# Behaviour of Nitrile Oxides towards Nucleophiles. Part III.[1] Dimerisation of Aromatic Nitrile Oxides catalysed by Trimethylamine

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Reactions of aromatic nitrile oxides (1) with trimethylamine in ethanol give the dimers (2) (3,5-diaryl-1,2,4-oxadiazole 4-oxides) among other products. Kinetic measurements of reaction rates show that the dimerisations are, at low trimethylamine concentrations, first order in both nitrile oxide and nucleophile; rate constants are much lower than those reported for the catalysed dimerisation of aromatic nitrile oxides to 3,6-diaryl-1,4,2,5-dioxadiazines (6). The production of two different kinds of dimer from aromatic nitrile oxides, according to the nucleophile employed as a catalyst, is ascribed to geometrical isomerisation of intermediate open-chain 1 : 2 adducts between the nucleophile and the nitrile oxide. These are thought to be produced in the *anti*-aryl configuration (leading to dioxadiazines), but with trimethylamine as nucleophile are isomerised to the more stable *syn*-aryl configuration (leading to oxadiazole oxides).

3,5-DIARYL-1,2,4-OXADIAZOLE 4-OXIDES (2) are the main reaction products from aromatic nitrile oxides (1) and trimethylamine in ethanol. Some such compounds (2) are known;[2-5] in one case (2; Ar = 2,4-dichlorophenyl) the structure was confirmed by deoxygenation to 3,5-bis-(2,4-dichlorophenyl)-1,2,4-oxadiazole, with phosphorus pentachloride. Further proof of structure was not considered necessary, as all the dimers (2) exhibit a characteristic low-frequency u.v. absorption, with maximum above 320 nm (Table 1).

Since aromatic nitrile oxides are reported to dimerise to 3,6-diaryl-1,4,2,5-dioxadiazines (6) with pyridine as catalyst,[1,6] we have obtained kinetic data for the dimerisation (1) $\longrightarrow$ (2), in the hope of explaining this difference.

*Kinetics*.—Concentrations of dimers (2) were evaluated by measuring the u.v. absorption of the reaction mixture at 330 nm. Since oxadiazole oxides (2) are not the sole reaction products, only the initial reaction rate $\{v_i = -d[(1)]/dt\}$ was measured, and related to the starting nitrile oxide concentration, *a*, according to equation (i).

$$v_i = k[\mathrm{NMe_3}]^m a^n \qquad \text{(i)}$$

With $[\mathrm{NMe_3}]$ kept constant, the apparent reaction order in nitrile oxide ($n$) is obtained (Table 2).

At low nucleophile concentrations, dimerisations are first-order in nitrile oxide; however $n$ increases with trimethylamine concentration. From those sets of data with $n$ reasonably close to unity, the reaction order in the nucleophile ($m$) can be evaluated: linear plots of $\log(v_i/a)$ *versus* $\log[\mathrm{NMe_3}]$, for each nitrile oxide, gave the slopes ($m$) reported in Table 2. With $[\mathrm{NMe_3}] < 0.1\mathrm{M}$, the reaction is also first-order in trimethylamine. Pertinent second-order rate constants ($k$), evaluated from equation (i) with $n = m = 1$, are reported in Table 2; they show the expected influence of substituents.

*Results*.—The illustrated reaction scheme, which

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[1] Presented in part at the Vth International Congress of Heterocyclic Chemistry, Ljubljana, 1975. Part II, F. De Sarlo and A. Guarna, *J.C.S. Perkin II*, 1976, 626.

[2] H. Wieland, *Ber.*, 1907, **40**, 1667.

[3] S. Morrocchi, A. Ricca, A. Selva, and A. Zanarotti, *Gazzetta*, 1969, **99**, 165.

[4] P. Caramella and E. Cereda, *Synthesis*, 1971, 433.

[5] P. Robin, *Compt. rend.*, 1920, **171**, 1153.

[6] F. De Sarlo, *J.C.S. Perkin I*, 1974, 1951.

TABLE 1

3,5-Diaryl-1,2,4-oxadiazole 4-oxides (2)

| Ar | M.p. (all decomp.) | Yields (%)[a] from (1) |  | Found |  |  |  | Formula | Required |  |  |  | $\lambda_{max.}$/nm (log ε)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  | R.t.† | 0 °C | C (%) | H(%) | N(%) | *M* |  | C (%) | H(%) | N(%) | *M* |  |
| Ph | 134[c] | 11 |  |  |  |  |  |  |  |  |  |  | 237 (4.41), 320 (4.02) |
| 4-$MeC_6H_4$ | 165—167 | 32 |  | 72.05 | 5.2 | 10.4 | 260 | $C_{16}H_{14}N_2O_2$ | 72.2 | 5.3 | 10.5 | 266.3 | 251 (4.50), 322 (4.11) |
| 4-$MeO\cdot C_6H_4$ | 180[d] | 49 | 52 | 64.3 | 4.7 | 9.3 | 301 | $C_{16}H_{14}N_2O_4$ | 64.4 | 4.7 | 9.4 | 298.3 | 266 (4.41), 328 (4.30) |
| 4-$ClC_6H_4$ | 194 | 61 | 61 | 55.05 | 2.65 | 8.95 | 298 | $C_{14}H_8Cl_2N_2O_2$ | 54.8 | 2.6 | 9.1 | 307.1 | 252 (4.53), 330 (4.13) |
| 4-$NO_2\cdot C_6H_4$ | 200 | 36 |  | 51.0 | 2.5 | 16.8 | 329 | $C_{14}H_8N_4O_6$ | 51.2 | 2.5 | 17.1 | 328.2 | 267 (4.41), 355 (4.09) |
| 2,4-$Cl_2C_6H_3$ | 167—168 | 43 | 46 | 45.0 | 1.7 | 7.3 | 370 | $C_{14}H_6Cl_4N_2O_2$ | 44.7 | 1.6 | 7.4 | 376.0 | 238sh (4.27), 322 (3.89) |

[a] Precipitate directly collected under standard conditions, except for the 4-nitrophenyl derivative. [b] Solvent rectified spirit. [c] Refs. 2—4. [d] Lit. m.p. 182° (ref. 5).

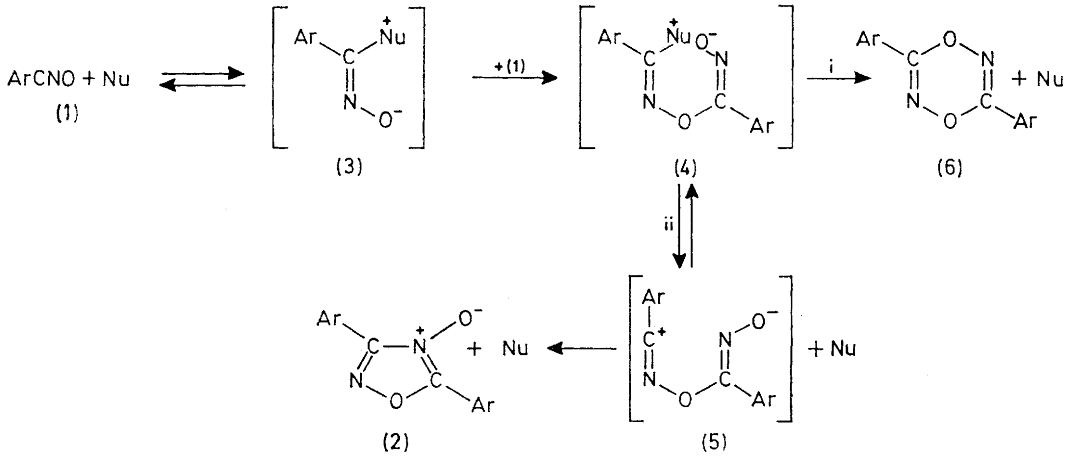
† Room temperature.

TABLE 2

Kinetics of dimerisation of nitrile oxides (1) to 1,2,4-oxadiazole 4-oxides (2) catalysed by trimethylamine, in ethanol, at 20 ± 0.2 °C

| Ar | [$NMe_3$]/M | Range of $10^2a$/M | *p* | *r* | *n* | log ($v_i/a$) (avge.) | *m* | $10^4k$ | $10^4k$ (avge.) |
|---|---|---|---|---|---|---|---|---|---|
| Ph | 0.13 | 0.64—1.83 | 7 | 0.998 0 | 1.21 |  |  |  |  |
|  | 0.08 | 1.2—3.8 | 9 | 0.993 9 | 1.05 | −4.56 | 0.92 | 3.4 | 3.7 |
|  | 0.050 5 | 1.2—3.9 | 7 | 0.997 4 | 1.02 | −4.71 |  | 3.86 |  |
|  | 0.02 | 2.2—4.3 | 7 | 0.996 5 | 0.98 | −5.11 |  | 3.85 |  |
| 4-$MeO\cdot C_6H_4$ | 0.336 | 0.39—1.18 | 7 | 0.999 6 | 1.22 |  |  |  |  |
|  | 0.244 | 0.34—1.14 | 8 | 0.993 9 | 1.56 |  |  |  |  |
|  | 0.218 | 0.37—0.94 | 7 | 0.992 3 | 1.55 |  |  |  |  |
|  | 0.136 | 0.48—1.7 | 7 | 0.998 1 | 1.31 |  |  |  |  |
|  | 0.044 5 | 0.49—1.13 | 10 | 0.997 7 | 1.13 | −4.81 | 0.94 | 3.5 | 3.5 |
|  | 0.037 6 | 0.63—1.4 | 10 | 0.995 1 | 1.08 | −4.88 |  | 3.5 |  |
|  | 0.020 3 | 0.52—1.47 | 8 | 0.998 8 | 1.01 | −5.13 |  | 3.65 |  |
| 4-$ClC_6H_4$ | 0.2 | 0.21—0.55 | 4 | 0.994 8 | 1.55 |  |  |  |  |
|  | 0.059 | 0.3—1.25 | 10 | 0.998 6 | 1.19 |  |  |  |  |
|  | 0.031 | 0.61—1.13 | 8 | 0.998 7 | 1.09 | −4.61 | 0.975 | 8.0 | 7.9 |
|  | 0.02 | 0.46—1.55 | 9 | 0.998 8 | 1.01 | −4.84 |  | 7.3 |  |
|  | 0.014 5 | 0.66—1.24 | 9 | 0.993 4 | 1.07 | −4.91 |  | 8.6 |  |

*a* = Initial nitrile oxide concentration; *p* = number of runs; *r* = correlation coefficient of linear plot log $v_i$ [or log ($\Delta E/\Delta t$)] *versus* log *a*; *n* = apparent reaction order in nitrile oxide, *i.e.* slope of the linear plot log $v_i$ [or log ($\Delta E/\Delta t$)] *versus* log *a*; *m* = reaction order in trimethylamine, *i.e.* slope of the linear plot log ($v_i/a$) *versus* log [$NMe_3$]; *k* in l $mol^{-1}$ $s^{-1}$.



SCHEME i, Nu = pyridine, substituted pyridine, or *N*-methylimidazole; ii, Nu = trimethylamine

includes the dimerisation to dioxadiazines (6) already illustrated in Part II,[1] rests upon the following observations. (*a*) Both the catalysed dimerisations of aromatic nitrile oxides (1) [to oxadiazole oxides (2) and to dioxadiazines (6)] are, under certain circumstances, second-order (first-order in each reagent). (*b*) In spite of the similarity in base strength of the two nucleophiles, the second-order rate constant for benzonitrile oxide and trimethylamine (Table 2) leading to the oxadiazole oxide (2; Ar = Ph) is *ca.* $10^4$ times lower than that[1] for the same nitrile oxide and 4-dimethylaminopyridine leading to the dioxadiazine (6; Ar = Ph).* (*c*) The reaction order in nitrile oxide is dependent on nucleophile concentration for the dimerisation to oxadiazole oxides (2), but is not for the dimerisation to dioxadiazines (6). (*d*) Nucleophilic additions to the nitrile oxide function

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* Such a difference in nucleophilic reaction rate between two classes of nucleophiles is not without precedent.[7]

[7] S. D. Ross and M. Finkelstein, *J. Amer. Chem. Soc.*, 1957, **79**, 6553.

occur with *trans*-stereochemistry, *i.e.* products have the nucleophile *trans* to the nitrogen lone pair; *cf.* addition of HCl [8,9] and polymerisation of acetonitrile oxide.[10] (*e*) Molecular models suggest that nucleophiles leading to dioxadiazines (6) should not hinder, in the intermediates (4), the approach of the charged oxygen atom to the carbon atom adjacent to the positive pole; but this reaction path appears to be sterically hindered by the trimethylammonium group.

It thus appears that the intermediates (4) are produced in the illustrated configuration and, only with trimethylamine as nucleophile, are isomerised to the *syn*-aryl configuration, which is presumably thermodynamically more stable because the two oxygen atoms lie *trans* to each other. The resulting intermediates (5) then give the dimers (2) rather than (6).

## EXPERIMENTAL

Molecular weights were measured with a Hitachi–Perkin-Elmer 115 osmometer (solvent chloroform); u.v. spectra were obtained with a Cary 14 spectrophotometer, and a Hilger-Watts spectrophotometer was used for u.v. readings at fixed wavelength.

Commercial rectified spirit was used as solvent. Aromatic nitrile oxides were prepared as described, and their purity was checked by measurements of $\nu_{C\equiv N}$ absorptions of standard solutions.[1]

*3,5-Diaryl-1,2,4-oxadiazole 4-Oxides* (2).—The nitrile oxide (100 mg) was dissolved in ethanol, and alcoholic trimethylamine was added to give 4 ml of solution *ca.* 2M in the nucleophile (30 ml for 4-nitrobenzonitrile oxide). After 3 h the precipitate was collected, dried *in vacuo* (conc. $H_2SO_4$), and weighed. Yields are in fact higher than the values reported in Table 1, since the dimers are not completely insoluble in the medium: by column chromatography the dimer (2; Ar = Ph) was isolated in 33% yield [silica gel (Merck; 70—325 mesh ASTM); eluant benzene–n-hexane (1 : 1)]. The dimers (2) are light-sensitive in solution. 3,5-Diaryl-1,2,4-oxadiazoles are always present as by-products.

*Deoxygenation of 3,5-Bis-(2,4-dichlorophenyl)-1,2,4-oxadiazole 4-Oxide*.—According to a described method,[11] the dimer (2; Ar = 2,4-dichlorophenyl) was heated at 100 °C with an excess of phosphorus pentachloride for 0.5 h. The resulting mixture was poured onto ice–water and the crude *product* was recrystallized from ethanol; m.p. 154—156° (yield 87%) (Found: C, 46.3; H, 1.8; N, 7.9. $C_{14}H_6Cl_4N_2O$ requires C, 46.7; H, 1.7; N, 7.8%).

*Estimation of Dimers* (2).—A control experiment was performed with 4-chlorobenzonitrile oxide. This was allowed to react in concentrated alcoholic solution with trimethylamine, then the reaction mixture was so diluted as to bring into solution all the precipitated dimer; another, identical reaction mixture, after removal of the precipitate, was diluted by the same amount. U.v. absorptions were compared in the range 300—350 nm: at 330 nm, the o.d. ratio was 10 : 1. Since the absorption of the filtered solution is due in part to the dimer dissolved, estimation of the dimer is practicable at this wavelength.

Another check was necessary, on the stability of the dimers under the reaction conditions. For the 4-chlorophenyl derivative in *ca.* 0.1M-trimethylamine only a 3% drop in optical density at 330 nm was found in 0.5 h; the dimers (2; Ar = Ph or 4-MeO·$C_6H_4$) are even more stable.

*Kinetics*.—The appropriate amount of alcoholic trimethylamine was added to a thermostatically controlled solution of the nitrile oxide, and the mixture was poured into the u.v. cell, within a thermostatted compartment. The change in optical density ($E$) at 330 nm was followed up to 2—4% of reaction, and plotted against time; after a short induction period, the reaction speed attained a constant value, and later began to decrease: the maximum slope was evaluated graphically to give the ratio $\Delta E/\Delta t$.

Each set of runs was carried out at fixed trimethylamine concentration and variable nitrile oxide initial concentration, $a$; the plot of log ($\Delta E/\Delta t$) *versus* log $a$ was in general a good straight line with slope $n$, the apparent reaction order in nitrile oxide. Average values of log ($\Delta E/\Delta t$) – log $a$, for those sets having $n = 1$, were converted into the values log ($v_i/a$) reported in Table 2 by use of the relation $v_i = -\mathrm{d}[(1)]/\mathrm{d}t = 2\ \mathrm{d}[(2)]/\mathrm{d}t = 2\ (\Delta E/\Delta t)/\varepsilon$, where $\varepsilon$ is the molar absorption coefficient of the dimer (2).

[6/130 *Received, 20th January,* 1976]

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[8] H. E. Ungnade, G. Fritz, and L. W. Kissinger, *Tetrahedron*, 1963, **19**, Suppl. 1, 235.

[9] J. P. Guetté, J. Armand, and L. Lacombe, *Compt. rend.*, 1967, **264**, 1509, quoted in Ch. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer-Verlag, New York, 1971, p. 154.

[10] A. Brandi, F. De Sarlo, and A. Guarna, following paper.

[11] H. Wieland, *Ber.*, 1907, **40**, 1674.