¹⁴C-Labeling of Bromobutide, 2-Bromo-3,3-dimethyl-*N*-(α,α -dimethylbenzyl)butyramide

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Bromobutide, a novel herbicide, was labeled with carbon-14 independently at the carbonyl group and the phenyl ring for use in metabolic studies. ¹⁴C-Carbonation of neopentylmagnesium chloride (3) gave 3,3-dimethyl[1-¹⁴C]butyric acid (4a) quantitatively. Chlorination of 4a with thionyl chloride followed by α -bromination with bromine yielded 2-bromo-3,3-dimethyl[1-¹⁴C]-butyryl halide (5a), which was subsequently condensed with α,α -dimethylbenzylamine (6a) to afford [carbonyl-¹⁴C]bromobutide (1a). The overall yield of 1a was 76% from barium [¹⁴C]-carbonate (2). Similarly, condensation of α,α -dimethyl[phenyl-¹⁴C]benzylamine (6b), which was prepared from α -methyl[phenyl-U-¹⁴C]styrene (7) in three steps, with 2-bromo-3,3-dimethylbutyryl halide (5b) gave [phenyl-¹⁴C]bromobutide (1b) in 67% yield after purification. The specific activities of 1a and 1b were 1.38 and 0.781 GBq/mmol (37.2 and 21.1 mCi/mmol), respectively.

Key Words: carbon-14, bromobutide, herbicide, 2-bromo-3,3-dimethylbutyryl halide, α,α -dimethylbenzylamine

1. Introduction

Bromobutide is a novel potent herbicide which provides strong herbicidal activity against wide variety of annual and perennial paddy weeds, and some combinations with other herbicides to increase its efficacy are now being developed as rice herbicides^{(1),(2)}. This agrochemical is composed of a blanchd aliphatic acid and a bulky benzylic amine. In order to assess its safety precisely, it was, therefore, required to prepare two sorts of radioactive bromobutide labeled independently at both components for detailed investigation of the metabolic and environmental fates. In this paper, we describe two methods for ¹⁴C-labeling of this herbicide.

2. Results and Discussion

2.1 ¹⁴C-Labeling at the carbonyl group

Retrosynthetic analysis of bromobutide for ¹⁴C-labeling at the carbonyl carbon in the acid component was shown in Fig. 1.

Commonly, acid amides such as bromobutide have been synthesized by condensation reaction between acid halides and amines⁽³⁾. And besides,

it was expected that 2-bromo-3,3-dimethylbutyryl halide, an acid halide for the synthesis of bromobutide, was readily derived from 3,3-dimethylbutyric acid, a simple derivative of acetic acid, by the well-known procedure (i.e., chlorination of carboxyl group with subsequent bromination at the α -position). Therefore, the ¹⁴C-labeling of 3,3-dimethylbutyric acid was considered to be the major task in this work.

Synthetic methods for the large-scale production of non-radioactive 3,3-dimethylbutyric acid have been reported^{(4),(5)}. These methods essentially rely upon the acid-catalyzed condensation of *t*-butyl alcohol and 1,1-dihaloethylene with subsequent hydrolysis. They were, however, impractical for the present ¹⁴C-labeling work due to many complicated processes and predicted low yields for the small-scale preparation of a proper ¹⁴C-labeled olefin. As shown in Fig. 1, two alternative methods seemed to be applicable to the present labeling. One is depended on ¹⁴C-cyanation with subsequent hydrolysis, and the other on ¹⁴C-carbonation. Initial attempts involving conventional ¹⁴C-cyanation^{(6),(7)} of neopentyl iodide, which was prepared according

Fig. 3 Synthesis of [phenyl- ^{14}C]bromobutide.

thyl[^{14}C]butyryl bromide and chloride (5a)³⁹. The brominated acid halide (5a) was condensed with α,α -dimethylbenzylamine (6a) in the presence of triethylamine to give the aimed amide (1a). The crude product was intensively purified by column chromatography and preparative high performance liquid chromatography to afford [carbonyl- ^{14}C]bromobutide (1a) with the purity more than 99% in 79% yield from the acid (4a).

2.2 ^{14}C -Labeling at the phenyl ring

Many methods for the synthesis of α,α -dimethylbenzylamine have been reported. They are mainly classified into three types of reactions: (A) Ritter reaction¹⁰ with subsequent hydrolysis; (B) Hofmann degradation^{11,12}, Curtis rearrangement¹³ and related types; (C) various kinds of addition to α -methylstyrene with subsequent proper amination such as reduction of the azide¹⁴ or hydrolysis of the isocyanate¹⁵. For the present ^{14}C -labeling, we selected a reaction sequence belonging under the type (C) (Fig. 3), because it had been known well that α -methyl[phenyl- ^{14}C]styrene (7), the starting material, could be readily obtained from bromo-[U- ^{14}C]benzene by Grignard reaction with acetone followed by dehydration of the resulting tertiary alcohol¹⁶.

In our preliminary experiments on the reaction sequence of Fig. 3, Markownikoff addition of hydrogen chloride to α -methylstyrene (7) gave α,α -dimethylbenzyl chloride (8) quantitatively. It was presumed that usual amination of the chloride (8) with ammonia or alkali amides would cause base-induced elimination to revive

the starting olefin (7). Therefore, we chose an alternative route to the desired amine (6b) via an isothiocyanate intermediate¹⁷. Treatment of the chloride (8) with sodium thiocyanate in water gave the corresponding isothiocyanate (9) in excellent yields more than 90%. Subsequent alkaline hydrolysis of 9 in ethylene glycol afforded the aimed amine (6b) in moderate yields (60–70%).

According to the procedures described above, the synthesis of α,α -dimethyl[phenyl- ^{14}C]benzylamine (6b) with a high specific activity was performed in cooperation with Amersham International plc. (England). The ring-labeled amine (6b) was condensed with 2-bromo-3,3-dimethylbutyryl halide (5b) in the manner similar to that described in the foregoing section to give [phenyl- ^{14}C]bromobutide (1b) in 67% yield after intensive purification.

3. Experimental

Radioactivity was measured by a TRI-CARB 460 liquid scintillation counter (Packard Instrument Co., USA) by using diluted Permafluor I (Packard) as the counting medium. Radio-thin layer chromatography (RTLC) was carried out on a Silica Gel 60 F₂₅₄ plate (Merck), and the radioactivity on the plate was determined by a JTC-601 Radiochromalyzer (Aloka, Japan). Radio-gas chromatography (RGC) was performed on a Yanaco G-180 gas chromatograph (detector FID; Yanagimoto Co., Ltd., Japan) equipped with a RD-4 gas-flow GM counter (Aloka), and a glass column (2 m $\times$ 3 mm ID) packed with Silicone XE-60 (5%) on Chromosorb W AW DMCS (60–80 mesh) was used for the analysis

of ^{14}C -labeled bromobutides (**1a**, **1b**) (column temperature raised from 100 to 200 °C at the rate of 10 °C/min, carrier gas He 27 ml/min; retention time: 16.7 min). Radio-high performance liquid chromatography (RHPLC) was conducted at ambient temperature on a LC-3A high performance liquid chromatograph (Shimadzu Co., Ltd., Japan) equipped with a SPD-2A UV detector (wave length 254 nm; Shimadzu Co.) and a RLC-551 Radioanalyzer (Aloka), and a stainless steel column (30 cm $\times$ 4 mm ID) packed with Lichrosorb SI-60 (5 μm , Merck) was used for the analysis of **1a** and **1b** (mobile phase *n*-hexane/ethyl acetate = 25/1 v/v, flow rate 1.0 ml/min; retention time 15.4 min). An infrared spectrum (IR) was measured by a IR-810 grating infrared spectrophotometer (JASCO Co., Japan), and the characteristic stretching absorptions (ν_{max}) were reported in cm^{-1} . A nuclear magnetic resonance spectrum (NMR) was determined on a H-90 NMR spectrometer (Hitachi Co., Ltd., Japan), and the chemical shifts (δ) for assigned protons were quoted in ppm downfield from tetramethylsilane as the internal standard.

3-1 3,3-Dimethyl[1- ^{14}C]butyric acid (**4a**)

To a stirred mixture of magnesium turnings (360 mg, 15.0 mmol), methyl iodide and iodine (each catalytic amount) in anhydrous ether (6 ml) was added dropwise a solution of neopentyl chloride (2.39 g, 22.6 mmol) in anhydrous ether (4 ml) to keep gentle reflux during the addition (about 20 min). After complete addition, the mixture was refluxed for 4 h. The Grignard reagent solution was then cooled, titrated (1.4 M), and charged into two flasks (2.5 ml and 1.7 ml, respectively), which were connected to a vacuum manifold and frozen in a liquid nitrogen bath. To one flask containing 3.5 mmol of neopentylmagnesium chloride was introduced carbon-14 dioxide liberated from barium [^{14}C]carbonate (**2**) (3.19 GBq, 86.3 mCi, 458 mg, 2.32 mmol) with concentrated sulfuric acid. The mixture was warmed to -20 °C and stirred at this temperature for 1.5 h. Then the remaining carbon-14 dioxide gas was confined in the other flask containing 2.4 mmol of the Grignard reagent, and this mixture was also

allowed to react under the same condition as described above. The two reaction mixtures were decomposed with 5% hydrochloric acid, combined and extracted with ether. The ethereal solution was re-extracted with 5% sodium carbonate. The alkaline solution was carefully acidified and extracted with ether again. The extract was washed with water and saturated sodium chloride solution, dried over anhydrous sodium sulfate, and the solvent was distilled off under atmospheric pressure to give 3,3-dimethyl[1- ^{14}C]butyric acid (**4a**) (3.07 GBq, 82.9 mCi, 96.1%) as a colorless oil; the purity 99% on RGC and RTLC (chloroform/methanol = 9/1 v/v, R_f 0.51). IR (liquid film): 3 500 (O-H), 1 700 (C=O); NMR (CDCl_3): 1.07 (9H, s, $(\text{CH}_3)_3\text{C}$ -), 2.25 (2H, s, $-\text{CH}_2$ -).

3-2 2-Bromo-3,3-dimethyl[1- ^{14}C]butyryl halide (**5a**)

A mixture of 3,3-dimethyl[1- ^{14}C]butyric acid (**4a**) (2.99 GBq, 80.9 mCi, 2.17 mmol) and thionyl chloride (410 mg, 3.45 mmol) in anhydrous benzene (2 ml) was stirred at 70 °C for 1.5 h. After addition of bromine (1.03 g, 6.45 mmol), the mixture was refluxed for 2.5 h. Then the solvent was distilled off together with excess amount of the halogenating agents to afford a mixture of 2-bromo-3,3-dimethyl[1- ^{14}C]butyryl bromide and chloride (**6a**) as an orange oil, which was supplied to the following condensation step without further purification.

3-3 [carbonyl- ^{14}C]Bromobutide (**1a**)

To a solution of 2-bromo-3,3-dimethyl[1- ^{14}C]butyryl halide (**5a**) (2.17 mmol) in anhydrous benzene (2 ml) were added α,α -dimethylbenzyl amine (**6a**) (870 mg, 6.43 mmol) and triethylamine (1.08 g, 10.6 mmol), and the mixture was stirred with reflux for 3 h. After dilution with water, the mixture was extracted with ethyl acetate. The extract was washed with 5% hydrochloric acid, water, 5% sodium carbonate and saturated sodium chloride solution, successively. After drying over anhydrous sodium sulfate, the extract was evaporated to give a residue, which was chromatographed on silica gel with chloroform. Evaporation of the main fraction gave a roughly purified product, which was dissolved

in chloroform and injected portionwise into the preparative HPLC [YMC Pack SH-043 column (S-15, SIL, 25 cm $\times$ 2 cm ID), *n*-hexane/ethyl acetate (25/1 v/v) as the solvent with a flow rate of 11.3 ml/min, at ambient temperature, monitored by UV absorbance at 254 nm]. The fraction containing the pure amide (retention time 25.0 min) was collected and evaporated to afford intensively purified [carbonyl- ^{14}C]bromobutide (**1a**) (2.37 GBq, 64.1 mCi, 581 mg, 79.2% from **4a**) as a colorless powder; the purity more than 99% on RGC, RHPLC and RTLC (chloroform, R_f 0.29; benzene, R_f 0.10; *n*-hexane/ethyl acetate=2/1 v/v, R_f 0.52). IR (Nujol): 3330 (N-H), 1660 (C=O); NMR (CDCl_3): 1.15 (9H, s, $-\text{C}(\text{CH}_3)_3$), 1.68 (3H, s, $\text{PhC}(\text{CH}_3)_2-$), 1.74 (3H, s, $\text{PhC}(\text{CH}_3)_2-$), 4.04 (1H, s, $-\text{CH}(\text{Br})-\text{CO}-$), 6.29 (1H, bs, $-\text{CO}-\text{NH}-$), 7.25–7.41 (5H, m, phenyl H).

3.4 [phenyl- ^{14}C]Bromobutide (**1b**)

To a mixture of α,α -dimethyl[phenyl- ^{14}C]-benzylamine(**6b**) (281 MBq, 7.60 mCi, 0.36 mmol; prepared by Amersham International plc, England) and triethylamine (443 mg, 0.61 mmol) in anhydrous benzene (2 ml) was added a solution of 2-bromo-3,3-dimethylbutyryl halide (**5b**) in benzene (0.17 M, 3.0 ml; **5b** 0.50 mmol), which was prepared from non-radioactive 3,3-dimethylbutyric acid (**4b**) in the manner similar to that described above. The mixture was then stirred under reflux for 3 h. The same work-up of the reaction mixture as conducted in the carbonyl-labeling gave a crude product, which was intensively purified by column chromatography on silica gel with benzene. The main fraction was evaporated to dryness to afford [phenyl- ^{14}C]-bromobutide (**1b**) (189 MBq, 5.11 mCi, 90.7 mg, 67.2%) as a colorless powder. The purity of **1b** was found to be 98% radiochemically and chemically on RGC, RHPLC and RTLC.

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要 旨

プロモブチド [2-プロモ-3,3-ジメチル-*N*-(α , α -ジメチル
ベンジル)ブチルアミド] の ^{14}C 標識化

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新規除草剤プロモブチドの代謝研究を行うために, そのカルボニル ^{14}C 標識体 (**1a**) およびフェニル ^{14}C 標識体 (**1b**) を調製した。 **1a** は, 3,3-ジメチル [$1\text{-}^{14}\text{C}$] 酪酸 (**4a**) を経由する方法により, [^{14}C] 炭酸バリウム (**2**) からの通算収率76%で合成した。一方, **1b** は, α -メチル [フェニル- ^{14}C] スチレン (**7**) より3工程を経て調製された α , α -ジメチル [フェニル- ^{14}C] ベンジルアミン (**6b**) から収率67%で得た。