Polychlorinated Biphenyls

VI.* 2,3,7,8-Tetrachlorodibenzofuran, a Critical Byproduct in the Synthesis of 2,2',4,4',5,5'-Hexachlorobiphenyl by the Ullmann Reaction

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In connection with structural studies of the components in commercial PCB-mixtures (polychlorinated biphenyls) we have synthesised a number of symmetrically and unsymmetrically substituted chlorinated biphenyls.[1-3] One of these compounds, 2,2',4,4',5,5'-hexachlorobiphenyl, a major component in PCB-mixtures,[4-6] was synthesised in larger amounts by an Ullmann coupling of 2,4,5-trichloroiodobenzene in order to be used in toxicological investigations.

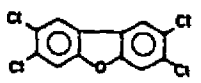
In a study concerning the Ullmann reaction of 2-chloroiodobenzene Nilsson[7] showed that under commonly used conditions dibenzofuran was formed as a by-product in the coupling reaction. The formation of minor amounts of 2,3,7,8-tetramethoxydibenzofuran in the coupling of 4-bromo-5-iodoveratrole has also been reported.[8] The occurrence of chlorinated dibenzofurans as contaminants in chlorobiphenyl samples prepared for toxicological experiments could be serious in view of the high toxicity of these compounds, recently detected by Vos *et al.*[9] as contaminants in some commercial PCB-mixtures. We have therefore studied the byproducts in the above coupling reaction with special attention to chlorinated dibenzofurans.

The coupling reaction was performed with commercial 2,4,5-trichloroiodobenzene which was thoroughly purified. The copper bronze was of the same quality as the one used by Nilsson[7] and contained a small amount of fatty acids. The use of very pure electrolytic copper did not significantly change the nature or yield of by-products. No precautions were taken to exclude air from the reaction mixture.

The crude coupling product was fractionated on a silica gel column with hexane as solvent. The fractions eluted after some starting material and the main product were investigated by mass spectrometry for the presence of compounds with the molecular ion 304 m.u. which corresponds to a tetrachlorinated dibenzofuran. Such a compound was also found eluted with some other byproducts, probably chlorinated terphenyls (MS) (*cf.* Ref. 7). The suspected tetrachlorodibenzofuran could more conveniently be isolated in a pure state by chromatography of the crude coupling product on an alumina column. The compound gave the expected analytical values and mass spectrum. The only peaks exceeding 10 % of the base peak (306 m.u.) in the mass spectrum was found at 241 – 243 m.u. (16 %) which corresponds to loss of ClCO from the molecular ion. This fragmentation was found also by Vos *et al.*[9] and could be compared with the loss of HCO from the molecular ion of the parent compound, dibenzofuran.[10]

The NMR spectrum showed singlet signals at δ 7.48 and δ 7.85, consistent only with a 2,3,7,8-tetrachlorodibenzofuran structure.

Treatment of 2,2',4,4',5,5'-hexachlorobiphenyl with potassium hydroxide at elevated temperatures gave small amounts of the same tetrachlorodibenzofuran (GLC, TLC), probably *via* a phenolic intermediate.



The results presented here show that any preparation of polychlorinated biphenyls synthesised *via* the Ullmann reaction using iodo-compounds with chlorine atoms in the *ortho*-positions must be thoroughly analysed for the presence of chlorinated dibenzofurans. A comparison of the toxicity of 2,2',4,4',5,5'-hexachlorobiphenyl, synthesised by the Ullmann method, and a commercial PCB-mixture (Aroclor 1254) was recently published.[11] No details of the purification of the product were given. However, our crude biphenyl contained *ca.* 3 % tetrachlorodibenzofuran and trace amounts of this compound were detected (GLC) even after repeated crystallisations from hexane, ethanol or acetic acid.

Experimental. The melting points were determined on a Kofler micro hot stage. Mass

* Part V, see Ref. 1.

spectra were recorded on an LKB 9000 spectrometer. The NMR spectrum was obtained on a Varian HA-100D instrument with tetramethylsilane as internal standard.

Gas chromatography. The products were characterised by GLC using a Hewlett-Packard 7620A instrument fitted with an EC detector. Glass columns (0.20 × 180 cm) containing 2 % (w/w) Apiezon L on Chromosorb W A/W DMCS (100–120 mesh) at 210° were used. The gas flow (argon-methane, 9:1) was about 25 ml/min.

Coupling reaction. 2,4,5-Trichloroiodobenzene (Koch-Light, recrystallised from ethanol or purified on a silica gel column with hexane as solvent, 10 g) was thoroughly mixed with copper-bronze (lithographic bronze, *cf.* Ref. 7; 9.3 g) and the mixture was heated from 180° to 235° during one hour with occasional stirring. Extraction of the reaction mixture in a Soxhlet apparatus with hexane and evaporation of solvent gave 5.7 g of crude product.

Isolation of 2,2',4,4',5,5'-hexachlorobiphenyl.[8,9,10] 2.5 g of the above product was added to a column (5.6 × 62 cm) of silica gel (Merck, <0.063 mm) which was eluted with hexane. After some starting material 2,2',4,4',5,5' hexachlorobiphenyl was obtained free from byproducts (GLC), 2.05 g, m.p. 103.5–104.5° (EtOH), λ_{max} (EtOH) 281 nm (ε 20 40), 290 nm (ε 1860).

After the major product the tetrachlorodibenzofuran eluted together with some other byproducts, most probably terphenyls (8 Cl) as shown by MS.

Isolation of 2,3,7,8-tetrachlorodibenzofuran. When 2.5 g of the crude product was chromatographed on neutral alumina (Merck, activity grade I, 4.2 × 72 cm) with hexane as solvent the biphenyl and the suspected terphenyls eluted together. The column was further eluted with hexane-ether (9:1). Finally elution with ether gave a fraction of 2,3,7,8-tetrachlorodibenzofuran (0.08 g) which crystallised from hexane. The compound recrystallised on the hot plate from ca. 150° to give needles, m.p. 223–226° (subl. from ca. 210°). [Found: C 47.0; H 1.3. M^+ 304 m.u. (4 Cl). $C_{12}H_4Cl_4O$ (306.0) requires C 47.1; H 1.3.] (NMR (CDCl$_3$) δ 7.48 (s) and δ 7.85 (s). λ_{max} (EtOH) 222.5 nm (sh) (ε 46 500), 228.5 nm (ε 50 200), 240 nm (sh) (ε 26 600), 251 nm (ε 17 400), 259.5 nm (ε 29 100), 298.5 nm (sh) (ε 24 500), 304 nm (ε 28 200), and 314 nm (ε 23 300).

Retention times on GLC, conditions as described above, for 2,2',4,4',5,5'-hexachlorobiphenyl and 2,3,7,8-tetrachlorodibenzofuran were 11.6 and 14.8 min, respectively. Retention times for the terphenyls were several hours under these conditions.

On TLC (silica gel-hexane) the tetrachlorodibenzofuran has an R_F value of 0.30 and the hexachlorobiphenyl 0.41.

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Differentiation between α-Glutamyl Peptides, γ-Glut Peptides, and α-Aminoacylglut Acids by PMR Spectrosco

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Numerous γ-glutamyl derivatives of acids and amines occur naturally methods for the unequivocal str determination of these compound therefore of importance. Whereas ard methods can be used to establi sequence of dipeptides containing glu acid the differentiation between α γ-glutamyl derivatives poses a sp problem. The only three reliable che solutions to this problem are synt quantitative decarboxylation with hydrin,[1] and deamination with n acid.[2] The latter two methods re structive and demand considerable am of material. The higher pK_a-value α-glutamyl α-amino acids than f glutamyl α-amino acids determine elution behaviour on strongly basic exchange resins in the acetate for glutamyl peptides being eluted last acetic acid. Differentiation between α γ-glutamyl peptides has been made amino acid analyser, where γ-glut peptides are eluted before and α glut peptides after the second amino acid a strongly acidic ion-exchange resin citrate buffer.[4] Various methods depe on paper chromatography, electrophe or acid lability for distinction betwee two isomer possibilities require isomers for reliable results.

The δ-value for the α-proton in glutamic acid moiety is larger f glutamyl amino acids than for γ glut amino acids in aqueous solution, and difference has been proposed as a m for differentiation between α- and glutamyl derivatives.[4] However, the value for the α-proton in γ-glutamy tamic acid (3.92 ppm) is higher than upper limit of 3.90 ppm given for th proton in γ-glutamyl derivatives,[4] similar to the shift for the α-prote glutamic acid in α-glutaroylphenylal