[CONTRIBUTION FROM RADIATION LABORATORY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Preparation of Demerol-N-methyl-C^{14} by Reductive Methylation[1]

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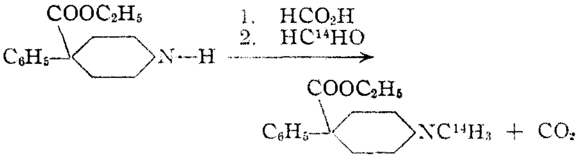
Demerol, the hydrochloride of N-methyl-4-phenyl-4-carbethoxypiperidine, is used as a sedative and analgesic similarly to morphine and is reported to be less toxic than morphine.[4] In order to study its action and distribution in animals,[5] demerol labeled with C^{14} in the N-methyl group has been synthesized using the formaldehyde–formate reductive methylation reaction.[6,7]



During this preparation the clarification of the role of formaldehyde and formic acid was undertaken by making each of these two reagents in turn radioactive. Although previous work had shown that in higher homologous reactions the N-alkyl group was derived from the aldehyde, this had never been proved for the first member of the series. In addition, there has been some question as to whether the aldehyde could contribute to the reduction as well as the formic acid.[7] In the preparation of the labeled demerol the alkylation of 4-phenyl-4-carbethoxypiperidine was carried out using radioactive formaldehyde and inactive formic acid. The demerol formed and the unreacted recovered formaldehyde were active, while the carbon dioxide given off contained only traces of C^{14}. Within experimental error the demerol and the formaldehyde used had the same specific activity.

In a check reaction, C^{14}-labeled formic acid and formaldehyde were used in this preparation. Neither the resulting demerol nor the unreacted formaldehyde was radioactive, but the carbon dioxide given off had the same specific activity as the starting formic acid. In Table I the data on these two runs are listed.

These figures support previous data that the RCHO molecule supplies the N-alkyl group in this reaction. The fact that the carbon dioxide evolved was radioactive only when C^{14}-labeled formic acid was used and not when labeled formaldehyde was employed shows that in the case of demerol the reduction is not effected appreciably by formaldehyde going to formic acid and thence to carbon dioxide, but appears to be exclusively an oxidation of formic acid to carbon dioxide. The data indicate that there was no exchange between the formaldehyde and formic acid under the conditions employed.

TABLE I

	Specific activity in μc/mmole[a]	
Reactants	With labeled formaldehyde	× 10^2 with labeled formic acid
4-Phenyl-4-carbethoxypiperidine	0	0
Formaldehyde	210	0
Formic acid	0	43
Products		
Demerol	215	0.30
Carbon dioxide	0.085	42
Recovered formaldehyde	155[b]	0

[a] All samples were counted to an accuracy of 2%. [b] Crude material (only 3 mg. of the dimethone derivative was recovered).

Experimental

The specific activity of the several samples was measured using thin window Geiger–Müeller tubes which were calibrated against standard samples from the Oak Ridge National Laboratory of the U. S. Atomic Energy Commission. The barium carbonate was counted using the procedure of Dauben, Reid and Yankwich[8] and the aliquots of the other samples were dissolved in appropriate solvents and thin films evaporated onto glass plates[9] which could be counted with no appreciable absorption correction.

Demerol-N-methyl-C^{14}.—Into a 10-ml., three necked, pear-shaped flask 1070 mg. (4.6 mmoles) of 4-phenyl-4-carbethoxypiperidine, m. p. 132–135°,[10] was weighed. The flask was fitted with a condenser, a micro dropper containing 598 mg. (4.2 mmoles) of a 21% solution in water of formaldehyde-C^{14}[11] (210 μc/mmole) and a capillary tube inlet for nitrogen (Fig. 1). The condenser was connected to a spiral trap cooled in a Dry Ice-bath and thence to a micro bubbler filled with 15 ml. of 2 N carbonate-free sodium hydroxide. The apparatus was protected at both ends with soda lime tubes.

To the reaction flask 547 mg. (10.7 mmoles) of commercial 90% formic acid was added at 0°. The system was then

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[4] R. Hazard, *Progrès. Méd.*, **72**, 289-292 (1944); *Chimie et Industrie*, **54**, 421 (1945).

[5] This work is in progress under the direction of Dr. H. H. Anderson, Division of Pharmacology and Experimental Therapeutics, University of California Medical Center, San Francisco.

[6] Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

[7] Staple and Wagner, *J. Org. Chem.*, **14**, 559 (1949).

[8] Dauben, Reid and Yankwich, *Anal. Chem.*, **19**, 827 (1947).

[9] Calvin, Heidelberger, Reid, Tolbert and Yankwich, "Isotopic Carbon," John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 109–113.

[10] We are indebted to Sterling–Winthrop Research Institute for supplying this material.

[11] This material was supplied via the Isotopes Division of the U. S. Atomic Energy Commission from the Organic Chemistry Group of the Oak Ridge National Laboratory. It contained, in addition to the formaldehyde, about 10% tracer activity in the form of methanol.

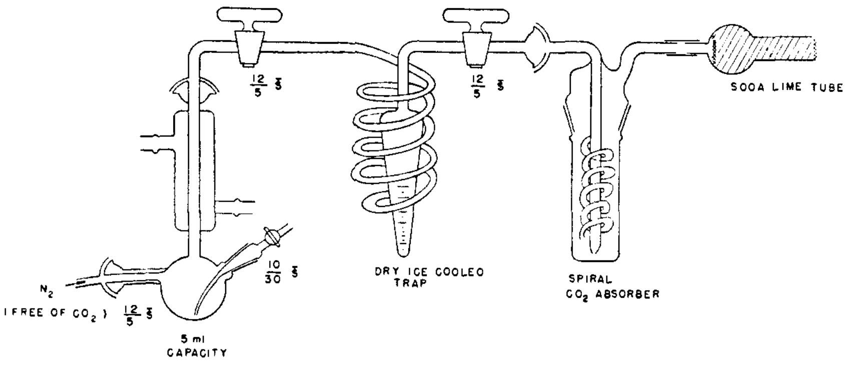

Fig. 1.

closed and swept with nitrogen. The formaldehyde was then added and the dropper rinsed with 0.4 ml. of water. The reaction mixture was slowly warmed to 100°. A rapid evolution of carbon dioxide started at 85° and continued for about twenty minutes. After this, the mixture was refluxed for four hours at 100–105°. The reaction mixture was cooled, 0.9 ml. of 6 *N* hydrochloric acid was added and the flask connected through the Dry Ice cooled trap to a vacuum line. Then the mixture was warmed under reflux for ten minutes.

The Dry Ice cooled trap was then removed and 3 mg. of the dimethone derivative of formaldehyde recovered and the specific activity determined.

To the sodium hydroxide solution 7 ml. of 4.4 *N* ammonium chloride and 43 ml. of 1.4 *M* barium chloride were added. The precipitate of barium carbonate was dried (1.02 g., 5.2 mmoles) and the specific activity determined.

The remaining volatile material in the flask, hydrochloric and formic acids, was then removed *in vacuo*. The crude product, a soft yellow solid was dissolved in chloroform, filtered, and the chloroform removed *in vacuo*. A first crop of 463 mg. of demerol was obtained by crystallization from acetone, m. p. 187–188°. The specific activity of this material was 215 μc/mmole, or 0.79 μc/mg. Second and third crops, totaling 455 mg., were crystallized from a chloroform–ether mixture. The combined yield was 78% based on the formaldehyde used to begin the synthesis. The analysis of an inactive sample prepared by the above method and corresponding to the first fraction with the same melting point is as follows: *Anal.* Calcd. for $C_{15}H_{22}O_2HCl$: C, 63.48, H, 7.81; N, 4.94; Cl, 12.49. Found: C, 63.69; H, 7.91; N, 5.14; Cl, 12.68.

The material was analyzed by two-dimensional paper chromatography using butanol–propionic acid in one direction and phenol–water in the other.[12] Only one radioactive spot was found when the paper was exposed to X-ray film.

Preparation Using Labeled Formic Acid.—The reaction was carried in the same manner as the previous run using, however, 4.4 mmoles of 4-phenyl-4-carbethoxypiperidine, 4.4 mmoles of formaldehyde and 9.4 mmoles of formic acid-C^{14}. Most of the excess formic acid (4.6 mmoles) was recovered from the cold trap as sodium formate as well as 3.4 mg. of the dimethone derivative of formaldehyde. The specific activity of the several fractions was measured.

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Summary

1. Demerol-N-methyl-C^{14} has been synthesized using the formate–formaldehyde reductive methylation method.

2. By the use of labeled formaldehyde in one reaction and labeled formic acid in another it has been shown that in this reaction the formaldehyde is the source of the N-methyl group, that the only major source of the reductive action is formic acid going to carbon dioxide, and that there is no exchange between the formic acid and formaldehyde.

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[12] Calvin, *et al.*, This Journal, **72**, 1710 (1950).

[Contribution from The School of Chemistry, Rutgers University, and from the Frick Chemical Laboratory, Princeton University]

Reactions of Organometallic Compounds with Alkyl Halides. II. On Sodium Ethyl and (+)2-Chlorooctane

By Stephen E. Ulrich,[1] Franklin H. Gentes, John F. Lane and Everett S. Wallis

The first paper of this series[2] presented the results of an investigation on the action of sodium ethyl on (−)2-bromooctane. The products of the reaction were shown to be octylene and octane, together with smaller amounts of the products of substitution, 3-methylnonane and 7,8-dimethyltetradecane. The first of these substitution products was almost completely (97%) racemized; the latter was optically inactive.

These results were considered in conjunction with the earlier finding of Wallis and Adams[3] that the action of sodium on (+)2-bromobutane gave optically inactive 3,4-dimethylhexane. It was pointed out that in both instances the optical inactivity of the di-*s*-alkyl hydrocarbon could have resulted from one of the three following causes:

(1) The hydrocarbon was produced by a concerted (S_N2) displacement reaction between sodium *s*-alkyl and *s*-alkyl halide in such a fashion as to give exclusively the *meso*-form.

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[1] American Chemical Society Fellow in Rutgers University, 1946–1949.

[2] Brink, Lane and Wallis, This Journal, **65**, 943 (1943).

[3] Wallis and Adams, *ibid.*, **55**, 3838 (1933).