THE SYNTHESIS OF ^{14}C -3- CHLORO -, 3 - BROMO - AND 3 - IODO - PROPAN - 1,2 - DIOL AND 2,3 - EPOXYPROPAN - 1 -OL

A.R. Jones.
Department of Pharmacology, Stopford Building,
University of Manchester, Oxford Road,
Manchester, M13 9PT. England.
Received on July 19, 1973

SUMMARY

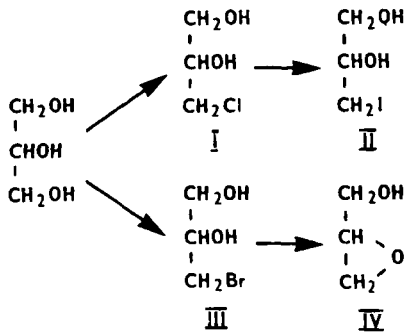
A convenient procedure has been developed for the synthesis of ^{14}C-3-chloropropan-1,2-diol (α-chlorohydrin, I) from ^{14}C-glycerol which can also be applied to the preparation of ^{14}C-3-bromopropan-1,2-diol (α-bromohydrin, III). These two compounds can be converted, respectively, by nucleophylic displacement with sodium iodide ^{14}C-3-iodopropan-1,2-diol (α-iodohydrin, II) and by alkaline epoxidation to ^{14}C-2,3-epoxypropan-1-ol (glycidol, IV). The use of readily available u-,1,3- or 2- ^{14}C-glycerol thus enables the title compounds to be synthesised readily and any desired labelling pattern as useful 3-carbon intermediates for further radioactive syntheses.

The compound 3-chloropropan-1,2-diol (α-chlorohydrin, I) is one of the simplest, yet most active, male rat antifertility agents at present known (1). In order to examine its in vivo distribution and metabolism, together with the comparative metabolism of the α-halohydrins in general, the title compounds were required labelled with carbon-14.

EXPERIMENTAL

The syntheses described give good yields of uniformly-labelled products of specific activity 4 μCi/mM from 250 μCi of u-^{14}C-glycerol.

The treatment of glycerol with either hydrogen chloride or hydrogen bromide using acetic acid as a catalyst is a modification of the method of Conant and Quayle (2). All compounds were radiochemically homogenous by thin-layer chromatography (Table) in three solvent systems; solvent 1, n-butanol saturated with water; solvent 2, chloroform : methanol 7:3; solvent 3, n-butanol : glacial acetic acid : water 4:2:1. Chromatograms were run on Merck 0.1 mm pre-coated kieselgel G plates and scanned on a Packard model 7201 Radiochromatogram Scanner. With the exception of glycidol, which could not be chromatographed due to rapid decomposition, the compounds gave a typical yellow colour for vicinal diols when sprayed with aqueous alkaline permanganate. Infra-red spectra (thin films) showed patterns characteristic of authentic compounds: α-chlorohydrin 745 cm^{-1} (C-Cl), α-bromohydrin 665 cm^{-1} (C-Br), glycidol 1260 cm^{-1} (epoxide).



Synthesis of ^{14}C-Labelled α-Halohydrins and Glycidol

Compound	Solvent 1	Solvent 2	Solvent 3
α-chlorohydrin	0.50	0.73	0.69
α-bromohydrin	0.52	0.57	0.53
α-iodohydrin	0.50	0.84	0.75
glycerol	0.25	0.37	0.38

u-^{14}C-α-chlorohydrin (I)

u-^{14}C-glycerol (250 μCi, 0.5 mg) was diluted with a methanolic solution of inactive glycerol (50 mg) in a reaction vessel prepared by sealing the end of a ground-glass air leak, and the solvent removed by a stream of nitrogen at 50°. The air leak was positioned in the side arm of a 250 ml 2-neck round bottom flask, containing refluxing iso-butanol*. Aqueous acetic acid (5%, 0.1 ml) was added to the glycerol and a steady stream of hydrogen chloride passed through the reaction solution for 1.5 hours via a Pasteur pipette. The reaction mixture was dried in vacuo, dissolved in anhydrous ethyl acetate and applied to a column of Whatmans SG-34 Chromedia (25 gm). Elution with ethyl acetate (200 ml) gave u-^{14}C-α-chlorohydrin (36-44 mg, 60-72%, 4 μCi/mg) as a pale yellow viscous oil. Further elution with ethyl acetate containing 10% methanol (150 ml) gave u-^{14}C-glycerol (12-16 mg, 24-32% of starting material). The yield of α-chlorohydrin, based on consumed glycerol, was 90% (average of 8 preparations). Attempts to improve the yield by increasing the chlorination time were unsuccessful. Beyond 2 hours, traces of an unidentified product of Rf 0.45 (solvent 1) appear which is not 1,3-dichloropropan-2-ol (3) (Rf 0.80). When the reaction is carried out on amounts of glycerol greater than 100 mg, the yield of α-chlorohydrin decreases to 50-70%.

u-^{14}C-α-iodohydrin (II)

A mixture of u-^{14}C-α-chlorohydrin (57.2 mg, 234.5 μCi) and anhydrous sodium iodide (85 mg) in methyl iso-butyl-ketone (5 ml) was stirred for 6 hours under reflux. The majority of the solvent was removed in a stream

* At this temperature (105-6°C), water distils from the mixture and condenses in the upper portion of the reaction vessel.

of nitrogen at 25° and the mixture finally dried in vacuo for several hours. The residue was suspended in anhydrous ethyl acetate and filtered directly onto a column of Whatmans SG-34 Chromedia (20 gm). Elution with ethyl acetate (250 ml) gave a yellow solution which was reduced in vacuo below 40° to a pale yellow oil. This was dissolved in ethyl acetate (2 ml), 40-60° petroleum ether (1 ml) added, the solution seeded with authentic α-iodohydrin (4) and left at 0° to crystallise. Recrystallisation from chloroform and 40-60° petroleum ether gave white plates of u-^{14}C-α-iodohydrin (37 mg, m.pt 48-50°) in 36% yield (2.2 μCi/mg). Thin-layer chromatograms of the original mother liquors (solvent 2) showed 2 radioactive components, α-chlorohydrin (19%) and α-iodohydrin (80%). Consequently inactive α-iodohydrin (50 mg) was dissolved in the mother liquors, crystallised and recrystallised to give a further 47 mg u-^{14}C-α-iodohydrin of specific activity 0.7 μCi/mg.

u-^{14}C-α-bromohydrin (III)

This compound was prepared by a method similar to that for α-chlorohydrin except that hydrogen bromide was passed through the reaction mixture for only 15 minutes. Purification by column chromatography on Whatmans SG-34 Chromedia gave the compound in the ethyl acetate eluate as a radiochemically homogenous brown oil in over 90% yield. Only trace amounts of glycerol can be recovered from the column and the high yield is maintained on amounts of glycerol up to 300 mg.

u-^{14}C-glycidol (IV)

This compound is prepared in quantitative yield by base epoxidation of u-^{14}C-α-bromohydrin. A quantity of α-bromohydrin (x mg, where x = 50-200 mg) is dissolved in 2N sodium hydroxide (1 ml) and kept for 2 minutes at 20°. The solution is neutralised with N acetic acid to give a solution containing 0.477x mg glycidol. Although the epoxidation is instantaneous and quantitative, temperatures higher than 20° result in decomposition (5);

e.g. the yield of glycidol (by titration) (6) is 73% after 10 minutes at 70° whereas it is 99.5% after 10 minutes at 20°.

The solution was saturated with sodium sulphate and extracted with ether (6 x 10 ml). The ether phase was dried and the solvent removed in a stream of dry nitrogen at 40° to give glycidol (2,3-epoxypropan-1-ol, IV) in 57-60% yield as a pale yellow oil. The purity of the product is 88-96% (6) with a half-life at 0° of 6 months.

REFERENCES

1. Ericsson R. J. J. Reprod. Fertil., 22, 213 (1970).
2. Conant J. B. and Quayle O. R. Organic Syntheses Coll. Vol. I, 294 (1941).
3. Conant, J. B. and Quayle O. R. Organic Syntheses Coll. Vol. I, 292 (1941).
4. Turner D. L., Holburn R. R., DeSipin M., Silver M. J. and Tocantins L. M. J. Lipid Res., 4, 52 (1963).
5. Ross W. C. J. J. Chem. Soc., 2257 (1950).
6. Ivashkiv E. and Dunham J. M. J. Pharm. Sci., 62, 285 (1973).