rachloride, 5 g of tin metal, and 50 mL of methanol was stirred for 1 h to give a blue solution. This solution was evacuated at 25 °C (0.1 mm) for 1 min to remove excess hydrogen chloride.

Titanium(III) Solution B: Titanium tetrachloride (4 mL) was added to 20 mL of benzene followed by 10 mL of methanol. After 10 min 50 mL of tetrahydrofuran and excess zinc metal were added and the mixture stirred for 4 h at room temperature to give a maroon solution.

Aliquots of each of these titanium(III) solutions gave brilliant blue-purple solutions with deoxygenated water indicating the presence of titanium(III). The deep purple potassium benzophenone ketyl solution used for the regeneration study in Table IV was obtained by stirring a solution of 1.0 g of benzophenone in 50 mL of tetrahydrofuran with excess potassium metal for 24 h.

Stoichiometric reduction of all Ti(IV) was assumed since an excess of reducing agent was present in the reduction solution preparation.

Summary

Cobalt(II) tetraarylporphyrins supported through carboxamide and sulfonamide linkages on aminated macroreticular polystyrene beads cross-linked with divinylbenzene provide an active and inexpensive catalyst for the valence isomerization of quadricyclane (II) to norbornadiene (I). The presence of unreacted pendant amino groups causes some difficulties in the analysis of the system both because of lack of a direct method for determining the porphyrin nitrogen and by providing a possible coordination site for nonporphyrin cobalt. In a practical system these difficulties appear acceptable in view of the simplicity of preparation of the catalyst.

These polystyrene-bound cobalt(II) tetraarylporphyrin catalysts exhibit fair stability in use. Catalyst deactivation appears to be caused by reaction with some extraneous component in the quadricyclane. We have not identified the component. Activity of the catalyst may be partially restored by treatment with mild reducing agents, e.g., Ti(III). Coupled with the visible spectral observation that the Co(III)/Co(II) ratio of the catalyst increases upon deactivation, this reactivation by reducing agents implies that the operative deactivation–reaction involves interconversion between Co(II) and Co(III). In a closed system, this mode of deactivation would presumably be limited to the first cycle.

Acknowledgments. The authors are indebted to the Division of Energy Storage Systems of the U.S. Department of Energy for partial support of this work under contract EY-76-S-09-0893. We thank Dow Chemical Co. for samples of the macroreticular polystyrenes used in this work. We acknowledge frequent helpful discussions with Professors C. R. Kutal and R. R. Hautala of the University of Georgia.

Registry No.—$TPPH_2$, 917-23-7; $H_2TPP(CO_2H)_4$, 14609-54-2; $(NH_4)_4H_2TPP(SO_3)_4$, 68438-24-4; $(Et_3NH)_4H_2TPP(SO_3)_4$, 68438-25-5; $Na_4H_2TPP(SO_3)_4$, 39050-26-5; quadricyclane, 278-06-8; norbornadiene, 121-46-0; polystyrene, 9003-53-6; Co(II), 22541-53-3; Ti(II), 22541-75-9.

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New Versatile Syntheses of 2-Substituted-2-amino Acid and 2,3-Dehydro-2-amino Acid Derivatives[1]

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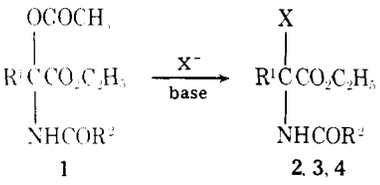
Received July 18, 1978

2-Substituted-2-amino acid derivatives were synthesized in high yields by reaction of 2-acetoxy-2-amino acid derivatives, which are synthetic potential intermediates, with various nucleophiles under basic conditions. Furthermore, the reaction of the 2-acetoxyamino acid derivatives with a nonnucleophilic base led to the synthesis of 2,3-dehydro-2-amino acid derivatives in excellent yields. In addition, the reaction in the presence of Lewis acid was carried out to afford the 2-substituted amino acid derivatives.

The synthesis of biologically active amino acids and their related compounds is one of the most attractive subjects in amino acid chemistry. In particular, syntheses of 2- or 3-substituted-2-amino acids and 2,3-dehydroamino acids have received increasing attention for preparation of pharmaceuticals such as antimicrobial agents. To synthesize such amino acids, we have selected two reactive species derived from the parent 2-amino acids which can be called an "anionic amino acid synthon" and a "cationic amino acid synthon". We have already reported useful syntheses[2] using isonitriles as anionic synthons of physiologically important amino acids such as 2-alkylamino acids,[3] 2-*C*-acylamino acids,[4] and 3-hydroxyamino acids.[5] In the present work, a synthetic method using the cationic synthon will be described.

0022-3263/79/1944-0391$01.00/0

Scheme I



1 2, 3, 4

R^1 = H, Me, $PhCH_2$; R^2 = Me, OCH_2Ph; X = SR^3, OR^3, $N(R^3)(R^4)$

With regard to the cationic synthon, 2-functionalized amino acids are currently of great interest as synthetic intermediates for the preparation of 2-substituted amino acids and 2,3-dehydroamino acids. Ben-Ishai et al.[6] developed 2-hydroxy- or 2-methoxyglycinate, which acts effectively as a reagent for introducing the glycine skeleton under strongly acidic conditions. Olsen et al.[7] reported the synthetic potentiality of 2-haloamino acids prepared in situ. Stammer et al.[8] described a synthesis of 2-substituted amino acid and 2,3-dehydroamino acid derivatives using tetrachlorodioxinone as a synthon. These studies suggest that the synthetic potential value depends on various structural features of the 2-functionalized amino acids. We[9] and Olsen et al.[10] have suggested that 2-acetoxyamino acids might be useful for introduction of other functional groups. To explore this we developed a synthesis of 2-acetoxyamino acid derivatives by anodic oxidation of *N*-acylaminomalonic acid monoester derivatives,[9] and now we report the reactivities of 2-acetoxyamino acid derivatives toward a variety of nucleophiles under basic and acidic conditions, and toward a nonnucleophilic base.

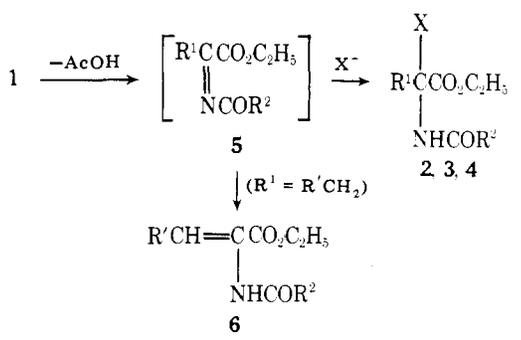
Results and Discussion

N-Acetyl- and *N*-carbobenzoxy-2-acetoxyamino acid esters (**1**) were prepared by anodic oxidation of the corresponding *N*-acylaminomalonic acid monoesters in acetic acid containing sodium acetate according to our preceding report.[9]

Reaction of **1** with various nucleophiles was carried out under basic conditions, as shown in Scheme I. For example, reaction of *N*-acetyl-2-acetoxyglycine ethyl ester with benzenethiol in the presence of 1 equiv of triethylamine in tetrahydrofuran at room temperature afforded *N*-acetyl-2-phenylthioglycine ethyl ester (**2a**) in an almost quantitative yield. In the same way, *N*-acyl-2-acetoxyalaninate and -phenylalaninate were treated with thiol compounds to afford the corresponding *N*-acyl-2-aryl- and -alkylthioamino acid derivatives (**2**) in excellent yields. Likewise, *N*-acyl-2-alkoxy- and -2-phenoxyamino acid derivatives (**3**) were synthesized by the reaction of **1** with alcohols and phenols in the presence of triethylamine, respectively. Interestingly, the substitution reaction with alcohols such as methanol and ethanol proceeded even in the absence of triethylamine at room temperature; the process seems to be a solvolytic displacement. Furthermore, reaction of **1** with 2 equiv of primary and secondary amines such as *tert*-butylamine, morpholine, and 4-toluidine in tetrahydrofuran at room temperature gave *N*-acyl-2-amino substituted amino acid derivatives (**4**) in excellent yields. The characterization of these products is described in the Experimental Section. The yields and physical constants of the products are listed in Tables I–III.

In the above reactions, direct substitution accompanying competitive elimination leading to 2,3-dehydroamino acids should normally be considered. In these reactions, however, only the substitution products were obtained. As suggested by Poisel et al.[11] and Stammer et al.,[8] these results also indicated that elimination of acetic acid from 2-acetoxyamino acids (**1**) would take place in the initial step to form *N*-acylimines (**5**) as transient intermediates; in the presence of nucleophiles, nucleophilic addition reaction to the azomethine

Scheme II



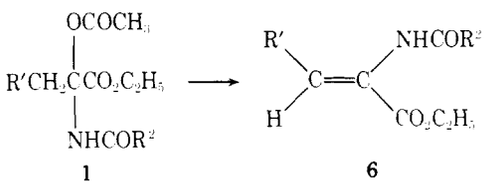
carbon of **5** to yield the 2-substituted amino acid should occur prior to the isomerization to 2,3-dehydroamino acids (Scheme II).

Based on the above mechanism, involving *N*-acylimine (**5**) as a key intermediate, a synthesis of 2,3-dehydroamino acid derivatives (**6**) was carried out using the reactive 2-acetoxyamino acids (**1**, $R^1 \neq H$) and a nonnucleophilic base as shown in Scheme III. For example, treatment of *N*-acyl-2-acetoxyalanine (**1**; R^1 = Me, R^2 = Me, OCH_2Ph) and -2-acetoxyphenylalanine (**1**; R^1 = $PhCH_2$, R^2 = Me, OCH_2Ph) derivatives with 1 equiv of triethylamine in tetrahydrofuran at room temperature for 20 h afforded the *N*-acyl-2,3-dehydroalanine and -dehydrophenylalanine derivatives (**6**), respectively, in high yields. In the case of *N*-acyl-2-acetoxybutyrine derivatives (**1**; R^1 = Et, R^2 = Me, OCH_2Ph), surprisingly, the reaction did not proceed smoothly under the same conditions. The use of DBU (diazabicyclo[5.4.0]undecene) in place of triethylamine, however, afforded exclusively the desired dehydrobutyrine derivatives in high yields (Table IV).

The stereochemistry of the resulting dehydroamino acid derivatives (**6**) was investigated on the basis of NMR spectra. The NMR spectrum of **6e**, for example, showed a doublet at δ 1.76 for the 3-methyl group and a quartet at δ 6.74 for olefinic protons. These chemical shifts were in accordance with those of the *Z* form reported.[11,12] All of the *N*-acyl-2,3-dehydroamino acid derivatives[12-14] formed under the basic conditions employed here were found to be thermodynamically stable *Z* isomers and not *E* isomers.

In addition to the basic conditions studied above, substi-

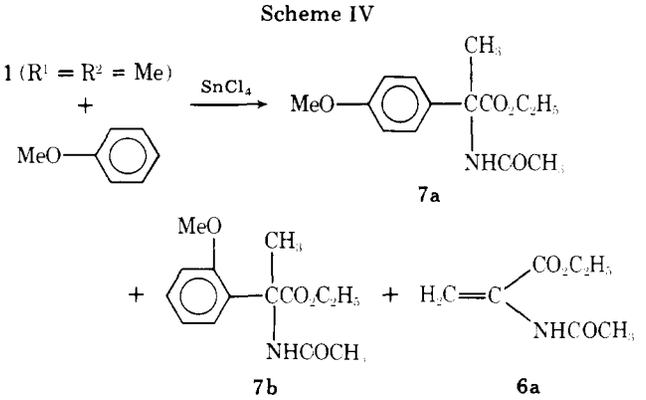
Scheme III



1 6

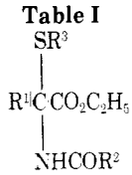
R' = H, Me, Ph; R^2 = Me, OCH_2Ph

Scheme IV



7a 7b 6a

Table I

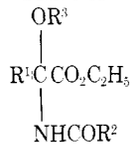


2

	R^1	R^2	R^3	mp, °C	yield, %	solvent[a]
a	H	Me	Ph	59–60	95	i-Pr_2O
b	Me	Me	Ph	122–123	96	i-Pr_2O
c	Me	Me	CH_2Ph	70–71	96	i-Pr_2O
d	$PhCH_2$	Me	CH_2Ph	91–92	98	i-Pr_2O–hexane
e	H	OCH_2Ph	CH_2Ph	53–54	96	hexane
f	H	Me	i-amyl	syrup	68	*b*

[a] Recrystallization solvent. [b] Purified by column chromatography on silica using $CHCl_3$; thin-layer chromatographically pure.

Table II

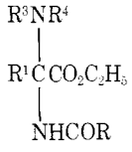


3

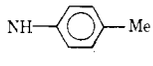
	R^1	R^2	R^3	mp, °C	yield, %	solvent[a]
a	H	Me	Me	syrup	98	*b*
b	Me	Me	Me	97–98	98	i-Pr_2O
c	Me	Me	Et	64–65	96	i-Pr_2O
d	H	Me	Ph	syrup	90	*b*
e	H	Me	p-NO_2Ph	103–105	82	AcOEt–i-Pr_2O

[a] Recrystallization solvent. [b] Purified by column chromatography on silica using $CHCl_3$; thin-layer chromatographically pure.

Table III



4

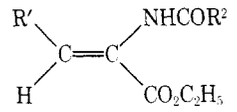
	R^1	R^2	NR^3R^4	mp, °C	yield, %	solvent[a]
a	H	Me	NH-t-Bu	58–59	98	hexane
b	H	OCH_2Ph	NH-t-Bu	66–67	96	hexane
c	H	Me		75–76	94	i-Pr_2O–hexane
d	Me	Me		97–98	94	i-Pr_2O
e	$PhCH_2$	Me		125–126	98	i-Pr_2O
f	H	OCH_2Ph		73–74	93	hexane
g	H	Me		112–113	74	i-Pr_2O

[a] Recrystallization solvent.

tution reaction under acidic conditions was investigated. A reaction of N-acetyl-2-acetoxyalanine ethyl ester (1; R^1 = Me, R^2 = Me) with phenylmethanethiol was carried out in acetonitrile at 0–5 °C in the presence of stannic tetrachloride as a typical Lewis acid. As a result, N-acetyl-2-benzylthioalanine ethyl ester (**2c**) was obtained in 76% yield. Similarly, the N-acetyl-2-acetoxyphenylalanine derivative (**1**; R^1 = $PhCH_2$, R^2 = Me) was treated with phenylmethanethiol to give the corresponding 2-benzylthiophenylalanine ethyl ester (**2d**) in good yield.

The Lewis acid catalyzed reaction, amidoalkylation,[15] was also applied to effect a new carbon–carbon bond formation leading to 2-substituted phenylglycine analogues, which are physiologically interesting amino acids such as the intermediates of semisynthetic β-lactam antibiotics.[16] As shown in Scheme IV, treatment of N-acetyl-2-acetoxyalanine ethyl ester (**1**; R^1 = Me, R^2 = Me) with anisole in the presence of 1 equiv of stannic tetrachloride afforded N-acetyl-2-methyl-2-(4-methoxyphenyl)glycine ethyl ester (**7a**, 58%) and its 2-methoxy isomer (**7b**, 29%). In this amidoalkylation, a small amount of 2,3-dehydroalanine derivative (**6a**) was also isolated.

Table IV



6

	R′	R²	mp, °C, or bp, °C/mmHg	yield, %	NMR ($CDCl_3$), δ R′	NMR ($CDCl_3$), δ H
a	H	CH_3	82–83/10	90	6.57 (s, 1 H)	5.88 (d)
b[a]	H	OCH_2Ph	syrup[b]	84	6.22 (s, 1 H)	5.68 (d)
(*Z*)-**c**	Ph	CH_3	96–97[c]	96	7.2–7.7 (m, 7 H, Ph + CH + NH)	
(*Z*)-**d**	Ph	OCH_2Ph	57–58[d]	90	7.1–7.7 (m, 6 H, Ph + CH)	
(*Z*)-**e**	CH_3	CH_3	64–65[e]	94	1.76 (d, 3 H)	6.74 (q)
(*Z*)-**f**	CH_3	OCH_2Ph	71–72[f]	88	1.76 (d, 3 H)	6.66 (q)

[a] NMR was measured in CCl_4. [b] Purified by column chromatography on silica gel with $CHCl_3$ as eluent. [c] Recrystallized from *i*-Pr_2O; lit.[12] mp 97–98 °C. [d] From *i* - Pr_2O; lit.[13] mp, 58 °C. [e] From hexane; lit.[12] mp 66–66.5 °C. [f] From hexane; lit.[13] mp 70–71 °C.

Thus, the 2-acetoxyamino acid derivatives can be used as an efficient synthon for the syntheses of biologically interesting 2-substituted amino acids and 2,3-dehydroamino acids.

Experimental Section[17]

Starting Materials. *N*-Acyl-2-acetoxyamino acid ethyl esters (**1**) were prepared by the method previously reported,[9] and the physical constants of new compounds are described below.

***N*-Carbobenzoxy-2-acetoxyalanine Ethyl Ester:** obtained as a syrup; IR ν_{max} (film) 3370, 1700–1760 (br) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H, $CO_2CH_2CH_3$), 1.93 (s, 3 H, CH_3), 2.02 (s, 3 H, $OCOCH_3$), 4.26 (q, 2 H, $CO_2CH_2CH_3$), 5.08 (s, 2 H, OCH_2Ph), 6.63 (s, 1 H, NH), 7.29 (s, 5 H, Ph).

***N*-Carbobenzoxy-2-acetoxyphenylalanine Ethyl Ester**: syrup, IR ν_{max} (film) 3370, 1700–1760 (br) cm^{-1}; NMR (CCl_4) δ 1.22 (t, 3 H, $CO_2CH_2CH_3$), 1.98 (s, 3 H, $OCOCH_3$), 3.11, 4.17 (AB q, 2 H, CH_2Ph, J = 13.2 Hz), 4.06 (q, 2 H, $CO_2CH_2CH_3$), 5.02 (s, 2 H, OCH_2Ph), 6.32 (s, 1 H, NH), 6.8–7.4 (m, 10 H, 2 × Ph).

***N*-Carbobenzoxy-2-acetoxybutyrine Ethyl Ester**: syrup; IR ν_{max} (film) 3350, 1700–1760 (br) cm^{-1}; NMR ($CDCl_3$) δ 0.97 (t, 3 H, CH_2CH_3, J = 7.2 Hz), 1.25 (t, 3 H, $CO_2CH_2CH_3$), 1.60–2.20, 2.60–3.20 (two m, 2 H, CH_2CH_3), 2.01 (s, 3 H, $OCOCH_3$), 4.22 (q, 2 H, $CO_2CH_2CH_3$), 5.07 (s, 2 H, OCH_2Ph), 6.56 (s, 1 H, NH), 7.28 (s, 5 H, Ph).

Basic Conditions. Synthesis of *N*-Acyl-2-oxy- and -2-thiosubstituted Amino Acid Esters (2 and 3). General Procedure. To a solution of **1** (10 mmol) in tetrahydrofuran (5 mL) was added a mixture of a nucleophile (10 mmol) and triethylamine (10 mmol) in tetrahydrofuran (10 mL) at 20–25 °C for a period of 10 min with stirring. After stirring was continued for 30 min at the same temperature, the reaction mixture was evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate. The solution was washed with water, dried over magnesium sulfate, and then evaporated to dryness in vacuo. The resultant product was purified by recrystallization or column chromatography on silica gel, as shown in Tables I and II.

***N*-Acetyl-2-phenylthioglycine Ethyl Ester (2a)**: IR ν_{max} (Nujol) 3370, 1730, 1680 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, 3 H, $CO_2CH_2CH_3$), 2.01 (s, 3 H, $COCH_3$), 4.20 (q, 2 H, $CO_2CH_2CH_3$), 5.86 (d, 1 H, CH, J = 7.8 Hz), 6.60 (br d, 1 H, NH, J = 7.8 Hz), 7.30–7.65 (m, 5 H, Ph). Anal. Calcd for $C_{12}H_{15}O_3NS$: C, 56.90; H, 5.97; N, 5.33; S, 12.63. Found: C, 56.82; H, 6.02; N, 5.49; S, 12.71.

***N*-Acetyl-2-phenylthioalanine Ethyl Ester (2b)**: IR ν_{max} (Nujol) 3350, 1735, 1670 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, $CO_2CH_2CH_3$), 1.75 (s, 3 H, CH_3), 1.90 (s, 3 H, $COCH_3$), 4.20 (q, 2 H, $CO_2CH_2CH_3$), 6.30 (br, 1 H, NH), 7.32 (s, 5 H, Ph). Anal. Calcd for $C_{13}H_{17}O_3NS$: C, 58.40; H, 6.41; N, 5.24; S, 11.99. Found: C, 58.27; H, 6.41; N, 5.22; S, 11.89.

***N*-Acetyl-2-benzylthioalanine Ethyl Ester (2c)**: IR ν_{max} (Nujol) 3230, 1740, 1640, 1530 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, $CO_2CH_2CH_3$), 1.76 (s, 3 H, CH_3), 1.89 (s, 3 H, $COCH_3$), 3.72 (s, 2 H, CH_2Ph), 4.21 (q, 2 H, $CO_2CH_2CH_3$), 6.28 (br, 1 H, NH), 7.30 (m, 5 H, Ph). Anal. Calcd for $C_{14}H_{19}O_3NS$: C, 56.35; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.60; H, 6.49; N, 4.61; S, 11.03.

***N*-Acetyl-2-benzylthiophenylalanine Ethyl Ester (2d)**: IR ν_{max} (Nujol) 3230, 1730, 1640, 1535 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (t, 3 H, $CO_2CH_2CH_3$), 1.78 (s, 3 H, $COCH_3$), 3.44, 3.99 (AB q, 2 H, $-CH_2Ph$, J = 14.4 Hz), 3.76 (s, 2 H, SCH_2Ph), 4.16 (q, 2 H, $CO_2CH_2CH_3$), 6.30 (br, 1 H, NH), 7.15, 7.25 (two s, 10 H, 2 × Ph). Anal. Calcd for $C_{20}H_{23}O_3NS$: C, 67.20; H, 6.49; N, 3.92; S, 8.97. Found: C, 66.92; H, 6.45; N, 3.90; S, 8.77.

***N*-Carbobenzoxy-2-benzylthioglycine Ethyl Ester (2e)**: IR ν_{max} (Nujol) 3350, 1730, 1690, 1515 cm^{-1}; NMR (Me_2SO-d_6) 1.20 (t, 3 H, $CO_2CH_2CH_3$), 3.87 (s, 2 H, SCH_2Ph), 4.12 (q, 2 H, $CO_2CH_2CH_3$), 5.08 (s, 2 H, $-OCH_2Ph$), 5.28 (d, 1 H, CH, J = 9.6 Hz), 5.76 (br d, 1 H, NH, J = 9.6 Hz), 7.23, 7.29 (two s, 10 H, 2 × Ph). Anal. Calcd for $C_{19}H_{21}O_4NS$: C, 63.51; H, 5.85; N, 3.90; S, 8.91. Found: C, 63.46; H, 5.90; N, 3.84; S, 8.99.

***N*-Acetyl-2-isoamylthioglycine Ethyl Ester (2f)**: IR ν_{max} (film) 3340, 1750, 1660, 1530 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (d, 6 H, $(CH_3)_2C$, J = 6.0 Hz), 1.35 (t, 3 H, $CO_2CH_2CH_3$), 1.45–1.75 (m, 3 H, $>CHCH_2-$), 2.10 (s, 3 H, $COCH_3$), 2.74 (t, 2 H, $-CH_2S-$, J = 7.2 Hz), 4.28 (q, 2 H, $CO_2CH_2CH_3$), 5.57 (d, 1 H, CH, J = 7.8 Hz), 6.58 (br d, 1 H, NH, J = 7.8 Hz). Anal. Calcd for $C_{11}H_{21}O_3NS$: C, 53.44; H, 8.50; N, 5.67; S, 12.96. Found: C, 53.21; H, 8.61; N, 5.44; S, 13.08.

***N*-Acetyl-2-ethoxyalanine Ethyl Ester (3c)**: IR ν_{max} (Nujol) 3320, 1740, 1680, 1545 cm^{-1}; NMR ($CDCl_3$) δ 1.19 (t, 3 H, OCH_2CH_3, J = 7.2 Hz), 1.31 (3 H, $CO_2CH_2CH_3$), 1.71 (s, 3 H, CH_3), 2.05 (s, 3 H, $COCH_3$), 3.52 (q, 2 H, OCH_2CH_3, J = 7.2 Hz), 4.25 (q, 2 H, $CO_2CH_2CH_3$), 7.21 (s, 1 H, NH). Anal. Calcd for $C_9H_{17}O_4N$: C, 53.20; H, 8.37; N, 6.90. Found: C, 53.23; H, 8.36; N, 6.92.

***N*-Acetyl-2-phenoxyglycine Ethyl Ester (3d)**: IR ν_{max} (film) 3330, 1750, 1680, 1600, 1530 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, $CO_2CH_2CH_3$), 2.08 (s, 3 H, $COCH_3$), 4.27 (q, 2 H, $CO_2CH_2CH_3$), 6.28 (d, 1 H, CH, J = 9.6 Hz), 6.85–7.45 (m, 6 H, Ph + NH). Anal. Calcd for $C_{12}H_{15}O_4N$: C, 60.76; H, 6.33; N, 5.91. Found: C, 60.94; H, 6.35; N, 5.84.

***N*-Acetyl-2-(4-nitrophenoxy)glycine Ethyl Ester (3e)**: IR ν_{max} (Nujol) 3250, 1770, 1675, 1610, 1590, 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, $CO_2CH_2CH_3$), 2.10 (s, 3 H, $COCH_3$), 4.31 (q, 2 H, $CO_2CH_2CH_3$), 6.38 (d, 1 H, CH, J = 9.6 Hz), 7.13 (br d, 1 H, NH, J = 9.6 Hz), 7.19, 8.19 (A_2B_2 q, 4 H, Ph, J = 10.2 Hz). Anal. Calcd for $C_{12}H_{14}O_6N_2$: C, 51.16; H, 4.96; N, 9.93. Found: C, 51.18; H, 4.92; N, 10.02.

N-Acetyl-2-alkoxyamino acid ethyl esters (**3a–c**) were also obtained as follows. A solution of **1** in methanol or ethanol was allowed to stand overnight. The solution was evaporated to dryness in vacuo, and the residue was extracted with ethyl acetate. The solution was washed with water, dried over magnesium sulfate, and evaporated to dryness in vacuo. The resulting products were purified by recrystallization or column chromatography. The physical constants of **3a** and **3b** were reported previously.[18]

Synthesis of *N*-Acyl-2-amino-substituted Amino Acid Esters (4). General Procedure. To a solution of **1** (10 mmol) in tetrahydrofuran (5 mL) was added a solution of an amine (20 mmol) in tetrahydrofuran (5 mL) at 20–25 °C for 10 min. After stirring for 30 min, the mixture was subjected to the same treatment as described above.

***N*-Acetyl-2-(*tert*-butylamino)glycine Ethyl Ester (4a)**: IR ν_{max} (Nujol) 3300, 3200, 1725, 1690, 1540 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (s, 9 H, $C(CH_3)_3$), 1.30 (t, 3 H, $CO_2CH_2CH_3$), 2.01 (s, 3 H, $COCH_3$), 2.10

(br, 1 H, NH), 4.20 (q, 2 H, $CO_2CH_2CH_3$), 5.36 (d, 1 H, CH, J = 7.2 Hz), 6.73 (br d, 1 H, NH, J = 7.2 Hz). Anal. Calcd for $C_{10}H_{20}O_3N_2$: C, 55.53; H, 9.12; N, 12.95. Found: C, 55.61; H, 9.22; N, 12.98.

***N*-Carbobenzoxy-2-(*tert*-butylamino)glycine Ethyl Ester (4b)**: IR ν_{max} (Nujol) 3300, 3200, 1700–1730 (br), 1550 cm^{-1}; NMR ($CDCl_3$) δ 1.12 (s, 9 H, $C(CH_3)_3$), 1.25 (t, 3 H, $CO_2CH_2CH_3$), 2.10 (br, 1 H, NH), 4.18 (q, 2 H, $CO_2CH_2CH_3$), 5.11 (d, 1 H, CH, J = 9.6 Hz), 5.13 (s, 2 H, OCH_2Ph), 5.45 (br d, 1 H, NH, J = 9.6 Hz), 7.31 (s, 5 H, Ph). Anal. Calcd for $C_{16}H_{24}O_4N_2$: C, 62.34; H, 7.79; N, 9.09. Found: C, 62.42; H, 7.81; N, 9.02.

***N*-Acetyl-2-morpholinoglycine Ethyl Ester (4c)**: IR ν_{max} (Nujol) 3300, 1730, 1680, 1525 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (t, 3 H, $CO_2CH_2CH_3$), 2.09 (s, 3 H, $COCH_3$), 2.38–2.70, 3.60–3.80 (two m, 8 H, morpholine protons), 4.26 (q, 2 H, $CO_2CH_2CH_3$), 5.26 (d, 1 H, CH, J = 7.8 Hz), 6.50 (br d, 1 H, NH, J = 7.8 Hz). Anal. Calcd for $C_{10}H_{18}O_4N_2$: C, 52.17; H, 7.83; N, 12.17. Found: C, 52.11; H, 7.88; N, 12.06.

***N*-Acetyl-2-morpholinoalanine Ethyl Ester (4d)**: IR ν_{max} (Nujol) 3250, 1740, 1640, 1530 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, $CO_2CH_2CH_3$), 1.80 (s, 3 H, CH_3), 2.03 (s, 3 H, $COCH_3$), 2.55–2.70, 3.60–3.80 (two m, 8 H, morpholine protons), 4.26 (q, 2 H, $CO_2CH_2CH_3$), 6.48 (br, 1 H, NH). Anal. Calcd for $C_{11}H_{20}O_4N_2$: C, 54.10; H, 8.20; N, 11.48. Found: C, 54.32; H, 8.19; N, 11.55.

***N*-Acetyl-2-morpholinophenylalanine Ethyl Ester (4e)**: IR ν_{max} (Nujol) 3350, 1735, 1675, 1520 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, 3 H, $CO_2CH_2CH_3$), 1.94 (s, 3 H, $COCH_3$), 2.55–2.90, 3.60–3.80 (two m, 8 H, morpholine protons), 3.20, 4.11 (AB q, 2 H, $-CH_2Ph$, J = 13.2 Hz), 4.29 (q, 2 H, $CO_2CH_2CH_3$), 6.35 (br, 1 H, NH), 7.00–7.30 (m, 5 H, Ph). Anal. Calcd for $C_{17}H_{24}O_4N_2$: C, 63.75; H, 7.50; N, 8.75. Found: C, 63.80; H, 7.48; N, 8.68.

***N*-Carbobenzoxy-2-morpholinoglycine Ethyl Ester (4f)**: IR ν_{max} (Nujol) 3200, 1740, 1700, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, 3 H, $CO_2CH_2CH_3$), 2.40–2.70, 3.50–3.75 (two m, 8 H, morpholine protons), 4.18 (q, 2 H, $CO_2CH_2CH_3$), 5.03 (d, 1 H, CH, J = 9.0 Hz), 5.10 (s, 2 H, OCH_2Ph), 6.17 (br d, 1 H, NH, J = 9.0 Hz), 7.29 (s, 5 H, Ph). Anal. Calcd for $C_{16}H_{22}O_5N_2$: C, 59.63; H, 6.83; N, 8.66. Found: C, 59.88; H, 6.88; N, 8.66.

***N*-Acetyl-2-(4-toluidino)glycine Ethyl Ester (4g)**: IR ν_{max} (Nujol) 3450, 3340, 1740, 1660, 1535 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, $CO_2CH_2CH_3$), 1.98 (s, 3 H, $COCH_3$), 2.25 (s, 3 H, CH_3Ph), 4.27 (2 H, $CO_2CH_2CH_3$), 5.85 (d, 1 H, CH, J = 7.2 Hz), 6.32 (br d, 1 H, NH, J = 7.2 Hz), 6.61, 7.03 (A_2B_2 q, 4 H, Ph, J = 8.4 Hz). Anal. Calcd for $C_{13}H_{18}O_3N_2$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.42; H, 7.23; N, 11.18.

Synthesis of 2,3-Dehydroamino Acid Derivatives (6). General Procedure. To a solution of *N*-acyl-2-acetoxyamino acid ethyl ester (1, 10 mmol) in tetrahydrofuran (10 mL) was added triethylamine (10 mmol) at room temperature. After stirring overnight, the mixture was evaporated to dryness in vacuo. The residue was extracted with ethyl acetate, and the solution was washed with water and dried over magnesium sulfate. Then the solution was concentrated in vacuo, and the resulting residue was purified by distillation, recrystallization, or column chromatography on silica gel using chloroform as an eluent.

In this method, *N*-acyl-2,3-dehydroalanine and -dehydrophenylalanine ethyl esters (**6a–d**) were prepared in satisfactory yields. However, the yields of dehydrobutyrine derivatives (**6e,f**) were about 50% from the NMR.

In the case of *N*-acyl-2-acetoxybutyrine ethyl esters (1; R^1 = Et, R^2 = Me, OCH_2Ph), DBU in place of triethylamine was used. The reaction mixture was stirred for 30 min at room temperature, following the same workup to yield 2,3-dehydrobutyrine derivatives. The yields and physicochemical properties are summarized in Table IV.

Acidic Conditions. Synthesis of *N*-Acetyl-2-benzylthioalanine Ethyl Ester (2c). To a mixture of *N*-acetyl-2-acetoxyalanine ethyl ester (1.0 g, 4.6 mmol) and phenylmethanethiol (0.62 g, 5 mmol) dissolved in acetonitrile (5 mL) was added stannic tetrachloride (0.58 mL, 5 mmol) at 0–5 °C under vigorous stirring. After the stirring was continued for an additional hour at the same temperature, the reaction was quenched by addition of saturated sodium bicarbonate solution (5 mL). The insoluble materials were filtered off, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in ethyl acetate. The solution was washed with brine, dried over magnesium sulfate, and then evaporated to dryness in vacuo. The resultant crystalline product was purified by recrystallization from diisopropyl ether to give 0.98 g of **2c** (76%). The physicochemical properties were identical with those described in the above section.

Synthesis of *N*-Acetyl-2-benzylthiophenylalanine Ethyl Ester (2d). 2d was obtained similarly by the reaction of *N*-acetyl-2-acetoxyphenylalanine ethyl ester (1.25 g, 4.8 mmol) with phenylmethanethiol (0.62 g, 5 mmol) in the presence of stannic tetrachloride (0.58 mL, 5 mmol), yield 1.23 g (72%). The physicochemical properties were the same as those for **2d** prepared above.

Synthesis of *N*-Acetyl-2-methyl-2-(4-methoxyphenyl)glycine Ethyl Ester (7a) and *N*-Acetyl-2-methyl-2-(2-methoxyphenyl)-glycine Ethyl Ester (7b). To a stirred solution of *N*-acetyl-2-acetoxyalanine ethyl ester (1.09 g, 5 mmol) dissolved in anisole (10 mL) was dropwise added stannic tetrachloride (0.58 mL, 5 mmol) at 0–5 °C. The same workup as above was carried out. The resulting syrup was chromatographed on silica gel with benzene–acetone (5:2) to afford **7a** (770 mg, 58%), **7b** (390 mg, 29%), and 2,3-dehydroalanine ethyl ester (**6a**; 35 mg, 4.5%), respectively.

Compound **7a**: mp 108–109 °C; IR ν_{max} (Nujol) 3240, 1740, 1630, 1560, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (t, 3 H, $CO_2CH_2CH_3$), 1.96 (s, 3 H, CH_3), 2.00 (s, 3 H, $COCH_3$), 3.77 (s, 3 H, OCH_3), 4.14 (q, 2 H, $CO_2CH_2CH_3$), 6.83, 7.34 (A_2B_2 q, 4 H, Ph, J = 9.0 Hz), 6.6–6.9 (br, 1 H, NH). Anal. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.27; H, 7.01; N, 5.33.

Compound **7b**: syrup, IR ν_{max} (film) 3400, 1730, 1660, 1600, 1585 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H, $CO_2CH_2CH_3$), 1.87 (s, 3 H, CH_3), 2.02 (s, 3 H, $COCH_3$), 3.73 (s, 3 H, OCH_3), 4.15 (q, 4 H, $CO_2CH_2CH_3$), 6.68–7.6 (m, 5 H, Ph + NH).

Acknowledgment. We wish to express our thanks to Dr. I. Chibata, Director of this Research Laboratory, for his encouragement in this study.

Registry No.—**2a,** 66569-38-8; **2b,** 66569-39-9; **2c,** 66569-37-7; **2d,** 66569-36-6; **2e,** 68225-93-4; **2f,** 66569-35-5; **3a,** 59223-85-7; **3b,** 59223-86-8; **3c,** 68184-93-0; **3d,** 68184-94-1; **3e,** 68184-95-2; **4a,** 68184-96-3; **4b,** 68201-11-6; **4c,** 68184-97-4; **4d,** 68184-98-5; **4e,** 68184-99-6; **4f,** 68185-00-2; **4g,** 68185-01-3; **6a,** 23115-42-6; **6b,** 68185-02-4; (*Z*)-**6c,** 62436-67-3; (*Z*)-**6d,** 50685-13-7; (*Z*)-**6e,** 66299-22-7; (*Z*)-**6f,** 50685-03-5; **7a,** 68185-03-5; **7b,** 68185-04-6; *N*-carbobenzoxy-2-acetoxyphenylalanine ethyl ester, 68185-05-7; *N*-carbobenzoxy-2-acetoxybutyrine ethyl ester, 68185-06-8; *N*-acetyl-2-acetoxyalanine ethyl ester, 62183-00-0; phenylmethanethiol, 100-53-8; *N*-acetyl-2-acetoxyphenylalanine ethyl ester, 59223-92-6; anisole, 100-66-3; *N*-carbobenzoxy-2-acetoxyalanine ethyl ester, 68185-07-9.

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