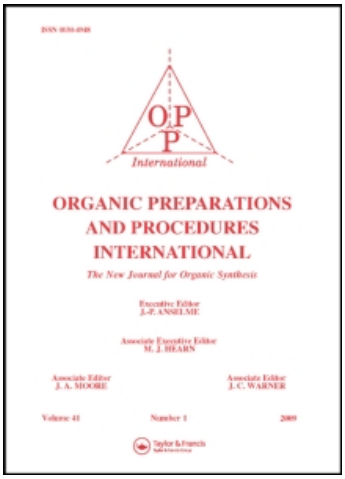

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AN EFFICIENT SYNTHESIS OF D,L-CARNITINE HYDROCHLORIDE

via THE ACYLATION OF AN α-AMINOKETONE

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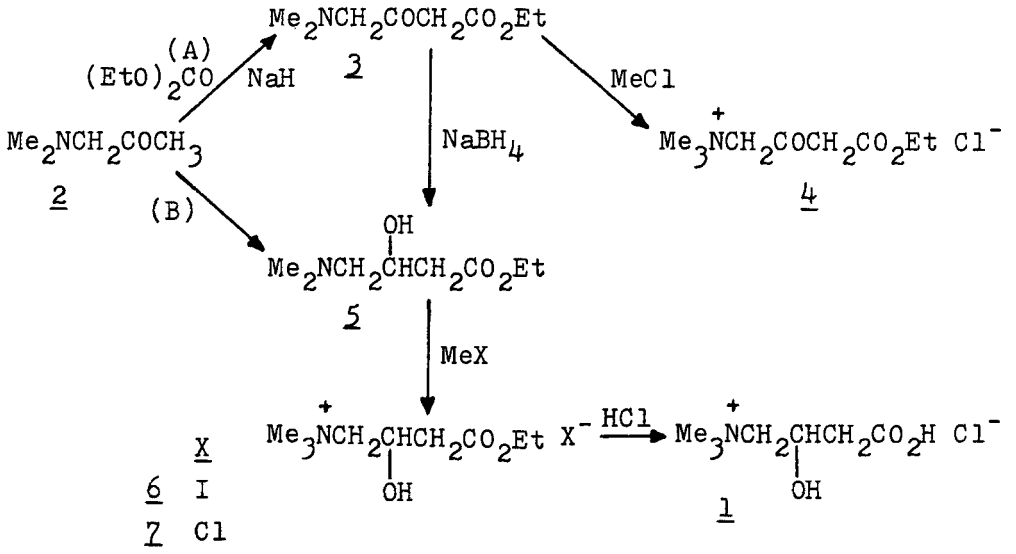
Carnitine, 1, is extremely important in mammalian systems[1] where it is required for the transport of long chain fatty acids into mitochondria. Recent interest related to this role has focused on carnitine's involvement in diabetes and heart function. In view of its physiological importance, it is not surprising that several synthetic approaches to D,L-carnitine have been reported.[2-10] However, most of these suffer from disadvantages including poor yield, numerous synthetic steps, inconvenience, and a lack of potentially versatile synthetic intermediates that might be utilized for preparing carnitine analogues.



We now report an improved synthesis of D,L-carnitine hydrochloride from commercially available dimethylaminoacetone in an overall yield of 50%. This procedure is the first carnitine synthesis to utilize C-acylation as a key step, and in particular incorporates an uncommon regioselective C-acylation of an α-aminoketone. Laborious ion exchange chromatography is not required. Additionally, the method described here offers the advantages of providing a synthetically versatile β-ketoester[11,12] intermediate and allowing for the ready incorporation of isotopic labels for biological studies.

A preparation in 30% yield of key intermediate 3 from ethyl 4-chloroacetoacetate and dimethylamine was previously reported;[13] our efforts to improve upon this preparation were unsuccessful. We therefore attempted to prepare 3 via the regioselective acylation of commercially available aminoketone 2 under conditions similar to that reported for acylating simple ketones.[14] Thus the reaction of 2 with NaH and diethyl carbonate proceeded smoothly to provide 3 (90%). Ketoester 3 was stable to distillation, could be stored for short periods of time, and when freshly distilled was satisfactory for subsequent reactions. However, in spite of protection from air, moisture and light or storage at 0°, 3 turned purple and degraded to several components in a few days. As a result we could not obtain a satisfactory elemental analysis for 3. Compound 3 was therefore quaternized with gaseous CH_3Cl to provide crystalline 4 (93%), which was completely characterized.

Freshly distilled ketoester 3 was reduced with $NaBH_4$ to give hydroxy-ester 5 (55%). Alternatively, 5 was more conveniently prepared directly from 2 in a one-pot reaction (Method B, Experimental Section), resulting in the same overall yield from 2.

The conversion of 5 to carnitine hydrochloride (1) was accomplished by two routes. The first involved the quaternization of 5 with CH_3I to provide the ammonium iodide ester 6. This was either hydrolyzed with HCl and converted to the chloride form on a Dowex 50 (H^+ form) column or converted to the hydroxide form with Ag_2O followed by heating in HCl to provide 1. A more direct route involved the quaternization of 5 with gaseous CH_3Cl to form 7, which was hydrolyzed in HCl to give 1.

In summary, the procedure described here represents a new, efficient synthesis of D,L-carnitine hydrochloride (1) from dimethylaminoacetone (2) in an overall yield of 50%.

EXPERIMENTAL SECTION

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. ^1H-NMR spectra were recorded on a Varian EM 360 spectrometer using $(CH_3)_4Si$ as internal standard. IR spectra were recorded on a Beckman Acculab 6 spectrophotometer. Elemental analyses were performed at Atlantic Microlab of Atlanta, GA.

Ethyl 4-(dimethylamino)-3-oxobutanoate (3).- To 2.11 g (44.0 mmol) of 50% NaH/mineral oil under N_2 was added 10 mL of DME followed by diethyl carbonate (4.81 g, 40.8 mmol). The heterogeneous mixture was heated nearly to reflux, and a solution of 2 (2.01 g, 19.9 mmol) in 10 mL DME was then added dropwise over 45 min. The mixture was heated for an additional 3 hrs, cooled to R.T. and 2.63 g (43.8 mmol) of HOAc was added slowly followed by 20 mL of H_2O. Most of the DME was removed *in vacuo* and the solution was acidified (pH 5.5) with additional HOAc. Residual mineral oil was then extracted with pentane (2 x 30 mL). The solution was adjusted to pH 8 (NaOH), extracted with 5 x 50 mL EtOAc, the combined extracts dried (Na_2SO_4), and the solvent removed to provide 3.1 g (90%) of 3 as an oil, bp. 74-75° (0.8 mm). Distillation provided 2.5 g of 3 as a colorless oil, which turned purple and degraded to several components in a few days despite protection from air, light, and moisture or storage at 0°.

^{1}H-NMR ($CDCl_3$): δ 1.27 (t, 3H, $CH_2\underline{CH_3}$), 2.3 (s, 6H, $N(CH_3)_2$), 3.23 (s, 2H, $N-CH_2$), 3.47 (s, 2H, $COCH_2CO$), 4.18 (q, 2H, $\underline{CH_2}CH_3$); IR (KBr): 1735, 1718 cm-1 (sh, C=O).

Ethyl 3-oxo-4-(trimethylammonium)butanoate chloride (4).- A solution of freshly distilled 3 (1.3 g, 7.5 mmol) in 15 mL of anhydrous acetone was placed in a 200 mL pear-shaped pressure bottle and cooled to -78°. Gaseous CH_3Cl was bubbled through the solution for 5 min. or less (until the weight increase indicated a 5 molar excess of CH_3Cl), the bottle was sealed, and the cooling bath was removed. The solution was stirred for 24 hrs at R.T., during which a white crystalline precipitate formed. This was filtered, washed with acetone and dried in vacuo to provide 1.6 g (93%) of 4, mp. 173-175° (dec.) (CH_3OH/Et_2O).

^{1}H-NMR (DMSO-d_6): δ 1.23 (t, 3H, $CH_2\underline{CH_3}$), 3.27 (s, 9H, $N(CH_3)_3$), 3.73 (s, 2H, $COCH_2CO$), 4.15 (q, 2H, $\underline{CH_2}CH_3$), 4.77 (s, 2H, $N-CH_2$); IR (KBr): 1740, 1720 cm^{-1} (C=O).

Anal. Calc. for $C_9H_{18}NO_3Cl$: C, 48.32; H, 8.11; N, 6.26; Cl, 15.85.

Found: C, 48.42; H, 8.12; N, 6.25, Cl, 15.85.

Ethyl 4-(dimethylamino)-3-hydroxybutanoate (5)

Method A.- A solution of freshly distilled 3 (1.72 g, 9.95 mmol) in 25 mL of 95% EtOH was chilled in an ice bath and adjusted to pH 7.5 (1N NaOH). To this was added, all at once, $NaBH_4$ (0.188 g, 4.97 mmol), and the resulting mixture was stirred at 0° for 4 hrs. While held at 0° the solution was adjusted to pH 5 (2 N HCl) and then adjusted to pH 13 (20% NaOH). The solvent was removed in vacuo at 30° and the residue triturated with EtOH to remove most of the salts. The EtOH extracts were concentrated and the oily residue applied to an alumina column (15 x 4.5 cm). This was eluted with $CHCl_3$, and the fractions containing material with R_f = 0.64 (alumina, $CHCl_3$) were combined and concentrated to give 0.96 g (55%) of

pure 5 as an oil, bp. 73° (0.4 mm) (lit.[16] bp. 90-93° at 4-5 mm). ^{1}H-NMR ($CDCl_3$): δ 1.28 (t, 3H, $CH_2\underline{CH_3}$), 2.3 (s, 6H, $N(CH_3)_2$), 2.2-2.6 (m, 4H, $\underline{CH_2}CH(OH)\underline{CH_2}$), 3.47 (br s, 1H, OH), 4.13 (m, 3H, $\underline{CH}(OH)$ and $\underline{CH_2}CH_3$); IR (KBr): 3410 (OH), 1715 cm^{-1} (C=O).

Anal. Calc. for $C_8H_{17}NO_3$: C, 54.83; H, 9.78; N, 7.99.

Found: C, 54.59; H, 9.81; N, 7.86.

Method B.- As described in the preparation of 3 (above), aminoketone 2 (3.00 g, 29.7 mmol) was treated with 2.85 g (59.6 mmol) of 50% NaH/mineral oil and 7.00 g (59.3 mmol) of diethyl carbonate in 20 mL of dry DME. Following extraction of the mineral oil with pentane, the solution was adjusted to pH 7.5 (20% NaOH), chilled to 0°, and $NaBH_4$ (1.14 g, 30.0 mmol) added all at once. After stirring at 0° for 4 hrs, the reaction mixture was treated as described above for the preparation of 5 (Method A). Chromatography of the crude product on alumina provided 2.6 g (50% overall yield from 2) of pure 5 that was identical in all respects to the material produced by Method A.

Ethyl 3-hydroxy-4-(trimethylammonium)butanoate iodide (6).- To a solution of 5 (1.20 g, 6.86 mmol) in 15 mL of acetone was added CH_3I (1.46 g, 10.28 mmol) and the mixture stirred for 18 hrs at R.T. The solvent was removed in vacuo to yield 2.1 g (97%) of 6 as a white, crystalline residue, mp. 133-4° (MeOH/Et_2O) (lit.[17] mp. 123-124°).

^{1}H-NMR (DMSO-d_6): δ 1.21 (t, 3H, $CH_2\underline{CH_3}$), 2.49 (d, 2H, $\underline{CH_2}CO_2Et$, $J_{2,3}$ = 6 Hz), 3.18 (s, 9H, $N(CH_3)_3$), 3.4 (d, 2H, $N\text{-}CH_2$, $J_{3,4}$ = 6 Hz), 4.1 (q, 2H, $\underline{CH_2}CH_3$), 4.1-4.7 (m, 1H, $\underline{CH}OH$), 5.62 (d, 1H, OH); IR (KBr): 3390 (OH), 1730 cm^{-1} (C=O).

Ethyl 3-hydroxy-4-(trimethylammonium)butanoate chloride (7).- A solution of 5 (0.520 g, 2.97 mmol) in 12 mL of acetone was placed in a 200 mL pear-shaped pressure bottle and cooled to -78°. Gaseous CH_3Cl was bubbled

through the solution until the weight increased by 4.10 g (81.3 mmol of CH_3Cl), which required about 2 min. The pressure bottle was capped, the cooling bath removed, and the mixture stirred at R.T. for 20 hrs. The solution was concentrated in vacuo to provide 0.67 g (100%) of 7 as a clear oil which crystallized on standing, mp. 129.5-130.5° (acetone/EtOH). ^{1}H-NMR (DMSO-d_6): δ 1.21 (t, 3H, $CH_2\underline{CH_3}$), 2.5 (d, 2H, $\underline{CH_2}CO_2Et$, $J_{2,3}$ = 6 Hz), 3.23 (s, 9H, $N(CH_3)_3$), 3.45 (d, 2H, NCH_2, $J_{3,4}$ = 6 Hz), 4.1 (q, 2H, $\underline{CH_2}CH_3$), 4.1-4.7 (m, 1H, $\underline{CH}OH$), 6.12 (d, 1H, $O\underline{H}$); IR (KBr): 3300 (OH), 1730 cm^{-1} (C=O).

Anal. Calc. for $C_9H_{20}NO_3Cl$: C, 47.89; H, 8.93; N, 6.21.

Found: C, 47.71; H, 9.32; N, 5.83.

D,L-Carnitine hydrochloride (1)

Method A.- Hydroxyester 6 (1.00 g, 3.16 mmol) was dissolved in 12 mL of 15% CH_3OH/H_2O and Ag_2O (0.731 g, 3.16 mmol) was added all at once. After stirring at R.T. for 24 hrs, the solution was filtered, CH_3OH removed from the filtrate in vacuo, and the resulting aqueous layer acidified with conc. HCl (pH 1). The solution was heated at 60° for 0.5 hr and the solvent removed in vacuo to give 0.62 g (100%) of 1, mp. 195-196° (dec.) (CH_3OH/Et_2O), lit.[4] mp. 195-197°.

Method B.- Hydroxy ester 6 (1.00 g, 3.16 mmol) was dissolved in 20 mL of conc. HCl and heated at 60° for 0.5 hr. The solvent was removed in vacuo and the residue was placed on a Dowex 50x8-200 column (H^+ form, 20 x 2.3 cm). The column was eluted with 200 mL of deionized H_2O followed by 500 mL of 2N HCl. Those fractions containing organic material (detected by spotting on a silica TLC plate without elution and staining with I_2) were combined and concentrated to give 0.57 g (91%) of 1, mp 196-197° (dec.) (CH_3OH/Et_2O).

Method C.- Hydroxyester 7 (100 mg, 0.44 mmol) was dissolved in 3 mL of conc. HCl and heated at 60° for 0.5 hr. The reaction mixture was concentrated in vacuo to provide 88 mg (100%) of 1, mp. 195-196° (dec.) (CH_3OH/Et_2O).

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