period of time (15 min). The resulting aqueous solution was immediately acidified to pH 1 with 1.0 M HCl and lyophilized to dryness. The resulting solid was suspended in 10 mL of methanol and filtered washing with 20 mL more of methanol. The filtrate was evaporated to dryness in vacuo three times with 20 mL of methanol. The resulting solid was suspended in a mixture of of 0.5 mL of water, 2 mL of methanol, and 10 mL of ethanol. The solid precipitate was collected by filtration and recrystallized from methanol to give 32.6 mg of **9** (6.1%). The amorphous crystals do not melt, but are transformed to long needles at 198–200 °C and then to a viscous glass between 243 and 267 °C: ^{1}H NMR (TFA) δ 1.54 (1 H, s), 3.06 (1 H, d, J = 17 Hz), 3.50 (1 H, d, J = 17 Hz), 4.09 (3 H, s, OCH_3), 5.23 (1 H, br s, $-CHOCH_3$), 7.95 (1 H, br s); mass spectrum, m/e (rel intensity) 250 ($M - OCH_3$, 4), 141 (17), 140 (3), 127 (58), 126 (100), 125 (100); λ_{max} (H_2O, pH 6) 264 mm. Thin-layer chromatography: silica gel–system C, R_f 0.38; system D, R_f 0.44. An analytically pure sample of **9** could not be obtained because of the ease with which it decomposes. Treatment of **9** with aqueous 1 N HCl gave **8** as a white solid. The ^{1}H NMR spectrum of **8** was virtually identical with that of **9** except the methoxyl protons were absent.

6-Amino-5-(α-thyminyl)uracil (11). 5-(Hydroxymethyl)uracil (170 mg, 1.20 mmol) was dissolved in 5 mL of TFA, and the mixture was stirred at room temperature for 2 h. 6-Aminouracil (150 mg, 1.18 mmol) was added, and the mixture was refluxed for 5.5 h and then condensed to dryness by rotary evaporation. The solid which was isolated was recrystallized by dissolution in 2 N ammonium hydroxide followed by reprecipitation by dropwise addition of concentrated hydrochloric acid, yielding 219 mg (70.1%) of white solid which did not melt on heating to 220 °C: ^{1}H NMR (TFA) δ 3.60 (2 H, s), 8.03 (1 H, broad d); IR (KBr) 3350, 3190, 3050, 2820, 1745, 1660, 1400, 1205, 1020, 830, 760 cm^{-1}. Anal. Calcd for $C_9H_9N_5O_4$: C, 43.0; H, 3.6; N, 27.9. Found: C, 43.7; H, 3.8; N, 27.7.

Acknowledgments. This investigation was funded by the Research Corporation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society, whom we gratefully thank for their support.

Registry No.—**4**, 67513-78-4; **5**, 69155-20-0; **6**, 28100-77-8; **8**, 69155-21-1; **9**, 69155-22-2; **11**, 69188-74-5; thymine, 65-71-4; 5,6-dihydrothymine, 696-04-8; 5-(hydroxymethyl)uracil, 4433-40-3; 6-aminothymine, 15828-63-4; 6-aminouracil, 873-83-6.

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Reaction of Alkanals and Amino Acids or Primary Amines. Synthesis of 1,2,3,5- and 1,3,4,5-Substituted Quaternary Pyridinium Salts

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The condensation of alkanals and amino acids or primary amines was studied under neutral condition at room temperature. From the reaction products of the glycine–propanal and L-α-leucine–propanal system, for example, the 1-(1-carboxymethyl)-2-ethyl-3,5-dimethylpyridinium betaine and the 1-(1-carboxy-3-methylpropyl)-4-ethyl-3,5-dimethylpyridinium betaine were isolated and identified. From the reaction products of the ethanolamine–alkanal system, the pyridinium salt with four substituents located at the 1,2,3,5 positions was also isolated. The substitution patterns of these pyridinium betaines are similar to that of the amino acids isodesmosine and desmosine. A mechanism involving the intermediacy of α,β-unsaturated aldimines is proposed, and evidence is presented that 2-ethyl-1,3,5-trimethyl- and 4-ethyl-1,3,5-trimethylpyridinium salts are formed by condensation of *N*-2-methyl-2-pentenilidenemethylamine with propanal in the presence of acetic acid. It may be concluded from the results that addition of alkanal to α,β-unsaturated aldimine occurred regiospecifically and was followed by ring closure and oxidation to give pyridinium salts.

The reaction of alkanals with amino acids or primary amines under neutral conditions is of interest in connection with the study of foodstuff deterioration.[1] In the course of our research on the reaction between alkanals and amino acids or primary amines under neutral condition at room temperature, quarternary pyridinium betaines **1** and salts **2** with four substituents located at the 1,2,3,5 and 1,3,4,5 positions were obtained.

Recently, two polyfunctional amino acids, desmosine and isodesmosine, derived from the cross-linkages in elastin have been isolated.[2,3] These isomers contain a pyridinium ring with four substituents located at the 1,3,4,5 and 1,2,3,5 positions. The structures suggested that the compounds may be formed from ring closure of four lysine residues.

While the reaction of pyridine ring formation, the "Chichibabin Pyridine Condensation", between carbonyl compounds and ammonia has been extensively investigated,[4] the formation of quarternary pyridinium salts by the reaction of carbonyls with primary amines has received little attention. In this paper we wish to report the identification and synthesis of quarternary pyridinium betaines **1** and pyridinium salts **2** which are condensation products of alkanals with amino acids

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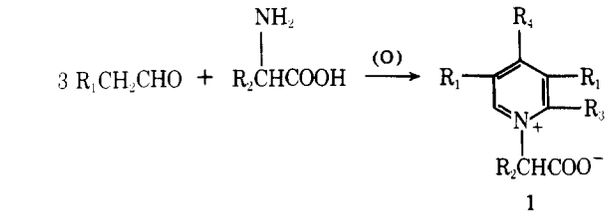
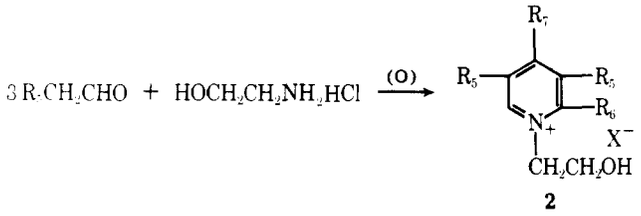
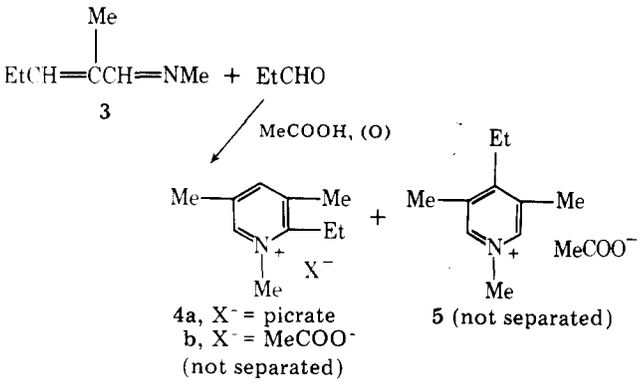


1a, R_1 = Me; R_2 = H; R_3 = Et; R_4 = H
b, R_1 = Et; R_2 = H; R_3 = Pr; R_4 = H
c, R_1 = $(CH_2)_4Me$; R_2 = H; R_3 = $(CH_2)_5Me$; R_4 = H
d, R_1 = Me; R_2 = Me; R_3 = Et; R_4 = H (not separated)
e, R_1 = Me; R_2 = Me; R_3 = H; R_4 = Et (not separated)
f, R_1 = Me; R_2 = $CH_2CH(Me)_2$; R_3 = H; R_4 = Et



2a, R_5 = Me; R_6 = Et; R_7 = H; X^- = picrate
b, R_5 = Me; R_6 = Et; R_7 = H; X^- = Cl^- (not separated)
c, R_5 = $(CH_2)_4Me$; R_6 = $(CH_2)_5Me$; R_7 = H; X^- = Cl^-
d, R_5 = $(CH_2)_4Me$; R_6 = H; R_7 = $(CH_2)_5Me$; X^- = Cl^-
(not separated)



4a, X^- = picrate
b, X^- = $MeCOO^-$
(not separated)

5 (not separated)

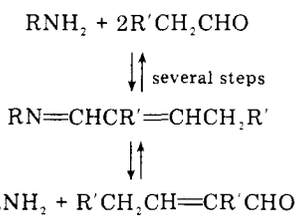
and with primary amines, respectively. We also wish to report the condensation of *N*-2-methyl-2-pentenilidenemethylamine (**3**) and propanal which gave not only 2-ethyl-1,3,5-trimethylpyridinium salt **4** but 4-ethyl-1,3,5-trimethylpyridinium salt **5**. These reactions may also be applied as a one-step procedure to the synthesis of various substituted pyridinium salts.

Results and Discussion

Structural Assignment of Pyridinium Betaines. As an example the reaction of propanal with glycine (Gly) and L-α-leucine (Leu) will be described.

Reaction of propanal with Gly resulted in an exothermic reaction after an induction period and water soluble reaction products giving on TLC a major spot (R_f 0.24) and five minor spots. The needles of **1a** that separated from ethyl acetate had an R_f value similar to that of the major spot. The structure of **1a** was established spectroscopically. Its UV spectrum which had λ_{max} 280 nm (ϵ 7350) in methanol and was not altered by addition of a trace amount of HCl and NaOH closely resembled that of 1,2,3,5-tetramethylpyridinium chloride[2] (λ_{max} 276 nm (ϵ 6940)); this suggested that the nitrogen atom was quarternized. On hydrogenation with palladium black catalyst in methanol at room temperature under normal pressure, **1a** did not take up hydrogen. The IR spectrum exhibited bands at 1635 (shoulder), 1595, 1510, and 1455 cm^{-1}, which suggested the presence of an aromatic nucleus. A strong absorption band for the ionized carboxyl group at 1645 and 1370 cm^{-1} disappeared on treatment with HCl, and an absorption of the carboxylic acid group appeared at 1743 cm^{-1}. Thus **1a** is an inner salting of carboxylic acid and pyridinium N. The ^{1}H-NMR spectrum showed two olefinic singlets at 8.69 (1 H) and 7.86 ppm (1 H) which were attributed to ring protons attached to the 4 and 6 positions of the pyridinium ring. Broadening of these singlets was due to long-range coupling to the adjacent alkyl groups. A six-proton singlet at 2.50 ppm was attributed to two methyls at the 3 and 5 positions. The ^{1}H-NMR spectrum closely resembled that of 2-ethyl-3,5-dimethylpyridine picrate as will be described later.

Scheme I



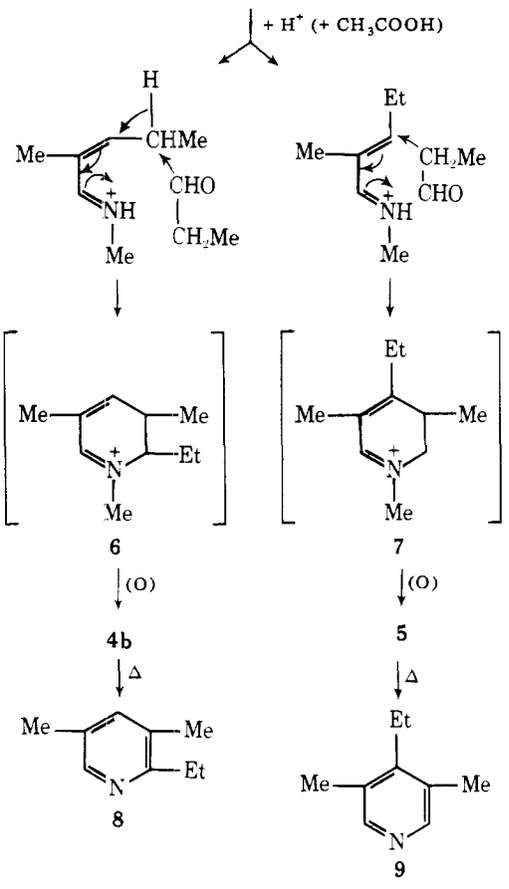
The rate of self-aldol condensation of propanal was faster than the rate of the condensation of Leu with propanal to form the pyridinium betaine, hence a large amount of propanal was consumed. The UV of the product **1f** recorded in methanol, λ_{max} 242 (ϵ 7950) and 270 nm (ϵ 5750), closely resembled that of 1,3,4,5-tetramethylpyridinium chloride. The IR spectrum showed the same pattern as **1a** and behaved similarly on treatment with HCl. The ^{1}H-NMR spectrum of **1f** was simple owing to the symmetry of the molecule.

Reaction of *N*-2-Methyl-2-pentenylidenemethylamine with Propanal. The exothermic reactions of *N*-2-methyl-2-pentenilidenemethylamine (**3**) with propanal in the presence of acetic acid gave noncrystalline products from which, after addition of picric acid, **4a** was separated. The appearance of a slight shoulder in the UV spectrum of the crude product was probably due to the presence of a small amount of **5**; however, this could not be isolated.

We studied the thermal degradation of the water soluble reaction products which resulted in the formation of 2-ethyl-3,5-dimethylpyridine (**8**) and 4-ethyl-3,5-dimethylpyridine (**9**) as volatile products in the ratio of 8:1 (GLC analysis). These pyridines can be separated easily as picrates. It seems reasonable to assume that the precursors of **6** and **7** were **2b** and **2d**, respectively.

Mechanistic Considerations. On the basis of the data described above, it may be concluded that an α,β-unsaturated aldimine is an intermediate in the formation of pyridinium salts. It is well recognized that α,β-unsaturated aldimines are formed as intermediates in amine-catalyzed aldol condensations[5,6] or condensations of α,β-unsaturated aldehyde with amines[7] as shown in Scheme I. Scheme II shows possible sequences for the formation of 2-ethyl-1,3,5-trimethylpyridinium acetate (**4b**) and 4-ethyl-1,3,5-trimethylpyridinium acetate (**5**). Protonation of *N*-2-methyl-2-pentenilidenemethylamine (**3**) by acetic acid is followed by attack of propanal and subsequent dehydration and ring closure to intermediates **6** and **7**. Formation of **6** would be analogous to a linear type polyaldol condensation in the presence of mild basic catalysts[8] and is supported by a report of Craig, Schaefgen, and Tyler,[9] who have obtained *N*-phenyl-3,5-diethyl-2-propyl-1,4-dihydropyridine with the same substitution pattern of **6** by reaction of 1-butanal with aniline in the presence of acetic acid. As regards formation of **7**, it seems plausible that because of the positive charge on the β carbon of protonated **3** neucleophilic attack by the α carbon of propanal is followed by ring closure and dehydration to give **7**. For Leu, the ring closure in the reaction leading to formation of **6** may be inhibited by steric hindrance. Attempts to separate dihydropyridinium salts from the reaction mixture failed.

Scheme II



It is generally assumed that the last step in the formation of pyridinium from dihydropyridinium salts requires oxygen. However, reaction of the Gly–propanal system in an oxygen atmosphere did not increase the yield of pyridinium salts, hence oxygen apparently is not required for the oxidation. To convert dihydropyridinium into pyridinium without oxygen, two possibilities may be envisioned: (1) disproportionation of dihydropyridinium to pyridinium and tetrahydropyridinium salts, and (2) oxidation by means of reactants. However, tetrahydropyridinium salts could not be detected in the reaction mixtures obtained in this study.

It seems likely that 2-ethyl-3,5-dimethylpyridine (**8**) and 4-ethyl-3,5-dimethylpyridine (**9**) are formed from **4b** and **5**, respectively, by a Hofmann degradation.

Experimental Section

UV spectra were obtained on Hitachi Perkin-Elmer 139 UV–vis spectrophotometer. IR spectra were recorded on a JASCO IR-S spectrophotometer. ^{1}H-NMR spectra were taken on JEOL JNM-ML-60 (60 NHz) and JEOL JNM-PS-100 (100 MHz) spectrometers with Me_4Si as an internal standard. All melting points were determined with a Yanagimoto melting point apparatus and were not corrected; boiling points were also uncorrected.

Chromatography. Reaction products were applied to a silicic acid (Mallinckrodt 100 mesh) column, and the column was eluted with the solvent systems specified below. Each fraction was examined by TLC, and the desired fractions were collected. Partion TLC was run on alminum sheet precorted with silica gel $60F_{245}$ (E. Merck) by using a mixture of 1-butanol–pyridine–water (6:4:3, v/v) as a solvent system and were developed by using a solvent system specified below. Spots on the TLC were visualized after spraying with Dragendorff reagent. The GLC analyses were performed with a Hitachi 063 instrument (flame ionization detector; 200 × 0.3 cm column packed with 10% DEGS on 80–100 mesh Diasolid L at 130 °C; nitrogen flow rate 10 mL min^{-1}).

Reagents. Gly, Leu, and other amino compounds used were of commercial G.R. grade. Commercial propanal and 1-butanal of C.P. grade were purified by redistillation, bp 46–48 °C and 74–75 °C, respectively. Commercial 1-heptanal of G.R. grade was used without further purification.

1-(1-Carboxymethyl)-2-ethyl-3,5-dimethylpyridinium Betaine (1a). The mixture of Gly (37 g, 0.5 mol) suspended in 50 mL of water and excess propanal (200 g, 3.5 mol) was stirred at room temperature. The reaction was exothermic and completed in ca. 5 h. The mixture was extracted with *n*-hexane (3 × 50 mL) and extracts were discarded. The residual water-soluble fraction was evaporated to a syrup and reextracted with chloroform. The chloroform layer was dried with anhydrous sodium sulfate and evaporated to dryness under reduced pressure. About 60 g of viscous syrup obtained was extracted with hot ethyl acetate. The hygroscopic needles of **1a** separated out by cooling and were repeatedly reprecipitated from ethyl acetate to give **1a** in 18% yield based on Gly: mp 135–136 °C dec; UV (MeOH) λ_{max} (ϵ) 280 nm (7350); IR (KBr) 2980 (CH), 1645 (COO^-), 1635 (shoulder), 1595, 1510, and 1455 (C=N and C=C), 1060, 1030, 900, 770 cm^{-1}, product by HCl treatment (**1a** hydrochloride) 2480–2700 and 1743 (COOH), 1635, 1595, 1510, 1455, 1195, 1060, 1025, 890, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (3 H, t, J = 7 Hz, CH_2CH_3), 2.50 (6 H, s, CH_3 × 2), 3.10 (2 H, q, J = 7 Hz, CH_2CH_3), 5.21 (2 H, s, NCH_2COO^-), 7.86 (1 H, s, pyridinium H), 8.69 (1 H, s, pyridinium H).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 67.90; H, 7.90; N, 7.21.

In a similar manner the following pyridinium betaines were prepared using Gly.

1-(1-Carboxymethyl)-3,5-diethyl-2-propylpyridinium Betaine (1b). The syrup (about 50 g) obtained by reaction of Gly (25 g, ca. 0.3 mol) with 1-butanal (150 g, ca. 2 mol) was reextracted with chloroform and subjected to column chromatgraphy with $CHCl_3$–MeOH (10:2, v/v). The fraction containing material with R_f 0.15 on TLC in the same solvent system was collected. Evaporation of the solvent gave a crystalline mass which was recrystallized from ethyl acetate to give hygroscopic colorless needles of **1b** in 11% yield: mp 118–119 °C dec; UV (MeOH) λ_{max} (ϵ) 281 nm (7700); IR (KBr) 2980 (CH), 1650 (COO^- and C=N), 1505, 1465, 1365, 900, 750 cm^{-1}, resultant of HCl treatment (**1b** hydrochloride)2975, 2480–2700, 1745 (COOH), 1630, 1590, 1505, 1390, 1320, 1200, 880, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (3 H, t, J = 7 Hz, $CH_2CH_2CH_3$), 1.32 (6 H, t, J = 7 Hz, CH_2CH_3 × 2), 1.5–2.0 (2 H, m, $CH_2CH_2CH_3$), 2.82 (4 H, q, J = 7 Hz, CH_2CH_3 × 2), 3.02 (2 H, t, J = 7 Hz, $CH_2CH_2CH_3$), 5.10 (2 H, s, NCH_2COO^-), 7.85 (1 H, s, pyridinium H), 8.62 (1 H, s, pyridinium H).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.30; H, 9.01; N, 5.88.

1-(1-Carboxymethyl)-2-hexyl-3,5-dipentylpyridinium Betaine (1c). After washing the reaction products obtained from Gly (15 g, ca. 0.2 mol) and 1-heptanal (200 g, ca. 1.5 mol) with hexane, the residual reaction products were extracted twice with chloroform. The combined chloroform solution was dried over sodium sulfate. The solvent was removed under reduced pressure to give a syrup (41 g). The syrup was chromatographed with $CHCl_3$ and $CHCl_3$–MeOH (10:2, v/v), successively. The eluate with the later solvent system was evaporated to dryness in vacuo to a syrup. After standing for 2 weeks in the refrigerator, crystallization of this syrup occurred. The crude crystals were recrystallyzed from dry ethyl ether to afford colorless hygroscopic needles which decomposed at room temperature in the desiccator during 1 to 2 months to give brown syrup: yield 14%; mp 95–96 °C dec; UV (MeOH) λ_{max} (ϵ) 241 (shoulder), 282 nm (9890); IR (KBr) 2980 (CH), 1650 (COO^- and C=N), 1510, 1470, 1365, 905, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.7–1.1 (9 H, m), 1.1–2.0 (14 H, m), 2.75 (4 H, t, J = 7 Hz, CH_2CH_2Pr × 2), 2.7–3.4 (2 H, m of tripret pattern, CH_2CH_2Bu), 5.10 (2 H, s, CH_2COO^-), 7.80 (1 H, s, pyridinium H), 8.55 (1 H, s, pyridinium H).

Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.58; H, 10.44; N, 3.81.

1-(1-Carboxy-3-methylpropyl)-4-ethyl-3,5-dimethylpyridinium Betaine (1f). The suspension of Leu (25 g, ca. 0.2 mol) in water (30 mL) and propanal (400 g, ca. 7 mol) was stirred with a magnetic stirrer at room temperature. The reaction was exothermic and completed in about 5 h. After washing with *n*-hexane twice, the residual reaction mixture was evaporated to a syrup, extracted with chloroform, and dried over sodium sulfate. The solvent was removed to afford a slightly brown oily residue (38 g) which was crystallized by treating with ethyl acetate to yield 18 g. Recrystallization from ethyl acetate afforded analytically pure, strongly hygroscopic colorless needles (6.5 g): mp 129–130 °C dec; UV (MeOH) λ_{max} (ϵ) 242 (7950) and 270 nm (5750); IR (KBr) 2960 (CH), 1645 and 1630 (COO^- and/or C=N), 1490, 1375, 1355, 760 cm^{-1}, resultant of HCl treatment (**1f** hydrochloride) 2960, 2280, 2540, 1755, 1640, 1500, 1490, 1395, 1205, 1160, 840, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (6 H, dd triplet pattern, J = 6 Hz, $CH_2CH(CH_3)_2$), 1.96 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.40 (1

H, m, $CH_2CH(CH_3)_2$), 1.9–2.2 (2 H, m, $CH(COO^-)CH_2CH(CH_3)_2$), 2.51 (6 H, s, $CH_3 \times 2$), 2.80 (2 H, q, J = 7.5 Hz, CH_2CH_3), 5.15 (1 H, dd J = 8.5 and 6.0 Hz, $NCH(COO^-)CH_2$), 8.60 (2 H, s, pyridinium H × 2).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.82. Found: C, 72.20; H, 9.33; N, 6.02.

Reaction of L-α-Alanine with Propanal. The mixture of L-α-alanine (4.5 g, ca. 0.05 mol) with propanal (100 g, ca. 0.7 mol) was reacted in the same manner. After treatment with n-hexane (3 × 100 mL), the n-hexane insoluble reaction product was purified by column chromatography; $CHCl_3$–MeOH (10:3, v/v) was used as solvent. The fractions containing material with R_f 0.2 on TLC in the same solvent system were collected. Evaporation of the solvent gave a syrup (7 g) containing a 1-(1-carboxyethyl)-2-ethyl-3,5-dimethylpyridinium betaine (**1d**) and 1-(1-carboxyethyl)-4-ethyl-3,5-dimethylpyridinium betaine (**1e**). Attempts to crystallize **1d** and **1e** from a syrup failed. The UV of a syrup in water showed the absorption maximum at 280 nm owing to the presence of **1d** and the shoulder absorption band at about 240 and 270 nm owing to the presence of **1e**: IR (neat) 1640 (C=N and COO^-), 1510, 1360, 760 cm^{-1}, resultant of HCl treatment 1745 (COOH), 1650, 1500, 1205, 840, 760 cm^{-1}. The ^1H NMR ($CDCl_3$) showed pyridinium H singlets at δ 7.85 and 8.67 due to **1d** and at δ 8.59 due to **1e**.

2-Ethyl-1-(2-hydroxyethyl)-3,5-dimethylpyridinium Picrate (2a). The suspension of ethanolamine hydrochloride (15 g, 0.15 mol) and propanal (100 g, ca. 1.7 mol) was stirred at room temperature. The reaction was exothermic and completed in about 3 h. After washing with n-hexane twice, the residual reaction mixture was evaporated to a syrup. The UV in methanol showed the absorption maximum at 279 nm which was due to the presence of 2-ethyl-1-(2-hydroxyethyl)-3,5-dimethylpyridinium chloride (**2b**). A syrup was dissolved in ethanol and treated with picric acid. The hygroscopic orange colored needles of 2-ethyl-1-(2-hydroxyethyl)-3,5-dimethylpyridinium picrate (**2a**) separated out and were repeatedly reprecipitation from ethanol to yield 11 g: mp 128–129.5 °C; IR (KBr) 3350 (OH), 1640, 1620 and 1495 (C=C and C=N), 1335 (NO_2), 1435, 1365, 1320, 1270, 1165, 1080, 910, 785, 740, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3 H, t, J = 7 Hz, CH_2CH_3), 2.40 (3 H, s, CH_3), 2.45 (3 H, s, CH_3), 3.15 (2 H, q, J = 7 Hz, CH_2CH_3), 3.8–4.1 (2 H, m of triplet pattern, CH_2CH_2OH), 4.64 (2 H, t, J = 6.5 Hz, NCH_2CH_2OH), 5.1–5.4 (1 H, m of triplet pattern, CH_2OH, disappeared by D_2O), 8.13 (1 H, s, pyridinium-H), 8.52 (2 H, s, picric acid H), 8.70 (1 H, s, pyridinium H).

Anal. Calcd for $C_{17}H_{20}N_4O_8$: C, 50.00; H, 4.94; N, 13.72. Found: C, 49.81; H, 5.12; N, 13.90.

1-(2-Hydroxyethyl)-2-hexyl-3,5-dipentylpyridinium Chloride (2c). A mixture of 15 g (ca. 0.15 mol) of ethanolamine hydrochloride and 120 g of 1-heptanal (ca. 1 mol) was stirred at room temperature. The reaction occurred exothermically and was complete in about 2 h. After washing with n-hexane twice and with water saturated with sodium chloride twice, the residual reaction mixture was extracted with chloroform and dried over anhydrous sodium sulfate. Evaporation of the chloroform gave a syrup (about 20 g). The UV in methanol of a syrup showed the absorption maximum at 245 and about 275 (shoulder) and 283 nm. The absorptions at 245 and about 275 nm were probably due to the presence of 1-(2-hydroxyethyl)-4-hexyl-3,5-dipentylpyridinium chloride **2d** (not separated). A syrup was stored in a refrigerator at 5 °C. The crude crystals were collected. A syrup was dissolved in dry ethyl ether and seeded with crude crystals. The colorless needles obtained were recrystallized from dry ethyl ether to afford strongly hygroscopic needles to yield 7 g: mp 71–71.5 °C; UV (MeOH) λ_{max} (ϵ) 283 nm (9800); IR (KBr) 3160 (OH), 2965 (CH), 1625, 1585 and 1500 (C=C and C=N), 1090, 870, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.7–1.1 (9 H, m), 1.1–2.0 (14 H, m), 2.75 (4 H, t, J = 7 Hz, $CH_2CH_2Pr \times 2$), 3.15 (2 H, m of triplet pattern, CH_2CH_2Bu), 4.05 (2 H, m of triplet pattern, CH_2CH_2OH), 4.90 (2 H, t, J = 7 Hz, NCH_2CH_2OH), 5.95 (1 H, m of triplet pattern CH_2OH, disappeared by D_2O), 7.9 (1 H, s, pyridinium H), 9.1 (1 H, s, pyridinium H).

Anal. Calcd for $C_{23}H_{42}NOCl$: C, 71.93; H, 11.02; N, 3.65; Cl, 9.23. Found: C, 71.65; H, 11.13; N, 3.69; Cl, 9.30.

2-Methyl-2-pentenal. 2-Methyl-2-pentenal was obtained from aldol condensation reaction of propanal catalyzed with Gly[6] to yield 55%: bp 136–138 °C (1 atm); IR (neat) 1685 (C=O), 1642, 1218, 1040 cm^{-1}; GLC t_R 1.1 min.

***N*-2-Methyl-2-pentenylidenemethylamine (3).** Aqueous 40% methylamine (50 mL) was added to 2-methyl-2-pentenal (30 g, 0.3 mol) with stirring at room temperature. The mixture become warm and the reaction was completed in ca. 30 min. The organic layer was extracted with ethyl ether and the extracts were dryed over sodium sulfate. The solution was distilled under atmospheric pressure, and after removal of the solvent the product was distilled at 138–140 °C, yielding 19 g (45%) of colorless liquid: UV (MeOH) λ_{max} (ϵ) 229 nm (21 200); IR (neat) 1650 and 1642 (C=C and/or C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (3 H, t, J = 7 Hz, CH_2CH_3), 1.82 (3 H, s, CH_3), 2.21 (2 H, m, $=CHCH_2CH_3$), 3.42 (3 H, s, CH_3), 5.76 (1 H, t, J = 7 Hz, $=CHCH_2$), 7.72 (1 H, s, N=CH).

Anal. Calcd for $C_7H_{12}N$: N, 12.73. Found: N, 12.01.

Reaction of *N*-2-Methyl-2-pentenylidenemethylamine (3) with Propanal. *N*-2-Methyl-2-pentenylidenemethylamine (**3**) (12 mL, ca. 0.1 mol) was cooled to 0 °C and added slowly to an acetic acid (8 mL, ca. 0.11 mol), keeping the temperature below 10 °C. Propanaol (10 mL, ca. 0.16 mol) was then added with stirring. The exothermic reaction occurred immediately and was complete in about 10 min. After 1 h, the mixture was treated with n-hexane three times. The aqueous layer obtained was evaporated to a syrup (18 g). The syrup (10 g) was dissolved in methanol and treated with picric acid. 2-Ethyl-1,3,5-trimethylpyridinium picrate (**4a**) was separated as needles (2.5 g) and recrystallized from methanol: mp 92.5–93 °C; IR (KBr) 3060, 1645, 1560, 1495, 1335, 1440, 1370, 1310, 1265, 1075, 905, 785, 745, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3 H, t, J = 7 Hz, CH_2CH_3), 2.50 (3 H, s, CH_3), 2.58 (3 H, s, CH_3), 3.16 (2 H, q, J = 7 Hz, CH_2CH_3), 4.48 (3 H, s, NCH_3), 7.98 (1 H, s, pyridinium H), 8.60 (2 H, s, picric acid H), 8.66 (1 H, s, pyridinium H).

Anal. Calcd for $C_{16}H_{18}N_4O_7$: C, 50.79; H, 4.80; N, 14.81. Found: C, 50.87; H, 4.86; N, 14.65.

The aqueous layer (8 g) was heated at 250 °C and then the volatile products (160–210 °C/1 atm) formed by thermal degradation were collected (6 mL): GLC t_R min (% of peak area) 1.1 (12), 1.6 (1), 1.9 (6), 2.4 (8), 3.0 (59), 5.5 (18), 6.4 (7), 8.1 (2). The volatile compounds (5 mL) were dissolved in methanol and treated with picric acid. 2-Ethyl-3,5-dimethylpyridine picrate (**8**) (3 g, yellow colored needles) and 4-ethyl-3,5-dimethylpyridine picrate (**9**) (0.1 g, orange colored needles) were obtained by fractional crystallization.

2-Ethyl-3,5-dimethylpyridine picrate (8): mp 157–158 °C (lit.[10] mp 156–157 °C); ^1H NMR ($CDCl_3$) δ 1.2 (3 H, t, J = 7 Hz, CH_2CH_3), 2.4 (6 H, s, $CH_3 \times 2$), 2.8 (2 H, q, J = 7 Hz, CH_2CH_3), 8.1 (1 H, s, pyridine H), 8.4 (2 H, s, and 1 H, s; picric acid H and pyridine H, respectively).

Anal. Calcd for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.47; H, 4.33; N, 15.54. GLC of **8** t_R 3.0 min.

4-Ethyl-3,5-dimethylpyridine picrate (9): mp 155–156 °C; ^1H NMR ($CDCl_3$) δ 1.3 (3 H, t, J = 7 Hz, CH_2CH_3), 2.5 (6 H, s, $CH_3 \times 2$), 2.9 (2 H, q, J = 7 Hz, CH_2CH_3), 8.3 (2 H, s, picric acid H), 8.7 (2 H, s, pyridine H).

Anal. Calcd for $C_{15}H_{16}N_4O_7$: C, 49.45; H, 4.43; N, 15.38. Found: C, 49.47; H, 4.48; N, 15.32. GLC of **9** t_R 6.4 min.

Registry No.—**1a**, 69188-76-7; **1a**·HCl, 69188-77-8; **1b**, 69188-78-9; **1b**·HCl, 69188-79-0; **1c**, 69188-80-3; **1d**, 69188-81-4; **1e**, 69188-82-5; **1f**, 69188-83-6; **1f**·HCl, 69188-84-7; **2a**, 53422-80-3; **2b**, 53422-78-9; **2c**, 53422-77-8; **2d**, 69188-85-8; **3**, 69188-86-9; **4a**, 69188-88-1; **8** picrate, 67498-69-5; **9** picrate, 69188-89-2; glycine, 56-40-6; leucine, 61-90-5; L-α-alanine, 56-41-7; propanal, 123-38-6; butanal, 123-72-8; ethanolamine hydrochloride, 2002-24-6; heptanal, 111-71-7; 2-methyl-2-pentenal, 623-36-9; methylamine, 74-89-5.

References and Notes

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