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Preparation of Ring Labelled Adamantane Derivatives II. 2-Adamantanone-2-^{14}C, Adamantane-2-^{14}C and 1-Methyladamantane-2 or 4-^{14}C

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SUMMARY

A high-yield, relatively simple synthetic route leading to incorporation of ^{14}C into the secondary position of the adamantane nucleus is described. The synthesis was achieved by the sequence shown in Figure 2. The key steps involved the introduction of a ^{14}C label by diazomethane-^{14}C ring expansion of adamantanone to give 4-homoadamantanone-4-^{14}C (I). Benzylic acid rearrangement of the corresponding homoadamantane diketone (II) gave hydroxy acid (III) which was converted by a novel reaction ($SOCl_2$/benzene) to 2-adamantanone-2-^{14}C (IV). The overall yield of labelled 2-adamantanone was 66 %. Wolff-Kishner reduction of (IV) gave adamantane-2-^{14}C (V). This was converted to the l-methyl derivative (VII) by treatment of the corresponding bromide (VI) with methylmagnesium bromide.

INTRODUCTION.

The use of radioactive labels has confirmed the hypothesis [1] that rearrangements of alkyl groups on adamantane do not proceed by simple 1,2-shift mechanisms [2]. We have previously reported [3] a synthesis of 2-methyl-adamantane-2-^{14}C, the compound which permitted the rearrangement mechanism to be probed [2]. Further studies required a different labeling pattern; consequently we have developed alternative approaches to the synthesis of ring labelled adamantane derivatives including a preparation of adamantane itself specifically labelled at the 2-position. The present synthesis,

like the earlier one [3], is based on a ring homologation-ring contraction approach. In both sequences carbon-14 was introduced by reaction of adamantanone with diazomethane-^{14}C [4]. In the present synthesis (Fig. 1) a different method of ring contraction giving higher yields with greater experimental convenience was employed.

Homoadamantan-4,5-dione-4-^{14}C (II) was prepared by SeO_2 oxidation of I [5]. Benzylic acid rearrangement of II produced the contracted product, 2-hydroxy-2-adamantane carboxylic acid (III) in which the label was distributed between the 2-position of the ring and the carboxyl group. This material, in principle, would permit the preparation of other adamantane derivatives doubly labelled in both the ring and in the side chain.

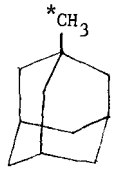
A novel method of converting 2-hydroxy acids to the corresponding ketones [6] was used to convert III to 2-adamantanone-2-^{14}C (IV). The reagent, thionyl chloride, presumably first formed a cyclic intermediate which decomposed to ketone and gaseous by-products :

Wolff-Kishner [7] reduction of IV gave adamantane-2-^{14}C (V). The overall chemical yield of V from unlabelled adamantanone was 59 %. The disadvantage with regard to radiochemical synthesis is the loss of half of the label during the conversion of III to IV. Nevertheless, the adamantane-2-^{14}C actually prepared was active enough (specific activity 21.80 nCi/mgC so that considerable dilution with unlabelled adamantane was possible before carrying out subsequent steps.

Bromination of V [8] gave 1-bromoadamantane-2 or 4-^{14}C (VI) which must have the label statistically distributed between the secondary carbons. Conversion of this bromide (VI) with excess methylmagnesium bromide [9] at 100° gave 1-methyladamantane-2 or 4-^{14}C with the same label distribution.

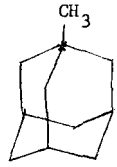
Since the synthetic sequences employed (Fig. 1) should not involve label scrambling other than that produced by symmetry considerations (and negligible isotope effects), we believe that the compounds prepared are specifically labelled.

Degradation studies on 1-methyladamantane-2 or 4-^{14}C (VII) were carried out by the modified Kuhn-Roth procedure [3, 10]. Starting with VII (specific act. 3.52 nCi/mgC) acetic acid (isolated as the thallium salt) [11] with a specific activity of 0.245 nCi/mgC was obtained. If the labelling pattern implied in VII was present in the starting material, and if no rearrangement had occurred on Kuhn-Roth oxidation the thallium acetate should not have contained any radioactivity. The position of the residual activity in the acetic acid was shown to be predominately at the methyl group by Schmidt degradation and analysis.



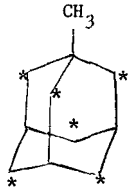
1. → CH_3—COOH (ref. 9)

100%	0%	expected
97%	0%	found[a]



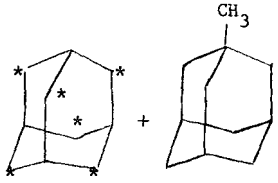
2. → CH_3—COOH (ref. 2)

0%	100%	expected
0%	90%	found[b]



3. →

CH_3—COOH		
0%	0%	expected
1.2%	~0.1%	found



4. →

CH_3—COOH		
0%	0%	expected
<2.6%	<0.06%	found[c]

inactive

1 : 1

[a] Specific activity in specified position/11 × specific activity starting material.

[b] Reasons for only 90 % of the activity being in the carboxyl group rather than 100 % are to be published (ref. 2).

[c] Specific activity in specified position/10 × specific activity of the adamantane Reaction was not run to completion.

FIG. 1. Results of Kuhn-Roth Degradation of Various Labelled 1-Methyladamantanes and Labelled Adamantanes.

Assuming that the methyl group in T1OAc does not originate from a bridgehead position, these results show that the 1-methyladamantane-2 or 4-^{14}C (VIII) was labelled at least to the extent of 99.6 % at the methylene positions [12]. The observation of substantial activity in the methyl group (as determined by the Schmidt degradation) is due, we believe, to the severity of the Kuhn-Roth degradation conditions permitting unexpected rearrange-

ments. We have observed similar scrambling previously. For example, 2-methyladamantane-2-^{14}C gave acetic acid with a radioactive content (79-89 % at the carboxyl group) which varied with the severity of the Kuhn-Roth conditions [3].

Figure 2 summarizes our results on Kuhn-Roth oxidation with a variety of labelled 1-methyladamantanes and labelled adamantane. These results show that the methyl group of the acetic acid obtained in the degradation is essentially derived from the methyl group of 1-methyladamantane (cf., oxidation numbers 1 and 3). A small amount of the methyl group in acetic acid obtained in the degradation is formed from the methylene group of the adamantyl nucleus (cf., oxidation numbers 3 and 4). Oxidation of 1-methyladamantane-1-^{14}C (cf., number 2) gave similar results but the starting material had been subjected to a variety of reactions and an explanation can be found in the forthcoming publication noted [2]. The oxidation of the mixture of labelled adamantane and unlabelled 1-methyladamantane gave a somewhat larger activity in acetic acid (~2.6 % as opposed to 1.2 % in number 3) reflecting the fact that the reaction was not taken to completion and that the rates of oxidation of adamantane and 1-methyladamantane are not the same. The results clearly demonstrate that essentially no acetic acid methyl is derived from a bridgehead position. The use of a carbon-13 label in conjunction with carbon-13 NMR would overcome the disadvantages inherent in the Kuhn-Roth method of analysis. Recent advances in carbon-13 NMR have made it possible to analyze for the label in a specific position at low levels of labelling and without the necessity for degradation.

Investigation of the rearrangements of labelled adamantane-2-^{14}C and 1-methyladamantane-^{14}C will be reported separately.

Experimental part.

The specific activities (average values of two samples) were determined in the gas phase. After combustion of the samples, the known amount of CO_2 was counted in an internal counter after 24 hour periods of equilibration.

Homoadamantan-4-one-5-^{14}C (I).

Homoadamantan-4-one-5-^{14}C (specific activity 37.92 nCi/mgC) was prepared in 85 % yield (radiochemical yield 53 %) as reported previously [2]. The product (I), after recrystallization from pentane, gave m.p. 269-271° C, lit. m.p. 270-271° C [4] and was shown by glc to have a purity exceeding 99 %.

Homoadamantan-4,5-dione-4-^{14}C (II).

Homoadamantan-4,5-dione-4-^{14}C (specific activity 38.61 nCi/mgC) was prepared by the SeO_2 oxidation of I as reported by Schlatmann *et al.* [5] in

87 % yield. Recrystallization from pet ether (30-60) gave yellow needles of m.p. 287° C (dec.), lit. m.p. 287° C (dec.) [5].

Benzylic Acid Rearrangement of Homoadamantan-4,5-dione to 2-Hydroxyadamantane-2-carboxylic acid.

In a typical experiment 16.0 g (0.096 mole) of homoadamantan-4,5-dione was dissolved in 780 ml of dioxane plus 360 ml of H_2O containing 80.0 g (1.43 moles) of KOH. The solution was refluxed for two hours. After cooling,

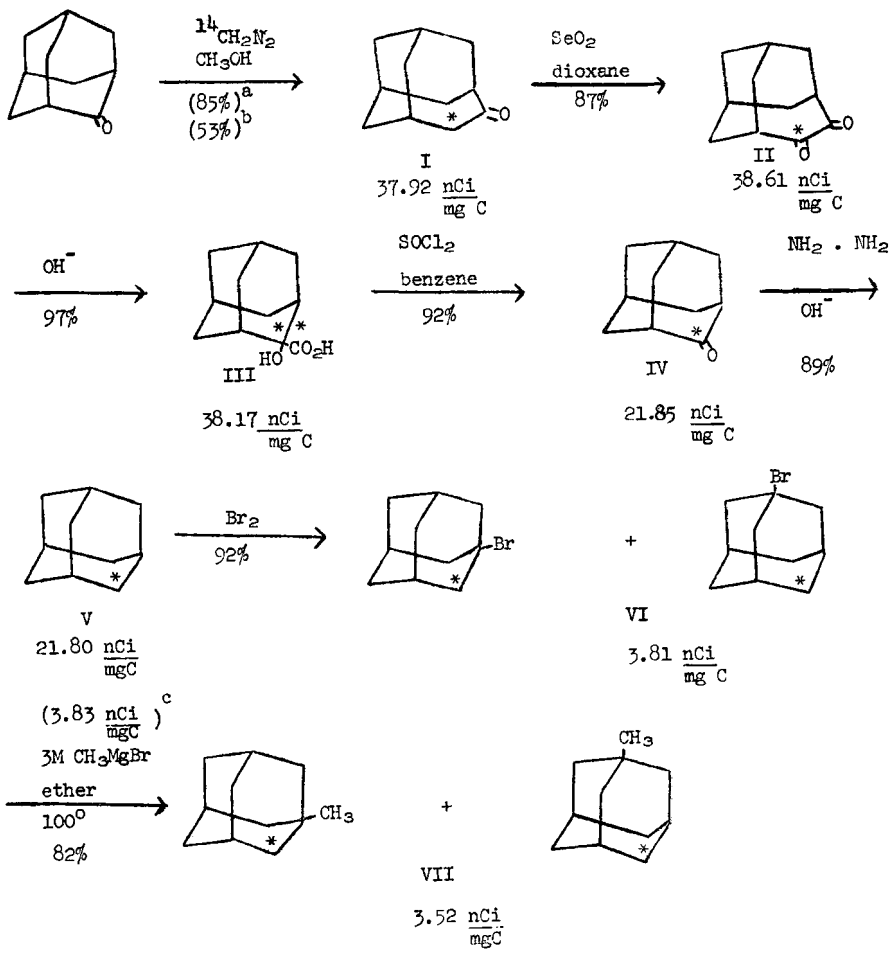


FIG. 2. Synthesis of Adamantane-2-^{14}C (V) and 1-methyladamantane-2 or 4-^{14}C (VII).

[a] Chemical yield.

[b] Radiochemical yield.

[c] Diluted V.

solvent was evaporated and the residue was dissolved in water. Extraction of the aqueous alkaline solution with ether (3 × 200 ml) was followed by acidification with conc. HCl to pH 1-2. The precipitated product was extracted with ether and removal of solvent left 18.3 g (0.093 mole, 97 %) of an off-white solid which was used directly in the next reaction. Recrystallization from carbon tetrachloride : benzene : : 1 : 1 gave white crystals (75 % recovery) of m.p. 210-211° C. IR (KBr) : 3,380 cm^{-1} (s), 2,660 (w) and 1,700 (s); nmr (CD_3 $COCD_3$) multiplet at 1.3-2.3 δ (14 H); Anal. Calcd. for $C_{11}H_{16}O_3$; C, 67.32; H, 8.22. Found : C, 67.6; H, 8.2. These data are consistent with the assigned structure of 2-hydroxyadamantane-2-carboxylic acid.

Conversion of 2-Hydroxyadamantane-2-carboxylic acid-2-1'-^{14}C (III) to 2-Adamantanone-2-^{14}C (IV).

III (10.1 g, 0.051 mole) (specific activity 38.17 nCi/mgC) directly prepared from the benzylic acid rearrangement of II was added to 65 ml of benzene immediately forming a suspension. Over a period of 5 minutes 4.1 ml (0.057 mole) of thionyl chloride was carefully added. The resulting suspension was refluxed with stirring for three hours. A clear, faint yellow solution resulted. Evaporation of solvent and sublimation of the residue gave 7.1 g (0.047 mole, 92 %) of white crystals whose nmr was identical with 2-adamantanone [14] and which gave one peak by glc analysis. M.p. 284-285° C, lit. m.p. 285-286° C [14], specific activity 21.85 nCi/mgC.

Adamantane-2-^{14}C (V).

A mixture of 6.75 g (45 mM) of 2-adamantanone-2-^{14}C (IV), 8.6 g (150 mM) of potassium hydroxyde, 6.3 ml (165 mM) of 85 % hydrazine hydrate and 65 ml of diethylene glycol was heated in an oil bath at 100-120° C for 2.5 hours. The reflux condenser was then replaced by a wide-neck Claisen-type adapter equipped with a thermometer, reflux condenser and receiving flask. The temperature of the oil bath was gradually increased to 200° C as water and excess hydrazine hydrate were distilled off. The reaction was allowed to continue for 4 hours at 200-220° C as adamantane-2-^{14}C (V) sublimed onto the Claisen-type adapter. The sublimed product was dissolved in pentane and the pentane solution was washed twice with water and dried over $MgSO_4$. The solvent was evaporated at room temperature and 5.5 g (89 %) of crude adamantane-2-^{14}C (~90 % (V), 10 % (IV) by glc) was obtained. Unreacted 2-adamantanone-2-^{14}C (IV) was completely removed (glc) by recrystallization from acetone to yield 4.5 g (32 mM, 73 %) of glc-pure adamantane-2-^{14}C (specific activity 21.80 nCi/mgC) m.p. 268-269° C, lit. m.p. 269° C [15].

Active V and 20.0 g of inactive adamantane were dissolved in pentane. Evaporation of the solvent gave 24.4 g of diluted V (specific activity 3.83 nCi/mgC) which was used in all subsequent reactions.

1-Bromoadamantane-2 or 4-^{14}C (VI).

Following the procedure of Stetter *et al.* [8] 5.0 g (37 mM) of V were brominated with 4.3 g (27 mM) of bromine yielding, after sublimation, 7.5 g (34 mM, 92 %) of 1-bromoadamantane-2 or 4-^{14}C (VI); specific activity 3.81 nCi/mgC.

1-Methyladamantane-2 or 4-^{14}C (VII).

By a recently developed procedure [9], 7.5 g (34 mM) of VI and 34 ml of 3 M methylmagnesium bromide in ethyl ether were heated at 100° C for 25 minutes in a Fisher bomb apparatus, thus yielding 4.2 g (28 mM, 82 %) of 1-methyladamantane-2 or 4-^{14}C (VII); specific activity 3.52 nCi/mgC; glc analysis gave one peak and the nmr spectrum of the product was identical with that reported for 1-methyladamantane [16].

Kuhn-Roth Oxidation of 1-methyladamantane-2 or 4-^{14}C (VII).

In a typical experiment ca. 800 mg of 1-methyladamantane-^{14}C (VII) were oxidized with 50 ml of 2.5 M chromium trioxide and 12.5 ml conc. sulfuric acid at 155° C for 16.5 hours in a heavy glass walled ampoule. The ampoule contents were treated as previously reported [2] and yielded 600 mg of TlOAc m.p. 126-127° C, lit. p.m. 126.5-127.5° C [17]. The specific activity of the thallous acetate was shown to be 0.245 nCi/mgC.

Degradation of Thallous Acetate.

The method used for the degradation of TlOAc was an adaptation [17] of the method of Phares [18] based on the Schmidt reaction. Counting tubes were filled with the CO_2 obtained in the degradation. The specific activity of CO_2 was found to be 0.0398 nCi/mgC. The methylamine produced was assayed as N-phenyl-N'-methylthiourea which was found to have a specific activity of 0.0556 nCi/mgC.

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12. This figure 99.6 % was calculated as follows : 0.0394 nCi/mgC (CO_2 obtained from TlOAc) × 4 (number of bridgehead carbons)/38.2 nCi/mgC (spec. act. of the adamantane nucleus × 10) × 100 = 0.4 %.
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