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THE ROLE OF FORMALDEHYDE AND FORMIC ACID IN THE
PREPARATION OF DEMEROL-N-METHYL-C¹⁴

Winifred Tarpey

December 29, 1949

Berkeley, California

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THE ROLE OF FORMALDEHYDE AND FORMIC ACID IN THE PREPARATION
OF DEMEROL-N-METHYL-C¹⁴

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December 29, 1949

ABSTRACT

1. Demerol-N-methyl-C¹⁴ has been synthesized using formaldehyde-C¹⁴ in the Wallach reaction.
2. The use of formaldehyde-C¹⁴ in one reaction and formic acid-C¹⁴ in another has shown that under the conditions of the reaction formaldehyde is the source of the N-methyl group formed, reduction is affected only by the formic acid and there is no exchange between the formic acid and formaldehyde.

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- 1 Present address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.
 - 2 The work described in this paper was sponsored by the Atomic Energy Commission.
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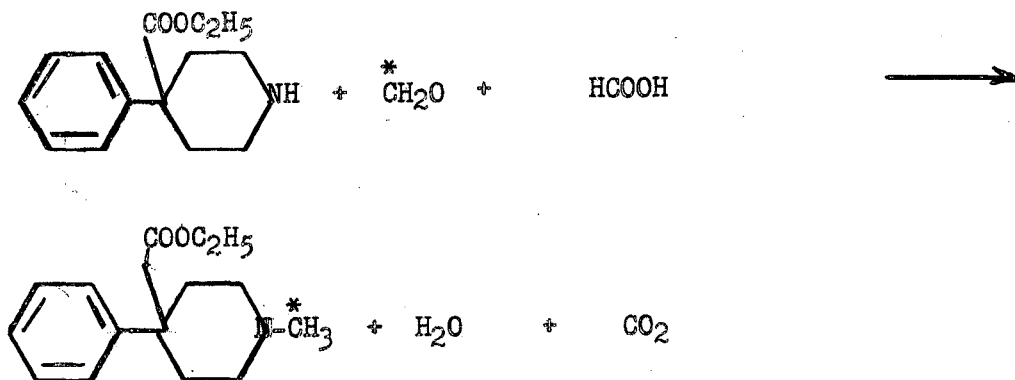
THE ROLE OF FORMALDEHYDE AND FORMIC ACID IN THE PREPARATION
OF DEMEROL-N-METHYL-C¹⁴

by

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Demerol (the hydrochloride salt of 1-methyl-4-phenyl-4-carbethoxy-piperidine) is used as a sedative and analgesic (similar to morphine) and is reported (3) to be less toxic than morphine. In order to study its action and distribution in animals, demerol labeled with C¹⁴ in the N-methyl position has been synthesized using the Wallach reaction (4).



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- (1) Present address: Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.
 (2) The work described in this paper was sponsored by the Atomic Energy Commission.
 (3) R. Hazard, Progrès. méd., 72, 289 (1944); Chimie and Industrie, 54, 421 (1945).
 (4) An extensive bibliography of this reaction is given by Staple and Wagner (5).
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In a recent study, Staple and Wagner (5) state that in methylations by formaldehyde and formic acid the reduction is affected by both compounds. By the use of C^{14} labeled reactants it seemed possible to clarify this question.

When the alkylation of 4-phenyl-4-carbethoxypiperidine was carried out using 4-phenyl-4-carbethoxypiperidine, formaldehyde- C^{14} and inactive formic acid (Run 1, Table I), only the demerol formed and the recovered formaldehyde were radioactive, while the carbon dioxide given off contained only traces of C^{14} . Within the experimental error, the demerol had the same specific activity as the formaldehyde used.

When the reaction was carried out with C^{14} -labeled formic acid and inactive formaldehyde (Run 2, Table I), neither the resulting demerol nor the unreacted formaldehyde was radioactive. The carbon dioxide produced had the same specific activity as the starting formic acid. The excess formic acid was recovered and found to be radioactive.

The fact that the carbon dioxide evolved was radioactive only when C^{14} -labeled formic acid was used but not when C^{14} -labeled formaldehyde was employed shows that in the case of demerol, the reduction is not affected by the formaldehyde going to formic acid and thence to carbon dioxide. Furthermore, there was no exchange between the formaldehyde and formic acid under the conditions employed.

(5) E. Staple and E. C. Wagner, J. Org. Chem., 14, 559 (1949).

EXPERIMENTAL PART

All melting points are corrected. Microanalyses were performed by V. H. Tashinian. The radioactive measurements were made using end-window Geiger-Müller tubes calibrated with standardized barium carbonate (6).

Demerol-N-methyl-C¹⁴ (Run 1): - 4-Phenyl-4-carbethoxypiperidine (1070 mg., 4.6 mmoles) (7) extracted from a basic solution of the hydrochloride salt (7) with ether and benzene was weighed into a 10 ml., three-necked, pear-shaped reaction flask equipped with a water-cooled condenser, a micro addition dropper and a capillary tube for maintaining a flow of nitrogen over the reaction mixture. The condenser was connected to a spiral trap cooled with carbon dioxide in isopropyl alcohol which was connected to a micro spiral bubbler filled with 15 ml. of carbonate-free 2N sodium hydroxide. Soda lime tubes were used at either end of the apparatus train. Formic acid (547 mg., 10.7 mmoles) (90%) was added to the amine at 0°C. The system was closed and swept out with a slow stream of high purity nitrogen. Twenty-one percent formaldehyde-C¹⁴ with a specific activity of 210 µc/mole (598 mg., 4.2 mmoles) (8) was added by means of the dropper which was then rinsed with 0.4 ml. distilled water. The reaction mixture was slowly warmed to 100°C. A rapid evolution of carbon dioxide occurred at 85°C and continued for 20 minutes. After the vigorous carbon dioxide evolution ceased, the reaction mixture was heated under reflux at

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- (6) W. G. Dauben, J. C. Reid and P. E. Yankwich, Anal. Chem., 19, 828 (1947).
(7) Received from Sterling-Winthrop Research Institute, m.p. 132-5°C.
(8) The solution received from Oak Ridge National Laboratory was reported to contain 660 mg. of 21% formaldehyde-C¹⁴ solution, 98 µc total activity, 210 µc/mole specific activity and 10% tracer activity methanol.
-

100-105° C for four hours. After cooling, 0.9 ml. of 6N hydrochloric acid was added and the flask was connected through a carbon dioxide-isopropyl alcohol cooled trap to a vacuum line. The mixture was heated under reflux for approximately 10 minutes and then the hydrochloric and formic acids were removed under vacuum.

Purification: -

Run 1. The barium carbonate precipitated from the sodium hydroxide solution with 7 ml. of 4.4M ammonium chloride and 43 ml. of 1.4M barium chloride, weighed 1.020 g. (5.2 mmoles) and the blank gave only 8 mg. of barium carbonate. In the previous inactive runs, the carbon dioxide given off was equivalent to the reactants used (Table I (a)). Three milligrams of the dimedone derivative of formaldehyde was recovered from the trap. The results of the radioactivity measurements are given in Table I.

Run 2. The reaction was carried out in the same manner as Run 1 using 4.4 mmoles of 4-phenyl-4-carbethoxypiperidine, 4.4 mmoles of formaldehyde and 9.4 mmoles of formic acid-C¹⁴. The excess formic acid was recovered from the cold trap as the sodium salt (crude weight 315 mg., 4.6 mmoles). Also recovered was 3.4 mg. of dimedone derivative of formaldehyde. Radioactivity measurements are given in Table I.

The crude product, a soft yellow solid, was removed from the reaction flask by dissolving it in chloroform. The chloroform was removed under vacuum and the crude demerol was recrystallized from dry acetone. The acetone was removed from the filtrate and second and third fractions were crystallized from chloroform-ether.

<u>Fraction</u>	<u>Weight</u> mg.	<u>% Yield</u>	<u>M.P.</u>
1	463	39	187-8
2	257	22	185-6
3	198	17	177-180

Melting points reported by Bergel et. al. (9), 188° C.

The analysis of an inactive sample, m.p. 187-8°, prepared according to the above method and corresponding to Fraction 1 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.

(9) F. Bergel, N. C. Hindley, A. L. Morrison and H. Rinderknecht,
U. S. Patent No. 2,418,289.

TABLE I

Reactants, Products, etc.	Run 1 (e)		Run 2 (f)	
	Molar Ratio	Spec. Act. $\mu\text{c}/\text{mmole}$	Molar Ratio	Spec. Act. $\mu\text{c}/\text{mmole}$
<u>Reactants</u>				
4-phenyl-4-carbethoxy-piperidine	1.0	--	1.0	--
Formaldehyde	1.0	210	1.0	--
Formic Acid	2.6	--	2.1	0.433
<u>Products</u>				
Demerol-C ¹⁴	0.39 Fr. 1 0.22 Fr. 2 0.17 Fr. 3	215 248 (b) 238	~0.65 (d)	0.003
CO ₂	1.2 (a)	0.08	1.0	0.418
Recovered formaldehyde (dimedone derivative)	3 mg.	155 (c)	3.4 mg.	0
Recovered formic acid	--	--	1.0	0.312 (c)
<p>(a) The source of the excess carbon dioxide in this reaction is unknown, but it may have resulted from the solution of CH₂O.</p> <p>(b) The higher specific activity of the less pure product indicates the presence of a radioactive impurity.</p> <p>(c) Radioactivity measurements were taken of the crude material.</p> <p>(d) The demerol was not recovered from the filtrates.</p> <p>(e) Radioactive formaldehyde and inactive formic acid were used in Run 1.</p> <p>(f) Inactive formaldehyde and radioactive formic acid were used in Run 2.</p>				

Acknowledgment:- The author wishes to thank Prof. M. Calvin, H. H. Anderson and R. T. Arnold for their help and encouragement.

SUMMARY

1. Demerol-N-methyl-C¹⁴ has been synthesized using formaldehyde-C¹⁴ in the Wallach reaction.
2. The use of formaldehyde-C¹⁴ in one reaction and formic acid-C¹⁴ in another has shown that under the conditions of the reaction, formaldehyde is the source of the N-methyl group formed, reduction is affected only by the formic acid, and there is no exchange between the formic acid and formaldehyde.