SYNTHESIS OF ^{14}C-LABELLED ISOTOPE-ISOMERIC ALKANES. I n-HEPTANE-1-^{14}C AND -2-^{14}C

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SUMMARY

The synthesis of n-heptane-1-^{14}C is described, starting from $^{14}CH_3I$ via $(^{14}CH_3)_2Cd$ and caproyl chloride; for obtaining n-heptane-2-^{14}C, n-pentyl bromide is converted into the Grignard reagent, carbonated with $^{14}CO_2$, and the resulted caproic acid is converted into its chloride and treated with dimethylcadmium. In both cases the labelled n-heptan-2-one is finally reduced to labelled n-heptane by the Kishner-Wolff method.

There are four possible singly C-labelled isotope-isomeric (1,2) n-heptanes, with the label in positions 1, 2, 3, or 4. We proposed to synthesize these carbon-labelled isotope-isomeric n-heptanes. In the present paper we report the preparation of n-heptane-1-^{14}C and -2-^{14}C.

Pines and Chen (3) described the preparation of n-heptane-1-^{14}C from n-hexylmagnesium bromide and $^{14}CO_2$, followed by reduction of the resulted oenantic acid-1-^{14}C with lithium aluminium hydride to n-heptanol-1-^{14}C. The last stages were dehydration and catalytic hydrogenation at 150° and 100 atm.(4)

Mitchell and Holder prepared n-heptane-1-^{14}C similarly up to the alcohol stage, then reduced the tosyl ester with $LiAlH_4$ obtaining some toluene as inactive by-product (probably from unreacted tosyl chloride) which had to be removed by silica gel adsorption.(5)

The first isotope-isomer of n-heptane reported in the literature (6) is n-heptane-4-^{14}C. McMahon reacted n-propylmagne-

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sium bromide with ethyl formate-carboxyl-${}^{14}C$, obtaining 4-heptanol-4-${}^{14}C$ which was acetylated, pyrolyzed to n-heptene, and this was hydrogenated over a platinum catalyst.$^{(6)}$

The synthesis of n-heptane-2-${}^{14}C$ or -3-${}^{14}C$ has not been reported. At present, n-heptane-1-${}^{14}C$ is commercially available, but no informations on the synthetic method are given.$^{(7)}$

In our choice of synthetic approaches to isotope-isomeric alkanes we considered the following requirements :

-to start from usual, simple compounds ;

-to introduce the label in the latest possible step ;

-to avoid as far as possible operations at high pressures or temperatures ;

-to devise approaches which may yield more than one isotope-isomer , if different starting materials are employed.

In the end, a procedure was selected which may yield both n-heptane-1-${}^{14}C$ and -2-${}^{14}C$, described in the present paper. The procedure consists in the reaction of caproyl chloride with dimethylcadmium, followed by a Kishner-Wolff reduction of the resulted 2-heptanone. According to whether (i) the dimethylcadmium or (ii) the caproyl chloride is labelled, this procedure affords 2-heptanone and n-heptane labelled in positions 1 and 2, respectively.

$$\text{(i)}\quad {}^{14}CH_3I \xrightarrow{Mg} {}^{14}CH_3MgI \xrightarrow{CdCl_2} ({}^{14}CH_3)_2Cd \xrightarrow{n\text{-}C_5H_{11}COCl}$$

$$\longrightarrow n\text{-}C_5H_{11}\text{-}CO\text{-}{}^{14}CH_3 \xrightarrow{N_2H_4} n\text{-}C_6H_{13}\text{-}{}^{14}CH_3$$

$$\text{(ii)}\quad n\text{-}C_5H_{11}Br \xrightarrow{Mg} n\text{-}C_5H_{11}MgBr \xrightarrow{{}^{14}CO_2} n\text{-}C_5H_{11}\text{-}{}^{14}COOH \xrightarrow{SOCl_2}$$

$$\longrightarrow n\text{-}C_5H_{11}\text{-}{}^{14}COCl \xrightarrow{(CH_3)_2Cd} n\text{-}C_5H_{11}\text{-}{}^{14}CO\text{-}CH_3 \longrightarrow$$

$$\xrightarrow{N_2H_4} n\text{-}C_5H_{11}\text{-}{}^{14}CH_2\text{-}CH_3$$

The use of organocadmium reagents $^{(8)}$ for the preparation of labelled ketones was first reported in 1950,$^{(9)}$ and applied to a variety of aromatic (10) or aliphatic ketones (11) in 1961-1962. This approach to labelled alkanes has not been reported in the literature, as far as we are aware.

For the reduction of 2-heptanone to n-heptane, the Clemmensen reduction (12) was also tested, but gave less satisfactory results in comparison with the Kishner-Wolff method.(13) The time necessary for the complete reduction by the latter method was established by following the course of the reduction of unlabelled 2-heptanone through infrared spectroscopy (disappearance of the CO stretching band around 1700 cm^{-1}).

The chemical purity of intermediate and final compounds was checked by fractional distillation, infrared spectroscopy, and refractive index. The n-heptane was also controlled by vapour phase chromatography, and found to have a chemical purity of 97 %.

For our purposes the necessary specific activity was relatively low. In preparations involving a few grams of material, the overall chemical and radiochemical yields for n-heptane-1-^{14}C were 40-45 %. Trial experiments with larger amounts gave yields above 50 %. The total yields for n-heptane-2-^{14}C are lower, because the yield in caproyl chloride-1-^{14}C from $^{14}CO_2$ is 55 % in small-scale preparations, leading to an overall yield of about 25 per cent.

EXPERIMENTAL PART

Reagents

Carbon dioxide-^{14}C was obtained from barium carbonate-^{14}C and phosphoric acid in a vacuum line.(14)

Methyl iodide-^{14}C was purified by shaking with mercury till it became colourless, followed by distillation on the vacuum line.

Cadmium chloride was dried at 110° to constant weight and kept in a dessicator over phosphoric anhydride.

Caproyl chloride was obtained from caproic acid and thionyl chloride. After refluxing for three hours, the mixture was fractionated on a small column, b. p. 151-153°/760 Torr.

Benzene and ethyl ether, thiophene- and peroxide-freed, were kept over, and distilled from, sodium wire.

n-Pentyl bromide was redistilled before use.

n-Heptane-1-^{14}C

Dimethylcadmium-^{14}C. In an oven-dried three-necked flask with efficient moisture-protected reflux condenser, stirrer and dropping funnel, 0.81 g (0.034 gram-atoms) magnesium turnings and 10 ml absolute ether were placed. The dropping funnel contained 0.5 mCi of methyl iodide-^{14}C diluted with inactive methyl iodide to a total of 4.8 g (34 mmol, 14.7 μCi/mmol) in 15 ml dry ether. The reaction was started with 2 ml of this solution, the remainder of which was added so as to maintain gentle refluxing. Then the mixture was refluxed under stirring for two additional hours. The solution was chilled in ice, the dropping funnel was replaced by a rubber-connected flask containing 3.3 g (17.8mmol) dry cadmium chloride. This reagent was added with stirring and cooling during ten minutes ; after removal of the $CdCl_2$ flask, the mixture was stirred for 15 minutes, then refluxed for 3 hours with stirring.

2-Heptanone-1-^{14}C. Most ether was removed by distillation discontinuing the water in the reflux condenser, which was now used as a fractionating column, connecting it with a downward condenser, and heating the flask on a water bath. Then 25 ml dry benzene was added, and 10 ml were distilled off to remove the ether. The benzene solution was cooled to 5° and a solution of 4.6 g caproyl chloride (34 mmol) in 10 ml benzene was added under stirring from the dropping funnel during 15 min. The mixture was then stirred for 3 hours at 15°, then 2 hours at room temperature. The mixture was then hydrolyzed with crushed ice and dil. sulphuric acid. The benzene layer was separated, the aqueous layer was extracted twice with 5 ml benzene. The combined benzenic solutions were washed successively with water, aqueous sodium hydrogen carbonate, and saturated sodium chloride solution. The benzenic solution was dried over sodium sulphate and distilled at normal pressure with a small column. After the benzene forerun, the 2-heptanone-1-^{14}C was collected at 148-151°/ 750 Torr. Chemical yield : 2.6 g (23 mmol, 67 %). Specific activity : 14 μCi/mmol. Radiochemical yield : 64 %.

n-Heptane-1-^{14}C. In a round-bottom flask with reflux condenser and thermometer reaching into the liquid, 5 g sodium were dissolved completely in 100 ml diethylene glycol. Then 2.5 g (22 mmol) from the above 2-heptanone-1-^{14}C and 2 g hydrazine hydrate were added. The mixture was refluxed for 20 hours (in trial experiments without radioactivity, the course of reduction had been checked by infrared spectroscopy in order to find out when the reduction was complete). After dilution with 400 ml water, the mixture was extracted four times with ether. The ethereal extracts were combined, dried over magnesium sulphate and fractionated, affording 1.4 g (14 mmol) n-heptane-1-^{14}C, b. p. 95-98°/ 760 Torr. Chemical yield : 63 %. Specific activity : 13.9 μCi/mmol. Radiochemical yield : 62.5 %. By v. p. c. the n-heptane-1-^{14}C had a purity of 97-98 %, with traces of 2-heptanone-1-^{14}C.

n-Heptane-2-^{14}C

Caproic acid-1-^{14}C. In a three-necked oven-dried 100 ml flask with efficient moisture-protected reflux condenser, dropping funnel and magnetic stirrer, 0.5 g (0.02 gram-atoms) of magnesium turnings, 5 ml absolute ether and a small crystal of iodine were placed. The dropping funnel contained 3 g (2.5 ml, 20 mmol) n-pentyl bromide in 15 ml ether. About one fifth of this solution was introduced into the flask. After the start of the reaction, the remaining solution was introduced dropwise so as to cause gentle refluxing. Then the mixture was refluxed for an additional hour.

The flask was then cooled in liquid nitrogen, stoppered, and attached to the vacuum line. The system was then evacuated to 10^{-3} Torr. Then $^{14}CO_2$ from 31.3 mg $Ba^{14}CO_3$ (3mCi) diluted with inactive $BaCO_3$ to a total weight of 200 mg barium carbonate, the gas being again flushed with inactive carbon dioxide to a total amount of 20 mmoles, i. e. a specific activity of 150µCi/mmol, was introduced into the flask. The temperature was raised to -20° with the aid of a bath with carbon tetrachloride and liquid nitrogen. The carbonation lasted 5 hours with stirring. Then the flask was taken off from the vacuum line and the mixture was hydrolyzed with ice and hydrochloric acid. The separated aqueous layer was extracted three times with ether, the combined ethereal extracts were dried over sodium sulphate, and the ether was evaporated under reduced pressure. The remaining caproic acid-1-^{14}C was further used without purification.

Caproyl chloride-1-^{14}C. An excess of thionyl chloride was added to the above acid, and the mixture was refluxed gently for three hours. Then the thionyl chloride was distilled off, and the labelled caproyl chloride was collected at 151-153° in a moisture-protected receiver flask. Chemical yield : 1.5 g, 56 % relatively to $^{14}CO_2$. Specific activity : 148 µCi/mmol. Radiochemical yield : 55 %.

2-Heptanone-2-^{14}C and n-heptane-2-^{14}C. The reaction of caproyl chloride-1-^{14}C with dimethylcadmium affording 2-heptanone-2-^{14}C and the subsequent reduction to n-heptane-2-^{14}C were performed as described above for n-heptane-1-^{14}C. The yields in the various stages were similar to those above, and the purity control was performed analogously with comparable results.

All radioactivity measurements were performed with a Packard Tri-Carb liquid scintillation spectrometer model 3375.

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