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).

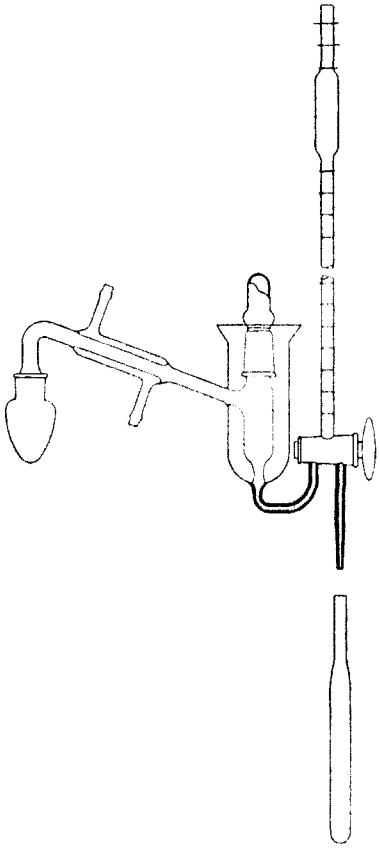

Fig. 1.—Distillation and aliquoting apparatus.

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.

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

OAK RIDGE, TENN. RECEIVED NOVEMBER 2, 1951

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).

$$C_6H_5OCH_2CHCH_3$$
$$C_6H_5\overset{*}{C}H_2—N—CH_2CH_2Cl\cdot HCl \qquad (I)$$

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.

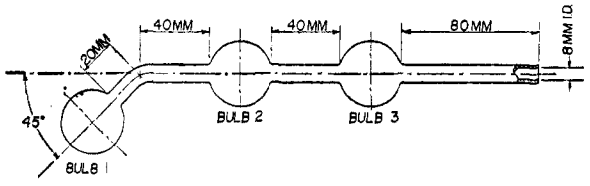

Fig. 1.—Inside diameter of all bulbs about 37 mm.

The residual aminoalcohol was distilled in high vacuum by first putting bulbs 1 and 2 of the distilling apparatus into a small metal box-shaped oven, fitted with a mica window on one side, a removable cover, a slit on one end and a thermometer, and heated with a bunsen burner. During the distillation, the slit in the box was covered with a piece of thick asbestos paper and wet cloth was wrapped around the bulbs remaining outside of the box.

A temperature of 142° was maintained inside of the oven for 15 minutes, allowing the forerun to distil at 0.15 mm. into bulb 3. After that period, the distilling apparatus was moved so that only bulb 1 remained in the box. Small amounts of the forerun condensed in bulb 2 were driven into bulb 3 by careful heating with a bunsen burner. The desired aminoalcohol was then distilled into bulb 2 as a colorless oil at 0.15 mm. and an oven temperature of 160–178°, the operation taking about 25 minutes.

Bulb 2 was then separated by cutting the connections to the other bulbs and the aminoalcohol (1.1205 g.) poured into a Pyrex tube of 100 mm. length and 22 mm. inside diameter. Three ml. of chloroform was used to wash the bottle.

(2) **C^{14}-Labeled N-Benzyl-N-(1-phenoxyisopropyl)-β-chloroethylamine Hydrochloride.**—The tube containing the chloroform solution of the aminoalcohol was cooled in an ice-bath and the procedure given in the literature[2] was followed in preparing the desired compound. Shiny white crystals (1.0414 g.) of the m.p. 137.5–140° (lit.[2] 137.5–140°) were obtained.

RESEARCH LABORATORIES OF GIVAUDAN-DELAWANNA, INC., AND
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A Convenient Synthesis of Uracil 2-C^{14} from Urea[1]

BY H. GEORGE MANDEL AND CURTIS L. BROWN

Uracil, a normal constituent of pentose nucleic acid, has been shown by many authors to act as a growth factor for various organisms.[2-6] It therefore became desirable to prepare this compound labeled with C^{14} in order to study its physiological disposition in several species. Since C^{14} urea is commercially available,[7] it was desirable to devise a synthesis with this substance as the limiting reagent. Non-radioactive uracil has been prepared in a 25% yield, based on urea, by Davidson and Baudisch.[8] The yield was improved slightly by temperature modifications introduced by Chi and Chen.[9] Hilbert[10] has observed that the amount of sulfur trioxide in the fuming sulfuric acid, the temperature of heating and the order of addition of the reagents influence the success of related condensation reactions.

The procedure outlined below permits the preparation of uracil in a better than 60% yield based on C^{14}-urea.

Experimental

Twenty ml. of fuming sulfuric acid (18% of SO_3) was placed in a three-necked 50-ml. flask equipped with a mercury seal stirrer, a thermometer and a funnel-shaped inlet tube. After cooling the solution in a Dry Ice–alcohol-bath to −5°, 4.4 g. (0.033 mole) of finely pulverized malic acid was added with stirring, keeping the temperature below 0°. When the material had been finely dispersed, 1.7 g. (0.028 mole) of urea, previously pulverized and desiccated, and containing 1 mc. of C^{14}-urea was introduced in small portions over a period of ten minutes, keeping the temperature below 5°, and stirring vigorously. The mixture was then slowly warmed to 80°, whereupon all solid material dissolved. The solution was stirred at 80–85° for one hour, cooled and poured over 60 g. of crushed ice. After 48 hours in the ice-box, the uracil had separated. It was centrifuged, resuspended repeatedly in ice water, filtered off and dried. Recrystallization from hot water, carried out with non-radioactive uracil, showed that this step was unnecessary.

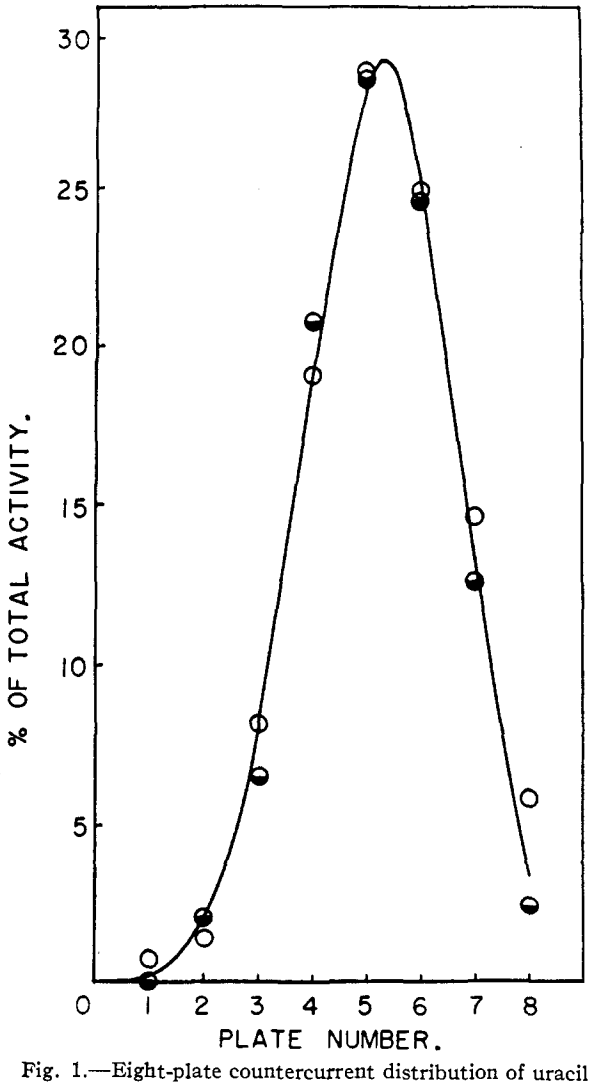

Fig. 1.—Eight-plate countercurrent distribution of uracil 2-C^{14}. Theoretical curve K = 1.85 system 1 M phosphate buffer pH 6.8, n-butanol and t-butanol; O, optical density at 260 mμ; ◒, radio assay.

(1) Aided by grants from the National Cancer Institute, of the National Institutes of Health, Public Health Service, and the Damon Runyon Fund.

(2) R. D. Housewright and S. A. Koser, *J. Infectious Diseases*, **75**, 113 (1944).

(3) S. H. Hunter, *Arch. Biochem.*, **4**, 119 (1944).

(4) R. E. Feeney, J. H. Mueller and P. A. Miller, *J. Bact.*, **46**, 559 (1943).

(5) E. Diczfalusy and H. v. Euler, *Arkiv Kemi, Mineral. Geol.*, **24A**, No. 38 (1947).

(6) G. W. Kidder, *Ann. N. Y. Acad. Sci.*, **49**, 99 (1947).

(7) Purchased from U. S. Atomic Energy Commission, Los Alamos Scientific Laboratory.

(8) D. Davidson and O. Baudisch, THIS JOURNAL, **48**, 2382 (1926).

(9) Y. F. Chi and Y.-H. Chen, *Trans. Science Soc. China*, **8**, 83 (1934).

(10) G. Hilbert, THIS JOURNAL, **54**, 2081 (1932).