THE SYNTHESIS OF ^{14}C-METHYLENE DIIODIDE AND ^{14}C-PROPANE-1,3-DIBROMIDE

A.R. Jones
Department of Pharmacology, Stopford Building, University of Manchester, Oxford Road, Manchester, M13 9PT, U.K.
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SUMMARY

Existing methods have been adapted for the small scale synthesis of the title compounds in high yield. Modification of the iodoform reaction enables 1,3-^{14}C-acetone (I) to be converted in over 95% yield to ^{14}C-iodoform (II) which is reduced by sodium aresenite to ^{14}C-methylene diiodide (III). Lithium aluminium hydride reduction of ^{14}C-diethyl malonate (IV) to ^{14}C-propane-1,3-diol (V), followed by acetylation and displacement with hydrobromic acid, produces ^{14}C-propane-1,3-dibromide (VII) in 87% overall yield. The use of u-, 2- or 1,3-^{14}C-diethyl malonate enables propane -1,3-dibromide to be synthesised in any desired labelling pattern. Compounds III, V and VII are useful difunctional 1- and 3-carbon intermediates for further radioactive syntheses.

Studies on the metabolism of alkylating compounds required a number of ^{14}C-labelled dihalo-alkanes, including methylene diiodide and propane-1,3-dibromide. These simple ^{14}C-compounds, which are not commercially available, have therefore been prepared in high yield by the improvement of standard methods and their adaptation to small-scale syntheses.

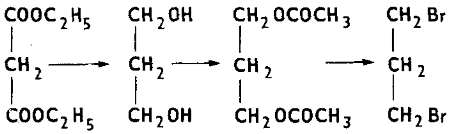
EXPERIMENTAL

^{14}C-Methylene diiodide is prepared by reducing ^{14}C-iodoform with sodium arsenite (1). Although iodoform may be prepared from a number of methyl ketones, the most economically suitable ^{14}C-precursor is 1,3-^{14}C-acetone, even though 50% of the radioactive label is lost at this stage. The hypoiodite oxidation of acetone to iodoform, the iodoform reaction, is well known, however the yield from this "classical" reaction rarely exceeds 25% of the theory even on a large scale (2). The present synthesis enables pure ^{14}C-iodoform to be prepared from 1,3-^{14}C-acetone in 96% yield, representing 48% incorporation of the radioactive label. Sodium arsenite reduction of the ^{14}C-iodoform gives ^{14}C-methylene diiodide in 90% yield. The identity of the product was confirmed by its reaction with silver methanesulphonate in acetonitrite (3) to give methylene dimethanesulphonate, m.pt 76-8^{o} (reported (3) m.pt 76-8^{o}).

$$\underset{\text{I}}{CH_3COCH_3} \longrightarrow \underset{\text{II}}{CHI_3} \longrightarrow \underset{\text{III}}{CH_2I_2}$$

Synthesis of ^{14}C-methylene diiodide

^{14}C-Propane-1,3-dibromide is conveniently prepared by a sequence of reactions from ^{14}C-diethyl malonate enabling the u-, 2- or 1,3-distribution of ^{14}C-label to be selected. Reduction of ^{14}C-diethyl malonate with lithium aluminium hydride gives ^{14}C-propane-1,3-diol in over 90% yield (based on conversion of the diol to its crystalline <u>bis</u>-α-naphthyl derivative, m.pt 164-6^{o}, reported (4) m.pt 164^{o}). Treatment with acetic anhydride produces ^{14}C-propane-1,3-diol-<u>bis</u>-acetate which without being isolated is refluxed with hydrobromic acid (5) to give ^{14}C-propane-1,3-dibromide, in 87% overall yield. Confirmation of the product was achieved by its conversion (3) to propane-1,3-dimethanesulphonate, m.pt 46^{o}C (reported (6) m.pt 46.5^{o}).



$$\begin{array}{ccccccc} COOC_2H_5 & & CH_2OH & & CH_2OCOCH_3 & & CH_2Br \\ | & & | & & | & & | \\ CH_2 & \longrightarrow & CH_2 & \longrightarrow & CH_2 & \longrightarrow & CH_2 \\ | & & | & & | & & | \\ COOC_2H_5 & & CH_2OH & & CH_2OCOCH_3 & & CH_2Br \end{array}$$

IV V VI VII

Synthesis of ^{14}C-diethylmalonate and ^{14}C-propane-1,3-dibromide

<u>^{14}C-methylene diiodide</u>

To a solution of 1,3-^{14}C-acetone (1 mCi, 2 mg) in water (20 ml) containing inactive acetone (300 mg), was added an ice-cooled solution of potassium iodide (7 gm) in water (12 ml). To this solution at 0^{o} was added an aqueous solution of sodium hypochlorite (commercial 14-15%, 60 ml) dropwise with stirring over 20 minutes and after a further 30 minutes, the precipitate of ^{14}C-iodoform (1.82 g) collected by filtration. The filtrate was kept at 0° with more sodium hypochlorite (20 ml) and after 16 hours a second crop of ^{14}C-iodoform (120 mg) was produced. The combined precipitates were washed with water (10 x 5 ml) and dried over anhydrous calcium chloride (not under vacuum) to give 1.92 gm (96%), m.pt 118-119°, s.a. 95 μCi/mm.

A reducing solution was prepared from arsenious oxide (1 g) and sodium hydroxide (2 g) in water (10 ml) and 1.5 ml added to ^{14}C-iodoform (1 g). The suspension was mixed by a stream of nitrogen and heated to 55-60° slowly over 30 minutes. A further amount of reducing solution (1.5 ml) was added during the following hour keeping the mixture at 55-60° during the addition and at this temperature for a further hour afterwards. The lower layer of ^{14}C-methylene diiodide was removed by decantation from the cooled solution and the aqueous phase extracted with ether (3 x 10 ml). The ether extracts and methylene diiodide were combined, dried with anhydrous calcium chloride, the ether removed and the product distilled to give ^{14}C-methylene diiodide (620 mg, 89.5%) as a pale straw liquid, b.pt 80° at 25 mm, s.a. 95 μCi/mmole.

^{14}C-propane-1,3-dibromide

1,3-^{14}C-diethyl malonate (500 μCi), diluted with inactive material (460 mg) in dry ether (20 ml), was added over 10 minutes to a stirred suspension of lithium aluminium hydride (500 mg) in dry ether (120 ml) and refluxed for 1.5 hours. The ice-cooled mixture was decomposed by cautious addition of 2N HCl (35 ml) and continuously ether extracted for 48 hours. The ether extract was dried over anhydrous sodium sulphate, and the ether removed in vacuo to give 1,3-^{14}C-propanediol as a brown oil (205 mg) in over 90% yield. This crude product was used without purification in the next sequence, however it can be purified by chromatography on a column of Florisil (60-100 mesh, 15 g) using ethyl acetate as eluent to give 1,3-^{14}C-propane-1,3-diol as a colourless viscous liquid (187 mg, 84%) s.a. 170 μCi/mm.

1,3-^{14}C-propane-1,3-diol (approximately 205 mg) was refluxed with acetic anhydride (1 ml) for 5 hours in an oil bath kept at 150-160°. The solution was cooled, hydrobromic acid (48%, 1.5 ml) added and refluxing continued for a further 5 hours. More hydrobromic acid (1.5 ml) was added and after an additional 5 hours refluxing, the cooled reaction mixture diluted with water (5 ml) and ether (10 ml). The mixture was carefully neutralised at 0° with potassium carbonate and extracted with ether (5 x 10 ml), the combined phases being washed with water (5 ml), dried over anhydrous potassium carbonate and the ether removed under gentle vacuum at 30°. 1,3-^{14}C-propane-1,3-dibromide was obtained as a pale yellow liquid, purified by distillation (b.pt 165°). The yield was 515 mg, 87% from diethyl malonate, of s.a. 165 μCi/mmole.

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