Synthesis of ^{14}C-Labeled 3-(4-Chlorophenyl)-1,1-Dimethylurea and 3-(3,4-Dichlorophenyl)-1,1-Dimethylurea

Fred S. Tanaka

3-(4-Chlorophenyl)-1,1-dimethylurea (monuron) and 3-(3,4-dichlorophenyl)-1,1-dimethylurea (diuron) were prepared with specific ^{14}C-labeling at the ring, carbonyl, and methyl positions. A reaction sequence was developed that affords satisfactory yields of monuron and diuron at microsynthetic levels. Methyl labeled-^{14}C monuron and diuron were prepared in 94 and 92% yields, respectively, in a two-step synthesis. Carbonyl labeled-^{14}C monuron and diuron were prepared in a four-step synthesis in 78.4 and 80.8% yields. Starting the radiochemical synthesis with aniline-^{14}C-hydrochloride, ring-^{14}C monuron was prepared through a nine-step synthesis in 53.5% yield, and ring-^{14}C diuron was prepared through a ten-step reaction sequence in 22.4% yield. The reaction sequence was developed for the preparation of ring-labeled diuron; however, the individual reactions may be useful in the synthesis of other radiochemical compounds.

The metabolic fate of monuron, 3-(4-chlorophenyl)-1,1-dimethylurea, and diuron, 3-(3,4-dichlorophenyl)-1,1-dimethylurea, in plant and animal systems have been studied with a great deal of interest. These studies have been greatly facilitated by the use of radiochemically labeled materials. However, in many instances, investigations were seriously hindered by the lack of key radiochemical compounds. This appears to be the case for ring-^{14}C diuron. The synthesis of radioactive diuron was first carried out by Todd (1953) with the preparation of the carbonyl labeled-^{14}C product. The preparation of ring-^{14}C diuron was recently reported by Onley *et al.* (1968) in their metabolic studies of diuron in corn seedlings. Although Onley *et al.* prepared ring-labeled diuron, their synthesis yielded a product of very low specific activity; and furthermore, no detailed description of their procedures for synthesis was reported. Therefore, the reaction sequence given in Figure 1 was developed for synthesis of ring-^{14}C diuron. With slight modification in the reaction order, preparation of ring-^{14}C monuron was also carried out by utilization of the same reactions.

EXPERIMENTAL

Radiochemical Compounds. For the radiochemical synthesis of specific labeled monuron and diuron, 1 mCi. of dimethylamine-^{14}C hydrochloride (9.5 mCi. per mmole), 1 mCi. of 4-chlorobenzoic acid-7-^{14}C (5.85 mCi. per mmole), 1 mCi. of 3,4-dichlorobenzoic acid-7-^{14}C (4.91 mCi. per mmole), and 10 mCi. of aniline-^{14}C (U)-hydrochloride (6.1 mCi. per mmole) were purchased from New England Nuclear Corp.

Analysis of Nonradiochemical Synthesis. The yields for nonradiochemical synthesis were measured by means of gas chromatography. Separation of monuron or diuron from by-products of reaction was carried out on a 6-foot glass column packed with 20% Apiezon L on 80- to 100-mesh Gas Chrom Q as described by Onley, Yip, and Aldridge (1968). The operating temperatures used in these analyses were as follows: Column 190° C., injection port 235° C., and detector 295° C. The instrument was equipped with a ^{63}Ni electron capture detector and operated with nitrogen carrier gas at a flow rate of 60 ml. per minute. Quantitative estimation of product yield was achieved by comparison of peak height with values on a standard curve prepared from samples of known concentration. All nonradiochemical syntheses were carried out more than four times, and an average value for the experiments was reported. The final product from the reaction sequence carried out with nonradioactive chemicals was characterized to be either monuron or diuron by the following data: Melting point, gas and thin-layer cochromatography, nuclear magnetic resonance, and infrared spectral analysis.

Analysis of Radiochemical Synthesis. The radiochemical product in each case was cleaned up by preparative thin-layer chromatography. Thin-layer plates of silica gel HF of 500-micron thickness were developed in a solvent system of benzene acetone (2 to 1) to effect chromatographic separation of the phenylurea compound from the reaction by-products. The chromatographic separation was carried out at least two times with each sample in order to isolate a pure product. Product removal from the thin-layer plates was achieved by vacuuming the silica gel into a small glass column, and elution from the silica gel was effected with anhydrous methanol. Estimation of yield for each radiochemical synthesis was carried out by means of liquid scintillation counting. The chemical level of each product was measured spectrophotometrically to determine the specific activity of the final products. Radiochemical purities of the final products were verified to be greater than 99% by thin-layer chromatography and autoradiography.

Acetanilide. Aniline is prepared from 1 gram of aniline hydrochloride by treatment with 0.5 ml. of 20*M* sodium hydroxide. Acetanilide is then formed by addition of 2 ml. of acetic anhydride to the flask containing the free aniline, and the reaction is allowed to go to completion. After heat is no longer evolved with occasional swirling of the contents in the flask, the reaction is stopped by addition of 10 ml. of water. The excess water and acetic acid are removed by rotary vacuum distillation with further drying being carried out in a vacuum desiccator. The crude product in approximately 100% yield is ready for Friedel-Craft acylation.

4-(Chloroacetyl)-Acetanilide. This compound is prepared by a method based on the procedure described by Leiserson and Weissberger (1955). A 200-ml. round-bottomed flask equipped with magnetic stirrer, reflux condenser, and calcium chloride drying tube is charged with 15 ml. of carbon di-

Crops Research Division, Agriculture Research Service, U.S. Department of Agriculture, Metabolism and Radiation Research Laboratory, Fargo, N.D. 58102

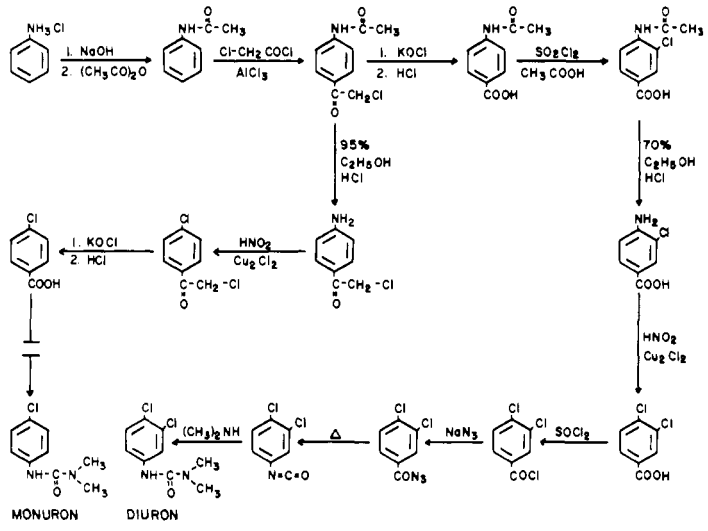

Figure 1. Synthesis of monuron and diuron

sulfide, 1 gram of acetanilide, and 4 grams of anhydrous aluminum chloride. The mixture is vigorously stirred until the carbon disulfide no longer refluxes freely. Temporary removal of the drying tube allows the addition of 1.5 ml. of chloroacetyl chloride down the condenser into the reaction vessel. After addition of chloroacetyl chloride, the mixture is stirred and refluxed in a water bath for a period of 30 minutes. Upon completion of reaction, the solvent is removed by volatilization with a stream of air. The red-brown complex is hydrolyzed by addition of an ice-water mixture into the flask. Care should be taken to avoid rapid generation of heat during the hydrolysis step. After sufficient water has been added so that no further reaction takes place, 2 ml. of concentrated hydrochloric acid is added to the flask, and the mixture is stirred for 5 minutes. The product is filtered and washed with water.

4-Acetaminobenzoic Acid. For preparation of basic potassium hypochlorite solution, 2.5 grams of commercial calcium hypochlorite (72% available chlorine), 35 ml. of warm water, 1.75 grams of potassium carbonate, and 0.5 gram of potassium hydroxide are placed in a 100-ml. round-bottomed flask. The flask is stoppered and shaken vigorously until the semi-solid gel which first forms becomes quite fluid. The hypochlorite solution is separated from the suspended solid by vacuum filtration.

For the haloform reaction 1 gram of 4-(chloroacetyl)-acetanilide and 5 ml. of 2.5*M* magnesium sulfate are added into a 100-ml. round-bottomed flask. While the contents in the flask are being stirred, 20 ml. of basic potassium hypochlorite solution is added. If the initial reaction becomes too vigorous, frequent cooling in an ice bath will control the reaction rate. The chloroform formed during the reaction is removed by a small stream of air introduced into the reaction vessel. Once the vigorous reaction has ceased, the mixture is allowed to stir for 1 hour in a 50° C. water bath. Upon reaction completion, the excess hypochlorite is destroyed by addition of 2 ml. of 2.5*M* sodium bisulfite. The solution should be tested with starch-potassium iodide paper to ensure that all hypochlorite has been destroyed. The product is precipitated with 4 ml. of 6*N* hydrochloric acid, collected on a sintered glass funnel, washed with water, and dried *in vacuo*.

3-Chloro-4-Acetaminobenzoic Acid. A round-bottomed flask equipped with efficient reflux condenser, calcium chloride drying tube, and gas absorption trap is set up in a fume hood. Into the flask are added 1 gram of 4-acetaminobenzoic acid, 5 ml. of glacial acetic acid, and 1 ml. of acetic anhydride. The contents in the flask are heated in an oil bath at 100° C. for 2 hours. Following this treatment the solution is cooled, and 10 ml. of sulfuryl chloride is added through the condenser into the reaction vessel. Further heating is carried out at a bath temperature of 85° C., and the mixture is allowed to reflux for 1.5 hours. After reaction is complete, the vessel is cooled and the excess sulfuryl chloride removed by rotary vacuum evaporation. Final traces of sulfuryl chloride are destroyed by addition of water into the reaction vessel. The solvent and by-products are then removed by rotary vacuum distillation.

3-Chloro-4-Aminobenzoic Acid and 4-(Chloroacetyl)-Aniline. For diuron synthesis 3-chloro-4-aminobenzoic acid is prepared by hydrolysis of 1 gram of 3-chloro-4-acetaminobenzoic acid with 20 ml. of 70% ethanol and 1 ml. of concentrated hydrochloric acid. For monuron synthesis 4-(chloroacetyl)-aniline is prepared by hydrolysis of 1 gram of 4-(chloroacetyl)-acetanilide with 20 ml. of 95% ethanol and 1 ml. of concentrated hydrochloric acid.

In both cases the solution is refluxed on a steam bath for 2 hours. After hydrolysis, the solvent is removed by rotary vacuum evaporation. In order to ensure removal of all volatile components, three separate 5-ml. aliquots of absolute ethanol are added and removed by vacuum distillation.

3,4-Dichlorobenzoic Acid. Ten milliliters of concentrated hydrochloric acid are pipetted into a beaker cooled in an ice bath, and 5 ml. of concentrated sulfuric acid is carefully added to the cold hydrochloric acid. Next, approximately 0.5 gram of a 1-gram sample of sodium nitrite is added slowly with stirring to the acid solution, being careful to keep the temperature at less than 5° C. Suspended in 20 ml. of glacial acetic acid, 1 gram of 3-chloro-4-aminobenzoic acid is added slowly with stirring to the nitrous acid solution while maintaining a reaction temperature of 5 to 10° C. After addition is complete, the solution is again cooled to less than 5° C., and the remaining 0.5 gram of sodium nitrite is added. The reaction mixture is stirred vigorously, removed from the ice bath, and allowed to warm to 15 to 20° C. with occasional stirring.

Fifteen milliliters of freshly prepared cuprous chloride (Marvel and McElvain, 1941) in concentrated hydrochloric

Table I. Yields for Nonradiochemical and Radiochemical Synthesis of Monuron and Diuron

Compound	Position Of Radiochemical Label	Starting Material for Synthesis	Quantity of Nonradiochemical Starting Material	% Yield Nonradiochemical Synthesis	Quantity of Radiochemical Starting Material	% Yield Radiochemical Synthesis	Specific Activity mCi./mmole
Monuron	Methyl	Dimethylamine–HCl	81.5 mg.	99	16.3 mg.	94.0	3.4
Monuron	Carbonyl	4-Chlorobenzoic acid	1.0 g.	91	22.8 mg.	78.4	5.8
Monuron	Ring	Aniline–HCl	1.0 g.	58	388 mg.	53.5	1.0
Diuron	Methyl	Dimethylamine–HCl	81.5 mg.	98	16.3 mg.	92.2	3.4
Diuron	Carbonyl	3,4-Dichlorobenzoic acid	1.0 g.	84	47.8 mg.	80.8	4.0
Diuron	Ring	Aniline–HCl	1.0 g.	40	908 mg.	22.4	1.0

acid are poured into a beaker and cooled in ice to approximately 5° C. The diazonium salt is added slowly to the cuprous chloride solution with vigorous stirring in order to break up the large quantity of foam produced. After addition is complete, the diazonium complex is hydrolyzed by addition of 10 to 20 ml. of distilled water and heating slowly over a 20-minute period to a maximum temperature of 80° C. Then an additional volume of 100 to 200 ml. of distilled water is added and the mixture is allowed to stand in an ice bath. The product is filtered, washed with water, and dried *in vacuo*.

3,4-Dichlorobenzoyl Azide. For preparation of 3,4-dichlorobenzoyl chloride, 1 gram of 3,4-dichlorobenzoic acid is dissolved in 15 ml. of thionyl chloride. The solution is refluxed for 2 hours in an oil bath. After reflux the excess thionyl chloride is removed by means of rotary vacuum evaporation. Acetone which has previously been dried over anhydrous potassium carbonate is added in three separate 5-ml. aliquots and removed by vacuum distillation to ensure complete removal of thionyl chloride.

The 3,4-dichlorobenzoyl chloride is dissolved in 3 ml. of dry acetone. Next, a solution of 0.8 gram sodium azide dissolved in 4 ml. of water is prepared in a round-bottomed flask equipped with magnetic stirrer. The flask is held in a water bath at a temperature of 20 to 25° C., and the 3,4-dichlorobenzoyl chloride solution is added dropwise with stirring to the aqueous sodium azide. Stirring is allowed to continue for 30 minutes after addition. Then 5 ml. of water is added and stirring is continued for an additional 30 minutes. The azide product is filtered, washed with water, and dried. However, for very small syntheses the azide may not precipitate from solution. In such cases, the azide is extracted from the reaction mixture with chloroform.

3-(3,4-Dichlorophenyl)-1,1-Dimethylurea. One gram of 3,4-dichlorobenzoyl azide is dissolved in 15 ml. of dry toluene and heated in an oil bath at 95 to 110° C. until nitrogen evolution ceases. Nitrogen evolution generally begins at 60° C. and the acid azide is usually completely decomposed after heating for a period of 2 hours. The solution of 3,4-dichlorophenylisocyanate in toluene is cooled in ice, and 5 ml. of 2*M* anhydrous dimethylamine in chloroform is added slowly with stirring to the isocyanate solution. The mixture is stirred for 15 minutes, and the solvent and excess dimethylamine are removed by rotary vacuum evaporation.

Methyl Labeled Diuron. For the preparation of methyl labeled diuron, 81.5 mg. (1 mmole) dimethylamine hydrochloride is placed in a vacuum system and converted to the free amine by addition of 0.5 ml. of 2.5*M* aqueous sodium hydroxide. In order to trap vaporized water, an ascarite drying tube is placed in the vacuum system between the sample and the cold trap. The dimethylamine is transferred by means of vacuum transfer techniques into a vessel containing 5 ml. of toluene, 5 ml. of chloroform, and 207 mg. (1.1 mmole) of 3,4-dichlorophenylisocyanate held in a cold bath of dry ice-2-propanol. After transfer the sample is removed from the cold bath and allowed to stand at room temperature for 4 hours in a sealed system.

DISCUSSION

Optimum experimental conditions for each reaction given in Figure 1 were developed using 1 gram of starting material. The 1-gram level was chosen because this quantity represented a level that was small enough for easy adjustment to microsynthetic levels, yet large enough for easy manipulation during reaction development. All reactions in the sequence gave crude product yields in excess of 80% after optimal conditions were attained. The experimental procedures are described on the basis of 1 gram of starting material rather than actual chemical levels realized during radiochemical synthesis so that each reaction procedure may be used as a general synthetic method. If the quantity of starting material in a given procedure should differ greatly from 1 gram, allowances in the concentration of reactants should be made accordingly. All procedures for preparation of diuron are directly applicable for preparation of monuron.

The per cent yields for nonradiochemical and radiochemical synthesis of monuron and diuron with respect to different labeling positions are presented in Table I. The yields derived from nonradiochemical synthesis give good indication of the relative yields that can be achieved by these reactions. The per cent yields given for radiochemical synthesis are the values resulting from one replication of the reaction sequence to produce the radioactive product. In all cases, the radiochemical synthesis produced lower yields in comparison to the values derived from nonradiochemical synthesis. This decrease in yield is due, in most cases, to the large reduction in quantity of starting material. But further examination of the product yields shows that radiochemical yields do not differ greatly from nonradiochemical yields. This result indicates that these reactions can effectively be adjusted to microsynthetic levels.

The preparation of monuron with the ^{14}C-label at the carbonyl position was first reported by Logan and Odell (1953). Starting with 122.4 mg. of 4-chlorobenzoic acid-7-^{14}C which was previously prepared by carbonation of a Grignard reagent, monuron was prepared in 69% yield. For preparation of the acid azide and subsequent Curtius rearrangement, they utilized the dry method of reaction which was carried out in

toluene with activated sodium azide. However, for acid chlorides that are immiscible with water, the dry method has been suggested (Smith, 1946) to be less desirable, in many instances, to the wet method where the acid azide is prepared from aqueous sodium azide. The wet method has been reported to be much more reliable, easier to control, and much faster. On the other hand, this method requires an extra isolation operation and could result in a slight reduction in yield. In this case, however, the wet method appears to result in an improved yield over the dry method of Logan and Odell.

Searle and Cupery (1954) have described a method for the preparation of ring-^{14}C monuron. Starting with 1.36 grams of aniline-^{14}C hydrochloride, ring-^{14}C monuron was prepared in 56% yield. In this synthesis, ring chlorination was carried out with *N*-chlorosuccinimide which resulted in chlorination at both the *ortho* and *para* positions of acetanilide. Hence, separation of the two isomeric products was necessary. Also, phosgene was used to generate the isocyanate from 4-chloroaniline hydrochloride. Utilization of this toxic gas for reaction requires greater handling care than preparation of the isocyanate by means of the acid azide. In overall comparison, however, the two synthetic methods for preparation of ring-labeled monuron resulted in approximately identical yields.

In Table I the radiochemical yield given for ring-^{14}C diuron was reported to be only 22.4%. This yield was much lower than that realized for nonradiochemical synthesis even though the quantity of starting material was approximately the same. The reason for reduction in yield was that one reaction step did not proceed as well as normally expected. However, the synthesis of diuron from aniline hydrochloride has been shown to produce a product yield ranging from 38 to 42%, and this is the yield that one can normally expect from this reaction sequence.

Reaction intermediates as well as final products resulting from the reaction sequence given in Figure 1 can be used as starting materials for preparation of other pesticides or pesticide metabolites. In this regard, tetrachloroazobenzene (Still and Tanaka, 1969) and monomethyl monuron have been prepared containing the ^{14}C-label in order to study the metabolic fate of these pesticide metabolites in plant systems. Other herbicides such as propanil, trifluralin, and 3,4-dichlorobenzyl methylcarbamate may also be prepared with the ring-^{14}C label by utilization of compounds prepared by this reaction sequence.

ACKNOWLEDGMENT

The author thanks R. G. Wien for carrying out the synthesis of the products and measurement of product yields for the nonradiochemical reactions.

LITERATURE CITED

Leiserson, J. L., Weissberger, A., "Organic Syntheses," Coll. Vol. III, pp. 183–184, Wiley, New York, 1955.
Logan, A. V., Odell, N. R., *Weeds* **2,** 135 (1953).
Marvel, C. S., McElvain, S. M., "Organic Syntheses," Coll. Vol. I, p. 170, Wiley, New York, 1941.
Onley, J. H., Yip, G., Aldridge, M. H., J. AGR. FOOD CHEM. **16,** 426 (1968).
Searle, N. E., Cupery, H. E., *J. Org. Chem.* **19,** 1622 (1954).
Smith, P. A. S., "Organic Reactions," Vol. III, p. 387, Wiley, New York, 1946.
Still, G. G., Tanaka, F. S., 157th ACS Meeting, Division of Agricultural and Food Chemistry, Minneapolis, Minn., April 1969.
Todd, C. W. (to E. I. du Pont de Nemours & Co.), U.S. Patent 2,655,445 (Oct. 13, 1953).

Received for review July 7, 1969. Accepted December 4, 1969. Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the U.S. Department of Agriculture, and does not imply its approval to the exclusion of other products that may also be suitable.