

THE PREPARATION OF ^{11}C -METHYL LABELLED
1,1'-DIMETHYL-4,4'-DIPYRIDINIUM DIODIDE

A.J. Palmer
Medical Research Council, Cyclotron Unit, Hammersmith Hospital,
Ducane Road, London, W12 0HS, U.K.
Received October 28, 1976
Revised November 29, 1976

SUMMARY

^{11}C -Methyl labelled 1,1'-dimethyl-4, 4'-dipyridinium diiodide has been prepared by reaction of ^{11}C -iodomethane with 4,4'-dipyridyl dihydrate. Radiochemical analysis of the product was by electrophoresis. The ^{11}C -iodomethane precursor was prepared rapidly from cyclotron produced $^{11}\text{CO}_2$ by reduction to methanol with lithium aluminium hydride followed by treatment with hydriodic acid.

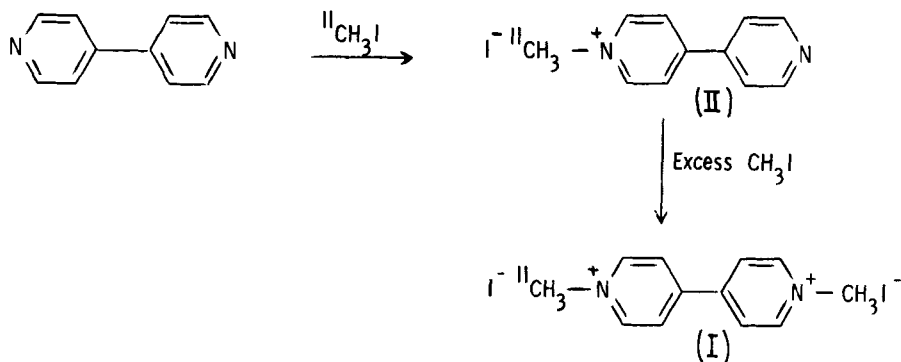
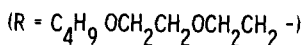
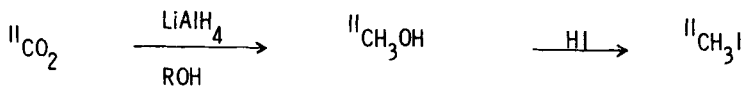
Key words: ^{11}C -methyl labelled 1,1'-dimethyl - 4,4'-dipyridinium diiodide, "paraquat", ^{11}C -iodomethane, electrophoresis.

INTRODUCTION

1,1'-Dimethyl-4,4'-dipyridinium dichloride is extensively used in agriculture as a weed-killer under the trade name "paraquat" (I.C.I. Ltd.). This compound is however toxic and the ^{14}C -methyl labelled material ⁽¹⁾ has been used to investigate its tissue distribution and pharmacology ^(2,3).

As a part of this programme the ^{11}C -methyl labelled material has now been synthesized (as the iodide). Carbon-11 decays by positron emission with a half-life of 20.4 min. This enabled the time course of the intracellular uptake of the compound in the lung of the dog to be followed over a period of 2-3 hours by means of external scintillation counting. Carrier-free

^{11}C in nitrogen is produced on the Medical Research Council Cyclotron by bombardment of nitrogen with 7.5 MeV protons ($^{14}\text{N}(p,\alpha)^{11}\text{C}$ reaction) (4,5). This was converted to ^{11}C -iodomethane by initial reduction to ^{11}C -methanol using lithium aluminium hydride followed by treatment with constant boiling hydriodic acid as reported previously (6-9). Reaction of the ^{11}C -iodomethane (plus carrier) with 4,4'-dipyridyl dihydrate in tributyl phosphate yielded ^{11}C -methyl labelled 1,1'-dimethyl-4,4'-dipyridinium diiodide (I). The total time required for the preparation from the end of cyclotron bombardment (EOB) was approximately 80 minutes.



EXPERIMENTAL

Apparatus

The apparatus used for the preparation of ^{11}C -iodomethane is shown in Fig. 1. All the tubing was of 0.125 in O.D. PTFE and the flasks had screw tops, being constructed from "Quickfit" screw thread adaptors*. The inserts for the flasks and drying tubes etc. were specially constructed from PTFE,

* ex Scientific Supplies Co. Ltd., Vine Hill, London EC1R 5EB.

and the teflon tubing was joined to these by means of "Chem inert" fittings**. This produced a system which was both gas-tight and easy to manipulate.

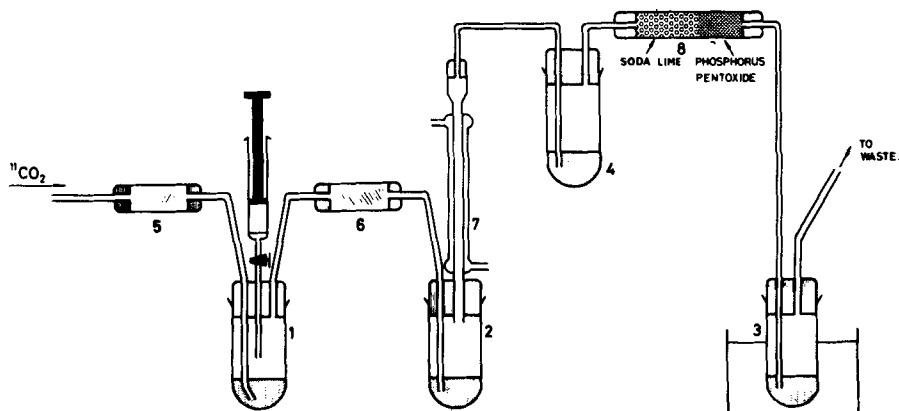


Fig. 1. Schematic diagram of the apparatus for the preparation of ^{11}C -iodomethane.

1. LiAlH_4 reaction flask.
2. HI reaction flask.
3. Receiver flask containing tributyl phosphate.
4. Trap containing water.
5. Magnesium perchlorate drying tube (20 x 2 cm).
6. Heated porapak Q column (5 x 0.8 cm).
7. Reflux condenser.
8. Sodalime - phosphorus pentoxide tube (30 x 1.2 cm).

Solvents

Either diethylene glycol dimethyl ether (diglyme) or diethylene glycol diethyl ether (diethyldigol) was used as solvent for the lithium aluminium hydride reduction stage. Both were freshly distilled under vacuum from lithium aluminium hydride before use, any storage being under nitrogen and in the absence of light. Diethylene glycol monobutyl ether (butyldigol) was heated under a reflux condenser to 100°C over stannous chloride for 2 hours and then distilled under vacuum, the middle fraction being collected. Tributyl phosphate was also redistilled under vacuum (B.P. $150\text{--}175^\circ\text{C}$).

**ex Anachem Ltd., 20A North St. Luton, Beds. LU 7QE.

TABLE I. Radiochemical yields for the preparation

Wt. LiAlH_4 (mg)	Int. Beam Current (μA hrs.)	Activity of CH_3I (mCi)	Wt. 4,4'-Dipyridyl dihydrate (mg)	Activity of (I) (mCi)	Specific activity of (I) ($\mu\text{Ci mg}^{-1}$)	Radiochemical yield of (I) (%)*
29	8.5	12 (55)	5.5	1.22 (100)	96.8	43
96	30	33 (30)	6.8	1.92 (80)	123.0	33
64	30	52 (23)	7.0	3.26 (78)	203.7	42
87	25	21 (33)	6.1	1.5 (82)	107.1	39

* Based on ^{11}C -iodomethane.

The activities of the products were measured at the times after EOB shown in parentheses (min), and are not corrected to EOB.

Preparation of ¹¹C-iodomethane

The carrier-free ¹¹CO₂ in nitrogen, was swept directly at a flow rate of 75 ml min⁻¹ from the cyclotron target (during irradiation) through the magnesium perchlorate drying tube and into the flask containing the lithium aluminium hydride (30-100 mg) in diglyme or diethyldigol (2 ml). After about 30 minutes the nitrogen flow was reduced to 50 ml min⁻¹ and butyldigol (1 ml) was added dropwise from the syringe. The flask was then heated to 120°C and the liberated ¹¹C-methanol distilled into the flask containing 55% hydriodic acid (2 ml) at 0°C., the porapak Q column being maintained at 90°C. This usually took 15-20 min. The flask (2) was then heated to 160°C and the ¹¹C-iodomethane was collected in the tributyl phosphate (1 ml) at 0°C in flask (3). This step took a further 5 minutes.

Preparation of ¹¹C-Methyl labelled 1,1'-Dimethyl-4,4'-dipyridinium Diiodide

4,4'-Dipyridyl dihydrate (6.1 mg, 0.032 mmole) and iodomethane (3μl, 0.048 mmole) were added to the flask (3) which was then sealed (screw cap) and heated at 155°C for 20 min with magnetic stirring. The flask was then cooled to 0°C, opened and further iodomethane (50μl, 0.80 mmole) was added. Heating at 155°C was then continued for a further 20 min after the flask had been resealed. After cooling, the tributyl phosphate containing the product (I) as a bright red precipitate, was transferred to a separating funnel containing diethyl ether (30 ml). The product (I) was then extracted into water (2 ml), the aqueous layer separated and nitrogen bubbled through to remove traces of iodomethane and ether. Finally the solution was passed through a millipore filter before use.

Analysis

The product was analysed by electrophoresis on cellulose acetate with a barbiturate buffer pH 8.6, coupled with autoradiography. Using this system the 1,1'-dimethyl-4,4'-dipyridinium cation (I) moved 8.0 cm under an applied voltage of 300 v for 20 minutes while the 1-methyl-4,4'-pyridyl-pyridinium cation (II) moved 5.2 cm. Autoradiography showed the radiochemical purity of the product to be > 98%.

RESULTS AND DISCUSSION

Details of several typical preparations are given in Table 1. The radiochemical yield of ^{11}C -labelled methanol was 60-70% (based on the activity trapped by the lithium aluminium hydride) and the yield of ^{11}C -iodomethane essentially quantitative (based on ^{11}C -methanol). The ^{11}C -methanol is not carrier-free due to pre-absorption of carbon dioxide in the lithium aluminium hydride. The porapak Q column in the methanol distillation line serves to remove traces of diglyme or diethyldigol from the gas stream. If this is not carried out cleavage of these compounds by the hydriodic acid results in the ^{11}C -iodomethane being diluted with miligram amounts of stable iodomethane or iodoethane respectively. The water, and soda lime plus phosphorous pentoxide traps remove traces of hydriodic acid and water from the final product. The ^{11}C -iodomethane was shown to have a chemical and radiochemical purity of > 99% by g.l.c. (5' x 0.125" porapak Q column at 100°C).

Radiochemical yields of ^{11}C -methyl labelled 1,1'-dimethyl-4,4'-dipyridinium diiodide (I) were in the range 30-50%. A large excess of iodomethane was necessary to complete the second stage of the reaction. The specific activities of the product (in the range 40-100 mCi/mmole) were sufficient for the purpose envisaged. Details of the pharmacological results will be published elsewhere.

ACKNOWLEDGMENTS

The author wishes to thank Dr. D.J. Silvester and Mr. J.C. Clark for their interest and advice and Mr. A.D. Nunn for help with developing the analytical procedure.

REFERENCES

1. Slade P. - *Weed Res.* 6: 158 (1966).
2. Litchfield M.H., Daniel J.W. and Longshaw S. - *Toxicology* 1: 155 (1973).
3. Davies D.S., Hawksworth G. and Bennett P. - *Proc. Eur. Soc. Toxicol.* (in press).
4. Clark J.C. and Buckingham P.D. - "Short Lived Radioactive Gases for Clinical Use". Butterworths, London, 1974.
5. Christman D.R., Finn R.D., Karlstrom K.I. and Wolf A.P. - *Int. J. appl. Radiat. Isotopes* 26: 435 (1975)
6. Comar D., Mazière M. and Crouzel C. ^{11}C "Synthèse et métabolisme de l'iodométhylate de chlorpromazine - ^{11}C " *Radiopharmaceuticals and Labelled Compounds*. Vol. 1, 461, IAEA Vienna, 1973.
7. Comar D., Cartron J., Mazière M. and Marazano C. - *Eur. J. nucl. Med.* 1: 11 (1976).

8. Langstrom B. and Lundqvist H. - Int. J. appl. Radiat. Isotopes 27: 357 (1976).
9. Marazano C., Maziere M. and Comar D. - Int. J. appl. Radiat. Isotopes (in press).