pound, thus producing two diastereoisomers which were seen separately via the singlets at δ 3.55 and 3.57 (also a slight difference was observed for the two protons in the propyl side chain: the two doublets, centered around δ 2.3 and 2.6, each consisted of two partially separated doublets). (+)-**34** ([α]$_{578}$ +4.81°) gave the di-(−)-menthyl ester with the singlet at δ 3.55 predominating, while the di-(−)-menthyl ester from (−)-**34** ([α]$_{578}$ −5.10°) had the singlet at δ 3.57 predominating. Anal. Calcd for $C_{34}H_{60}O_4S_2$: C, 68.41; H, 10.13; S, 10.74. Found: C, 68.70, 68.87; H, 10.09, 10.25; S, 10.42, 10.55.

3-[2,2-(Ethylenedithio)propyl]-3-methylheptanoic Acid (38). Distillation of crude (+)-**34** (25.5 g, [α]$_{578}$ +4.81°) gave the decarboxylated acid: bp 168–171 °C (0.03 mm); 14.83 g (53.7 mmol, 74% yield based on the (−)-cinchonidine salt of **34**). It has a very small specific rotation ([α]$_{578}$ +0.1°) which was influenced by small impurities (**38** obtained from other fractions of **34** showed rather variable specific rotations): ^{1}H NMR (CCl_4) δ 0.7–1.6 (m, 12 H), 1.8 (s, 3 H), 2.2 (s, 2 H), 2.45 (s, 2 H), 3.25 (s, 4 H), 12.0 (s, 1 H). Anal. Calcd for $C_{13}H_{24}O_2S_2$: C, 56.48; H, 8.75; S, 23.19. Found: C, 56.61, 56.52; H, 8.86, 8.77; S, 23.06, 23.11.

3-Methyl-3-propylheptanoic Acid (25). A Raney nickel catalyst, W-5, prepared from nickel–aluminum alloy (175 g) and sodium hydroxide (225 g) in water (840 mL) was heated under reflux for 4 h with 4.37 g of **38** (52.1 mmol), sodium carbonate (18 g), water (1300 mL), and ethanol (100 mL). The mixture was filtered while hot, and the catalyst was washed with boiling sodium carbonate solution (300 mL of a 5% solution), boiling ethanol (300 mL), and boiling water (300 mL), respectively. The combined filtrates were acidified with concentrated hydrochloric acid, and the acid **25** was extracted with chloroform (3 × 300 mL). The combined chloroform layers were washed with water, dried, evaporated, and distilled to give **25**: bp 118–120 °C (1 mm); 8.84 g (47.5 mmol, 91%).

In all desulfurizations of **38** with Raney nickel, the product **25** contained small variable amounts of impurities which could not be removed by distillation.

Acknowledgment. This investigation was supported by the Netherlands Foundation for Chemical Research (SON).

Registry No. (+)-**10**, 73636-61-0; (−)-**10**, 73636-62-1; **11**, 73651-43-1; **12** (isomer 1), 73636-63-2; **12** (isomer 2), 73679-16-0; **13**, 73636-64-3; **14**, 73636-65-4; **15**, 73636-66-5; **16**, 73636-67-6; **17**, 18795-91-0; **18**, 73636-68-7; **19**, 35205-69-7; **20**, 73636-69-8; **21**, 73636-70-1; **22** (isomer 1), 73636-71-2; **22** (isomer 2), 73679-37-5; (+)-**24**, 73636-72-3; (−)-**24**, 67752-85-6; (+)-**25**, 73636-73-4; (−)-**25**, 67727-45-1; (+)-**26**, 73636-74-5; (+)-**26** tosylate, 73636-75-6; (−)-**26**, 73636-76-7; (−)-**26** tosylate, 73636-77-8; **28**, 60934-88-5; **29**, 73636-78-9; (±)-**30**, 73636-79-0; **31**, 73636-80-3; (±)-**32**, 73636-81-4; (±)-**33**, 73636-82-5; (±)-**34**, 73636-83-6; (±)-**34** (−)-cinchonidine salt, 73636-84-7; (+)-**34**, 73636-85-8; (+)-**34** (−)-cinchonidine salt, 73636-86-9; (−)-**34**, 73636-87-0; **36**, 485-71-2; **37** (isomer 1), 73651-44-2; **37** (isomer 2), 73636-88-1; (±)-**38**, 73636-89-2; (+)-**38**, 73636-89-2; (−)-menthol, 2216-51-5; diethyl malonate, 510-20-3; 2-pentanone, 107-87-9; 2-hexanone, 591-78-6; 4-octanone, 589-63-9; 4-nonanone, 4485-09-0; 5-decanone, 820-29-1; 2-bromothiophene, 1003-09-4; acetylacetone, 123-54-6; cyanoacetamide, 107-91-5; ethyl (±)-3-acetonyl-3-methylheptanoate, 73636-90-5.

Synthesis of Carnitine Homologues. Reactions of Tertiary Amines with Epoxy Esters

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Received November 2, 1979

A series of new carnitine homologues, 4-hydroxy-5-(trialkylammonio)pentanoates (**2**) and 5-hydroxy-6-(trialkylammonio)hexanoates (**3**), has been synthesized. The key step in this synthesis was the reaction of an epoxy ester with a tertiary amine to effect epoxide opening and hydrolysis in one step. The generality of this reaction is discussed, and the synthetic approach to **2** and **3** is compared to previously published routes to carnitine and its analogues. Attempts to apply the new reaction scheme to carnitine itself are described.

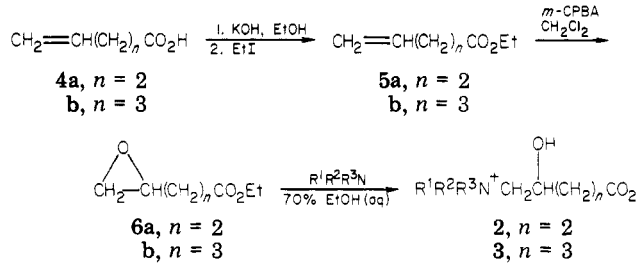
The role of carnitine (**1**), often referred to as vitamin B_T,

$$(CH_3)_3N^+CH_2CH(OH)CH_2CO_2^-$$
1

in the transport of fatty acids across membranes is now well established[1] though research in this area continues.[2] Several analogues of carnitine have also been investigated. For example, Norum studied the effect of various ammoniobutyrates on the carnitine transport system.[3] In 1975 the synthesis and evaluation of several dialkylaminohydroxybutyric acid hydrochlorides and methochlorides as potential hypoglycemic agents were reported.[4]

Our interest in hydroxylated quaternary ammoniocarboxylates led us to the development of an efficient route to their synthesis. We report here the successful preparation of several hydroxylated (trialkylammonio)pentanoates (**2**) and hexanoates (**3**), new carnitine homologues.

Scheme I



$$R^1R^2R^3N^+C^5H_2C^4H(OH)C^3H_2C^2H_2C^1O_2^-$$
2

$$R^1R^2R^3N^+C^6H_2C^5H(OH)C^4H_2C^3H_2C^2H_2C^1O_2^-$$
3

The key step in this sequence is a one-step epoxide ring opening and ester hydrolysis which to our knowledge has

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0022-3263/80/1945-2763$01.00/0

Table I. Reactions of Tertiary Amines with Epoxy Esters 6

epoxy ester	amine R¹	amine R²	amine R³	product	yield, %
6a	CH_3	CH_3	CH_3	$(CH_3)_3N^+CH_2CH(OH)(CH_2)_2CO_2^-$ (2b)	61
6a	C_2H_5	C_2H_5	C_2H_5	$(C_2H_5)_3N^+CH_2CH(OH)(CH_2)_2CO_2^-$ (2b)	66
6a	n-$C_{14}H_{29}$	CH_3	CH_3	n-$C_{14}H_{29}N^+(CH_3)_2CH_2(OH)CH(CH_2)_2CO_2^-$ (2c)	69
6b	CH_3	CH_3	CH_3	$(CH_3)_3N^+CH_2CH(OH)(CH_2)_3CO_2^-$ (3a)	70
6b	C_2H_5	C_2H_5	C_2H_5	$(C_2H_5)_3N^+CH_2CH(OH)(CH_2)_3CO_2^-$ (3b)	50
6b	n-C_4H_9	n-C_4H_9	n-C_4H_9	$(n$-$C_4H_9)_3N^+CH_2CH(OH)(CH_2)_3CO_2^-$ (3c)	48
6b	$PhCH_2$	CH_3	CH_3	$PhCH_2N^+(CH_3)_2CH_2CH(OH)(CH_2)_3CO_2^-$ (3d)	60
6b	n-$C_{22}H_{45}$	CH_3	CH_3	n-$C_{22}H_{45}N^+(CH_3)_2CH_2CH(OH)(CH_2)_3CO_2^-$ (3e)	66

not been previously reported. Conceptually, this procedure was designed to effect ester hydrolysis by hydroxide ion generated in situ as epoxide opening proceeds.[5] Our attempts to apply this method to the preparation of the corresponding butyrates are also discussed.

Results and Discussion

The approach developed for the preparation of **2** and **3** is depicted in Scheme I. The potassium salt of the appropriate olefinic acid **4** was esterified with ethyl iodide.[6] Epoxidation of **5** with *m*-chloroperbenzoic acid proceeded smoothly to afford the epoxy ester **6**. Reaction of **6** with tertiary amine in 70% aqueous ethanol at 50–60 °C produced directly the desired hydroxy ammoniocarboxylate (**2**, **3**) in 48–70% yield (Table I).

In most cases the product of epoxy ester ring opening hydrolysis was initially isolated as an oil which slowly crystallized under high vacuum. Attempts to recrystallize products containing short-chain nitrogen substituents (**2a,b**, **3a–d**) were unsuccessful. However, stirring with hot dry acetone followed by chilling produced extremely hygroscopic white crystalline products which from all spectral and TLC data appeared pure. Products containing long-chain nitrogen substituents (**2c**, **3e**) crystallized on workup and were easily recrystallized from hexane–ethanol. These zwitterionic products proved to be moderately hygroscopic.

^{13}C NMR spectroscopy proved useful in confirming the direction of epoxide opening. An off-resonance-decoupling experiment on **3a** showed that the absorption assigned to the carbon bearing the hydroxyl group (66.9 ppm) split into a doublet due to coupling with the methine proton. Furthermore, the absorption due to the carbon bearing the ammonio group (71.9 ppm) split into a triplet as a result of coupling with the two methylene protons. These data plus the lack of any unaccountable absorptions indicate that the vast majority of epoxide opening (>97%) occurs from the least hindered side.

Field-desorption mass spectral data further support the proposed structures of **2** and **3**. In addition to the expected protonated molecular ions $(M + H)^+$ and lower molecular weight fragments, these spectra also contain protonated cluster ions $(xM + H)^+$, where x = 2–4, and species derived from alkyl group transfer from nitrogen to the carboxylate oxygen. Similar behavior has been observed previously in related compounds.[7] A detailed description of the mass spectra of **2** and **3** will appear elsewhere.[8]

The generality of this epoxy ester ring opening hydrolysis process is evidenced by the wide variety of tertiary amines which react. Not only relatively unhindered amines react (e.g., Me_3N) but also those with much greater steric bulk (e.g., $PhCH_2NMe_2$) react successfully (Table I) in comparable yields. Also, the reaction scale presents no particular problem. We have conducted experiments on both milligram and multigram scales with similar results.

Several synthetic approaches to carnitine[9–13] and its butyrate analogues[4] have been published. Application of the latest and most efficient of these methods, by Boots and Boots,[4,13] to the synthesis of **2** and **3** would involve epoxide ring opening of **6** with the hydrochloride salt of an appropriate tertiary amine followed by a separate ester hydrolysis step. Our scheme offers an alternative approach which is more convenient in that it reduced the number of steps required, while producing yields similar to or better than those expected by application of this previous method.

A limitation of our reaction scheme was discovered when its application to the synthesis of carnitine itself (**1**) was tested. In only one instance were we able to isolate a pure, crystalline product (15% yield) whose ^1H NMR spectrum was consistent with that of carnitine.[13] Generally, our reaction conditions produced varying amounts of a dark red oil from which **1** could not be isolated. Concentration of the ether extracts from workup produced material which was shown to be a single compound by TLC and GLC. Spectral data of this byproduct were consistent with those of ethyl 4-hydroxy-2-butenoate (**7**).[14] Higher concentrations of amine minimized the amount of **7** produced but did not noticeably aid in the isolation of pure **1**. Apparently when the epoxide ring is directly bonded to the activated methylene group, proton abstraction with opening of the epoxide is competitive with ester hydrolysis.[15]

$$HOCH_2CH{=}CHCO_2Et$$
7

Experimental Section

Melting points and boiling points are uncorrected. Proton magnetic resonance spectra were obtained with Varian T-60 and HA-100 spectrometers; ^{13}C spectra were recorded on a Varian CFT-20 instrument. Infrared spectra were determined on a

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Table II. ^{13}C NMR Data for Compounds 2 and 3[a]

compd	C-1	C-2	C-3	C-4	C-5	C-6	R^1	R^2	R^3
2a	183.0	34.1[b]	32.8[b]	66.8	71.6		55.3	55.3	55.3
2b	182.7	34.0[b]	33.1[b]	66.2	62.3		8.00, 54.7	8.00, 54.7	8.00, 54.7
2c	182.2	34.4[b]	33.2[b]	66.5	69.1		53.2	52.8	15.0, 23.8, 27.4, 30.4, 31.1, 69.4
3a	183.6	36.0[b]	22.6	38.2[b]	66.9	71.9	55.4	55.4	55.4
3b	184.0	36.1[b]	22.6	38.0[b]	66.2	62.4	7.9, 54.6	7.9, 54.6	7.9, 54.6
3c	183.5	36.1[b]	22.6	37.9[b]	66.2	63.8	14.1, 20.3, 24.4, 60.2	14.1, 20.3, 24.4, 60.2	14.1, 20.3, 24.4, 60.2
3d	183.9	35.9[b]	22.5	38.1[b]	66.5	69.7	51.4	51.9	70.5, 128.3, 130.3, 131.9, 134.2
3e[c]	179.2	36.5[b]	22.2	38.2[b]	66.5	69.0	51.8	52.0	14.2, 22.8, 23.0, 26.5, 29.5, 29.8, 32.0, 64.9

[a] All spectra obtained in D_2O with Me_4Si standard (capillary) unless noted. Shifts are in parts per million. [b] Interchangeable values. [c] Spectrum obtained in $CDCl_3$ with Me_4Si standard.

Perkin-Elmer Model 257 instrument. Electron-impact (EI) mass spectra were recorded on an AEI/Kratos MS-30 spectrometer at an ionization potential of 70 eV. Field-desorption (FD) mass spectra were obtained on a modified Varian SM-1B spectrometer at emitter currents of 10–20 mA. Satisfactory elemental analyses for long-chain zwitterionics were obtained from combustion data (Galbraith Laboratories) in conjunction with water determination by Karl Fischer titration. Short-chain ammoniocarboxylates were too hygroscopic for similar analysis. Preparative VPC work was done on a Varian 3700 instrument equipped with a thermal conductivity detector and using a 2 ft × $^1/_8$ in., 5% OV-101 on Chrom G column.

Ethyl 4-Pentenoate (5a). 4-Pentenoic acid (12.0 g, 0.120 mol; Tridom Chemicals) was dissolved in 200 mL of dry EtOH, and KOH pellets (7.1 g, 0.126 mol) were added. The mixture was stirred at room temperature until homogeneous. Ethyl iodide (24.3 g, 0.156 mol) was added and the solution refluxed for 48 h. The cooled solution was poured onto H_2O (600 mL) and extracted with pentane (200 mL). The organic extract was washed with H_2O (2 × 500 mL) and dried ($MgSO_4$). Solvent removal afforded 10.0 g (65%) of **5a**: bp 142–143 °C (lit.[16] 144–146 °C); NMR ($CDCl_3$, Me_4Si) δ 6.16–5.44 (m, 1), 5.20 (br d, 1), 4.84 (br s, 1), 4.19 (q, 2, J = 7 Hz), 2.42 (br s, 4), 1.23 (t, 3, J = 7 Hz); IR (neat) 1737 (s), 1639 (w), 1172 (s) cm^{-1}.

Ethyl 4,5-Epoxypentanoate (6a). Ethyl 4-pentenoate (9.90 g, 77.3 mmol) and *m*-chloroperbenzoic acid (18.5 g, 92.8 mmol, of 85% assay) were dissolved in 300 mL of CH_2Cl_2 and stirred for 18 h in an oil bath at 50 °C. The mixture was then filtered and washed with 10% $NaHSO_3$, saturated $NaHCO_3$ (2×), and H_2O (2×) before being dried ($MgSO_4$). Concentration under slight vacuum at room temperature followed by distillation (32 °C, 0.07 mm) afforded 6.1 g (55%) of **6a**: NMR ($CDCl_3$, Me_4Si) δ 4.09 (q, 2, J = 7 Hz), 3.11–2.79 (m, 1), 2.71 (t, 1, J = 4.5 Hz), 2.56–2.27 (m, 3), 2.04–1.68 (m, 2), 1.25 (t, 3, J = 7 Hz); IR (neat) 1737 (s), 1256 (m), 1180 (s), 840 (m) cm^{-1}.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 57.87; H, 8.07.

Ethyl 5-Hexenoate (5b). 5-Hexenoic acid[17] (**4b**) was converted to **5b** in 85% yield by the procedure used for esterification of **4a**: bp 162 °C (760 mm) [lit.[18] 58–60 °C (15 mm)]; NMR ($CDCl_3$, Me_4Si) δ 6.21–5.50 (m, 1), 5.13 (br d, 1), 4.91 (br s, 1), 4.28 (q, 2, J = 7 Hz), 2.52–1.52 (m, 6), 1.26 (t, 3, J = 7 Hz); IR (neat) 1737 (s), 1639 (w), 1172 (s) cm^{-1}.

Ethyl 5,6-Epoxyhexanoate (6b). Distilled ethyl 5-hexenoate (**5b**) was converted to the epoxy ester (**6b**) in 70% distilled yield by the procedure used for epoxidation of **5a**: bp 45 °C (0.2 mm); NMR ($CDCl_3$, Me_4Si) δ 4.06 (q, 2, J = 7 Hz), 3.02–2.56 (m, 2), 2.56–2.09 (m, 3), 2.09–1.45 (m, 4), 1.24 (t, 3, J = 7 Hz); IR (neat) 1734 (s), 1246 (m), 1175 (s), 830 (m) cm^{-1}.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.91; H, 8.70.

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Typical Preparation of Short-Chain Hydroxylated Ammoniocarboxylates. To a solution of epoxy ester **6a** (1.00 g, 6.94 mmol) in 16 mL of 70% aqueous EtOH was added Et_3N (7.03 g, 69.4 mmol). The mixture was placed in an oil bath at 55–60 °C and stirred for 24 h before the solvent was removed under vacuum. The residue was dissolved in H_2O (10 mL) and washed with Et_2O (3 × 10 mL). The aqueous layer was concentrated by using CH_3CN to azeotropically remove the final traces of H_2O, affording a light yellow oil which crystallized overnight under high vacuum. Stirring with hot, dry acetone followed by cooling overnight in a refrigerator produced white crystals which were isolated by filtration under argon. Drying under high vacuum afforded 997 mg (66%) of **2b** as an extremely hygroscopic white solid: mp 168–170 dec; NMR (D_2O) δ 4.32–3.86 (m, 1), 3.86–3.59 (m, 8, J = 7 and 7 Hz), 2.19 (t, 2, J = 6.5 Hz), 1.79 (t, 2, J = 6.5 Hz), 1.29 (t, 9, J = 7 Hz); IR (KBr) 3400 (br, s), 1566 (m), 1459 (s), 1373 (s) cm^{-1}; mass spectrum (FD), m/e 174 [$(M + H - CO_2)^+$], 218 $(M + H)^+$, 391 [$(2M + H - CO_2)^+$], 435 [$(2M + H)^+$], 608 [$(3M + H - CO_2)^+$], 652 [$(3M + H)^+$].

4-Hydroxy-5-(trimethylammonio)pentanoate (2a): mp 202 dec; NMR (D_2O) δ 4.17 (m, 1, J = 6 Hz), 3.34 (d, 2, J = 6 Hz), 3.17 (s, 9), 2.30 (t, 2, J = 8 Hz), 1.77 (t, 2, J = 7 Hz); IR (KBr) 3200 (br, s), 1564 (s), 1457 (s), 1375 (s) cm^{-1}; mass spectrum (FD), m/e 132 [$(M + H - CO_2)^+$], 176 [$(M + H)^+$], 307 [$(2M + H - CO_2)^+$], 351 [$(2M + H)^+$], 482 [$(3M + H - CO_2)^+$], 526 [$(3M + H)^+$].

5-Hydroxy-6-(trimethylammonio)hexanoate (3a): mp 182 dec; NMR (D_2O) δ 4.40–4.10 (m, 1), 3.39 (d, 2, J = 6 Hz), 3.13 (s, 9), 2.42–2.00 (t, 2, J = 8 Hz), 1.79–1.42 (m, 4); IR (KBr) 3250 (br s), 1570 (s), 1461 (s), 1385 (s) cm^{-1}; mass spectrum (FD), m/e 146 [$(M + H - CO_2)^+$], 190 [$(M + H)^+$], 335 [$(2M + H - CO_2)^+$], 379 [$(2M + H)^+$], 568 [$(3M + H)^+$].

5-Hydroxy-6-(triethylammonio)hexanoate (3b): mp 205–206 dec; NMR (D_2O) δ 4.33–3.90 (m, 1), 3.61–3.07 (m, 8), 2.19 (t, 2, J = 6 Hz), 1.76–1.45 (m, 2), 1.30 (t, 9, J = 7 Hz); IR (KBr) 3370 (br, s), 1574 (s), 1458 (s), 1373 (s) cm^{-1}; mass spectrum (FD), m/e 188 [$(M + H - CO_2)^+$], 232 [$(M + H)^+$], 421 [$(2M + H - CO_2)^+$], 463 [$(2M + H)^+$], 650 [$(3M + H - CO_2)^+$], 694 [$(3M + H)^+$].

5-Hydroxy-6-(tri-*n*-butylammonio)hexanoate (3c): semisolid, light yellow oil; NMR (D_2O) δ 4.27–3.94 (m, 1), 3.64–3.10 (m, 8), 2.29–2.07 (m, 2), 1.96–1.14 (m, 16), 1.10–0.77 (m, 9); IR (KBr) 3250 (br, s), 1580 (s), 1462 (s), 1383 (s) cm^{-1}; mass spectrum (FD), m/e 272 [$(M + H - CO_2)^+$], 316 [$(M + H)^+$], 587 [$(2M + H - CO_2)^+$], 631 [$(2M + 1)^+$].

6-(Benzyldimethylammonio)-5-hydroxyhexanoate (3d): mp 190–192 dec; NMR (D_2O) δ 7.56 (s, 5), 4.55 (s, 2), 4.47–4.10 (m, 1), 3.27 (d, 2, J = 6 Hz), 3.16 (s, 6), 2.46–2.09 (m, 2), 1.87–1.39 (m, 4); IR (KBr) 3300 (br, s), 1575 (s), 1365 (s) cm^{-1}; mass spectrum (FD), m/e 222 [$(M + H - CO_2)^+$], 266 [$(M + H)^+$], 280 [$(M + CH_3)^+$], 312 [$(M + CH_2Ph - CO_2)^+$], 356 [$(M + CH_2Ph)^+$], 531 [$(2M + H)^+$], 545 [$(2M + CH_3)^+$], 577 [$(2M + CH_2Ph - CO_2)^+$], 621 [$(2M + CH_2Ph)^+$].

4-Hydroxy-5-(tetradecyldimethylammonio)pentanoate (2c). To a solution of epoxy ester **6a** (0.500 g, 347 mmol) in 16 mL of 70% aqueous EtOH was added tetradecyldimethylamine (8.36 g, 34.7 mmol). The mixture was stirred at 50 °C for 72 h.

Solvent removal produced crystals which were purified by recrystallization from hexane–EtOH. Drying under high vacuum afforded 857 mg (69%) of the desired product as white crystals: mp 156–159 °C; NMR (D_2O) δ 4.33–3.95 (m, 1), 3.63–2.97 and 3.14 (br m plus s, 10), 2.30 (t, 2, J = 6 Hz), 1.78 (t, 2, J = 6 Hz), 1.33 (br s, 24), 0.90 (t, 3, J = 2.5 Hz); IR (KBr) 3400 (br s), 1566 (s), 1460 (m), 1392 (m) cm^{-1}; mass spectrum (FD) m/e 314 [$(M + H - CO_2)^+$], 325 [$(M - MeOH)^+$], 340 [$(M + H_2O)^+$], 358 [$(M + H)^+$], 372 [$(M + CH_3)^+$].

Anal. Calcd for $C_{21}H_{43}NO_3 \cdot 0.14H_2O$: C, 70.0; H, 12.1; N, 3.9. Found: C, 69.6; H, 12.5; N, 3.7.

6-(Docosyldimethylammonio)-5-hydroxyhexanoate (3e). To a solution of epoxy ester **6b** (3.00 g, 19.0 mmol) in 50 mL of 70% aqueous EtOH was added docosyldimethylamine (6.71 g, 19.0 mmol). The mixture was stirred at 80 °C for 42 h. The solvent was removed under vacuum, and the resulting crystals were purified by recrystallization from hexane–EtOH. Drying under high vacuum afforded 5.70 g (62%) of **3e** as white crystals: mp 188–190; NMR (D_2O) δ 4.35–4.00 (m, 1), 3.60–3.03 and 3.16 (br m plus s, 10), 2.37–2.80 (m, 2), 1.30 (br s, 44), 0.84 (t, 3, J = 6 Hz); IR (KBr) 3330 (s), 1571 (s), 1462 (m), 1386 (m); mass spectrum (FD), m/e 440 [$(M + H - CO_2)^+$], 451 [$(M - MeOH)^+$], 484 [$(M + H)^+$], 498 [$(M + CH_3)^+$].

Anal. Calcd for $C_{30}H_{61}NO_3 \cdot 0.86H_2O$: C, 72.2; H, 12.7; N, 2.8. Found: C, 72.6; H, 12.7; N, 2.8.

^{13}C NMR Spectra. Spectral data are given in Table II. Assignments are based upon off-resonance-decoupling experiments and comparison with values for unhydroxylated ammoniohexanoates[19] and other known systems.[20]

Acknowledgment. The author wishes to express his gratitude to Drs. E. P. Gosselink and R. G. Laughlin for valuable advice and discussions and to Drs. T. W. Keough, A. J. Destefano, and S. A. Goldman for assistance in attaining and interpreting spectral data.

Registry No. 2a, 73697-53-7; **2b**, 73697-54-8; **2c**, 73697-55-9; **3a**, 73697-56-0; **3b**, 73697-57-1; **3c**, 73712-26-2; **3d**, 73697-58-2; **3e**, 73697-59-3; **4a**, 591-80-0; **4b**, 1577-22-6; **5a**, 1968-40-7; **5b**, 54653-25-7; **6a**, 73697-60-6; **6b**, 73697-61-7; Et_3N, 121-44-8; Me_3N, 75-50-3; Bu_3N, 102-82-9; $PhCH_2NMe_2$, 103-83-3; $Me_2N(CH_2)_{13}CH_3$, 112-75-4; $Me_2N(CH_2)_{21}CH_3$, 21542-96-1.

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Acylations of Thiol Ester Enolate Anions

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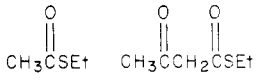
Received June 28, 1979

The synthetic utility of thiol ester enolate anions has been explored. Claisen condensations of thiol esters with isopropylmagnesium bromide base proceed in good yield. The Dieckmann reaction of diethyl thiolpimelate to form a six-membered ring proceeds in 74% yield, but the corresponding reaction of diethyl thioladipate to provide a five-membered ring gives only 26% yield. Neither alkylation of ethyl thiolacetate nor a Michael-type adduct with methyl vinyl ketone could be achieved. The mechanism of the Claisen condensation as it applies to thiol esters is discussed.

Chain elongation in fatty acid biosynthesis proceeds by a succession of thiol ester Claisen condensations.[1b-3] By contrast to the ubiquitous nature of the biochemical transformation, thiol ester condensation studies in organic chemistry are rare,[4-6] having been reported only three times. In 1929, Baker and Reid induced ethyl thiolacetate to condense with itself at 50 °C using sodium as a base.[4] These authors obtained a 15% yield of ethyl acetothiolacetate, but in the Experimental Section they made note of the fact that a solid residue, identified as dehydracetic acid, was obtained from the vacuum distillation. A mixed ester condensation of ethyl thiolacetate and ethyl acetate with sodium was also carried out, giving 93% ethyl acetothiolacetate and 2% ethyl acetoacetate.

Cronyn, Chang, and Wall[5] reported a 67% yield of ethyl acetothiolacetate (**2**) from the self-condensation of ethyl thiolacetate (**1**) using isopropylmagnesium bromide at 0 °C and a 20% yield of *tert*-butyl acetothiolacetate from the self-condensation of *tert*-butyl thiolacetate.



1 **2**

Sheehan and Beck[6] allowed phenyl thiolacetate to condense at 0 °C using isopropylmagnesium bromide and obtained a 49% yield of phenyl acetothiolacetate. In addition, they allowed *N*,*S*-diacetylcysteamine to condense using mesitylmagnesium bromide at room temperature and obtained a 32% yield of *N*-acetyl-*S*-(acetoacetyl)cysteamine.

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