onto cracked ice. The title compound precipitated as a white solid. Filtration, washing with water, and air-drying gave the product: 0.93 g (66.5%); mp 145 °C. Recrystallization from ethyl acetate provided the analytical sample: mp 147–148 °C; $^1$H NMR ($Me_2SO$-$d_6$) δ 5.98 (s, 2, $CH_2$), 7.95 (s, 1, H-2), 9.75 (br s, 1, NH); mass spectrum (70 eV), *m/e* (relative intensity) 188 ($M^+$, 23), 142 (M – $NO_2$, 17), 46 ($NO_2^+$, 94).

Anal. Calcd for $C_4H_4N_4O_5$: C, 25.55; H, 2.14; N, 29.79. Found: C, 25.74; H, 2.27; N, 29.65.

**[4-Nitro-1-(tetrahydropyran-2-yl)imidazol-5-yl]methyl Nitrate (6).** Dihydropyran (5.3 mL, 58.6 mmol) in ethyl acetate (60 mL) was added dropwise to a refluxing solution of **5** (10.2 g, 54.2 mmol) and bis(*p*-nitrophenyl) phosphate (75 mg) in ethyl acetate (100 mL). After complete addition, the reaction mixture was refluxed for an additional hour. A second portion of dihydropyran (3 mL) was then added, and refluxing was continued until all the starting material was consumed. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (250 g), eluting with chloroform. The product was obtained as a yellow oil (10.7 g, 72.6%) which, when cooled, crystallized: mp 79–80 °C; $^1$H NMR ($CDCl_3$) δ 1.3–2.6 (m, 6, C-3′, C-4′, C-5′ $H_2$), 3.5-4.4 (m, 2, C-6′ $H_2$), 5.47 (m, C-2′ H), 5.93 and 6.2 (AB q, 2, $CH_2$–O, *J* = 13 Hz), 7.82 (s, 1, H-2).

Anal. Calcd for $C_9H_{12}N_4O_6$: C, 39.71; H, 4.44; N, 20.59. Found: C, 39.73; H, 4.49; N, 20.40.

**4-Nitro-1-(tetrahydropyran-2-yl)imidazole-5-carboxaldehyde (7).** To a stirred and chilled (4 °C) solution of **6** (1.38 g, 5.06 mmol) in chloroform (23 mL) was added, dropwise, a solution of 1,5-diazabicyclo[4.3.0]non-5-ene (0.66 mL, 5.31 mmol) in chloroform (8 mL). After 1 min, the reaction mixture was washed with 0.1 N HCl (3 × 20 mL) and water (2 × 10 mL), dried over magnesium sulfate, filtered, and evaporated to dryness to give a brown oil (1.95 g). Purification by column chromatography, eluting with chloroform, provided the product (1.06 g, 100%) as a yellow oil which solidified on standing: mp 49–50 °C; $^1$H NMR ($CDCl_3$) δ 1.5–2.5 (m, 6, C-3′, C-4′, C-5′ $H_2$), 3.4–4.5 (m, 2, C-6′ $H_2$), 6.1 (m, 1, C-2′ H), 8.15 (s, 1, H-2), 10.63 (s, 1, CHO).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.93; N, 18.66. Found: C, 48.06; H, 4.78; N, 18.42.

**2-Nitro-1-[(4-nitro-1-(tetrahydropyran-2-yl)imidazol-5-yl]ethanol (8).** To a stirred, chilled (4 °C) solution of **7** (155 mg, 0.69 mmol) and nitromethane (0.075 mL) in 95% ethanol (5 mL) was added 10% aqueous sodium hydroxide (0.2 g). After 20 min, 2% aqueous acetic acid (2.1 mL) was added. Extraction with chloroform, drying, and evaporation gave a residue which was crystallized from ethyl acetate–hexane (2:1): mp 137 °C; 180 mg (91%); $^1$H NMR ($Me_2SO$-$d_6$) δ 1.27–2.27 (m, 6, C-3′, C-4′, C-5′ $H_2$), 3.43–4.3 (m, 2, C-6′ $H_2$), 4.82–5.05 (m, 2, $CH_2NO_2$), 5.64–5.95 (m, 1, C-2′ H), 6.08–6.55 (m, 1, CHOH), 6.82 (m, 1, OH), 8.13 (s, 1, H-2).

Anal. Calcd for $C_{10}H_{14}N_4O_6$: C, 41.96; H, 4.90; N, 19.58. Found: C, 41.84; H, 4.77; N, 19.31.

**2-Acetoxy-2-[4-nitro-1-(tetrahydropyran-2-yl)imidazol-5-yl]acetonitrile (9).** To a stirred solution of **7** (2.85 g, 12.7 mmol) in chloroform (20 mL) were added acetic anhydride (1.62 mL, 14 mmol) and potassium cyanide (1.0 g, 20.4 mmol). After stirring at room temperature for 4 h, additional acetic anhydride (0.16 mL) and potassium cyanide (0.1 g) were added, and stirring was continued for another 4 h. Filtration of the solid followed by washing the filtrate with water (3 × 20 mL), drying, and evaporation gave a gummy residue. Purification by column chromatography on silica gel, with ethyl acetate–hexane (1:1) as an eluent, afforded the product: 3.2 g (86%); $^1$H NMR ($CDCl_3$) δ 1.4–2.5 (m, 6, C-3′, C-4′, C-5′ $H_2$), 2.22, 2.25 (s, 6, $CH_3$), 3.55–4.42 (m, 2, C-6′ $H_2$), 5.72–6.17 (m, 1, C-1′ C-2′ H), 7.57, 7.70 (2 s, 1, CH, OAc), 7.97 (s, 1, H-2); IR ($CHCl_3$) 2198 $cm^{-1}$ (CN).

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**Registry No.** 1, 81246-34-6; 3, 81246-35-7; 4, 81246-36-8; 6, 81246-37-9; 7, 81246-38-0; 8, 81246-39-1; 9, 81246-40-4; 4(5)-(hydroxymethyl)imidazole hydrochloride, 29452-13-9.

# A Mild and Efficient Route to Schiff Base Derivatives of Amino Acids

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Our interest in the preparation of imines (Schiff bases or azomethines) is based on the use of benzophenone Schiff base derivatives of glycine alkyl esters or aminoacetonitrile as an α anion of glycine equivalent for the synthesis of higher amino acids by phase-transfer alkylations.[1] In the

$$Ph_2C{=}NCH_2CO_2R \qquad Ph_2C{=}NCH_2CN$$

past, a major limitation in this preparation of amino acids has been the tedious synthesis of the starting Schiff bases.

A commonly used method for the preparation of imines is the condensation of an aldehyde or ketone with a primary amine.[2,3] Aldimines are readily prepared by simply mixing equimolar amounts of an aldehyde and the amine with provision for the removal of water. On the other hand, when the carbonyl component is a ketone, forcing conditions (high reaction temperatures, nonstoichiometric amounts of reagents, added protic or Lewis acids, and/or long reaction times) are generally required for the preparation of ketimines. More recent studies have shown that it is often possible to prepare ketimines by a room-temperature condensation in the presence of combined catalysts–drying reagents such as $TiCl_4$,[4] molecular sieves,[5] or a catalyst prepared from molecular sieves, silica gel, and alumina.[6] Such procedures have not proven successful in our case because the amine component, e.g., glycine ethyl ester, readily self-condenses to form 2,5-dioxopiperazine (glycine anhydride) when extended reaction times are required.[7] In addition, the use of excess amine or carbonyl component is not desirable, especially if the method is to be extended to the preparation of Schiff base derivatives of higher amino acids.[8]

## Results and Discussion

We now report a mild, simple, and high-yield preparation of the benzophenone Schiff base derivatives of amino acid esters (**3**). The procedure is based on transimina-

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(8) We have previously prepared the benzophenone Schiff base derivatives of glycine ethyl ester[1a] and aminoacetonitrile[1b] in 82% and 70% isolated yields, respectively, by condensation of the free amine with benzophenone in refluxing xylene or toluene with added $BF_3$·$Et_2O$. The products were purified by high-temperature vacuum distillation (to separate tars and unreacted benzophenone) followed by recrystallization.

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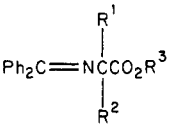
Table I. Synthesis of Schiff Bases 3

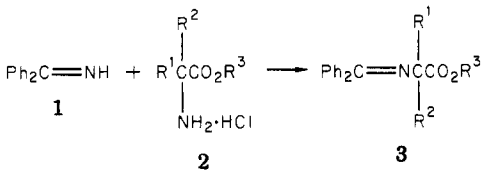


3

| compd | $R^1$ | $R^2$ | $R^3$ | % yield[a] |
|---|---|---|---|---|
| 3a | H | H | $CH_3$ | 91 |
| 3b | H | H | $CH_2CH_3$ | 97 |
| 3c | H | H | $CH_2Ph$ | 76[b] |
| 3d | H | H | $CHPh_2$ | 87[b] |
| 3e | H | H | $C(CH_3)_3$ | 91 |
| 3f | H | H | $CO_2R^3$ = CN | 93 |
| DL-3g | H | $CH_3$ | $CH_2CH_3$ | 92 |
| DL-3h | H | $CH_2Ph$ | $CH_2CH_3$ | 90 |
| L-3h | H | $CH_2Ph$ | $CH_2CH_3$ | 93 |
| DL-3i | H | Ph | $CH_2CH_3$ | 90 |
| L-3j | H | $CH_2$-(4-hydroxyphenyl) | $CH_2CH_3$ | 93 |
| DL-3k | H | $CH_2$-(3,4-dihydroxyphenyl) | $CH_3$ | 84 |
| L-3l | H | $CH_2$-(3-indolyl) | $CH_3$ | 91 |
| L-3m | H | $CH_2$-[4(5)-imidazolyl] | $CH_3$ | 89[c] |
| 3n | $CH_3$ | $CH_3$ | $CH_3$ | 60[c,d] |
| 3o | H | H | $CO_2R^3 = CONHCH_2CO_2CH_3$ | 91 |
| 3p | H | H | $CO_2R^3 = CH_2CH_2CO_2CH_3$ | 94 |

[a] Isolated yields. [b] Prepared from the tosylate. [c] See the Experimental Section for details. [d] Purified by chromatography; see the Experimental Section.

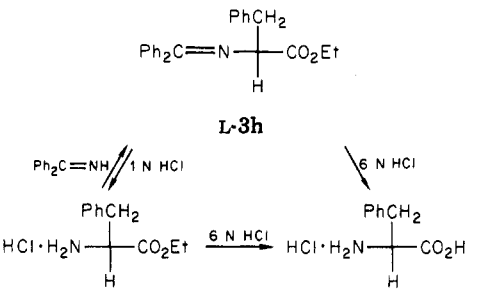
tion[9,10] of the reactive benzophenone equivalent, benzophenone imine (1),[11] with the amino ester salt (2), which is often available commercially or can be readily prepared from the corresponding amino acid. In most cases the



1 2 3

reaction is accomplished by simply stirring equimolar amounts of the two reagents in methylene chloride overnight at room temperature. Filtration and an aqueous workup followed by recrystallization leads to excellent yields of the Schiff bases (3; see Table I). With use of this general procedure, the benzophenone Schiff bases of a variety of glycine alkyl esters (**3a–3e**) and that from aminoacetonitrile (**3f**) are easily prepared. In addition, we have also synthesized the imines from a number of higher monoalkyl amino acids (**3g–3m**) as well as the Schiff base derived from the $\alpha,\alpha$-disubstituted amino acid $\alpha$-aminoisobutyric acid (**3n**). In the latter case the reaction was conducted in refluxing 1,2-dichloroethane and the crude product was purified by chromatography on deactivated alumina. Finally the Schiff base derivatives of a simple dipeptide, glycylglycine, as well as 4-aminobutyric acid (GABA; **3o** and **3p**, respectively) have also been prepared. This last example as well as the Schiff bases derived from tyrosine (**3j**), DOPA (**3k**), tryptophan (**3l**), and histidine (**3m**) are of special interest because of the biological significance of the associated amino acids.

Scheme I



L-3h

L-4a, $[\alpha]^{25}_D$ +35.6 ± 0.5° L-5a, $[\alpha]^{25}_D$, −6.3 ± 0.4°
L-4b, $[\alpha]^{25}_D$ +35.4 ± 0.2° L-5b, $[\alpha]^{25}_D$, −6.6 ± 0.3°

Hydrolysis of the Schiff base derivatives 3 is readily accomplished to yield either the amino ester hydrochloride (2) or the free amino acid. Thus, a mild two-phase hydrolysis with 1 N HCl/ether gives 2 (which can be saponified to yield the amino acid), while refluxing the Schiff base 3 in 6 N HCl gives the amino acid directly (see Experimental Section for a typical example).

Preparation of the Schiff base from a chiral amino acid should give a chiral Schiff base provided basic conditions, which are known to promote racemization of imine derivatives,[12] are avoided. Indeed this proved to be the case as shown in Scheme I. Esterification of L-phenylalanine yields L-phenylalanine ethyl ester hydrochloride (L-**4a**) which has the same specific rotation within experimental error as the product L-**4b** obtained by preparation of the optically active Schiff base L-**3h** followed by mild acid hydrolysis back to the amino ester hydrochloride. Similarly, hydrolysis of the Schiff base L-**3h** directly to the amino acid yields product L-**5b** with the same rotation as the amino acid (L-**5a**) obtained from direct hydrolysis of the starting ester (L-**4a**). Both of these results indicate that the transimination reaction occurs with retention of configuration at the $\alpha$-carbon.

(9) (a) For transimination of *N*-acyl derivatives of benzophenone imine with primary amines, see: Drach, B. S.; Dolgushina, I. Y.; Sinitsa, A. D.; Kirsanov, A. V. *Zh. Obshch. Khim.* **1972**, *42*, 785–91. (b) For transimination to prepare imidates, see: Tarzia, G.; Schiatti, P.; Selva, D.; Favara, D.; Ceriani, S. *Eur. J. Med. Chem.* **1976**, *11*, 263–70 and references cited therein.

(10) For a mechanistic study of a transimination reaction, see: Hogg, J. L.; Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 4772–8.

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## Experimental Section

Melting points are uncorrected. Proton NMR spectra were determined on a Varian EM-390 spectrometer using $CDCl_3$ as solvent and $Me_4Si$ as internal standard. The $^{13}C$ spectra were obtained on a Varian CFT-20 spectrometer. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Ultraviolet spectra were obtained on a Cary 118 spectrophotometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Midwest Microlab, Ltd. of Indianapolis, IN.

Benzophenone imine was prepared by the method of Pickert and Tolbert.[11] The amino ester salts were purchased (Aldrich Chemical Co. or United States Biochemical Corp.) or synthesized from the corresponding amino acid.[13] No special precautions were taken to dry solvents or exclude oxygen from the reactions unless specifically noted.

**General Procedure.** In a typical experiment 1.00 g (5.52 mmol) of benzophenone imine, an equimolar amount of finely ground amino acid ester hydrochloride (**2**) and 20 mL of methylene chloride were stirred at room temperature for 24 h with the exclusion of moisture ($CaCl_2$ tube). The reaction mixture was filtered to remove $NH_4Cl$ and evaporated to dryness on a rotary evaporator. The residue was taken up in 20 mL of ether, filtered, washed with 20 mL of water, and dried ($MgSO_4$). Filtration and solvent removal were followed by recrystallization (ether/hexane) in most cases and chromatography for **3n**. The reaction was also conducted on a larger scale (25 g, 0.138 mol of **1**) to make **3b**, using the above procedure, with no reduction in yield. The following compounds were prepared as described above unless otherwise noted.

**Methyl *N*-(diphenylmethylene)glycinate (3a)**: 91%; mp 42.5–43 °C; NMR $\delta$ 3.7 (3 H, s), 4.1 (2 H, s), 7.1–7.8 (10 H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 51.6, 55.5, 127.6, 128.0, 128.7, 130.4, 136.0, 139.3, 170.6, 171.4; $^{13}C$ NMR ($Me_2SO$-$d_6$) $\delta$ 51.6, 55.2, 127.4, 128.2, 128.3, 128.8, 128.9, 130.5, 135.5, 139.0, 170.4, 170.5; IR (KBr) 1745, 1615 $cm^{-1}$. Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.98; H, 5.71; N, 5.76.

**Ethyl *N*-(diphenylmethylene)glycinate (3b)**:[1a] 97%; mp 51–52 °C; NMR $\delta$ 1.2 (3 H, t), 4.0 (2 H, q), 4.0 (2 H, s), 6.9–7.5 (10 H, m); IR (KBr) 1745, 1615 $cm^{-1}$; UV (hexane) 247 nm ($\epsilon$ 14 400). Anal. Calcd for $C_{17}H_{17}NO_2$: C 76.38; H, 6.41; N, 5.24. Found: C, 76.46; H, 6.29; N, 5.16.

**Benzyl *N*-(diphenylmethylene)glycinate (3c)**: prepared from the tosylate salt;[13b] 76%; mp 86.5–87 °C; NMR $\delta$ 4.1 (2 H, s), 5.1 (2 H, s), 7.0–7.7 (15 H, m); IR (KBr) 1745, 1620 $cm^{-1}$. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.17; H, 5.79; N, 4.48.

**Benzhydryl *N*-(diphenylmethylene)glycinate (3d)**: prepared from the tosylate salt;[13c] 87%; mp 92–94 °C; NMR $\delta$ 4.2 (2 H, s), 6.9 (1 H, s), 7.0–7.8 (20 H, m); IR (KBr) 1740, 1625 $cm^{-1}$. Anal. Calcd for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 82.75; H, 5.51; N, 3.44.

***tert*-Butyl *N*-(diphenylmethylene)glycinate (3e)**: 91%; mp 111–112 °C; NMR $\delta$ 1.5 (9 H, s), 4.2 (2 H, s), 7.1–7.9 (10 H, m); IR (KBr) 1730, 1620 $cm^{-1}$. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.18; H, 7.08; N, 4.82.

**[(Diphenylmethylene)amino]acetonitrile (3f)**:[1b] 93%; mp 81–82 °C; NMR $\delta$ 4.2 (2 H, s), 7.1–7.8 (10 H, m); IR (KBr) 2250 (weak), 1615 $cm^{-1}$. Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49. Found: C, 81.56; H, 5.46.

**Ethyl *N*-(diphenylmethylene)-DL-alaninate (DL-3g)**:[1a] 92%; oil; NMR $\delta$ 1.2 (3 H, t), 1.4 (3 H, d), 4.1 (3 H, m), 7.1–7.8 (10 H, m); IR (KBr) 1730, 1630 $cm^{-1}$. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.57; H, 6.84; N, 4.73.

**Ethyl *N*-(diphenylmethylene)-DL-phenylalaninate (DL-3h)**:[1a] 90%; mp 68.5–69 °C; NMR $\delta$ 1.2 (3 H, t), 3.1–3.3 (2 H, m), 4.2 (2 H, q), 4.2 (1 H, m), 6.5–7.6 (15 H, m); IR (KBr) 1725, 1615 $cm^{-1}$. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.48; N, 3.92. Found: C, 80.57; H, 6.43; N, 3.90.

**Ethyl *N*-(diphenylmethylene)-L-phenylalaninate (L-3h)**: 93%; oil; $[\alpha]^{25}_D$ −246.1° (*c* 2, $CHCl_3$); NMR $\delta$ 1.2 (3 H, t), 3.1–3.3 (2 H, m), 4.2 (2 H, q), 4.2 (1 H, m), 6.5–7.6 (15 H, m); IR (KBr) 1730, 1615 $cm^{-1}$. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.48; N, 3.92. Found: C, 80.65; H, 6.46; N, 3.72.

**Ethyl α-[(diphenylmethylene)amino]-(±)-benzeneacetate (DL-3i)**: 90%; mp 65–65.5 °C; NMR $\delta$ 1.2 (3 H, t), 4.1 (2 H, q), 5.1 (1 H, s), 7.0–7.8 (15 H, m); IR (KBr) 1745, 1615 $cm^{-1}$. Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.62; H, 6.16; N, 4.35.

**Ethyl *N*-(diphenylmethylene)-L-tyrosinate (L-3j)**: 93%; mp 101–102 °C; $[\alpha]^{25}_D$ −233.8° (*c* 2, $CHCl_3$); NMR $\delta$ 1.2 (3 H, *t*), 3.0–3.2 (2 H, m), 4.0–4.3 (3 H, m), 5.7 (1 H, br s), 6.5–7.7 (14 H, m); IR (KBr) 3410, 1740, 1620 $cm^{-1}$; UV (MeOH) 248 nm ($\epsilon$ 14 200), 280 (4000, sh). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 76.96; H, 6.13; N, 3.60.

**Methyl *N*-(diphenylmethylene)-DL-3-hydroxytyrosinate (DL-3k)**: 84%; mp 137–138 °C; NMR $\delta$ 3.0–3.2 (2 H, m), 3.7 (3 H, s), 4.2–4.4 (1 H, m), 5.5–6.0 (2 H, br s), 6.3–7.6 (13 H, m); IR (KBr) 3460, 1730, 1610 $cm^{-1}$; UV (MeOH) 246 nm ($\epsilon$ 14 100), 280 (5000, sh). Anal. Calcd for $C_{23}H_{21}NO_4$: C 73.59; H, 5.64; N, 3.73. Found: C, 73.50; H, 5.88; N, 3.70.

**Methyl *N*-(diphenylmethylene)-L-tryptophanate (L-3l)**: 91%; mp 114–115 °C; $[\alpha]^{25}_D$ −297.9° (*c* 2, $CHCl_3$); NMR $\delta$ 3.0–3.5 (2 H, m), 3.6 (3 H, s), 4.3–4.5 (1 H, m), 6.5–7.6 (15 H, m), 8.0 (1 H, br s); IR (KBr) 3290, 1735, 1600 $cm^{-1}$; UV (MeOH) 246 nm ($\epsilon$ 15 100), 280 (7200, sh), 290 (6000, sh). Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H 5.80; N, 7.32. Found: C, 78.75; H, 5.55; N, 7.53.

**Methyl *N*-(Diphenylmethylene)-L-histidinate (L-3m).** Benzophenonimine (1.00 g, 5.52 mmol), finely ground L-histidine methyl ester dihydrochloride (1.34 g, 5.53 mmol), freshly distilled triethylamine (0.558 g, 5.51 mmol), and 20 mL of methylene chloride were reacted as described previously. Recrystallization was accomplished with ether/methylene chloride followed by addition of hexane: 89%; mp 143–146 °C; $[\alpha]^{25}_D$ −145.7° (*c* 2, $CHCl_3$); NMR $\delta$ 3.1 (2 H, d), 3.6 (3 H, s), 4.3 (1 H, t), 6.7 (1 H, s), 6.8–7.7 (12 H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 31.0, 52.0, 65.9, 119.5, 127.6, 128.1, 128.4, 128.6, 128.8, 130.4, 132.3, 134.6, 136.0, 139.5, 171.3, 172.3; IR (KBr) 3090, 1730, 1625 $cm^{-1}$; UV (MeOH) 248 nm ($\epsilon$ 13 900). Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.04; H, 5.93; N, 12.64.

**Methyl *N*-(Diphenylmethylene)-2-methylalaninate (3n).** Benzophenone imine (1.00 g, 5.52 mmol), finely ground 2-methylalanine methyl ester hydrochloride (5.09 g, 33.14 mmol), freshly distilled triethylamine (2.79 g, 27.57 mmol), and 25 mL of 1.2-dichloroethane were refluxed with stirring under argon, for 72 h. Workup as described previously yielded 1.93 g (theoretical yield 1.55 g) of a brown oil. A 0.40-g sample of the crude oil was chromatographed on a 2 × 20 cm column of Grade V basic alumina (3% ethyl acetate in hexane) to yield 0.21 g (65%) of **3n**. An analytical sample was prepared by recrystallization from ether/hexane: 60%; mp 41–41.5 °C; NMR $\delta$ 1.5 (6 H, s), 3.2 (3 H, s), 7.0–7.6 (10 H, m); IR (KBr) 1735, 1630 $cm^{-1}$. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.06; H, 6.99; N, 5.11.

**Methyl *N*-[*N*-(diphenylmethylene)glycyl]glycinate (3o)**: 91%; 95–96 °C; NMR $\delta$ 3.7 (3 H, s), 4.0 (2 H, s), 4.1 (2 H, d), 7.0–7.7 (10 H, m), 8.0 (1 H, br m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 40.9, 52.2, 56.4, 127.3, 128.2, 128.5, 128.9, 129.0, 130.7, 136.1, 138.8, 170.3, 170.4, 170.9; IR (KBr) 3360, 1745, 1665, 1630 $cm^{-1}$; UV (MeOH) 248 nm ($\epsilon$ 14 000). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.60; H, 5.93; N, 9.27.

**Methyl 4-[(diphenylmethylene)amino]butanoate (3p)**: 94%; oil; NMR $\delta$ 1.9 (2 H, quintet), 2.3 (2 H, t), 3.3 (2 H, t), 3.5 (3 H, s), 7.0–7.6 (10 H, m); IR (KBr) 1730, 1615 $cm^{-1}$; UV (MeOH) 246 nm ($\epsilon$ 14 000). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.09; H, 6.93; N, 5.10.

**Hydrolyses.** A stirred solution of 1.79 g (5.00 mmol) of Schiff base DL-**3h** in 10 mL of ether was chilled in an ice bath. Six milliliters of 1 N HCl (6 mmol, 1.2 equiv) was added dropwise over 30 min, the ice bath was allowed to melt, and the two-phase mixture was stirred overnight at room temperature. The layers were separated, and water was removed in vacuo from the aqueous layer to yield 1.15 g (100%) of the amino ester hydrochloride

(13) (a) Methyl and ethyl ester hydrochlorides: Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109–15. (b) Glycine benzyl ester tosylate: Miller, H. K.; Waelsch, H. *J. Am. Chem. Soc.* **1952**, *74*, 1092–3. (c) Glycine benzhydryl ester tosylate: Aboderin, A. A.; Delpierre, G. R.; Fruton, J. S. *ibid.* **1965**, *87*, 5469–72. (d) Glycine *tert*-butyl ester hydrochloride: Moore, A. T.; Rydon, H. N. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, pp 586–9.

DL-**2h**, mp 122–124 °C (lit.[14] mp 127 °C).

The ester DL-**2h** can be saponified to DL-phenylalanine as follows. Sodium hydroxide (6 N, 4.5 mL, 27 mmol, 3 equiv) was added to 2.00 g (8.71 mmol) of DL-**2h** and the mixture was stirred at room temperature for 2 h. The pH of the solution was adjusted to the isoelectric point with 1 N HCl to obtain 1.17 g (81%) of crystalline DL-phenylalanine, mp 268–271 °C dec (lit.[15] mp 271–273 °C dec).

The Schiff base DL-**3h** can be converted directly to the amino acid by refluxing a mixture of DL-**3h** (4.00 g, 11.2 mmol) in 20 mL of 6 N HCl under argon for 6 h. The solution was cooled and washed several times with ether, and the layers were separated. Water and excess HCl were removed from the aqueous layer, distilled water was added, and the aqueous solution was taken to the isoelectric point with aqueous NaOH to yield 1.69 g (91%) of DL-phenylalanine, mp 250–251 °C dec (commercial sample, U.S. Biochemical Corp., mp 258–259 °C dec; mmp 248–249 °C dec).

All three hydrolysis products described above showed one spot on TLC which was identical with an authentic sample.

**Optical Rotation Studies.** The starting L-phenylalanine ethyl ester hydrochloride (L-**4a**) used in this study was prepared from L-phenylalanine (Aldrich) by the method of Brenner and Huber.[13a] Two grams of L-**4a** was hydrolyzed to the amino acid L-**5a** as described above. Five grams of the amino ester hydrochloride L-**4a** was converted to the Schiff base L-**3h** by the general transimination procedure. Part (2.0 g) of this Schiff base (L-**3h**) was hydrolyzed back to L-phenylalanine ethyl ester hydrochloride (L-**4b**) and another portion (2.0 g) of L-**3h** was hydrolyzed directly to L-phenylalanine (L-**5b**) according to the procedures described previously. All four products were recrystallized (ethanol/ether for the esters L-**4a** and L-**4b** and water/ethanol for the amino acids L-**5a** and L-**5b**) and dried in a vacuum oven [60 °C (1 mmHg)]. Three solutions (~2g/100 mL) of each product were prepared, and the optical rotation of each solution was measured 3 times at a constant temperature of 25 °C. The resulting optical rotations and literature references are listed below. The various reactions as well as the average rotations are presented in Scheme I.

L-**4a**: $[\alpha]^{25}_D$ +35.90°, +35.05°, +35.88°; average $[\alpha]^{25}_D$ +35.6 ± 0.5° (*c* 2, EtOH); lit.[16] $[\alpha]^{20}_D$ +33.5° (EtOH).

L-**4b**: $[\alpha]^{25}_D$ +35.57°, +35.13°, 35.55°; average $[\alpha]^{25}_D$ +35.4 ± 0.2° (*c* 2, EtOH).

L-**5a**: $[\alpha]^{25}_D$ −6.70°, −5.95°, 6.14°; average $[\alpha]^{25}_D$ −6.3 ± 0.4° (*c* 2, 1 N HCl); lit.[17] $[\alpha]^{25}_D$ −4.47° (*c* 1–2, 5 N HCl); lit.[18] $[\alpha]_D$ −7.4° (5 N HCl).

L-**5b**: $[\alpha]^{25}_D$ −6.38°, −6.44°, −6.88°; average $[\alpha]^{25}_D$ −6.6 ± 0.3° (*c* 2, 1 N HCl).

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**Registry No.** **1**, 1013-88-3; **2a**·HCl, 5680-79-5; **2b**·HCl, 623-33-6; **2c** tosylate, 81477-92-1; **2d** tosylate, 5042-82-0; **2e**·HCl, 27532-96-3; **2f**·HCl, 6011-14-9; DL-**2g**·HCl, 617-27-6; DL-**2h**·HCl, 3182-93-2; L-**2h**·HCl, 3182-93-2; DL-**2i**·HCl, 72651-17-3; DL-**2j**·HCl, 4089-07-0; DL-**2k**·HCl, 40611-00-5; L-**2l**·HCl, 26988-71-6; L-**2m**·HCl, 22888-60-4; **2n**·HCl, 15028-41-8; **2o**·HCl, 2776-60-5; **2p**·HCl, 13031-60-2; **3a**, 81167-39-7; **3b**, 69555-14-2; **3c**, 81477-91-0; **3d**, 81477-93-2; **3e**, 81477-94-3; **3f**, 70591-20-7; DL-**3g**, 69555-16-4; DL-**3h**, 69555-18-6; L-**3h**, 81477-95-4; DL-**3i**, 81477-96-5; L-**3j**, 81477-97-6; DL-**3k**, 81477-98-7; L-**3l**, 81167-36-4; L-**3m**, 81477-99-8; **3n**, 81478-00-4; **3o**, 81478-01-5; **3p**, 81478-02-6; L-**4a**, 3182-93-2; L-**5a**, 17585-69-2.

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## Anomalous Hydrogen–Deuterium Exchange of Cyclic β-Keto Sulfides[1]

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The effect of divalent sulfur in enhancing the acidity of protons attached to an adjacent carbon atom has been known for over 40 years.[2] The size of this influence is typically more than 3 orders of magnitude.[3] The work reported here was stimulated by the observation of an apparent anomaly: the protons at C4 display a higher kinetic acidity than those at C2 in 3-thiolanone (**4**) when hydrogen–deuterium exchange is catalyzed by pyridine. The purpose of this study was to measure and compare the rates of hydrogen–deuterium exchange of **4** and a series of related ketones. An objective was to determine whether the kinetic acidity at C4 is enhanced or that at C2 is suppressed in **4**. The former was found to be true.

### Experimental Section

**General Methods.** Melting points are uncorrected. A Varian Model A-60 NMR spectrometer equipped with a Model V-6040 variable-temperature controller was used to obtain analytical 60-MHz $^1$H NMR spectra of various compounds and to follow the kinetics of deuteration reactions. Chemical shifts are reported with respect to $Me_4Si$ as internal reference. Constant temperature baths were used to control the temperature of samples involved in the longer studies to within ±0.1 °C. Both temperature control systems were adjusted by use of thermometers calibrated against a thermometer that had been tested at the National Bureau of Standards.

**Substrates.** Commerical 3-pentanone (**1**) and cyclopentanone (**2**) were purified by distillation, bp 101–103 °C (lit.[4] bp 102 °C) and bp 130–131 °C (lit.[5] bp 129 °C), respectively.

1-(Methylthio)-2-propanone (**3**) contained substantial byproducts as evidenced by $^1$H NMR analysis when prepared by the method of Cain and Cunneen.[6] The following synthesis eliminated that problem. Metallic sodium (34.5 g, 1.50 mol) was dissolved in 700 mL of anhydrous EtOH under nitrogen. Methanethiol (72 g, 1.5 mol) was added slowly and the mixture was allowed to stand for 1 h. This solution was added dropwise with stirring to bromoacetone[7] (206 g, 1.5 mol) in 200 mL of anhydrous EtOH at a rate sufficient to keep the reaction mixture boiling gently under reflux. The mixture was heated to maintain boiling an additional 20 min and was then poured into 200 mL

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