Preparation of Ring-Labelled Adamantane Derivatives. I. 2-Adamantanecarboxylic Acid-2-^{14}C and 2-Methyladamantane-2-^{14}C

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Received March 10, 1970

SUMMARY

A relatively simple route to 2-substituted adamantane derivatives labelled with ^{14}C at the 2-position in the adamantane skeleton was developed. The approach used (Figure I) involved ring expansion of adamantanone by labelled diazomethane, conversion of the resulting 4-homoadamantanone (II) to diazoketone IV, followed by photolytic Wolff ring contraction to 2-adamantanecarboxylic acid-2-^{14}C (VI). Reduction of the carboxylic acid by conventional procedures gave 2-methyladamantane-2-^{14}C (IX).

INTRODUCTION.

Rearrangements involving the migration of substituents between the 1- and 2-positions of adamantane are more complicated than simple expectation suggests [1]. In order to study the mechanism of these processes, appropriately ring labelled adamantane compounds were required [1b]. Specifically, the synthetic objective described in this paper was the preparation of 2-methyladamantane-2-^{14}C (IX).

Two general methods which might give the desired compound appear to offer promise. The first was based on the total synthesis of 2-adamantanecarboxylic acid (VI) reported by Stetter, Held and Mayer [2]. This synthesis constructs the adamantane skeleton by condensation of the biseneamine of bicyclo [3.3.1] nona-2,6-dione with methyl dibromoacetate. A repetition of this synthesis using methyl dibromoacetate-2-^{14}C would eventually lead to 2-adamantanecarboxylic acid-2-^{14}C (VI). We were deterred from using

* Research performed under the auspices of the U. S. Atomic Energy Commission.

this route because of low yields and the number of steps involving the manipulation of labelled compounds.

Instead, an entirely different approach, starting with the adamantane skeleton already formed, was adopted. The required label was introduced by the ring enlargement-ring contraction sequence summarized in Figure 1.

As diazomethane homologation of adamantanone (I) to 4-homoadamantanone (II) had already been worked out in our laboratory [3], it was an easy matter to prepare labelled II using commercially available diazomethane-^{14}C precursor. Two ring contraction reactions were investigated. Use of the Favorskii rearrangement was frustrated by our inability to prepare the required precursor, 5-bromo-4-homoadamantanone in good yield. Monobromination of homoadamantanone is hard to effect; a considerable amount of dibromide is produced, and separation from the monobromide is difficult [4]. This route was abandoned in favor of a sequence based on the photolytic Wolff [5,6] ring contraction of diazoketone (IV). This rearrangement is known to proceed through intermediate ketene formation [6] (e.g., via V), and no label scrambling is expected.

In fact, irradiation of IV in basic aqueous tetrahydrofuran gave 2-adamantanecarboxylic acid-2-^{14}C (VI), readily isolated in pure form. The overall yield of VI from II was 23 %. Diazoketone (IV) was obtained as a yellow oil in two reaction steps from 4-homoadamantanone-5-^{14}C (II). Treatment of II with n-butyl nitrite and potassium *t*-butoxide produced 5-oximino-4-homoadamantanone-5-^{14}C (III), which was converted to IV by treatment with chloramine solution [6,7]. Reduction of 2-adamantanecarboxylic acid-2-^{14}C (VI) by the standard sequence shown in Figure 1 led to the desired 2-methyladamantane-2-^{14}C (IX).

The specific activities of II, VI, and IX were the same within the precision of the assay : 8.44, 8.51 and 8.52 nCi/mgC, respectively. The nmr and infrared spectra of all compounds were as anticipated and the physical properties of the labelled compounds agreed excellently with those of known unlabelled materials. Gas chromatographic analysis of 2-methyladamantane-2-^{14}C (IX) indicated a purity of over 99 %.

For this work, a sample of inactive 2-methyladamantane (IX) was prepared by a new route : a modified Wittig reaction on adamantanone [8], followed by Pd/C catalyzed hydrogenation of the resulting 2-methyleneadamantane. Active 2-methyladamantane (IX) was diluted with inactive material (resulting specific activity 0.69 nCi/mgC) and then subjected to the Kuhn-Roth oxidation [9]. The acetic acid formed was isolated as thallous acetate [10] (m.p. 126-7°); the specific activity observed (3.36 nCi/mgC) corresponded to 89 $\pm$ 2 % of the activity present in the starting material [(spec. act. T1OAc $\times$ 2/spec. act. diluted IX $\times$ 11) 100]. The thallous acetate was subjected to the Schmidt degradation; CO_2 with a specific activity of 6.62 nCi/mgC was produced. Methylamine, the second product, proved to be inactive within the limits of detection of the assay method. The carboxyl

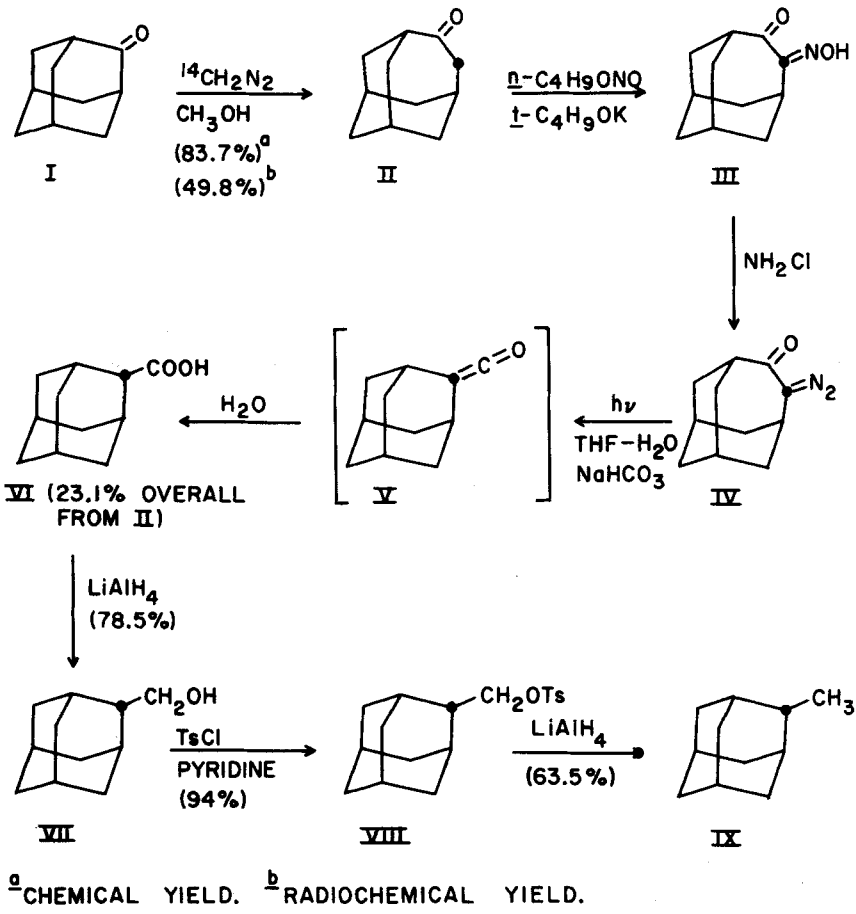
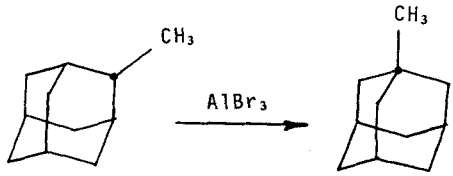


FIG. 1. Reaction sequence for preparation of 2-methyladamantane-2-^{14}C.

group is therefore shown to contain all of the activity within the error limits of the assay method. This proves that at least 89 % of the active carbon was indeed at the 2-position in IX. We were somewhat surprised that this value was not higher. However, the specific activity of the thallous acetate produced by Kuhn-Roth oxidation was found to vary somewhat (3.00-3.36 mCi/mgC, corresponding to 79-89 %) depending upon the oxidation conditions. It is possible, therefore, that the synthetic sequence led to 2-methyladamantane (IX) with virtually all of the radioactivity located at the 2-position, but some rearrangement occurred during the oxidation-degradation. This hypothesis was not established experimentally, since the labelled compounds prepared sufficed for our purposes.



IX X

We are reporting separately [1b] that the rearrangement of 2-methyladamantane-2-^{14}C (IX) by aluminum halide catalysis gives 1-methyladamantane-1-^{14}C (X) assaying for 90 % of the activity at position 1. Consequently, this rearrangement represents a route to 1-position labelled adamantanes.

Experimental part.

The activities of all samples reported were determined by combustion of each sample to CO_2 followed by counting the CO_2 in an internal counter after a 24 hour period of equilibration. Each value represents the average of three determinations. The precision of the method is $\pm$ 3 % (A.D.) on the value reported.

Homoadamantane-4-one-5-^{14}C (II). — Homoadamantane-4-one-5-^{14}C (specific activity 8.44 nCi/mgC) was prepared in 83.7 % yield (radiochemical yield 49.8 %) by the reported procedure [3] from adamantanone (I) (12.0 g, 80 mM) and diazomethane-^{14}C in methanolic KOH. Commercial Diazald-^{14}C (New England Nuclear Corporation) was used as the $^{14}CH_2N_2$ precursor. The active Diazald (150 nCi) was added to the suspension of adamantanone in the reaction medium together with the first half of the total amount of inactive diazald used (36 g, 168 mM). The product, II, after recrystallization from pentane, had m.p. 269-271° C, lit. m.p. 270-271° C [3] and analysis by glpc indicated a purity exceeding 98 %.

5-Oximino-4-homoadamantanone-5-^{14}C (III). — A solution of 10.7 g (65 mM) of II in 400 ml of *t*-butanol (distilled from CaH_2) was added to a stirred solution of 38.5 g (343 mM) of potassium *t*-butoxide in 235 ml of dry *t*-butanol. While maintaining a nitrogen atmosphere, n-butyl nitrite was added dropwise in two portions (15.0 g, 145 mM initially and 6.5 g, 63 mM 90 minutes later). The stirring was continued for an additional 2.5 hours under nitrogen; 2 l of water was then added and the solution acidified to pH 6 with 5 N hydrochloric acid. Extraction was carried out with a 1 l and three 0.5 l portions of ether; these combined ether extracts were washed with two 300 ml portions of saturated aqueous $NaHCO_3$ solution, 650 ml of saturated aqueous NaCl solution and finally with 350 ml of saturated

aqueous NH_4Cl solution. After drying over Na_2SO_4, the ether solution was evaporated on a rotary evaporator yielding 12.5 g (99 %) of a crude, yellowish solid. The crude product was used directly in the next step since the purification leads to considerable loss of material. Ir (Nujol): 3.1, 5.8, 6.2 μ bands characteristic of α-oximinoketones [6b,c,e].

5-Diazo-4-homoadamantanone-5-^{14}C (IV). — This compound was obtained as a stable oil by a modification of Forster's [7] procedure for the conversion of oximoketones to diazoketones by treatment with chloramine produced *in situ*. To a solution of 12.5 g (64.5 mM) of III in 90 ml of tetrahydrofuran was added 1300 ml of ether, 70 ml of 5 N NaOH and 110 ml of 58 % aqueous NH_4OH solution. The reaction mixture was stirred under a nitrogen atmosphere and treated with three 120 ml portions of 6 % sodium hypochlorite solution injected through a syringe cap at 1.5 h intervals. After 5 hours total reaction time the aqueous layer was separated and extracted with three 150 ml portions of ether. The ether layer was combined with these ether extracts; after drying with Na_2SO_4, evaporation *in vacuo* yielded 8 g of a wet, yellow oil. The infrared spectrum (neat) displayed bands at 4.8 and 6.1 μ, characteristic of α-diazoketones [6b-e,11]. This crude diazoketone was used in the next step directly without further purification, in order to conserve material.

2-Adamantanecarboxylic Acid-2-^{14}C (VI). — Crude diazoketone (IV) (8 g) was dissolved in 750 ml of tetrahydrofuran and a solution of 1.9 g of $NaHCO_3$ in 250 ml water was added. Irradiation was effected under a nitrogen atmosphere at 15° C using a 550 w Hanovia medium-pressure lamp (quartz insert). After two hours, the irradiation was stopped. Solid $NaHCO_3$ was added in small portions until two layers separated. After evaporation of two thirds of the organic layer, 200 ml pentane was added and the resulting solution was extracted with two 250 ml and three 100 ml portions of saturated aqueous $NaHCO_3$ solution. The combined $NaHCO_3$ extracts were washed with two 100 ml pentane portions and acidified with 5 N hydrochloric acid (to pH 3). Liberated acid (a white fluffy precipitate) was extracted with two 200 ml and three 100 ml portions of ether. The combined extracts were dried over Na_2SO_4. Evaporation of the solvent yielded a yellowish solid which, after recrystallization from methanol, gave 2.7 g (15 mM) of VI; m.p. 141-143° C, lit. m.p. 143.5-144.5° C [2]. The overall yield based on II was 23.1 %. Specific activity: 8. 51 nCi/mgC. The nmr, ir and mass spectra were identical to those of an authentic sample [2,*].

(2-Adamantyl-2-^{14}C)-carbinol (VII). — (2-Adamantyl-2-^{14}C)-carbinol was obtained in 78.5 % yield by lithium aluminum hydride (0.76 g, 20 mM)

* The sample (obtained by a different route) was kindly supplied by B. Bentley and S. H. Liggero.

reduction of VI (2.0 g, 11.1 mM) in anhydrous ether. m.p. 93-95° C, lit. m. p. 94.9-95.8° C [12].

(2-Adamantyl-2-^{14}C)-carbinyl tosylate (VIII). — This tosylate was prepared in 94 % yield from VII by the usual tosylation procedure.

2-Methyladamantane-2-^{14}C (IX). — To a stirred suspension of 1.0 g (26.3 mM) of lithium aluminum hydride in 50 ml of dry ether was added dropwise an ether solution of 2.65 g (8.2 mM) of VIII over a period of 30 minutes. The mixture was stirred overnight at gentle reflux. First 50 ml of pentane was added followed by an excess of 10 % aqueous H_2SO_4 solution. The aqueous layer was separated and was extracted with three 40 ml portions of pentane. These extracts, combined with the organic layer, were washed with two 30 ml portions of saturated aqueous $NaHCO_3$ solution, and two 30 ml portions of water. After drying the extract over Na_2SO_4, the solution was passed through 10 g of neutral alumina (activity 1). The solvent was distilled through a Vigreux column and the residue sublimed *in vacuo* (4 mm) at 70-80° C to give 780 mg (63.5 %) of white, waxy, crystals, m.p. 144-146° C, lit. m.p. 143.8-146.0° C [13]. Gas chromatography showed the purity of the 2-methyladamantane (IX) so formed to be greater than 99 %. Specific activity: 8.52 nCi/mgC. Nmr, ir and mass spectra were identical to those of authentic 2-methyladamantane prepared as described below.

2-Methyleneadamantane (XI). — This compound was prepared from adamantanone (I) following a procedure [8a] based on a modified Wittig reaction [8b]. Sodium hydride (5.9 g, 0.14 M as a 56 % dispersion in mineral oil) was washed in the reaction flask with several portions of pentane to remove the mineral oil. A nitrogen atmosphere was maintained during the entire preparation. Dimethyl sulfoxide (75 ml, freshly distilled from CaH_2) was introduced *via* syringe, and the resulting mixture was stirred for *ca.* 1 hour at 70-80° C. The mixture was then cooled to room temperature and 52.5 g (0.13 M) of methyltriphenyl phosphonium iodide was added in 125 ml of dry dimethyl sulfoxide. To the resulting bright yellow-green solution, 15.0 g (0.1 M) of adamantanone (I) (dried over P_2O_5 *in vacuo*) in 125 ml of warm dry dimethyl sulfoxide was added. The mixture was stirred for 20 hours at 57-59° C, then poured into 175 ml of water and extracted with two 200 ml and three 100 ml portions of pentane. These extracts were washed with two 150 ml portions of a 1 : 1 water-dimethyl sulfoxide solution and two 150 ml portions of 50 % saturated aqueous NaCl solution. The pentane layer was then dried over Na_2SO_4 and passed through 75 g of neutral alumina (activity 1). The alumina was eluted with pentane until no more solid was obtained. The solvent was removed through a Vigreux column and the residue was sublimed *in vacuo* (4 mm) at 70-75° to give 10.5 g (70.8 %) of 2-methyleneadamantane (XI) (purity $\geqslant$ 99 % by glpc). M.p. 134-136° C, lit. m.p. 135.8-136 5°C. [13].

2-Methyladamantane (X). — 2-Methyladamantane was obtained in 96.5 % yield by Pd/C (1 g) catalyzed hydrogenation of XI (9.0 g, 60.7 mM) under atmospheric pressure at 0° C. Methyl formate (150 ml) was used as the solvent. Gas chromatographic analysis indicated a purity greater than 99 %; m.p. 145-146° C (lit. m.p. 143.8-146.0° C) [13].

Kuhn-Roth Oxidation [9]. — Active IX was diluted with inactive carrier [SA 0.69 nCi/mgC (*ca.* 450 mg, 3 mM)] and 50 ml of aqueous CrO_3-H_2SO_4 solution (see below) were sealed in heavy glass-walled ampoules (3 × 30 cm) and heated for 4.5-20 hours. The concentrations of CrO_3 and H_2SO_4, the reaction times, and the temperatures were varied as shown in the table. At the end of the reactions, the ampoules were cooled in dry ice-acetone baths until freezing began then opened carefully. The black solution which resulted was neutralized with 1/1 hydrazine hydrate-water mixture at 0° C and then steam distilled. Approximately 500-800 ml of distillate was collected. Titration of this distillate with 0.1 N aqueous TlOH solution to the phenolphtalein end point converted the acetic acid to its thallium salt [10]. A white solid was recovered by evaporating the aqueous solution to dryness on a rotary evaporator. This solid was extracted with five 3-ml portions of boiling ethanol. The insoluble material was separated by centrifugation, and the mother liquor was evaporated to near dryness by a gentle flow of nitrogen. The resulting precipitate was recrystallized twice from ethanol, then dried over P_2O_5 *in vacuo* at 64° C. This gave yields on the order of 200-300 mg of pure TlOAc, m.p. 126-127° C, lit. m.p. 126.5-127.5° C [14]. The specific activity of TlOAc varied with changes in the reaction conditions. See Table 1.

TABLE 1. Variation in thallous acetate activity with varying reaction conditions.

TlOAC (nCi/mgC)	[CrO_3] (mol/l.)	[H_2SO_4] (mol/l.)	Temp. (° C)	Reaction Time (h)
3.00	2.0	3.7	152	20
3.22	4.4	2.1	152	4.5
3.36	4.4	2.1	122	9.0

Degradation of Thallous Acetate. — The method used for the degradation of TlOAc was a modification [14] of Phares' method [15] based on the Schmidt reaction. Counting tubes were filled with the CO_2 obtained from the decarboxylation of thallous acetate. The methylamine was assayed as the N-phenyl-N′-methyl-iso-thiourea derivative.

ACKNOWLEDGMENTS.

The authors wish to express their thanks and appreciation to Dr D. R. Christman for carrying out the carbon-14 activity determinations and Miss C. S. Redvanly for carrying out the micro Schmidt degradations.

REFERENCES

1. (a) SCHLEYER, P. V. R. — *Angew. Chem.*, **81** : 539 (1969); (b) MAJERSKI, Z., WOLF, A. P. and SCHLEYER, P. V. R. — In press.
2. STETTER, H., HELD, H. and MAYER, J. — *Ann.*, **658** : 151 (1962).
3. SCHLEYER, P. V. R., FUNKE, E. and LIGGERO, S. H. — *J. Am. Chem. Soc.*, **91** : 3965 (1969).
4. LIGGERO, S. H. — Unpublished observations.
5. WOLFF, L. — *Ann.*, **394** : 25 (1912).
6. (a) HORNER, L. and SPIETSCHKA, E. — *Ber.*, **88** : 934 (1955); (b) MEINWALD, J. and GASSMAN, P. G. — *J. Am. Chem. Soc.*, **82** : 2857 (1960); (c) MATEOS, J. L., CHAO, O. and FLORES, H. — *Tetrahedron*, **19** : 1051 (1963); (d) CAVA, M. P., LITTLE, R. L. and NAPIER, D. R. — *J. Am. Chem. Soc.*, **80** : 2257 (1958); KIRMSE, W. — *Angew. Chem.*, **69** : 106 (1957); (e) CAVA, M. P. and VOGT, B. R. — *J. Org. Chem.*, **30** : 3775 (1965); *Tetrahedron Ltrs.*, 2813 (1964).
7. FORSTER, M. O. — *J. Chem. Soc.*, **107** : 260 (1915).
8. (a) FRY, J. L. — Unpublished results; (b) COREY, E. J. and CHAYKOVSKY, M. — *J. Am. Chem. Soc.*, **84** : 866 (1962); GREENWALD, R., CHAYKOVSKY, M. and COREY, E. J. — *J. Org. Chem.*, **28** : 1128 (1963).
9. KUHN, R. and ROTH, H. — *Ber.*, **66** : 1274 (1933); KIRSTEN, W. and STENHAGEN, E. — *Acta Chem. Scand.*, **6** : 682 (1952); FRANCK, B. and KNOKE, J. — *Ber.*, **95** : 579 (1962).
10. WALTER, R. — *Ber.*, **59** : 962 (1926).
11. YATES, P., SHAPIRO, B. L., YODA, N. and FUGGER, J. — *J. Am. Chem. Soc.*, **79** : 5756 (1957); BOSE, A. K. and YATES, P. — *J. Am. Chem. Soc.*, **74** : 4703 (1952).
12. BURKHARD, J., VAIS, J. and LANDA, S. — *Z. Chem.*, **9** : 29 (1969).
13. SCHLEYER, P. V. R. and NICHOLAS, R. D. — *J. Am. Chem. Soc.*, **83** : 182 (1961).
14. WOLF, A. P., REDVANLY, C. S. and ANDERSON, R. C. — *J. Am. Chem. Soc.*, **79** : 3717 (1957).
15. PHARES, E. F. — *Arch. Biochem. Biophys.*, **33** : 173 (1951).