Deoxygenation of Aromatic Sulphoxides by Thionyl Chloride in the Presence of Cyclohexene. Synthesis of Substituted Phenoxathiins

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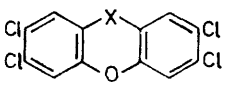
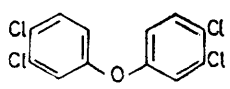
2,3,7,8-Tetrachlorophenoxathiin (1b) and bis-3,4-dichlorophenyl ether (2), structural analogues of the highly toxic pollutant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (1a), have been synthesized. The preparation of (1b) by the aluminium chloride-catalysed condensation of (2) with thionyl chloride involves deoxygenation, and some aromatic chlorination also occurs. The scope of the latter reactions for the preparation of substituted phenoxathiins has been studied. Aromatic sulphoxides undergo deoxygenative chlorination upon treatment with thionyl chloride, but only deoxygenation occurs in the presence of cyclohexene, which traps the by-product chlorine.

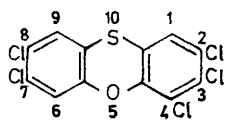
2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (1a) is one of the most toxic synthetic compounds known,[1] but its biological mode of action remains obscure.[2,3] It is an environmental hazard,[2] being a common contaminant of the herbicide 2,4,5-trichlorophenoxyacetic acid. The molecule of (1a) in the crystalline state [1] is almost planar. The toxicity of (1a) is dependent on both its chlorine content and its ring structure; [4] other chlorinated dioxins are less toxic.[3,4] We set out to prepare structural analogues of (1a) in order to study structure–activity relationships.



(1) a; X = O
b; X = S



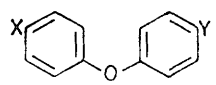
(2)



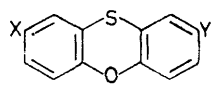
(3)

The ether (2) was prepared from 3,4-dichlorophenol and 1,2-dichloro-4-iodobenzene. Its aluminium chloride-catalysed condensation with an excess of thionyl chloride yielded mainly 2,3,7,8-tetrachlorophenoxathiin (1b) along with 2,3,4,7,8-pentachlorophenoxathiin (3) (or an isomer) as a by-product. The latter was identified from the characteristic isotope pattern of molecular ion in the mass spectrum of the product mixture (containing 2% of pentachloro-compound). The intermediate sulphoxide, usually obtained in Friedel–Crafts reactions of thionyl chloride with an excess of aromatic substrate,[5] is apparently reduced by unchanged thionyl chloride, and electrophilic chlorination is responsible for the by-product.[6,7]

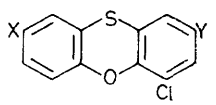
The synthetic potential of this reaction led us to study its scope. The ethers (4a—e) reacted with thionyl chloride in the presence of aluminium chloride in carbon disulphide to give mainly compounds (5a—e) and (6a—e). In the absence of the catalyst the reactants were unchanged. Product mixtures were analysed by mass spectrometry (see later). N.m.r. could not be used for this purpose owing to coincidence of the signals arising



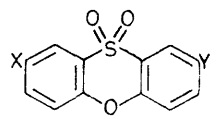
(4)



(5)



(6)



(7)

a; X = Y = F b; X = Y = Cl c; X = Y = Br
d; X = Y = Me e; X = F, Y = Br

[1] F. P. Boer, F. P. van Remoortere, and W. W. Muelder, *J. Amer. Chem. Soc.*, 1972, **94**, 1006, and references therein.
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[4] V. K. Rowe, J. M. Norris, G. L. Sparschu, B. A. Schwetz, and P. J. Gehring, Abstracts 162nd Amer. Chem. Soc. National Meeting, 1971, PEST, Abstract No. 86.
[5] I. Granoth, A. Kalir, and Z. Pelah, *J. Chem. Soc.* (*C*), 1969, 2424.
[6] F. Loth and A. Michaelis, *Ber.*, 1894, **27**, 2540.
[7] C. W. Bird, *J. Chem. Soc.* (*C*), 1968, 1230.

from compounds (5) and (6), and column chromatography and t.l.c. were ineffective separation methods. Occasionally, when the ratio (5) : (6) was relatively high (*e.g.*, 5—6 : 1), fractional crystallization could be used to obtain a pure sample of (5). Oxidation to the sulphone (7) sometimes aided isolation of pure compounds.

Low temperature and low thionyl chloride concentration increased the ratio (5) : (6). However, even with a 1 : 1 molar ratio of (4) and thionyl chloride, only sulphides, rather than sulphoxides, were obtained, and the chlorinated derivatives (6) were always found. A large excess of thionyl chloride (used as solvent) and prolonged refluxing led in addition to various amounts of dichlorinated derivatives of (5), and in the case of (4d) a trichloro-analogue was also detected.

These findings show that the deoxygenation occurs under all conditions studied, but that the extent of chlorination depends on the reaction conditions. Chlorination does not occur to the same extent as deoxygenation and may well be the last step in the overall process. It has been suggested [7] that the thionyl chloride-induced deoxygenative chlorination of heterocyclic sulphoxides proceeds through generation of a ' chlorinating species ' produced on deoxygenation of the sulphoxide. We suggest that this ' chlorinating species ' is simply elemental chlorine, produced according to equation (i).

$$Ar_2SO + SOCl_2 \longrightarrow Ar_2S + Cl_2 + SO_2 \qquad (i)$$

In order to obtain evidence supporting this suggestion, several aromatic sulphoxides, available from an earlier study,[5] were treated with boiling thionyl chloride in the presence and in the absence of cyclohexene. Indeed, in the presence of cyclohexene, the appropriate sulphides were obtained together with 1,2-dichlorocyclohexane. This reaction thus provides a new method [5] for deoxygenation of aromatic sulphoxides. The same sulphoxides and thionyl chloride, in the absence of cyclohexene, yield mixtures of sulphides and their chloro-derivatives.

Thus the formation of phenoxathiins from the ethers (2) and (4) apparently proceeds by deoxygenation of the intermediate sulphoxide, followed by chlorination by molecular chlorine. This accounts for the relatively small amount of compound (3) produced along with (1b). The already high chlorine content of (1b) renders it less accessible to further chlorination by chlorine. However the use of cyclohexene as a chlorine scavenger in attempted syntheses of (5) proved unsuccessful: such reactions yielded only tars.

Mass Spectra.—Mass spectrometry has been recommended [8,9] as an analytical method for the detection of (1a) and chlorinated pesticides. The molecular ions of the various phenoxathiins studied appear as the most intense peaks in the mass spectra. The characteristic isotope patterns of those ions generated from the chlorine- and bromine-containing derivatives are especially useful for analyses of mixtures.

The mass spectral fragmentation of phenoxathiin [10] proceeds mainly by two competing paths: (a) consecutive elimination of CO, H, and CS from the molecular ion, and (b) stepwise loss of S and CHO. This pattern also applies in the case of 2,8-difluorophenoxathiin (5a). However, the presence of the fluorine atoms enables also the one-step expulsion of CFO from the molecular ion, indicated by the appropriate metastable transition at *m/e* 151·4. This process is reminiscent of a similar rearrangement observed in the electron-impact-induced decompositions of some 2,8-difluorophenoxaphosphine derivatives.[11]

The introduction of several chlorine or bromine atoms changes the breakdown of these compounds in the mass spectrometer. The main cracking pattern of the molecular ion of (1b), for example, involves elimination of Cl followed by either CO or another Cl. Loss of sulphur is also observed. The occurrence of a one-step loss of CClO from (1b) or its fragments [12] is not supported by observation of a metastable transition.

The biological activity of some of the compounds described here is being studied and will be reported elsewhere.

EXPERIMENTAL

M.p.s were taken with a Thomas Hoover capillary apparatus. U.v. spectra were recorded for solutions in 96% ethanol with a Bausch and Lomb Spectronic 505 instrument. N.m.r. spectra were run for solutions in $CDCl_3$ with Me_4Si as internal standard with a JEOL C-60 HL high resolution spectrometer. Mass spectra were obtained with a Hitachi–Perkin-Elmer RMU 6 spectrometer at 70 eV by using the direct insertion probe and source temperature 150—200°. 20 eV Spectra were used to determine the compositions of mixtures by observing the relative intensities of the molecular ions.

Bis-3,4-dichlorophenyl Ether (2).—3,4-Dichlorophenol (65·2 g), potassium hydroxide (18·6 g), 1,2-dichloro-4-iodobenzene [13] (82 g), and copper-bronze (2·0 g) were refluxed for 2 h. The mixture was cooled, treated with 10% sodium hydroxide (200 ml), and extracted with chloroform. Fractional distillation gave unchanged dichloroiodobenzene (45·0 g), b.p. 81—82° at 0·2 mmHg, and the *ether* (2) (12·5 g), b.p. 160—162° at 0·2 mmHg, m.p. 70° (from ethanol) (Found: C, 46·9; H, 2·3; Cl, 45·8. $C_{12}H_6Cl_4O$ requires C, 46·8; H, 2·0; Cl, 46·1%); δ 6·88 (2H, dd, H-6 and -6′), 7·13 (2H, d, H-2 and -2′), and 7·45 (2H, d, H-5 and -5′).

2,3,7,8-*Tetrachlorophenoxathiin* (1b).—Thionyl chloride (4·0 g), the ether (2) (7·7 g), aluminium chloride (8·0 g), and carbon disulphide (200 ml) were stirred and refluxed for 5 h and the mixture was then decomposed with ice–water. The organic layer yielded the *phenoxathiin* (1b) (3·5 g), m.p. 220—222° (from acetic acid) (Found: C, 42·3; H, 1·1; Cl, 42·3; S, 10·0. $C_{12}H_4Cl_4OS$ requires C, 42·6; H, 1·2; Cl,

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[10] J. Heiss, K. P. Zeller, and B. Zeeh, *Tetrahedron*, 1968, **24**, 3255.
[11] I. Granoth, A. Kalir, Z. Pelah, and E. D. Bergmann, *Israel J. Chem.*, 1970, **8**, 621.
[12] I. Granoth, *J.C.S. Perkin II*, 1972, 1503.
[13] G. M. Kraay, *Rec. Trav. chim.*, 1930, **49**, 1083.

42·0; S, 9·5%); δ 7·07 (2H, s, H-4 and -6) and 7·13 (2H, s, H-1 and -9); *m/e* 336 (77%, $M^{+\cdot}$), 304 (14, M^+ — S), 301 (41, M^+ — Cl), 273 (17, M^+ — Cl — CO), and 266 (20, M^+ — 2Cl); $\lambda_{max.}$ 246 (log ε 4·24) and 306 nm (3·46).

2,8-*Difluorophenoxathiin* (5a).—(*a*) Bis-4-fluorophenyl ether (4a) (5·2 g), thionyl chloride (3·0 g), aluminium chloride (4·5 g), and carbon disulphide (80 ml) were stirred for 1 h at 20°. The mixture was then refluxed for 1 h and decomposed with ice–water (100 ml). The residue obtained from the organic layer was thrice recrystallized from ethanol, giving the phenoxathiin (5a) [14] (1·4 g), m.p. 98—99° (Found: C, 61·2; H, 2·3; F, 16·4; S, 13·5. Calc. for $C_{12}H_6F_2OS$: C, 61·0; H, 2·5; F, 16·1; S, 13·6%); $\lambda_{max.}$ 237 (log ε 4·47), 274 (3·25), and 302 nm (3·56); *m/e* 236 (100%, $M^{+\cdot}$), 208 (18, M^+ — CO), 207 (43, M^+ — CHO), 204 (30, M^+ — S), and 189 (10, M^+ — CFO).

(*b*) When this reaction was carried out with (4a) (5·2 g), thionyl chloride (50 ml), and aluminium chloride (4·5 g) at 50° for 4 h, a mixture of (5a) (70%), (6a) (25%), and a dichloro-derivative (5%) was obtained (estimated from the mass spectrum). Similar results were obtained with compounds (4b—e) under these conditions.

(*c*) When the reaction described in (*a*) was performed in the presence of cyclohexene (3·0 g) only tar was obtained.

2,8-*Dimethylphenoxathiin* 10,10-*Dioxide* (7d).—Di-*p*-tolyl ether (5·0 g), thionyl chloride (6·0 g), aluminium chloride (4·5 g), and carbon disulphide (100 ml) were stirred for 6 h at 0°. The product, obtained as above, was treated for 1 h with 30% hydrogen peroxide (15 ml) in acetic acid (100 ml) at 60°. Dilution with water (200 ml), filtration, and two recrystallizations from ethanol yielded the sulphone (7d) [15] (3·1 g), m.p. 170° (Found: C, 64·4; H, 4·8; S, 12·0. Calc. for $C_{14}H_{12}O_3S$: C, 64·6; H, 4·6; S, 12·3%); $\lambda_{max.}$ 243 (log ε 4·15), 270sh (2·99), 283sh (3·31), 297 (3·58), and 303 nm (3·62); δ 2·43 (6H, s, CH_3), 7·20 (2H, d, H-4 and -6), 7·42 (2H, dd, H-3 and -7), and 7·82 (2H, d, H-1 and -9).

2,8-*Dibromophenoxathiin* 10,10-*Dioxide* (7c).—Prepared as for (7d), by treatment of bis-4-bromophenyl ether (3·0 g) with thionyl chloride (3·5 g), aluminium chloride (2·5 g), and carbon disulphide (50 ml), followed by oxidation with hydrogen peroxide (8 ml) in acetic acid (70 ml), the *sulphone* (7c) (1·4 g) had m.p. 182° (from ethanol) (Found: C, 36·5; H, 1·3; S, 8·1. $C_{12}H_6Br_2O_3S$ requires C, 36·9; H, 1·5; S, 8·2%); $\lambda_{max.}$ 249 (log ε 4·29), 276 (3·11), 290sh (3·24), 302 (3·41), and 309 nm (3·46).

Reduction of Sulphoxides with Thionyl Chloride.—General procedure. The sulphoxide [5] (0·01 mol) was added to a stirred mixture of thionyl chloride (0·03 mol) and cyclohexene (0·015 mol), and kept for 1 h at 70°. The mixture was decomposed with ice–water (50 ml) and extracted with chloroform, and the product was isolated (85—90% yield; see Table) and identified as described earlier.[5] 1,2-Dichlorocyclohexane was isolated by fractional distillation of the mother liquor from the recrystallization of the product sulphide, and was identified by comparison of its i.r. and n.m.r. spectra with those of an authentic sample.

Substituted diphenyl sulphides from the reduction of the sulphoxides [5]

Subst.	M.p. of sulphoxide (°C)	M.p. of sulphide (°C)	Yield (%)
	71		85
4,4′-Me_2	92	59	87
4,4′-Cl_2	145	94	92
4-Br,4′-Cl	144	106	90
4-Cl,4′-F	76	34	85
2-Br,4′-Cl	98	66	90
4-NO_2,4′-Cl	151	87	90

When this reaction was conducted in the absence of cyclohexene, a mixture of the sulphide and 20—30% of its monochloro-derivative was obtained, as shown by mass spectrometry.

I thank Dr. A. Vincze for advice.

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