Ethyl Chlorocarbonate-^{14}C and its Application to the Synthesis of N-Methyl-^{14}C-amines

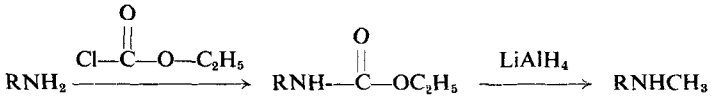
F. J. MARSHALL and R. E. MCMAHON
The Lilly Research Laboratories, Indianopolis, Indiana 46206.
Received February 6, 1970.

SUMMARY

A convenient method for the preparation of ethyl chlorocarbonate-^{14}C is described. This has led to a facile synthesis of N-methyl-^{14}C secondary amines by lithium aluminum hydride reduction of an intermediate ^{14}C-carbamate. The reaction has also been employed in the preparation of N-methyl-$^{2}H_3$- and N-methyl-^{3}H-amines by using lithium aluminum hydride-$^{2}H_4$ and lithium aluminum hydride-^{3}H.

INTRODUCTION.

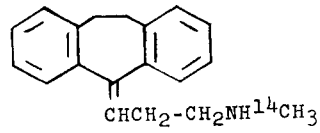
The preparation of N-methyl labeled tertiary amines can usually be accomplished by one of a number of available methods [1]. The preparation of the corresponding secondary amines frequently presents a more formidable problem. A number of years ago Easton and co-workers [2] described the preparation of β-5-methylamino-4, 4-diphenyl-2-heptanol by the following general reaction scheme.



This seemed to offer a promising and versatile approach to the synthesis of methyl labeled secondary N-methylamines.

The application of this method to the synthesis of N-methyl-^{14}C-amines, however, required the development of a practical method of preparation of ethyl chlorocarbonate-^{14}C. A thoroughly satisfactory method for the preparation of this reagent from phosgene-^{14}C has now been devised. The procedure is described below in detail.

Among the labeled compounds which have now been prepared utilizing the labeled ethyl chlorocarbonate in the Easton procedure was the antidepressant, nortriptyline :



N-methyl-^{14}C-3-phenylpropylamine has also been prepared.

Although this procedure has been used in the present study to prepare labeled secondary amines, it can be used equally well to prepare methyl-labeled tertiary amines by starting with the appropriate secondary amine.

The reduction of non-labeled carbamates with either lithium aluminum deuteride ($LiAl^2H_4$) [3] or lithium aluminum hydride-^{3}H ($LiAlH_3{}^3H$) was also explored. Some of the hydrogen-labeled amines prepared in the present study are listed in Table I.

EXPERIMENTAL.

Materials and Methods.

The phosgene-^{14}C, lithium aluminum deuteride and lithium aluminum hydride-^{3}H were all obtained commercially and were used as received from the suppliers.

Thin-layer chromatography of the various amines was carried out using Silica gel-GF plates (E. Merck) and a solvent system of ethanol-ethyl acetate (1 : 1) in an ammonia atmosphere. Eastman Blue Brand X-ray film was used for the autoradiographs.

Ethyl Chlorocarbonate-^{14}C. — A dry 25 ml 2-neck flask containing a magnetic stirring bar and fitted with a dropping funnel was connected to a vacuum system. After addition of 2 ml of a solution of phosgene in toluene (49.5 mg/ml), the flask was chilled in liquid nitrogen and was evacuated at 0.1 mm pressure. There was then introduced by vacuum transfer 9.89 mg (0.1 mmole, 1.5 mCi) of phosgene-^{14}C to give a total of 1.1 mmoles of phosgene. After 5 minutes the frozen solution was allowed to melt and then was refrozen and remelted.

One and two-tenths ml of a dry toluene solution containing 133 mg (1.1 mmoles, 0.145 ml) of purified collidine (distilled from barium oxide) and 46 mg (1 mmole, 0.056 ml) of absolute ethanol (distilled from sodium and diethyl phthalate) was added dropwise to the stirred phosgene solution which was cooled in ice water. The reaction was kept in the ice bath for 2 hours and was then stirred at room temperature for 18 hours. The product was used immediately for the next step without isolation.

5-(γ-N-Carbethoxy-^{14}C-aminopropylidene) - dibenzo[a, d] - cyclohepta - [1, 4] diene. — A solution of 249 mg (1 mmole) of 5-(γ-aminopropylidene)-dibenzo [a, d]-cycloheptа [1, 4] diene, freshly prepared from its hydrochloride, and 0.5 ml of purified collidine in 1 ml of dry toluene was added to the above solution of ethyl chlorocarbonate-^{14}C and stirring was continued for 2 hours. The mixture was diluted with benzene and was washed three times each with water, 1N hydrochloric acid, water, 1N sodium hydroxide and water. After drying over magnesium sulfate, the solvents were removed under reduced pressure and the carbamate, which crystallizes on standing, was used without further purification or assay for radioactivity. Yields of the carbamate ranged from 63-71 % based on phosgene.

A sample of non-labeled carbamate was crystallized from benzene-petroleum ether (b.p. 60-68°). It melted at 110-112°.

Anal. — Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21. Found : C, 78.40; H, 7.25.

5-(γ-Methyl-^{14}C-aminopropylidene) - dibenzo[a, d] - cyclohepta - [1,4] diene (Nortriptyline-N-methyl-^{14}C). — The crude carbamate was dissolved in 10 ml of dry ether and was added, dropwise with stirring, to 0.5 g(13.2 mmoles) of lithium aluminum hydride in 40 ml of dry ether. The mixture was stirred and refluxed overnight. It was then chilled in ice water and was hydrolyzed by dropwise addition of 0.5 ml of ethanol, 0.5 ml of water, 0.5 ml of 20 % sodium hydroxide solution and 1.5 ml of water. The ether was decanted and the residue was extracted by stirring with three 20 ml portions of boiling benzene. The ether-benzene solution was extracted with three 10 ml portions of 1N hydrochloric acid and then with three small portions of water. About 6 drops of concentrated hydrochloric acid were added to the combined aqueous solutions to produce immédiate crystallization of the hydrochloride salt of labeled nortriptyline. After chilling overnight, the product was isolated by filtration and was dried in air and then in a desiccator over anhydrous calcium sulfate. The yield of labeled nortriptyline hydrochloride was 132 mg (40 % overall based on the starting phosgene) with a melting point of 212-214°. The specific activity was 4.5 μCi/mg, 1.36 mCi/mmole.

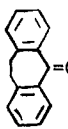
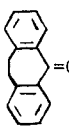
The labeled product was co-chromatographed on thin-layer with authentic cold material. Liquid scintillation counting of sections of the chromatogram showed that all the radioactivity was present in the product spot visible under UV light.

In a subsequent run, if recovered carbamate were considered, the overall yield was 49 %.

N-Methyl-^{14}C-3-phenylpropylamine was prepared by the same general procedure as the nortriptyline-N-methyl-^{14}C except that the acid extracts were made basic and the free base was extracted with ether. After drying over magnesium sulfate, hydrogen chloride gas was passed over the surface of the solution and the resulting hydrochloride was crystallized from ethanol-

TABLE I. Deuterium and Tritium Labeled Amines by Reduction of Carbamates

$$RR'N\text{-}\overset{\overset{O}{\|}}{C}\text{-}OC_2H_5$$

R	R'	MMole	Reducing Agent MMole	Product	Yield[a], %
$C_6H_5\text{-}CH_2CH_2CH_2\text{-}$	H	9.7	$LiAl^2H_4$, 20	$C_6H_5\text{-}CH_2CH_2CH_2\text{-}NHC^2H_3$[b]	76
$C_6H_5\text{-}CH_2CH_2CH_2\text{-}$	C^2H_3	10.6	$LiAl^2H_4$, 20	$C_6H_5\text{-}CH_2CH_2CH_2N(C^2H_3)_2$	14[c]
	H	0.5	$LiAlH_3{}^3H$, 0.53 (25mCi) $LiAlH_4$, 0.53 $LiAlH_4$, 2.1[e]		25

[a] Yields of the amine hydrochlorides are based on starting carbamates.

[b] Anal. Calcd. for $C_{10}H_{13}{}^2H_3ClN$: C, 63.64; H + ^{2}H, 10.15. Found : C, 63.41; H + ^{2}H, 9.84. The melting point was 137-139°.

[c] This is an overall yield for three steps ($LiAl^2H_4$ reduction, preparation of carbamate, $LiAl^2H_4$ reduction). The product melted at 138-140°.

[d] The non-labeled carbamate was prepared in pyridine solution by the procedure described for non-labeled ethyl N-3-phenyl-propyl-carbamate. It was used without purification.

[e] This large excess fo $LiAlH_4$ was added after 8 hours of reflux and heating was continued for another 8 hours.

[f] The product melted at 212-214°. Thes pecifica ctivity was 73.6 μCi/mg, 22 mCi/mmole. A thin-layer chromatogram and autoradiograph showed that the single radioactive spot corresponded to authentic material. Rf approximately 0.5.

ether. The product from a 2 mmole (1 mCi of phosgene-^{14}C) reaction was obtained in 31 % overall yield based on the starting phosgene. The melting point of 143-145° is in agreement with that reported in the literature [4] for non-labeled material. The nature and purity of the product was verified by thin-layer chromatography and authoradiography. It was shown to be a single spot and to have an Rf of about 0.3. The specific activity was 2.45 μCi/mg, 0.46 mCi/mmole.

Ethyl N-3-phenylpropylcarbamate. — To a well stirred solution of 0.1 mole of 3-phenylpropylamine in 50 ml of dry pyridine was added 12 g (0.1 mole, 10.5 ml) of ethyl chlorocarbonate at a dropwise rate. Ether was added and the mixture was washed thoroughly with water, 1N hydrochloric acid and water. After drying over anhydrous magnesium sulfate the ether was removed under reduced pressure and the resulting product, ethyl N-3-phenylpropyl-carbamate, boiled at 146-150°/0.1 mm.

Anal. — Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H. 8.27. Found : C, 69.51; H, 8.47.

N-Methyl-$^2H_3$- and N-methyl-^3H-amines. — To 2 mmoles of lithium aluminum deuteride, or a mixture of 1 mmole of lithium aluminum hydride-^3H ($LiAlH_3{}^3H$) and 1 mmole lithium aluminum hydride, in 10 ml of dry ether was added a solution of 1 mmole of the ethyl carbamate of the appropriate amine in 5 ml of dry ether at a dropwise rate. The mixture was stirred and refluxed for 8 hours. It was then chilled in ice water and hydrolyzed by the addition of 0.076 ml of water, 0.076 ml of 5N sodium hydroxide solution and 0.238 ml of water. After filtration and thorough washing of the residue with benzene, the hydrochloride was precipitated from the filtrate by addition of gaseous hydrogen chloride and was recrystallized from methanol-ethyl acetate. See Table I for compounds prepared by this procedure.

The identity of the deuterated 3-phenylpropylamine derivatives was confirmed by comparison of their mass spectra (Hitachi RMU-6-Mass Spectrometer) with those of the corresponding hydrogen compounds. The pertinent data showed, where R = 3-phenylpropyl : $RNHCH_3$, mol. wt. 149, mass ion 149, strong ion peak at 44 for $CH_2 = N^+HCH_3$; $RNHC^2H_3$, mol. wt. 152, mas ion 152, strong ion peak at 47 for $CH_2 = N^+HC^2H_3$; RN $(CH_3)_2$ [5], mol. wt. 163, mass ion 163, strong ion peak at 58 for $CH_2 = N^+ (CH_3)_2$; RN $(C^2H_3)_2$, mol. wt. 169, mass ion 169, strong ion peak at 64 for $CH_2 = N^+(C_2H_3)_2$.

REFERENCES

1. McMahon, R. E. and Marshall, F. J. — *Advances in Tracer Methodology*, **4** : 29 (1968).
2. Easton, N. R., Lukach, C. A., Nelson, S. J. and Fish, V. B. — *J. Am. Chem. Soc.* **80** : 2519 (1958).
3. See Elison, C., Elliott, H. W., Look, M. and Rapoport. H. — *J. Med. Chem.*, **6** : 237 (1963), for the preparation of morphine-N-methyl-$^2H_3$ by this method.
4. Cope, A. C. and McElvain, S. M. — *J. Am. Chem. Soc.*, **53** : 1587 (1931).
5. McMahon, R. E. — *J. Med. Chem.*, **9** : 790 (1966).