COMMUNICATIONS

Preparation of Tritium-Labeled Tetramethylcyclopropanecarboxylic Acid and Insecticidal Esters from It

When tetramethylcyclopropanecarboxylic acid is refluxed with potassium hydroxide in [*hydroxy*-^3H]-ethylene glycol, generated *in situ* with tritiated water, the α proton exchanges with tritium, giving the specifically labeled *1*-^3H-tetramethylcyclopropanecarboxylic acid. This, esterified with 5-benzyl-3-furylmethyl alcohol, (+)-pyrethrolone, (±)-allethrolone, or *N*-hydroxymethyltetrahydrophthalimide gives the *1*-^3H-tetramethylcyclopropanecarboxylates, each with a specific activity of approximately 30 mCi/mmol. Nuclear magnetic resonance and mass spectral data for the 1-^{2}H analog of the acid (made using deuterium oxide in place of tritiated water) establishes that the only proton exchanged is that at C-1 on the cyclopropane ring.

Esters of tetramethylcyclopropanecarboxylic acid (Figure 1, X = H) with (±)-allethrolone (Matsui and Kitahara, 1967), 5-benzyl-3-furylmethyl alcohol (Berteau and Casida, 1969; Barlow *et al.*, 1971), and (+)-pyrethrolone (Barlow *et al.*, 1971) have activity comparable to that of corresponding esters of natural (+)-*trans*-chrysanthemic acid against some insect species. However, the oral toxicity to rats of 5-benzyl-3-furylmethyl tetramethylcyclopropanecarboxylate is sixty times greater than that of the (+)-*trans*-chrysanthemate (bioresmethrin) (Elliott, 1971) but the two esters are approximately equally toxic to houseflies (Barlow *et al.*, 1971). Such differences in toxicity to mammals between the esters of the two acids may be general, and probably result from differences in rates of metabolism and/or in metabolic pathways. Therefore, it is important to prepare appropriate radio-labeled compounds to determine the sites and rates of metabolism of these tetramethylcyclopropanecarboxylates. This paper describes a simple method for making such esters, labeled with tritium in the acid moiety.

MATERIALS AND METHODS

Procedures for column chromatography, thin-layer chromatography (tlc), nuclear magnetic resonance (nmr) spectrometry, and mass spectrometry are described by Elliott and Casida (1972).

SYNTHESES

***1*-^3H-Tetramethylcyclopropanecarboxylic Acid** (Figure 1, X = ^{3}H). Tetramethylcyclopropanecarboxylic acid (Mescheryakov and Dolgii, 1960) (1.0 g, 0.0071 mol), potassium hydroxide (2.2 g, 0.039 mol), and ethylene glycol (10 ml, 0.32 mol) were heated until all traces of water had been distilled and the temperature of the boiling liquid had reached 200°C. After cooling, tritiated water (1.0 ml, 39.5 Ci/ml; 720 mCi/mmol) was added and the mixture was heated until the water had distilled and the liquid temperature had again reached 200°C; this temperature was maintained for 2.5 hr. After cooling, the product was poured into water (100 ml) and acidified (concentrated hydrochloric acid). The ^{3}H-acid precipitated was collected and dried (0.86 g; mp 117.5–118°C after purification by sublimation at 1 mm; 56 mCi/mmol).

***1*-^2H-Tetramethylcyclopropanecarboxylic Acid** (Figure 1, X = ^{2}H). Tetramethylcyclopropanecarboxylic acid, potassium hydroxide, and ethylene glycol, in the proportions used for the ^{3}H experiment, were heated as above to remove residual water and, after cooling, deuterium oxide (isotopic purity > 99.5%, 1.0 ml) was added. The mixture was heated until the water had distilled and until the liquid reached 200°C; this temperature was maintained for 3 hr. To increase the proportion of protons replaced by deuterium, the same procedure was repeated with nine successive 1.0-ml portions of deuterium oxide. The ^{2}H-acid formed was precipitated and purified [0.80 g; mp 117.5–118°C; nmr peaks in pyridine at τ 8.51 (s, C-1 H, 0.20 H), 8.59 (s), 8.87 (s) (4 × CH_3, 12 H)], as described above for the ^{3}H-acid.

5-Benzyl-3-furylmethyl *1*-^3H-Tetramethylcyclopropanecarboxylate. Pure *1*-^3H-tetramethylcyclopropanecarboxylic acid (71 mg) was refluxed in benzene (1.2 ml) with thionyl chloride (purified with triphenyl phosphite; Fieser and Fieser, 1967) (120 μl) for 5 hr. Solvents and excess reagents were then evaporated in a stream of dry nitrogen and additional benzene (1.0 ml) was added. Then, the mixture was evaporated to remove residual volatile impurities. 5-Benzyl-3-furylmethyl alcohol (Elliott *et al.*, 1971) (122 mg) was added in benzene (0.5 ml) with pyridine (60 μl) at 0°C. After 12 hr at room temperature, the reaction mixture was transferred with hexane to a column of Florisil (50 g) in hexane. The ester was eluted with ether–hexane mixtures (starting with 2.5% ether and following with 5% ether, 10% ether, and so on) and it was recovered from the fraction eluted with 5% ether in hexane, by the procedure described for ^{3}H-pyrethrin I (Elliott and Casida, 1972). The product obtained (138 mg; 89% yield; 36 mCi/mmol) was identical (tlc) with a nonradioactive preparation (Berteau and Casida, 1969).

Other Esters. Similarly were prepared from ^3H-tetramethylcyclopropanecarboxylic acid (3 × 71 mg); with pyrethrolone from the hydrate (Elliott, 1964; Maciver, 1968) (127 mg), *(+)-pyrethronyl-1-*^3H*-tetramethylcyclopropanecarboxylate:* (91 mg, 61%), 34 mCi/mmol, eluted with 12.5% ether in hexane; *(±)-allethronyl-1-*^3H*-tetramethylcyclopropanecarboxylate* (90 mg, 65%), 34 mCi/mmol, eluted with 12.5% ether in hexane; *tetrahydrophthalimidomethyl-1-*^3H*-tetramethylcyclopropanecarboxylate* (106 mg, 74%), 33 mCi/mmol, eluted with 25% ether in hexane. These esters were pure by tlc.

RESULTS AND DISCUSSION

Atkinson *et al.* (1968) showed that the α protons in carboxylic acids are replaced by deuterium when sodium or potassium salts are treated with basic deuterium oxide. With most of the

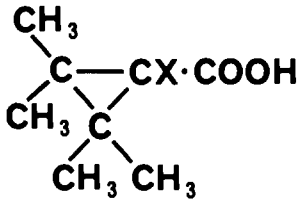

Figure 1. Structure of tetramethylcyclopropanecarboxylic acid, X being H, ^2H, or ^3H

acids they investigated, the reactions were complete in a reasonably short time when conducted in a stainless steel bomb at 150°C. However, even at this elevated temperature, the α proton in cyclopropanecarboxylic acid was not exchanged to a satisfactory degree. In the study reported here, it was found that the exchange of deuterium or tritium for the α proton in a tetramethylcyclopropanecarboxylic acid takes place to a considerable extent in a relatively short time when the reaction temperature is raised to 200°C by using refluxing ethylene glycol as solvent for the base. These convenient conditions may be suitable for deuterium or tritium exchange of protons in other organic acids.

To confirm the course of the reaction, tetramethylcyclopropanecarboxylic acid was treated repeatedly with deuterium oxide under the conditions above and the nmr spectra of the deuterated and undeuterated acids were compared. In pyridine [but not in deuterochloroform or carbon tetrachloride (Barlow *et al.*, 1971)] the signal from the C-1 proton is clearly separate from the signals due to the methyl groups and after deuteration had an intensity relative to them only one-fifth as great as that of the corresponding signal in the undeuterated acid. Further, in the mass spectrum of the undeuterated acid, peaks from M^+ and $M^+ - CH_3$ appeared at 142 and 127. In the deuterated preparation, the corresponding peaks were at 143 and 128, respectively. The relative peak intensities corresponded to a content of 79% of a species in which one proton had been replaced by deuterium. This evidence from the nmr and mass spectra showed that only the C-1 proton is displaced under the reaction conditions, so that, with tritium oxide, an acid labeled specifically at this position would be obtained.

ACKNOWLEDGMENT

The authors thank N. F. Janes, Rothamsted Experimental Station, for determinations and discussion of spectral data, Meryl Petersen for technical assistance, and the following for their suggestions or assistance: J. E. Engel, E. C. Kimmel, and Louis Lykken, Division of Entomology, University of California, Berkeley, Calif.

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Received for review August 2, 1971. Accepted November 12, 1971. Studies supported in part by grants from the following sources: U.S. Atomic Energy Commission [Contract AT(04-3)-34, Project 113]; U.S. Public Health Service, National Institutes of Health (Grant ES-00049); S. C. Johnson & Son, Inc., Racine, Wis. [1] *On leave from the Department of Insecticides and Fungicides, Rothamsted Experimental Station, Harpenden, Hertfordshire, England.*

Rapid Fluorometric Evaluation of the Deposition and Persistence of Carbaryl in the Presence of an Adjuvant on Bean and Tomato Leaves

A rapid analytical procedure for determining carbaryl on the leaves of bean and tomato plants was developed and used to evaluate the effectiveness of an adjuvant, β-pinene polymer, in spray formulations. Small aliquots of methylene chloride extracts of treated leaves were placed into glass vials and the solvent was allowed to evaporate. Sodium hydroxide solution was then added to hydrolyze carbaryl into 1-naphthol, which is leached out into the clear aqueous solution for measurement of the fluorescence intensity. No significant difference was found in the initial deposit (~1000 ppm) or the chemical lifetime of carbaryl when the spray did or did not contain this adjuvant. The method may readily be applied to other studies with carbaryl.

Stickers, surfactants, and other adjuvants are sometimes added to spray formulations to increase the effectiveness of pesticides on sprayed plants. This method of regulating the rate of loss of a pesticide on sprayed plants could make control less expensive for the farmer by requiring the use of less pesticide. Thus, an adjuvant that increases the effectiveness of degradable organophosphorus and carbamate pesticides would be highly desirable. A comprehensive study of the effect of 74 adjuvants in prolonging the toxicity of two organophosphorus compounds on lima bean foliage was reported by Smilowitz and Dewey (1969), who used a bicassay of two insect species to make their determinations.

Carbaryl, a widely used carbamate insecticide, is relatively insoluble in water and is usually applied as a wettable powder in aqueous spray formulations. Blazquez *et al.* (1970) added an adjuvant, a β-pinene polymer, to this spray mix and reported that it increased the initial deposit of carbaryl on tomato leaves sevenfold and the life of the compound three-