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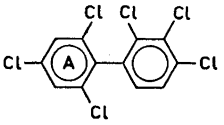
Polychlorinated Biphenyls
III.* Synthesis of Two ^{14}C-Labelled Hexachlorobiphenyls

GÖRAN SUNDSTRÖM and
CARL AXEL WACHTMEISTER

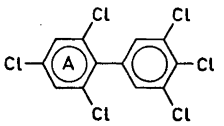
Wallenberglaboratoriet, Stockholms Universitet, Lilla Frescati, S-104 05 Stockholm, Sweden

Polychlorinated biphenyls (PCB) which find use, *e.g.*, in the electrical industry, are complex mixtures of compounds with one to ten chlorine atoms per molecule.[2,3] Their occurrence in fish and wildlife from various parts of the world has recently been the subject of comprehensive reviews.[4,5]

We recently reported a synthesis of two ^{14}C-tetrachlorobiphenyls.[6] In the present communication the synthesis of a mixture of 2,2′,3,4,4′,6′-hexachlorobiphenyl (I) and 2,3′,4,4′,5′,6-hexachlorobiphenyl (II), labelled in the A rings with a specific activity of *ca.* 25 Ci/mol is described. These compounds were required for current investigations into the distribution and excretion of PCB in mice and quails.[7-9]



I



II

Chlorination with sodium chlorate in hydrochloric acid [10] of uniformly labelled acetanilide-^{14}C afforded 2,4,6-trichloroacetanilide-^{14}C. This was hydrolysed and the 2,4,6-trichloroaniline-^{14}C produced was used in the arylation of 1,2,3-trichlorobenzene following the general procedure described by Cadogan.[11] The biphenyl mixture obtained contained the labelled isomers I and II in the approximate ratio 2:1 (GLC), chromatographically indistinguishable from the two main components formed in the same coupling reaction using unlabelled 2,4,6-trichloroaniline.

The latter products were isolated in a pure state by chromatography on a silica gel column. Based on their relative retention times by GLC (*cf.* Ref. 2), the major and minor components were formulated as 2,2′,3,4,4′,6′-hexachlorobiphenyl (I) and 2,3′,4,4′,5′,6-hexachlorobiphenyl (II), respectively. The structural assignments were confirmed by UV spectrometry. Compound I gives a distinct long-wave band (about 270–280 nm), similar to that produced by 2,2′,3,6′-tetrachlorobiphenyl.[1] By comparison, compound II, similarly to 2′,3,4,6′-tetrachlorobiphenyl, exhibits a shoulder only in this region.[1] This spectral difference, which has previously been found also in the spectra of 2,2′,6-trimethylbiphenyl and 2,6-dimethylbiphenyl has been interpreted as indicating a progressive disappearance of the conjugation band about 230 nm with an increasing number of *ortho*-substituents.[12]

Final confirmation of the assigned structures was provided by the 100 MHz NMR spectra of the two compounds.[3]

Experimental. Activities were measured with a Packard Tri-carb model 3320 liquid scintillation spectrometer. UV-spectra were measured on a Perkin-Elmer 124 spectrophotometer. Melting points were determined on a Kofler micro hot stage. Mass spectra were recorded on an LKB 9000 spectrometer. NMR spectra were obtained on a Varian HA-100 instrument with tetramethylsilane as internal standard. All reagents used were of analytical grade unless otherwise stated.

Gas chromatography. The hexachlorobiphenyls were characterised by GLC using a Varian 1400 instrument fitted with an electron capture detector. Glass columns (0.18×160 cm) containing 4 % (w/w) SF 96 on Chromosorb W A/W DMCS (100–120 mesh) at 173°

* Part II, Ref. 1.

were used. The gas flow (nitrogen) was about 30 ml/min.

Acetanilide-^{14}C. Aniline-^{14}C hydrogen sulphate (5 mCi, 50 Ci/mol, produced by The Radiochemical Centre, Amersham), in the original ampoule, was stirred magnetically with acetic anhydride (3 ml) for 7 h at room temperature. The acetic anhydride was evaporated under controlled pressure in a vacuum desiccator over molecular sieves (Union Carbide, 8 Å). The residue, containing sulphuric acid, was dissolved in ethyl acetate (5 ml) and filtered through a column (0.8 × 5 cm) of silica gel (Merck, 0.05–0.2 mm). Elution with ethyl acetate and evaporation of solvent gave acetanilide-^{14}C (4.25 mCi).

2,4,6-Trichloroacetanilide-^{14}C. Acetanilide-^{14}C (4.25 mCi, 0.085 mmol), in a Pyrex tube fitted with a screw cap, was dissolved in acetic acid (100 %, 2.5 ml) and hydrochloric acid (12 M, 1 ml). The mixture was stirred magnetically. A solution of sodium chlorate (2 M, 1.4 ml) was added in small portions (0.1 ml) at room temperature at 30 min intervals. The screw cap was kept tightly closed during the reaction. After the last addition, the mixture was stirred for another half hour and then cooled in an ice bath. A cooled solution of sodium hydrogen sulphite (2.5 M) was slowly added until the solution was discoloured (*ca.* 5 ml).

The reaction mixture was extracted in the tube with chloroform (8 × 1 ml). The chloroform phase was filtered through a column (0.8 × 3.5 cm) of aluminium oxide (Merck, neutral, activity grade I). The solvent was evaporated, finally in a vacuum desiccator over sodium hydroxide and silica gel at about 360 mm. The residue, dissolved in chloroform, was transferred to two thin layer plates (Merck, Kieselgel HF_{254}, 20 × 20 × 0.1 cm) which were developed twice with chloroform. The band containing 2,4,6-trichloroacetanilide-^{14}C was removed and eluted with acetone into a 25 ml pear-shaped flask (2.81 mCi, 0.056 mmol, 66 %). A band containing 2,4-dichloroacetanilide-^{14}C was also collected (0.20 mCi, 0.004 mmol, 5 %).

2,4,6-Trichloroaniline-^{14}C. After evaporation of the acetone a molar equivalent of 2,4,6-trichloroaniline (Schuchardt, 99 %, recrystallised from ethanol and sublimed *in vacuo*) was added to the crystalline residue of the above 2,4,6-trichloroacetanilide-^{14}C. Hydrochloric acid (12 M, 2 ml) and acetic acid (100 %, 0.5 ml) were added and the mixture was stirred for 5 h at 90°. The acids were cautiously evaporated in a vacuum desiccator over sodium hydroxide and silica gel to give a residue of 2,4,6-trichloroaniline-^{14}C and its hydrochloride.

2,2',3,4,4',6'- and 2,3',4,4',5',6-Hexachlorobiphenyl-^{14}C. 2,4,6-Trichloroaniline-^{14}C (2.81 mCi, 0.112 mmol) was mixed with 1,2,3-trichlorobenzene (Merck, for synthesis, recrystallised from ethanol, 1.5 g) and heated to a melt (about 60°). Isoamyl nitrite (0.1 ml) was added with stirring and the temperature was slowly raised to 100° and kept there for 1.5 h. Excess trichlorobenzene was then distilled off (60–70°/1–3 mm) and collected in a trap chilled with dry ice. (This step must be performed with extreme caution. To prevent foaming it is important to keep the temperature slightly above the m.p. of the trichlorobenzene while the pressure is slowly lowered). Activity measurements showed the presence of low boiling byproducts (1.18 mCi) in the cold trap. Most of the activity was shown by autoradiography to originate from 1,3,5-trichlorobenzene-^{14}C.

The residue was dissolved in chloroform and transferred to a preparative thin layer plate as described above. This was developed three times with hexane. The desired zone was removed and eluted with chloroform. Evaporation of solvent gave the two biphenyls as an oil, 0.60 mCi, 21 %.

GLC analysis of the labelled product gave two peaks of retention times corresponding to those of the unlabelled biphenyls analogously prepared (see below).

Synthesis of unlabelled material. 2,4,6-Trichloroaniline (0.5 g) and 1,2,3-trichlorobenzene (5 g) were heated to a melt. Isoamyl nitrite (1 ml) was added with stirring. The mixture was slowly heated to about 100° and kept at this temperature for 1.5 h. The trichlorobenzene was evaporated at 140–150° under a flow of nitrogen. The residue was dissolved in a small amount of hexane-chloroform (1:1) and transferred to an aluminium oxide column (2 × 11 cm, Merck, neutral, activity grade I). Elution with hexane and removal of solvent gave a mixture of biphenyls I and II (0.33 g).

The two components were separated on a silica gel column (3 × 65 cm, Merck, <0.08 mm), with hexane as eluent. Recrystallisation from methanol and sublimation *in vacuo* gave 2,2',3,4,4',6'-hexachlorobiphenyl (I), m.p. 69.5–71° (Found: C 40.1, H 1.3, M^+ 358 m.u. (6 Cl) $C_{12}H_4Cl_6$ (360.9) requires C 39.9, H 1.1), λ_{max} (EtOH) 275 nm (log ε 2.73), NMR: ($CDCl_3$) δ 7.04 (d, J = 8.7 Hz, H_6), δ 7.45 (s, $H_{3',5'}$), δ 7.49 (d, J = 8.7, H_5) and 2,3',4,4',5',6-hexachlorobiphenyl (II), m.p. 110–111° (Found: C 39.8, H 1.1, M^+ 358 m.u. (6 Cl) $C_{12}H_4Cl_6$ (360.9) requires C 39.9, H 1.1), NMR: ($CDCl_3$) δ 7.27 (s, $H_{2',6'}$), δ 7.43 (s, $H_{3,5}$). Only a weak shoulder at 285 nm (log ε

2.85) was observed in the UV spectrum (EtOH) of biphenyl II.

GLC at 173° as described above showed a retention time of 19.2 min for biphenyl I and 23.5 min for biphenyl II.

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