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Enamine/Imine Tautomerism in α,β-Unsaturated-α-Amino Acids

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Abstract: Investigation of the α,β-unsaturated-α-amino acids—dehydrovaline, dehydrophenylalanine, and dehydropipecolinic acid—revealed that these compounds undergo rapid hydrolysis in neutral aqueous medium, via the imine tautomers, even when the corresponding esters and sodium salts exist as the enamine tautomers. This is true even for dehydropipecolinic acid which had been reported to be stable for 10–18 h in dilute aqueous neutral solution.

Vinyl amines (enamines) are known to exist in equilibrium with their imine tautomers; the latter hydrolyze quite rapidly to give the corresponding aldehyde or ketone and the amine.[1] Only limited studies exist regarding the factors controlling enamine-imine tautomerizations and the relative energies of the tautomers. It is known that the stability of enamine tautomers, relative to the imine tautomers, is greater in tertiary systems and least in primary unsaturated amines,[1] but even primary and secondary enamines can be stabilized by appropriate substitution at the β-carbon.[1] In addition, it has been shown that polar solvents favor enamization.[2] A recent computational study of the parent tautomer pair, vinylamine/acetaldimine, estimated the energy difference between the tautomers at 3.9 kcal/mol in favor of the imine;[3] only small effects were calculated for changes in dielectric constant of the medium. Medium effects on enamine-imine tautomerism have been extensively studied in the quinoxaline system. Enamine-imine mixtures are observed in dimethyl sulfoxide solutions of 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines[4] and 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines,[5] but the enamine tautomers predominate in chloroform solutions of 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines.[4] Protonation stabilizes the imine tautomer for 3-alkoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxalines, but for 3-(arylhydrazono)methyl-2-oxo-1,2-dihydroquinoxalines the enamine is favored.[5] In related compounds the enamine tautomer is preferred in all solvents as well as by protonation.[4] Studies of o-substituted aromatic azomethines have shown that the enolimino tautomer is preferred in the gas phase and in apolar solvents, and this result has been confirmed by computational methods.[6]

There are also a few literature examples of α,β-unsaturated-α-amino acids.[7-12] In particular, a study of dehydropipecolinic acid (**1c**) was intriguing since it was reported that this compound, when isolated as the sodium salt, exists as the enamine while the hydrochloride salt exists as the imine.[13] It was also reported that the compound has a reasonable lifetime in dilute solution at neutral pH; the nature of the tautomer in neutral medium was not reported. We undertook to study the open chain aliphatic α,β-unsaturated-α-amino acid dehydrovaline (**1a**), an open chain aliphatic α,β-unsaturated-α-amino acid with a β-substituent capable of extending the conjugation of the enamine double bond, dehydrophenylalanine (**1b**), and the cyclic aliphatic α,β-unsaturated-α-amino acid dehydropipecolinic acid (**1c**).

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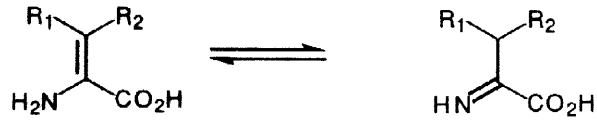
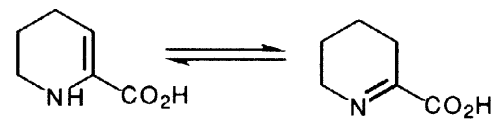


	R_1	R_2
1a	CH_3	CH_3
1b	Ph	H



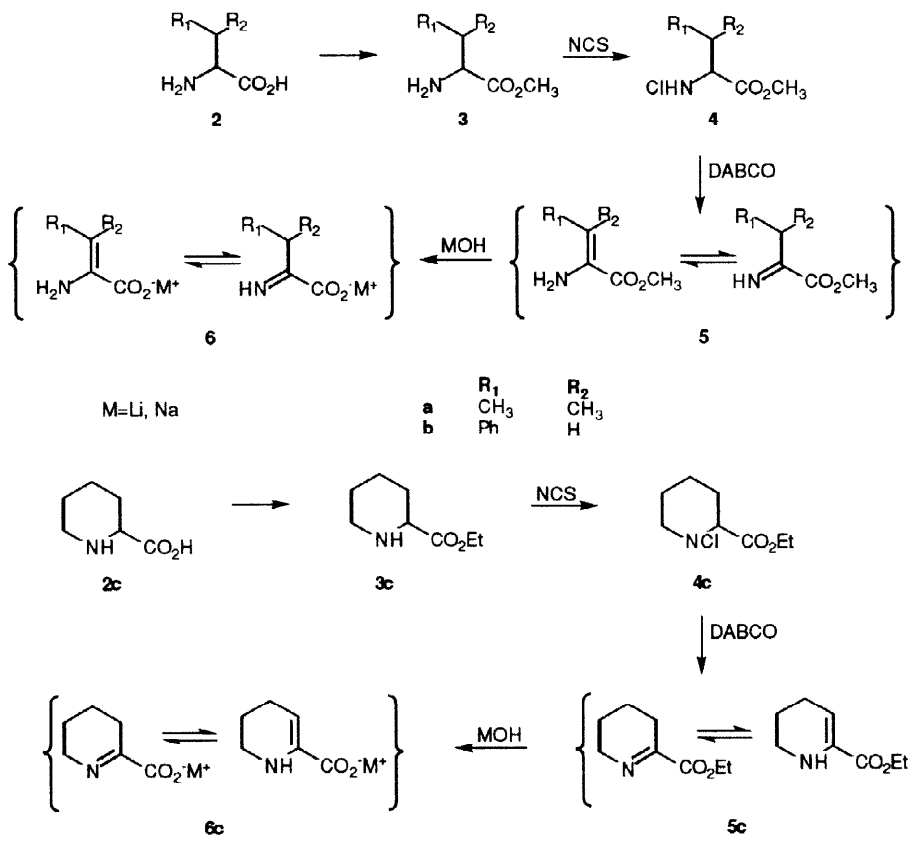
1c

RESULTS

Synthesis

The synthetic approach to the preparation of α,β-unsaturated-α-amino acids was *via* the N-chloro derivatives of the corresponding α-amino acid esters (Scheme). Carefully monitored N-chlorination of the methyl or ethyl ester (**3**) of the appropriate saturated α-amino acid, using N-chlorosuccinimide (NCS), afforded the desired N-chloro-α-amino acid ester (**4**). Treatment of the light sensitive chloramines with one equivalent of 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effected the elimination of hydrochloric acid and gave the unsaturated esters **5**. These esters were susceptible to

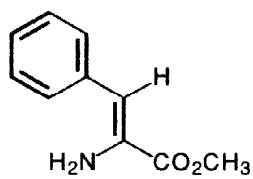
Scheme



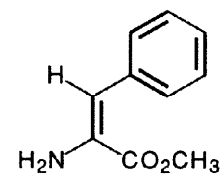
moisture and air but could be stored at low (<20 °C) temperatures in the presence of radical scavengers for a few weeks. Saponification with one equivalent of lithium hydroxide in aqueous tetrahydrofuran or of sodium hydroxide in aqueous dioxane produced the lithium or sodium carboxylate salts **6**, respectively.

Spectral Studies

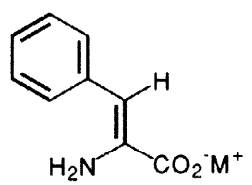
The proton nuclear magnetic resonance spectra of the esters of dehydrovaline (**5a**), dehydrophenylalanine (**5b**), and dehydropipecolinate (**5c**) in chloroform indicate that the esters **5a** and **5b** exist entirely in their enamine forms. Specifically, no signals which would be expected for the imine tautomer of **5a**, *e.g.* a multiplet for the β-proton, doublet methyl resonances, are observed for **5a**, and, similarly, no aliphatic proton resonances are exhibited in the proton NMR of **5b**. The nuclear Overhauser effect on the vinyl resonance (δ 6.48 ppm), resulting from irradiation of the methyl resonance (δ 3.86 ppm), shows dehydrophenylalanine enamine to be in *Z* (phenyl *anti* to carboxyl) configuration. On the other hand, ethyl dehydropipecolinate (**5c**) appears as an equimolar mixture of imine and enamine tautomers (see experimental section). In aqueous solution the sodium salts of all three amino acids (**6a–c**) show resonances consistent with mixtures in which the imine predominates (60–85%). In a dimethyl sulfoxide solution of the sodium salt of dehydrophenylalanine (**6b**) a slight excess of the enamine (~66%), as a near equimolar mixture of *E* and *Z* isomers, is observed. These results are summarized in the Table.



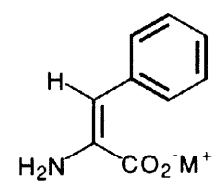
Z-**5b**



E-**5b**



Z-**6b**



E-**6b**

Table
Enamine-Imine Tautomeric Equilibria[a]

Compound	Solvent	Composition (%)	
		Enamine	Imine
5a	$CDCl_3$	100	0
6a	D_2O	17	83
5b	$CDCl_3$	100	0
6b	D_2O	40	60
	DMSO-d_6	67[b]	33
5c	$CDCl_3$	50	50
6c	D_2O	25	75

[a] Determined by integration of the appropriate ^1H NMR resonances
[b] Equimolar mixture of *Z* and *E* isomers

Examination of the sodium salts of the three dehydroamino acids (**6a-c**) by UV shows absorbance at λ_{max} 250–300 nm immediately after dissolution in strong base (pH =14). For **6b** this absorbance persists for several days, but for **6a** and **6c** it disappears overnight. Dissolution of **6b** in aqueous buffer at pH 7.4 gives the identical absorbance pattern observed at pH 14. This pattern disappears within 5–10 minutes. At pH 8 the pattern lasts for about one hour. The salts **6a** and dehydropipecolinate **6c** show no significant absorbance in aqueous solution at pH 7.4.

The IR spectrum of sodium dehydropipecolinate **6c** (nujol mull) exhibited the following bands (cm^{-1}): 3355, 1609, 1397, 1373, 1329, 1117, 923. Thus, although it was similar to the literature[13] spectrum [which had the following bands (cm^{-1}): 2400, 1667, 1610, 1407, 1335, 1110, 910], the band at 1667 cm^{-1} was absent in our spectrum.

DISCUSSION

The observed predominance of some enamine tautomers, relative to the imine tautomeric forms, in trifluoroacetic acid[4,5] suggests that protonation may stabilize the enamine tautomer. On the other hand, the presence of a $C=N^+$ group (1713 cm^{-1}) in the IR spectrum of the hydrochloride salt of α,β-dehydropipecolinic acid indicates that this salt exists as an imine tautomer.[13] These apparent discrepancies suggest that the factors affecting tautomeric equilibria in quinoxaline analogs and in α,β-unsaturated-α-amino acids such as **1c** are significantly different.

For α,β-dehydropipecolinic acid (**1c**) the observed C=C bond (1667 cm^{-1}) in the IR spectrum of its sodium salt **6c** is consistent with the carboxylate anion existing as the enamine tautomer; at the same time, the cationic hydrochloride salt exists as the imine. It follows that, since there is good evidence that α-amino acids exist primarily as zwitterions, **1c**, which contains the elements of a carboxylate anion and of a protonated nitrogen, would exist as an equilibrium mixture of enamine and imine tautomers. The reported[13] stability of **1c** over an 18-hour period in neutral aqueous solution does not support this conjecture, since, if this were the case, hydrolysis to an α-keto acid *via* the imine should have been rapid. The results of our study fail to confirm both the reported[13] stability of dehydropipecolinate in neutral medium and the existence of the sodium salt of dehydropipecolinate predominantly in the enamine form. Thus, whereas our Nujol spectrum of sodium α,β-dehydropipecolinate (**6c**) resembles the published spectrum and exhibits no bands in the region between 1670–2730 cm^{-1}, the NMR spectrum of an aqueous solution of sodium dehydropipecolinate (**6c**) shows a 3:1 mixture of imine and enamine tautomers. Since the IR spectrum was recorded as a Nujol mull, this discrepancy might be ascribed to the existence of different tautomeric forms in the solid (IR) and in solution (NMR). In fact, the dependency of enamine-imine tautomeric equilibria on the matrix is not only likely *a priori*, it is supported by the literature[2,4,5] and by our observations in the dehydrophenylalanine (**6b**) system. Thus, in dimethyl sulfoxide, the sodium salt **6b** exists as an equimolar mixture of imine, *E* enamine, and *Z* enamine, while in water it is a 3:2 mixture of imine and *Z* enamine.

The discrepancy between our results and the literature[13] regarding the stability of dehydropipecolinate in neutral solution is more serious. Since our NMR studies show that the sodium salts of all three dehydro α-amino acids (**6a-c**) exist to some extent (15–40%) in the enamine form, the UV absorbance (>250 nm), which they all demonstrate at pH 14, is likely to be associated with the enamine tautomer. This is supported by the observation that the UV spectrum of dehydrophenylalanine at pH 7.4 is initially identical to the spectrum recorded at pH 14 but rapidly changes and becomes identical to the spectrum of phenylpyruvic acid, consistent with conversion of the enamine to the imine followed by hydrolysis. Again, this interpretation is consistent with the NMR observations, which show that while the characteristic carbonyl resonance of phenylpyruvic acid (205 ppm) is absent from the ^{13}C NMR spectrum of dehydrophenylalanine at pH 14 in water, the spectrum of dehydrophenylalanine in neutral water is identical to that of phenylpyruvic acid. For sodium dehydropipecolinate (**6c**) in dilute (10^{-4} M) basic aqueous solution, λ_{max} 260 nm is observed, consistent with what might be expected for an α,β-unsaturated acid with an amino α-auxochrome[14] and consistent with the detection of 25% enamine in an aqueous solution by NMR. Recording of the UV

spectrum of sodium dehydropipecolinate (**6c**) immediately after dissolution in a pH 7.4 buffer reveals no absorbance >210 nm, indicating that the enamine has disappeared. That the spectrum observed at pH 7.4 is not that of the imine is shown by the fact that re-basification of the sample fails to reproduce the spectrum observed at pH 14. In fact, none of the characteristics of the sample (TLC, NMR) survive lowering of the pH to neutrality, even for a moment.

CONCLUSIONS

The enamine tautomers of the three α,β-unsaturated-α-amino acids—dehydrovaline, dehydropipecolinic acid, and dehydrophenylalanine—are more stable than their respective imine tautomers in the esters of the open chain analogs dehydrovaline and dehydrophenylalanine but are equienergetic with the imine tautomer in the cyclic dehydropipecolinate ester. On the other hand, the enamine tautomers are less stable than their respective imine tautomers in basic aqueous medium, unless the enamine double bond is stabilized by extended conjugation. Hydrolysis of α,β-unsaturated-α-amino acids to the α-keto acids occurs in less than five minutes in neutral aqueous solution.

EXPERIMENTAL

General

Diethyl ether and THF were distilled form sodium/benzophenone under nitrogen. Methylene chloride was distilled from calcium hydride under nitrogen. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-250, using $CDCl_3$ or D_2O as the solvent. The infrared spectra were taken on a Shimadzu IR-460 spectrometer. UV measurements were carried out on a Cary 3G UV-Visible spectrometer. Mass measurements were recorded on a Hewlett Packard 5989A mass spectrometer. All reactions were routinely followed by thin-layer chromatography on commercial TLC plates Merck 60 F_{254}. Flash column chromatography was conducted on Merck silica gel 60 (230–400 mesh). A Kugelrohr apparatus was used for vacuum distillation of products. Unless otherwise specified, all nonaqueous reactions were carried out under nitrogen atmosphere, using oven-dried glassware.

Synthesis of Sodium Salt of α,β-Dehydrovaline (6a)

A solution of valine methyl ester **3a** (2.77 g, 23.6 mmol) in anhydrous Et_2O (100 mL) was cooled to 0–5 °C with an ice-water bath and was treated under N_2 with 1.0 eq of N-chlorosuccinimide[15,16] (3.15 g, 23.6 mmol) in a flask covered with aluminum foil. To minimize the formation of N-dichloramine, the N-chlorosuccinimide was dissolved in benzene or cyclohexane (60 mL) and added dropwise to the reaction vessel over a period of 2 h. The reaction mixture was stirred at 0–5 °C for another 4 h until TLC (AcOEt/CH_2Cl_2, 1:1) indicated total consumption of the starting material. Since N-chloramines[17] are light sensitive, all the following workup and handling of the product were done with exclusion of light. The solvent was evaporated, and petroleum ether (60 mL) was added. The white solid was removed by filtration and washed with petroleum ether (20 mL) several times. The filtrate was concentrated in vacuo, and the product N-chlorovaline methyl ester (**4a**) was obtained as a colorless oil (3.07 g, 78%) which was immediately used in the dehydrochlorination reaction. The NMR data of **4a** were consistent with literature values.[9] ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 0.93 (d, J = 6.9 Hz, 3H, CH_3), 0.96 (d, J = 6.9 Hz, 3H, CH_3), 1.91 (m, 1H, βCH), 3.37 (dd, J = 11.3 Hz, 6.4 Hz, 1H, αCH), 3.77 (s, 3H, OCH_3), 4.58 (d, J = 11.3 Hz, 1H, NH). ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 18.7, 19.1, 31.7, 52.0, 73.6, 173.3.

A solution of **4a** (1.00 g, 6.0 mmol) in anhydrous Et_2O (60 mL) was treated under N_2 with 1.0 eq of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.92 g, 6.0 mmol) in a flask covered with aluminum foil. The reaction mixture was stirred at room temperature for 2 h. It was cooled to 0 °C, and the white solid was removed by filtration. The ethereal solution of the resulting iminoacid ester was treated at -78 °C with 1.0 M HCl in anhydrous Et_2O (7.2 mL). The solution was stirred at -78 °C for 15 min and at 0 °C for 5 h. It was then kept

in a refrigerator overnight. The solution was concentrated to dryness in vacuo and the resultant residue was digested with anhydrous Et_2O and collected by filtration. The collected crystalline product was dissolved in anhydrous $CHCl_3$, and dry NH_3 was passed through the solution at 0–5 °C for 15 min. The white solid was removed by filtration, and the filtrate was concentrated in vacuo. A light yellow oil was obtained. Kugelrohr distillation under vacuum afforded the pure α,β-dehydrovaline methyl ester (**5a**) (581 mg, 75%), b.p. 65 °C/6 torr. The NMR data were consistent with literature values.[11] ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 1.62 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 3.16 (br, 2H, NH_2), 3.63 (s, 3H, OCH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 20.8, 51.2, 120.9, 127.2, 165.4.

A solution of NaOH (155 mg, 3.87 mmol) in H_2O (10 mL) was added to a solution of **5a** (500 mg, 3.9 mmol) in 1,4-dioxane (10 mL). The reaction mixture was stirred overnight and lyophilized to afford a pale yellow solid (530 mg, 100%). Examination of the ^1H NMR spectrum at 250 MHz in D_2O provided evidence for the presence of two tautomers in solution, namely the sodium salts of α,β-dehydrovaline and α-iminovaline in a 1:5 ratio. The ^{13}C NMR spectrum taken in D_2O was consistent with the presence of the sodium salt of the enamine, *i.e.* two olefinic carbon signals were present at δ 117.5 and 134.1. The effect of pH on the NMR and UV spectra of this compound was studied. At neutral or acidic pH both the NMR and the UV spectra changed rapidly consistent with immediate hydrolysis to the keto acid. In basic solution the UV exhibited λ_{max} 262 nm; this absorbance disappeared after overnight. The material can be stored as a solid sodium salt under nitrogen in refrigerator for months without evident decomposition. ^1H NMR (250 MHz, D_2O) δ (ppm): (enamine) 1.64 (s, 3H, CH_3), 1.86 (s, 3H, CH_3); (imine) 1.12 (d, J = 6.9 Hz, 6H, $(CH_3)_2$), 3.0 (m, 1H, CH).

Synthesis of Sodium Salt of α,β-Dehydrophenylalanine (6b)

A solution of phenylalanine methyl ester **3b** (2.00 g, 11.16 mmol) in anhydrous Et_2O (20 mL) was cooled to 0–5 °C with an ice water bath and was treated under nitrogen atmosphere with 1.0 eq of N-chlorosuccinimide (1.49 g, 11.16 mmol) in a flask covered with aluminum foil. To minimize the formation of N-dichloramine, the N-chlorosuccinimide was dissolved in benzene or cyclohexane (60 mL) and added dropwise to the reaction vessel over a period of 2 h. The reaction mixture was stirred at 0–5 °C for another 4 h until TLC (AcOEt/Hxn 1:10) indicated total consumption of the starting material. The following workup and handling of the product chloramine were done with exclusion of light. The solvent was evaporated, and petroleum ether (60 mL) was added. The white solid was removed by filtration and washed with petroleum ether (20 mL) several times. The filtrate was concentrated in vacuo, and the product N-chlorophenylalanine methyl ester **4b** was obtained as a colorless oil (2.30 g, 97%) pure enough for immediate use in the dehydrochlorination reaction. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 3.03 (d, J=7.5 Hz, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.90 (m, 1H, dt, J=9.5, 6.8 Hz, αCH), 4.59 (m, 1H, d, J=9.5 Hz, NH), 7.14–7.37 (m, 5H, ArH); ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 37.7, 52.3, 68.3, 127.1, 128.6, 129.1, 135.6, 172.3.

A solution of **4b** (2.30 g, 10.76 mmol) in dry Et_2O (60 mL) was treated with 1.2 eq of 1,4-diazabicyclo[2.2.2]octane (DABCO) (1.45 g, 12.92 mmol) under nitrogen in a flask covered with aluminum foil. The reaction mixture was stirred at room temperature for 6 h. The white solid was removed by filtration, and the ethereal solution was washed with cold 20% aq $NaHCO_3$. The solution was concentrated in vacuo and a colorless oil was obtained. Kugelrohr distillation under vacuum afforded Z-α,β-dehydrophenylalanine methyl ester **5b** as a single product (0.96 g, 50%). The slightly low yield may be due to the decomposition and polymerization of the product during vacuum distillation. The Z-configuration was confirmed by NOE experiments on the vinyl and methyl protons using a Bruker AMX-500. The NMR data were consistent with the literature values,[12] b.p. 180 °C/6 torr. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): 3.86 (s, 3H, OCH_3), 4.23 (br, 2H, NH_2), 6.48 (s, 1H, =CH), 7.17–7.50 (m, 5H, ArH). ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm): 52.6, 109.2, 126.8, 128.3, 128.8, 132.1, 136.2 166.3 IR (neat) cm^{-1}: 3445, 3045, 1715, 1632, 1585, 1489, 1438, 1402, 1323, 1267, 1224, 1193, 1166, 1074, 984. MS (EI, 70 eV) m/z (relative intensity): 177 (M^+, 100), 117 (95), 91 (39), 65 (10).

A solution of NaOH (97.1 mg, 2.43 mmol) in H_2O (10 mL) was added to a solution of **5b** (430 mg, 2.43 mmol) in 1,4-dioxane (10 mL). The reaction mixture was stirred overnight and lyophilized to afford a pale yellow solid (435 mg, 98%). Examination of the ^1H NMR (250 MHz) in D_2O provided evidence for the presence of two tautomers in solution, namely the sodium salts of α,β-dehydrophenylalanine (δ 6.40 ppm, s, 1H, =CH, 7.40 ppm, m, 5H, ArH) and α-iminophenylalanine (δ 4.11 ppm, s, 2H, CH_2, 7.40 ppm, m, 5H, ArH) in a 2:3 ratio. ^1H NMR in DMSO-d_6 indicated the presence of a mixture of imine, (δ 3.96 ppm, s, 2H, CH_2, 7.25 ppm, m, 5H, ArH), E enamine (δ 6.08 ppm, s, =CH, 1H, 7.25 ppm, m, 5H, ArH), and Z enamine (δ 6.15 ppm, s, 1H, = CH, 7.25 ppm, m, 5H, ArH) in 1:1:1 ratio. The effects of pH on the NMR and UV spectra of the compound were studied. At acidic or neutral pH, both the NMR and the UV spectra changed rapidly, indicating immediate decomposition of the material. The sodium salt of α,β-dehydrophenylalanine (0.90 mg, 4.9×10^{-3} mmol) was quickly dissolved in 1 N HCl (10 mL), potassium phosphate buffer (pH 7.4) (0.05 M, 10 mL), sodium phosphate buffer (pH 8.5) (0.2M, 10 mL), and 1 N NaOH (10 mL), respectively. Immediately after the preparation of the solutions, UV measurements were recorded every 5 min over a period of 1 h. In acidic medium the spectra were identical to those of phenylpyruvic acid exhibiting λ_{max} 210 nm, consistent with hydrolysis of the imine to produce phenylpyruvic acid. Furthermore, treatment of **6b** with 6 N HCl quantitatively afforded a product identical to authentic phenylpyruvic acid. At pH 7.4 the absorbance at λ_{max} 295 nm diminished rapidly to yield a spectrum identical to that of phenylpyruvic acid. At pH 8.5 the process was much slower; enamine was still present 1 h after the solution was prepared, as judged by the absorbance at λ_{max} 295 nm. In basic solution, absorbance at λ_{max} 295 nm was observed; no spectral change was observed over a 24-h period. The sodium salt of α,β-dehydrophenylalanine can be stored as a solid, under nitrogen, in a refrigerator, for months without evident decomposition. ^1H NMR (250 MHz, D_2O) δ (ppm): (enamine isomer) 6.40 (s, 1H, =CH), (imine isomer) 4.11 (s, 2H, CH_2), 7.40 (m, 5H, ArH).

Synthesis of Sodium Salt of α,β–Dehydropipecolinate (6c)

A solution of ethyl pipecolinate (**3c**) (2.00 g, 12.7 mmol) in dry Et_2O (50 mL) was cooled to 0–5 °C with an ice water bath and was treated under N_2 atmosphere with 1.2 eq of N-chlorosuccinimide (2.04 g, 15.3 mmol) in a flask covered with aluminum foil. The reaction mixture was stirred at 0–5 °C for another 4 h until TLC indicated total consumption of the starting material. The following workup and handling of the product were done with exclusion of light. The solvent was evaporated, and petroleum ether (60 mL) was added. The white solid was removed by filtration and washed with petroleum ether (20 mL) several times. The filtrate was concentrated in vacuo, and the product ethyl N-chloropipecolinate (**4c**) was obtained as a colorless oil (2.08 g, 85%) which was immediately used in the dehydrochlorination reaction. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J = 7.2 Hz, 3H, CH_3), 1.60–1.82 (br, 6H, $CH_2CH_2CH_2$), 2.88 (m, 1H, αCH), 3.41–3.54 (m, 2H, NCH_2), 4.18 (q, J = 7.2 Hz, 2H, OCH_2). ^{13}C NMR (63 MHz, $CDCl_3$) δ (ppm) 14.0, 22.3, 26.8, 30.9, 61.0, 62.7, 74.0, 170.9. IR (neat) cm^{-1}: 2930, 1750, 1463, 1377, 1274, 1182, 1055.

A solution of **4c** (1.22 g, 6.4 mmol) in dry Et_2O (30 mL) was treated with 1.0 eq of 1,4-diazabicyclo[2.2.2]octane (DABCO) 0.71 g, 6.4 mmol) under N_2 in a flask covered with aluminum foil. The reaction mixture was stirred at room temperature for 6 h. The white solid was removed by filtration, and the ethereal solution was washed with cold 20% aq $NaHCO_3$. The solution was concentrated in vacuo, which provided the product ethyl α,β-dehydropipecolinate (**5d**) (889 mg, 90%) as a near equimolar tautomeric mixture of enamine and imine. ^1H NMR (250 MHz, $CDCl_3$) δ (ppm): (enamine) 1.22 (t, J = 7.2 Hz, 3H, CH_3), 1.73 (m, 2H, CH_2), 2.12 (m, 2H, CH_2), 3.10 (dd, 2H, CH_2), 4.14 (q, J = 7.2 Hz, 2H, OCH_2), 5.59 (t, J = 4.3 Hz, 1H, =CH); (imine) 1.30 (t, 7.2 Hz, 3H, CH_3), 1.56, 1.65 (2m, 2H, CH_2), 2.41 (m, 2H, CH_2), 3.78 (m, 2H, CH_2), 4.23 (q, J = 7.2 Hz, 2H, OCH_2); IR (neat) cm^{-1}: 3405, 2975, 2855, 1703, 1639, 1477, 1440, 1382, 1330, 1271, 1245, 1137, 1098. MS (EI, 70 eV) m/e (relative intensity): 155 (M^+, 39), 127 (12), 126 (41), 82 (78), 54 (100).

A solution of NaOH (258 mg, 6.4 mmol) in H_2O (10 mL) was added to a solution of **5c** (1.0 g, 6.4 mmol) in 1,4-dioxane (10 mL). The reaction mixture was stirred overnight and lyophilized to afford a pale yellow solid (960 mg, 99%). Examination of the ^1H NMR spectrum at 250 MHz in D_2O provided evidence for the

presence of the enamine and imine tautomers in solution in a 1:3 ratio. The ^{13}C NMR spectrum taken in D_2O was consistent with the presence of the sodium salt of the enamine, *i.e.* two olefinic carbon signals were present at δ 112.3 and 141.1 ppm. The sodium salt **6c** (0.70 mg, 4.7×10^{-3} mmol) was quickly dissolved in 1 N HCl (10 mL), potassium phosphate buffer (pH 7.4) (0.05 M, 10 mL), sodium phosphate buffer (pH 8.5) (0.2 M, 10 mL), and 1 N NaOH (10 mL), respectively. Immediately after preparation of the solutions, UV measurements were recorded every 5 min over a period of 1 h. At acidic or neutral pH both the NMR and the UV spectra changed rapidly indicating immediate decomposition of the material. At basic pH, **6c** exhibited λ_{max} 260 nm; no major change was observed over 24 h. The material can be stored as a solid sodium salt, under nitrogen, in a refrigerator, for months without evident decomposition. ^1H NMR (250 MHz, D_2O) δ (ppm): (enamine) 1.64 (m, 2H, CH_2), 2.15 (m, 2H, CH_2), 3.04 (m, 2H, NCH_2), 5.69 (t, J = 4.1 Hz, 1H, =CH); (imine) 1.64 (br, 4H, CH_2 CH_2), 2.40 (m, 2H, CH_2), 3.55 (m, 2H, NCH_2).

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REFERENCES

1. Capon, B.; Wu, Z.-P. *J. Org. Chem.* **1990,** *55*, 2317.
2. Clark, R. A.; Parker, D. C. *J. Am. Chem. Soc.* **1971,** *93*, 7257.
3. Lammerstma, K.; Prasad, B. V. *J. Am. Chem. Soc.* **1994,** *116*, 642.
4. Kurasawa, Y.; Takada, A. *Heterocycles* **1986,** *24*, 2321.
5. Kurasawa, Y.; Hosaka, T.; Takada, A.; Kim, H. S.; Okamoto, Y. *J. Heterocycl. Chem.* **1995,** *32*, 445.
6. Hofmann, H.-J.; Cimiraglia, R.; Tomasi, J.; Bonaccorsi, R. *Z. Chem.* **1990,** *30*, 443.
7. Cutolo, M.; Fiandanese, V.; Naso, F.; Sciacovelli, O. *Tetrahedron Lett.* **1983,** *24*, 4603.
8. Denis, J. M.; Niamayoua, R.; Vata, M.; Lablache-Combier, A. *Tetrahedron Lett.* **1980,** *21*, 515.
9. Poisel, H.; Schmidt, U. *Chem. Ber.* **1975,** *108*, 2547.
10. Poisel, H.; Schmidt, U. *Chem. Ber.* **1975,** *108*, 2917.
11. Poisel, H.; Schmidt, U. *Angew. Chem. Int. Ed. Engl.* **1976,** *15*, 294.
12. Poisel, H. *Chem. Ber.* **1977,** *110*, 942.
13. Macholan, L.; Vencalkova, J. *Chem. Ber.* **1963,** *96*, 237.
14. Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. ^{13}C NMR spectrometry. In *Spectrometric Identification of Organic Compounds*; John Wiley & Sons: New York, 1981; pp. 305.
15. Ruschig, H.; Fritscj, W.; Schmidt-Thome, J.; Haede, W. *Berichte de Deutsche Chemische Gesellschaft* **1955,** *88*, 883.
16. Kimura, M.; Ban, Y. *Synthesis* **1976**, 201.
17. Kovacic, P.; Lowery, M. K.; Field, K. W. *Chem. Rev.* **1970,** *70*, 639.