α,β-Unsaturated Carboxylic Acid Derivatives. VI. New Synthesis of *N*-Acyl-α-dehydroamino Acid Esters[1]

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A new synthetic route to α,β-unsaturated *N*-acyl-α-amino acid esters (*N*-acyl-α-dehydroamino acid esters) is described. The dehydroamino acid esters were prepared by the dehydration of α-(*N*-acylhydroxyamino) acid esters (**10**), derived from the acylation of α-hydroxyamino acid esters (**2** and **6**), and by the elimination of carboxylic acid from α-(*N*-acyl-*O*-acetyl), α-(*N,O*-diacetyl, dipropionyl and diethoxycarbonyl-hydroxyamino) acid esters, obtained by the acylation of **2**, **6** and **10**, in the presence of triethylamine.

It is known that synthetic methods of 2-(2-substituted-acetamino)-2-alkenoic acids,[2] *i.e.*, *N*-acyl-α-dehydroamino acids (**4** and **8**) were derived in the following ways. Greenstein *et al.* and Wieland *et al.* reported the preparation of several *N*-acyl-α-dehydroamino acids (**4**; free acid) by treating a mixture of α-oxocarboxylic acids and acetonitrile[3] or acetamide[4] with dry hydrogen chloride or concentrated sulfuric acid, respectively. However, the yields are low, and isolation and purification of the products is difficult.[3-5] A convenient synthesis of *N*-chloroacetyl-α-dehydroamino acid esters by the condensation of several ethyl α-oxocarboxylates with chloroacetamide in the presence of concentrated sulfuric acid or phosphoryl chloride was recently reported.[6]

Bergmann *et al.*[7] and other workers[8-10] described another preparative method of **4** *via* the corresponding 4-alkylidene and arylidene-2-substituted-oxazolones.

Shin *et al.* reported that compound **4** was obtained by acylation of β-substituted-α-amino-α-alkenoic acid esters obtained by the reduction of the corresponding nitroolefins or β-methoxy-α-nitro compound.[11]

This paper deals with another route for the preparation of *N*-acyl α-dehydroamino acid esters from the α-hydroxyamino acid esters (**2** and **6**) *via* α-(*N*-monoacylhydroxyamino) (**10**) and α-(*N,O*-diacylhydroxyamino) acid esters (**3** and **7**).

Results and Discussion

Preparation of 2 and 6. *t*-Butyl α-hydroxyamino carboxylates (**2**) were obtained by the reaction of *t*-butyl α-bromocarboxylates (**1**),[12] obtained by the esterification of the corresponding acid bromide with hydroxylamine in methanol in the presence of triethylamine in good yields. However, ethyl α-hydroxyamino carboxylates (**2**), which could not be obtained directly by the reaction of ethyl α-bromocarboxylates with hydroxylamine, were prepared by the esterification of the free α-hydroxyamino carboxylic acids (**2**; R^1=H)[13] obtained by the saponification of **2** (R^1=*t*-Bu) with concentrated hydrochloric acid.

By a method reported recently,[11b] ethyl 2-hydroxyamino-3-methoxy-3-phenylpropanoate (**6**) was prepared by the reduction of ethyl 3-methoxy-2-nitro-3-phenylpropanoate (**5**), derived from ethyl 2-nitrocinnamate and methanol in the presence of sodium methoxide, with aluminum-amalgam in ether at room temperature.

The IR spectra of the products (**2**) and (**6**) showed N–OH and N–H bands at 3450—3250 and 3275—3150 cm^{-1} regions. The results are summarized in Table 1.

Acylation of 2 and 6. Acylation of **2** and **6** was performed mainly by the following two routes. When an equimolar mixture of **2** or **6**, pyridine and acyl chloride was stirred in dry benzene at room temperature, the corresponding *N*-acyl derivatives (**10**) were obtained as crystals, together with a reddish syrup, which was confirmed to be the *O*-acyl isomers (**9**).[14]

Further acetylation of **10** with acetic anhydride at 100—110 °C for half an hour gave the corresponding *N,O*-diacyl derivatives (**3** and **7**) in good yields. These compounds were also obtained directly from **2** or **6** under similar conditions by use of more than 2 equimolar amounts of acid anhydride or ethyl chloroformate, respectively. Only the *N*-phthaloylglycyl-*O*-acetyl derivatives (**3** and **7**) were obtained as colorless needles or prisms.

Structures of the monoacyl (**9** and **10**) and diacyl derivatives (**3** and **7**) were characterized by elementary analysis and infrared spectrum. **10** showed deep violet coloration with methanolic ferric chloride. Isomerization of **9** to **10** even in the absence of alkali[14] at room temperature was confirmed by the coloration. The syrup (**9**) could not be isolated in a pure state. It showed a N–H band in the 3300—3100 cm^{-1} region, the absorption shifting towards 3450—3250 cm^{-1} region (OH band) with the progress of isomerization. The results are summarized in Tables 2 and 3.

Synthesis of N-*Acyl-α-dehydroamino Acid Esters.* Treatment of **3** or **7** with more than 2 equimolar amounts of triethylamine in dry benzene under reflux or at room temperature gave the expected α-dehydroamino acid esters (**4** and **8**) in pure state in good yields. It was found that **10** was directly dehydrated to give **4** in higher yield than in the above experiment, by refluxing in benzene for a longer time in the presence of triethylamine. Structures of these α-dehydroamino acid esters were confirmed by elementary analyses and their infrared absorption spectra which were similar to those of the α-dehydroamino derivatives obtained earlier.[5,6,9,11,15] The results are summarized in Table 4.

TABLE 1. ETHYL AND *t*-BUTYL α-HYDROXYAMINOALKANOATES (**2**) (R-CH_2-CH-$COOR^1$ / NHOH)

Substituents R	Substituents R^1	Yield (%)	mp °C (bp °C/mmHg)	Formula	Found, % C	Found, % H	Found, % N	Calcd, % C	Calcd, % H	Calcd, % N	IR Spectrum cm^{-1}, in KBr
H	*t*-Bu	98.0	70.5—71.5[a]	$C_7H_{15}NO_3$	52.43	9.42	8.57	52.15	9.38	8.69	3260, 3150, 1750
CH_3	Et	55.6	(80—82/2)[b]	$C_6H_{13}NO_3$	48.96	9.04	9.50	48.96	8.90	9.52	3450, 3275, 1740
CH_3	*t*-Bu	96.7	50—52[a]	$C_8H_{17}NO_3$	54.75	9.74	7.86	54.83	9.78	7.99	3260, 3150, 1740
C_2H_5	Et	74.5	(80—80.5/1)[b]	$C_7H_{15}NO_3$	52.21	9.30	8.63	52.15	9.38	8.69	3430, 3270, 1745
C_2H_5	*t*-Bu	97.4	65.5—69.0[a]	$C_9H_{19}NO_3$	57.33	10.17	7.40	57.11	10.12	7.40	3250, 3150, 1745
C_6H_5	Et	39.0	47.5—48.0[c][d]	$C_{11}H_{15}NO_3$	63.29	7.27	6.66	63.14	7.23	6.69	3250, 3200, 1735

a) Colorless needles from benzene and petroleum ether. b) Colorless viscous oil. c) Colorless needles from di-*n*-butyl ether. d) R^1=H, yield 75.0%, mp 150 °C (mp 156—157 °C).[16]

TABLE 2. ETHYL AND *t*-BUTYL α-(*N*-ACYLHYDROXYAMINO)ALKANOATES (**10**) (R-CH_2-CH-$COOR^1$ / N(OH)-CO-X)

Substituents R	Substituents R^1	Substituents X	Yield (%)	mp °C[b]	Formula	Found, % C	Found, % H	Found, % N	Calcd, % C	Calcd, % H	Calcd, % N	IR Spectrum cm^{-1}, in KBr
H	*t*-Bu	P. T[a]	61.5	149.5—150.0	$C_{17}H_{20}N_2O_6$	58.89	5.77	8.02	58.61	5.79	8.04	3260, 1740, 1660
CH_3	Et	P. T	81.4	118—119	$C_{16}H_{18}N_2O_6$	57.60	5.27	8.33	57.48	5.43	8.38	3160, 1735, 1645
CH_3	*t*-Bu	P. T	52.3	170.0—171.5	$C_{18}H_{22}N_2O_6$	59.76	6.06	7.73	59.66	6.12	7.73	3380, 1715, 1685
CH_3	*t*-Bu	C_6H_5	37.6	85—86	$C_{15}H_{21}NO_4$	64.73	7.80	4.99	64.49	7.58	5.01	3280, 1720, 1620
C_2H_5	Et	P. T	62.0	134—136	$C_{17}H_{20}N_2O_6$	58.97	5.65	8.06	58.61	5.79	8.04	3400, 1725, 1670
C_2H_5	*t*-Bu	P. T	22.1	149.5—150.5	$C_{19}H_{24}N_2O_6$	61.07	6.43	7.44	60.62	6.43	7.44	3400, 1715, 1685
C_6H_5	Et	P. T	26.4	143—145	$C_{21}H_{20}N_2O_6$	63.85	5.08	7.31	63.63	5.09	7.07	3300, 1725, 1670

a) P. T=Phthalyliminomethyl group. b) Colorless needles from benzene and petroleum ether.

Table 3. Ethyl and *t*-butyl α-(*N*,*O*-diacyl-hydroxyamino)alkanoates (**3**) $\left(\begin{array}{l} R\text{-}CH_2\text{-}CH\text{-}COOR^1 \\ \quad\quad\quad\quad | \\ \quad\quad\quad N\text{-}CO\text{-}X \\ \quad\quad\quad\quad | \\ \quad\quad\quad O\text{-}CO\text{-}Y \end{array}\right)$

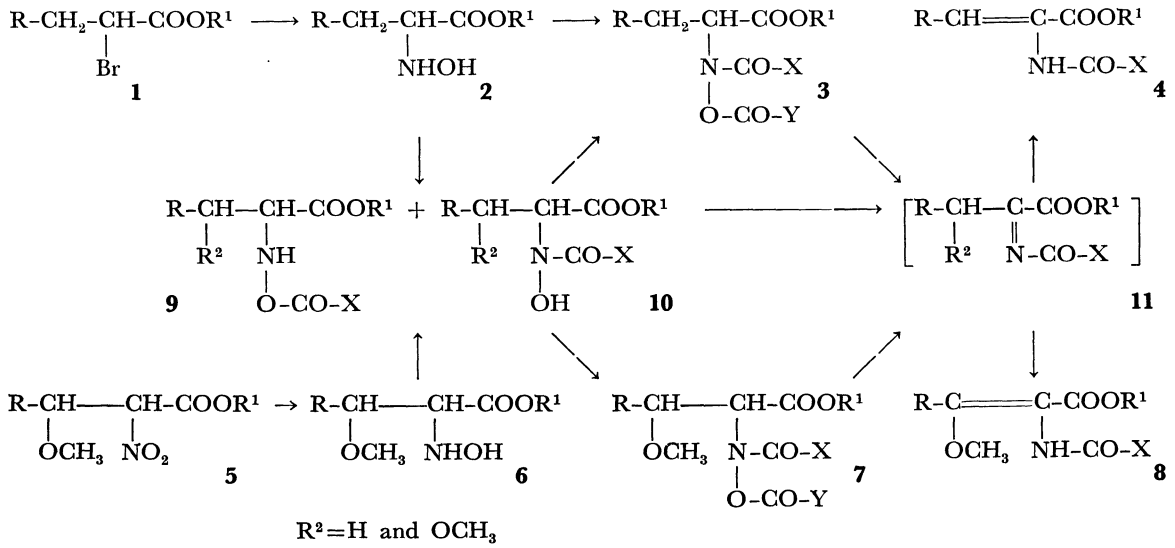
Substituents				Yield (%)	mp °C (bp °C/mmHg)	Formula	Found, %			Calcd, %			IR Spectrum cm^{-1}, in KBr
R	R^1	X	Y				C	H	N	C	H	N	
H	*t*-Eu	P. T[a]	CH_3	83.0	111—112[b]	$C_{19}H_{22}N_2O_7$	58.53	5.68	7.09	58.45	5.68	7.18	1800, 1730, 1705
CH_3	Et	P. T	CH_3	97.8	syrup[c]								1800, 1720
CH_3	*t*-Bu	P. T	CH_3	89.9	90.0—91.5[b]	$C_{20}H_{24}N_2O_7$	59.38	6.02	6.92	59.10	5.98	6.93	1805, 1725, 1685
CH_3	Et	P. T	CH_3	98.2	syrup[c]								1800, 1725
C_2H_5	*t*-Bu	P. T	CH_3	90.0	128—129[d]	$C_{21}H_{26}N_2O_7$	60.04	6.27	6.65	60.28	6.26	6.70	1800, 1730, 1700
C_2H_5	*t*-Bu	CH_3	CH_3	76.2	(114—115/1)[e]	$C_{13}H_{23}NO_5$	57.52	8.63	5.41	57.12	8.48	5.13	1800, 1740, 1700
C_2H_5	*t*-Bu	C_2H_5	C_2H_5	71.5	(123—128/3)[e]	$C_{15}H_{27}NO_5$			4.78			4.65	1800, 1740, 1700
C_2H_5	*t*-Bu	OC_2H_5	OC_2H_5	54.5	(123—126/3)[e]	$C_{15}H_{27}NO_7$			4.33			4.20	1800, 1740
C_6H_5	Et	P. T	CH_3	99.0	syrup[c]								1800, 1725

a) P. T=Phthalyliminomethyl group. b) Colorless needles from di-*n*-butyl ether. c) Unstable colorless syrup, structure of which was confirmed by means of IR spectra and conversion into compound **4**. d) Colorless tablets from di-*n*-butyl ether. e) Colorless oil.

Table 4. Ethyl and *t*-butyl *N*-acyl-α-amino-α-alkenoates (**4**) $\left(\begin{array}{l} R\text{-}CH{=}C\text{-}COOR^1 \\ \quad\quad\quad | \\ \quad\quad NH\text{-}CO\text{-}X \end{array}\right)$

Substituents			Yield (%)		mp °C (bp °C/mmHg)	Formula	Found, %			Calcd, %			IR Spectrum cm^{-1}, in KBr
R	R^1	X	A[a]	B[b]			C	H	N	C	H	N	
H	*t*-Bu	P. T[c]	87.5		194—195[d]	$C_{17}H_{18}N_2O_5$	61.59	5.42	8.44	61.81	5.49	8.48	3350, 1720, 1700
CH_3	Et	P. T	97.3		176—179[e]	$C_{16}H_{16}N_2O_5$	60.87	5.11	9.29	60.75	5.10	8.86	3250, 1730, 1680
CH_3	*t*-Bu	P. T	64.8	71.8	152—152.5[e]	$C_{18}H_{20}N_2O_5$	62.92	5.88	8.26	62.78	5.85	8.14	3170, 1740, 1675
C_2H_5	Et	P. T	84.5		173—174.5[e]	$C_{17}H_{18}N_2O_5$	61.71	5.57	8.48	61.81	5.49	8.48	3270, 1740, 1685
C_2H_5	*t*-Bu	CH_3	76.0	80.6	(136—138/3)[f]	$C_{11}H_{19}NO_3$	61.47	9.04	6.85	61.94	8.98	6.57	3260, 1730, 1670
C_2H_5	*t*-Bu	C_2H_5	82.6		(128—131/1)[f]	$C_{12}H_{21}NO_3$	62.77	9.19	5.77	63.11	9.31	6.16	3270, 1730, 1670
C_2H_5	*t*-Bu	OC_2H_5	86.8		(115—117/1)[f]	$C_{12}H_{21}NO_4$			5.68			5.76	3330, 1730, 1670
C_2H_5	*t*-Bu	P. T	93.4		124—126[e]	$C_{19}H_{22}N_2O_5$			7.83			7.82	3260, 1730, 1685
C_6H_5	Et	P. T	92.5		191—193[e]	$C_{21}H_{18}N_2O_5$	66.75	4.89	7.55	66.66	4.80	7.40	3260, 1725, 1690

a) From compound **3**. b) From compound **10**. c) P. T=Phthalyliminomethyl group. d) Colorless prisms from glacial acetic acid. Decomposition. e) Colorless needles from ethanol and water. f) Colorless viscous oil.



Scheme 1

Conversion of **3**, **7** and **10** into **4**, **8** and **4**, respectively, is deduced to proceed through the corresponding *N*-acyl-α-imino intermediate (**11**), which subsequently isomerizes to a more stable form.[15] This is supported by the fact that ethyl α-(*N*-acyl-hydroxyamino)-β-methoxycarboxylates react with ethanolic ammonia to afford 4-imidazolidone derivatives instead of the expected 2,5-piperazinedione derivatives[14] and that chloroacetylation of ethyl 2-imino-3-methylbutanoate gives the isomerized compound; ethyl 2-(2-chloroacetamido)-3-methyl-2-butanoate.[15]

Experimental

All boiling and melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-S2 Spectrometer.

Material. Ethyl 3-methoxy-2-nitro-3-phenylpropanoate (**5**) was prepared by the method reported.[11b] Yield 91.6%, colorless prisms from benzene and petroleum ether, mp 81—83 °C. IR(KBr): 1760, 1565, 1380 cm^{-1}. Found: C, 57.01; H, 6.17; N, 5.46%. Calcd for $C_{12}H_{15}NO_5$: C, 56.71; H, 5.97; N, 5.53%.

*t-Butyl α-Bromoalkanoates (**1**).* α-Bromoalkanoic acid bromide (0.443 mol) was added dropwise, with stirring, to a mixture of pyridine (0.447 mol) and *t*-butyl alcohol (120 ml) at a temperature below 30 °C. After being stirred at room temperature for 6 hr, the reaction mixture was allowed to stand overnight at room temperature. After removal of the pyridinium salt separated out, benzene (300 ml) was added to the resulting solution, which was washed successively with water, 3M-hydrochloric acid twice, saturated aqueous solution of sodium hydrogen carbonate and then finally with water. The benzene layer was dried over anhydrous magnesium sulfate and then evaporated. The residual oil was distilled under reduced pressure to give colorless oil. *t*-Butyl 2-bromopropanoate, yield 87.1%, bp 64—65 °C/18 mmHg (bp 62 °C/13 mmHg).[12] *t*-Butyl 2-bromobutanoate, yield 86.7%, bp 71—75 °C/12 mmHg. Found: C, 43.51; H, 6.55%. Calcd for $C_8H_{15}O_2Br$: C, 43.32; H, 6.73%. *t*-Butyl 2-bromopentanoate, yield 84.0%, bp 98—100 °C/19 mmHg. Found: C, 45.77; H, 6.98%. Calcd for $C_9H_{17}O_2Br$: C, 45.57; H, 7.18%.

*t-Butyl α-Hydroxyaminoalkanoates (**2**).* When a solution of **1** (0.37 mol), hydroxylamine (made from hydroxylamine hydrochloride (0.41 mol) and sodium (0.41 mol)) and triethylamine (0.37 mol) in methanol (300 ml) was refluxed for 30 hr and then evaporated, a residual syrup was obtained. After addition of dry ether (300 ml) to the syrup and removal of the triethylamine hydrogen bromide separated out, the ether layer was evaporated to give a residual syrup, which was gradually crystallized or distilled under reduced pressure. The results are summarized in Table 1.

*α-Hydroxyaminoalkanoic Acids (**2**; $R^1=H$).* *t*-Butyl α-hydroxyaminoalkanoate (**2**; 0.246 mol) was dissolved in concentrated hydrochloric acid (350 ml) and then the solution was allowed to stand at room temperature for a day. After evaporation of the reaction solution under reduced pressure, the acidic residual syrup was dissolved in water (30 ml) and maintained within the pH range 6—7 with concentrated aqueous ammonia. After being allowed to stand overnight in a refrigerator, the colorless crystals separated out were collected and then washed with cold water. Recrystallization from water gave colorless prisms. 2-Hydroxyaminobutanoic acid, yield 78.0%, mp 189—191 °C (mp 193—194 °C).[13] 2-Hydroxyaminopentanoic acid, yield 78.3%, mp 192—194 °C (mp 194—195 °C).[13]

*Ethyl α-Hydroxyaminoalkanoates (**2**; $R^1=Et$).* When concentrated sulfuric acid (40 ml) was added dropwise, with stirring, to a suspension of **2** ($R^1=H$, 0.125 mol) in ethanol (100 ml) under cooling, the crystals gradually dissolved. The solution was allowed to stand at room temperature for two days and poured into ice water (200 ml) and then neutralized with solid sodium bicarbonate. After extraction of the reaction solution with ether several times, the ether extracts were washed with water and then dried over anhydrous magnesium sulfate. After concentration of the extracts, the residual syrup was distilled under reduced pressure to give pale yellow oil (See Table 1).

*Ethyl 2-Hydroxyamino-3-methoxy-3-phenylpropanoate (**6**).* This compound was prepared by the reduction of **5** according to the method reported.[11b] Recrystallization from benzene and petroleum ether gave colorless prisms, yield 28.9%, mp 84—85 °C. IR(KBr): 3400, 3250, 1738 cm^{-1}. Found: C, 60.66; H, 7.20; N, 6.03%. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85%.

*Ethyl and t-Butyl α-(N-Acyl-hydroxyamino)alkanoates (**10**).* To a solution of **2** (0.0272 mol) and pyridine (0.0272 mol) in dry benzene (40 ml) was added with stirring a solution of appropriate acyl chloride (0.0272 mol) in dry benzene (15 ml)

dropwise at room temperature. After stirring for several hours, the resulting benzene layer was washed successively with water, aqueous solution of sodium hydrogen carbonate, 3M-hydrochloric acid and then finally with water. The benzene solution was dried over anhydrous magnesium sulfate and then evaporated. The residual crystals were collected, washed with water and then recrystallized. The results are summarized in Table 2.

Reaction of **6** *with Phthaloylglycyl Chloride.* To a solution of **6** (0.0083 mol) and pyridine (0.0087 mol) in dry benzene (20 ml) was added with stirring a solution of phthaloylglycyl chloride (0.0092 mol) in dry benzene (10 ml) dropwise at room temperature. After stirring for several hours, crystals separated out were collected and washed with water. Recrystallization from ethanol gave colorless needles, which were identified as ethyl 3-methoxy-3-phenyl-2-(*N*-phthaloylglycylhydroxyamino)propanoate (**10**), yield 65.1%, mp 170—172 °C. IR (KBr): 3300, 1700, 1664 cm^{-1}. Found: C, 62.25; H, 5.05; N, 6.76%. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.96; H, 5.20; N, 6.57%.

The benzene filtrate was washed successively with water, 3M-hydrochloric acid and with water, and dried over anhydrous magnesium sulfate and then evaporated. The residual oil was chromatographied on silica-gel column with benzene and the effluent was condensed under reduced pressure to give a pale yellow syrup, which was identified as ethyl 3-methoxy-3-phenyl-2-(*O*-phthaloylglycylhydroxyamino)propanoate (**9**), yield 8.5%. IR(KBr disk): 3250, 1730 cm^{-1}. Found: C, 62.31; H, 5.29; N, 6.38%. Calcd for $C_{22}H_{22}N_2O_7$: C, 61.96; H, 5.20; N, 6.57%.

t-*Butyl 2-(*N,O-*Diacetyl- or Dipropionyl-hydroxyamino)pentanoate (***3***;* R^1*=Et).* A mixture of *t*-butyl 2-hydroxyaminopentanoate (0.053 mol) and appropriate acid anhydride (27 ml) was heated at 100—110 °C for half an hour. After concentration of the reaction solution under reduced pressure, the residual syrup was distilled under reduced pressure to give colorless oil (See Table 3).

t-*Butyl 2-(*N,O-*Diethoxycarbonylhydroxyamino)pentanoate (***3***;* R^1*=Et).* To a solution of *t*-butyl 2-hydroxyaminopentanoate (0.0265 mol) and pyridine (0.053 mol) in dry benzene (40 ml) was added dropwise with stirring a solution of ethyl chloroformate (0.053 mol) in dry benzene (10 ml) at room temperature. After stirring for 3 hr and removal of pyridinium salt separated out, the benzene layer was concentrated to give a syrup. The syrup was distilled under reduced pressure to give colorless oil (See Table 3).

Ethyl and t-*Butyl* α-*(*O-*Acetyl-*N-*phthaloylglycyl-hydroxyamino)-alkanoates (***3***) and Ethyl 3-Methoxy-3-phenyl-2-(*O-*acetyl-*N-*phthaloylglycylhydroxyamino)-propanoate (***7***).* A mixture of **10** (0.00585 mol) and acetic anhydride (22 ml) was heated at 100—110 °C for half an hour. After concentration of the reaction solution under reduced pressure, a viscous syrup, which was gradually crystallized, or crystals were obtained. The results are summarized in Table 3. Ethyl 3-methoxy-3-phenyl-2-(*O*-acetyl-*N*-phthaloylglycyl-hydroxyamino)propanoate (**7**) was also obtained in 45.5% yield as colorless needles from ethanol, mp 124—126 °C. IR(KBr): 1800, 1720 cm^{-1}. Found: C, 61.34; H, 5.15; N, 6.07%. Calcd for $C_{24}H_{24}N_2O_8$: C, 61.53; H, 5.16; N, 5.98%.

Ethyl and t-*Butyl* N-*Acyl-*α*-amino-*α*-alkenoates (***4***).* *a) From 3*: A solution of **3** (0.0011 mol) and triethylamine (0.0026 mol) in dry benzene (10 ml) was stirred at room temperature for 24 hr. After being allowed to stand at room temperature for over a day, the reaction solution was neutralized by 3M-hydrochloric acid and washed with water and then dried over anhydrous magnesium sulfate. Evaporation of the benzene layer under reduced pressure gave colorless crystals or syrup. The results are summarized in Table 4.

b) From ***10***: When a solution of **10** and triethylamine in dry benzene was refluxed for 12 hr in an analogous manner to the case of **3**, compound **4** was obtained in good yield (See Table 4).

*Ethyl 3-Methoxy-3-phenyl-2-(*N*-phthaloylglycylamino)-2-propenoate (***8***).* In an analogous manner to the case of **3**, compound **7** was treated with triethylamine to give compound **8** in 87.5% yield as colorless needles from benzene, mp 178—179 °C. IR(KBr): 3250, 1725, 1660 cm^{-1}. Found: C, 64.76; H, 4.96; N, 6.89%. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86%.

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