

The Synthesis and Purification of Pentachlorophenol- $^{14}\text{C}_6$

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Received 1st version, August 10, 1970

Revised version, September 1st, 1970

SUMMARY

Pentachlorophenol- $^{14}\text{C}_6$ was synthesized by chlorinating phenol- $^{14}\text{C}_6$ using aluminum chloride as a catalyst. Purification of the labeled pentachlorophenol involved the precipitation of the labeled product from an aqueous alkali solution with hydrochloric acid and two sublimations. Proof of radiochemical purity was determined using thick layer chromatography and autoradiography. Internal liquid scintillation counting techniques were used to determine the specific activity of the compound.

INTRODUCTION.

Pentachlorophenol has been manufactured for commercial purposes in the United States since 1936⁽¹⁾. The compound has many applications in industry and agriculture. Pentachlorophenol has been used extensively in the lumber and construction industries as a wood preservative and has been used as a pesticide, fungicide, bactericide and mothproofing agent in fabrics⁽²⁾. The widespread use of this compound presents the possibility of potential environmental and toxicological problems.

Radioisotope tracer techniques often furnish information previously undisclosed by other methods of approach. Therefore, pentachlorophenol, labeled with a radioactive nuclide could be extremely useful for the investigation and evaluation of some of these problems.

A review of the literature revealed two references concerning the use or preparation of radionuclide labeled pentachlorophenol. Jaworski⁽³⁾ reported the use of pentachlorophenol-1- ^{14}C in tracer studies in cotton in 1956. Details

of the synthesis were not given nor could they be found by exhaustive literature survey; however, the author did mention that the techniques of the labeling of pentachlorophenol with carbon-14 in the 1 position were those used by the Tracer Laboratory Company. Bubner and Schmidt ⁽⁴⁾ reported the synthesis of pentachlorophenol-³⁶Cl₅ in 1963. This was accomplished by the exhaustive chlorination of phenol with chlorine-³⁶Cl₂ to yield hexachloro-2,5-cyclohexadien-1-one-³⁶Cl₆ which was reduced to pentachlorophenol-³⁶Cl₅ by means of a sulfur dioxide reduction.

In 1938 Stoesser ⁽⁵⁾ reported a process for the preparation of unlabeled pentachlorophenol involving the direct chlorination of phenol or an intermediate chlorophenol in the presence of an aluminum chloride catalyst with or without the aid of a solvent. The method involves bubbling chlorine gas into a mixture of phenol and the aluminum chloride catalyst and gradually increasing the temperature over a period of about ten hours. The author claims that pentachlorophenol may be produced in high yield without the concurrent formation of large quantities of alkali insoluble products.

In the work reported in this paper the synthesis of pentachlorophenol-¹⁴C₆ was accomplished by the direct chlorination of phenol using aluminum chloride as a catalyst. The procedure was similar to one described by Stoesser ⁽⁵⁾, except that the proportions of the reactants were varied considerably. The yield of pentachlorophenol-¹⁴C₆ was 46.6 % after purification. The melting point was 190.4° C. The proof of radiochemical purity was shown using thick layer chromatography and autoradiography.

EXPERIMENTAL.

Pentachlorophenol-¹⁴C₆. — Into a 25 ml 3-necked pear-shaped flask was placed 0.9760 g (10.3 millimoles) of freshly distilled phenol and 3.6 mg (26.9 mCi/millimole) of phenol-¹⁴C₆ *. The labeled phenol was transferred into the reaction flask using four 2 ml diethyl ether washes to effect the transfer. The ether was stripped using a water aspirator and was condensed in a trap which was placed in a dry ice-methyl cellosolve bath. The flask was fitted with a 70 cm water cooled condenser, a capillary delivery tube for chlorine gas and a stopper. The flask was placed in an oil bath equipped with a magnetic stirring bar and a thermometer and heated to 67° C. Chlorine gas was bubbled into the melted phenol through the capillary delivery tube at a rate which did not cause the phenol to splash on the sides of the reaction vessel. Immediately, 0.100 g (0.75 millimole) of anhydrous aluminum chloride was added, and the flask was stoppered. The temperature was increased to a final temperature of 190° C during a period of four hours and forty-five minutes. There was obtained a black oil which did not solidify.

* Amersham/Searle Corp., Des Plaines, Ill.

The black oil was dissolved in 30 ml of 5 % sodium hydroxide and filtered; 10 % hydrochloric acid was added to the clear filtrate, precipitating a light brown material. When the mixture was heated, the precipitate dissolved. Re-precipitation occurred when the mixture had cooled to room temperature. The precipitate was collected on a Buchner funnel, air dried and transferred into a sublimation apparatus *. Most of the material sublimed under reduced pressure (water aspirator) at 100° C, a temperature known to be below that necessary to sublime pentachlorophenol. The sublimed material and 0.0970 g of aluminum chloride were placed back in the reaction flask. The mixture was chlorinated for an additional two hours and thirty minutes over a temperature range of 110°-190° C. There was obtained 1.8 g (64.3 % yield) of dark brown solid product.

Purification of the Crude Product. — The reaction mixture was placed in a 250 ml beaker and dissolved in 50 ml of 5 % sodium hydroxide. Most of the reaction mixture dissolved after considerable breaking up and stirring with a glass rod. The solution was filtered through Whatman Number 1 filter paper into a 400 ml beaker. The filter was washed with 50 ml of distilled water. The pentachlorophenol was precipitated by adding 10 % hydrochloric acid to the clear filtrate until the mixture was about pH 2. The pH was determined using Hydrion pH indicating paper. The acidified mixture was heated with constant stirring on a hot plate to a temperature of about 90° C. The mixture was set aside, covered, and allowed to cool to room temperature. The precipitated product was filtered on a Buchner funnel by suction filtration, washed with about 50 ml of distilled water and allowed to air dry. The dry product was transferred into the sublimation apparatus. Inserted between the sublimation apparatus and the water aspirator was a trap submerged in a dry ice-methyl cellosolve bath to prevent radioactivity from being lost to the environment. The pentachlorophenol was sublimed at 150° C under reduced pressure (water aspirator). There was obtained 1.56 g (55.7 % yield) of white crystals melting at 187.1° C.

The sublimed product was subjected to thin layer chromatographic and autoradiographic analysis. The procedure was as follows :

Thin layer plates were prepared by coating 20 × 20 cm glass plates with 200 μ layers of purified Silica Gel G with fluorescent indicator ** in a slurry form. The preparation of 5 plates required a slurry containing 30 g of adsorbant and 45 ml of distilled water, The chromatographic plates were allowed to air dry until set and were then placed in a 110° C oven for one hour prior to use.

Two thin layer plates were spotted with 10 μl each of a 1.0 μg/μl acetone solution of unlabeled pentachlorophenol and a 1.0 μg/μl acetone solution of

* Kontes Glass Company, Franklin Park, Ill.

** Adsorbasil-1-P with 10 % binder, Applied Science Laboratories, State College, Pa.

the sublimed pentachlorophenol- $^{14}\text{C}_6$. One plate was developed in a 95:5 benzene-methanol solution and the other plate was developed in chloroform. In both systems, the unlabeled pentachlorophenol and the sublimed product were comparable to each other in position and size when observed under a long wave ultraviolet lamp.

A portion of the pentachlorophenol- $^{14}\text{C}_6$ solution was diluted 100 times with acetone. A 10 μl portion of the diluted solution was spotted on the upper right corner of the plate for the purpose of showing the intensity of a 1 % impurity on an autoradiogram.

Autoradiograms were made using No Screen Kodak Medical X-Ray Film *. The thin layer chromatogram of the labeled product was sprayed with Neotan **, allowed to dry, and placed in a ten by twelve casset. The film was centered over the chromatogram. After the proper exposure time, the film was developed with Kodak *** chemicals in accordance with the manufacturer's instructions.

Two autoradiograms, one exposed for three days and the other exposed for thirty days, showed the presence of an impurity. The spot was about 1 cm above the pentachlorophenol spot and was slightly darker than the 1 % sensitivity spot.

Further purification of the sample was attempted by a second sublimation. The labeled product was sublimed under reduced pressure (water aspirator) at 100° C for 1 hour and 15 minutes. The small amount of sublimed material was washed from cold finger of the sublimator. The temperature was raised to 150° C and the remainder of the labeled product was sublimed under reduced pressure. There was obtained 1.3 g (46.6 % yield) of white, needle-like crystals melting at 190.4 °C; reported ⁽⁶⁾ m.p. 191° C. A mixture of the labeled compound and an authentic sample of unlabeled pentachlorophenol showed no melting point depression.

The twice sublimed product was subjected to thick layer chromatographic and autoradiographic analysis. Thick layer plates were used in place of thin layer plates because greater concentrations of the labeled compound could be chromatographed permitting a shorter exposure time for a 1 % impurity to be seen on an autoradiogram. The thick layer chromatography procedure followed closely that of the thin layer procedure. Thick layer plates were prepared by coating 20 × 20 cm glass plates with 1,000 μ layers of purified Silica Gel G with fluorescent indicator **** in a slurry form. The preparation of 5 plates required a slurry containing 120 g of adsorbant and 180 ml of distilled water. The chromatographic plates were allowed to air dry until set and were then placed in a 110° C oven for one hour prior to use.

* Eastman Kodak Co., Rochester, N. Y.

** Brinkmann Instruments, Inc., Wesbury, L. I., N. Y.

*** Eastman Kodak Co., Rochester, N. Y.

**** Adsorbasil-1-P with 10 % binder, Applied Sciences Laboratories, State College, Pa.

Thin layer and thick layer plates were spotted and chromatographed as previously described utilizing both solvent systems. Under a long wave length ultraviolet lamp, the spots were identified against the fluorescent background. The pentachlorophenol-¹⁴C₆ and the unlabeled pentachlorophenol were near the origin and were comparable to each other in position and size. No other spots were seen.

An autoradiogram of a thick layer chromatogram was prepared. The film was exposed for 72 hours. The autoradiogram showed one spot, much lighter than the 1 % impurity spot, 1 cm above the labeled pentachlorophenol spot.

The radiopurity of the purified compound was determined by scraping four separate zones and a blank from the origin to the solvent front into counting vials containing 15 ml of scintillation fluid. The scintillation fluid was composed of 0.4 % PPO (2,5-diphenyloxazole) in an equal volume of toluene and 2-ethoxyethanol. The separate zones consisted of the origin, the pentachlorophenol, the area above the pentachlorophenol, and the solvent front. A Packard Tri-Carb internal liquid scintillation counter was used to quantitate the amount of radioactivity present in each vial. Carbon-14 toluene was used as the internal standard for the determination of absolute disintegration. Radiochemical purity was calculated as the fraction of activity of the pentachlorophenol zone divided by the total activity of the four zones and was expressed as percent. Two plates, one from each solvent system, were assayed and showed the radiopurity of the labeled pentachlorophenol to be 99.57 % and 99.52 %.

The specific activity was determined using internal liquid scintillation counting techniques. The specific activity was found to be 0.270 μ Ci/mg. The compound gave a melting point of 190.4° C; reported 191° C⁽⁶⁾.

ACKNOWLEDGMENTS.

This research was supported in part by U.S. Public Health Service Training Grant No. 5-TO1-ES00071 from the National Institute of Environmental Health Sciences.

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