Synthesis of *N*-(1-Hydroxy-2-fluorenyl-1-C^{14})-acetamide with a High Specific Activity[1]

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Previous work[2-4] has implicated the metabolite *N*-(1-hydroxy-2-fluorenyl)acetamide in a series of reactions resulting in the protein binding of the carcinogen *N*-2-fluorenylacetamide *in vitro*. In connection with further studies concerned with the metabolism and mechanism of action of *N*-2-fluorenylacetamide, carbon-14 ring-labeled *N*-(1-hydroxy-2-fluorenyl)acetamide with a high specific activity was desired.

A chemical synthesis utilizing potassium cyanide-C^{14} for the introduction of carbon-14 into the fluorene nucleus in a route to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide has been reported by Morgan and Gutmann. The preparation[5] involved treatment of 3-(3-indenyl)propyl bromide with potassium cyanide-C^{14} to give 4-(3-indenyl)butyronitrile-1-C^{14} and cyclization of the nitrile to 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}. The carbon-14 labeled ketone was dehydrogenated yielding 1-hydroxyfluorene-1-C^{14}, which was converted to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide in four steps.

In the present paper, a modification of this synthesis, which is more economical than that reported previously, is presented. The major modification is in the use of barium carbonate-C^{14} instead of potassium cyanide-C^{14} for the introduction of the radioactivity. Barium carbonate-C^{14} is available commercially at less than one sixth the cost of potassium cyanide-C^{14} per millicurie of radioactivity.

The Grignard reagent prepared from 3-(3-indenyl)propyl bromide[6] was carbonated with carbon-C^{14} dioxide generated from barium carbonate-C^{14}. Ring closure of the resulting 4-(3-indenyl)butyric-1-C^{14} acid was accomplished with anhydrous hydrogen fluoride yielding 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}. The radioactive yield from the barium carbonate to the tetrahydrofluorenone was 61% compared to a yield of 42% from the potassium cyanide to the ketone in the previous synthesis.[5] The labeled ketone was converted to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide in four steps using slight modifications of published methods as indicated below. The over-all radioactive yield from barium carbonate to *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide, having a specific radioactivity of 4.99 millicuries per mmole was 10.6%. Morgan and Gutmann obtained a yield of 5.1%, and the product had a specific radioactivity of 0.66 millicurie per mmole.

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Radioactivity measurements were made using a Tri Carb liquid scintillation spectrometer.

4-(3-Indenyl)butyric-1-C^{14} Acid.—3-(3-Indenyl)propylmagnesium bromide was prepared from 0.54 g. (22 mmoles) of magnesium and 4.8 g. (20 mmoles) of freshly redistilled 3-(3-indenyl)propyl bromide[6] (b.p. 130°/0.4 mm., $n^{28}D$, 1.5870) in 30 ml. of anhydrous ether under an atmosphere of dry nitrogen. After stirring and refluxing for 3 hr. the reaction mixture was cooled to room temperature and an aliquot was removed for titration. The mixture contained 0.48 mmole of Grignard reagent per ml. At once, 11.5 ml. of the solution, containing 5.5 mmoles of Grignard reagent, was transferred to a carbonation flask containing 10 ml. of anhydrous benzene in an atmosphere of dry nitrogen. Carbonation was carried out at −5° at a pressure of 0.2 mm. in an apparatus similar to that described by Gutmann *et al.*[7] Carbon-C^{14} dioxide was generated by addition of concd. sulfuric acid to barium carbonate-C^{14} (0.987 g., 5.01 mmoles; 25.4 mc.). After standing at room temperature for several hours, 10 ml. of 10% hydrochloric acid was added to the carbonation reaction mixture with stirring. The ether layer was washed with 5 ml. of water and extracted twice with 2 *N* sodium hydroxide. The sodium hydroxide extracts (25 ml. total) were combined and warmed to remove ether. Activated charcoal was added to the warm solution, which was then filtered through Celite. The filtrate was cooled and acidified with concd. hydrochloric acid. After standing at 4° overnight, the product was collected, washed with water, and dried *in vacuo* over phosphoric anhydride. The yield was 0.922 g. (4.56 mmoles, 91%) of 4-(3-indenyl)-butyric-1-C^{14} acid, m.p. 88–92°. The indenylbutyric acid could be recrystallized from petroleum ether (b.p. 90–100°) but was used without purification for the next reaction step. In some nonradioactive preparations, the melting point of the recrystallized product mixed with authentic 4-(3-indenyl)butyric acid,[6] m.p. 90–92° (reported[6] m.p. 91–93°), was not depressed.

1,2,3,4-Tetrahydrofluoren-1-one-1-C^{14}.—4-(3-Indenyl)-butyric-1-C^{14} acid (0.922 g., 4.56 mmoles) was dissolved in 5–6 ml. of anhydrous hydrogen fluoride, and the solution was allowed to stand overnight at room temperature in a closed 15-ml. polypropylene centrifuge tube. The hydrogen fluoride was evaporated, and the residue was taken up in 25 ml. of ether. The ether solution was washed with 10% sodium carbonate and then with water. Evaporation of the ether under a stream of nitrogen gave 0.560 g. (3.04 mmoles, 67% yield) of 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}, m.p. 101–105°, after drying *in vacuo* over phosphoric anhydride. Recrystallization of the crude product in some nonradioactive preparations gave pure 1,2,3,4-tetrahydrofluoren-1-one, m.p. 105° (reported[6] m.p. 104–106°) which showed no depression in melting point when mixed with authentic 1,2,3,4-tetrahydrofluoren-1-one.[6] The yield of crude tetrahydrofluorenone was markedly dependent upon the purity of the 4-(3-indenyl)butyric acid used as starting material. In nonradioactive runs using recrystallized indenylbutyric acid, the yield of crude ketone was 90–95%.

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1-Hydroxyfluorene-1-C^{14}.—1,2,3,4-Tetrahydrofluoren-1-one-1-C^{14} (0.560 g., 3.04 mmoles) was dehydrogenated according to the method described by Morgan and Gutmann,[5] except dichloromethane instead of ether was used in the extraction of the crude reaction mixture. There was obtained 0.414 g. (2.27 mmoles, 75% yield) of 1-hydroxyfluorene-1-C^{14}.

1-Hydroxy-2-nitrofluorene-1-C^{14}.—1-Hydroxyfluorene-1-C^{14} (0.414 g., 2.27 mmoles) was nitrated by the procedure reported by Weisburger and Weisburger.[8] Chromatography of the crude nitration product on alumina (Merck, acid-washed) gave 0.211 g. (0.93 mmole, 41% yield) of 1-hydroxy-2-nitrofluorene-1-C^{14}.

1-Hydroxy-2-aminofluorene-1-C^{14} Hydrochloride.—1-Hydroxy-2-nitrofluorene-1-C^{14} (0.211 g., 0.93 mmole) was reduced[8] with zinc dust. The hot reaction mixture was filtered through Celite into 1.9 ml. of concd. hydrochloric acid, and the zinc was washed with ethanol. The filtrate and washings were combined and the ethanol was removed under reduced pressure at 40°. The mixture was then cooled in an ice bath, and the product was transferred to a sintered glass funnel with the aid of a small volume of ice-cold concd. hydrochloric acid. After drying *in vacuo* over potassium hydroxide, there was obtained 0.159 g. (0.68 mmole, 73%) of 1-hydroxy-2-aminofluorene-1-C^{14} hydrochloride.

***N*-(1-Hydroxy-2-fluorenyl-1-C^{14})acetamide.**—The hydrochloride of 1-hydroxy-2-aminofluorene-1-C^{14} (0.159 g., 0.68 mmole) was acetylated by the method of Weisburger and Weisburger,[8] yielding 0.160 g. (0.67 mmole, 99%) of crude *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide. Chromatography of the crude product on alumina (Merck, acid-washed) with ethyl acetate as eluent, followed by recrystallization from dilute ethanol, gave 0.126 g. (0.529 mmole, 78% yield) of *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide as white needles, m.p. 211–212° (reported[8] m.p. 208°), after drying *in vacuo* at 78° over phosphoric anhydride. The specific radioactivity of the *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide was 4.99 mc. per mmole.

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Asymmetric Synthesis of (+)-Bicyclo[2.2.2]-octanol-2[1]

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Brown and Zweifel[2] have recently reported that they obtained nearly complete asymmetric stereoselectivity[3] by the addition of diisopinocampheylborane to various olefines. This remarkable achievement prompted us to apply this method to the synthesis of optically active bicyclo[2.2.2]-octanol-2.

We wish to report that the addition of diisopinocampheylborane (from (−)-α-pinene) to bicyclo-[2.2.2]octene-2 produced *S*-(+)-bicyclo [2.2.2]-octanol,[4] m.p. 214–217°, $[\alpha]^{25}D$ +6.9° (*c* 2.37, chloroform).

Based on the known absolute configuration[5] of (−)-α-pinene and by the application of the Prelog-Cram rule[6] one would predict the *R* configuration for the resulting alcohol. This was not found to be the case and is therefore inconsistent with the absolute configurational assignment of *S*-(+)-bicyclo[2.2.2]octanol-2 which has been determined by a different method.[4]

Experimental[7]

***S*-(+)-Bicyclo[2.2.2]octanol-2.**—To a solution of 3.12 g. (0.083 mole) of sodium borohydride in 75 cc. of anhydrous diglyme was added 27.2 g. of α-pinene,[8] $[\alpha]^{25}D$ −47.88. The solution was cooled to 0° and while under an atmosphere of argon 14.2 g. of freshly distilled boron trifluoride-etherate was added at a rate which maintained the temperature between 0–5°. The mixture was stirred for an additional hour at 0–2° and then 10.4 g. (0.1 mole) of bicyclo[2.2.2]-octane-2[9] was added. Stirring was continued for 4 hr. at 0–2° and finally at room temperature for 12 hr.

The reaction mixture was hydrolyzed by the addition of water, 31 cc. of 3 *N* sodium hydroxide and finally, 31 cc. of 30% hydrogen peroxide at a sufficient rate so that the temperature of the solution was kept between 30–35°. The reaction mixture was extracted with pentane, and the extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled at 85 mm. to yield 3.55 g. of material, b.p. 60–75°. Fractional sublimation of the waxy product gave fractions, the specific rotations of which varied from +6 to +7°. Recrystallization of the sublimed material from pentane yielded 2.61 g. of bicyclo[2.2.2]octanol-2, m.p. 214–217° (s.t.), $[\alpha]^{28}D$ +6.9° (*c* 2.32, chloroform), the infrared spectrum of which was identical with that of an authentic sample. Vapor phase chromatography showed that the sample was not contaminated with isopinocampheol. Recrystallization of the residue from the above distillation yielded an additional 1.04 g. of alcohol, $[\alpha]^{28}D$ +6.3° (*c* 2.15, chloroform) making the total yield of alcohol 30%.

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(3) A. comparable degree of stereoselectivity has been previously reported [J. A. Berson and M. A. Greenhaum, *ibid.*, **80**, 445 (1958)] in an atrolactic acid synthesis.

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(7) Melting points and boiling points are uncorrected.

(8) We wish to thank Prof. H. C. Brown, Purdue University and the Glidden Co., Jacksonville, Fla., for supplying us with generous samples of α-pinene.

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Some Free Radical-Catalyzed Additions of Perfluoroalkyl Iodides to Olefins

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The free radical-catalyzed addition of one- and two-carbon perhaloalkyl iodides to simple olefins has been investigated extensively, principally