[CONTRIBUTION FROM THE CHEMISTRY DIVISION OF OAK RIDGE NATIONAL LABORATORY]

Carbon-14 Synthetic Studies. 2-Methyl-1,4-naphthoquinone-8-C^{14} [1,2]

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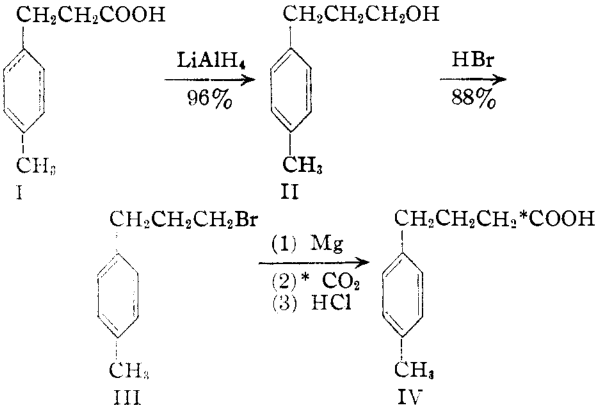
2-Methyl-1,4-naphthoquinone-8-C^{14} has been synthesized from 4-(*p*-tolyl)-butanoic-1-C^{14} acid. The acid has been prepared by a new method, involving carbonation with carbon-C^{14} dioxide of β-(*p*-tolyl)-propylmagnesium bromide. The over-all yield, based on carbon dioxide, was 25%. An apparatus useful for the carbonation of Grignard reagents with carbon-C^{14} dioxide of high specific activity is described.

Introduction

The antihemorrhagic properties of 2-methyl-1,4-naphthoquinone are well known. Because of the interest in this compound, a synthesis in which carbon-14 is incorporated in the 8-position has been effected, utilizing conventional procedures, and starting with 4-(*p*-tolyl)-butanoic-1-C^{14} acid (IV). The latter compound has been prepared by a new method.



β-(*p*-Tolyl)-propyl bromide (III) was prepared by the reaction series (I → II → III). The carbonation with C^{14}O$_2$ of the Grignard reagent prepared from the bromide (III) proceeded in yields of 85–95% at temperatures below −40°, but the yields were reduced at higher temperatures, and when temperatures above −20° were employed, the main product consisted of nonacidic material. Ring closure of the acid (IV)[3] was followed by reduction[3,4] and dehydrogenation[5] to yield 2-methylnaphthalene-8-C^{14}. Chromic acid oxidation[6] of the hydrocarbon produced 2-methyl-1,4-naphthoquinone-8-C.^{14}

Experimental

β-(*p*-Tolyl)-propyl Alcohol (II).—Utilizing the procedure of Nystrom and Brown[7] for ether-insoluble acids, 10.5 g. of acid (I),[8] m.p. 117–118°, yielded 9.13 g. of liquid carbinol (96.2%), after distillation *in vacuo;* boiling point of II, 248–250° at 741 mm. Although several attempts were made at purification, consistent carbon and hydrogen analyses could not be obtained. The *p*-nitrobenzoate melted at 58.2–59.0° (cor.).

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.2; H, 5.7. Found: C, 67.97, 68.11; H, 5.42, 5.70.

β-(*p*-Tolyl)-propyl Bromide (III).—The procedure employed was analogous to that described for *n*-dodecyl bromide,[9] 8.72 g. of alcohol yielding 9.90 g. of liquid β-(*p*-tolyl)-propyl bromide (III) (88.3%) after distillation under high vacuum. Boiling point of III, 210–213° at 741 mm. pressure; n^{27}_{D} 1.5362.

Anal. Calcd. for $C_{10}H_{13}Br$: Br, 37.6. Found: Br, 37.78, 37.48.

4-(*p*-Tolyl)-butanoic-1-C^{14} Acid (IV).—The carbonation apparatus shown in Fig. 1 was used for this reaction.[10] In flask B was placed 0.90 g. of magnesium turnings, 25 ml. of dry ether and 5.0 ml. (6.37 g.) of β-(*p*-tolyl)-propyl bromide (III). A chloroform–carbon tetrachloride mixture was added to powdered Dry Ice in the reflux condenser D (the fitting S, for cold water reflux, was removable). Dry Ice-baths surrounded traps K and L. Trap M contained Drierite. A half-concentrated barium hydroxide solution was drawn into the chamber G through the sintered glass disc at F. Six (6.00) grams of BaC^{14}O$_3$ and 5 ml. of distilled water had previously been placed in flask A. The length of the capillary inlet tube was such that it did not at this time extend below the surface of the aqueous suspension. The entire apparatus was swept with dry helium gas, which was introduced through inlets P and T and a positive pressure of helium was maintained throughout the experiment. A Mariotte bottle connected to the outlet at 10 maintained a slight negative pressure at this point. Stopcock 5 was closed to flask B, and stopcock 8 was open to B and M. Stopcocks 6, 9 and 11 were closed. A hot-water-bath was then raised about flask B, and the Grignard reaction started immediately. It was vigorously stirred by means of a magnetic bar, and refluxed for 1 hour, at which time the stopcock 8 was closed to M and opened to B and L, and the hot-water-bath was replaced with a Dry Ice–carbon tetrachloride–chloroform-bath adjusted to a temperature of −40 to −45°. Below this temperature, the Grignard reagent precipitated. Keeping a positive pressure of helium at P, stopcock 1 was opened, and stopcock 4 was opened to A and K. Stopcock 8 was opened, and stopcock 5 was opened to K and B. The barium carbonate in flask A was then slowly decomposed (one-half hour) with 5 *M* perchloric acid, by addition through stopcock 2, and the mixture was agitated with a magnetic stirring bar. The carbon dioxide-addition product in flask B began to precipitate almost immediately. During an early experiment, the temperature of the bath surrounding flask B was allowed to rise momentarily to −20°, at which temperature the precipitate completely dissolved, and the yield was considerably decreased. Carbon dioxide not absorbed by the Grignard solution was trapped in the barium hydroxide bubbler G. After the barium carbonate was completely decomposed, the sweep was continued an additional 5 minutes, with the mechanical stirrer still in operation, and 50 ml. of an aqueous solution containing 7 ml. of concentrated phosphoric acid was slowly added through the funnel, C, until the ether level rose to the inlet tube to flask E. The Dry Ice-bath surrounding flask B was removed to prevent freezing of the water. The mixture

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[1] This document is based upon work performed for the Atomic Energy Commission at the Oak Ridge National Laboratory.

[2] Presented before the Division of Organic Chemistry at the 115th meeting of The American Chemical Society, San Francisco, California, March, 1949.

[3] F. Krollpfeiffer and W. Schafer, *Ber.*, **56**, 620 (1920).

[4] K. Kindler and Dschi-Yin Kwok, *Ann.*, **554**, 9 (1943).

[5] R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

[6] L. F. Fieser, W. P. Campbell, E. M. Fry and M. D. Gates, THIS JOURNAL, **61**, 3218 (1939).

[7] R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 2548 (1947).

[8] The β-(*p*-tolyl)propionic acid was prepared by a normal pressure hydrogenation with 3% palladium-on-carbon catalyst of *p*-methylcinnamic acid. This compound was kindly supplied by Professor W. G. Brown of the University of Chicago.

[9] E. E. Reid, J. R. Ruhoff, and R. E. Burnett, "Organic Syntheses," Coll. Vol. II, p. 246, John Wiley and Sons, New York, N. Y., 1943.

[10] This apparatus (Fig. 1) was designed for the carbonation of Grignard reagents with C^{14}O$_2$ in levels of radioactivity up to 20 mc., and could be used, if necessary, for much higher levels. For carbonation experiments with tracer amounts of carbon-14, a more conventional apparatus is entirely suitable.

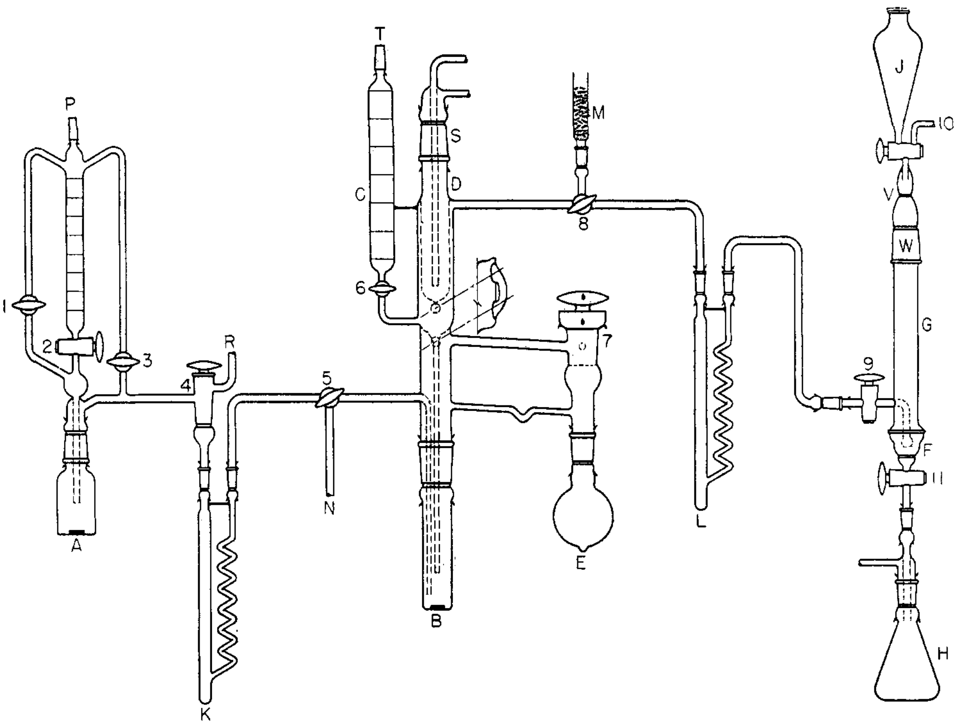

Fig. 1.—Grignard carbonation apparatus: A, carbonate decomposition flask; B, Grignard flask; C, acid funnel; D, reflux condenser; E, ether flask; F, sintered glass funnel; G, $Ba(OH)_2$ bubbler; H, filter flask; J, water funnel; K and L, Dry Ice traps; M, Drierite; N, waste outlet; P, helium inlet; R, emergency outlet; S, removable joint; T, helium inlet; V, sintered glass frit; W, removable joint.

was allowed to warm to room temperature, and the helium sweep was continued 1 hour, during which time a considerable amount of carbon dioxide was recovered from the hydrolysis mixture. Stopcock 9 was closed, and 5 was closed to B. Stopcock 8 was opened to B and M. The stopcock 7 was opened and ether, which had been placed in flask E prior to the experiment, was allowed to reflux gently, effecting for 4 hours a continuous extraction of the product in flask B. The residue in flask B was removed through N. The ether solution was concentrated to a colorless oil which solidified on standing. To this solid was added 75 ml. of saturated sodium bicarbonate solution, and the mixture was stirred with a magnetic stirring bar for 1 hour. The aqueous solution was washed with 3–5-ml. portions of ether using the extractor described previously.[11] The bicarbonate layer was acidified with 20 ml. of concentrated hydrochloric acid, and the white precipitate was removed by a continuous ether extraction. Concentration and desiccation yielded 2.60 g. of crude 4-(*p*-tolyl)-butanoic-1-C^{14} acid (IV), melting 54–55° (softening 51°).[3] Since 2.62 g. of barium carbonate was recovered from the bubbler, after aeration for 4 hours with carbon dioxide-free air, the yield of acid based on unrecovered $BaC^{14}O_3$ was 85.5%. During the aeration, the solution in bubbler G was heated with an infrared lamp. (Several model runs with β-phenylpropyl bromide yielded 90–96% phenylbutyric acid.) Recrystallization from petroleum ether gave white plates melting sharply at 57.5–59°.

Anal. 485 microcuries carbon-14 per millimole.

2-Methyl-1,4-Naphthoquinone-8-C^{14}.—Ring closure of the acid chloride prepared from 1.26 g. of crude acid (IV) was effected using the stannic chloride method of Bachmann and Thomas.[12] The product, obtained in 91% yield, was reduced by the method of Kindler[4] in 85–90% yield to produce 7-methyl-1,2,3,4-tetrahydronaphthalene-1-C^{14}. This hydrocarbon was dehydrogenated with 30% palladium-on-carbon catalyst[5,13] to yield 0.57 g. of 2-methylnaphthalene-8-C^{14}. A portion of this hydrocarbon was diluted with 2-methylnaphthalene and oxidized with chromic oxide to the desired 2-methyl-1,4-naphthoquinone-8-C^{14}. The yield was 3.52 g. (52–55%), melting at 104–105.5°.

Anal. 35.9 microcuries carbon-14 per millimole.

Reductive acetylation yielded a diacetate, m.p. 109.5–111.5°.

Anal. 36.1 microcuries carbon-14 per millimole.

Analytical Determinations.—Radioactive assays were carried out as previously described.[11] Microanalyses were performed by the Oakwold Laboratories, Alexandria, Virginia.

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[11] C. J. Collins, THIS JOURNAL, **70**, 2419 (19 8).

[12] W. E. Bachmann and D. G. Thomas, *ibid.*, **64**, 94 (1942).

[13] N. D. Zelinski and M. B. Turowa-Pollak, *Ber.*, **58**, 1295 (1935).