazolo[2,3-*a*]quinoline-1-*N*-oxide (**5**); 2-(3,5-dichloro-2,4,6-trimethylphenyl)-[1,2,4]triazolo[2,3-*a*]quinoline (**6**); 3,5-di(3,5-dichloro-2,4,6-trimethylphenyl)-1,2,4-oxadiazole (**7**).

Apart from **7**, which has already been described,[5] the products are new, to our best knowledge.



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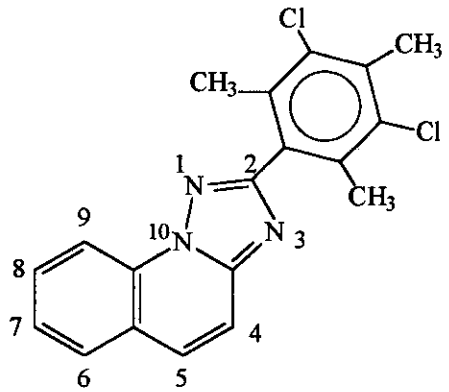

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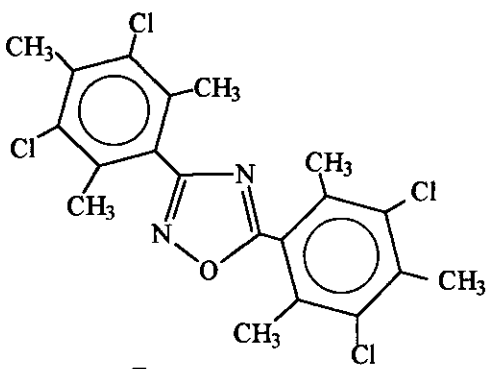


7

In order of elution, the first product was the diaryloxadiazole (**7**), deriving from a dimerization of **1**; the adduct (**3**), the unreacted diazepine, and the products (**4**, **5** and **6**) followed. Products (**3**, **4** and **5**) were mainly identified on the basis of their nmr and mass spectra; **6**, besides this, was the object of an X-ray diffraction analysis.

The overall yields of identified products were in the range 76-93%. Melting points and elemental analyses of products are collected in Table 1. For spectra, see Experimental.

Table 1 - Analytical Data of Products.[a]

Product	mp °C	Formula	C%	H%	N%
3	182	$C_{19}H_{17}N_3OCl_2$	61.14	4.22	11.33
			(60.98	4.58	11.23)
4	179	$C_{19}H_{15}N_3OCl_2$	61.20	4.11	11.30
			(61.31	4.06	11.29)
5	195	$C_{19}H_{15}N_3OCl_2$	61.23	4.17	10.91
			(61.31	4.06	11.29)
6	235	$C_{19}H_{15}N_3Cl_2$	64.03	4.57	11.69
			(64.06	4.24	11.80)

[a] Required values in parentheses.

Kinetic measurements and product distribution

Kinetic runs were carried out at temperatures from 40 to 70°C. They were followed by ir analysis, on the band at 2300 cm^{-1}, typical of nitrile oxide (**1**), to measure the overall rate coefficient (k). As in previous work,[1,3] TCE-DMF mixtures, of composition 90:10, 70:30, 50:50, v/v, were chosen as solvents.

The product distribution was studied in the same conditions as for the kinetic runs, using hplc, usually at "infinity time". Values of selectivity in the conversion of nitrile oxide into the main products, however, showed no regular trends as a function of temperature and solvent composition, because of the uncertainty of experimental measurements.

Average values are presented in Table 2.

By substituting CCl_4 for TCE in the 70:30 mixture with DMF, it was found that the main products are still **3**, **4** and **7**, with selectivities in the range of the average values for TCE/DMF in Table 2. When, however, pure CCl_4 was used as solvent, the product

distribution considerably changed, as shown in Table 2, particularly in favour of product (**4**), at the expenses of product (**7**) and of other products.

Table 2 - Selectivities from Nitrile Oxide (**1**) to Reaction Products

	Selectivity to Products				
	3	**4**	**5**	**6**	**7**
TCE/DMF mixed solvents [a]	0.33 ±0.04	0.20 ±0.03	0.03 ±0.02	0.01 ±0.01	0.43 ±0.07
CCl_4 [b]	0.30 ±0.01	0.37 ±0.01	0.01 ±0.01	traces	0.32 ±0.02

[a] average values for a DMF content from 10 to 50 vol.% (temperature range 40-70 °C);
[b] temperature 50 °C.

Similar analyses carried out during the progress of a reaction in TCE/DMF 70:30 at 60 °C gave, within experimental error, the same results, so evidencing a scheme of parallel reactions of the same kinetic order. The study of the overall kinetics showed that reactions are first-order with respect to both reactants (**1**) and (**2**).

The measured values of overall rate coefficient k were not markedly dependent on solvent composition, when runs were effected in TCE/DMF 90:10, 70:30 and 50:50. To a first approximation, they can be considered unaffected by changing the fraction of DMF from 10 to 50%. Values measured in TCE/DMF 70:30 at different temperatures are shown in Table 3.

Table 3 - Overall Kinetic Coefficients[a] as a Function of Temperature

Temperature (°C)	40	50	60	70
10^4k (l mol^{-1} s^{-1})	5.44 ±0.03	10.27 ±1.01	19.42 ±0.27	38.36 [b] ±2.32

Apparent activation energy = 58.0 ± 1.8 kJ mol^{-1}

Apparent activation entropy = - 131.7 ± 8.2 J mol^{-1}K^{-1}

[a] measured in TCE/DMF 70:30; [b] similar values, within experimental error, were found in TCE/DMF mixtures 90:10 and 50:50.

DISCUSSION

Among the most abundant products, **7** does not derive, in a stoichiometric sense, from diazepine (**2**): however, there is an evidence that it derives from a reaction that involves **2**, since (i) nitrile oxide (**1**) is usually stable, in the reaction conditions, without reactant (**2**), and (ii) kinetic measurements revealed a system of parallel reactions of the same order, hence also for the production of **7** the rate determining step appears to be a bimolecular reaction between **1** and **2**, as it is for the accompanying cycloadditions. The overall stoichiometry for the formation of **7** could be the following one:

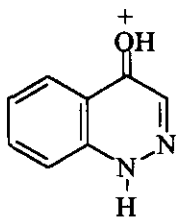
$$\underset{(1)}{2\ C_{10}H_9NOCl_2} + \underset{(2)}{C_9H_8N_2} \longrightarrow \underset{(7)}{C_{20}H_{18}N_2OCl_4} + \underset{(?)}{C_9H_8N_2O}$$

We ignore whether benzodiazepine (**2**) is altered or not by the reaction: in any case, there is a loss of an oxygen atom by the "dimer" of nitrile oxide (**1**). In a previous work,[5] the same nitrile oxide, in the presence of 1,4-diaryl-1-aza-1,3-butadiene, gave the same dimerization with loss of an oxygen atom. Therefore it seems that the presence of some

aza-derivatives reduces the stability of **1**, which is otherwise well known as a stable nitrile oxide. The runs in pure CCl_4 as solvent indicated that the interaction of **1** and **2** in order to give the "dimer" **7** is favoured when a polar component is present in the solvent (S_7 = 0.32 in CCl_4, 0.43 in TCE/DMF; see Table 2).

The products of real addition between nitrile oxide and benzodiazepine shall now be considered. The cycloadduct (**3**) was identified because of its ^{1}H-nmr spectrum, which in several details is analogous to that of benzodiazepine (**2**) (for instance: the signals of protons 4-H, 5-H and 9-H appear at, δ 5.96, 6.84 and 7.19 respectively, in **2**, at δ 5.85, 6.62 and 7.18 in **3**), while the signal assigned to H-3a appears at δ 6.22 ppm, in the range of similar products of [3+2] cycloaddition of arylnitrile oxides to the C=N bond of 1,2-diazepine;[1-3] one of these cycloadducts had the structure determined by X-ray diffraction analysis.[1,2] Further commenting on the ^{1}H-nmr spectrum, it should be noticed that the two *ortho* CH_3 groups were found non-equivalent: one of them is strongly affected by the shielding effect of the benzodiazepine; furthermore, the NH proton does not exchange with D_2O. In the mass spectrum of **3**, the molecular peak is correctly present at m/z = 373; the most intense peak has m/z = 144 (benzodiazepine$^+$), evidence of a process of retrocycloaddition.

The nmr spectrum of product (**4**) is evidence of a compound with an extended conjugated system (for protons corresponding to those of **3**, signals are at lower fields). In agreement with elemental analysis, it indicates that **4** has two hydrogen atoms less than **3**. Further evidence of this fact is given by the mass spectrum, in which the molecular peak (also the most intense one) appears at m/z = 371. Other intense peaks in the ms are at m/z = 147 (attributable to fragmentation with loss of ArCNC and H-shift; an ion can be envisaged having formula **8**) and at m/z = 120 (the previous ion - HCN).



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The structure of a product of cycloaddition to the C=C bond, accompanied by dehydrogenation, was therefore assigned to **4**. The nmr spectrum indicates equivalent *ortho* CH_3 groups, a result consistent with a cycloaddition with the proposed orientation. The NH proton gives normal exchange with D_2O.

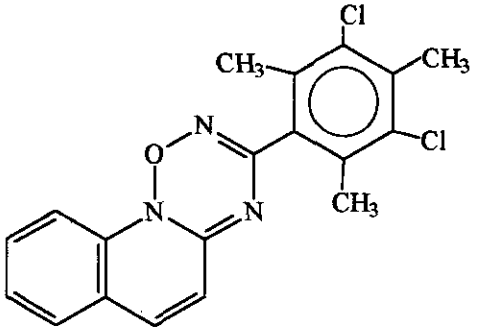
Of products **(3)** and **(4)**, the former is more abundant than the latter in solvent mixtures of TCE/DMF type: it had already been found that, on a diazepinic ring containing both C=N and C=C bonds, the preferred position of attack is the C=N bond.[1-3]

Among minor products **(5)** and **(6)**, it was found that **6**, whose identification was not obvious, gave crystals suitable for an X-ray diffraction study (see below).

The structure assignment to product **(5)** has not as strong foundations as that of **6**, but is rather based on a comparison between the spectral properties of the two products: both have the ms with an intense peak at m/z = 128 (quinoline$^+$-H); their ^{1}H-nmr spectra give evidence of the "quinolinic" part of the molecules by quite similar peaks, except for the protons assigned to the position on the benzo group closer to the quinoline nitrogen (9-H):

		(4-H)	(5-H)	(6-H)	(7-H)	(8-H)	(9-H)
in **5**:	δ	7.55	7.83	7.93	7.67	7.79	10.0
in **6:**	δ	7.66	7.87	7.87	7.53	7.73	8.48

The one last mentioned is apparently the region where the structures of **5** and **6** are more different, because of the extra oxygen atom of **5**. So we propose for **5** the structure of an *N*-oxide of compound **(6)**.



5a

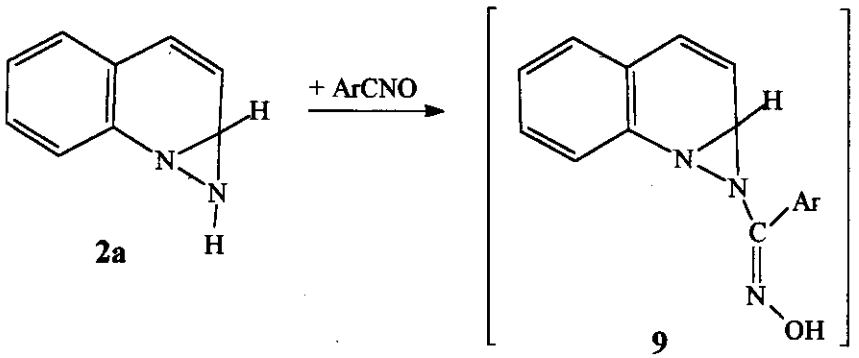
However, these similarities and differences could perhaps be explained by an isomeric structure for compound (**5**), labelled **5a**, and corresponding to a 1,2,4,6-oxatriazinic derivative.

From what is known about similar couples of isomers (an aromatic azine *N*-oxide and the corresponding expanded ring including the oxygen atom), as for instance in the case treated by Gainsford and Woolhouse,[6] it may happen that the isomers are both thermally stable compounds, with similar ir and nmr spectra, so that it is difficult to distinguish them on this ground. However, in the case of mass spectra there is a typical property of heterocyclic *N*-oxides, which tend to lose oxygen from their molecular ion, giving an $(M-16)^+$ fragment ion,[7,8] possibly associated with an $(M-17)^+$ ion. On the contrary an $(M-16)^+$ peak is not reported for heterocycles containing oxygen and one or more nitrogen atoms within their ring,[6,9-11] although intense $(M-17)^+$ peaks were reported for a series of 1,2,4,5-oxatriazine derivatives.[12] Therefore in the present case structure (**5**) has been preferred to **5a**, due to the presence, in the ms of the product, of a weak peak at m/z = 371 and a more intense peak at m/z = 355.

As to the reason of the formation of products (**5**) and (**6**), one might think that the reactant benzodiazepine contains small quantities of 2-aminoquinoline, commonly a minor product from the preparation of **2**, as a residual impurity, and that products (**5**) and (**6**) derive from reactions of 2-aminoquinoline with nitrile oxide (**1**). However such a hypothesis had to be discarded, since a study of the reaction of **1** with 2-aminoquinoline revealed a series of products, among which **6** was found to be only about 1%. On the other hand, the purity of benzodiazepine (**2**) has been proved by hplc and mass spectrometry.

An other possible route could involve a diaziridinic isomer of the benzodiazepine (molecule **2a**, the same that is considered as an intermediate in the photochemical preparation of the benzodiazepine).[13] In various cases, diaziridines are stable molecules,[14] able to give, possibly through intermediate azomethine imine isomers, [3+3] cycloadditions, for instance with nitrones.[15] Similar reactions could take place with nitrile oxide (**1**), but they would give rise to products other than **5** (or even **5a**) and **6**: from the [3+3] cycloaddition of aryl nitrile oxides and hydrazones, a series of 1,2,4,5-

oxatriazine derivatives were obtained.[12] In order to justify the minor products (**5**) and (**6**) as deriving from **2a**, there should be a reaction of **2a** and nitrile oxide (**1**), to give an open adduct (**9**) and, from the latter, product (**6**) by loss of H_2O or product (**5**) by loss of H_2, .



The problem with **2a** is that, in the reaction mixture and at the reaction temperature, we found no ^{1}H-nmr signal around δ 2 ppm, which should be typical of a diaziridinic NH,[16] operating both in $CDCl_3$ and in a mixture of $CDCl_3$ and deuterated DMF. Hence the isomer (**2a**), if present during the reaction, should represent such a small fraction of the system as to be not detected by the nmr technique.

In conclusion, we can speculate that there is an equilibrium between **2** and **2a**, largely favouring the former as in the photochemical preparation of the benzodiazepine,[13] but with a non-zero fraction of **2a**; during the reaction with the nitrile oxide, such isomer would be consumed to give **5** and **6**, but continously regenerated, so producing detectable amounts of the by-products.

Diazepines previously considered and benzodiazepine of the present work show, besides differences of behaviour, one common reaction with benzonitrile oxide (**1**), that is the cycloaddition at the C=N bond, which is in any case the main reaction. A comparison is possible between kinetic measurements performed at 70 °C in TCE/DMF mixed solvents, particularly in TCE/DMF in a 70:30 ratio: for 1-ethoxycarbonyl-4-methyl, 5-methyl, and 6-methyl-1,2-diazepines, values of 10^4k_3 (l mol^{-1} s^{-1}) around 5 were measured;[1,3] for the present benzodiazepine the corresponding value is 12.8 (from the k-value in

Table 3 and the selectivity in Table 2). The presence of the benzo group and the absence of the ethoxycarbonyl and methyl substituents on the diazepine slightly increase the reaction rate.

Crystal structure determination of 6.

For compound (**6**) the crystal structure, as determined by means of X-ray diffraction, revealed an unexpected system of three condensed cycles bonded to a polysubstituted phenyl derivative. A structural feature (the absence of N-H bonds) was already foreseen from ^{1}H-nmr and ir spectra.

According to the Cambridge Structural Database[17] Version 5.10 (October 1995), no crystal structure determination has been performed on similar triazoloquinoline derivatives.

Compound (**6**) crystallizes with two molecules in the asymmetric unit (see Fig.1);[18] they are related by an approximate screw axis $2_{1/2}$, at x= 0.605(11), y= 0.728(22), parallel to z with Δz= 0.256(13).[19]

The two independent molecules show a very similar geometry. The condensed rings are planar within 0.014(3)Å (molecule A) and 0.022(4)Å (molecule B); their LS-planes form dihedral angles of 68.8(1)° and 71.5(1)° with those of the phenyl rings, for molecules A and B respectively.

Geometric parameters are in the normal range; in particular, C-N, C=N and N-N bond lengths are generally in good agreement with accepted average values.[20] Selected bond distances and bond angles are reported in Table 4.

The conformation of **6** is even the same in both molecules, the concerned torsion angle τ, N7-C8-C14-C15 having the value of -70.1(3)° and -71.0(3)° in molecule A and B, respectively. The 1...5 non-bonded distances N7...C21 and N9...C20 do assume reasonable values, ranging between 3.15 and 3.28 Å. Intermolecular distances are normal, with only one slightly short contact with respect to the sum of van der Waals radii. Each of the *ortho* methyl groups (C20A, C21A, C20B, C21B) is bonded to the phenyl ring defining two bond angles whose difference ranges between 0.1 and 1.1°, showing no steric hindrance effects due to the tricyclic moiety. No hydrogen bonds are

present. In the crystal, no packing anomalies have been observed; there are only few voids with a radius larger than 1 Å (R_{max}= 1.29 Å).[21]

On the whole, these features allow to formulate the hypothesis that packing forces in the crystal of **6** should play a small role on the molecular conformation.

To test this point, the geometry of an isolated molecule of **6** has been fully optimized[22] at the HF level with the 3-21G* basis set (266 basis functions), starting from the experimental coordinates as obtained for molecule A; the final value calculated for the τ angle is -63.5°. Some further single point calculations[22] have been performed using the 6-31G* basis set (398 basis functions), always with the experimental geometry but for different values of the τ angle in the range 0 to -100°, at intervals of 20° (and finally of 5° in the last calculations). The minimum of energy occurs for an angle τ between -70 and -75°. These results are in fair agreement with the experimental value and give support to the above hypothesis for the present case.

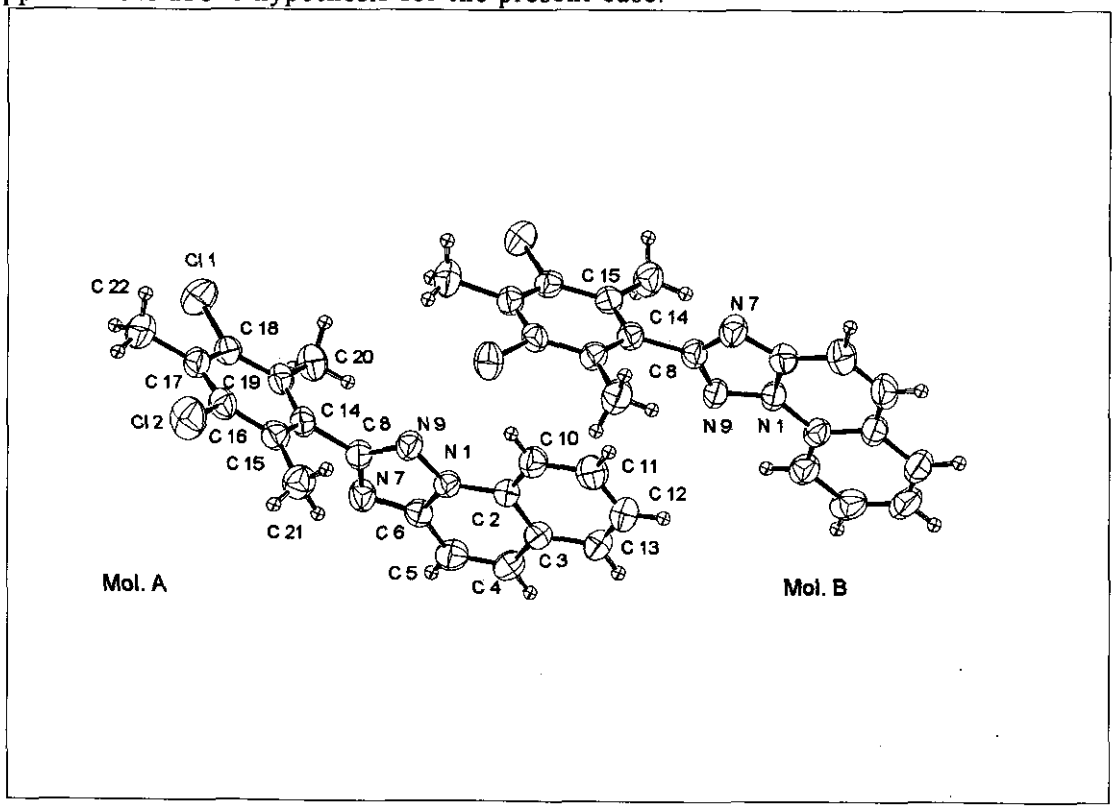


Figure 1. ORTEP drawing of the asymmetric unit of **6** and adopted numbering of atoms. Thermal ellipsoids are at the 50% probability level; hydrogen atoms, treated as isotropic, are on an arbitrary scale.

Table 4. Selected Bond Lengths and Bond Angles in the Crystal Structure of **6**

	mol.A	mol.B		mol.A	mol.B
			Bond lengths (Å)		
N1 - C6	1.363(3)	1.353(3)	C4 - C5	1.339(4)	1.343(4)
C6 - N7	1.335(3)	1.335(3)	C5 - C6	1.420(4)	1.427(4)
N7 - C8	1.362(3)	1.351(3)	C2 - C10	1.382(4)	1.385(4)
C8 - N9	1.330(3)	1.329(3)	C10 -C11	1.372(4)	1.371(4)
N1 - N9	1.363(3)	1.368(3)	C11 - C12	1.383(4)	1.394(4)
N1 - C2	1.391(3)	1.394(3)	C12 - C13	1.360(5)	1.348(5)
C2 - C3	1.409(3)	1.407(4)	C13 - C3	1.401(4)	1.408(4)
C3 - C4	1.421(4)	1.424(4)	C8 - C14	1.486(3)	1.491(3)
			Bond angles (°)		
N1 - C6 - N7	109.5(2)	109.7(2)	C4 -C5 -C6	119.2(3)	118.8(3)
C6 - N7 - C8	102.7(2)	102.6(2)	N1 - C6 - C5	118.5(2)	118.7(2)
N7 - C8 - N9	115.7(2)	116.1(2)	C2 - C10 - C11	118.6(3)	118.7(3)
C8 - N9 - N1	101.9(2)	101.4(2)	C10 -C11 - C12	121.1(3)	120.3(3)
C6 - N1 - N9	110.2(2)	110.1(2)	C11 -C12 - C13	120.3(3)	120.9(3)
C6 -N1 - C2	124.5(2)	124.9(2)	C12 -C13 - C3	121.2(3)	121.1(3)
N1 - C2 - C3	116.1(2)	115.9(2)	C3 - C2 - C10	121.9(2)	122.1(2)
C2 - C3 - C4	119.6(2)	119.8(2)	C2 - C3 - C13	117.0(2)	116.8(2)
C3 - C4 - C5	122.1(3)	122.1(3)			

EXPERIMENTAL

Melting points are uncorrected. ^{1}H and ^{13}C-nmr spectra were recorded with a Varian VXR300 MHz spectrometer (Me_4Si as internal standard, $CDCl_3$ as the solvent). Proton decoupling experiments were performed to gain further evidence for the assignment of

the spectra of products (**5**) and (**6**). Mass spectra were recorded, at 70 eV, with a HP 5989A mass spectrometer, using the DIP (direct insertion probe) method. Ir spectra were recorded and kinetics followed with a Nicolet FT-ir 205 spectrophotometer. Reagent grade reagents and solvents were used. Crystal diffraction data (**6**) were collected with an Enraf-Nonius CAD-4 diffractometer.

Materials

Aryl nitrile oxide (**1**) was obtained as previously described.[23] The 1*H*-1,2-benzodiazepine was prepared starting from *N*-iminoquinoline dimer obtained as described.[13]
A solution of *N*-iminoquinoline dimer (3 g, 0.01 mol) in dichloromethane (1500 ml), added of acetic acid (12 ml, 0.21 mol), was irradiated, under nitrogen and internal cooling to 15-18°C, with a 500 W high pressure lamp, for 12 h. After acetic acid was removed by extraction with saturated aqueous solution of sodium bicarbonate, the reaction solution was washed with water, dried on anhydrous sodium sulphate and evaporated to dryness. The resulting residue was chromatographed over alumina, using petroleum ether (bp 40-70°C)-dichloromethane (1:1, v/v) as eluant. Recrystallization from isopropyl ether-benzene gave the 1*H*-1,2-benzodiazepine (**2**), mp 64°C (lit.[13] 63-64°C); obtained 0.9 g, yield 30%. The purity of diazepine was determined by hplc and mass spectrometry analysis.

General procedure for the reaction of aryl nitrile oxide 1 with the diazepine 2.

A solution of **1** (1.2 g, 0.005 mol) and **2** (1.8 g, 0.0125 mol) in a mixture of TCE -DMF (70:30, v/v), was kept at 70°C, for 24 h. The solvent was then evaporated under reduced pressure and the residue was fractionated by flash chromatography, on a Merck 60 silica gel (230-400 mesh) column of 50 cm length and 2.5 cm internal diameter, eluting initially with a mixture of petroleum ether-ethyl acetate (90:10, v/v) to obtain the 3,5-diaryl-1,2,4-oxadiazole (**7**), the cycloadduct (**3**) and the diazepine in excess. Successively the separation was continued eluting with a mixture of petroleum ether-ethyl acetate (70:30, v/v) to obtain other cycloadducts (**4**, **5** and **6**).

From the reaction of **1** with **2** the products listed below have been obtained:

1-(3,5-Dichloro-2,4,6-trimethylphenyl)-3a*H*,10*H*-[1,2,4]oxadiazolo[4,5-*b*][1,2]benzodiazepine (**3**): mp 182°C (petroleum ether/ethyl acetate); ^{1}H-nmr (δ ppm): 7.18 (1H, d, J = 7.2 Hz, 9-H); 6.93 (1H, t, J = 7.5 Hz, 8-H); 6.80 (1H, t, J = 7.5 Hz, 7-H); 6.62 (1H, d, J = 12.3 Hz, 5-H); 6.22 (1H, s_b, 3a-H); 5.94 (1H, d, J = 7.8 Hz, 6-H); 5.85 (1H, dd, J = 12.6 Hz, 4-H); 5.22 (1H, s, NH); 2.48 (3H, s, CH_3 *para*); 2.45 (3H, s, CH_3 *ortho*); 1.62 (3H, s, CH_3 *ortho)*. Ir (Nujol): 3326 cm^{-1} (NH). EI ms m/z(%): 373 (M^+, 31.4); 215 (22.0)($ArCO^+$); 213 (19.8)($ArCN^+$); 180 (11.8); 178 (35.5); 144 (100) (benzodiazepine$^+$); 129 (10.7)(quinoline$^+$); 117 (46.8)(m/z 144-HCN); 116 (12.9); 115 (20.4); 89 (12.8); 77 (28.1).

3-(3,5-Dichloro-2,4,6-trimethylphenyl)-6*H*-isoxazolo[4,5-*d*][1,2]-benzodiazepine (**4**): mp 179°C (petroleum ether/ethyl acetate); ^{1}H-nmr (δ ppm): 7.48 (1H, d, J = 7.8 Hz, 7-H); 7.27 (1H, t, J = 7.5 Hz, 8-H); 7.02 (1H. t, J = 7.8 Hz, 9-H); 6.77 (1H, s, 4-H); 6.60 (1H, s_b, NH); 6.58 (1H, d, J = 8.1 Hz, 10-H); 2.49 (3H, s, CH_3 *para*); 2.14 (6H, s, CH_3 *ortho*). Ir (Nujol): 3420 cm^{-1} (NH broad). EI ms m/z(%): 371 (M^+, 100); 311 (12.5); 310 (17.1); 309 (37.8); 308 (33.5) (M^+-CO-Cl); 147 (34.3)(M^+-$C_{11}H_8NCl_2$); 120 (47.5)(m/z 147-HCN); 119 (10.9); 116 (11.0); 115 (21.8); 102 (12.9); 92 (11.9); 76(10.8); 51 (12.4).

2-(3,5-Dichloro-2,4,6-trimethylphenyl)-[1,2,4]triazolo[2,3-*a*]quinoline-1-*N*-oxide (**5**): mp 195°C (ethanol); ^{1}H-nmr (δ ppm): 10.0 (1H, d, J = 9.0 Hz, 9-H); 7.93 (1H, d, J = 7.8 Hz, 6-H); 7.83 (1H, d, J = 9.3 Hz, 5-H); 7.79 (1H, t, J = 7.8 Hz, 8-H); 7.67 (1H, t, J = 7.8 Hz, 7-H); 7.55 (1H, d, J = 9.3 Hz, 4-H); 2.60 (3H, s, CH_3 *para*); 2.26 (6H, s, CH_3 *ortho)*. EI ms m/z(%): 371 (M^+, 2.8); 357 (20.3); 356 (22.7); 355 (30.8) (M^+-O); 354 (26.5); 344 (10.4); 343 (44.8); 342 (19.0); 341 (70.5)(M^+-NO); 321 (10.7); 320 (29.3)(M^+-O-Cl); 319 (15.0); 215 (18.4)($ArCO^+$); 213 (27.7)($ArCN^+$); 180(13.6) ($ArCO^+$-Cl); 178(41.4)($ArCN^+$-Cl); 142 (7.4)(M^+-ArCNO); 129 (35.0) (quinoline$^+$); 128 (100)(quinoline$^+$-H); 115 (12.8)(m/z 142-HCN); 102 (11.1) (quinoline$^+$-HCN); 101 (19.0)(m/z 128-HCN); 77 (11.1);51 (12.7); 44 (17.1).

2-(3,5-Dichloro-2,4,6-trimethylphenyl)-[1,2,4]triazolo[2,3-*a*]quinoline (**6**): mp 235°C (ethanol); H-nmr (δ ppm): 8.48 (1H, d, J = 8.4 Hz, 9-H); 7.87 (2H, d, J = 9.4 Hz, 5-H and 6-H); 7.73 (1H, t, J = 7.8 Hz, 8-H); 7.66 (1H, d, J = 9.5 Hz, 4-H); 7.53 (1H, t, J = 7.6 Hz, 7-H); 2.57 (3H, s, CH_3 *para*); 2.16 (6H, s, CH_3 *ortho)*. ^{3}C-nmr (δ): 163.0 (2-C); 149.6 (3a-C); 135.4 (14-C); 134.6 (12-C, 16-C); 133.7 (11-C); 133.3 (9a-C); 131.0 (9-C); 130.4 (6-C); 128.8 (13-C, 15-C); 125.9 (5-C); 123.3 (5a-C); 116.1 (4-C); 115.0 (8-C, 7-C); 19.1 (CMe *para*); 18.9 (CMe *ortho*). EI ms m/z(%): 358 (21.9); 357 (65.2); 356 (68.7); 355 (M,$^+$ 100); 354 (78.7); 322 (27.9); 320 (83.9) (M^+-Cl); 319 (41.8)(M^+-HCl); 284 (14.5)(m/z 319-Cl); 227 (10.7); 178 (12.8) ($ArCN^+$-Cl); 129 (25.1) (quinoline$^+$); 128 (43.4)(quinoline$^+$-H); 115 (17.2); 102 (13.3) (quinoline$^+$-HCN); 101 (19.1)(quinoline$^+$-H-HCN); 77 (16.4); 63 (12.6); 51 (15.7).

3,5-Di(3,5-Dichloro-2,4,6-trimethylphenyl)-1,2,4-oxadiazole (**7**): mp 200°C (as in lit.[5]). EI MS m/z(%): 444 (M^+, 5.0); 442 (3.84); 429 (12.0); 427 (9.4); 401 (8.1); 230 (5.8); 229 (4.3) ($ArCNO^+$); 219 (10.5); 218 (8.6); 217 (61.3); 216 (23.0); 215 (100)($ArCO^+$); 214 (21.3); 178 (9.4); 151 (9.6); 116 (13.8); 115 (21.6); 85 (10.8); 83 (14.9); 77 (4.8).

X-ray Crystallography of 6.

The crystals used for the X-ray study were obtained from ethanol.

Crystal data: $C_{19}H_{15}N_3Cl_2$, mp 235°C, M= 356.25, monoclinic, $P2_1/c$, a= 8.600(2), b= 14.299(6), c= 27.224(4) Å, β= 91.12(2)°, V= 3347(2) Å^3, Z= 8, λ (Mo Kα)= 0.7107 Å, μ= 0.393 mm^{-1}, δ_c= 1.414 g cm^{-3}

Data collection: Colourless plate sample 0.30 x 0.36 x 0.48 mm, $2\theta_{max}$ = 50°, 5856 unique intensities [4305 with $F_o > 4\sigma(F_o)$], ψ -scan absorption correction.[24]

Structure solution and refinement: Direct methods (applied to difference structure factors by means of DIRDIF),[25] refined on F^2 (program SHELXL-93),[26] the weighting scheme being $w = [\sigma^2(F_o^2) + (0.0595P)^2 + 0.78P]^{-1}$, with $\sigma(F_o^2)$ from the counting statistics and $P = (F_o^2 + 2F_c^2)/3$, R1= 0.043 (over 4305 reflections), wR2= 0.114 (over all 5856 reflections), 523 parameters, S= 1.02, $\Delta\rho_{max}$= 0.24 e Å^{-3}, $\Delta\rho_{min}$= -0.21e Å^{-3}

All non-hydrogen but the two chlorine atoms were initially considered as carbon atoms; their identity was assessed during the refinement, on the basis of values obtained for bond distances and isotropic thermal factors. All the hydrogen atoms were located on the difference Fourier maps and were included in the subsequent refinement with isotropic thermal parameters.

Final refinement utilized anisotropic thermal parameters for all heavy atoms.

Tables of atomic coordinates, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, U.K.

Reaction selectivities

Besides the excess of diazepine, the analysis revealed the occurrence of the cycloadducts above described. The adducts were determined in the reaction mixtures, after reaction for *ca.* 10 half-lives of the nitrile oxide (0.02 mol l^{-1}) with the benzodiazepine (0.09-0.15 mol l^{-1}), in solvent mixtures containing 1,1,2,2-tetrachloroethane (TCE) and *N*,*N*-dimethylformamide (DMF) in the ratio (v/v) 90:10, 70:30, 50:50, respectively. The samples were diluted with chloroform and analyzed by reversed-phase hplc analysis. A column C_6H_5 (length 25 cm, i.d. 4.6 mm) was employed. The eluant (1 cm^3 min^{-1}) was usually a mixture methanol-water (water content 27%, v/v) and the uv detector was positioned at 242 nm. All determinations were carried out on the basis of the calibration plots on the pure compounds. 5-(4-Chlorophenyl)tetrazole was used as a reference. At least duplicated analyses were carried out and the results averaged.

Selectivity values S were obtained from the molar concentrations with formulas of the type:

$$S_3 = C_3 / (C_3 + C_4 + C_5 + C_6 + 2C_7)$$

apart from S_7, obtained as

$$S_7 = 2\ C_7 / (C_3 + C_4 + C_5 + C_6 + 2C_7)$$

taking into account that two molecules of **1** are required to form **7**.

Kinetics

The reactions were carried out in a thermostatted 0.5 mm sodium chloride cell (FH-0.1 variable temperature cell) in a FT-ir spectrophotometer. The temperature was kept constant within ± 0.2 °C. Quantitative analyses were made of the band at 2300 cm^{-1} typical of nitrile oxide (**1**). The concentration of the latter was *ca.* 0.02 mol l^{-1} while for the benzodiazepine (**2**) was in the range 0.09-0.15 mol l^{-1}. Absorbance values were obtained from the peak heights and the concentration read from calibration plots. Kinetic runs were carried out for up to two half-lives and results interpreted by the equation for second order reactions [equation (1)]:

$$\ln (c_2/c_1) = (c_2^\circ - c_1^\circ)kt + \text{constant} \qquad (1)$$

Values of c_2 were obtained as $c_2 = c_2^\circ - (c_1^\circ - c_1)$, neglecting the fact that the reaction giving rise to product (**7**) presumably does not have the 1:1 stoichiometry of the other reactions. The consequent approximation is quite good, since **2** is in excess with respect to **1**, so that even a pseudo-first order approximation would have been reasonably good, but the one adopted is certainly better.

Kinetic parameters for the single parallel reactions giving rise to the main products (**3**, **4** and **7**) could be obtained by splitting the overall kinetic coefficient k on the basis of the selectivity values S_3, S_4 and S_7 as for parallel reactions of the same order:

$$k_3 = kS_3; \quad k_4 = kS_4; \quad 2\,k_7 = kS_7 \qquad (2)$$

Splitted values are not reported for brevity.

A check of the occurrence of parallel reactions of the same order was effected by hplc analysis of samples taken at different times, during a run with 0.02 mol **1**/l and 0.11 mol **2**/l at 60°C in solvent TCE:DMF 70:30. In the region of fractional conversion beyond 50%, where products are present in concentrations suitable for a more precise determination, selectivities S_3, S_4 and S_7 were found not dependent on time within

experimental error. Therefore all parallel reactions were considered to be first-order with respect to nitrile oxide (**1**) and first-order with respect to benzodiazepine (**2**). On the other hand, the plots corresponding to equation (1) were straight lines, with no bending attributable to the presence of reactions of different orders.
Duplicate kinetic runs were always carried out with good reproducibility.

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