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PREPARATION OF LABELED ZINC LACTATE FROM PROPIONIC ACID

D. M. Hughes, R. Ostwald and B. M. Tolbert

May 31, 1950

Berkeley, California

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PREPARATION OF LABELED ZINC LACTATE FROM PROPIONIC
ACID

By

D. M. Hughes, R. Ostwald and B. M. Tolbert
Radiation Laboratory and Department of Chemistry
University of California, Berkeley*

ABSTRACT

May 31, 1950

Zinc lactate-1-C¹⁴, zinc lactate-2-C¹⁴ and zinc lactate-3-C¹⁴
have been prepared in yields of 76-87% based on labeled propionic acid.
Details of this preparation for a 6-12 mmole scale are described.

* The work described in this paper was sponsored by the Atomic Energy
Commission.

PREPARATION OF LABELED ZINC LACTATE FROM PROPIONIC

ACID

By

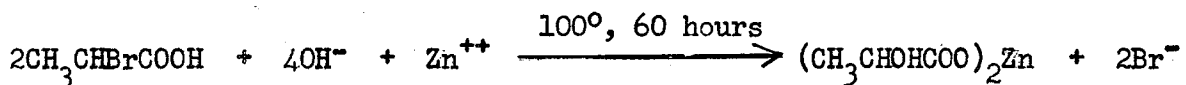
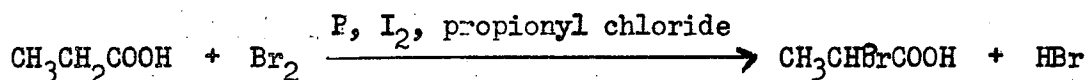
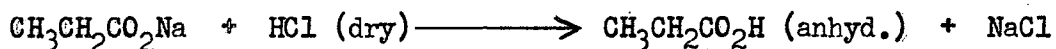
D. M. Hughes, R. Ostwald and B. M. Tolbert

Radiation Laboratory and Department of Chemistry

University of California, Berkeley*

Lactic acid, α -hydroxypropionic acid, is an important naturally occurring organic compound. It is found as a product of bacterial action on sugars, it is believed to be an important factor in muscular activity and occurs in most plant and animal foodstuffs.

As propionic acid labeled with C^{14} in any of the three positions was available, the preparation of the three labeled lactic acids from these compounds was undertaken as follows:

Experimental

Propionic Acid. - Sodium propionate-1- C^{14} was prepared in 95%

* The work described in this paper was sponsored by the Atomic Energy Commission.

yield by direct carbonation of ethyl Grignard (1). Sodium propionate-2-C¹⁴

-
- (1) "Isotopic Carbon", Calvin, Heidelberger, Reid, Tolbert and Yankwich, John Wiley and Sons, Inc., New York, 1949, pp 178-179.
-

was prepared from acetic acid-1-C¹⁴ by reduction of this material to ethanol, bromination, conversion to the Grignard and carbonation (2).

-
- (2) Unpublished material, Ostwald, Adams, and Tolbert.
-

Sodium propionate-3-C¹⁴ was prepared from sodium acetate-2-C¹⁴ (3) in the same way the two-labeled propionate was made.

-
- (3) B.M. Tolbert, J. Biol. Chem., 173, 205 (1948).
-

α -Bromopropionic Acid.- Anhydrous propionic acid was prepared by heating 1.2215 g. dry sodium propionate-3-C¹⁴ (6.52 mc.) with dry HCl (dried over phosphorus pentoxide) in a gas-solid reactor (Figure 1). The excess HCl was removed under a vacuum at Dry Ice-isopropyl alcohol temperature.

The propionic acid was then distilled into the bromination vessel (Fig. 2) which contained 0.04 g. red phosphorus, 0.02 g. iodine and 0.2 cc. propionyl chloride. The mixture was allowed to reflux on the steam bath for one-half hour to react with any traces of water, and then 1.5 cc.

of repurified Br_2 was added dropwise and refluxing continued for three or more hours. The condenser was kept at Dry Ice-isopropyl alcohol temperature and the apparatus (Fig. 2) was kept open to the air but protected by a Drierite filled tube.

At the completion of the reaction the apparatus unit was closed from the air and the reaction mixture frozen with liquid nitrogen to distill any material from the sidewalls and condensed it into the main body of liquid. Water was then added carefully to the cold mixture to hydrolyze the acid chloride. Finally, a total of 20 ml. of water was added and the material transferred to a 60 cc. flask to which a condenser was attached. The excess Br_2 was reduced by adding 1N sodium bisulfite dropwise until the color disappeared; 15 ml. was required. Six grams of zinc oxide was added, and the hydrolysis of the bromide carried out at steam bath temperature for 2-1/2 days. The excess zinc oxide was filtered from the hot solution and washed five or six times with hot water. The filtrate and wash water were combined and evaporated a volume of about 6 cc. and placed in the refrigerator for two to three days to crystallize.

Purification of the Zinc Lactate. - The crystals were filtered off and recrystallized from 5 cc. 0.1 N zinc chloride solution. All crystallizations were slow, requiring one or more days to reach completion. The crystals were filtered and dried under vacuum for twenty-four hours. This material was then permitted to stand in the laboratory (relative humidity 50%) in a dust-free place for three days. Yield -

anhydrous, 1.3251 g.; hydrated, 1.6235 g. $[\text{Zn}(\text{Lac})_2 \cdot 3\text{H}_2\text{O}]$ or 72.8% theoretical.

A second crop was obtained by adding 0.3 g. non-radioactive zinc lactate to the filtrate and recrystallizing. The resulting crystals were further recrystallized from fresh 0.1 N zinc chloride. Yield - anhydrous, 0.2771 g.; 0.877 $\mu\text{c}/\text{mg}$. or 3.7% of activity.

Anal. A low activity run analyzed as follows: C, 24.10%; H, 5.36%; residue, 27.3%. Theoretical (based on the formula $(\text{CH}_3\text{CHOHCO})_2\text{Zn} \cdot 3\text{H}_2\text{O}$): C, 24.16%; H, 5.43%; residue (zinc oxide), 27.28%.

Discussion

The yields, specific activities and scale of reaction for these several preparations are listed below in Table I.

Table I

<u>Compound</u>	<u>Scale of Reaction</u>	<u>First Crop</u>		<u>Second Crop</u>	<u>Total</u>
		<u>% Yield</u>	<u>Sp. Act.</u>	<u>% Yield</u>	<u>% Yield</u>
Zinc lactate-1-C ¹⁴ DH-46-22	12.1 mmoles	59.2	5.30 $\mu\text{c}/\text{mg}$.	28.2	8.74
Zinc lactate-1-C ¹⁴ DH-46-19	6.3 mmoles	66.9	3.85 $\mu\text{c}/\text{mg}$.	14.9	8.18
Zinc lactate-2-C ¹⁴ DH-46-24	13.5 mmoles	74.5	6.90 $\mu\text{c}/\text{mg}$.	9.5	84.0
Zinc lactate-3-C ¹⁴ DH-46-26	12.7 mmoles	72.8	3.09 $\mu\text{c}/\text{mg}$.	3.7	76.3

This material, the zinc salt, can be easily and quantitatively converted to the free acid by shaking a solution of the salt with excess Dowex 50 ion exchange resin. The resin, with the zinc, is then filtered off,

washed to give a filtrate containing no zinc. This, or a similar procedure, is necessary in most biological experiments, for zinc is quite toxic.

Attempts to recrystallize the crude zinc lactate from distilled water resulted in a product with a low C analysis, even assuming adequate water of crystallization. Since crystallization from dilute zinc chloride solution corrected this difficulty it is presumed this effect was due to partial hydrolysis of the zinc lactate.

In order to produce a stable material of uniform hydration, the procedure described, of first dehydration followed by atmospheric hydration, was adopted. Evidence for exactly three waters of hydration was obtained not only from the analytic work (C, H, ash) but also from the weight of the anhydrous to the hydrated material. The calculated value is 0.819 (244/298); the observed value is 0.816.

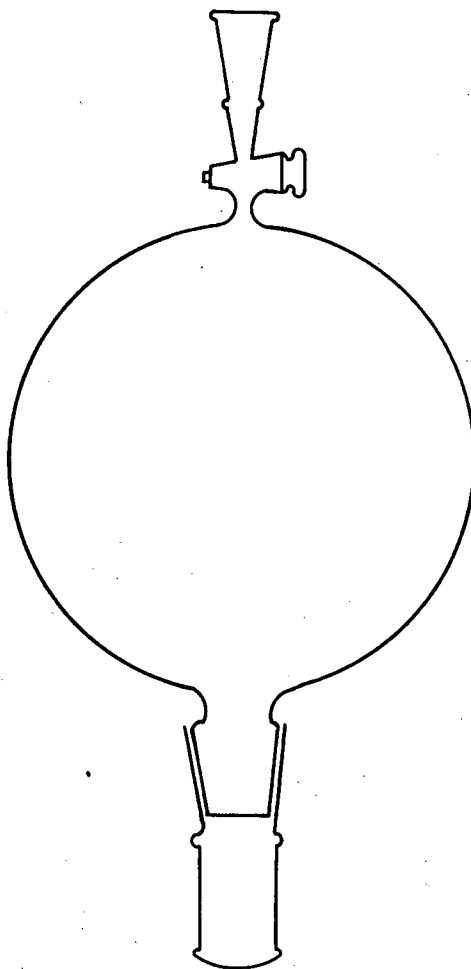
Two-dimensional paper chromatography (phenol-water and butanol-propionic acid) and radioautographs of the chromatograms showed only one radioactive spot for the first two crops, thus indicating the radiopurity of this material. A trace of excess zinc chloride is probably present, however.

A third crop containing 2.8% of the initial activity was obtained in the same manner as the second crop. This material contained 3-6% of a radioactive impurity.

Acknowledgments: The authors would like to thank Prof. M. Calvin for his continued help and encouragement in this work.

Summary

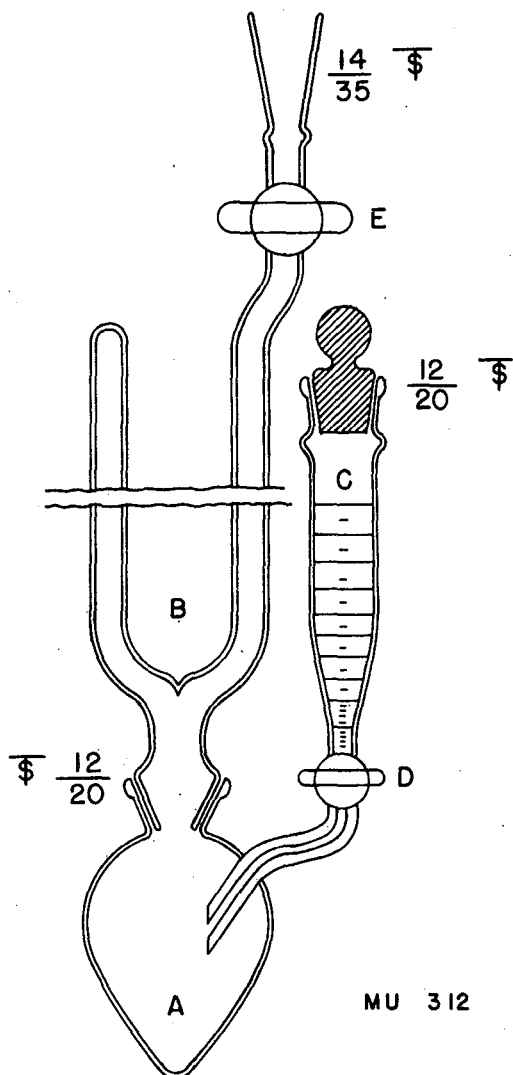
Zinc lactate-1-C¹⁴, zinc lactate-2-C¹⁴ and zinc lactate-3-C¹⁴ have been prepared in yields of 76-87% based on labeled propionic acid. Details of this preparation for a 6-12 mmole scale are described.



GAS SOLID REACTOR
(CAPACITY = 2L)

MU 310

FIG. 1



SEMI-MICRO BROMINATION VESSEL: A, 30 ml CONICAL FLASK; B, DRY ICE REFLUX CONDENSER; C, 12 ml GRADUATED CENTRIFUGE TUBE; D + E, 2 AND 3 mm BORE STOPCOCKS, RESPECTIVELY. FIG. 2