## Behaviour of Nitrile Oxides towards Nucleophiles. Part I. Pyridine-catalysed Dimerisation of Aromatic Nitrile Oxides

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When treated with pyridine in ethanol, non-hindered aromatic nitrile oxides dimerise to 3,6-diaryl-1,4,2,5-dioxadiazines, whose structures have been proved by the results of catalytic hydrogenation. The dimerisation of 2,4-dichlorobenzonitrile oxide has been shown to be second-order in the nitrile oxide and first-order in the nucleophile. A reaction scheme is suggested in which an intermediate adduct between nitrile oxide and pyridine reacts with more nitrile oxide to give the dimer.

TREATMENT of non-hindered aromatic nitrile oxides (1) with pyridine in alcoholic solution produces 3,6-diaryl-1,4,2,5-dioxadiazines (2) in excellent yields. This reaction was first noted [1] for benzonitrile oxide; later the same product (2; Ar = Ph) was obtained by dimerisation in acidic solution (excess of $BF_3$ in benzene).[2] The structure of some of the dimers (2) has been proved through their conversion by catalytic hydrogenation into aromatic amides in yields exceeding 50%; had the yields been lower than 50%, other structures

[1] G. Speroni and M. Bartoli, ' Sopra gli ossidi di benzonitrile,' nota VIII, Stabilimento Tipografico Marzocco, Firenze, 1952; quoted in ref. 4, p. 82.

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

could not have been excluded. U.v. and i.r. data for the dimers (2) are summarised in Table 2.
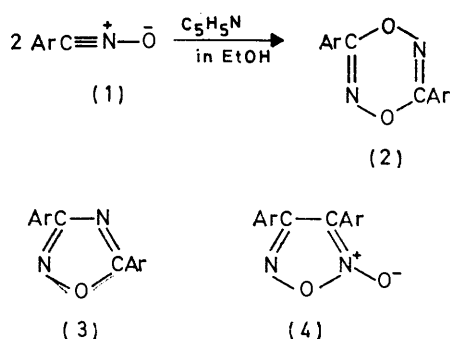


SCHEME 1

The influence of the solvent on the dimerisation (1) ⟶ (2) is indicated by the observation that the yield of dimer from (1; Ar = 4-ClC$_6$H$_4$) gradually increases with the solvent dielectric constant (see Experimental section). Several by-products are formed [among them, 3,5-bis-$p$-chlorophenyl-1,2,4-oxadiazole (3; Ar = 4-Cl-C$_6$H$_4$) and the corresponding 4-oxide]; however, under our experimental conditions, the 3,4-bis($p$-chlorophenyl)-1,2,5-oxadiazole 5-oxide (4; Ar = 4-ClC$_6$H$_4$), which is usually produced in neutral medium, is scarcely detectable, even in carbon tetrachloride solution.†

A preliminary kinetic study on 2,4-dichlorobenzonitrile oxide has shown that the dimerisation to (2; Ar = 2,4-Cl$_2$C$_6$H$_3$) is second order in nitrile oxide and first order in pyridine; the catalytic constants are given in Table 1, and the activation parameters evaluated

TABLE 1

Kinetic data for the dimerisation of 2,4-dichlorobenzo-nitrile oxide with pyridine

| Temp. (°C) | Concentration range (M) | | $k =$ $k_{obs}/[C_5H_5N]$ * |
|---|---|---|---|
| | Nitrile oxide | Pyridine | |
| 0 | 0·0118—0·0313 | 0·151—0·359 | 0·0133 ± 0·0003 |
| 20 | 0·0160—0·0335 | 0·108—0·499 | 0·0222 ± 0·0006 |
| 30 | 0·0133—0·0388 | 0·096—0·497 | 0·0286 ± 0·0009 |

* Average of six (at 0 and 20°) or eleven runs (at 30°).

therefrom are: $E_a = 17\cdot5 \pm 0\cdot8$ kJ mol$^{-1}$; $\Delta H^{\ddagger} = 15\cdot1 \pm 0\cdot8$ kJ mol$^{-1}$; $\Delta S^{\ddagger} = -225 \pm 3$ J mol$^{-1}$ K$^{-1}$ (at 20 °C).

On the basis of the postulated reversible formation of inner salts from tertiary amines and nitrile oxides
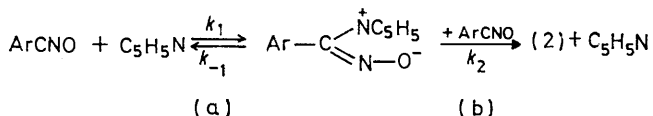


SCHEME 2

(ref. 4, p. 167), Scheme 2 represents a reasonable reaction pathway, stage (b) being the slow step. Use of the

† The rate of dimerisation of (1; Ar = 4-ClC$_6$H$_4$) to the corresponding 1,2,5-oxadiazole oxide in carbon tetrachloride has been reported [3] to be unaffected by the addition of tertiary amines; however, the pyridine concentration in those experiments (0·02 or 0·04M) was so low as not to alter the course of dimerisation to oxadiazole oxide significantly.

steady-state approximation for the polar intermediate yields the pertinent rate equation (i). Since that the

$$-d[(1)]/dt = 2k_1k_2[(1)]^2[C_5H_5N]/\{k_{-1} + k_2[(1)]\} \quad (i)$$

reaction has been found to be second order in (1) and that equilibrium (a) lies well to the left,[4] $k_2[(1)]$ can be neglected with respect to $k_{-1}$, and equation (i) becomes: $-d[(1)]/dt = 2k_1k_2[(1)]^2[C_5H_5N]/k_{-1}$. This agrees with the kinetic findings reported in Table 1, where $k = 2k_1k_2/k_{-1}$.

The low value of $\Delta H^{\ddagger}$ is expected for a reaction involving chemical catalysis, and the high negative value of $\Delta S^{\ddagger}$ is in agreement with a transition state involving three reacting molecules and presumably several solvent molecules. The solvent effect outlined above would be expected if the intermediate is polar, as indicated.

For a more detailed interpretation of stage (b), further data are needed. Studies of the influence of base strength and of aryl substituents in (1) on reaction rates are in progress.

EXPERIMENTAL

The following instruments were used: a Hitachi–Perkin-Elmer osmometer model 115 (for molecular weights), Perkin-Elmer 457 (for i.r.) and Cary 14 (for u.v.) spectrometers, and a Hilger–Watts spectrometer for u.v. readings at fixed wavelength.

*Benzohydroxamoyl Chlorides.*—These were in general prepared according to the reported method, by chlorination of the corresponding oximes. 2,4-Dichlorobenzohydroxamoyl chloride, obtained by chlorination of 2,4-dichlorobenzaldehyde oxime in ice-cold chloroform (yield 78%), had m.p. 95—98° (decomp.) (from petroleum) (lit.,[5] 100—105°) (Found: C, 37·9; H, 1·8; N, 6·3. Calc. for C$_7$H$_4$Cl$_3$NO: C, 37·45; H, 1·8; N, 6·2%).

*Nitrile Oxides.*—A slight excess of ethereal triethylamine was added in the cold to the appropriate benzohydroxamoyl chloride in distilled ether. After 10 min the precipitate of amine hydrochloride was removed and washed. The ethereal solution was washed with dilute sulphuric acid, then with water until neutral, and dried (CaCl$_2$). Concentration under vacuum gave the crude nitrile oxide. Benzonitrile oxide was more conveniently prepared in aqueous medium, according to the literature method.[6]

*2,4-Dichlorobenzonitrile oxide* ‡ had m.p. 85—86° (from

‡ The only record of the 2,4-dichlorobenzonitrile oxide relates to its i.r. spectrum,[5] the product being directly prepared in carbon tetrachloride solution; a solid derivative, m.p. 159—160°, was also recorded, and reported to be the corresponding 1,2,5-oxodiazole oxide. After we had prepared and purified the nitrile oxide (1; Ar = 2,4-Cl$_2$C$_6$H$_3$) we tried to convert it into the 1,2,5-oxadiazole oxide by simple heating, and obtained a dimer melting at 97—98°: attempts to obtain the compound reported [5] with m.p. 159—160° were unsuccessful. To make sure that the compound melting at 97—98° was in fact the 1,2,5-oxadiazole oxide, we converted it by catalytic hydrogenation into a dioxime: this was then hydrolysed to 2,2',4,4'-tetrachlorobenzil, identical with a sample prepared directly from 2,4-dichlorobenzaldehyde. Other data in ref. 5 are incorrect: for instance, 3,4-bis-$p$-chlorophenyl-1,2,5-oxadiazole oxide has m.p. 144—145° rather than the reported 180—181°.

[3] G. Barbaro, A. Battaglia, and A. Dondoni, *J. Chem. Soc. (B)*, 1970, 588.

[4] Ch. Grundmann and P. Grünanger, ' The Nitrile Oxides,' Springer-Verlag, New York, 1971.

[5] R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, 1960, 25, 546.

[6] A. Quilico and G. Speroni, *Gazzetta*, 1946, 76, 159.

ethanol) [Found: C, 45·15; H, 1·8; N, 7·5%; M, 194 (in benzene at 40°). $C_7H_3Cl_2NO$ requires C, 44·7; H, 1·6; N, 7·45%; M, 188]. Cycloadducts have been prepared from this nitrile oxide with N-benzylidenemethylamine [yield 57%; m.p. 90—92° (from ethanol) (Found: C, 58·6; H, 3·8; N, 9·0. Calc. For $C_{15}H_{12}Cl_2N_2O$: C, 58·7; H, 3·9; N, 9·1%)] and with phenylacetylene [yield 70%; m.p. 98—100° (from ethanol) (Found: C, 62·0 H, 3·0; N, 4·7. $C_{15}H_9Cl_2NO$ requires C, 62·1; H, 3·1; N, 4·8%)]. When heated above its m.p., this nitrile oxide produced 3,4-bis-(2,4-dichlorophenyl)-1,2,5-oxadiazole 5-oxide, m.p. 97—98° (from methanol) [Found: C, 44·3; H, 1·85; N, 7·2%; M, 376 (cryoscopic in benzene). $C_{14}H_6Cl_4N_2O_2$ requires C, 44·7; H, 1·6: N, 7·45%; M, 376]. The last compound was

128°; 4-$ClC_6H_4$, 70%, 170—174, 170, or 179°; 2,4-$Cl_2C_6H_3$, 64%, 186—190, 193—194°.

*Solvent Effect on the Dimerisation of the Nitrile Oxide* (1; Ar = 4-$ClC_6H_4$).—A *ca.* 0·05M-solution of the nitrile oxide in the appropriate solvent was treated at room temperature with 0·04 vol. of pyridine (*i.e.* concentration *ca.* 0·5M). After several hours the dimer (2; Ar = 4-$ClC_6H_4$) was collected, dried (conc. $H_2SO_4$), and weighed. Solvents and yields were as follows (figures in parentheses are those obtained by making allowance for the dimer remaining in solution): EtOH 94 (98), AcMe 57 (70), $CH_2Cl_2$ 29 (47), $Et_2O$ 0 (max. 3), $CCl_4$ 0 (max. 8), $C_6H_6$ 0 (max. 12%). T.l.c. showed the formation, in $CCl_4$ or $C_6H_6$, of 3,5-bis-*p*-chlorophenyl-1,2,4-oxadiazole, its 4-oxide, and other

TABLE 2

3.6-Diaryl-1,4,2,5-dioxadiazines (2)

| Ar | M.p. (°C) (all decomp.) | Found | | | | Formula | Required | | | | U.v.*b* | | i.r.*e* heterocyclic ring modes (cm⁻¹) (approximate descriptions) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | C(%) | H(%) | N(%) | M *a* | | C(%) | H(%) | N(%) | M | λmax. | log ε | ν(C–N) | νas(C–O–N) | νs(C–O–N) | |
| Ph | 101—102 | | | | | | | | | | 249 *c* | 4·54 *c* | 1615m | 1340vs | 1090m | 850m |
| 4-MeC6H4 | 167—168 | 72·0 | 5·1 | 10·5 | 252 | $C_{16}H_{14}N_2O_2$ | 72·2 | 5·3 | 10·5 | 266·3 | 258 | 4·62 | 1610s | 1340vs | 1080s | 862ms |
| 4-MeO·C6H4 | 180 | 64·0 | 4·7 | 9·1 | 293 | $C_{16}H_{14}N_2O_4$ | 64·4 | 4·7 | 9·4 | 298·3 | 278 | 4·61 | 1605s | 1340s | 1080m | 867m |
| 4-ClC6H4 | 220—221 | 55·0 | 2·5 | 9·3 | 300 | $C_{14}H_8Cl_2N_2O_2$ | 54·8 | 2·6 | 9·1 | 307·1 | 259 | 4·65 | 1620m | 1340vs | 1094s | 870m |
| 2,4-Cl2C6H3 | 170—171 | 45·0 | 1·8 | 7·5 | 370 | $C_{14}H_6Cl_4N_2O_2$ | 44·7 | 1·6 | 7·4 | 376·0 | 250 *d* | 4·46 | 1628m | 1337s | 1102s | 857m |
| 4-NO2·C6H4 | 219—220 | 51·5 | 2·5 | 16·9 | 313 | $C_{14}H_8N_4O_6$ | 51·2 | 2·5 | 17·1 | 328·2 | 272 | 4·46 | 1625w | 1335vs | 1078s | 867m |
| 3-NO2·C6H4 | 177—179 | 51·4 | 2·45 | 16·75 | 333 | $C_{14}H_8N_4O_6$ | 51·2 | 2·5 | 17·1 | 328·2 | 242 | 4·67 | 1615s | 1335vs | | 868m |

*a* Osmometric in benzene, except (2; Ar = 4-$ClC_6H_4$ or 4-$NO_2·C_6H_4$), in chloroform. *b* Solvent EtOH: λ in nm. *c* Ref. 2. *d* Shoulder at *ca.* 280 nm. *e* KBr pellets.

hydrogenated in ethanol over Raney nickel, at room temperature and *ca.* 3 atm pressure. The product, washed with ether, had m.p. 258° (decomp.) (Found: C, 45·2; H, 2·7; Cl, 36·9; N, 7·0. Calc. for $C_{14}H_8Cl_4N_2O_2$: C, 44·5; H, 2·1; Cl, 37·5; N, 7·4%). This dioxime was hydrolysed by heating at 180—190° for 9 h with conc. hydrochloric acid. in a sealed tube: the resulting 2,2′,4,4′-tetrachlorobenzil had m.p. 147—148° (from ethanol) (Found: C, 47·6; H, 2·2. Calc. for $C_{14}H_6Cl_4O_2$: C, 48·3; H, 1·7%), and was identical with that obtained from 2,4-dichlorobenzaldehyde by benzoin condensation and nitric acid oxidation (m.p., mixed m.p., and i.r. spectra).

*3,6-Diaryl-1,4,2,5-dioxadiazines* (2).—An ethanolic solution of the nitrile oxide became yellow as soon as an excess of pyridine was added. After a few minutes precipitation of small needles usually started: the dimers (2) are, in general, sparingly soluble in ethanol. When the colour had faded or disappeared, the product was collected (yields often >80%) and crystallised from ethanol. Analytical and spectroscopic data are collected in Table 2.

*Catalytic Hydrogenation of the Dimers* (2).—Some of the dimers (2) were hydrogenated (2 h) to the corresponding amides, in dioxan solution, at room temperature, over Raney nickel at 2—3 atm pressure. Aryl groups (Ar), yields of crystallised amide ($ArCONH_2$), m.p.s, and literature m.p.s are as follows: Ph, 71%, 124—127°,

unidentified products, as well as small amounts of (2; Ar = *p*-$ClC_6H_4$) and 3,4-bis-*p*-chlorophenyl-1,2,5-oxadiazole 5-oxide.

*Kinetics.*—Owing to the poor solubility of the reaction products (2) [*e.g.* a saturated solution of (2; Ar = 2,4-$Cl_2C_6H_3$) in EtOH at room temperature is about 4 × $10^{-4}$M], it is necessary to follow the reaction by observing the disappearance of the nitrile oxide. U.v. analysis is only practicable in the case where Ar = 2,4-$Cl_2C_6H_3$, for which [probably owing to the non-coplanarity of the heterocyclic and aromatic rings in (2)] the spectra of (1) and (2) are different enough. From the values of the absorption coefficients at 233 and 271 nm [(1; Ar = 2,4-$Cl_2C_6H_3$): $\varepsilon_{233}$ = 1900, $\varepsilon_{271}$ = 15,400; (2; Ar = 2,4-$Cl_2C_6H_3$): $\varepsilon_{233}$ = 16,750, $\varepsilon_{271}$ = 5220] it follows that the nitrile oxide concentration is $(3·21E_{271} - E_{233})/47,500$.

*Materials.*—Ethanol was commercial rectified spirit. Commercial pyridine was refluxed over KOH flakes, then distilled into a standard flask and weighed in order to obtain a standard ethanolic solution.

*Procedure.*—Clear samples were periodically withdrawn with a U-shaped pipette carrying in the middle a plate of porous sintered glass, then appropriately diluted for u.v. readings.