Synthesis of C^{14}-Labeled 3,4-Dichlorobenzyl Methylcarbamate (UC 22463 Herbicide)

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UC 22463, 3,4-dichlorobenzyl methylcarbamate, has been synthesized with carbon-14 labeling at two different positions: the benzyl-C^{14} tag obtained via a four-step synthesis originating with 3,4-dichlorophenyl magnesium bromide and carbon-C^{14} dioxide, and the *N*-methyl-C^{14} tag obtained by reaction of the appropriate benzyl alcohol with methyl-C^{14} isocyanate. An animal metabolite, 3,4-dichlorohippuric acid, has also been synthesized utilizing glycine-C^{14}.

A new pre-emergence herbicide (Herrett and Berthold, 1965), 3,4-dichlorobenzyl methylcarbamate (Union Carbide 22463), formulated with 20% of its 2,3-isomer as an emulsifiable concentrate, has been under active development for use on both grass and broadleaf weeds. Its potential use on food crops has necessitated an understanding of its metabolic breakdown in plants and animals. To implement these studies, the compound was synthesized with two different carbon-14 labels. In addition, a suspected animal metabolite, 3,4-dichlorohippuric acid, was prepared.

EXPERIMENTAL

Yields are based on the radioactive intermediate employed in each instance. Syntheses utilizing tagged compounds were preceded by a series of experiments with nonlabeled materials to optimize techniques and yields. In every case, the resultant products were identical to authentic compounds as determined by infrared and NMR spectra and by melting point. Radiochemical purities were determined by GLC analyses of the *N*-acetyl derivatives of UC 22463 and of the methyl ester of the hippuric acid (Knaak and Sullivan, 1968), or by TLC analyses of the parent compounds. Melting points are uncorrected.

3,4-Dichlorobenzoic-C^{14} Acid. A solution of 3,4-dichlorophenyl magnesium bromide was prepared by the reaction of 5.65 grams (25 mmoles) of 3,4-dichlorobromobenzene with 0.673 gram (28 mmoles) of magnesium metal in 100 ml. of anhydrous ether. The Grignard reagent was transferred under nitrogen pressure to a dry nitrogen-filled volumetric flask via a tube containing a loose plug of glass wool. After dilution to the mark, the molarity of the solution was determined by transferring an aliquot to a standard hydrochloric acid solution, and back-titrating with standard sodium hydroxide to a methyl orange end point.

A Grignard carbonation apparatus similar to that described by Murray and Williams (1958) was flushed with dry nitrogen, and the reaction flask charged with 15.1 ml. (3.85 mmoles) of the ethereal Grignard solution. The carbon dioxide generator was charged with 494 mg. (2.5 mmoles) of nonlabeled barium carbonate and 98.7 mg. (0.5 mmole) of barium carbonate-C^{14} (specific activity 10 mc. per mmole, Tracerlab, Waltham, Mass.). Concentrated sulfuric acid (5 ml.) was added dropwise to the barium carbonate-C^{14}, and the liberated carbon-14 dioxide was condensed in the Grignard mixture under reduced pressure as described by Murray and Williams. When the reaction was complete, the vacuum was released with nitrogen, and the Grignard complex decomposed with dilute hydrochloric acid. The product was taken up in three 25-ml. portions of ether, and the resultant solution was cautiously extracted with three 25-ml. portions of 20% aqueous potassium carbonate solution. The aqueous phase was extracted once with 25 ml. of ether, and then acidified carefully with dilute hydrochloric acid. The liberated acid was taken up in ether, dried over magnesium sulfate, and concentrated to give 480 mg. (84%) of 3,4-dichlorobenzoic-C^{14} acid (m.p. 208–9° C.).

3,4-Dichlorobenzyl-C^{14} Alcohol. A stirred mixture of 240 mg. (6.3 mmoles) of lithium aluminum hydride in 35 ml. of anhydrous ether was treated at 25° C. with the dropwise addition of a solution of 467 mg. (2.45 mmoles) of 3,4-dichlorobenzoic-C^{14} acid in 30 ml. of anhydrous ether. Addition was completed after 15 minutes, and the mixture was heated at reflux for 5.5 hours. The mixture was cooled to 10–15° C., and the excess hydride was destroyed by the cautious, dropwise addition of 30 ml. of 30% sulfuric acid. After standing overnight, the layers were separated, and the aqueous phase was extracted with three 25-ml. portions of ether. The organic extracts were then washed once with 25 ml. of 1*N* potassium hydroxide solution followed by 25 ml. of water. The solution was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give 399 mg. (92%) of 3,4-dichlorobenzyl-C^{14} alcohol as a pale yellow oil which crystallized on standing (m.p. 33–35° C.).

3,4-Dichlorobenzyl-C^{14} Methylcarbamate. A solution of 389 mg. (2.2 mmoles) of 3,4-dichlorobenzyl-C^{14} alcohol

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and one drop of triethylamine catalyst in 0.6 ml. of anhydrous ether was introduced into a 10-ml. flask. The flask was fitted to the vacuum manifold by means of an adapter with its own stopcock, and after freezing in liquid nitrogen, the system was evacuated to 0.1 micron. After isolating the manifold from the pump, 2.5 mmoles of methyl isocyanate were condensed into the reaction mixture, and the flask was sealed with its stopcock. The flask was warmed to room temperature, and allowed to stand overnight. The solution was then concentrated under a slow stream of dry nitrogen to remove any excess isocyanate, after which the residue was taken up in ether. After washing with two 3-ml. portions of water, the organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under vacuum to give 472 mg. of pale yellow oil which crystallized on standing. Recrystallization of the product from 40 ml. of hot heptane yielded 302 mg. of slightly tacky solid (m.p. 37–42° C.). The mother liquor was concentrated, and 188 mg. of pure, nonradioactive 3,4-dichlorobenzyl methylcarbamate was added. Recrystallization as above from 20 ml. of heptane gave 242 mg. of long, white needles. Combination of the crystalline fractions obtained in the two instances above, and recrystallization from 50 ml. of heptane, gave 134 mg. of high purity UC 22463 (m.p. 53–54° C.). An additional 173 mg. (m.p. 51–51.5° C.) was obtained by chilling the mother liquor. The various mother liquor solutions were then combined, concentrated, and taken up in 30 ml. of 1 to 1 ether-hexane solution. The solution was added to a column of 55 grams of activated Florisil slurried in hexane, and the product eluted in 30- to 40-ml. fractions as follows:

Fraction No.	Solvent(s)
1 to 5	Hexane
6 to 13	2 to 1 hexane-ether
14 to 21	1 to 1 hexane-ether
22 to 29	1 to 2 hexane-ether
30 to 39	Ether
40 to 49	2 to 1 ether-acetone

The individual fractions were analyzed by TLC (Eastman silica gel sheets with fluorescent indicator, 1 to 1 ether-hexane solvent), and the spots were located by short-wavelength ultraviolet light. Fractions 18 to 27 were concentrated to give 59 mg. of unreacted 3,4-dichlorobenzyl-C^{14} alcohol, and fractions 35 to 45 gave 240 mg. of UC 22463-C^{14} as a yellow oil. Crystallization of the oil from 20 ml. of heptane gave 147 mg. of additional 3,4-dichlorobenzyl-C^{14} methylcarbamate (m.p. 50–50.5° C.). The total yield was 454 mg. (65%) of the desired carbamate. The infrared spectra of the labeled crystalline fractions were identical to the spectrum of pure UC 22463, with no evidence of isomeric impurities.

3,4-Dichlorobenzyl Methyl-C^{14}-carbamate. Methyl-C^{14} isocyanate was prepared by the pyrolysis of a mixture of 163 mg. (2.42 mmoles) of methyl-C^{14}-amine hydrochloride (specific activity 3.98 μc. per mg.) and 420 mg. (2.59 mmoles) of *N,N'*-carbonyldiimidazole (Paul and Anderson, 1960; Staab, 1957) by the procedure described previously (Bartley *et al.*, 1966). The liberated isocyanate was distilled into a frozen (liquid nitrogen) mixture of 356 mg. (2.01 mmoles) of 3,4-dichlorobenzyl alcohol and four drops of triethylamine in 0.5 ml. of anhydrous ether as in the preceding experiment. The mixture was warmed to room temperature and allowed to stand overnight, after which the solution was treated with five drops of nonlabeled isocyanate, and allowed to stand 4 hours at room temperature to convert any excess alcohol to the carbamate. Concentration of the solution, followed by recrystallization from 40 ml. of hot heptane, gave 453 mg. (80%) of 3,4-dichlorobenzyl methyl-C^{14}-carbamate (m.p. 47–48° C.).

3,4-Dichlorohippuric-C^{14} Acid. A solution of 765 mg. (4.0 mmoles) of 3,4-dichlorobenzoic acid in sodium-dried tetrahydrofuran was treated with 652 mg. (4.0 mmoles) of *N,N'*-carbonyldiimidazole (Paul and Anderson, 1960) added in two portions over a 5-minute period. A vigorous evolution of carbon dioxide ensued and continued for about 30 seconds. After stirring at 25° C. for 1 hour to allow for complete reaction, a mixture of 1.5 mg. of glycine-1-C^{14} (specific activity, 5 mg. per mmole; Nuclear Chicago) and 299 mg. (4.0 mmoles total) of nonlabeled glycine in 4.0 mmoles of 0.957*N* sodium hydroxide solution was added in one portion. The temperature climbed to 35° C. immediately after addition, and then subsided after about 10 minutes. The mixture was stirred overnight at 25° C., and the following morning the solution was treated with 4 ml. of 5*N* hydrochloric acid. The product was liberated in the form of a white solid which, after vacuum distillation of the tetrahydrofuran, was taken up in 10 ml. of ether. After thorough mixing, the layers were separated, and the aqueous phase was re-extracted with two additional 10-ml. portions of ether. The organic extracts were dried over magnesium sulfate and filtered, and the solution was treated with 1.00 gram (10.0 mmoles) of triethylamine to precipitate the hippuric acid salt selectively. The mixture was allowed to stand for 3 hours at 25° C. to complete crystallization, after which the ether was decanted off, and the residual crystals were washed with two additional 10-ml. portions of fresh ether. The salt was dissolved in 10 ml. of water, and the aqueous phase was washed with 10 ml. of ether to remove the last traces of unreacted 3,4-dichlorobenzoic acid. The ether extracts were washed once with 5 ml. of water, and then the combined aqueous extracts were neutralized with 2*N* hydrochloric acid. The liberated hippuric acid was extracted with three 10-ml. portions of ether, and the resultant solution was dried, filtered, and concentrated to yield 722 mg. (73%) of white, powdery 3,4-dichlorohippuric-C^{14} acid (m.p. 145.5–46.5° C.).

The infrared, NMR, and elemental analyses of a nonlabeled sample (m.p. 146–47° C.) prepared in an identical manner were in agreement with the postulated hippuric acid structure.

DISCUSSION

Benzyl-C^{14}-labeled UC 22463 (III) was synthesized by the sequence of reactions summarized in Figure 1. The preparation originated with the carbonation of 3,4-dichlorophenyl magnesium bromide with carbon-14 dioxide to give 3,4-dichlorobenzoic acid (I) in 84% yield. The acid was smoothly reduced with lithium aluminum hydride in refluxing ether to yield 92% of the corresponding benzyl alcohol (II). Finally, carbamylation of II with methyl

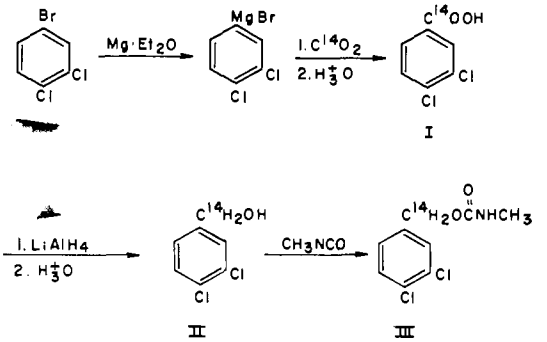

Figure 1. Synthesis of 3,4-dichlorobenzyl-C^{14} methylcarbamate (III)

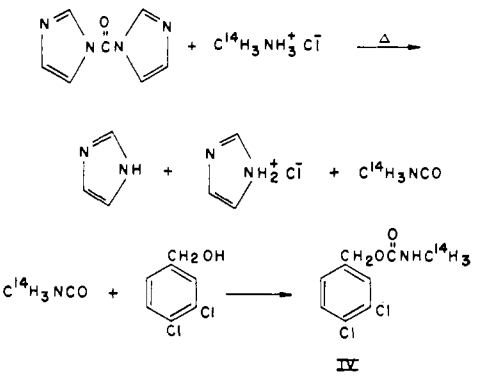

Figure 2. Synthesis of 3,4-dichlorobenzyl methyl-C^{14}-carbamate (IV)

isocyanate gave, in 50% over-all yield, the desired 3,4-dichlorobenzyl-C^{14} methylcarbamate (III).

Figure 2 illustrates the synthesis of 3,4-dichlorobenzyl methyl-C^{14}-carbamate (IV) utilizing methyl-C^{14} isocyanate. The isocyanate was conveniently prepared by heating a mixture of methyl-C^{14}-amine hydrochloride and *N,N'*-carbonyldiimidazole (Staab and Benz, 1961) in vacuo as previously reported (Bartley *et al.*, 1966). The liberated methyl-C^{14} isocyanate was condensed directly into a reaction vessel containing 3,4-dichlorobenzyl alcohol to produce *N*-methyl-labeled UC 22463 in 80% over-all yield.

Animal metabolism studies (Knaak and Sullivan, 1968) have shown that UC 22463 is degraded readily by the rat, and excreted primarily as the 3,4-dichlorohippuric acid conjugate (VI, Figure 3). To aid in the confirmation of this structure, a sample of VI labeled with carbon-14 on the glycine function was prepared by an adaptation of the method of Paul and Anderson (1960). This synthesis, summarized in Figure 3, employed the reaction of stoichiometric quantities of *N,N'*-carbonyldiimidazole and 3,4-dichlorobenzoic acid under anhydrous conditions. The initial product was the imidazolide (V) (Paul and Anderson, 1960) which was not isolated, but was converted directly to the desired product (VI) by reaction with an aqueous solution of sodium glycinate-C^{14}. Selective precipitation of the more acidic hippuric acid (VI) as its triethylamine salt was employed to remove a small amount of 3,4-dichlorobenzoic acid impurity. Acidification of the hippurate salt gave 3,4-dichlorohippuric-C^{14} acid in 73% over-all yield.

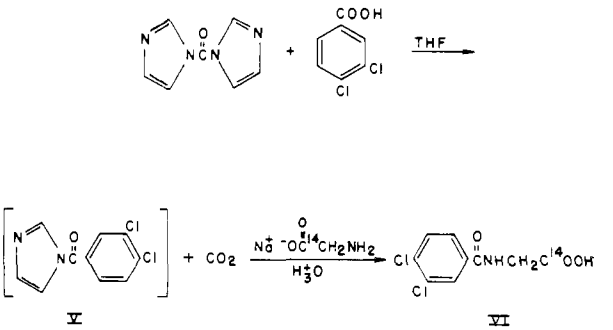

Figure 3. Synthesis of 3,4-dichlorohippuric-C^{14} acid (VI)

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