SYNTHESIS OF METHYL 3-OXO-4,4-DIMETHYLPENTANOATE-1,3-^{14}C.

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SUMMARY

A description of the preparation of methyl 3-oxo-4,4-dimethylpentanoate-1,3-^{14}C. The Grignard reagent prepared from 2-chloro-2-methylpropane is carbonated with $^{14}CO_2$ and the resulting trimethylacetic acid treated with methyllithium. 3,3-Dimethyl-2-butanone is treated with $NaNH_2$, the resulting enolate is carbonated with $^{14}CO_2$, and this ketoacid treated immediately after workup with excess diazomethane.

In the interest of preparing methyl 3-oxo-4,4-dimethylpentanoate-1,3-^{14}C, the following sequence of reactions was proposed:

<u>i</u> $(CH_3)_3CCl \xrightarrow{Mg} (CH_3)_3CMgCl \xrightarrow{^{14}CO_2} (CH_3)_3C^{14}CO_2H$

<u>ii</u> $(CH_3)_3C^{14}CO_2H + 2CH_3Li \longrightarrow (CH_3)_3C^{14}COCH_3$

<u>iii</u> $(CH_3)_3C^{14}COCH_3 \xrightarrow{NaNH_2} (CH_3)_3C^{14}COCH_2^-Na^+ \xrightarrow{^{14}CO_2}$

$(CH_3)_3C^{14}COCH_2{}^{14}CO_2H$

<u>iv</u> $(CH_3)_3C^{14}COCH_2{}^{14}CO_2H \xrightarrow{CH_2N_2} (CH_3)_3C^{14}COCH_2{}^{14}COCH_3$

During preliminary work with unlabelled compounds, an attempt was made to carbonate the Grignard reagent prepared from 2-bromo-2-methylpropane according to <u>i</u>. No acid was isolated. A literature

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search revealed successful preparations[1,2] of this acid by way of 2-chloro-2-methylpropane. This method was tested and found to be quite satisfactory.

The reaction of dimethylcadmium with trimethylacetyl chloride was investigated for the preparation of the ketone ii, in view of prior successful preparations of methyl ketones by this method in our laboratory. Repeated attempts, using the general method reviewed by Cason[3], gave unacceptably low yields of ii. The reaction of trimethylacetic acid with two equivalents of methyllithium in diethyl ether at room temperature followed by a brief reflux[4] afforded ii in greater than 90% yield, and proved much simpler mechanically than the method using dimethylcadmium.

For the preparation of the title compound from the ketone ii, the two step mothod of Levine[5] was modified to make most efficient use of both the labelled ketone and the $^{14}CO_2$ for the carbonation. Whereas Levine prepared the sodium amide in situ from sodium and liquid ammonia, a good commercial grade of sodium amide is now available and was used as purchased in this preparation. An excess of sodium amide was avoided in order to minimize the formation of sodium carbamate, which results not only in reduced yields of the desired product, but also in the release of radioactive carbon dioxide during the hydrolysis step. The ketone ii, sodium amide and $^{14}CO_2$ were therefore used in stoichiometric equivalence for this carbonation. The time required for nearly complete conversion of the ketone ii to the sodium enolate by sodium amide in refluxing diethyl ether was determined to be four hours by preliminary experiments performed in our laboratory. After working up the acid iii, which tends to decarboxylate, it was treated immediately with excess diazomethane to avoid any further decomposition. None of the intermediates i, ii, iii required purification. The final product iv was separated from diethyl ether and a trace of the ketone ii by

preparative gas chromatography. The overall radiochemical yield, based on barium carbonate used, was 41.6%.

EXPERIMENTAL

Reagents

$^{14}CO_2$ was prepared by the addition of lactic acid to $Ba^{14}CO_3$ on a vacuum line, passing the liberated $^{14}CO_2$ through a dry ice-acetone cooled trap at -78°C to remove water, and trapping the $^{14}CO_2$ in a liquid nitrogen cooled receiver, where it was stored for subsequent use.

Diethyl ether, where used as a reaction solvent, was taken from a freshly opened can of high grade commercial product.

Diazomethane was prepared by the alkaline hydrolysis of N-methyl-N-nitroso-p-toluenesulfonamide, distilling off the diazomethane with diethyl ether. A typical run yielded approximately 1.5g diazomethane in 100ml of ether.

All other reagents were used as purchased from commercial suppliers. All radioactivity measurements were performed with a NE liquid scintillation spectrometer model LSC-2.

Trimethylacetic acid-1-^{14}C. In a 200ml round bottom flask equipped with a magnetic stir bar, a condenser topped with a dropping funnel, the system under a slight positive pressure of nitrogen and vented through a mineral oil bubbler, was placed 1.459g (60 mmol) -50 mesh powdered magnesium, a small chip of iodine and 10ml diethyl ether. The dropping funnel contained 6.526ml (60 mmol) of 2-chloro-2-methylpropane in 100ml diethyl ether. Stirring was begun and approximately half the alkyl chloride solution was run in at once. The flask was warmed with a heat gun until self sustaining reflux was obtained. The remainder of the alkyl chloride solution was let in at such a rate as to maintain a gentle reflux. The flask

was stirred two more hours at room temperature, at which time a majority of the magnesium had dissolved. The flask was attached to a vacuum line, frozen in liquid nitrogen and evacuated. 20 mmol $^{14}CO_2$ at a specific activity of 10 mCi/mmol was frozen into the flask, the flask isolated from the line by a stopcock, thawed to room temperature and stirred 20 min. The flask was filled with nitrogen through the vacuum line, removed from the line, and the mixture carefully hydrolysed with 30ml water while stirring in an ice bath. The aqueous layer was acidified with 7ml 50% sulfuric acid(w/w), extracted with three 35ml portions of ether, the ether solution dried over $MgSO_4$ and filtered. The bulk of the ether was distilled off through a 12 cm 14/20 column packed with 0.5 cm glass chips, leaving 4.37g residue in the pot. G.C. analysis(col.packing: OV-101, 10%; col.temp.: 125^{0}C) showed the residue to contain only ether and trimethylacetic acid. By comparison with chromatographs of standard solutions of known composition the residue was determined to contain approximately 40% by weight of the acid(1.75g, 17.1 mmol, 86% chemical yield from $Ba^{14}CO_3$). The volume was brought up to 25ml with fresh diethyl ether.

3,3-Dimethyl-2-butanone-2-^{14}C. In a 100ml pear shaped flask equipped with a magnetic stir bar, a condenser topped with a dropping funnel, the system maintained as above under an atmosphere of nitrogen, was placed the trimethylacetic acid solution from the previous step. The dropping funnel contained 23.7ml 1.56M ethereal methyllithium(37 mmol). The methyllithium solution was run in slowly enough to maintain a gentle reflux. At the end of the addition, the flask was stirred at reflux in an oil bath for 30 min. The flask was cooled to room temperature and the mixture carefully hydrolyzed with 10ml water. The ether was removed and the aqueous layer extracted with two 20ml portions of ether. The combined extracts were dried over $MgSO_4$ and filtered. The bulk of the ether was distilled off as above, leaving 5.36g of residue in the pot. G.C.

analysis(col.temp.:60^{0}C) showed the residue to contain only ether and 3,3-dimethyl-2-butanone. The residue was standardized as in the previous step and found to contain approximately 30% by weight of the ketone(1.61g, 16.1 mmol, 94% chemical yield from the acid). The volume was brought up to 10ml with fresh diethyl ether.

3-Oxo-4,4-dimethylpentanoic acid-1,3-^{14}C. In a 200ml round bottom flask equipped with a magnetic stir bar, a dropping funnel, and maintained as before under an atmosphere of nitrogen, was suspended 0.624g(16 mmol) sodium amide in 25ml diethyl ether. The dropping funnel contained the ether solution of the ketone from the previous step, which was run in slowly. The mixture was refluxed by heating in an oil bath for four hours, at which time the initially vigorous evolution of ammonia had slowed considerably. The flask was attached to a vacuum line, evacuated briefly to remove any remaining ammonia, then frozen in liquid nitrogen and evacuated completely. 16 mmol $^{14}CO_2$ at a specific activity of 10 mCi/mmol was frozen into the flask, the flask isolated from the line by a stopcock, thawed to room temperature and stirred one hour. The flask was filled with nitrogen through the vacuum line, removed from the vacuum line and the mixture carefully hydrolyzed with 10ml water. The ether was removed, the aqueous layer extracted with 15ml ether. The combined extracts contained approximately 50 mCi, which was assumed to be unreacted ketone ii, and were set aside. The aqueous layer was cooled in an ice-salt bath and slowly acidified to pH 2 with 20% sulfuric acid(w/w). Very little gas evolution was observed during the addition of the acid. The acidic solution was extracted with three 30ml portions of ether, the combined extracts dried over $MgSO_4$ and filtered.

Methyl 3-oxo-4,4-dimethylpentanoate-1,3-^{14}C. In a 250ml flask without a ground glass joint and equipped with a magnetic stir bar was placed the ether solution of ketoacid from the previous step. 50ml of ethereal diazomethane containing approximately 0.75g

(17.8 mmol) of diazomethane was pipetted slowly into the flask, which was cooled in an ice-salt bath. After approximately 30ml had been added(10.7 mmol diazomethane), the yellow color persisted and gas evolution ceased. After stirring 5 min., glacial acetic acid was added until the yellow color was discharged and the solution tested acidic to pH paper. The solution was extracted with two 30ml portions of 10% aqueous sodium hydrogen carbonate(w/w), dried over $MgSO_4$ and filtered. The bulk of the ether was distilled off as before. G.C. analysis(col.temp.:170^{0}C) showed the residue to contain predominantly ether and the ketoester product, as well as a trace of 3,3-dimethyl-2-butanone. The product was purified by preparatory G.C.(OV-101, 170^{0}C) and trapped under an atmosphere of nitrogen maintained as before, with the receiver cooled to -78^{0}C in a dry ice-acetone bath. The trapped material was transferred by vacuum distillation to a tared flask, yielding 1.09g of water white liquid. G.C. analysis(col.temp.:170^{0}C) showed the material to be 98% pure methyl 3-oxo-4,4-dimethylpentanoate, the impurity being composed of approximately equal amounts of diethyl ether and 3,3-dimethyl-2-butanone. Chemical purity: 98%, radiochemical purity: 99%. Specific activity measured at 21.83 mCi/mmol. 1.09g, 6.86 mmol 150 mCi, 41.6% radiochemical yield from $Ba^{14}CO_3$.

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