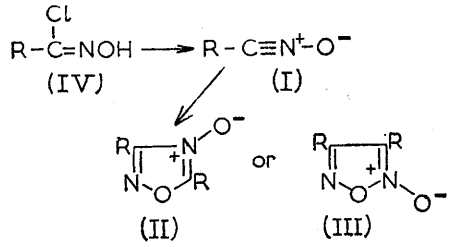
N-Oxides and Related Compounds. Part XXXVI.[1] Isomerism in the Oxadiazole Series

By **A. J. Boulton, P. Hadjimihalakis, A. R. Katritzky,* and A. Majid Hamid,** School of Chemical Sciences, University of East Anglia, Norwich

The structures of the dimerisation products of *p*-chlorobenzonitrile oxide have been established. Products derived from anethole by the action of nitrous acid are shown to be the isomeric furoxans and the equilibration of these isomers is described.

THE dimerisation of nitrile oxides (I) can occur in two ways, to give 1,2,4-oxadiazole 4-oxides (II) or 1,2,5-oxadiazole 2-oxides (III).[2]† Usually the furoxan structure (III) is obtained. Wiley and Wakefield [3] prepared a compound, m.p. 180—181°, described as 3,4-bis-(*p*-chlorophenyl)furoxan (III; R = *p*-C_6H_4Cl) by the dehydrochlorination of the chloro-oxime (IV; R = *p*-C_6H_4Cl) using aqueous sodium hydroxide. Quilico,[4] however, has listed the same furoxan (III; R = *p*-C_6H_4Cl), prepared by dimerisation of the nitrile oxide, having m.p. 144—145°, and Truce and Naik [5] reported 139—142°. Ruggeri,[6] in the course of a study on nitrolic acids, quoted 193—194° for the m.p. of 'di-*p*-chlorobenzil dioxime peroxide,' also listed in Beilstein as the furoxan.‡

In our hands, the procedure of Wiley and Wakefield gave, in small yield, a product, m.p. 143—144°. The same material was obtained by dehydrochlorination of the chloro-oxime (IV; R = *p*-C_6H_4Cl) with triethylamine in benzene, in considerably improved yield (50%). We were unable to isolate any material of m.p. 180°. We subsequently learnt that Berg,[7] attempting to repeat the above preparation by a modification of the published [3] route (specifically, using 14% aqueous sodium hydroxide at 0°), obtained two isomeric products, m.p. 145—146° (36%) and 190° (5%).



We have now established that the lower-melting isomer, identical with our product, is the furoxan (III; R = *p*-C_6H_4Cl), by mass spectrometry and by an unambiguous synthesis, and that the higher-melting product, presumably identical with that of Ruggeri,[6] is the 1,2,4-oxadiazole 4-oxide (II; R = *p*-C_6H_4Cl). Mass spectra of furoxans have been briefly reported, in particular by Ungnade and Loughran,[8] and Grundmann and his co-workers.[9] The latter group established the structure of mesitonitrile oxide dimer as the corresponding furoxan by this method, and, in agreement with

† A third dimerisation mode, catalysed by BF_3 and forming 1,4-dioxa-2,5-diazines, has recently been reported (S. Morocchi, A. Ricca, A. Selva, and A. Zanarotti, *Gazzetta*, 1969, **99**, 165).

‡ Ruggeri's product has recently been established to be *p*-chlorobenzoic anhydride (M. Calleri, G. Ferraris, and D. Viterbo, *Atti Accad. Sci. Torino*, 1965—1966, **100**, 1). We thank Dr. Calleri for correspondence on this point.

[1] Part XXXV, A. R. Katritzky and E. Lunt, *Tetrahedron*, 1969, in the press.

[2] J. H. Boyer, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, vol. 7, Wiley, New York, 1961, p. 514.

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

[4] A. Quilico, in 'Chemistry of Heterocyclic Compounds,' ed. A. Weissberger, vol. 17, Interscience, New York, 1962, p. 21.

[5] W. E. Truce and A. R. Naik, *Canad. J. Chem.*, 1966, **44**, 297.

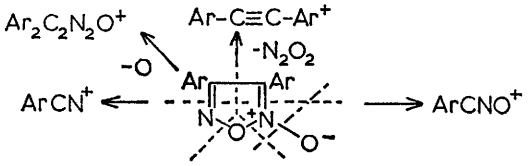
[6] G. Ruggeri, *Gazzetta*, 1923, **53**, 691; Beilstein, *EII*, 1955, **27**, 645.

[7] Dr. S. S. Berg (May and Baker, Ltd., Dagenham, Essex), personal communication.

[8] H. E. Ungnade and E. D. Loughran, *J. Heterocyclic Chem.*, 1964, **1**, 61.

[9] C. Grundmann, H.-D. Frommeld, K. Flory, and S. K. Datta, *J. Org. Chem.*, 1968, **33**, 1464.

them, we find that diarylfuroxans behave in a characteristic manner on electron impact, giving $(M - O)^+$, $(M - N_2O_2)^+$, $(ArCN)^+$, and $(ArCNO)^+$ as major fragment ions (Scheme). We have also observed that $(M - N_2O_2)^+$ ions figure prominently in the spectra of other furoxans and benzofuroxans. Berg's isomeric compound, m.p. 190°, had a very intense $(M - O)^+$ peak, with little below that until the $(ArCNO)^+$ fragment is reached. Other bands, corresponding to $(ArCN)^+$ and $(ArCO)^+$, leave no doubt that the isomer is the 1,2,4-oxadiazole 4-oxide (II; R = *p*-C_6H_4Cl). Both compounds were deoxygenated by triethyl phosphite, and the fragmentation patterns of the products were also consistent with their structures, assigned as the corresponding 1,2,5- and 1,2,4-oxadiazoles. No peak corresponding to $ArCO^+$ was found in the spectrum of the furoxan or the furazan; however, it was fairly weak in that of the 1,2,4-oxadiazole, and is not therefore proposed as a general diagnostic criterion for the latter structure. The



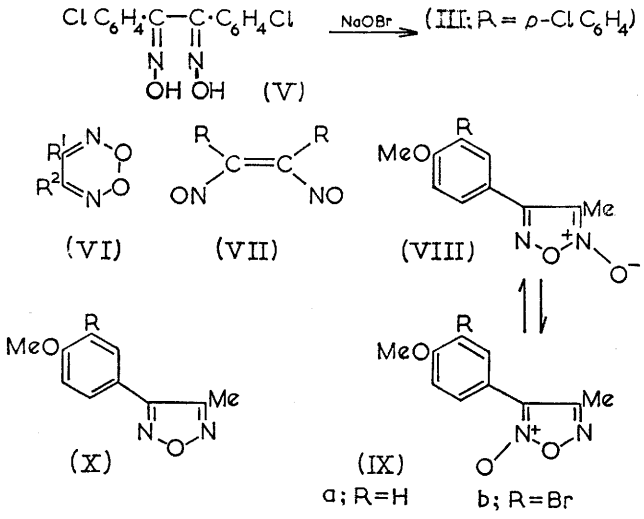
SCHEME

furoxan (III; R = *p*-C_6H_4Cl) was also prepared by oxidation of 4,4′-dichlorobenzil dioxime (V), thus confirming the presence of the heteroannular C–C bond, suggested by the mass spectrum.

When the two substituent groups of a furoxan (III) are different, further isomerism can arise, depending on their positions relative to the *N*-oxide group. Several instances of such isomerism exist,[10] and although in the past it has been held that the isomerism was structural, between furoxan (III) and dioxadiazine (glyoxime peroxide) (VI) structures, the view that it is positional now generally prevails, and an *X*-ray structure determination has confirmed this for one isomer pair.[11] Interconversion of isomers, *via* the dinitrosoethylene intermediate (VII), has been studied by Mallory and Cammarata,[12] who assigned structures to isomers of dialkyl- and phenylmethyl-furoxans based on n.m.r. criteria. At the time that their paper appeared, we were studying the isomerism [(VIII) ⇌ (IX)] of certain arylalkylfuroxans: we here present a brief account of the work, and correct some literature structural assignments.

Reaction of anethole (*p*-propen-1-ylanisole) with nitrous acid [13-15] leads to a compound, m.p. 99°, assigned the furoxan structure (VIIIa or IXa) by Ponzio.[13,16,17] When this compound was refluxed in acetic anhydride, or simply heated alone, then treated in each case with sodium ethoxide, an isomer, m.p. 80—81° was obtained, to which he assigned the dioxadiazine structure (VI; R^1 = *p*-C_6H_4·OMe, R^2 = Me). Ponzio also reduced the compound, m.p. 99°, to the furazan (Xa) and brominated it to give a monobromo-derivative, m.p. 109°. The last compound could be isomerised by heat, followed by treatment with alkali, to a compound, m.p. 155—116°, and these two compounds were listed as a dioxadiazine and a furoxan, respectively.

In our hands, all these compounds were readily obtained from anethole by the methods described by the earlier workers. In addition, *both* the furoxan, m.p. 99°, and its supposed 'dioxadiazine' isomer, m.p. 80—81°, were smoothly deoxygenated by triethyl phosphite to 3-*p*-methoxyphenyl-4-methylfurazan (Xa), m.p. 65—66°. The isomerisation of the isomer of m.p. 99° was observed by heating a solution in tetrachloroethylene–bromoform containing a few drops of tetramethylsilane in a sealed tube at 130—140°, and examining the n.m.r. spectrum at intervals during 8 hr. Initially, the 'methyl region' contained a single peak, τ 7·68, which was joined by another, τ 7·51, after heating. An equilibrium was established and the final ratio of the peak heights was 1·6 : 1. The isomer, m.p. 80—81°, also



showed a single peak, τ 7·51, and on heating under the same conditions as the first gave a second peak at τ 7·68, which soon exceeded the intensity of the first. The spectra of the two compounds on equilibration were identical, both in the τ 7—8 region and in that part of the 'aromatic' region unobscured by the solvent. The monobromo-derivatives behaved similarly on heating; the equilibrium mixture contained the isomers of m.p. 109° and 116—117° in a ratio 1·6 : 1.

The structures of the isomers are as indicated in the

[10] J. V. R. Kaufman and J. P. Picard, *Chem. Rev.*, 1959, **59**, 429.
[11] M. Calleri, G. Ferraris, and D. Viterbo, *Tetrahedron Letters*, 1967, 4549.
[12] F. B. Mallory and A. Cammarata, *J. Amer. Chem. Soc.*, 1966, **88**, 61. The correctness of the n.m.r. assignments has been confirmed by n.m.r. investigation of the bromophenyl methyl isomers studied in ref. 11 (Altaf-ur-Rahman and A. J. Boulton, unpublished work, 1969).
[13] G. Ponzio, *Ber.*, 1928, **61**, 1316; *Gazzetta*, 1928, **58**, 329.
[14] P. Toennies, *Ber.*, 1880, **13**, 1845.
[15] G. Boeris, *Gazzetta*, 1893, **23***II*, 165.
[16] G. Ponzio, *Gazzetta*, 1929, **59**, 713.
[17] G. Ponzio and M. Milone, *Gazzetta*, 1928, **58**, 844.

Table. These assignments are based principally on the chemical shifts of the methyl groups: those adjacent to

	M.p.	$\tau(CH_3)$	$\lambda_{max.}(m\mu)$ (ε)
(VIIIa)	99°	7·68	238 (15,200), 272 (13,000)
(VIIIb)	109	7·68	
(IXa)	80—81	7·51	242·5 (18,400), 291 (9800)
(IXb)	116—117	7·48	

the *N*-oxide (VIII) give signals upfield of those of isomers (IX).[12] These conclusions are in agreement with the chemical evidence provided (but incorrectly interpreted) by Ponzio:[13,16,17] the 'isoxazolinic rearrangement' of methylfuroxans results in isomer (VIII) being readily degraded by alkali, hence the necessity for the alkali treatment in the conversion of isomers (VIII) into (IX). The equilibrium constants imply a ΔG° value of *ca.* 0·4 kcal./mole (at 135°) in favour of isomer (VIII). For phenylmethylfuroxan, Mallory and Cammarata[12] have reported an equilibrium constant (at 136·3°) of 0·796, corresponding to a ΔG° value of *ca.* 0·2 kcal./mole, also in favour of the isomer with the methyl group adjacent to the *N*-oxide oxygen.

EXPERIMENTAL

3,4-*Bis*-(p-*chlorophenyl*)*furoxan* (III; R = *p*-ClC_6H_4).—(a) *p*-Chlorobenzaldoxime, m.p. 109—110°, and *p*-chlorobenzohydroxamoyl chloride, m.p. 78—79°, were prepared by standard methods[18] (lit.,[18] 110° and 76—77°, respectively). The hydroxamic acid chloride (5·0 g.) was set aside in benzene (50 ml.) and triethylamine (5 ml.) at 20° for 12 hr. Triethylamine hydrochloride was filtered off, excess of base was removed by extraction with dil. hydrochloric acid, and the solvent was removed from the filtrate, leaving the furoxan, which crystallised from ethanol as white needles (2·0 g., 50%), m.p. 143—144° (lit.,[4] 144—145°; lit.,[5] 139—140°).

(b) 4,4′-Dichlorobenzoin was prepared[19] from *p*-chlorobenzaldehyde, and was oxidised ($CuSO_4$–pyridine)[20] to the benzil (34%), yellow needles, m.p. 195—196° (lit.,[19] 194—196°). 4,4′-Dichlorobenzil (20 g.) was heated under reflux for 5 hr. with hydroxylamine hydrochloride (19 g.) and methanol (110 ml.). The *dioxime*, which unlike the benzil and its mono-oxime was fairly soluble in methanol, was recovered by evaporation of the solvent and crystallised from aqueous methanol as white needles, m.p. 226° (decomp.) (Found: C, 54·3; H, 3·3; N, 8·9. $C_{14}H_{10}Cl_2N_2O_2$ requires C, 54·4; H, 3·2; N, 9·1%). The dioxime was oxidised to the furoxan as described by Grundmann[9] for dimesityl diketone dioxime. The product was identical with the dimer, m.p. 143—144°, of *p*-chlorobenzonitrile oxide prepared as already described.

3,4-*Bis*-(p-*chlorophenyl*)*furazan*.—The furoxan (III; R = *p*-ClC_6H_4) (2·0 g.) was deoxygenated by refluxing for 26 hr. with triethyl phosphite (25 ml.). Pouring into water (150 ml.), containing 10N-hydrochloric acid (*ca.* 5 ml.) to accelerate the hydrolysis of the excess of phosphite, gave the *furazan* (1·39 g., 73%), which crystallised from ethanol as elongated white prisms, m.p. 138—140° (Found: C, 57·7; H, 2·6; N, 9·8. $C_{14}H_8Cl_2N_2O$ requires C, 57·7; H, 2·75; N, 9·65%). Trimethylphosphite gave a reflux temperature too low for the reduction to proceed satisfactorily.

3,5-*Bis*-(p-*chlorophenyl*)-1,2,4-*oxadiazole*.—A sample of the corresponding 4-oxide (II; R = *p*-ClC_6H_4) (0·1 g.), m.p. 190° (supplied by Dr. S. S. Berg[7]), was deoxygenated as already described, to give the oxadiazole (0·08 g., 85%) as white needles, m.p. 180—181° (lit.,[6] 180—181°).

4-*p*-Methoxyphenyl-3-methylfuroxan (VIIIa), m.p. 98—99° (lit.,[13] 99°), and 3-*p*-methoxyphenyl-4-methylfuroxan (IXa), m.p. 80—81° (lit.,[13] 80—81°), were prepared as described by Boeris[15] and Ponzio.[13]

4-(3-*Bromo*-4-*methoxyphenyl*)-3-*methylfuroxan* (VIIIb).—4-*p*-Methoxyphenyl-3-methylfuroxan (1·0 g.) was brominated in acetic acid,[14] and crystallised from ethanol, giving plates or short needles (1·1 g., 80%), m.p. 109° (lit.,[14] 109—110°).

3-(3-*Bromo*-4-*methoxyphenyl*)-4-*methylfuroxan* (IXb).—Prepared by bromination of 3-*p*-methoxyphenyl-4-methylfuroxan (1·0 g.), this product, m.p. 116° (lit.,[13] 115—116°) (1·2 g., 88%), formed needles from ethanol, and was identical with a sample prepared by rearrangement of 4-(3-bromo-4-methoxyphenyl)-3-methylfuroxan.[13]

3-p-*Methoxyphenyl*-4-*methylfurazan* (Xa).—(a) 4-*p*-Methoxyphenyl-3-methylfuroxan (1·0 g.) was deoxygenated with triethyl phosphite (10 ml.) in the usual way, giving elongated prisms from ethanol (0·9 g., 96%), m.p. 65—66° (lit.,[17] 65—66°).

(b) The same product (compared by m.p., mixed m.p., and i.r. and u.v. spectra) (0·85 g., 91%) was obtained on deoxygenation of 3-*p*-methoxyphenyl-4-methylfuroxan (1·0 g.), τ (4-CH_3) 7·45, $\lambda_{max.}$ 266·5 mμ (ε 10,700).

In a similar way, 3-(3-bromo-4-methoxyphenyl-4-methylfurazan (Xb), m.p. 76—77° (lit.,[14] 76°) was prepared from both isomeric bromomethoxyphenyl methyl furoxans, and in both cases in nearly quantitative yields; τ (4-CH_3) 7·45.

N.m.r. spectra were taken with a Perkin-Elmer 40 Mc./sec. spectrometer. Samples to be heated were dissolved in tetrachloroethylene–bromoform (2 : 1), to reduce the danger of explosion of the tubes. The rest of the spectra were of solutions in chloroform. Tetramethylsilane was used as internal reference.

Mass spectra were run with a Perkin-Elmer–Hitachi RMU-6E instrument. Inlet temperatures were generally between 180° and 250°; and ionisation potential 70 ev.

We thank Dr. S. S. Berg[7] for sending samples of the *p*-chlorobenzonitrile oxide dimers, and Dr. E. Lunt for calling our attention to this work. We also thank the British Council for the award of a visiting fellowship, the University of Thessaloniki for leave of absence (to P. H.), and the Pakistan Council of Scientific and Industrial Research (Lahore) for granting study leave (to A. M. H.).

[9/505 *Received, March* 21*st*, 1969]

[18] T. Farley, F. H. Rathmann, and D. Tangen, *Proc. N. Dakota Acad. Sci.*, 1959, **13**, 61 (*Chem. Abs.*, 1960, **54**, 5619).

[19] A. Hantzsch and W. H. Glower, *Ber.*, 1907, **40**, 1519.

[20] H. T. Clarke and E. E. Dreger, *Org. Synth.*, 1932, Coll. Vol. I, 87.