Synthesis of N-[1-(1-Substituted 2-oxopropyl)]acrylamides and -methacrylamides. Isolation and Some Reactions of Intermediates of the Dakin–West Reaction

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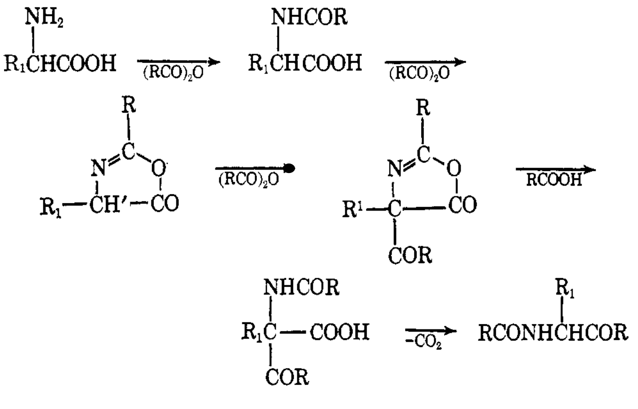
The Dakin–West reaction of N-methacryloyl-α-amino acids was carried out at a low temperature, and the intermediates of this reaction, 4-acetyl-5-oxazolones (III), which had been presumed but had never been obtained, were isolated. Some reactions of these intermediates were studied. The reaction with acetic acid in pyridine gave N-acyl-α-amino ketones, N-[1-(1-substituted 2-oxopropyl)]methacrylamides (VII), which were the usual products of the Dakin–West reaction, and some by-products. From the results, the mechanism of the reaction was discussed. The reaction of compounds III with aniline yielded N-methacryloyl-α-amino acid anilides (VIII) and acetanilide. In the case of N-acryloyl-α-amino acids, the intermediates could not be isolated, and final products (VII) were obtained. The compounds (VII) were also prepared by the reaction of α-amino ketone hydrochlorides with acid chlorides in the presence of alkali.

The Dakin–West reaction[1] consists in the synthesis of N-acyl-α-amino ketones by treatment of α-amino acids or N-acyl-α-amino acids[2] with acid anhydrides under the catalytic influence of a base such as pyridine.

A number of studies[1–5] have been made of the mechanism of this reaction. The most probable mechanism involves azlactonization of N-acyl-α-amino acid first formed, base-catalyzed acylation at the reactive 4 position, cleavage to β-keto acid, and decarboxylation to N-acyl-α-amino ketone. This mechanism is well known, but no 4-acetyl-5-oxazolones have been isolated in this reaction and the step involving the cleavage of 4-acetyl-5-oxazolone to β-keto acid had been hypothetical. (See Chart I.)

CHART I



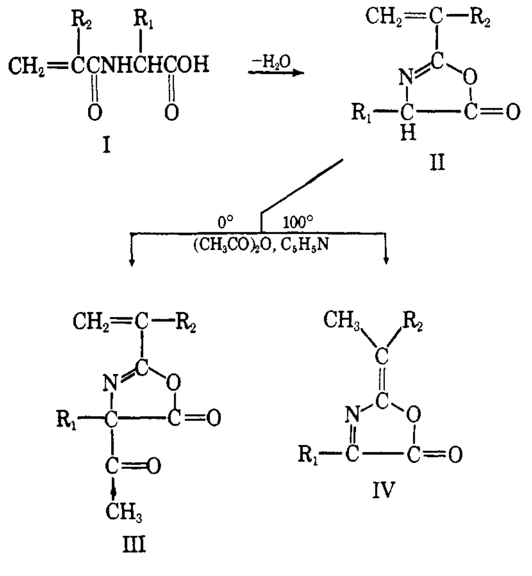
In this investigation, this type of reaction was carried out under various conditions using N-acryloyl-α-amino acids and N-methacryloyl-α-amino acids as starting materials for the purpose of the preparation of new monomers for polymer synthesis. In the reaction of N-methacryloyl-α-amino acids, the intermediates of this reaction, 2-isopropenyl-4-acetyl-5-oxazolones, were isolated. The isolation and some reactions of these intermediates provide information about the mechanism of the Dakin–West reaction.

Results and Discussion

The acylation of α-amino acids, DL-alanine, DL-leucine, DL-phenylalanine, and DL-valine, was accomplished by treatment with acryloyl chloride and with methacryloyl chloride in the presence of sodium hydroxide- The melting points, yields, and analyses of the N-acyl. α-amino acids (I) are shown in Table I.

First, according to Carter's method,[6] methacryloylalanine (Ia) was treated with an equal amount of acetic anhydride in pyridine under cooling for the purpose of the preparation of 2-isopropenyl-5-oxazolone (IIa). However, only a small amount of a product, which was not IIa, was obtained. This product was identified as 2-isopropenyl-4-methyl-4-acetyl-2-oxazolin-5-one (IIIa). Attempts to increase the yield were attempted under various conditions. The reaction carried out at 100° afforded no 4-acetyl-5-oxazolones (III), but rather the isomerized 5-oxazolones (IV, 2-alkylidene-4-substituted 3-oxazolin-5-ones) in high yield[7] (Chart II). These compounds (IV), formed by migration of double bonds in oxazolones of type II, were not affected by the further action of acetic anhydride in pyridine. The reaction at 50° gave about equal amounts of 4-acetyl-5-oxazolones (III) and isomerized 5-oxazolones (IV). The reaction of N-methacryloylamino acids (except methacryloylvaline) with excess acetic anhydride in pyridine at 0° gave rise to 4-acetyl-5-oxazolones (III, 2-isopropenyl-4-

CHART



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[1] H. D. Dakin and R. West, *J. Biol. Chem.*, **78**, 91, 745, 757 (1928).

[2] S. Searles and G. J. Cvejanovich, *J. Am. Chem. Soc.*, **72**, 3200 (1950).

[3] G. H. Cleland and C. Niemann, *ibid.*, **71**, 841 (1949).

[4] R. H. Wiley, *Science*, **111**, 259 (1950).

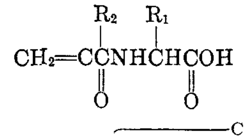
[5] J. W. Cornforth and D. F. Elliott, *ibid.*, **112**, 534 (1950).

[6] H. E. Carter, P. Handler, and D. B. Melville, *J. Biol. Chem.*, **129**, 359 (1939).

[7] Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron Letters*, 4427 (1966).

TABLE I

N-ACYL-α-AMINO ACIDS (I)



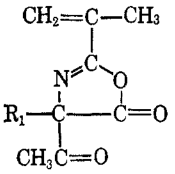
$CH_2{=}\overset{\overset{R_2}{|}}{C}\underset{\underset{O}{\|}}{C}NH\overset{\overset{R_1}{|}}{C}H\underset{\underset{O}{\|}}{C}OH$

Substituents		Yield,	Mp,		Calcd, %			Found, %		
R_1	R_2	%	°C	Formula	C	H	N	C	H	N
CH_3	H	65	130	$C_6H_9NO_3$	50.34	6.34	9.79	50.23	6.40	9.59
CH_3	CH_3	70	118	$C_7H_{11}NO_3$	[a]					
$C_2H_3(CH_3)_2$	H	90	82	$C_9H_{15}NO_3$	58.36	8.16	7.56	58.12	7.95	7.54
$C_2H_3(CH_3)_2$	CH_3	90	106	$C_{10}H_{17}NO_3$	[a]					
$CH_2C_6H_5$	H	75	119	$C_{12}H_{13}NO_3$	65.74	5.98	6.39	65.62	6.10	6.22
$CH_2C_6H_5$	CH_3	80	104	$C_{13}H_{15}NO_3$	66.93	6.48	6.01	67.20	6.22	6.32
$CH(CH_3)_2$	CH_3	75	102	$C_9H_{15}NO_3$	[b]					

[a] Y. Iwakura, F. Toda, and Y. Torii, *J. Org. Chem.*, **31**, 2875 (1966). [b] J. W. Lynn, *ibid.*, **24**, 1030 (1959).

TABLE II

2-ISOPROPENYL-4-SUBSTITUTED 4-ACETYL-2-OXAZOLIN-5-ONES (III)



Substituent	Yield,	Bp, °C		Calcd, %			Found, %		
R_1	%	(mm)	Formula	C	H	N	C	H	N
CH_3	80	79 (0.15)	$C_9H_{11}NO_3$	59.66	6.12	7.73	59.95	6.36	7.97
$C_2H_3(CH_3)_2$	76	92 (1)	$C_{12}H_{17}NO_3$	64.55	7.68	6.27	64.48	7.58	6.42
$CH_2C_6H_5$	78	130 (1)	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	70.47	5.94	5.53

substituted 4-acetyl-2-oxazolin-5-ones) in *ca.* 80% yields in the other three cases. The reaction of methacryloylvaline gave no 4-acetyl-5-oxazolone (III), but gave 2-isopropenyl-4-isopropyl-5-oxazolone (II). Under such mild conditions, the steric hindrance of the isopropyl group would prevent the acetylation of C-4.

The structures of the 4-acetyl-5-oxazolones (III) were confirmed by elemental analyses and infrared spectral data described in the Experimental Section. The yields, boiling points, and elemental analyses of these 4-acetyl-5-oxazolones (III) are given in Table II.

These compounds (III) had been presumed as the intermediates of the Dakin–West reaction, but had never been isolated. The isolation of the intermediates lends conclusive support to the mechanism involving the base-catalyzed acylation of oxazolone type (II).

4-Acetyl-5-oxazolones (III) were readily converted into N-methacryloyl-α-amino ketones (VII) by heating with acetic acid in pyridine, the reaction being accompanied by the evolution of carbon dioxide. However, the reaction of the isobutyl derivative (IIIb) gave rise to an equal amount of a by-product, isomerized 5-oxazolone IVb, owing to elimination of the acetyl group and isomerization of IIb. The elimination reaction of the acetyl group would be promoted by the steric hindrance of the substituent R_1 at C-4. Actually, only a small amount of isomerized 5-oxazolone IVa was obtained in the reaction of 4-methyl derivative (IIIa). The 4-acetyl-5-oxazolones (III) have two reactive sites (A and B), which are susceptible to nucleophilic attack. When acetate anion attacks site A, the elimination of the acetyl group at the 4 position would occur, and oxazolone of type II and acetic anhydride would be re-formed. On the other hand, a mixed acid anhydride (V) would be afforded when base-catalyzed nucleophilic addition to the site B takes place. This mixed acid anhydride (V) would react with acetic acid at once, and would be converted into acetic anhydride and a β-keto acid (VI), followed by decarboxylation to the N-acyl-α-amino ketone (VII). (See Chart III.)

From the formation of the by-product resulting from the elimination of acetyl group and the isomerization, it can be considered that there is an equilibrium shown in Chart IV.

Rondestvedt and his co-workers[8] have indicated stoichiometrically the requirement of 3 moles of acetic anhydride in the Dakin–West reaction of α-amino acid, and have rejected the mechanism involving the re-formation of acetic anhydride. However, the equilibrium described above would not shift sufficiently to the right without the presence of an excess amount of acetic anhydride.

In order to increase the yields of N-acyl-α-amino ketones (VII), the reaction of 4-acetyl-5-oxazolones (III) with acetic acid in the presence of acetic anhydride was carried out. This method gave N-acyl-α-amino ketones (VII) in high yield. Occasionally, a small amount of isomerized 5-oxazolone (IV) was also formed, but in many cases its formation could not even be detected. From the results, N-acyl-α-amino ketones (VII) can also be prepared without isolation of 4-acetyl-5-oxazolones (III) by heating the reaction mixture after the acetylation at a low temperature.

The reaction of 4-acetyl-5-oxazolones (III) with excess aniline yielded N-methacryloyl-α-amino acid anilides (VIII) and acetanilide, since the nucleophilic attack of aniline took place at the both sites because of its stronger nucleophilicity. These compounds (VIII)

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[8] C. S. Rondestvedt, Jr., B. Manning, and S. Tabibian, *J. Am. Chem. Soc.*, **72**, 3183 (1950).

CHART III

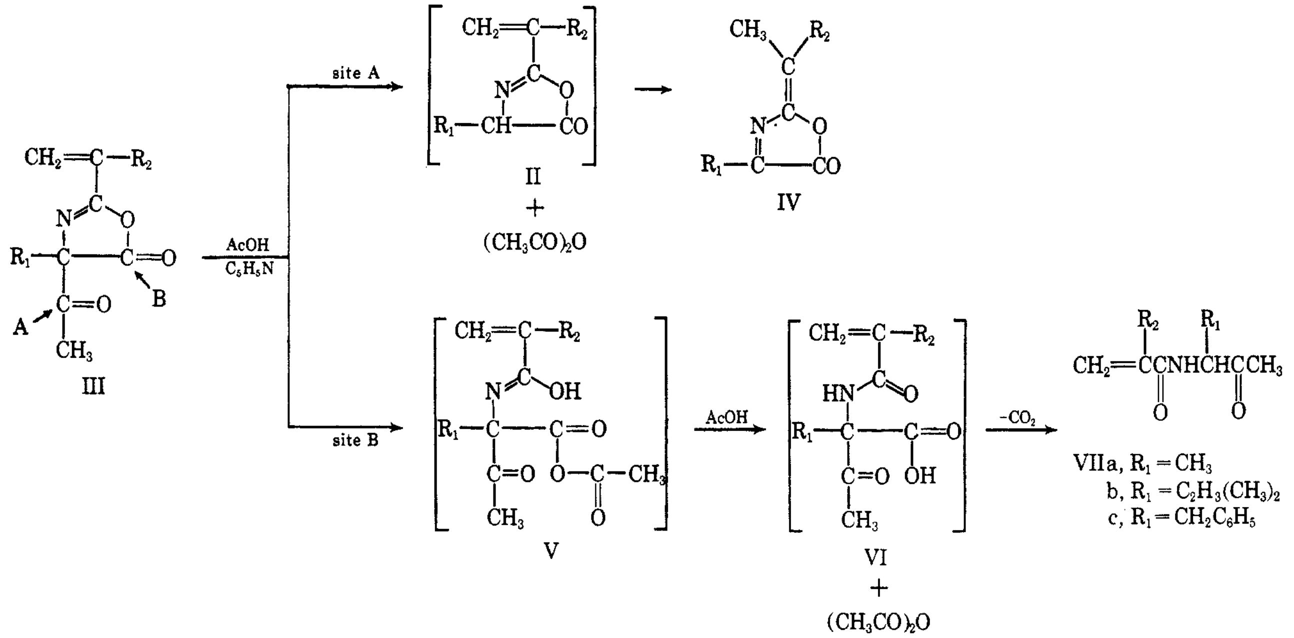
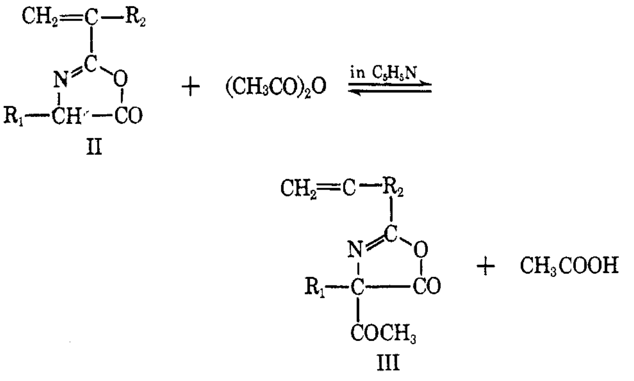
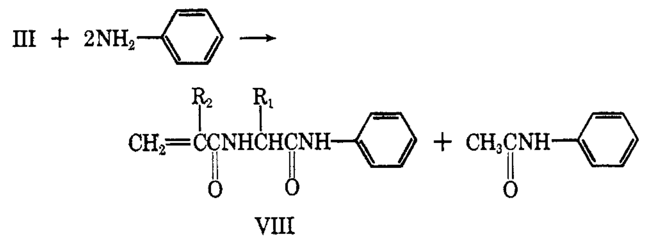


CHART IV



were identified by the complete agreement of the melting points and infrared spectra with those of compounds which were obtained in the reaction of 2-isopropenyl-5-oxazolones with aniline.[7]



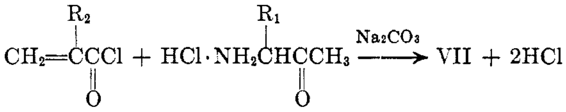
VIII

The Dakin-West reaction of N-acryloyl-α-amino acids gave no 4-acetyl-5-oxazolones (III), but gave N-acryloyl-α-amino ketones (VII). In this case, 2-vinyl-4-acetyl-5-oxazolones would be formed initially, but are probably so unstable that when the cooling is stopped decarboxylative decomposition would occur at once to yield N-acryloyl-α-amino ketones (VII). In fact, the evolution of carbon dioxide from the reaction mixture was observed even at a low temperature.

Acylated glycine, DL-valine, and DL-phenylglycine were also applied as starting materials, but neither 4-acetyl-5-oxazolones (III) nor N-acyl-α-amino ketones (VII) were obtained. In the case of glycine, only a resinous product was obtained. This might be due to the occurrence of the isomerization of oxazolone type II once formed under a mild condition, followed by the rapid polymerization. The steric hindrance of R_1 of valine and phenylglycine would prevent the acetylation of C-4 under a mild condition under which the isomerization of 5-oxazolones II does not take place.

The structures of the ketones (VII) were confirmed by elemental analyses and infrared spectral data described in the Experimental Section. The presence of a ketone group was confirmed by the formation of hydrazones by treatment with 2,4-dinitrophenylhydrazine.

N-[1-(1-Substituted 2-oxopropyl)]acrylamides and -methacrylamides (VII) were also prepared by the Schotten–Baumann reaction of α-amino ketone hydrochlorides with corresponding acid chlorides. This method can be used for compounds which cannot be prepared by the Dakin–West procedure, but the yields are generally low because of the formation of the byproduct, 2,5-dimethyl-3,6-disubstituted pyrazine, which arises by the dimerization of α-amino ketone hydrochloride in the influence of alkali. The compounds



$$\mathrm{CH_2{=}\overset{R_2}{C}\underset{\overset{\|}{O}}{C}Cl + HCl\cdot NH_2\overset{R_1}{C}H\underset{\overset{\|}{O}}{C}CH_3 \xrightarrow{Na_2CO_3} VII + 2HCl}$$

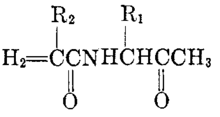
(VII) prepared by the latter method were identified by the complete agreement of the physical properties and infrared spectra with those of the compounds yielded by the former procedure.

Experimental Section

Acylation of α-Amino Acids.—One-half mole of α-amino acid (DL-alanine, DL-leucine, and DL-phenylalanine) and 80 g of sodium hydroxide were dissolved in 200 ml of water. To this solution, an equimolar amount of acryloyl chloride or methacryloyl chloride was added dropwise under cooling in an ice bath during 1 hr while the reaction temperature was maintained at 0 to 10°. After the addition was completed, stirring was continued for 1 additional hr. The mixture was neutralized with 85 ml of concentrated HCl. The precipitated product was filtered with suc-

TABLE III

N-[1-(1-SUBSTITUTED 2-OXOPROPYL)]ACYLAMIDES (VII)



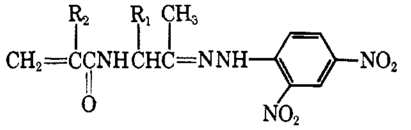
$$CH_2{=}\overset{R_2}{\overset{|}{C}}\underset{\underset{O}{\|}}{C}NH\overset{R_1}{\overset{|}{C}}H\underset{\underset{O}{\|}}{C}CH_3$$

Substituents		Yield, %[a]		Bp, °C	Mp,		Calcd, %			Found, %		
R_1	R_2	A	B	(mm)	°C	Formula	C	H	N	C	H	N
H	H	0	20	110 (1)	...	$C_6H_9NO_2$	56.68	7.14	11.02	56.95	7.43	11.23
H	CH_3	0	18	110 (2)	...	$C_7H_{11}NO_2$	59.55	7.95	9.92	59.71	8.21	10.11
CH_3	H	62	45	115 (4)	64	$C_7H_{11}NO_2$	59.55	7.95	9.92	59.60	8.19	10.06
CH_3	CH_3	78	55	95 (2)	35	$C_8H_{13}NO_2$	62.20	7.85	9.08	61.92	8.08	9.08
$C_2H_3(CH_3)_2$	H	65		137 (2)	45	$C_{10}H_{17}NO_2$	65.54	9.35	7.64	65.50	9.18	7.44
$C_2H_3(CH_3)_2$	CH_3	72		121 (2)	43	$C_{11}H_{19}NO_2$	66.97	9.71	7.10	66.58	9.52	6.82
$CH_2C_6H_5$	H	60	75	...	130	$C_{13}H_{15}NO_2$	71.86	6.96	6.45	71.94	6.89	6.61
$CH_2C_6H_5$	CH_3	90	80	...	92	$C_{14}H_{17}NO_2$	72.70	7.41	6.06	72.75	7.28	6.31

[a] A, by the Dakin-West reaction; B, by the Schotten-Baumann reaction.

TABLE IV

2,4-DINITROPHENYLHYDRAZONES OF VII



Substituents		Mp,		Calcd, %			Found, %		
R_1	R_2	°C	Formula	C	H	N	C	H	N
H	H	141	$C_{12}H_{10}N_5O_5$	46.90	4.26	22.80	46.70	4.60	22.68
H	CH_3	168	$C_{13}H_{15}N_5O_5$	48.59	4.77	21.80	48.74	5.05	21.77
CH_3	H	158	$C_{13}H_{15}N_5O_5$	48.59	4.77	21.80	48.80	4.75	21.60
CH_3	CH_3	159	$C_{14}H_{17}N_5O_5$	50.14	5.11	20.89	50.21	5.18	21.05
$C_2H_3(CH_3)_2$	H	180	$C_{16}H_{21}N_5O_5$	52.88	5.83	19.28	52.75	5.82	19.16
$C_2H_3(CH_3)_2$	CH_3	194	$C_{17}H_{23}N_5O_5$	54.10	6.14	18.50	54.17	6.41	18.57
$CH_2C_6H_5$	H	208	$C_{19}H_{19}N_5O_5$	57.42	4.82	17.63	57.63	5.00	17.56
$CH_2C_6H_5$	CH_3	185	$C_{20}H_{21}N_5O_5$	58.38	5.15	17.02	58.34	5.08	17.28

tion and purified by recrystallization from water (N-acryloyl derivative) or benzene (N-methacryloyl derivative).

The yields, melting points, and elemental analyses of these N-acyl-α-amino acids are shown in Table I.

Isolation of 4-Acetyl-5-oxazolones (III).—A stirred solution of 0.25 mole of N-acyl-α-amino acid (I) in 200 ml of pyridine was treated dropwise with 200 ml of acetic anhydride under cooling in an ice bath. After the addition, stirring was continued for 4 hr while the temperature was kept at 0 to 10°. Then pyridine, excess acetic anhydride, and acetic acid, which had been formed by the reaction, were carefully removed under reduced pressure, and the residual reaction product was distilled under highly reduced pressure to give the pure substance, 2-isopropenyl-4-substituted 4-acetyl-2-oxazolin-5-one (III). These compounds have some typical infrared absorptions at 1830, 1720, 1660, and 1600 cm^{-1}, corresponding to $\nu_{C=O}$ (carbonyl in the cyclic system), $\nu_{C=O}$ (ketone), $\nu_{C=N}$, and $\nu_{C=C}$ respectively. The yields, boiling points, and elemental analyses are shown in Table II.

Reaction of 4-Acetyl-5-oxazolones (III) with Aniline.—The mixture of 4-acetyl-5-oxazolone (III) and an excess amount of aniline was allowed to stand at a room temperature, until the reaction product precipitated. The product was filtered with suction and recrystallized from alcohol to give the purified N-methacryloyl-α-amino acid anilide (VIII).

The melting point and nitrogen analysis of each derivative obtained are as given below.

Alanine derivative had mp 154°. *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: N, 12.10. Found: N, 12.10.

Leucine derivative had mp 175°. *Anal.* Calcd for $C_{16}H_{22}N_2O_2$: N, 10.21. Found: N, 10.57.

Phenylalanine derivative had mp 170°. *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: N, 9.09. Found: N, 8.89.

Preparation of N-[1-(1-Substituted 2-oxopropyl)]acrylamides and -methacrylamides (VII). A. The Dakin-West Reaction.—The procedure was the same one used in the preparation of 4-acetyl-5-oxazolones (III). The reaction of N-acryloyl-α-amino acids, however, required a longer reaction period (*ca.* 8 hr) because of their lower reactivities. After the acetylation of 5-oxazolone was completed, the reaction temperature was raised to 100°, and stirring was continued for an additional 1 hr. After the evolution of carbon dioxide ceased, pyridine, acetic anhydride, and acetic acid were removed under reduced pressure. The residual product was purified by distillation or recrystallization (phenylalanine derivative).

B. The Schotten-Baumann Reaction.—To a vigorously stirred, aqueous solution of α-amino ketone hydrochloride, equimolar amounts of corresponding acid chloride in ether and aqueous solution of sodium carbonate were added dropwise under cooling in an ice bath. After the addition, stirring was continued for 1 hr. In the case of aminoacetone hydrochloride[9] and 2-aminobutan-3-one hydrochloride[10] as starting materials, the reaction products were extracted with three portions of diethyl ether. The extracted solution were dried over anhydrous sodium sulfate. After the removal of ether, the products were distilled under reduced pressure. In the reaction of 1-phenyl-2-aminobutan-3-one hydrochloride,[11] the precipitated product was filtered with suction and recrystallized from water to give the pure substance.

These compounds (VII) show some typical infrared absorption bands at 3300, 1720, 1660, 1620, and 1520 cm^{-1} characteristic of ν_{NH}, $\nu_{C=O}$ (ketone), $\nu_{C=O}$ (amide), $\nu_{C=C}$, and so-called amide band II, respectively. The yields by both methods, physical properties, and elemental analyses of these compounds (VII) are summarized in Table III.

2,4-Dinitrophenylhydrazones of VII.—N-Acyl-α-amino ketone (VII) was heated with an equimolar amount of 2,4-dinitrophenylhydrazine in alcohol under the catalytic action of a trace of concentrated HCl. The reaction mixture was allowed to stand at a room temperature, until the yellow crystal of hydrazone precipitated. The crystallization of acrylamide derivatives required a deep cooling or an addition of water. These hydrazones were filtered with suction and were purified by recrystallization from alcohol or a mixture of alcohol and a small amount of water, if required. The melting points and elemental analyses of hydrazones are shown in Table IV.

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(9) S. Gabriel and J. Colman, *Ber.*, **35**, 3805 (1902).

(10) H. Künne, *ibid.*, **28**, 2036 (1895).

(11) P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **79**, 100 (1928).