

SYNTHESIS OF 1,5,9-CYCLODODECATRIENE- x - $^{14}\text{C}_6$

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SUMMARY

A small-scale synthesis of 1,5,9-cyclododecatriene- x - $^{14}\text{C}_6$ is described. 1,3-Butadiene-1,4- $^{14}\text{C}_2$, specific activity of 1.15 mCi/mmmole, was prepared via the thermal decomposition of tetramethylene-1,4- $^{14}\text{C}_2$ -bis-(trimethylammonium hydroxide) and immediately converted to a mixture of stereoisomers of 1,5,9-cyclododecatriene- x - $^{14}\text{C}_6$ using a Ziegler catalyst prepared in situ. The overall radiochemical yield was 15% (based on K^{14}CN).

Key words: 1,5,9-Cyclododecatriene- x - $^{14}\text{C}_6$, 1,3-Butadiene-1,4- $^{14}\text{C}_2$

INTRODUCTION

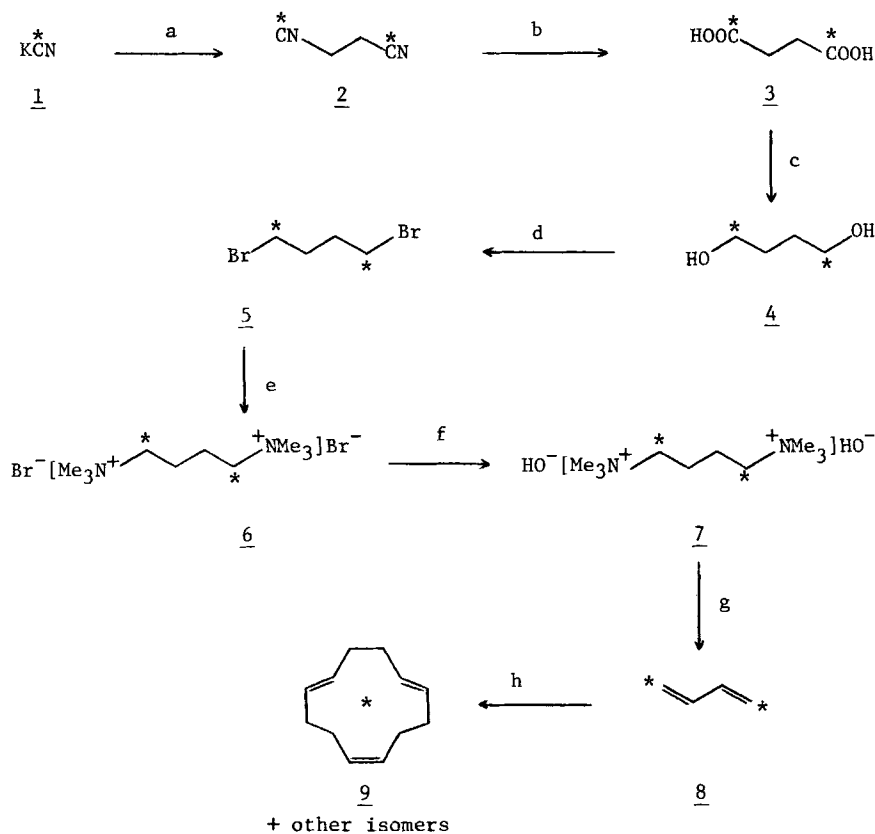
1,5,9-Cyclododecatriene has proven to be an important intermediate in the synthesis of a continuously increasing number of organic compounds which are difficult to obtain by other methods [1]. The need for ^{14}C -labeled 1,5,9-cyclododecatriene and 1,2,5,6,9,10-hexabromocyclododecane (a known flame retardant) for environmental and/or related studies prompted our investigation aimed at defining an efficient small-scale radiochemical synthesis route for the title compound. The results of this work are reported below.

DISCUSSION

The synthesis route utilized for the preparation of 1,5,9-cyclododecatriene- x - $^{14}\text{C}_6$, **9**, from K^{14}CN is based on procedures described in the literature for the nonlabeled analogs and is depicted in Scheme I. Trimerization of 1,3-butadiene-1,4- $^{14}\text{C}_2$ would appear to give 1,5,9-cyclododecatriene-3,4,7,8,11,12- $^{14}\text{C}_6$. However, once double bond isomerization under the reaction conditions (Ziegler catalyst- $\text{Et}_2\text{AlCl/TiCl}_4$) cannot be ruled out, we feel the notation of choice is 1,5,9-cyclododecatriene- x - $^{14}\text{C}_6$.

Succinic-1,4- $^{14}\text{C}_2$ acid, **3**, was prepared in 93% yield by the hydrolysis of succinonitrile-1,4- $^{14}\text{C}_2$, **2** [2], which, in turn, was prepared from K^{14}CN and 1,2-dibromoethane. The conversion of **3** to 1,4-butanediol-1,4- $^{14}\text{C}_2$, **4**, was then

Scheme I



a 1,2-Dibromoethane, EtOH, Δ ; b conc. HCl, reflux; c B_2H_6 , THF; d HBr conc., 95° ; e NMe_3 in EtOH, reflux; f Ag_2O ; g $160\text{--}250^\circ$; h Ziegler catalyst

accomplished in 92% yield by treating 3 in THF with a diborane-THF solution according to the procedure of H. C. Brown et al. [3]. Conversion of 4 to 1,4-dibromobutane-1,4- $^{14}\text{C}_2$, 5, was achieved in 80% yield by simply refluxing 4 in 48% hydrobromic acid.

The synthesis of 1,3-butadiene-1,4- $^{14}\text{C}_2$, 8, and 1,5,9-cyclododecatriene-x- $^{14}\text{C}_6$ in millimole quantities presented some special problems. That is, procedures had to be developed which would allow handling and recycling of small

amounts of $\underline{8}$, such that a maximum yield of $\underline{9}$ could be obtained, as well as to avoid or minimize the radiation-induced linear polymerization of $\underline{8}$ [4]. Thus, $\underline{5}$ was converted to $\underline{8}$, having a specific activity > 1 mCi/mmole, in 59% yield utilizing an adaptation of the method of Mann and Nystrom [5]. Subsequent trimerization of $\underline{8}$ at atmospheric pressure using a Ziegler catalyst, prepared *in situ* [6], gave a 64% yield of a mixture of stereoisomers of 1,5,9-cyclododecatriene- x - $^{14}\text{C}_6$, containing 98% of the trans-trans-cis-isomer and 2% of the all-trans isomer.

EXPERIMENTAL

Potassium cyanide- ^{14}C was purchased from Amersham Corporation, Chicago, Illinois. Radioactivity was determined by means of a Packard Model 2425 liquid scintillation counter using Liquifluor (New England Nuclear). Radiochemical purity was determined by autoradiography and radiochromatogram scanning of TLC plates. Radiochromatogram scans were obtained using a Packard Model 7201 radiochromatogram scanner. Analytical standards were used for comparison on TLC or GLC with the ^{14}C -labeled compounds prepared as additional proof of their identity. Silica gel plates (Brinkman 60F-254) were used for TLC utilizing one of the following systems as the developing solvent: (a) benzene:acetic acid (9:1); (b) ethanol:ammonium hydroxide:water (80:16:4). The GLC analyses were performed using a Varian 2400 gas chromatograph equipped with a flame-ionization detector and temperature programming.

Succinonitrile-1,4- ^{14}C , $\underline{2}$

A mixture of dibromoethane (1.878 g, 10 mmole) and ethanol (6.5 ml) was heated to boiling, after which a concentrated solution of K^{14}CN (0.347 g, 5.32 mmole, 250 mCi) in 0.8 ml of water was added dropwise with stirring. Heating was continued for 4 hr, and nonradioactive potassium cyanide (1.08 g, 16.6 mmole dissolved in 2.5 ml of water) was added. The reaction mixture was refluxed for a total of 48 hr and the progress of the reaction was followed by TLC (solvent system a). After cooling to room temperature the liquid was decanted from the KBr crystals, and the solid was washed with a total of 30 ml of ethanol. The

combined liquid and ethanol washes were evaporated, yielding 242 mCi (9.6 mmole) of crude succinonitrile-1,4- $^{14}\text{C}_2$.

Succinic-1,4- $^{14}\text{C}_2$ Acid, $\underline{3}$

The crude $\underline{2}$ (9.6 mmole, 242 mCi) was refluxed in 4 ml of conc. HCl for 20 hr. After cooling, the reaction mixture was transferred with a total of 10 ml of water into a liquid-liquid extractor. Continuous ether extraction for 4 days followed by evaporation of the solvent (*in vacuo*) gave 1.096 g (9.28 mmole, 231 mCi) of succinic-1,4- $^{14}\text{C}_2$ acid. The radiochemical purity ($\geq 98\%$) was established by TLC radiochromatogram scanning (solvent system b), $R_f = 0.5$.

1,4-Butanediol-1,4- $^{14}\text{C}_2$, $\underline{4}$

Commercial diborane, 1 molar solution in THF (25 ml, 25 mmole) was added over a period of 15 min to a solution of $\underline{3}$ (1.096 g, 9.28 mmole, 231 mCi) in 10 ml of THF (freshly distilled from LAH). After the addition was completed, the reaction mixture was allowed to warm up to room temperature during 1 hr. TLC analysis of the crude reaction mixture (solvent system b) showed complete conversion of the acid ($R_f \sim 0.5$) to the corresponding diol ($R_f = 0.8$). The reaction mixture was carefully treated with 2 ml of a 1:1 mixture of THF:water at 0° followed by addition of ~ 2 g of solid potassium carbonate. Continuous ether extraction of the resulting aqueous mixture afforded 0.768 g (8.52 mmole, 213 mCi) of $\geq 98\%$ pure 1,4-butanediol-1,4- $^{14}\text{C}_2$.

1,4-Dibromobutane-1,4- $^{14}\text{C}_2$, $\underline{5}$

A mixture of $\underline{4}$ (0.768 g, 8.52 mmole, 213 mCi) and 12 ml of 48% hydrogen bromide was stirred at 95° for 5 hr. The product was extracted with ether and dried over KOH pellets, yielding 1.47 g (6.8 mmole, 170 mCi) of $\geq 98\%$ pure 1,4-dibromobutane-1,4- $^{14}\text{C}_2$. The purity of $\underline{5}$ was determined by GLC (column: 20% SP-2100/0.1% Chromosorb W, 10 ft x 1/8 in.; column temperature: 115° ; detector temperature: 205° ; injector temperature: 185° ; helium gas flow: 35 ml/min).

Tetramethylene-1,4- $^{14}\text{C}_2$ -bis-(trimethylammonium bromide), $\underline{6}$

A portion of $\underline{5}$ (4.32 g, 20 mmole, 23 mCi) was mixed with 30 ml of absolute ethanol which had been saturated at 10° with anhydrous trimethylamine. The resulting reaction mixture was refluxed for 2 hr under anhydrous conditions and

left overnight at room temperature. Absolute ether (100 ml) was subsequently added to the reaction mixture to precipitate the quaternary salt. The mother liquor was removed by decantation and the solid was washed with dry ether (3 x 50 ml). The yield of tetramethylene-1,4- $^{14}\text{C}_2$ -bis-(trimethylammonium bromide) was 5.38 g (16.1 mmoles, 18.4 mCi).

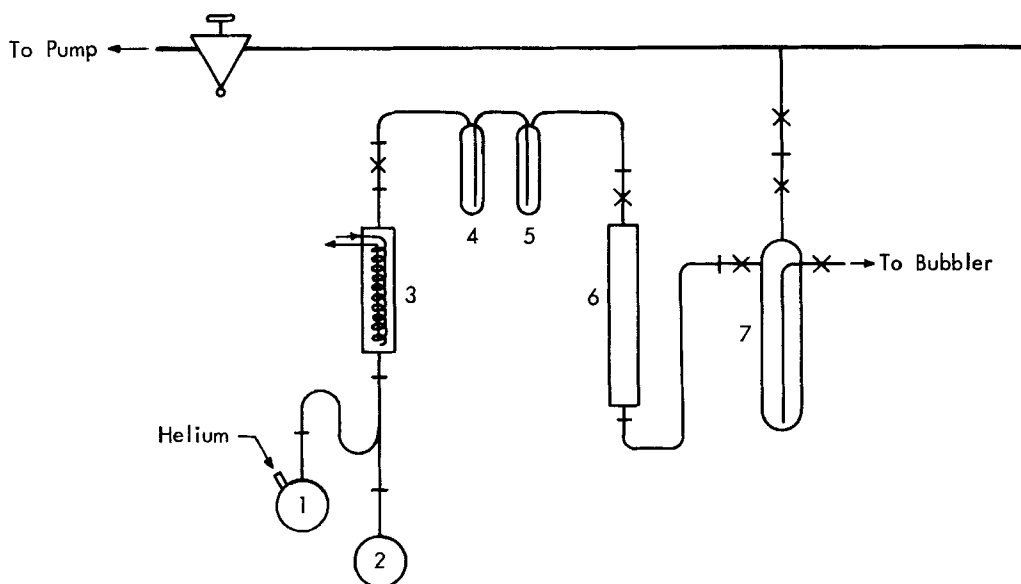
Tetramethylene-1,4- $^{14}\text{C}_2$ -bis-(trimethylammonium hydroxide), 7

A solution of 7.4 g of silver nitrate in 74 ml of water was heated to 85° and treated with an equally warm solution of 1.7 g of sodium hydroxide in 74 ml of water. The precipitated silver oxide was washed with six portions of hot water and used without further purification.

The diquaternary bromide, 6 (5.38 g, 16.1 mmole, 18.4 mCi), was dissolved in 38 ml of water and then added at room temperature with vigorous stirring to a suspension of the silver oxide in 15 ml of water. After 0.5 hr, the resulting precipitate was filtered and washed with three 10-ml portions of water. The filtrates were collected (75 ml total volume) and assayed, indicating a yield of 16.4 mCi (14.3 mmoles) of tetramethylene-1,4- $^{14}\text{C}_2$ -bis-(trimethylammonium hydroxide), which was immediately taken to the next step.

1,3-Butadiene-1,4- $^{14}\text{C}_2$, 8

The thermal decomposition of 7 was carried out by using the high-vacuum manifold apparatus depicted in Figure 1. The aqueous solution of 7 (14.3 mmole, 16.4 mCi) was transferred into flask (1) (100 ml capacity, equipped with a side-arm, septum, and stirring bar). Helium flow was established via a needle in (1) in order to sweep the whole system from (1) through the trap (7) which was cooled with liquid nitrogen. Further, heat was applied to the flask (1) by means of an oil bath maintained at 160°. Most of the water distilling out of flask (1) was removed from the gas stream by a cold water condenser (3) and/or trapped in the flask (2) while the trimethylamine evolved was absorbed by bubbling through 2 N sulfuric acid contained in trap (5). Finally, the last traces of water were removed by passing through a column filled with indicating Drierite, and the resulting dry 1,3-butadiene-1,4- $^{14}\text{C}_2$ was condensed in trap (7). As the decomposition proceeded, the temperature was allowed to rise to 250° and the reaction was



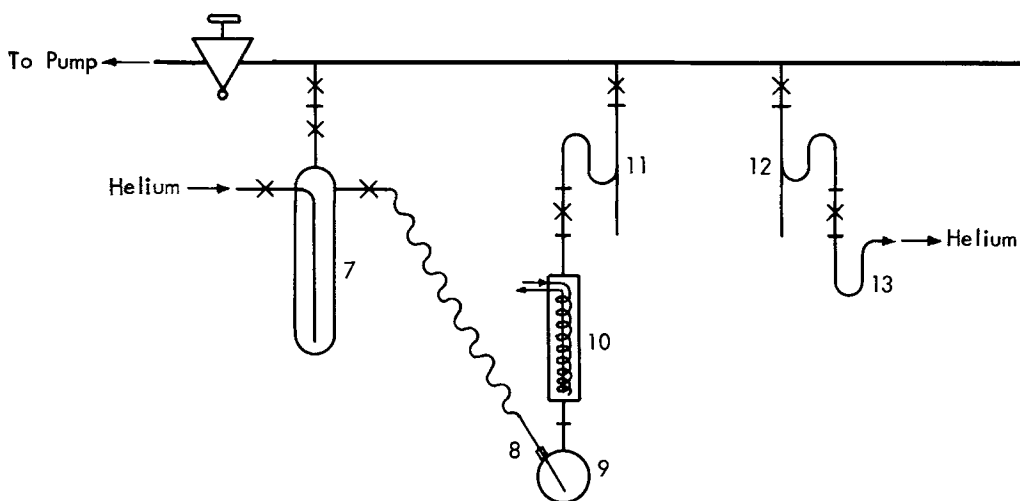
Legend:

- 1 - Reaction flask with side arm and septum
- 2 - Flask for collection of water
- 3 - Reflux condenser
- 4 - Empty trap
- 5 - Trap with 2N H₂SO₄
- 6 - Drying column with indicating Drierite
- 7 - 250ml collection trap for 1,3-butadiene - (1,4 - ¹⁴C₂)

Figure 1 - Vacuum Manifold Apparatus for the Preparation of
1,3-Butadiene-1,4-¹⁴C₂

completed when flask (1) was practically empty and no more gas evolution was evident from the residue. A yield of 11.8 mmoles of 1,3-butadiene-1,4-¹⁴C₂ was obtained (based on manometric measurements). The purity of the compound ($\geq 98\%$) was determined by GLC (column: 20% SP-2100/0.1% Chromosorb W, 10 ft x 1/8 in.; column temperature: 100°; detector temperature: 160°; injector temperature: 125°; helium gas flow: 35 ml/min). The total radioactivity was calculated to be 13.6 mCi, based on the specific activity of 1.15 mCi/μmole for 5.
1,5,9-Cyclododecatriene-x-¹⁴C, 9 (Mixture of Isomers)

The technique used in the synthesis of 9 is described below and was carried out by means of the vacuum manifold apparatus depicted in Figure 2.



Legend:

- 7 - 250ml trap containing 1,3-butadiene - 1,4 - $^{14}\text{C}_2$
- 8 - Side arm with septum and long needle
- 9 - Reaction flask
- 10 - Reflux condenser
- 11, 12 - Traps cooled with liquid nitrogen
- 13 - Gas bubbler with silicon oil

Figure 2 - Vacuum Manifold Apparatus for the Synthesis of
1,5,9-Cyclododecatriene- x - ^{14}C

a. Preparation of the catalyst: The Ziegler type catalyst was prepared in the flask (9). Thus, benzene (50 ml) was distilled from LAH into (9) and then the vacuum was released using dry helium. Next, diethyl aluminum chloride (25% solution in hexane) (4.82 ml, 10 mmole) was added all at once, followed by dropwise addition of titanium tetrachloride (0.110 ml, 1.0 mmole). The catalyst precipitated as a fine brown suspension which was stirred at room temperature for 1 hr. The preparation of the catalyst was synchronized with the trimerization of g such that the ^{14}C -butadiene was used within 1 hr.

b. Trimerization of g : Helium pressure was applied to the inlet of trap (7) and g was flushed out and thus bubbled through the suspension of the Ziegler catalyst contained in (9) at room temperature. Any unreacted g was condensed in

two traps (11 and 12) cooled with liquid nitrogen and the carrier gas was allowed to escape through the bubbler (13). After 0.5 hr at a bubbling rate of ~ 60 /min, the traps (7), (11) and (12) were isolated, cooled with liquid nitrogen, then evacuated to 10^2 torr. The unreacted ξ was then vacuum transferred into flask (7) and the entire cycle described above repeated until all of the ξ had reacted as indicated by the vapor pressure readings obtained from traps (11) and (12).

The catalyst was decomposed by addition of 1 ml of acetone and the reaction mixture was assayed for radioactivity. A total of 12.3 mCi of activity was found, indicating a 90% conversion of ξ to products. Distillation of benzene at atmospheric pressure, followed by repeated distillation of the final product using high vacuum techniques, gave 8.8 mCi of 1,5,9-cyclododecatriene- x - $^{14}\text{C}_6$. The GLC analysis of this solution (column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport; column temperature: 125° ; detector temperature: 250° ; injector temperature: 220° ; H_2 gas flow: 60 ml/min) was compared against unlabeled standards [7], and showed that the ^{14}C -labeled product contained 98% of the trans-trans-cis-1,5,9-cyclododecatriene- x - $^{14}\text{C}_6$ isomer and 2% of the all-trans isomer.

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