Peptides. V. Some Carbonates of Ethyl 2-Hydroximino-2-cyanoacetate and Related Compounds as Esterification Reagents for Peptide Synthesis

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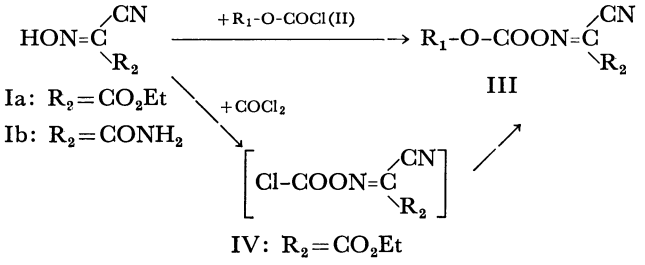
Some carbonates (III) of ethyl 2-hydroximino-2-cyanoacetate (Ia) and 2-hydroximino-2-cyanoacetamide (Ib) were prepared and utilized as simple esterification reagents for acylamino acids.

The applications of some carbonates in the preparation of acylamino acid esters[1,2] have been reported, but the reactivity of these carbonates is rather low and these applications have been limited to the preparation of aryl esters. The present author wishes to report a generally-applicable esterification of acylamino acids by the use of carbonates (III) of strongly acidic oximes such as ethyl 2-hydroximino-2-cyanoacetate (Ia),[3] which has previously been proposed as an additive for racemization suppression.[4]

The oxime carbonates were prepared, as is shown in Scheme 1, by the reaction of oximes with alkyl or aryl chloroformates under the conditions of a Schotten-Baumann reaction (method A), or through a labile chloroformate, ethyl 2-chloroformyloximino-2-cyanoacetate (IV), prepared from Ia with phosgene in an anhydrous organic solvent (method B). The carbonates thus prepared are listed in Table 1. These carbonates are generally stable enough and remain unchanged over one year in closed bottles, but some of them are extremely unstable and are difficult to prepare. Ethyl 2-*t*-amyloxycarbonyloximino-2-cyanoacetate (IIIm; R_1=*t*-amyl), for example, was prepared by Method B, but it decomposed instantly after characterization by taking its infrared (IR) spectrum.



Scheme 1.

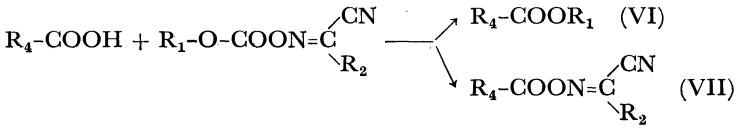
Preliminary experiments on the reaction of oxime carbonates with *N*-benzyloxycarbonylglycine in an attempt to prepare the corresponding esters were done in the presence of a tertiary base at room temperature; by the help of thin layer chromatography (tlc) on silica gel G, it was noticed that the reaction does not take place in the absence of base or in the presence of water. The reactivity of carbonates (III) is parallel to the acidity of the parent oximes, and the carbonates of 2-hydroximinopropane,[5] 1-hydroximinoethane,[6] 1-hydroximino-2-propanone[7] (pK_a 8.4), and diethyl 2-hydroximinomalonate[8] (pK_a 7.1) were less reactive. Thus, Ia (pK_a 4.6) and 2-hydroximino-2-cyanoacetamide[9] (Ib, pK_a 5.2) were selected as suitable parent oximes from among them. The rate of esterification depends largely on the basicity of the tertiary amines

TABLE 1. SOME CARBONATES OF VARIOUS OXIMES

R_1-O-COON=C(R_2)(R_3) (III)

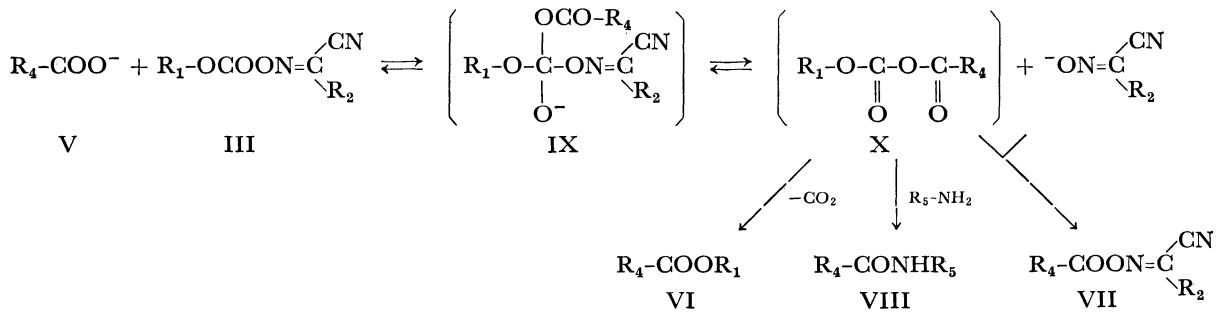
	R_1	R_2	R_3	Method	Yield (%)	IR $\nu^{C=O}$ (cm^{-1})
IIIa	Me	$CONH_2$	CN	A	82	1810, 1720, 1685
b	Et	$CONH_2$	CN	A	84	1800, 1715, 1685
c	Bu (iso)	$CONH_2$	CN	A	58	1795, 1720, 1690
d	Me	COOEt	CN	A	82	1800, 1740
				B	87	
e	Et	COOEt	CN	A	74	1805, 1755, 1735
f	Bu (iso)	COOEt	CN	A	58	
g	Bzl	COOEt	CN	A	80	1795, 1735
h	Allyl	COOEt	CN	A	62	1810, 1735
i	C_6H_4-NO_2 (*p*)	COOEt	CN	B	37	1810, 1735
j	C_6H_2-Cl_3 (2, 4, 5)	COOEt	CN	B	83	1815, 1740
k	C_6Cl_5	COOEt	CN	B	42	1820, 1745
l	CH_2CCl_3	COOEt	CN	A	80	1810, 1755
m	Amyl (*t*)	COOEt	CN	A	40	1810, 1740
n	Et	Me	Me	A	80	1770
o	Et	H	Me	A	33	1765
p	Et	H	COMe	A	45	1780, 1700
q	Et	COOEt	COOEt	A	79	1795, 1745

Table 2. The yields of esters VI and VII under the various conditions



	R_1	R_2	R_4	Base/Solvent	Yield (%) VI	Yield (%) VII
1	Me	COOEt	C_6H_5-	TEA/MeOH	66.1	0
2	Me	COOEt	C_6H_5-	DMA/CH_2Cl_2	0	56.8
3	Et	$CONH_2$	C_6H_5-	TEA/THF	66.7	11.2
4	Et	COOEt	C_6H_5-	TEA/EtOAc	44.0	36.6
5	Bu (iso)	COOEt	C_6H_5-	TEA/EtOAc	95.5	trace
6	Et	$CONH_2$	-$(CH_2)_2$-[a]	TEA/THF	64.4	11.9
7	Et	COOEt	$HOCH_2$-[a]	TEA/THF	95.0[17]	
8	Me	COOEt	Z-Gly-	NEM/CH_2Cl_2	90.9	
9	Me	$CONH_2$	Z-Gly-	TEA/$CHCl_3$-MeOH (2 : 1)	98.0	
10	Et	$CONH_2$	Z-Gly-	TEA/EtOAc-THF (1 : 1)	92.4	
11	Bu (iso)	COOEt	Z-Gly-	TEA/THF	98.0	
12	Bzl	COOEt	Z-Gly-	TEA/Dioxane	95.0	
13	Et	COOEt	Z-Trp-	TEA/EtOAc	92.9	
14	Et	$CONH_2$	Z-Phe-	TEA/EtOAc	95.0	
15	Me	COOEt	H-Phe-[a]	TEA/$CHCl_3$	50.6	

a) Two equivalents of reagents were used. TEA = triethylamine, DMA = *N*,*N*-dimethylaniline, NEM = *N*-ethylmorpholine. Abbreviations used throughout this work are those recommended by IUPAC-IUB commission on biochemical nomenclature (*J. Biol. Chem.*, **247**, 977 (1972)).



Scheme 2.

used and on the polarity of the solvents used. The reaction was completed fast by the use of a stronger base in a polar solvent.

When benzoic acid was used as a model, reverse esters, ethyl 2-benzoyloximino-2-cyanoacetate (VIIa) or 2-benzoyloximino-2-cyanoacetamide (VIIb), were obtained as by-products, accompanied by ordinary esters. The yield of the reverse esters varied depending upon the substituents of the carbonates, bases, and solvents used. The yield of VIIa increased up to 56.8% when the reaction of benzoic acid with ethyl 2-methyloxycarbonyloximino-2-cyanoacetate (IIId) was carried out using *N*,*N*-dimethylaniline in dichloromethane, while it was suppressed completely by the use of triethylamine in methanol.

In the case of *N*-benzyloxycarbonylglycine, on the contrary, the yields of such reverse esters are negligible. The esters prepared are summarized in Table 2. IIId and ethyl 2-ethyloxycarbonyloximino-2-cyanoacetate (IIIe) were also allowed to react with L-phenylalanine and hydroxyacetic acid to afford fully-protected acids, methyl *N*-methyloxycarbonyl-L-phenylalaninate and ethyl ethyloxycarbonyloxyacetate respectively. Some of the esters prepared were subjected to gas chromatography (Examples 6 and 7 in Table 2) and to mass spectrometry (Examples 8, 12, and 15 in Table 2) in order to characterize them. This procedure might be suitable for obtaining a simple characterization of multifunctional acids.

This esterification may proceed through a mixed anhydride-type intermediate (X), as is shown in Scheme 2. When the intermediate, X, is stable enough and when its decarboxylation is rather slow, it may react with the oxime anion to afford the reverse ester, VII. This mechanism is supported by the peptide formation from *N*-benzyloxycarbonylamino acids with amino acid esters, using ethyl 2-isobutyloxycarbonyloximino-2-cyanoacetate (IIIf) as a coupling reagent, at −15 °C. However, its use does not show remarkable advantages over the usual mixed anhydride method, because it requires conditions similar to the usual ones and it will act as an esterification reagent

Table 3. Some active esters of acylamino acids

$$R_4\text{-COOH} + R_1\text{-O-COON=C}\begin{matrix}\text{CN}\\ R_2\end{matrix} \longrightarrow R_4\text{-COOR}_1 + \text{HON=C}\begin{matrix}\text{CN}\\ R_2\end{matrix}$$

R_1	R_2	R_4	Base/Solvent	Yield (%)	Ref.
$-C_6H_4$-NO_2 (*p*)	$CONH_2$	Z-Phe	TEA/THF	60.0	10a
$-C_6H_4$-NO_2 (*p*)	COOEt	Z-Phe	NEM/CH_2Cl_2	47.0	
$-C_6H_4$-NO_2 (*p*)	COOEt	Z-Pro	TEA/EtOAc	54.0	10a
$-C_6H_4$-NO_2 (*p*)	COOEt	Z-Gly	TEA/EtOAc	63.0	11
$-C_6H_4$-NO_2 (*p*)	COOEt	Z-Cys (Bzl)	TEA/EtOAc	62.0	12
$-C_6H_4$-NO_2 (*p*)	COOEt	Z-Glu	TEA/DMF	44.3	12
$-C_6H_2Cl_3$ (2,4,5)	COOEt	Z-Phe	TEA/EtOAc	79.5	11
$-C_5H_2Cl_3$ (2,4,5)	COOEt	Z-Gly	TEA/EtOAc	80.2	14
$-C_6Cl_5$	COOEt	Z-Gly	TEA/EtOAc	78.6	10b, 11
$-C_6Cl_5$	COOEt	Z-Glu	TEA/DMF	62.5	13

for acylamino acid unless the reaction is performed at low temperature.

The aryl esters of *N*-benzyloxycarbonylamino acids were prepared by the use of ethyl 2-(*p*-nitrophenyl)-oxycarbonyloximino-2-cyanoacetate (IIIi), ethyl 2-(2,4,5-trichlorophenyl)-oxycarbonyloximino-2-cyanoacetate (IIIj) and ethyl 2-(pentachlorophenyl-)oxycarbonyloximino-2-cyanoacetate (IIIk), in moderate yields, as is shown in Table 3.

Experimental

The capillary melting points were observed on a Hoover "Uni-Melt" apparatus and are uncorrected. The optical rotations were determined with a JASCO optical rotatory dispersion recorder, Model ORD/UV-5. The gas-liquid chromatographic work was done with a Varian Aerograph, Model A-700, using a column (3/8 in×10 ft) packed with SF-96 on Neopak (60/80), and on a Shimadzu gas chromatograph, GC-2C, using a column (3 mm×1.5 m) packed with 5% SE-30 on Shimailte W (60/80). The spectrometers used throughout this work were as follows: IR spectra: Hitachi Model EPI-S2; nuclear magnetic resonance spectra: Varian A-60, and mass spectra: JEOLCO Model JMS 01 SG.

Materials. Commercially-available methyl, ethyl, isobutyl, trichloroethyl, and benzyl chloroformates were purchased and used for the preparation of the carbonates. The allyl chloroformate was prepared according to the literature.[15]

The Preparation of Oxime Carbonates (III). A-i) In an Aqueous Solution: Chloroformate (II, 0.1 mol) was added dropwise to a suspension of ethyl 2-hydroximino-2-cyanoacetate sodium salt[3] (16.4 g, 0.1 mol) or 2-hydroximino-2-cyanoacetamide sodium salt[3] (13.5 g, 0.1 mol) in a mixture of acetone (15 ml) and water (100 ml) at 0—+5 °C. The mixture was then stirred for 3 hr while the pH of the solution was maintained at 7—8. The product was then extracted from the solution by ether (IIId,e,n,o,p, and q) or ethyl acetate (EtOAc) (IIIf,g and h). The extract was washed with water and dried over magnesium sulfate. After evaporation, the residue was distilled or recrystallized from a suitable solvent, as will be shown below. In some cases (IIIb,c and g), a crude product was obtained by the filtration of the reaction mixture. The compounds (III, R_1–O–COON=CR_2R_3) prepared in this manner are as follows: (R_1, R_2, R_3, mp °C or bp °C/mmHg, recrystallization solvent, elemental analysis (calcd) shown) IIIb: Et, $CONH_2$, CN, 194—196, EtOAc, C, 39.12; H, 3.69; N, 22.78% (C, 38.92; H, 3.81; N, 22.70%); IIIc: *iso*-Bu, $CONH_2$, CN, 156—158, EtOAc, C, 44.86; H, 5.27; N, 19.57% (C, 45.07; H, 5.20; N, 19.71%); IIId: Me, COOEt, CN, 69—71, C_6H_6-hexane, C, 41.99; H, 3.90; N, 14.10% (C, 42.00; H, 4.03; N, 14.00%); IIIe: Et, COOEt, CN, 127.5/0.8, ···, C, 45.08; H, 4.63; N, 13.17% (C, 44.86; H, 4.71; N, 13.08%); IIIf: *iso*-Bu, COOEt, CN, 60—62, EtOAc-petroleum ether, C, 56.98; H, 4.30; N, 10.25% (C, 56.52; H, 4.38; N, 10.14%); IIIh: allyl, COOEt, CN, 122—124/0.9, --, C, 47.56; H, 4.40% (C, 47.79; H, 4.46%); IIIn: Et, Me, Me, 66—66.5/5, --, C, 49.81; H, 7.68% (C, 49.65; H, 7.64%); IIIo: Et, H, Me, 67—70/6, --, C, 46.38; H, 7.01; N, 10.49% (C, 45.80; H, 6.92; N, 10.68%); IIIp: Et, H, COMe, 81—85/8.5, --, C, 44.96; H, 5.62; N, 8.45% (C, 45.28; H, 5.70; N, 8.80%); IIIq: Et, COOEt, COOEt, 120/0.1, C, 46.27; H, 5.69; N, 5.53% (C, 45.98; H, 5.78; N, 5.36%).

A-ii) In Organic Solvents; A typical example is as follows. A solution of *β,β,β*-trichloroethyl chloroformate (10.5 g, 0.05 mol) in benzene (C_6H_6)(35 ml) was added dropwise to a solution of ethyl 2-hydroximino-2-cyanoacetate (Ia, 7.2 g, 0.05 mol) and triethylamine (TEA)(7.0 ml, 0.05 mol) in C_6H_6 (50 ml) under ice-cooling. The mixture was then stirred for 1 hr below 10 °C and allowed to stand overnight at room temperature. The solution was washed with water and dried over magnesium sulfate. After evaporation, the residue was triturated with petroleum ether and filtered to give IIIl; 12.3 g, mp 50—52 °C. A part of the sample was recrystallized from EtOAc-petroleum ether; mp 51—53 °C.

Found: C, 30.59; H, 2.14; N, 9.29; Cl, 32.70%, Calcd for $C_8H_7O_5N_2Cl_2$: C, 30.26; H, 2.22; N, 8.82; Cl, 33.50%.

For the preparation of IIIa, chloroform was used as the solvent. For IIIm, a solution of Ia and TEA in C_6H_6 was added to a solution of *t*-amyl chloroformate in an ether–toluene mixture.[16] The carbonates prepared in this manner are as follows: (R_1, R_2, R_3, mp °C, recrystallization solvent, elemental analysis (calcd) shown) IIIa: Me, $CONH_2$, CN, 174—175 (decomp), EtOAc, C, 35.33; H, 2.99; N, 24.31% (C, 35.09; H, 2.95; N, 24.56%); IIIm: *t*-Amyl, COOEt, CN, oil, ···, ···. This decomposed spontaneously after IR measurement.

B-i) Preparation of Ethyl 2-Chlorocarbonyloximino-2-cyanoacetate (IV): A solution of Ia (7.2 g) and TEA (7.0 ml) in dry C_6H_6 (50 ml) was added dropwise to a solution of phosgene in C_6H_6 (52.5 ml, 0.05 mol) at 5 °C. The mixture was stirred for 2 hr, allowed to stand overnight, and used for the next step without further treatment. In another run, the

reaction mixture was filtered and evaporated to dryness under reduced pressure. The pale yellow oil (8.6 g) thus obtained showed IR absorptions at 1870 and 1740 cm^{-1} and was very unstable toward moisture.

B-*ii) Preparation of Oxime Carbonates (III)*: A typical example is as follows. A solution of pentachlorophenol (13.3 g, 0.05 mol) and *N,N*-dimethylaniline (6.0 g, 0.05 mol) in CH_2Cl_2 (50 ml) and C_6H_6 (50 ml) was added dropwise into the stirred solution of IV described in B-i) at 5—10 °C. The mixture was then stirred for 2 hr and allowed to stand overnight. The mixture was subsequently washed with water, dried over magnesium sulfate, and evaporated to dryness under reduced pressure. The residue was filtered with a small amount of ether to give a crude powder; 5.5 g. Recrystallization from EtOAc-petroleum ether gave needles (IIIk); mp 122—124 °C.

Found: C, 33.02; H, 1.09; N, 6.25; Cl, 40.70%. Calcd for $C_{12}H_5O_5N_2Cl_5$: C, 33.17; H, 1.16; N, 6.45; Cl, 40.80%.

IIId, IIIi and IIIj were prepared by a similar procedure except for the following modifications: C_6H_6 (40 ml) for IIId, CH_2Cl_2 (50 ml) for IIIi and pyridine in C_6H_6 (50 ml) for IIIj. The following are the R_1, R_2, R_3, mp °C, recrystallization solvent, elemental analysis (calcd) shown; IIId: Me, COOEt, CN, 68—70, C_6H_6-hexane, ···; IIIi; C_6H_4-$NO_2(p)$, COOEt, CN, 90—93, C_6H_6-petroleum ether, C, 47.41; H, 2.90; N, 13.77% (C, 46.91; H, 2.95; N, 13.68%); IIIj: $C_6H_2Cl_3(2,4,5)$, COOEt, CN, 101—103, C_6H_6-petroleum ether, C, 39.29; H, 1.88; N, 6.95; Cl, 29.18% (C, 39.42; H, 1.93; N, 7.66; Cl, 29.10%.)

Preliminary Reactions of N-*Benzyloxycarbonylglycine with Some Oxime Carbonates. A) A Comparison of The Reactivity of Carbonates by The Help of Tlc*: The stoichiometric amount of oxime carbonate (2 mmol) cited below was added to a solution of *N*-benzyloxycarbonylglycine (0.42 g, 2 mmol) and TEA (0.28 ml, 2 mmol) in dioxane (5.0 ml) at room temperature. The reaction mixture was checked by tlc on silica gel G (solvent: $CHCl_3$–MeOH (9 : 1)). With 2-ethyloxycarbonyloximinopropane (IIIn), ethyloxycarbonyloximinoethane (IIIo), 1-ethyloxycarbonyloximinopropan-2-one (IIIp) and diethyl 2-ethoxycarbonyloximinomalonate (IIIq), the reaction did not take place at all. When dimethylformamide was used as the solvent, the reaction proceeded slightly with only IIIq. The reaction was completed with ethyl 2-ethoxycarbonyloximino-2-cyanoacetate (IIIe) and 2-ethoxycarbonyloximino-2-cyanoacetamide (IIIb) within 20 min and 2 hr respectively.

B) Comparison of The Solvent Effects: 2-Isobutyloxycarnyloximino-2-cyanoacetamide (IIIc, 0.43 g, 2 mmol) was allowed to react with *N*-benzyloxycarbonylglycine (0.42 g, 2 mmol) and TEA (0.28 ml, 2 mmol) in the following solvent (5.0 ml) for 3 hr at room temperature. The rate of ester formation was compared by tlc as has been described in A). The rate increased in the following order: THF≒dioxane<MeCN<dimethylformamide.

General Procedure for The Preparation of Esters. Oxime carbonate (III, 0.01 or 0.02 mol, according to the number of functional groups) was added portionwise to a solution of carboxylic acid (0.01 mol) and tertiary amine (0.01 or 0.02 mol) in a suitable solvent (20 ml), as is shown in Table 2, at room temperature. The mixture was then stirred for a further 2 hr and extracted with EtOAc, $CHCl_3$ (ex. 6) or ether (ex. 7). The organic layer was washed with water, 1M $NaHCO_3$ solution, water, 1M HCl and water successively, and dried over magnesium sulfate. The subsequent evaporation of the solvent gave a product, which was purified or analyzed by the method cited below for each section. Reverse esters (VII) were less soluble than normal esters (VI) and were easily separated by treatment with EtOAc containing petroleum ether. Remarks on each experiment shown in Table 2 follows: ex. 2) ethyl 2-benzoyloximino-2-cyanoacetate (VII), mp 99—101 °C (from EtOAc-petroleum ether), C, 58.60; H, 3.93; N, 11.60% (calcd for $C_{12}H_{10}O_4N_2$: C, 58.53; H, 4.09; N, 11.38%), IR (Nujol, cm^{-1}) 1770, 1745; ex. 3) 2-benzoyloximino-2-cyanoacetamide (VII), mp 223—226 °C (from THF), C, 55.69; H, 3.05; N, 19.30% (calcd for $C_{10}H_7O_3N_3$: C, 55.30; H, 3.25; N, (19.35%), IR (Nujol, cm^{-1}) 1770, 1695; ex. 6) diethyl adipate (VI) was checked by gas-liquid chromatography (glc) and identified with an authentic sample; 1,4-bis(α-cyano-α-carbamoylmethyleniminoxycarbonyl)butane (VII), mp 200—202 °C (from THF), C, 42.63; H, 3.54; N, 24.67% (calcd for $C_{12}H_{12}O_6N_6$: C, 42.86; H, 3.60; N, 24.99%), IR (Nujol, cm^{-1}) 3450, 3200, 1795, 1705; ex. 7) ethyl 2-ethoxycarbonyloxyacetate (VI), fractionated by preparative glc, IR (neat, cm^{-1}) 1745, nuclear magnetic resonance (in $CDCl_3$, ppm) 1.29 (methyl, 3H, triplet, J=7.5 Hz), 1.31 (methyl, 3H, triplet, J=7.5 Hz), 4.25 (two methylene, 4H, quartet, J=7.5 Hz), 4.61 (methylene, 2H, singlet); ex. 8) mass spectrometry *m/e* 223 (M^+), IR (neat, cm^{-1}) 3350, 1740, 1700; ex. 11) IR (neat, cm^{-1}) 3350, 1730, 1700; ex. 12) mass spectrometry *m/e* 299 (M^+); ex. 13) ethyl *N*-benzyloxycarbonyl-L-tryptophanate, mp 80—83 °C (from EtOAc-petroleum ether), C, 68.56; H, 6.05; N, 7.64% (calcd for $C_{21}H_{22}O_4N_2$: C, 68.83; H, 6.05; N, 7.65%), IR (Nujol, cm^{-1}) 3350, 1730, 1700; ex. 14) ethyl *N*-benzyloxycarbonyl-L-phenylalaninate, checked by tlc and identified with an authentic sample, IR (neat, cm^{-1}) 3350, 1730, 1700; ex. 15) methyl *N*-methoxycarbonyl-L-phenylalaninate, mass spectrometry *m/e* 237 (M^+), IR (neat, cm^{-1}) 3350, 1730, 1700.

Peptide Formation by the Use of Ethyl 2-isobutyloxycarbonyloximino-2-cyanoacetate (IIIf). A) Ethyl N-*Benzyloxycarbonylglycyl-*L-*leucinate*: To a solution of *N*-benzyloxycarbonylglycine (1.05 g, 5 mmol) and TEA (0.70 ml, 5 mmol) in EtOAC (15 ml), a solution of IIIf (1.21 g, 5 mmol) in EtOAc (10 ml) was added dropwise at −15 °C. The mixture was then stirred for 30 min at the same temperature. A solution of ethyl L-leucinate hydrochloride (1.0 g) and TEA (0.70 ml) in CH_2Cl_2 (15 ml) was subsequently added dropwise to the solution described above, and the mixture was stirred for 1 hr. The product was taken up into EtOAc. The extract was washed with water, 1M $NaHCO_3$ solution, water, 1M HCl, and water again, and dried over magnesium sulfate. Evaporation gave an oily product; 1.4 g (80%). To confirm the structure, the product was saponified to give *N*-benzyloxycarbonylglycyl-L-leucine; mp 100—102 °C (lit,[18] 101—102 °C). The sample was identified with an authentic specimen by means of its IR spectra.

B) Methyl N-*Benzyloxycarbonylglycyl-*L-*phenylalaninate*: This compound was prepared in a similar manner in an 86% yield. A part of the product was saponified to give *N*-benzyloxycarbonylglycyl-L-phenylalanine; mp 124—126 °C (lit,[19] mp 125—126 °C). An admixture of the sample and an authentic specimen melted at 124—126 °C.

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