

The Preparation of Polyvinyl Acetate Phthalate*- $^{14}\text{C}_1$

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SUMMARY

Polyvinyl acetate phthalate- $^{14}\text{C}_1$ (PVAP) was prepared by condensing radioactive phthalic anhydride with polyvinyl alcohol. The radioactive anhydride was prepared from ethyl anthranilate. The chemical purity and the authenticity of the PVAP so prepared was ascertained by a comparison of its acid number and thin layer chromatography to an authentic sample. The specific activity was determined using liquid scintillation counting.*

INTRODUCTION

Polyvinyl acetate phthalate (PVAP), a polymer which has been claimed to have excellent enteric coating properties, was developed by Millar ⁽¹⁾ in 1959. The toxicity, absorption, and metabolism of the product have not been studied in either humans or animals nor have there been any closely related studies done on other polymers of the type used for enteric coating. The only type of toxicity studies which have been reported ^(2,3) entail acute and chronic investigations which do or do not show visceral changes. Conventional procedures for toxicity, absorption and metabolic type of biological

* The name of this product, polyvinyl acetate phthalate, indicates that there are acetyl groups present, yet in the method of preparation acetylation does not occur. The explanation for the presence of acetyl groups is that polyvinyl alcohol (Du Pont's product Elvanol, grade 51-05) is not pure alcohol but has been shown to have an acetyl content of 1.6 to 6.0 %. The presence of the acetyl groups was established by infrared spectrometry; the product has a carbonyl absorption band at $5.80\ \mu$ and an ester absorption band at $8.00\ \mu$. The polyvinyl alcohol has a molecular weight range of 25,000 to 40,000 which corresponds to a polymer of 600 to 800- $\text{CH}_2\text{-CH(OH)}$ -units. When the alcohol is esterified with phthalic anhydride, PVAP is formed with a phthalyl content of 60-70 % and 24-38 % free hydroxyl groups remain. The compound was labelled with ^{14}C in the carboxyl carbon position.

studies are not as easily performed or readily applicable as more modern isotope tracer techniques. Thus, the need arose for a sample of labelled PVAP for such contemplated work.

The proposed synthesis for PVAP required the need for radioactive phthalic anhydride. Labelled phthalic acid from which the anhydride could be prepared readily had been explored earlier in our Laboratories ⁽⁴⁾. In the published procedure the tagged carbon atom was introduced by reacting the Grignard reagent prepared from the reaction of magnesium and o-bromotoluene with labelled carbon dioxide generated from radioactive barium carbonate. The resultant product was subsequently oxidized to phthalic acid. The use of gaseous carbon dioxide required a closed system and necessitated care in the manipulative procedure. A further need for phthalic acid presented an opportunity to investigate the utilization of ¹⁴C cuprous cyanide in a diazonium reaction as a second way to introduce the tagged atom and thus be able subsequently to compare the two procedures. The latter method described in this paper is more convenient to run and gave almost a 10 % better yield without any manipulative risk with the radioactive reagents. The complete synthesis entails reacting cuprous cyanide with the diazonium salt of ethyl anthranilate, base catalyzed hydrolysis of the nitrile so obtained and finally acidification of the salt obtained from the hydrolysis to give the acid. Cuprous cyanide was prepared from available labelled potassium cyanide.

The chemical purity and authenticity of the PVAP prepared by reacting phthalic anhydride with polyvinyl alcohol was ascertained by making a comparison of the acid number and thin layer chromatography of the resultant product to an authentic sample as the point of reference.

The radioactive purity was established by obtaining an autoradiograph of the thin layer chromatographic plate, and the product was found to be comparable to the spots obtained from an authentic sample.

EXPERIMENTAL

ETHYL ANTHRANILATE.

To 84.0 g (0.43 mole) of ethyl o-nitrobenzoate there was added 120 ml of ethanol (99.6 %) and one teaspoonful of Raney nickel. The mixture was hydrogenated in a Parr High Pressure Hydrogenator at 80-90° C and at an initial pressure of 700 p.s.i. Additional hydrogen was added as required. After the hydrogenation appeared to have stopped the mixture was shaken for an additional five hours to insure complete reduction. The catalyst was then filtered off, and the ethanol was removed under reduced pressure. There was obtained 66.5 g (93.0 %) of product which distilled at 105-106° C/0.35 mm; reported ⁽⁵⁾ b.p. 145-147° C/15 mm.

CUPROUS CYANIDE- ^{14}C (6, 7).

To a solution of 4.20 g (0.0168 mole) of pentahydrated cupric sulfate and 0.98 g (0.0168 mole) of sodium chloride in 50 ml of water, there was added dropwise with constant stirring and a slight amount of heat an alkaline solution of sodium sulfite [1.13 g (0.0110 mole) of sodium bisulfite and 0.74 g (0.0185 mole) of sodium hydroxide in 15 ml of water]. The white precipitate which resulted was washed several times by decantation with water, and the solid was suspended in 15 ml of water.

Crystalline potassium cyanide- ^{14}C (2 mCi weighing 3.7 mg) was dissolved in water and added to the constantly stirred cuprous chloride. To the mixture there was further added a solution of 2.73 g (0.042 mole) of unlabelled potassium cyanide dissolved in 10 ml of water. To the clear cuprous cyanide solution there was added 70 ml of toluene and the mixture was then cooled to 0-5 °C using a dry ice-acetone bath.

ETHYL O-(CYANO- ^{14}C) BENZOATE (8).

To a mixture of 35 ml of water and 17 ml of concentrated hydrochloric acid, there was added 2.77 g (0.0168 mole) of ethyl anthranilate. To the mixture cooled to 0-5° C using a dry ice-acetone bath, a solution of 1.16 g (0.0168 mole) of sodium nitrite in 20 ml of water was added with constant stirring. After the addition was complete, the diazonium solution was allowed to stir for 20 minutes to insure complete reaction. After this period of distinct and permanent reaction for free nitrous acid was present as evident from testing with potassium iodide-starch paper as the indicator. The mixture was then carefully neutralized by adding dry sodium carbonate to a pH of 7 using pHydriion paper as the indicator.

The cold diazonium solution was added cautiously with vigorous stirring to the cold cyanide solution prepared above. After the addition was complete, the mixture was stirred for 30 minutes at 0-5° C; then it was allowed to rise to room temperature. The mixture was then heated slowly with constant stirring to 50° C in order to break the complex formed, and then it was allowed to cool to room temperature.

The water layer which was separated from the toluene layer containing most of the organic nitrile was extracted five times with 10 ml portions of toluene. All toluene extractions were combined, and the solvent was then removed under reduced pressure to give a solid residue of the radioactive nitrile.

PHTHALIC ACID- $^{14}\text{C}_1$.

To the crude nitrile there was added a solution of 30 ml of methanol in 10 ml of water which contained 4 g of sodium hydroxide. The mixture was refluxed gently for 64 hours. The methanol and water were removed

under reduced pressure to give the disodium salt of phthalic acid. The salt was redissolved in 5 ml of water, the solution was filtered, and the filter paper was washed free of radioactive material with successive portions of water. The filtrate and combined washings were acidified and then allowed to stand overnight. The phthalic acid crystals which formed was filtered off and air dried. A yield of 2.60 g (93.2 %, based on the amount of ethyl anthranilate used) was obtained. The melting point was about 200-201° C; reported ⁽⁹⁾ 191° C, sealed tube. The product was not recrystallized. A mixed melting point gave no depression.

PHTHALIC ANHYDRIDE-¹⁴C₁ ⁽¹⁰⁾.

A mixture of 2.6 g of the labelled phthalic acid and 50 ml of acetic anhydride was refluxed for 10 hours. The solvent was removed under reduced pressure. A yield of 2.16 g (93.1 %) of unrecrystallized phthalic anhydride was obtained. Its melting point was 130-132° C; reported ⁽¹¹⁾ 131.2° C. Mixed melting point gave no depression.

POLYVINYL ACETATE PHTHALATE-¹⁴C₁ ⁽¹²⁾.

To a mixture of 10 ml of glacial acetic acid and 2.16 g of labelled phthalic anhydride at a temperature of 70° C, there was added with constant stirring 1.44 g of polyvinyl alcohol *. The temperature of the reaction mixture was then raised to 115° C and held at that temperature for 4½ hours. To the mixture previously cooled to 85° C there was added 10 ml of acetic acid (60 %). After stirring the mixture for thirty minutes it was poured slowly into 200 ml of vigorously stirred ice water (0-5° C). The gummy mass was removed and washed by decantation with ice water (0-5° C) until a pH of 4 was obtained. The polymer was placed in a vacuum oven at a pressure of 0.45 mm and a temperature of 50° C for 24 hours. A yield of 3.00 g (83.3 %) of product was obtained.

The radioactive compound was found to be quantitatively comparable to an authentic sample. The acid number of the radioactive sample based on an average titration of 2.57 ml of 0.0923 N potassium hydroxide per 70 mg of product was 190.9; for the authentic sample the acid number was 200.5 based on an average titration of 2.70 ml of 0.0923 N potassium hydroxide per 70 mg of sample.

Methanolic solutions (1 %) of the authentic and radioactive sample were prepared for thin layer chromatographic comparison. On a thin layer chromatographic plate which had a 250 μ support of Silica Gel H, there was spotted 5 μl of each solution. The plate was placed in a tank containing a solvent system of 1 part methanol to 1 part water.

* See footnote page 150.

The plate was developed using iodine. The authentic and radioactive samples gave identical R_f values.

An autoradiograph of the thin layer plate was made using an X-ray emulsion film to determine the radiopurity of the labelled polymer. Only one radioactive spot at the R_f of the authentic sample was found to be present indicating that the sample of PVAP- ^{14}C was radioactively pure.

The specific activity of the PVAP- ^{14}C was found to be 63.1 nCi/mg based on determinations using the liquid scintillation counting technique.

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