THE SYNTHESIS OF CHLORINATED DIPHENYL ETHERS

G. Sundström and O. Hutzinger Laboratory of Environmental Chemistry, University of Amsterdam, Nieuwe Achtergracht 166, Amsterdam, The Netherlands.

(Received in UK for publication 23 August 1976)

in our studies on the chemistry and environmental behaviour of industrial products similar to compounds which have caused environmental problems, such as PCBs (polychiorinated biphenyls) and PBBs (polybrominated biphenyls), we have surveyed the literature on polychiorinated diphenyl ethers (PDEs). PDEs have been the subject of a large number of patents and have been suggested for uses similar to those of PCBs and PBBs. This includes use as flame retardants, electric insulators, plasticisers, lubricants and as hydraulic fluids - although we do not know to what extent chlorinated diphenyl ethers are used or manufactured at present.

The structural similarity between PDEs and PCBs or PBBs indicates that any leakage of such compounds into the biosphere may cause similar problems as with the latter products regarding bioaccumulation <u>etc.</u> It has recently been shown that PDEs are present as impurities in fungicidal and herbicidal chlorophenol preparations which may therefore be a source of contamination with PDEs¹⁻³.

A certain toxicity potential of PDEs to organisms is indicated by the suggestions to use low-chlorinated diphenyl ethers as acaricides⁴, miticides⁵ and against lice⁶. PDEs may also be used as synergists together with pyrethrins⁷ or pesticides of both phosphate and chlorinated hydrocarbon type⁸. The bioconcentration potential of diphenyl ether and 2,2',4,4'-tetrachlorodiphenyl ether were investigated by Neely <u>et al.</u> by calculation of partition coefficients between <u>n</u>-octanol and water and by measuring uptake and clearance rates in trout⁹. The tetrachlorro compound showed a bioconcentration factor of a value similar to the very persistent compound hexachlorobenzene. Furthermore, it was recently shown that highly toxic chlorinated dibenzofurans are formed upon photolysis of PDEs and may be a reaction of environmental significance^{10,11}.

As is evident from above there is very limited data on both biological, toxicological and chemical properties on PDEs. To facilitate studies on the environmental behaviour of PDEs we have synthesised a number of pure PDEs and collected data on synthetic routes useful for the preparation of chlorinated diphenyl ethers of known structure. This work is summarised below.

305

SYNTHESIS OF CHLORINATED DIPHENYL ETHERS.

A. Direct chlorination of diphenyl ether.

The direct chlorination of diphenyl ether have been investigated by Weingarten and Schisla using tetrachloromethane as solvent with SnCl₄, FeCl₃ or AlBr₃ as catalysts or acetic acid without catalysts¹². Substitution initially occurr in the 2- and 4-positions and unsubstituted diphenyl ether, 2-chloro- and 4-chlorodiphenyl ether give the 2,2'-, 2,4'- and 4,4'--dichloro compounds as major products. 2-Chloro- and 4-chlorodiphenyl ether also give traces of the 2,4-dichloro isomer and from the 2-chloro compound also traces of 2,6-dichlorodiphenyl ether was detected. No traces of a 3,4-dichlorosubstituted ether was found as claimed by Brewster and Stevenson¹³.

Further chlorination of diphenyl ether give good yields of 2,2',4,4'-tetrachlorodiphenyl ether, unambiguously structurally determined by Norström <u>et al.</u>¹⁰ although originally being. claimed to be the 2,2',6,6'-tetrachloro isomer¹⁴.

The chlorination reactions are usually performed in the presence of a solvent $(CCI_4^{10,14,15})$ or HOAc¹³) and often without catalysts when low-chlorinated diphenyl ethers are to be synthesised. However, even in the preparation of octa-, and decachiorodiphenyl ethers solvents may be used, boiling tetrachioromethane¹⁶ and boiling tetrachioroethylene¹⁷. Decachiorodiphenyl ether can also be obtained by treatment of diphenyl ether with the BMC reagent $(SO_2CI_2-AICI_3-S_2CI_2)^{18}$.

Industrial chlorination processes are mostly performed without solvent and except for chlorine only sulfuryl chloride seem to have used as chlorinating $agent^{19,20}$. It has been claimed that the usual ratio of para to ortho substitution of 4:1 obtained upon monochlorination of diphenyl ether can be increased to 9:1 by not using solvent or catalyst²¹. Increased amounts of meta isomers (64-80%) can be obtained by heating the chlorination mixture with alumium chloride²² or by chlorination in the gas phase²³. The rate of chlorination of diphenyl ether in chlorobenzene solution has been examined but no products were identified²⁴.

A number of highly chlorinated ethers have been synthesised by direct chlorination but since no structures were assigned these compounds have not been included in Table 1 below^{16,25}.

B. The Ulimann ether synthesis and modifications.

The classical Ulimann ether synthesis -coupling of phenol salts with halogenated benzenes in the presence of copper catalyst²⁶- have been used for the preparation of a number of chloro substituted diphenyl ethers (<u>cf.</u> Table 1). Originally the reaction was performed without solvent but recent modifications successfully employ the use of high-bolling solvents such as diglyme^{27,28} and dimethyl sulfoxide^{29,30}. In the former solvent Cu_2Cl_2 and KI were used as catalysts while no catalysts were used when the reaction was performed in dimethyl sulfoxide solution. Copper and mercury have been used as catalysts in the synthesis of 4-chlorodiphenyl ether from 4-chlorobromobenzene and phenol in the absence of base³¹.

In the synthesis of two pentachlorodiphenyl ethers we used the modification of the Ulimann ether synthesis using diglyme as solvent to obtain 2,4-dinitro-2',4',5'-trichloro- and 3,4--dinitro-2',4',5'-trichlorodiphenyl ether whereafter the nitro groups were substituted for

<u>Table 1</u> .	. Known chlorinate	d diphenyl e	thers.		Table 1	<u>1.</u> continued.			r.
Compor	pun	synthetic method	m.p. b.p. (mm)	Ref.	Сотро	und	synthetic method	ш.р. b.р.(mm)	Ref.
2-	Q Q	B	435 152-3(15) 147-675	(E7) (6E)	2,5-	ڳ ج	B	306-7(762)	õ
			47-8 4,2-6(12) oil	13 13 Mork	- 4 /E		A,C	160-3(7)	1 3
		ш	I OI	(9E)	3,5-		ß	(†9L)LLE	0£
Ļ		B	16 8-9 (30) 155-6(20)	(E1) 71	2,2 ^t -		ш	I	(36)
4		≺ മ	14.6-50(7) 284-5(760) 14.0-2(7) 133-9(5) 133-9(5)	13 15 (4,4) 30	2,4'-		8 0 9	31 170-4(8) oil -	27 (39) this work (36)
		ح	149-52(8) 161-2(19) 160(20) _G il	(39) 42 (43)	3'3 '		ß	12 313(760)	LZ LZ
	-	ыш	5 15	32	3,4 <mark>′-</mark>		ß	-10 113(0.5)	28 28
2,4-		80	n ²⁵ 1.5982 oil	46 this work cont.		5			cont.

Table 1. continued.				Table 1. continued.			
Compound	synthefic method	а.р. b.р. (mm)	Ref.	Compound	synthetic method	т.р. bp.(mm)	Ref.
44 ⁻ ~0~~	A	R	£	22441- J. O. J.	A	8-98	6
	:	168-72(7)	ŧ			68	4
		312-14 (760)	ħ			2	(84)
		i	(19)			205-7(12)	(8+)
		150-3(3)	(20)		в	22	(6E)
		310-2(760)	(20)		B+F	73-3.5	(EE)
	8	ጽ	77	5	Ч Н	70-2	(] 4)
		õ	(39)	24,45- 200	0	oila	this work
1	J	õ	47	r Y	I	i	
2 ^{4,5-}	۵	oil	this work	234,4-	J	oil	this work
) c)-C C							
2,2/4- 2,2/4	8	180-5(6)	(6E)	םליין מישיים -איונד	٥	oil	this work
	ш	I	(36)				
לאסלאם -152	Ω	oil	this work	23456-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0-0	8	132-3	56
`							
244- 200	8	21	(6E)	274.45- J O J	1+F	a jo	٢F
	J	54-5 300	۲. ۲			5 65-6	ነ ස
		59 53 73	ĥ 88	н С П			
	ц.,	51-2	10				cont.
			cont.				

308

Ref.

32

(39)

29

17

18

216

224-5

Compound	synthetic method	m.p. b.p. (mm)
	B≁E	oil ^a
22'4,4,6-	B	36
	R	1/.7-8

Table 1. continued.

^a solidifies around room temperature.

chlorine by the Ponomarenko reaction (see below)³². Two japanese groups synthesised diphenyl ethers with nitro and chloro substituents by coupling of chlorophenol salts with 2,5-dichloronitrobenzene whereby substitution occurrs in the 2-position^{33,34}.

C. The Sandmeyer reaction.

A number of mainly low-chlorinated diphenyl ethers have been synthesised by exchange of amino groups for chlorine <u>via</u> the Sandmeyer reaction (<u>cf</u>. Table 1). It may be pointed out that attempts in this laboratory to exchange amino groups in the position <u>ortho</u> to the ether linkage for chlorine have been unsuccessful although the corresponding deamination reaction via diazotation have given good yields of products (see below).

D. Deamination reactions.

We have synthesised a number of chlorinated diphenyl ethers from commercially available amino-chlorosubstituted diphenyl ethers (Aldrich Chem. Co.) by deamination <u>via</u> treatment with amyl nitrite in boiling tetrahydrofuran³⁵.

E. Miscellaneous substitution reactions.

Chlorine have been introduced into the diphenyl ether system by direct substitution of nitro or sulfonyl groups. The 2-chloro-, 4-chloro-, 2,2',4,4',5-tetrachloro- and 2,3'4,4'5-

-tetrachlorodiphenyl ethers were synthesised by the Ponomarenko reaction which involves treatment of nitro compounds with tetrachloromethane at elevated temperatures. Deactivated aromatic compounds usually give high yields of products and the reaction may be used for the synthesis of a number of specifically chlorinated aromatic systems³².

Matsui et al. substituted nitro and sulfuryl groups for chlorine treatment with thionyl chloride at high temperatures³³. Finally, exchange of nitro groups for chlorine by the use of chlorine gas at high temperatures have been described in a patent³⁶.

<u>Refs.</u> 37-39 contain data on a number of nitro-chloro substituted diphenyl ethers which may be used in any of the above reactions for the synthesis of PDEs of known structure.

F. Miscellaneous coupling reactions.

The aryl ether synthesis described by Crowder <u>et al.</u>⁴⁰ have been used for the synthesis of 2,4,4'-trichlorodiphenyl ether by coupling of sodium 2,4-dichlorophenolate with 4,4'-dichloroblaryliodonium chloride¹⁰. Finally, an octachlorodiphenyl ether of unknown structure were obtained when diphenyl sulphate was chlorinated in the presence of Iron in an attempts to synthesise 4,4'-dichlorodiphenyl sulphate⁴¹.

In Table 1 is summarised data on chlorinated diphenyl ethers of known structure. References that give limited information on synthetic procedures are given in parentheses. If two synthetic methods have been used in a sequence this is indicated with an arrow (A+B) while two independent routes are separated by a comma (A,B).

Acknowledgements. The technical assistance by Mr. F. van der Wielen and Mr. J. van der Steen is gratefully acknowledged.

REFERENCES.

- 1. Firestone, D., Ress, J., Brown, N.L., Barron, R.M. and Damico, J.N., <u>J. Ass. Off. Anal.</u> Chemists, <u>55</u>, 85 (1972).
- 2. Nilsson, C.A. and Renberg, L., J. Chromatog., 89, 325 (1974).
- 3. Buser, H.R., J. Chromatog., 107, 295 (1975).
- 4. Metcalf, R.L., J. Econ. Entomol., 41, 875 (1948).
- 5. Cross, H.F. and Snyder, F.M., Soap Sanit. Chemicals, 25, 135 (1949).
- 6. Blanton, F.S., J. N. Y. Entomol. Soc., 61, 217 (1953).
- 7. Gersdorff, W.A. and Schechter, M.S., Soap Sanit. Chemica Ds, 24, 155 (1948).
- Yana, A., Doc. Techn. Inst. Nat. Rech. Agron. Tunisic., No. 24, 1966. {Chem. Abstr., 70, 27933d (1969)}.
- 9. Neely, W.B., Branson, D.R. and Blau, G.E., Environ. Sci. Technol., 8, 1113 (1974).
- 10. Norström, X., Andersson, K. and Rappe, C., <u>Chemosphere</u>, <u>1976</u>, 21.

- 11. Choudry, G., Sundström, G. and Hutzinger, O., in preparation:
- 12. Weingarten, H. and Schisla, R.M., J. Org. Chem., 27, 4103 (1962).
- 13. Brewster, R.Q. and Stevenson, G., J. Amer. Chem. Soc., 62, 3144 (1940).
- 14. Ger. 1,139,847, Nov. 22, 1962. {<u>Chem. Abstr.</u>, <u>58</u>, P 11277c (1963)}.
- 15. Mailhe, A. and Murat, M., Compt. Rend., 154, 601 (1912).
- 16. D.R.P. 705,530, March 27, 1941. {Chem. Abstr., 36, 1946 (1942)}.
- 17. Denivelle, L., Fort, R. and Van Hoi, P., Bull. Soc. Chim. France, 1960, 1538.
- Hutzinger, O., Jamieson, W.D.J., Safe, S. and Zitko V.Z., <u>J. Ass. Off. Anal. Chemists</u>, <u>56</u>, 982 (1973).
- 19. U.S.S.R. 170,525, April 25, 1965. {Chem. Abstr., 63, P 13155e (1965)}.
- Voronkova, Z.V., Bessudnova, G.M. and Khvostov, J.V., <u>Metody Pollycheniya Khim. Reaktivov</u> <u>i Preparatov</u>, <u>13</u>, 49 (1965). {Chem. Abstr., <u>65</u>, 5390e (1966)}.
- 21. U.S. 3,022,252, Feb. 20, 1962. {Chem. Abstr., 58, 7174e (1962)}.
- 22. Brit. 917,950, Feb. 13, 1963. {Chem. Abstr., 59, 5078d (1963)}.
- 23. Engelsma, J.W. and Kooljman, E.C., Rec. Trav. Chim., 80, 526 (1961).
- 24. Roberts, R.E. and Soper, F.G., J. Chem. Soc., 1932, 1979.
- Babin, E.P., Skavinskii, Y.P., Andrukhov, N.A., Sedlova, L.N., Litoshenka, N.A. and Rudavskii, V.P., <u>Khim. Tekhnol. (Kiev)</u>, <u>1973</u>, 48. {<u>Chem. Abstr.</u>, <u>79</u>, 78259s (1973)}.
- 26. Ulimann, F. and Sponagel, P., Ber., 38, 2211 (1905).
- 27. Neth. Appl. 6,512,264, March 22, 1966. {Chem. Abstr., 65, PC 10530f (1966)}.
- 28. Neth. Appl. 6,512,286, March 22, 1966. {Chem. Abstr., 65, PC 7104h (1966)}.
- 29. Fr. 1,514,721, Feb. 23, 1968. {Chem. Abstr., 70, P. 77449f (1969)}.
- 30. Fr. 1,576,298, July 25, 1969. {Chem. Abstr., 72, P 79667r (1970)}.
- 31. Brit. 912,340, Dec. 5, 1962. {Chem. Abstr., 58, 11280b (1963)}.
- 32. Sundström, G., Chemosphere, 1976, 191.
- Matsui, K., Oda, K. and Seino, J., <u>Yuki Gosei Kogaku Kyokai Shi</u>, <u>14</u>, 401 (1956). {<u>Chem.</u> <u>Abstr., 51</u>, 10415f (1957)}.
- Wakabayashi, S. and Matsubara, Y., <u>Nippon Kagaku Zasshi</u>, <u>80</u>, 1179 (1959). {<u>Chem. Abstr.</u>, <u>55</u>, 4420e (1961)}.
- 35. Cadogan, J.I.G. and Molina, G.A., J. Chem. Soc. Perkin Trans. 1., 1973, 541.
- 36. U.S. 3,072,728, Jan. 8, 1963. {Chem. Abstr., 58, P 11277a (1963)}.
- 37. Groves, L.G., Turner, E.E. and Sharp, G.I., J. Chem. Soc., 1929, 512.

- 38. Raiford, L.C., Thiessen, G.W. and Wernert, I.J. J. Amer. Chem. Soc., 52, 1205 (1930).
- 39. Dahlgard, M. and Brewster, R.Q, <u>J. Amer. Chem. Soc.</u>, <u>80</u>, 5861 (1958).
- 40. Crowder, J.R., Glover, E.E., Grunden, M.F. and Kaempfen, H.X., J. Chem. Soc., 1963, 4578.
- 41. Bollinger, J.L., Buil. Soc. Chim. France, 1948, 156.
- 42. Suter, C.M. and Green, F.O., J. Amer. Chem. Soc., 59, 2578 (1937).
- 43. Sanesi, M., Gazz. Chim. Ital., 86, 1246 (1956).
- 44. Sperry, J.A., <u>U.S. Dept. Com., Office Tech. Serv., PB Rept. 145</u>, 953 (1959). {<u>Chem. Abstr.</u>, <u>58</u>, 4592d (1963)}.
- 45. U.S. 3,110,683, Nov. 12, 1963. {Chem. Abstr., 60, 2846g (1964)}.
- 46. Fr. 1,327,189, May 17, 1963. {Chem. Abstr., 59, P 12709b (1963)}.
- 47. Le Fèvre, R.J.W., Saunders, S.L.M. and Turner, E.E., J. Chem. Soc., 1927, 1168.
- 48. D.R.P. 673,522, March 23, 1939. {Chem. Abstr., 33, 6342 (1939)}.