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Franco Mazzetti and Richard M. Lemmon

August 2, 1956

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ABSTRACT

The synthesis of DL-carnitine hydrochloride via an oxazolidine intermediate has been simplified and improved. The crystalline product is obtained in a 5-step synthesis from epichlorohydrin with an over-all yield of 32%.

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We have recently been interested in studying the radiation sensitivity of DL-carnitine hydrochloride, $\left[(CH_3)_3NCH_2CH(OH)CH_2CO_2H\right]^+Cl^-$. The first synthetic route to carnitine, involving a Gabriel-type synthesis, was described by Tomita;[1] however, the yields were poor. Another synthesis, based on an oxazolidine intermediate of Bergmann's,[2] has been given by Carter.[3] A final procedure, recently given by Strack et al.,[4] involves the preparation of the mononitrile from $ClCH_2CH(OH)CH_2Cl$, followed by reacting the chloronitrile with trimethylamine, and finally hydrolyzing the -CN group to $-CO_2H$. This latter procedure was of little interest to us, as the over-all yields were also low and because we wished to introduce C^{14} into the carnitine molecule, via $C^{14}H_3I$, at the last step of a reaction sequence. We therefore turned our attention to the Bergmann-Carter synthesis. It is carried out as follows:

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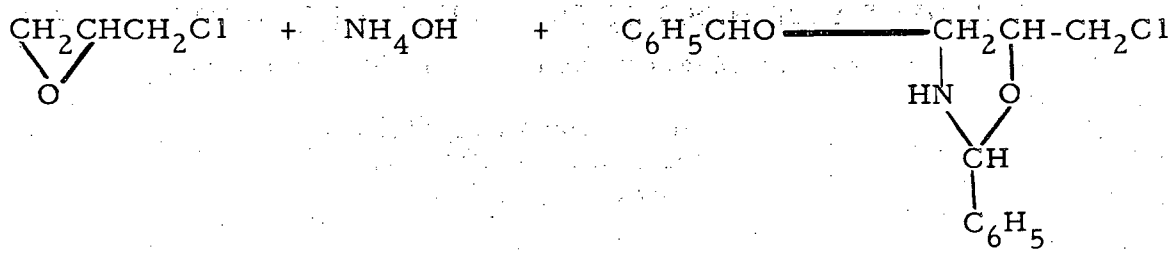
* U.S. Foreign Operations Administration Fellow, 1954-1956.

1 M. Tomita, Z. physiol. Chem. 124, 253 (1922).

2 Bergmann, Brand, and Weinmann, Z. physiol. Chem. 131, 1 (1923).

3 H. E. Carter and P. K. Bhattacharyya, J. Am. Chem. Soc. 75, 2503 (1953).

4 Strack, Röhnert, and Lorenz, Chem. Ber. 86, 525 (1953).



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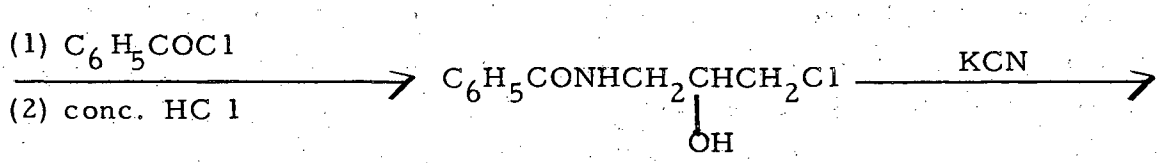

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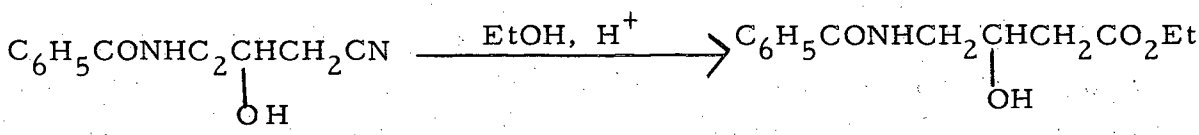

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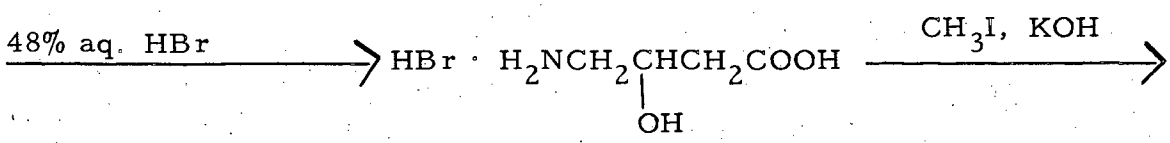

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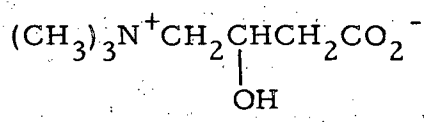

carnitine

VI

We have found that this reaction sequence can be simplified by going directly from the benzoylaminonitrile (III) to the amino acid (V) in a single step. The final step in the sequence, the methylation of the amino acid, is surprisingly difficult. The amino acid is very susceptible to lactamization in dilute alkaline solution and, furthermore, it is difficult to separate the carnitine from the cation of the base used to effect the methylation. The best methylation procedure for this amino acid now available[3] is difficult, particularly for a small-scale preparation with C^{14}, because it involves successive extractions with phenol, countercurrent washings with water, and final washings of aqueous extracts with ether. We have found that the use of barium hydroxide as the base in the methylation, removal of barium with H_2SO_4, and exchange of other anions for hydrozide on an ion-exchange column leads to an 88% yield of recrystallized DL-carnitine hydrochloride from the amino acid. The experimental conditions for the improved synthesis of carnitine are described below. (All melting points are uncorrected.)

EXPERIMENTAL

5-Chloromethyl-2-phenyloxazolidine (I). The directions given by Carter[3] are excellent. It is desirable to use freshly purified benzaldehyde and epichlorohydrin, and to add the epichlorohydrin very slowly (to decrease polymerization). We have obtained a yield of 85% of impure oxazolidine by this procedure and, after crystallization, the analytically-pure compound was obtained in 76% yield; m.p. 71°. Use of the 76% of pure product gives a higher yield in the next step than does the corresponding 85% of impure material.

Anal. Calc'd for $C_{10}H_{12}ClNO$: C, 60.76; H, 6.11. Found: C, 60.90; H, 6.06.

3-Benzoylamino-1-chloro-2-hydroxypropane (II). This is a modification of the procedure given by Bergmann et al.[5] To a solution of 40 g (0.2 mole) of pure oxazolidine in 150 ml of chloroform was added 16 g (0.2 mole) of pyridine. The solution was cooled to -40° in a dry ice-isopropyl alcohol bath and removed from the bath, and 28 g (0.2 mole) of benzoyl chloride was added

[5] Bergmann, Radt, and Brand, Chem. Ber. 54, 1645 (1921).

dropwise, with stirring. During this addition the temperature of the reaction mixture reached a maximum of 0°. The mixture was then left overnight at room temperature; however, another experiment indicated that the overnight standing was unnecessary.

Concentrated HCl (200 ml) was then added and the mixture stirred for 5 minutes. Finally, 500 ml of water and 500 ml of petroleum ether (b.p. 60–70°) were added and the flask was placed in a refrigerator. Crystals soon appeared in the upper (pet. ether) phase, and the crystallization was complete in 1 to 2 hours. The yield of the crystallized benzoylamino-chlorohydroxypropane was 26.8 g (yield 79%); m.p. 108°.

Anal. Calc'd for $C_{10}H_{12}ClNO_2$: C, 56.20; H, 5.66. Found: C, 55.94; H, 5.63.

3-Benzoylamino-1-cyano-2-hydroxypropane (III). Ten grams (47 millimoles) of crystallized benzoylaminochlorohydroxypropane (II) was dissolved in 60 ml of 67% ethanol and 5 g (77 millimoles) of KCN, and 50 mg of KI were added. The solution was left at room temperature for 72 hours. The alcohol and water were removed by evaporation at reduced pressure, and the crystalline residue was washed with ice water, filtered, rewashed with ice water, and dried. It was recrystallized from acetone–petroleum ether, giving 7.7 g (yield 80%) of pure nitrile, m.p. 126°.

Anal. Calc'd for $C_{11}H_{12}N_2O_2$: C, 64.67; H, 5.93. Found: C, 64.41; H, 5.80.

3-Amino-2-hydroxybutyric acid (V). The cyano group of III was hydrolyzed to carboxyl and the benzoyl group was simultaneously removed as follows:

To 1.60 g (7.8 mmoles) of the pure benzoylaminonitrile was added 10 ml of reagent-grade 48% aqueous HBr, and the solution was refluxed for 45 minutes; times that were shorter (10, 20, or 30 min) or longer (1 or 3 hr) led to lesser yields. The benzoic acid freed by the hydrolysis was filtered off and washed with a few ml of water (which was added back to the reaction mixture), and the remainder of the benzoic acid in solution was extracted by ether. Gaseous ethylene oxide was then passed into the solution until a final pH of about 6 was reached. Two-thirds of the water was removed under reduced pressure and 25 ml of ethanol was added to give an ethanol: water ratio of about 3:1. A few drops of conc. NH_4OH were added to bring the pH to 7; this causes crystallization of the amino acid. The product was

washed with 30 ml of 3:1 ethanol-water and recrystallized from the same solvent mixture. The yield was 0.70 g (75%) of amino acid with a melting point of 212°.

Anal. Calc'd for $C_4H_9NO_3$: C, 40.33; H, 7.62. Found: C, 40.11; H, 7.64.

DL-Carnitine hydrochloride (VI). To a suspension of 6.6 g (70 meq) of $Ba(OH)_2 \cdot H_2O$ in 20 ml of water was added 1.0 g (8.4 mmoles) of recrystallized amino acid. Ten grams (70 mmoles) of methyl iodide was added and brought into solution with the addition of 100 ml of methanol. The reaction flask was tightly stoppered and stirred overnight at room temperature. Seventy meq of H_2SO_4 (11.6 ml of 6 N) was added and the barium sulfate removed by centrifugation. The supernatant liquid and washings, containing carnitine, iodide, and sulfate ions, was then passed into 50 ml of Dowex 1-X anion-exchange resin in the hydroxide form. The solumn was washed with about 25 ml of distilled water (until aliquot portions of the effluent gave, after removal of the methanol, negative reineckate[6] tests for carnitine) and the effluent was then made acid with a slight excess of dilute HCl. This solution was evaporated to dryness and the carnitine hydrochloride was recrystallized from methanol-ether solution to give 1.46 g (yield 88%). The over-all yield from epichlorophydrin to carnitine hydrochloride was 32%.

Anal. Calc'd for $C_7H_{16}ClNO$: C, 42.51; H, 8.16. Found: C, 42.60; H, 8.01.

This work was done under the auspices of the U.S. Atomic Energy Commission.

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[6] David Glick, J. Biol. Chem. 156, 643 (1944).