New Convenient Syntheses of α-C-Acylamino Acids and α-Amino Ketones[1]

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α-C-Acylamino acid esters (3-oxo-2-amino acid esters, **6**) were prepared in good yields by the acid hydrolysis of α-acyl-α-isocyanoacetate analogs (**5**) and oxazole-4-carboxylate derivatives (**4**), which were easily obtained by the reaction of α-isocyanoacetate analogs (**1**) with acyl halides (**2**) or acid anhydrides (**3**) in the presence of metallic or organic bases. Further, the hydrolysis of **6** and **4** gave the α-amino ketones (**7**) in high yields.

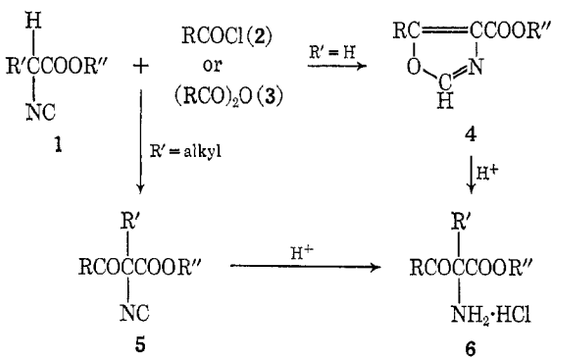
α-C-Acylamino acids are pharmaceutically interesting compounds and important intermediates for the synthesis of β-hydroxyamino acids.[2-5] Most recently, α-C-acylamino acids have been used for the preparation of β-keto esters.[6]

A few methods for the synthesis of α-C-acylamino acids have been reported. Bolhofer[2] and Sallay, *et al.*,[3] described a partial reduction of acyldiazoacetates which were prepared by the diazotization of β-keto esters and by the acylation of diazoacetates, respectively. Pines, *et al.*, reported the synthesis of *N*-acetyl-α-benzoylglycine derivatives by a reaction of azlactone with Grignard reagents in about 30% yield.[4] However, these methods require various limiting conditions.

In the course of our studies on the synthesis of amino acids, we have reported the reaction of isocyano compounds with various electrophiles,[5,7-9] among which the synthesis of aroylamino acids has been published in a preliminary communication.[8] In the present paper, we wish to report in detail a new convenient synthesis of various α-C-acylamino acid esters (**6**), using the reaction of isocyano compounds (**1**) with acyl halides (**2**) or acid anhydrides (**3**) as shown in Scheme I.

The reaction of α-isocyanoacetate[10] (**1**, R′ = H) with benzoyl chloride analogs (**2**, R = aromatic group) in the presence of triethylamine to produce oxazole-4-carboxylates (**4**) (method A) (Table I, **4g-k**) was previously described.[8] Schöllkopf and Schröder also reported that the reactions of α-isocyanoacetate with acyl halides and acyl amides in the presence of metallic bases gave oxazole (**4**).[11] Furthermore, we have studied reactions using acylating reagents other than acyl halides and acyl amides. We have found that reaction of α-isocyanoacetate with various acid anhydrides

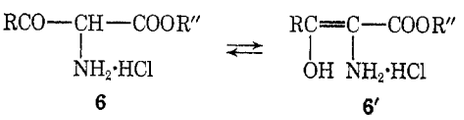
Scheme I



(**3**) proceeds easily in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)[12] which is a very strong organic base,[13] and consequently various oxazole-4-carboxylates (**4**) are obtained in good yields as listed in Table I (method B). The same reaction took place also in the case of cyclic acid anhydrides such as succinic anhydride or glutaric anhydride and subsequently yielded dicarboxylic acid oxazole compounds (**4e** and **4f**) which are new and interesting substances, in 65 and 60% yields, respectively.

It was also found that the oxazole compounds prepared according to method A or B were readily converted to α-C-acylamino acid derivatives (**6**, R′ = H) by heating at 40–50° in 3 *N* HCl–MeOH for 4 hr in high yields. These results are listed in Table II. The conversion of the oxazole compounds (**4e** and **4f**) to α-C-acylamino acid esters was accompanied by esterification of the ω-carboxylic acid group; the corresponding esters were identified as 2-amino-3-oxyhexanedioic acid dimethyl ester hydrochloride (**6e**) and 2-amino-3-oxyheptanedioic acid dimethyl ester hydrochloride (**6f**).

The α-C-acylamino acid ester hydrochlorides (**6**, R′ = H) prepared by the hydrolysis of the oxazole compounds (**4**) may exist in keto–enol tautomeric forms as shown in the following equation.



For example, the ir spectrum (KBr disk) of α-(3,4-dichloro)benzoylglycine (**6j**) showed the characteristic

(1) Synthesis of Amino Acids and Related Compounds. 6. Part 5: ref 6.

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TABLE I

FORMATION OF OXAZOLE COMPOUNDS (4)

Compd	R	R''	Method[a]	Yield, %	Mp, °C [bp, °C (mm)]	Formula	Analysis, % C	H	N
4a	CH_3	Me	B	78	46–48	$C_6H_7O_3N$	51.06[f]	5.00	9.93
					[55–57 (0.1)]		51.28[g]	4.99	9.85
4b	$CH_3CH_2CH_2$	Et	B	85	[85–88 (1.2)]	$C_9H_{13}O_3N$	59.00	7.15	7.65
							59.27	7.00	7.56
4c	$(CH_3)_2CHCH_2$	Me	A	25	[78–80 (0.35)]	$C_9H_{13}O_3N$	59.00	7.15	7.65
			B	75			58.87	7.32	7.60
4d	$C_6H_5CH_2$	Et	B	70	[125–128 (0.1)[b]]	$C_{13}H_{13}O_3N$	67.52	5.67	6.06
							67.18	5.52	5.99
4e	$HOOCCH_2CH_2$[c]	Me	B	65	121–123	$C_8H_9O_5N$	48.24	4.56	7.03
							48.39	4.40	6.83
4f	$HOOCCH_2CH_2CH_2$[d]	Me	B	60	84–85	$C_9H_{11}O_5N$	50.70	5.20	6.57
							50.96	5.17	6.38
4g	C_6H_5	Me	A	90	91–93	$C_{11}H_9O_3N$	65.02	4.46	6.89
			B	85			64.86	4.40	6.89
4h	3,4-Methylenedioxy Ph	Me	A	92	130–132	$C_{12}H_9O_5N$	58.30	3.67	5.67
							58.17	3.67	5.52
4i	3,4,5-Trimethoxy Ph	Me	A	79	137–139	$C_{14}H_{15}O_6N$	57.33	5.16	4.78
							57.56	5.26	4.96
4j	3,4-Dichloro Ph	Me	A	88	142–143	$C_{11}H_7O_3NCl_2$	48.55	2.59	5.14
							48.37	2.63	5.10
4k	2-Naphthalene[e]	Me	A	85	111–113	$C_{15}H_{11}O_3N$	71.14	4.37	5.53
							70.74	4.50	5.44

[a] Method A, from acyl halides; method B, from acid anhydrides. [b] Lit.[11] bp 135° (0.1 mm). [c] Reaction using succinic anhydride. [d] Reaction using glutaric anhydride. [e] Reaction using β-naphthoyl chloride. [f] Calculated. [g] Found.

TABLE II

FORMATION OF α-*C*-ACYLAMINO ACID DERIVATIVES (6, R' = H)

Compd	R	R''	Yield, %	Mp, °C[b] dec	Formula	Analysis, % C	H	N
6a	CH_3	Me	73	146–148	$C_5H_{10}O_3NCl$	35.83[c]	6.01	8.35
						35.89[d]	6.00	8.44
6b	$CH_3CH_2CH_2$	Et	84	125–126	$C_8H_{16}O_3NCl$	45.82	7.69	6.68
						45.64	7.66	6.79
6c	$(CH_3)_2CHCH_2$	Me	77	110–113	$C_8H_{16}O_3NCl$	45.82	7.69	6.68
						45.77	7.52	6.80
6d	$C_6H_5CH_2$	Et	80	144–146	$C_{12}H_{16}O_3NCl$	55.92	6.25	5.43
						55.79	6.14	5.58
6e	$MeOOCCH_2CH_2$	Me	83	143–146	$C_6H_{14}O_5NCl$	40.09	5.88	5.84
						40.17	5.69	5.88
6f	$MeOOCCH_2CH_2CH_2$	Me	87	Oil[a]				
6g	C_6H_5	Me	84	185–186	$C_{10}H_{12}O_3NCl$	52.29	5.28	6.10
						52.26	5.39	6.11
6h	3,4-Methylenedioxy Ph	Me	85	170–171	$C_{11}N_{12}O_5NCl \cdot H_2O$	45.29	4.80	4.79
						45.20	4.90	4.83
6i	3,4,5-Trimethoxy Ph	Me	80	174–175	$C_{13}H_{18}O_6NCl$	48.82	5.67	4.38
						48.63	5.56	4.30
6j	3,4-Dichloro Ph	Me	80	165–167	$C_{10}H_{10}O_3NCl_3 \cdot {}^3/_2H_2O$	36.58	4.02	4.29
						36.86	3.96	4.56
6k	2-Naphthalene	Me	85	169–170	$C_{14}H_{14}O_3NCl$	60.11	5.04	5.00
						60.28	5.38	4.81

[a] Identified by ir and nmr spectra. [b] Recrystallization from ethyl acetate–methanol. [c] Calculated. [d] Found.

absorption of the ester group at 1750 cm^{-1} and of the ketone group at 1690 cm^{-1}, respectively. These results suggested that the keto form (**6**) should be preferred. On the other hand, the nmr spectrum (DMSO-d_6) of compound **6j** showed one proton signal for the hydroxy at δ 6.35 which disappeared on deuterium exchange and obtained no signal for the methine proton. From these results, the stability of the enol form (**6'**) was high in solution. Similar behavior was also shown by other various α-*C*-acylamino acid ester hydrochlorides (**6**, R' = H).

In the reaction of α-alkylisocyano compounds [**1**, R' = CH_3, CH_2CH_3, $CH(CH_3)_2$] with various acyl halides in the presence of metallic base such as NaH or organic base such as DBU, the oxazoles were not formed, but α-acyl-α-isocyano compounds (**5**) were obtained. Part of the products (**5**, R = C_6H_5, R' = CH_3, R'' = Me) was distilled for purification and identified by the ir spectrum, which exhibited bands at 2120, 1750, and 1700 cm^{-1} due to the NC, COOMe, and CO, respectively, and by the nmr spectrum. The other compounds (**5**) were subsequently hydrolyzed without purification with 2 *N* HCl–MeOH for 1 hr at 40° to afford the various α-alkyl-α-*C*-acylamino acid methyl ester hydrochlorides (**6**, R' = alkyl) in 50–65% yields as summarized in Table III.

Table III
Formation of α-Alkyl-α-aroylamino Acid Derivatives (6, R'' = Me)

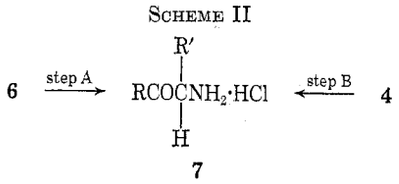
Compd	R	R'	Yield,[a] %	Mp, °C[c] dec	Formula	Analysis, % C	H	N
6l	C_6H_5	CH_3	50 (65[b])	154–155	$C_{11}H_{14}O_3NCl$	54.21[d]	5.79	5.74
						53.95[e]	5.82	5.71
6m	3,4-Methylenedioxy Ph	CH_3	58	146–147	$C_{12}H_{14}O_5NCl \cdot H_2O$	47.15	5.28	4.58
						46.85	5.26	4.58
6n	3,4,5-Trimethoxy Ph	CH_3	62	155–157	$C_{14}H_{20}O_6NCl \cdot H_2O$	47.79	6.30	3.98
						47.51	6.42	3.99
6o	C_6H_5	CH_2CH_3	52	166–167	$C_{12}H_{16}O_3NCl$	55.93	6.08	5.44
						55.98	6.31	5.41
6p	3,4-Methylenedioxy Ph	CH_2CH_3	58	163–164	$C_{13}H_{16}O_5NCl$	51.75	5.35	4.64
						51.41	5.53	4.44
6q	3,4,5-Trimethoxy Ph	CH_2CH_3	53	142–145	$C_{15}H_{22}O_6NCl \cdot H_2O$	49.24	6.61	3.83
						49.04	6.68	3.85
6r	C_6H_5	$CH(CH_3)_2$	65	167–168	$C_{13}H_{18}O_3NCl$	57.46	6.68	5.15
						57.42	6.81	5.23
6s	3,4-Methylenedioxy Ph	$CH(CH_3)_2$	55	152–153	$C_{14}H_{18}O_5NCl \cdot H_2O$	50.37	6.04	4.20
						50.08	6.07	4.20
6t	3,4,5-Trimethoxy Ph	$CH(CH_3)_2$	60	132–134	$C_{16}H_{24}O_6NCl \cdot H_2O$	50.59	6.89	3.68
						50.81	6.58	3.70
6u	2-Naphthalene	$CH(CH_3)_2$	55	142–143	$C_{17}H_{20}O_3NCl \cdot H_2O$	60.00	6.52	4.12
						59.81	6.47	4.38

[a] Reaction of isocyano compounds with acyl halides in the presence of NaH. [b] Reaction of isocyano compounds with benzoic anhydride in the presence of DBU. [c] Recrystallization from ethyl acetate–methanol. [d] Calculated. [e] Found.

On the other hand, α-amino ketones are also useful compounds for the synthesis of amino alcohols, which include such physiologically interesting substances as ephedrine and adrenaline. Several methods for the preparations of amino ketones have been reported.[14] For example, the hydrolysis of the quaternary salt obtained from phenacyl bromide and hexamethylenetetramine,[15] the reduction of α-oximino acetone derivatives[16] or α-nitroacetone derivatives,[17] the Neber rearrangement of the tosylate of acetophenone oxime derivatives,[18] and the rearrangement of *N,N*-dichloro-*sec*-alkylamine[19] are generally known.

We previously reported a method for the preparation of phenacylamine derivatives from aroylamino acids and oxazoles as shown in Scheme II.[8] In the

Scheme II



present study, the method is extended to various aliphatic α-*C*-acylamino acid esters and oxazoles.

When the α-*C*-acylamino acid ester hydrochlorides (**6**) were treated with 6 *N* hydrochloric acid under heating at 90–95° for 4 hr, the corresponding α-amino ketone hydrochlorides (**7**) were obtained in high yields by decarboxylation (step A). Furthermore, hydrolysis of the oxazoles (**4**) carried out under conditions similar to the method of step A afforded the corresponding α-amino ketone hydrochlorides (**7**, R' = H) (step B). These results are summarized in Table IV.

It appears that these synthetic methods will be generally useful for the preparation of α-*C*-acylamino acids and α-amino ketones.

Experimental Section[20]

Typical Procedures for Preparation of Oxazoles (4). Method A.—This method has been described previously.[8] Various oxazoles (**4g–k**) were prepared in the same way. The yields, melting points, and elemental analyses of the compounds are shown in Table I.

Method B. Methyl 5-Methyloxazole-4-carboxylate (4a).—To a mixture of methyl α-isocyanoacetate (2.97 g, 0.03 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4.5 g, 0.03 mol) in THF (40 ml) was added a mixture of acetic anhydride (**3**, R = CH_3, 3.06 g, 0.03 mol) and THF (10 ml) at 10° with stirring. After the solution was stirred for 10 hr at room temperature, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 ml) and the solution was washed with water. The solution was dried over magnesium sulfate and the solvent was evaporated *in vacuo*. The residual oil was distilled under reduced pressure, bp 55–57° (0.1 mm), yield 3.3 g (78%). The product solidified on standing and was recrystallized from a mixture of isopropyl ether and *n*-hexane: mp 46–48°; ir (Nujol) 3100 (CH), 1695 (COOMe), 1600 (C=N), 1510 cm^{-1} (C=C); nmr (CCl_4) δ 7.84 (s, 1, CH), 3.92 (s, 3, OCH_3), 2.65 (s, 3, CH_3).

Other oxazole compounds (**4b–d** and **4g**) were prepared in a similar way. The results are summarized in Table I.

4-Methoxycarbonyl-5-oxazolepropionic Acid (4e).—A mixture of succinic anhydride (3.0 g, 0.03 mol) and THF (30 ml) was gradually added to a solution of methyl α-isocyanoacetate (2.97 g, 0.03 mol) and DBU (9.0 g, 0.06 mol) in THF (40 ml) for a period of 30 min at 30–33° with vigorous stirring. After stirring was continued for 4 hr at room temperature, the reaction mixture was neutralized with acetic acid under cooling and evaporated to remove the solvent under reduced pressure. The residue was dissolved in water (70 ml) and the solution was washed out with benzene. The separated aqueous layer was acidified with concentrated hydrochloric acid (15 ml) and then saturated with sodium chloride. The solution was sufficiently

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(20) All the melting points and the boiling points were uncorrected. All the melting points were measured by the use of the Yamato melting point apparatus. The infrared spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. The nmr spectra were obtained using a Hitachi Perkin-Elmer R-20A high resolution nmr spectrometer with tetramethylsilane as internal standard.

TABLE IV
FORMATION OF α-AMINO KETONE HYDROCHLORIDES (7)

Compd	R	R′	Yield, %[a]	Yield, %[b]	Mp, °C[c] dec	Formula	Analysis, % C	Analysis, % H	Analysis, % N
7a	CH_3	H	75	70	70–72[d]	C_3H_8ONCl	32.88[i]	7.36	12.78
							33.01[k]	7.19	12.50
7b	$CH_3CH_2CH_2$	H	90	85	172–174[e]	$C_5H_{12}ONCl$	43.63	8.78	10.17
							43.71	8.58	10.22
7c	$(CH_3)_2CHCH_2$	H	85	80	177–178[f]	$C_6H_{14}ONCl$	47.52	9.30	9.23
							47.34	8.97	9.19
7d	$C_6H_5CH_2$	H	95	93	200–202[g]	$C_9H_{12}ONCl$	58.22	6.51	7.54
							58.47	6.46	7.49
7g	C_6H_5	H	90	92	190–191[h]	$C_8H_{10}ONCl$	55.98	5.87	8.16
							56.32	5.93	8.37
7h	3,4-Methylenedioxy Ph	H	93	94	187–191[i]	$C_9H_{10}O_3NCl$	50.12	4.67	6.49
							50.19	4.68	6.48
7i	3,4,5-Trimethoxy Ph	H	91	94	243–244	$C_{11}H_{16}O_4NCl$	50.48	6.16	5.73
							50.24	6.06	5.41
7k	2-Naphthalene	H	91	90	256	$C_{12}H_{12}ONCl$	65.01	5.45	6.31
							64.88	5.46	6.41
7m	3,4-Methylenedioxy Ph	CH_3	93		206	$C_{10}H_{12}O_3NCl$	52.30	5.27	6.10
							52.11	5.30	6.31
7n	3,4,5-Trimethoxy Ph	CH_3	95		237	$C_{12}H_{18}O_4NCl$	52.27	6.58	5.08
							51.90	6.57	5.10
7r	C_6H_5	$CH(CH_3)_2$	87		198–199	$C_{11}H_{16}ONCl$	61.82	7.54	6.55
							61.73	7.42	6.60
7t	3,4-Methylenedioxy Ph	$CH(CH_3)_2$	86		227–229	$C_{12}H_{16}O_3NCl$	55.92	6.26	5.44
							55.68	6.21	5.63

[a] From step A in Scheme II. [b] From step B in Scheme II. [c] Recrystallization from ethyl acetate-methanol. [d] Lit. mp 75° dec: S. Gabriel and G. Pinkus, *Ber.*, **35**, 3806 (1902). [e] Lit. mp 163–164° dec: M. Jackman, M. Klenk, B. Fishburn, B. F. Tuller, and S. Archer, *J. Amer. Chem. Soc.*, **70**, 2884 (1948). [f] Lit.[e] mp 179–180°. [g] Lit.[e] mp 190–193° dec. [h] Lit.[19] mp 185–186° dec. [i] Lit. mp 193° dec: P. W. Neber, A. Burgard, and W. Thier, *Justus Liebigs Ann. Chem.*, **526**, 277 (1936). [j] Calculated. [k] Found.

extracted with ethyl acetate (50 ml) three times and the combined extract was dried over magnesium sulfate and then evaporated *in vacuo*. The obtainable crystals were washed with ether and collected by filtration. Recrystallization from ethyl acetate gave **4e** as colorless needles: yield 3.9 g (65%); mp 121–123°; ir (Nujol) 3120 (CH), 1728 (COOMe), 1708 (COOH), 1608 (N=C), 1525 cm^{-1} (C=C); nmr ($CDCl_2$) δ 10.37 (s, 1, COOH), 7.85 (s, 1, CH), 3.90 (s, 3, OCH_3), 3.45 (t, 2, CH_2), 2.75 (t, 2, CH_2).

4-Methoxycarbonyl-5-oxazolebutyric Acid (4f).—A mixture of glutaric anhydride (3.42 g, 0.03 mol) and THF (20 ml) was added dropwise to a solution of methyl α-isocyanoacetate and DBU (9.0 g, 0.06 mol) in THF (40 ml) for a period of 20 min at 30–33° with vigorous stirring. After additional stirring was continued for 1 hr at room temperature, the same treatment as described above was carried out to afford the oxazole compound **4f**. Recrystallization from ethyl acetate gave colorless needles: yield 3.8 (60%); mp 83–85°; ir (Nujol) 3150 (CH), 1722 (COOMe), 1710 (COOH), 1625 (N=C), 1515 cm^{-1} (C=C); nmr ($CDCl_3$) δ 11.08 (s, 1, COOH), 7.87 (s, 1, CH), 3.90 (s, 3, OCH_3), 3.16 (t, 2, CH_2), 2.90 (t, 2, CH_2), 2.10 (m, 2, CH_2).

General Procedure for Preparation of α-*C*-Acylamino Acid Derivatives (6a–k) *via* Oxazole Compounds (4a–k).—Oxazole compound **4** (0.01 mol) was dissolved in a mixture of concentrated hydrochloric acid (5 ml) and methanol (15 ml) and the solution was heated at 45–50° for 4 hr. After the reaction was complete, methanol was removed under reduced pressure below 30°. To the residue was added water (10 ml) and the acidic solution was washed with ether (10 ml). The separated aqueous layer was treated with activated charcoal and was concentrated to dryness *in vacuo* below 30°. The residue was dissolved in methanol and the mixture was then evaporated *in vacuo*. Such a treatment was repeated more than five times to remove completely excess hydrochloric acid. The resulting precipitates were washed with ether and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol gave various α-acylamino acid derivatives in good yields. The yields, physical properties, and elemental analyses of these compounds are listed in Table II.

Preparation of α-Benzoyl Alanine Methyl Ester Hydrochloride (6l).—To a mixture of DBU (6.0 g, 0.04 mol) and dimethylformamide (DMF, 40 ml) was added a mixture of methyl α-isocyanopropionate (3.39 g, 0.03 mol) and DMF (10 ml) at room temperature with stirring for a period of 10 min. After stirring was continued for 3 hr at the same temperature, benzoic anhydride (6.78 g, 0.03 mol) dissolved in DMF (10 ml) was added dropwise to the mixture for a period of 30 min at 30° with vigorous stirring. After the reaction mixture was stirred for 3 hr, water (100 ml) was added to the mixture under cooling and the solution was extracted with ethyl acetate (100 ml). The extract was washed with water (2 × 50 ml) and 10% sodium bicarbonate (2 × 30 ml) and dried over magnesium sulfate. After the solvent was removed, the residual oil was distilled under reduced pressure to afford methyl α-benzoyl-α-isocyanopropionate (**5**, R = Ph; R′ = CH_3; R″ = Me): bp 95–97° (0.15 mm); yield 4.2 g (65%); ir (film) 2120 (NC), 1750 (COOMe), 1700 cm^{-1} (CO); nmr (CCl_4) δ 8.10–7.70 (m, 5, aromatic H), 3.75 (s, 3, OCH_3), 1.88 (s, 3, CH_3).

Subsequently, the isocyano compound (2.17 g, 0.01 mol) was dissolved in 2 *N* methanolic hydrochloric acid solution (30 ml) and the solution was heated at 40° for 1 hr. After the reaction was over, the solvent and the excess hydrochloric acid were removed under reduced pressure below 30°. The obtainable crystals were washed with ethyl acetate and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol gave α-benzoylalanine methyl ester hydrochloride (**6l**): yield 2.4 g (quantitative); mp 154–155° dec; ir (Nujol) 1750 (COOMe), 1690 cm^{-1} (CO); nmr (DMSO-d_6) δ 9.50 (br, 3, $NH_2 \cdot HCl$), 8.00–7.50 (m, 5, aromatic H), 3.80 (s, 3, OCH_3), 1.90 (s, 3, CH_3).

A method using NaH was reported previously.[8] In a similar manner, several α-alkyl-α-*C*-acylamino acid ester hydrochlorides (**6l–u**) were prepared and these results are shown in Table III.

Typical Hydrolysis of α-*C*-Acylamino Acid Ester 6b to α-Amino Ketone Hydrochloride 7b (Step A).—α-Butyrylglycine ester hydrochloride (**6b**, 0.5 g, 0.0024 mol) was dissolved in 6 *N* hydrochloric acid (20 ml) and the solution was heated at 90–95° for 4 hr. After the reaction was over, the solution was removed under reduced pressure. The crystals were washed with ethyl acetate and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol afforded colorless leaflets: yield 0.29 g (90%); mp 172–174° dec; ir (Nujol) 1720 cm^{-1} (CO); nmr (DMSO-d_6) δ 8.50 (br, 3, $NH_2 \cdot HCl$), 3.88 (s, 2, CH_2), 2.52 (t, 2, CH_2), 1.50 m, 2, CH_2), 0.88 (t, 3, CH_3).

In a similar way, other α-amino ketone hydrochlorides (**7**) were prepared and these results are summarized in Table IV.

General Procedure for Preparation of α-Amino Ketone Hydrochlorides (7, R′ = H) from Oxazole Compounds (4) (Step B).—After a mixture of the oxazole compounds (**4**, 0.01 mol) and 6 *N* hydrochloric acid (30 ml) was heated at 95–100° for 5 hr, the solution was washed with benzene, treated with activated charcoal, and then evaporated *in vacuo*. The obtainable crystals were washed with ethyl acetate and collected by filtration. Recrystallization from a mixture of ethyl acetate and methanol afforded various α-amino ketone hydrochlorides (**7a–k**, R′ = H) in good yields as listed in Table IV. The physicochemical properties of the resulting products in this way agreed with those obtained by step A.

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Registry No.—**1** (R′ = H; R″ = Me), 105-34-0; **1** (R′ = H; R″ = Et), 105-56-6; **3** (R = Me), 108-24-7; **3** (R = Pr), 106-31-0; **3** (R = *i*-Bu), 1468-39-9; **3** (R = CH_2Ph), 1555-80-2; **3** (R = Ph), 93-97-0; **4a**, 41172-57-0; **4b**, 41172-58-1; **4c**, 41172-59-2; **4d**, 32998-96-2; **4e**, 41172-61-6; **4f**, 41172-62-7; **4g**, 38061-18-6; **4h**, 38061-19-7; **4i**, 38061-20-0; **4j**, 38061-21-2; **4k**, 38061-22-2; **5** (R = Ph; R′ = Me; R″ = Me), 41172-68-3; **5** (R = 3,4-methylenedioxy Ph; R′ = Me; R″ = Me), 41265-39-8; **5** (R = 3,4,5-trimethoxy Ph; R′ = Me; R″ = Me), 41172-69-4; **5** (R = Ph; R′ = Et; R″ = Me), 41172-70-7; **5** (R = 3,4-methylenedioxy Ph; R′ = Et; R″ = Me), 41172-71-8; **5** (R = 3,4,5-trimethoxy Ph; R′ = Et, R″ = Me), 41172-72-9; **5** (R = Ph; R′ = *i*-Pr; R″ = Me), 41172-73-0; **5** (R = 3,4-methylenedioxy Ph; R′ = *i*-Pr; R″ = Me), 41172-74-1; **5** (R = 3,4,5-trimethoxy Ph; R′ = *i*-Pr; R″ = Me), 41172-75-2; **5** (R = 2-naphthalene; R′ = *i*-Pr; R″ = Me), 41172-76-3; **6a**, 41172-77-4; **6b**, 41172-78-5; **6c**, 41172-79-6; **6d**, 38603-81-5; **6e**, 6317-41-5; **6f**, 41172-82-1; **6g**, 38061-23-3; **6h**, 38061-24-4; **6i**, 38061-25-5; **6j**, 38061-26-6; **6k**, 38061-27-7; **6l**, 40846-67-1; **6m**, 38061-28-8; **6n**, 38061-29-9; **6o**, 40846-68-2; **6p**, 40846-71-7; **6q**, 40846-74-0; **6r**, 38061-30-2; **6s**, 38061-31-3; **6t**, 40846-73-9; **6u**, 38061-32-4; **7a**, 7737-17-9; **7b**, 41172-98-9; **7c**, 21419-26-1; **7d**, 41173-00-6; **7g**, 5468-37-1; **7h**, 38061-34-6; **7i**, 38061-35-7; **7k**, 38061-36-8; **7m**, 38061-37-9; **7n**, 38061-38-0; **7r**, 33119-73-2; **7t**, 38061-40-4; succinic anhydride, 108-30-5; glutaric anhydride, 108-55-4; DBU, 6674-22-2.

Selective Hydrolysis of Dihydrocinnamate Ester Protecting Groups by α-Chymotrypsin. Further Studies on the Scope and Limitations of the Method

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Further examples of the preparative feasibility of exploiting the aromatic acyl group specificity of α-chymotrypsin as a useful addition to the methods of protecting group chemistry have been provided by studies on representative decalin and tropane acetate–dihydrocinnamate diesters. When the hydroxide-ion susceptibility of both ester functions is approximately equal, α-chymotrypsin catalysis exposes only the hydroxyl group protected as its dihydrocinnamate ester. On the other hand, when hydroxide-ion selectivity of hydrolysis is possible, enzymic hydrolysis of the dihydrocinnamate function can be used to complement or reverse the chemical specificity. The alcohol moiety binding site of the enzyme is hydrophobic in character and tolerates wide structural variations and the method appears applicable to a broad range of organic compounds provided that a marginal solubility in aqueous solutions is preserved. The approach seems most appropriate for alkaloids where partial conjugate acid formation can enhance the water solubility of the substrate. The mild, pH 7.8, conditions used are synthetically attractive since they minimize the problems of epimerization, isomerization, racemization, rearrangement, etc., often encountered during acid- or base-mediated hydrolyses of ester protecting groups.

In view of the increasing availability of purified enzymes and their immobilized derivatives, there can be little doubt that preparative exploitations of enzymes as selective and/or stereospecific catalysts of organic reactions will become far more widespread in the future. One of the areas in which the synthetic advantages of enzymatic catalysis has already been recognized is in the use of α-chymotrypsin to effect selective removal of aromatic amino acid and related acyl protecting groups from hydroxyl and amino functions of nucleosides.[1–4] Our preliminary studies[5] indicated that the method might be generally applicable and this communication provides further data on the scope and limitations of the technique when extended to mixed esters of other classes of organic compounds.

Choice and Syntheses of Some Representative Diols and their Esters.—In our initial survey,[5] it was found that, whereas simple acetate and dihydrocinnamate esters were hydrolyzed at almost equivalent rates by hydroxide ion,[6] α-chymotrypsin-catalyzed cleavage of the dihydrocinnamoyl moiety was achieved with complete specificity with acyclic acetate–dihydrocinnamate diesters. Accordingly, mixed diesters of this type were used to evaluate the preparative selectivity of α-chymotrypsin toward the dihydrocinnamoyl group in molecules of more general structural interest to organic chemists.

It was desired to evaluate the feasibility of achieving preferential removal of the α-chymotrypsin-sensitive acyl group from acetate dihydrocinnamates for which differences in the rates of chemical hydrolysis of each ester function were small or nonexistent. Alternatively, for compounds where preferential chemical cleavage of one ester group was possible, exploitation of α-chymotrypsin's specificity to reverse the chemical selectivity was the goal. Mixed esters of *trans*-decalin-1,6-diols and of tropane-3α,6β-diol appeared to satisfy most of the requirements for such evaluation and selected mixed ester derivatives were prepared as described below.

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