SYNTHESIS OF ^{14}C-LABELED 2,2-DICHLOROPROPIONIC ACID

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SUMMARY

A widely used herbicide, 2,2-dichloropropionic acid (dalapon), was synthesized with ^{14}C-labeling in the C-1 or C-2 positions. The carboxyl labeled material was prepared in 55% yield by carbonation of 1,1-dichloroethyllithium at approximately -104°. Starting with trichloroacetic acid, the C-2 labeled product was prepared in an overall yield of 39% by means of a 4-step reaction sequence which involved the removal of a chlorine atom and the addition of a methyl group.

INTRODUCTION

Sodium 2,2-dichloropropionate (sodium dalapon) is an important herbicide used for the selective control of grasses. The absorption, translocation, and metabolism of 2,2-dichloropropionic acid (dalapon) has been extensively studied in plants (1-4). Degradation of dalapon by soil microorganisms has also been investigated (5-7). The synthesis of sodium dalapon-^{14}C-2 was previously reported (8) where propionic-^{14}C-2 acid was directly chlorinated in two successive steps. Difficulty was encountered, however, in the purification of the radiolabeled product

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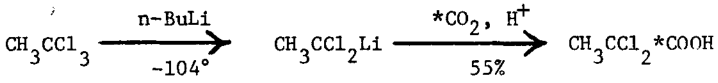
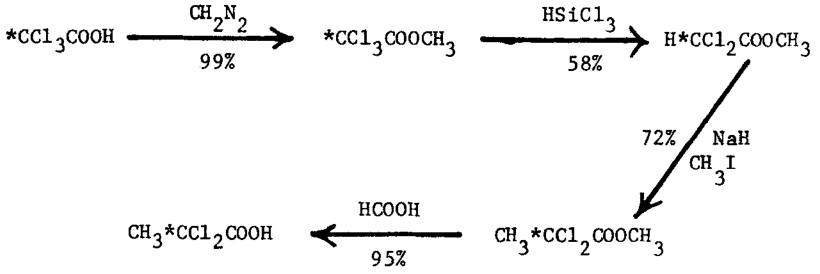
because a variety of similarly chlorinated acids were produced. Thus, a product of 96% radiochemical purity was obtained.

Using nonlabeled materials, we have examined the photochemistry (9) and hydrolysis (10) of dalapon and sodium dalapon, respectively. The use of radioactive materials could greatly facilitate further studies. Therefore, dalapon-^{14}C-1 and dalapon-^{14}C-2 were prepared. Carboxyl labeled dalapon was synthesized by the reaction sequence given in Scheme I.



Scheme I

Dalapon-^{14}C-2 was prepared by the series of reactions given in Scheme II.



Scheme II

In addition, if dalapon-^{14}C-3 was desired, this material could be prepared by implementation of the last two steps of Scheme II using methyl-^{14}C iodide.

EXPERIMENTAL

Materials and Methods. Diazald (N-methyl-N-nitroso-p-toluenesulfonamide) was purchased from Aldrich Chemical. Trichlorosilane, n-butyl lithium (2.4 M in n-hexane), and sodium hydride (57% dispersion in mineral oil) were obtained from Alfa Inorganics. The radioactive starting materials, barium carbonate-^{14}C (5 mCi) and trichloroacetic-^{14}C-2 acid (3 mCi), were purchased from New England Nuclear and Amersham/Searle Corporation, respectively.

Methyl iodide was dried by distillation over phosphorous pentoxide. Dimethylformamide (DMF) was dried over molecular sieve 4A, and tetrahydrofuran (THF) was dried over sodium hydride; both were freshly distilled before use. Commercial 1,1,1-trichloroethane was purified by washing with concentrated hydrochloric acid, 10% aqueous potassium carbonate, and 10% aqueous sodium chloride (11). Following this treatment, the material was dried over anhydrous calcium chloride and distilled.

The reaction yields were estimated by comparison with authentic samples of known concentration using gas-liquid chromatography (10), and the identity of each synthesized product was verified by nuclear magnetic resonance spectrometry. Radioactivity measurements were taken on a Packard 3375 liquid scintillation counter (12).

Synthesis of 2,2-Dichloropropionic-^{14}C-1 Acid

Preparation of 1,1-dichloroethyllithium. This reaction was based on a procedure for the preparation of dichloromethyllithium (13). A 250-ml 3-necked round bottom flask was equipped with mechanical stirrer, cold temperature thermometer, and pressure equalizing addition funnel closed with a rubber serum cap. The reaction flask was initially flushed with dry nitrogen, and then 2.4 ml (24 mmol) of 1,1,1-trichloroethane and 80 ml of THF were added. The vessel was placed in a 2,2,4-trimethylpentane (isooctane) bath which was partially frozen to a slurry (-107°) with liquid nitrogen. A mechanical stirrer was used to agitate the bath to avoid solidification of the isooctane. As the trichloroethane solution was being cooled to approximately -104°, 10.2 ml (24 mmol) of n-butyllithium solution was introduced into the addition funnel through the serum cap by means of a hypodermic syringe. The butyllithium was slowly added to the trichloroethane over a 30 min period, and care was taken to maintain the reaction temperature at approximately

-104°. After the reaction mixture was allowed to stir for an additional 1.5 hr at the same reduced temperature, the dichloroethyllithium solution was ready for transfer to the carbonation vessel.[1]

Generation of carbon dioxide-^{14}C. While the dichloroethyllithium solution was stirred, the $^{14}CO_2$ was generated (14) and trapped for the carbonation reaction. The apparatus shown in the right portion of Fig. 1 was employed for this reaction, with a glass stopper placed at (K). Radioactive barium carbonate (5 mCi, 197 mg, 1 mmol) and nonradioactive carrier (197.4 mg) were placed in the generating flask (E). A fine wadding of glass wool was positioned inside at the bottom of the CO_2-trap (H). The system was then assembled and evacuated with a water aspirator. Stopcocks (D) and (J) were closed and the system was disconnected at (I). With a hypodermic syringe, 1.2 ml of 40% perchloric acid was introduced into the reservoir (C) through the rubber serum cap (B). A liquid nitrogen bath (G) was used to cool the CO_2-trap (H). Just the end of the trap was submerged into the liquid nitrogen in order to freeze most of the $^{14}CO_2$ on the glass wool. Stopcock (D) was carefully opened and small quantities of perchloric acid were added to the $Ba^{14}CO_3$. Addition of the acid was stopped each time the evolution of $^{14}CO_2$ became moderately vigorous. Approximately 15 min were required for total addition of perchloric acid. The generating flask (E) was gently heated to release the remaining $^{14}CO_2$ that was held either as trapped bubbles or dissolved gas. The system was returned to atmospheric pressure by introducing a small stream of nitrogen through serum cap (B) using a hypodermic needle. The $^{14}CO_2$ was now ready for the addition of the 1,1-dichloroethyllithium solution.

Dichloropropionic acid (carbonation reaction). The mechanical stirrer (Q) was stopped in the dichloroethyllithium flask, and the thermometer

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[1] During the preliminary studies, an estimation of dichloroethyllithium formation was determined. For this measurement, about 75 g of pulverized dry ice were added to the reaction mixture. The vessel was removed from the isooctane bath and allowed to warm to ambient temperature. Yield of DCP based on 1,1,1-trichloroethane was approximately 75%.

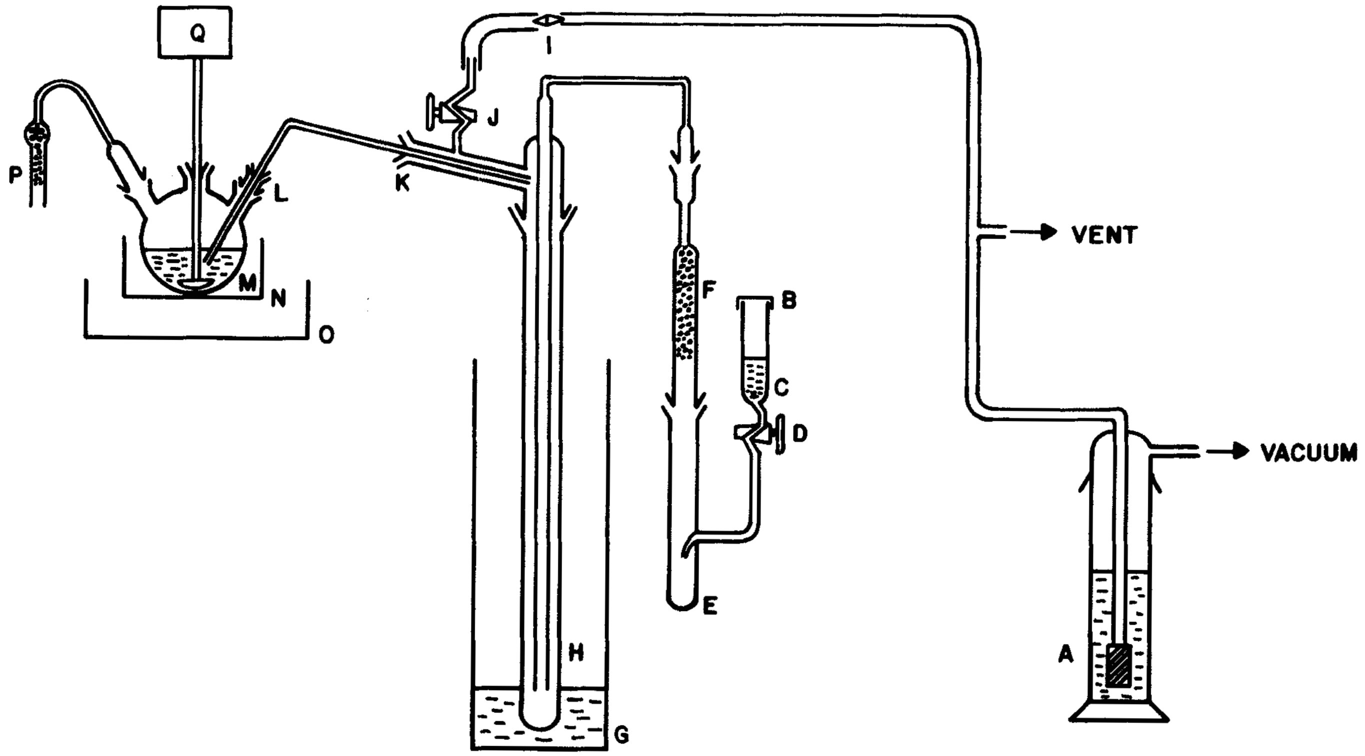

Fig. 1.--Apparatus for the carbonation of dichloroethyllithium. A, washing tower (6 M NaOH); B, rubber serum cap; C, 40% $HClO_4$; D, stopcock; E, CO_2 generation flask; F, anhydrone; G, liquid N_2 bath; H, CO_2 trap; I, quick connector; J, stopcock; K, ground glass connection; L, adapter; M, dichloroethyllithium; N, isooctane bath; O, liquid N_2 bath; P, NaOH pellets; Q, mechanical stirrer.

was removed and replaced with a drying tube filled with sodium hydroxide pellets (P). From the opposite side arm, the addition funnel was removed and the solid adapter was inserted at (L). Stopcock (J) was opened and the glass stopper at (K) was removed. The cold trap (H) was positioned so that the delivery tube was able to connect flask (M) with the cold trap at positions (K) and (L), respectively. During connection, the delivery tube was introduced very slowly into flask (M) to avoid pressure buildup (pressure buildup causes the dichloroethyllithium solution to move slowly up the delivery tube and decompose). After the two systems were joined, the vacuum line was connected at (I); thus, at this point, the entire system appeared exactly as illustrated in Fig. 1. The dichloroethyllithium solution was rapidly drawn into the cold trap with the assistance of vacuum. The rate and amount delivered was easily controlled by operating the vent on the vacuum line. By this technique, about 90% of the dichloroethyllithium solution was quickly transferred without any discoloration. Following addition, the delivery tube was removed and the system was closed at (K) with a glass stopper. The vacuum line was disconnected at (I), and replaced with a drying tube filled with ascarite. The liquid nitrogen bath was removed, and as the reaction mixture slowly warmed to ambient temperature, a medium brown solution was produced. The vacuum line was reconnected at (I), and nitrogen was introduced through serum cap (B). With stopcocks (D) and (J) open, the unreacted $^{14}CO_2$ was swept under reduced pressure from the reaction vessel and trapped in 6 M sodium hydroxide in the washing tower (A).

The mixture was transferred into a separatory funnel with ethyl ether, and hydrolysis was achieved by addition of 100 ml of cold aqueous 1% sulfuric acid. The ether and water layers were separated, and the water layer was extracted three additional times with ether. Product yield was 55%.

Synthesis of 2,2-Dichloropropionic-^{14}C-2 Acid

Preparation of methyl trichloroacetate. For esterification, an ethereal nonalcoholic solution of diazomethane was prepared from Diazald according to the procedure of de Boer and Backer (15). A solution containing 490 mg (3 mCi, 3 mmol) of trichloroacetic-^{14}C-2 acid in 4 ml of ethyl ether was placed in a 50-ml pear-shaped flask. Diazomethane solution was carefully pipetted into the trichloroacetic acid until the yellow color of the diazomethane persisted. The reaction was allowed to stand for about 15 min with occasional swirling of the contents in the flask. To decompose the excess diazomethane, the solution was gently warmed until the yellow color disappeared. Yield was greater than 99%.

Preparation of methyl dichloroacetate. This reaction employed a dechlorination procedure reported by Benkeser and Smith (16). A 50-ml pear-shaped flask fitted with reflux condenser and drying tube was charged with about 532 mg (0.36 ml, 3 mmol, 3 mCi) of methyl trichloroacetate-^{14}C-2, 20 ml of anhydrous dichloromethane, and 950 mg (0.75 ml, 7.5 mmol) of trichlorosilane. The sample was thoroughly mixed, and 310 mg (0.40 ml, 1.6 mmol) of tri-n-butylamine was added as catalyst. The reaction was heated at 48° for 2.5 hr. Hydrolysis was then carried out by transfering the solution into a beaker containing about 10 g of crushed ice, 20 ml of saturated aqueous sodium chloride, and 5 ml of 1 M hydrochloric acid. The product was extracted from the aqueous phase with aliquots of ethyl ether. The ether extracts were combined and dried over anhydrous calcium sulfate. After drying, the ethereal solution was filtered and concentrated for the next reaction. Product yield was 58%.

Preparation of methyl dichloropropionate. This procedure was based on an alkylation reaction of some substituted acetoacetates (17) using alkyl halides with sodium hydride. A 50-ml 3-necked round bottom flask was equipped with magnetic stirrer, pressure equalizing addition funnel with nitrogen inlet, and reflux condenser with drying tube. In the flask was added 0.23 g (5.5 mmol) of sodium hydride dispersion and 25 ml of DMF-THF (1:1 v/v). Under an atmosphere of nitrogen, the mixture was heated with stirring at approximately 65° for 1 hr. The reaction vessel was then placed in crushed ice, and cooled to a temperature of -10 to -15° by addition of small chips of solid carbon dioxide into the crushed ice bath. At this temperature, 4.1 g (1.8 ml, 29 mmol) of methyl iodide dissolved in 10 ml of DMF-THF was added and allowed to mix thoroughly into solution. Then 0.43 g (0.31 ml, 3.0 mmol) of methyl dichloroacetate-^{14}C-2 (1.71 mmol of ^{14}C from the previous synthesis and 1.29 mmol of nonradioactive carrier) dissolved in 10 ml of DMF-THF was slowly added with stirring at a temperature of -10 to -12°. After addition, the reaction was placed in an oil bath at about 36° and stirred magnetically for 2 hr. The material was then transferred into a beaker containing 10 g of crushed ice, 20 ml of saturated aqueous sodium chloride, and 5 ml of 1 M hydrochloric acid. The product was extracted with aliquots of ethyl ether. Product yield was 72%.

Preparation of dichloropropionic acid. Methyl 2,2-dichloropropionate-^{14}C-2 (0.34 g, 2.2 mmol) was transferred into an Erlenmeyer flask and diluted to approximately 200 ml with anhydrous ethyl ether. Then 3 ml of 90% formic acid were added, and the ethereal solution was dried for 2 days over anhydrous sodium sulfate. The solution was filtered, placed in a 50-ml pear-shaped flask fitted with a 2-ball Snyder column, and the ether removed. The remaining solution was held at gentle reflux for approximately 40 hr for the transesterification reaction. Product yield was 95%.

Purification of products. The synthesized dalapon-^{14}C-1 and dalapon-^{14}C-2 were purified by liquid chromatography. A Waters Associates ALC-100 liquid chromatograph equipped with an ultraviolet light (254 nm) detector was used. Separation was achieved on a Waters micro-bondapak C_{18} nonpolar column (30 cm) using distilled water that contained 0.1% methanol as the eluting solvent. The liquid chromatograph pump was set at 4000 psi with a flow rate of 2 ml/min. Under these conditions, the retention times for formic, dichloroacetic, and dichloropropionic acid were 2.9, 4.1, and 5.4 min, respectively. The samples were introduced into the chromatograph by stop-flow injection, and fractions were manually collected according to recorder response. The purified dalapon-^{14}C was titrated to neutrality with 0.2 N sodium hydroxide, and taken to dryness under vacuum.

Purity of the products was determined by thin-layer chromatography on silica gel H. The eluting solvent system (8) was 100 ml of 1-pentanol equilibrated with 100 ml of 5 M aqueous formic acid. By autoradiography of the thin-layer plates, dalapon-1-^{14}C appeared to be homogeneous, and the radiochemical purity of dalapon-2-^{14}C was approximately 98%. The specific activity of dalapon-1-^{14}C was 2.5 mCi/mmol, and that of dalapon-2-^{14}C was 0.57 mCi/mmol.

DISCUSSION

Initial attempts were made to prepare 1,1-dichloroethyllithium by reaction of 1,1-dichloroethane with butyllithium. Using dichloroethane, however, approximately 15% of the acid product after carbonation was the monochloropropionic acid. When 1,1,1-trichloroethane was used, the presence of monochloropropionic acid was not observed. Another important factor in this synthesis was the maximum temperature of reaction. If the reaction temperature was allowed to rise above -100°, a significant loss in product yield occurred. The temperature, however, could be reduced to the point that THF began to solidify without any loss in dichloroethyllithium formation.

In the dechlorination reaction using trichlorosilane, yields of approximately 87% were achieved during trial studies. These yields were in general agreement with the 82% yield reported by Benkeser and Smith (16). Therefore, the 58% yield that was obtained for the radiochemical synthesis was not anticipated. Consequently, to reach the desired chemical level required for the next reaction, it was necessary to add additional nonradioactive methyl dichloroacetate. Since diazomethane was the only reagent added prior to the trichlorosilane reaction, one possible explanation for this loss in yield is that all diazomethane was not destroyed before the next reaction was performed. Another possibility is reaction interference by alcohol since a small quantity of alcohol was present in the shipping vial to inhibit the radiolysis of the trichloroacetic-^{14}C acid. Although the amount present was believed to be insignificant, the question of alcohol interference still remains.

In the transesterification reaction of methyl dalapon with formic acid, it was necessary to remove as much water as possible. Not all the water was removed because 90% formic acid was used in this reaction. If the material was not initially stored over a drying agent, a significant quantity of product might be lost owing to the fact that dalapon can hydrolyze at the temperature of the transesterification reaction.

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