yield, including the less pure compound, was approximately 77% calculated on the same basis.

Both samples of IPC were counted as $BaCO_3$, corrected for self absorption. The first sample (m.p. 84–85°) showed an activity of 7.78×10^5 counts/min./mg. The second sample (m.p. 79–80°) showed an activity of 6.69×10^5 counts/min./mg.

Acknowledgment.—Funds for the purchase of the isotopes used were provided by the General Research Council, Oregon State College.

DEPARTMENT OF CHEMISTRY
OREGON STATE COLLEGE
CORVALLIS, OREGON RECEIVED JANUARY 28, 1952

Synthesis of Carbon-14 Labeled Urea[1,2]

BY ALBERT L. MYERSON[3]

Carbon-14 labeled urea was conveniently synthesized in small quantities through the direct combination of carbon dioxide and ammonia at room temperature, to form ammonium carbamate. The latter compound was sealed in a capillary and heated to 135°, to form urea. The first reaction is quantitative, while the second reaches equilibrium at 40% conversion.

This synthesis constitutes one of the simplest operations by which radioactive carbon dioxide can be incorporated into an organic compound on a micro scale. The preparation of urea from carbon dioxide and ammonia was originally reported[4] using 10 to 20 g. quantities, where maximum conversion was obtained by heating 16 g. of carbamate in a volume of 37 cc. In the present work, two radioactive syntheses were carried out employing 30 and 300 mg. of barium carbonate, respectively, the total activity in each case being 0.35 mc. The m.p. of the white crystals of urea was 131.5° without recrystallization, compared to reported values of 132 to 133°.

(1) For experimental details of this synthesis order Document 3493 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35-mm. motion picture film) or $1.00 for photocopies (6 × 8 inches) readable without optical aid.

(2) Reported at a symposium "Isotopes and Medicine," at the University of Wisconsin, Madison, Wis., in September, 1948.

(3) The Franklin Institute, Philadelphia, Pa.

(4) F. Fichter and B. Becker, *Ber.*, **44**, 3473 (1911).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON, WIS. RECEIVED DECEMBER 22, 1951

A Synthesis of Formaldehyde-C^{14} [1]

BY A. R. JONES AND W. J. SKRABA

Methanol-C^{14} has been converted to formaldehyde-C^{14} by the chlorination of methyl-C^{14} acetate followed by hydrolysis of the chlorinated product. The reactions, first studied by Henry[2] and Michael[3] gave a 60% yield of product when isolated with the aid of inert formaldehyde.[4]

(1) This document is based upon work performed under Contract Number W-7405 eng. 26 for the Atomic Energy Commission at the Oak Ridge National Laboratory.

(2) L. Henry, *Ber.*, **6**, 739 (1873).

(3) A. Michael, *Am. Chem. J.*, **1**, 418 (1879).

(4) Since the preliminary report of this procedure (Jones and Skraba, *Science*, **110**, 332 (1949)), another synthesis has been proposed by A. Murray and A. R. Ronzio, AECU-991; LADC-778.

Since the hydrolysis of carefully purified chloromethyl acetate[5] gave a quantitative yield of formaldehyde, efforts to improve the over-all yield of formaldehyde from methanol were confined to the acetylation and chlorination steps. The over-all yield was not improved by conducting the acetylation at atmospheric pressure under reflux, and was considerably decreased when a mole proportion of pyridine was added before acetylation.

The chlorination yield was not affected by ultraviolet irradiation of the reaction mixture, nor by varying the reaction temperature from 20–60°. The over-all yields of formaldehyde were best when a slightly less than molar proportion of chlorine was used.

To avoid the competing chlorination of the methyl group of the acetate moiety, the methyl esters of chlorocarbonic, oxalic, chloroacetic, trichloroacetic, bromoacetic, benzoic and *p*-toluenesulfonic acids were chlorinated. Poor yields were obtained in all cases. A mixture of methyl bromoacetate and bromine was decolorized after two days at room temperature, but hydrolysis of the product yielded only a small amount of formaldehyde.[6]

Experimental

Acetylation.—Methanol-C^{14}, 332 mg., 10.4 mmoles, 21.43 microcuries (2.06 microcuries/mmole) and acetyl chloride, 816 mg., 10.4 mmoles, were consecutively high-vacuum distilled[7] into the liquid nitrogen cooled nipple of a one-liter bulb. The reaction vessel was isolated from the manifold and the frozen reagents were warmed to 40–50° for 45 minutes with a heat lamp. The contents were then frozen into the nipple by immersing the latter in liquid nitrogen. To remove a part of the hydrogen chloride, the nipple was warmed to −80° (Dry Ice and trichloroethylene) and the bulb was evacuated to 10^{-4} mm.

Chlorination.—The Dry Ice–trichloroethylene-bath was replaced by liquid nitrogen and 1400 ml. (27° and 12.9 cm. pressure), 9.6 mmoles, of commercial chlorine gas, from which impurities non-condensable with liquid nitrogen had been removed, was distilled into the reaction bulb. The pressure of chlorine was determined with a manometer in which the mercury was protected by a layer of sulfuric acid. The bulb was isolated from the manifold and the contents were allowed to warm to room temperature in subdued light. Loss of the chlorine color began while the reactants were still quite cold. The contents of the bulb were recondensed and allowed to return to room temperature several times to ensure thorough mixing. When all trace of chlorine color had disappeared, one to two hours, part of the hydrogen chloride was removed as described above.[8]

Hydrolysis.—A 25-ml. hydrolysis bulb containing 3 ml. of distilled water and equipped with a spring-loaded 4-mm. straight-bore stopcock was attached to the manifold, im-

(5) M. Descude, *Compt. rend.*, **132**, 1567 (1901).

(6) Radioactive paraformaldehyde was prepared by treating chloromethyl-C^{14} acetate with sufficient commercial formalin solution to furnish the water for hydrolysis. This procedure produced a paste which left a residue of dry polymeric formaldehyde when the volatile material was removed under high vacuum.

In attempts to prepare an isolable solid derivative from which formaldehyde would be easily recoverable, formaldehyde oxime, hexamethylenetetramine and the methylol derivatives of saccharin and phthalimide were investigated. None gave sufficiently high yields of derivative from reaction with aqueous formaldehyde.

Direct oxidation of dilute methanol to formaldehyde with potassium persulfate (P. D. Bartlett and J. D. Cotman, THIS JOURNAL, **71**, 1419 (1949)) was attempted as a preparative method, but was not found feasible because of the difficulty of recovering formaldehyde from the dilute aqueous solution necessary for reaction to take place.

(7) All joints and stopcocks were greased with Dow-Corning silicone vacuum grease.

(8) After a number of runs the reaction bulb contained a trace of white non-volatile material and the over-all yields of formaldehyde decreased. Replacement of the bulb corrected the matter.

mersed in liquid nitrogen, and evacuated. After the crude chloromethyl-C^{14} acetate was transferred to the hydrolysis bulb, the stopcock was closed and the vessel was removed from the vacuum line, and immersed to the stopcock in boiling water for thirty minutes to allow hydrolysis to take place.[9] The flask was cooled to room temperature and with the aid of a file mark on the stem, the stopcock was removed and the contents were transferred to a 20-ml. pear-shaped flask. Five milliliters of 37% commercial formalin solution containing approximately 60 mmoles of formaldehyde was used to rinse the hydrolysis bulb and complete the transfer. The mixture was made slightly basic with potassium hydroxide pellets, and then barely acidified to phenolphthalein with acetic acid. A neutral formalin solution which weighed 9.027 g. was obtained by distillation to dryness at atmospheric pressure into the ice-cooled receiver of the aliquoter (Fig. 1).

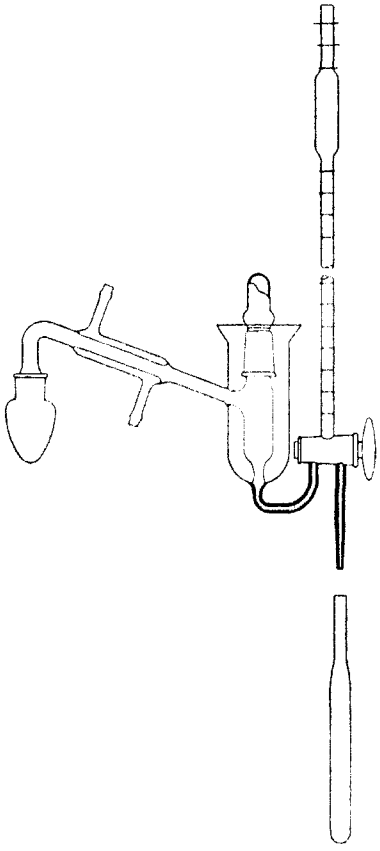

Fig. 1.—Distillation and aliquoting apparatus.

Analysis.—A 75-microliter aliquot (78 mg.) of this solution was added to a solution of 0.40 g. of dimedon reagent in 100 ml. of water. After standing for 24 hours at room temperature, the dimedon derivative of formaldehyde was filtered off, washed with water and dried. In this way, 159 mg. of dimedon-formaldehyde was obtained.

The dry combustion of a 22.6-mg. sample of the derivative gave 181 ml. of carbon dioxide (28.5° and 13.7 cm. pressure) which produced an ion current of 6.80×10^{-14} amperes when the radioactivity assay was made with a dynamic condenser electrometer. The factors 1.17×10^{-16} ampere per disintegration per second and 3.7×10^{4} disintegrations per second per microcurie were used to convert the ion current to microcuries. The total activity of the formaldehyde in the neutral distillate was calculated to be 12.9 microcuries, a radiochemical yield of 60.5%.

To show that no isotopic dilution had occurred, a run was made starting with 258 mg. of methanol-C^{14}, 8.06 mmoles, 96.75 microcuries (sp. act. 12.00 microcuries per millimole). A 0.295-g. aliquot of the acid hydrolysis solution (3.755 g. total weight) gave 100 mg. of formaldehyde-dimedon derivative, 0.342 mmole, 4.17 microcuries (sp. act. 12.18 microcuries per millimole). From these figures both the radiochemical yield (51%) and the chemical yield (59%) can be calculated.

For the analysis of production runs, where the isotopic ratio was much greater, a small aliquot of the neutral distillate was diluted with carrier formaldehyde solution and aliquots of this mixture were analyzed radiochemically by the method given above.

OAK RIDGE, TENN. RECEIVED NOVEMBER 2, 1951

(9) There has been no failure of either bulb or stopcock observed in more than fifty hydrolyses.

Adrenergic Blocking Agents. V. Synthesis of N - Benzyl - N - (1 - phenoxyisopropyl) - β - chloroethylamine Hydrochloride Labeled with C^{14}

BY EDWARD J. NIKAWITZ, WILLIAM S. GUMP, JAMES F. KERWIN AND GLENN E. ULLYOT

RECEIVED JULY 18, 1951

Since the discovery[1] of the remarkable adrenergic-blocking ability of N,N-dibenzyl-β-chloroethylamine hydrochloride following intravenous administration, our attention has been directed toward the development of a compound effective at a tolerated dosage level with the view that such an agent might find practical therapeutic application. Progress toward this goal has been achieved recently in the synthesis of N-benzyl-N-(1-phenoxyisopropyl)-β-chloroethylamine hydrochloride.[2] In order that further studies regarding the absorption, distribution, fate, site of action and mechanism of action of an adrenergic blocking drug of this type might be undertaken, it was deemed desirable to prepare a quantity of this compound labeled with C^{14}. Because of the availability of labeled benzyl chloride and because of the desire to label a group which might be expected to remain with the nitrogen containing moiety of a possible breakdown product we chose to prepare the compound labeled at the methylene of the benzyl group (see I).

$$\begin{array}{l} C_6H_5OCH_2CHCH_3 \\ \qquad\qquad\quad | \\ C_6H_5\overset{*}{C}H_2\text{—}N\text{—}CH_2CH_2Cl\cdot HCl \end{array} \qquad (I)$$

The synthetic procedure was that previously employed but adapted to a suitable scale.

Experimental[3]

(1) **C^{14}-Labeled N-Benzyl-N-(1-phenoxyisopropyl)-2-aminoethanol.**—Benzyl chloride (0.684 g.) labeled with C^{14} in the side chain,[4] N-(1-phenoxyisopropyl)-2-aminoethanol (1.09 g.), anhydrous sodium carbonate (0.29 g.) and 7 ml. of absolute alcohol were heated under reflux at 85–90° for 10 hours. The alcohol was then removed by sucking the vapors away by means of an inverted glass funnel and vacuum. The remaining salt and oil were mixed with small amounts of water and ether. The ether solution was separated, dried, concentrated to a small volume and transferred into bulb 1 of a distilling apparatus having 3 bulbs (Fig. 1). A small portion of additional ether was used to wash the flask. The ether was then removed by heating bulb 1 in a water-bath at 40–50°.

(1) M. Nickerson and L. S. Goodman, *Federation Proc.*, **5**, 194 (1946); *J. Pharm. Expt. Therap.*, **89**, 167 (1947); Nickerson and Gump, *ibid.*, **97**, 25 (1949).

(2) J. F. Kerwin, G. C. Hall, F. J. Milnes, I. H. Witt, R. A. McLean, E. Macko, E. J. Fellows and G. E. Ullyot, THIS JOURNAL, **73**, 4162 (1951).

(3) The synthesis with the tagged material was carried out in the laboratories of U. S. Testing Co., Inc., Hoboken, N. J.

(4) Obtained from Tracerlab, Inc., Boston, Mass., with a specific activity of 1.3 mc./mM.