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Polyhalogenoaromatic Compounds. Part XII.¹ Synthesis and Cycloaddition Reactions of Pentafluoro- and Pentachloro-benzonitrile N-Oxide

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Pentafluoro- and pentachloro-benzonitrile N-oxide were prepared from the corresponding pentahalogenobenzaldehyde oximes. The fluoro-compound dimerised to 3,4-bis(pentafluorophenyl)furoxan, whereas the chlorocompound was stable. Both the nitrile oxides readily underwent cycloadditions with styrene and phenylacetylene. to give the appropriate 3-pentahalogenophenyl-5-phenyl-isoxazolines and -isoxazoles.

NITRILE N-OXIDES are versatile and readily available reagents for the synthesis of heterocyclic compounds by 1,3-dipolar cycloadditions.² A characteristic reaction of these dipolar compounds, which is frequently en-

¹ Part XI, E. Ager, B. Iddon, and H. Suschitzky, *J. Chem.* Soc. (C), 1970, 193. ² C. Grundmann, Fortschr. Chem. Forsch., 1966, 7, 62.

countered as an undesirable side reaction, is their dimerisation, generally to furoxans.^{2,3}

The effect of steric factors on the rate of dimerisation is straightforward; thus, aryl-nitrile N-oxides with bulky ortho-substituents, such as mesitonitrile N-oxide,

⁸ (a) R. Koreff, Ber., 1886, **19**, 176; (b) S. Morrocchi, A. Ricca, A. Selva, and A. Zanarotti, Gazzetta, 1969, **99**, 165.

dimerise slowly and only under certain conditions.^{4,5} The influence of polar factors is less straightforward. A preliminary study of a limited number of compounds indicated that the dimerisation followed second-order kinetics, and that the reaction was slowed by electronreleasing substituents.⁶ Earlier semi-quantitative observations suggested that the reaction was slowed both by electron-releasing, and, particularly, by electronwithdrawing substituents; for example, m-nitrobenzonitrile N-oxide was dimerised completely only after 20-25 days at 18°, compared with 30-60 min. for benzonitrile N-oxide.7

Fluorine atoms in the ortho-positions are too small to prevent dimerisation by steric hindrance; 5a we prepared pentafluorobenzonitrile N-oxide (IIIa) in the hope of obtaining a compound in which dimerisation would be prevented or drastically slowed by the influence of the five electron-withdrawing substituents.

Attempts to prepare pentafluorobenzonitrile N-oxide (IIIa) via the chloro-oxime (IIa) met with only limited success. Direct chlorination of pentafluorobenzaldehyde oxime (Ia)^{8,9} failed to yield the chloro-oxime (IIa). However, treatment of the oxime (Ia) with nitrosyl chloride ¹⁰ gave an oil, which could not be purified, but whose i.r. spectrum showed peaks at 3500-3300 cm.⁻¹ (OH) but not at 3010 cm.⁻¹ (=CH), and whose ¹H n.m.r. spectrum showed a singlet at $\tau -1.0$ (exchangeable, OH) but not at τ 1.8 (CH=N·OH). On treatment with p-toluidine the chloro-oxime (IIa) gave pentafluoro-



Reagents: i, Cl₂ or NOCl; ii, NaOH; iii, Pb(OAc)₄; iv, PhCH $:CH_2$; v, PhC:CH.

N-p-tolylbenzamide oxime (VII). When treated with base, or in the absence of reagent, crude chloro-oxime (IIa) yielded only a compound whose molecular formula was that of a dimer of pentafluorobenzonitrile N-oxide, and which was presumably 3,4-bis(pentafluorophenyl)-

⁵ (a) C. Grundmann and J. M. Dean, *J. Org. Chem.*, 1965, **30**, 2809; (b) C. Grundmann, H.-D. Frommeld, K. Flory, and S. K. Datta, ibid., 1968, 33, 1464.

⁶ A. Dondoni, A. Mangini, and S. Ghersetti, Tetrahedron Letters, 1966, 4789.

⁷ A. Quilico, in 'Chemistry of Heterocyclic Compounds,' vol. 17, ed. R. H. Wiley, Interscience, New York, 1962, p. 21.

furoxan (IVa). However, when the i.r. spectrum of the solution was examined shortly after treatment with base, a strong peak at 2300 cm.⁻¹, attributable to the nitrile oxide 9 was observed. Treatment of pentafluorobenzaldehyde oxime (Ia) with sodium hypobromite 5a gave a



solution whose i.r. spectrum showed absorption at 2300 cm.⁻¹, but the peak was weak, and the yield of nitrile oxide was clearly low. Pentafluorobenzonitrile N-oxide (IIIa) was most satisfactorily prepared by dehydrogenation of the oxime (Ia) with lead tetraacetate;¹¹ this reaction led to a solution which showed strong i.r. absorption at 2300 cm.⁻¹, and which slowly deposited dimer, presumably the furoxan (IVa). Our expectation that the nitrile oxide (IIa) would dimerise only slowly was not fulfilled; evaporation of the solution at room temperature led only to dimer.

In contrast to pentafluorobenzaldehyde oxime (Ia), pentachlorobenzaldehyde oxime (Ib) could not be oxidised directly to pentachlorobenzonitrile N-oxide (IIIb) by lead tetra-acetate, but was converted into the stable chloro-oxime (IIb) by chlorine. Treatment of the chloro-oxime (IIb) with base then gave pentachlorobenzonitrile N-oxide (IIIb), which was remarkably stable; it could be recrystallised from hot ethanol without any dimerisation being observed, and could be stored indefinitely at room temperature. Attempts to obtain the dimer by maintaining solutions at $ca. 60^{\circ}$ (cf. ref. 5b) led to recovery of monomer, and at higher temperatures (ca. 140°), only unidentified decomposition products were obtained.

2,6-Dichlorobenzonitrile N-oxide is reported ⁷ to be completely dimerised in 30-35 days at 18°. The greater stability of pentachlorobenzonitrile N-oxide (IIIb) may be attributed to greater steric hindrance to dimerisation caused by the 'buttressing effect' of the additional chlorine atoms, with possibly some additional stabilisation due to their electron-withdrawing effect.

Despite their greatly differing tendencies towards dimerisation, both pentafluoro- (IIIa) and pentachlorobenzonitrile N-oxide (IIIb) reacted readily, and under similar conditions, to give good yields of cycloadducts with styrene and phenylacetylene. Thus, pentafluorobenzonitrile N-oxide (IIIa) gave 3-pentafluorophenyl-5-phenyl-isoxazoline (Va) and -isoxazole (VIa), respectively, and pentachlorobenzonitrile N-oxide (IIIb) gave the analogous pentachlorophenyl derivatives (Vb) and

⁸ G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, J. Amer. Chem. Soc., 1957, 79, 462. * R. H. Wiley and B. J. Wakefield, J. Org. Chem., 1960, 25,

546.

H. Rheinboldt, Annalen, 1926, 451, 161. 10

¹¹ G. Just and K. Dahl, *Tetrahedron Letters*, 1966, 2441; G. Just and W. Zehetner, *ibid.*, 1967, 3389; G. Just and K. Dahl, Tetrahedron, 1968, 24, 5251.

⁴ S. Califano, R. Moccia, R. Scarpati, and G. Speroni, J. Chem. Phys., 1957, **26**, 1777.

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(VIb). Although cycloadditions of nitrile oxides to monosubstituted ethylenes and acetylenes have been generally reported to yield only the 5-substituted isoxazolines and isoxazoles,⁷ it has been recently reported 12 that mixtures of the 4- and 5-substituted compounds are in fact formed in many cases. In our experiments, only the 5-substituted compounds were isolated, but the experimental procedure was not designed to recover small proportions of isomeric products. The ¹H n.m.r. spectra of the adducts (see Experimental section) are consistent with the structures assigned. In particular, the signal for the heterocyclic ring proton in the pentafluorophenylisoxazole (VIa) is split into a triplet by the ortho-fluorine atoms, and the signal for the heterocyclic ring proton in the pentachlorophenylisoxazole (VIb) is at much too high a field for it to be located at the 5-position.

EXPERIMENTAL

Pentafluorobenzaldehyde Oxime .--- This was prepared from pentafluorobenzaldehyde by a standard procedure; ¹³ m.p. $130-131^{\circ}$ (lit., ¹⁴ 131-132°), τ 1.8 (1H, s, CH) and -2.3(1H, s, exchangeable, OH).

a-Chloropentafluorobenzaldehyde Oxime.--Nitrosyl chloride was passed into a solution of pentafluorobenzaldehyde oxime (1.002 g.) in dry chloroform (30 ml.) at room temperature for 30 min. The solvent was evaporated off under reduced pressure, to leave a pale yellow oil (1.145 g.), $v_{max.}$ (film) 3500–3300 (OH) and 1655 (C=N) cm.⁻¹, τ - 1.0br (s, exchangeable, OH).

2,3,4,5,6-Pentafluoro-N-p-tolylbenzamide Oxime.-A solution of p-toluidine (0.507 g.) in dry ether (10 ml.) was added to a solution of crude α -chloropentafluorobenzaldehyde oxime (0.582 g.) in dry ether (10 ml.). The mixture was set aside at room temperature for 22 hr. and then filtered, and the precipitate (p-toluidine hydrochloride) was washed with ether. The combined ether solutions yielded a tacky brown solid (0.81 g.), which was washed with light petroleum (5 ml.), and redissolved in ether (25 ml.); a further amount of p-toluidine hydrochloride was filtered off. The ether solution yielded an oil, (0.28 g.) which solidified slowly and which gave crystals (0.200 g., 27%), m.p. 116-117° (from light petroleum), v_{max} (Nujol) 3410, 3400–3100, 1655, and 810 cm.⁻¹, τ (CCl₄) 0.65br (1H, s, exchangeable, NH), 2.65br (1H, s, exchangeable, OH), 3.00 (2H, d, J 8 Hz, ArH), 3.30, (2H, d, J 8 Hz, ArH), and 7.75 (3H, s, Me) (Found: C, 53.1; H, 2.85; N, 8.8%; M⁺ 316. C₁₄H₉F₅-N₂O requires C, 53.2; H, 2.85; N, 8.9%; M, 316).

Pentafluorobenzonitrile N-Oxide.-(a) From pentafluorobenzaldehyde oxime. To the oxime (0.211 g.) in methylene chloride (10 ml.) a solution of lead tetra-acetate * (0.45 g.) in methylene chloride (15 ml.) was added dropwise, with stirring, during 5 min. The mixture was stirred for a further 5 min., then filtered, and the filtrate was dried (MgSO₄) for 15 min. The i.r. spectrum of the solution showed strong peaks at 2300 and 1385 cm.⁻¹.

(b) From α -chloropentafluorobenzaldehyde oxime. A solu-

* A freshly opened bottle of lead tetra-acetate, moistened with acetic acid, gave satisfactory results. Certain other samples gave much lower yields.

¹² M. Christl and R. Huisgen, Tetrahedron Letters, 1968, 5209. ¹⁸ R. P. Linstead and B. C. L. Weedon, 'Qualitative Organic Chemical Analysis,' Butterworth, London, 1956.

tion of the crude chloro-oxime (0.522 g.) in chloroform (20 ml.) was stirred with 4N-sodium hydroxide (2.0 ml.). The dried chloroform layer showed i.r. absorption corresponding to the nitrile oxide.

3,4-Bis(pentafluorophenyl)furoxan.-When solutions of pentafluorobenzonitrile oxide, prepared as described above, were set aside, or when the solvent was evaporated off, 3,4-bis(pentafluorophenyl)furoxan (80-95%) was obtained as white crystals, m.p. 149-150° (from aqueous enthanol), v_{max}, 1655 and 1620 (C=N), 1340 (N=O), and 1140, 990, 865, and 845 (furoxan) cm.⁻¹ (Found: C, 40.0; H, nil; N, 6.5%; M^+ , 418. $C_{14}F_{10}N_2O_2$ requires C, 40.2; H, nil; N, 6.7%; M, 418).

Cycloadditions of Pentafluorobenzonitrile N-Oxide.-(a) With Styrene. A solution of the nitrile oxide in methylene chloride [prepared as in (a), previous experiment] was added dropwise during 15 min. to a boiling solution of styrene (0.104 g.) in methylene chloride (10 ml.). The mixture was heated under reflux for 45 min. and then filtered; the filtrate was dried and evaporated to give an oil (0.301 g., 96%), which solidified when cool. The solid 3-(pentafluorophenyl)-5-phenylisoxazoline gave white needles (0.180 g., 57%), m.p. 105–106° (from aqueous ethanol), ν_{max} 3100– 3020, 1655, 1585, 755, and 700 cm.⁻¹, τ [CD₃)₂CO] 2.55 (5H, s, Ph), 4.1 (1H, dd, J 11 and 9 Hz, 5-H), and 5.7-6.8 (2H, complex m, 4-H) (Found: C, 56.9; H, 2.7; N, 4.4. $C_{15}H_8F_5N$ requires C, 57.5; H, 2.6; N, 4.5%.

(b) With phenylacetylene. By a similar procedure, phenylacetylene (0.102 g.) gave 3-(pentafluorophenyl)-5-phenylisovazole (5102 g.) gave 5 (penultuolopheny) 5-phenylisovazole (72% crude, 28% recrystallised), m.p. 130—131°, ν_{max} 3140, 1660, 1615, 770, and 695 cm.⁻¹, τ [(CD₃)₂CO] 2·0 (2H, m, o-H), 2·4 (3H, m, m- and p-H), and 2.70 (1H, t, J 1.5 Hz, 4-H) (Found: C, 57.4; H, 1.8; N, 4.3. C₁₅H₆F₅N requires C, 57.9; H, 1.9; N, 4.5%).

2,3,4,5,6-Pentachlorotoluene.--A solution of n-butyllithium (0.118 mole) in hexane (47 ml.) was added to a stirred suspension of hexachlorobenzene (30.0 g., 0.105 mole) in dry ether (300 ml.) at -75° . The mixture was stirred as it warmed to room temperature, and until most of the solid had dissolved (15 min.). The mixture was re-cooled to -75° , and dimethyl sulphate (13.2 g., 0.105 mole) was added. The suspension was stirred as it warmed to room temperature, and during a further 2 hr. Conc. aqueous ammonia (50 ml.) was added cautiously. Work-up gave crystals (21.4 g.), which were recrystallised twice from benzene to give 2,3,4,5,6-pentachlorotoluene (16.5 g., 59%), m.p. $214-216^{\circ}$ (lit.,¹⁵ 218°), τ 7.4 (s).

Pentachlorobenzaldehyde Oxime.-Photochlorination of 2,3,4,5,6-pentachlorotoluene ¹⁶ gave $\alpha, \alpha, 2, 3, 4, 5, 6$ -heptachlorotoluene, which on hydrolysis with sulphuric acid 17 gave pentachlorobenzaldehyde, which was converted into the oxime, m.p. 204-205° (lit., 18 201°), by a standard procedure.13

 α ,2,3,4,5,6-Hexachlorobenzaldehyde Oxime.—Chlorine was passed into a solution of pentachlorobenzaldehyde oxime (1.00 g.) in chloroform (30 ml.) during 30 min. at room temperature. The resulting green solution was dried and evaporated under reduced pressure to give a white solid (1.14 g.), m.p. 152-155° (decomp.). Recrystallisation

¹⁴ E. V. Aroskar, P. J. N. Brown, R. G. Plevey, and R. Stephens, *J. Chem. Soc.* (C), 1968, 1569.

 ¹⁵ F. Beilstein and A. Kuhlberg, Annalen, 1869, 150, 286.
¹⁶ M. Ballester, Memorias real. acad. ciencias y artes de Barcelona, 1948, 29, 271. ¹⁷ M. Weiler, U.S.P. 998,140/1911.

¹⁸ G. Lock, Ber., 1939, 72, 300.

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from light petroleum removed a little insoluble hexachlorobenzene to give α ,2,3,4,5,6-hexachlorobenzaldehyde oxime, m.p. 154—157° (decomp.), ν_{max} (Nujol) 3315 and 1640, τ (CDCl₃) 1.8 (s, exchangeable) (Found: C, 25.9; H, 0.8; N, 4.45. C₇H₂Cl₅NO requires C, 25.9; H, 0.3; N, 4.3%).

Pentachlorobenzonitrile N-Oxide.—To a solution of α ,2,3,4,5,6-hexachlorobenzaldoxime (0.500 g.) in chloroform (20 ml.) was added dropwise, with stirring, 4N-sodium hydroxide (2.0 ml.). Stirring was continued for 30 min., and the organic layer was then separated, dried, and evaporated, to give *pentachlorobenzonitrile* N-oxide (0.398 g., 89%), m.p. 225—229° (decomp.), ν_{max} (CHCl₃) 2300 and 1350 cm.⁻¹ (Found: C, 29.1; N, 4.5%; M^+ , 289. C₇Cl₅NO requires C, 28.8; N, 4.8%; M, 289).

Cycloadditions of Pentachlorobenzonitrile N-Oxide.—(a) With styrene. A solution of pentachlorobenzonitrile Noxide (from the chloro-oxime, 0.701 g.) in chloroform (20 ml.) was added to a solution of styrene (0.22 g.) in chloroform (10 ml.), and the mixture was heated under reflux for 1 hr. The solvent was evaporated off, and the residue (0.86 g.) was recrystallised from ethanol to give 3-(*pentachlorophenyl*)-5-*phenylisoxazoline* (0.513 g., 61%), m.p. 141—142°, $v_{\text{max.}}$ (Nujol) 3065, 3035, 755, and 695 cm.⁻¹, τ (CDCl₃) 2.55 (5H, s, Ph), 4.10 (1H, dd, J 11 and 9 Hz, 5-H), and 6.0—7.0 (2H, complex m, 4-H) (Found: C, 45.8; H, 2.2; N, 3.8. C₁₅H₈Cl₅NO requires C, 45.4; H, 2.0; N, 3.5%).

(b) With phenylacetylene. By a similar procedure, phenylacetylene (0·102 g.) gave 3-(pentachlorophenyl)-5-phenylisoxazole (quantitative yield crude, 31% from ethanol), m.p. 194—195°, v_{max} . (Nujol) 3120, 1610, 760, and 675 cm.⁻¹, τ (CDCl₃) 2·15 (2H, m, o-H), 2·55 (3H, m, m- and p-H), and 3·45 (1H, s, 4-H) (Found: C, 45·9; H, 1·9; N, 3·3. C₁₅H₆Cl₅NO requires C, 45·75; H, 1·5; N, 3·6%).

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