[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Cyanoethylation of α-Amino Acids. IV. N-2-Carbalkoxyethyl Derivatives

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N-2-Cyanoethyl derivatives of α-amino acids reacted with alcoholic hydrogen chloride to give N-2-carbalkoxyethyl derivatives of amino acid esters. The properties of these esters and of some of their N-acetyl and N-benzoyl derivatives are described.

Previous communications have described the reaction of acrylonitrile with α-amino acids to produce mono- and dicyanoethyl derivatives.[2] This paper describes the preparation and properties of N-2-carbalkoxyethyl derivatives of amino acid esters of the type shown in the formula

$$R_3—N(R_1—CH—COOR_2)—CH_2—CH_2COOR_2$$

where R_1 is derived from the amino acid, *i.e.*, H for glycine, CH_3 for alanine, etc., R_2 is an alkyl group, and R_3 is H or an acyl group. These derivatives were investigated because of their possible application as plasticizers and as polymer intermediates.

Monocyanoethyl derivatives of the α-amino acids were treated with alcoholic hydrogen chloride to produce the imidic ester hydrochlorides by the method of Pinner.[3] Upon refluxing the reaction mixture, the imidic ester hydrochlorides were converted to the ester hydrochlorides and ammonium chloride. After filtering the reaction mixture to remove the ammonium chloride, the hydrochlorides of the N-2-carbalkoxyethyl derivatives of amino acid esters could be isolated, but this step was usually omitted. The alcoholic solution of the ester hydrochlorides was neutralized with sodium bicarbonate, the alcohol removed by distillation and the pure ester isolated by vacuum distillation. Ethyl N-(2-carbethoxyethyl)-tyrosinate could not be distilled without considerable decomposition. A fairly pure sample was isolated by omitting the vacuum distillation. Diethyl N-(2-carbethoxyethyl)-glutamate could not be distilled without cyclization to give the pyroglutamate.[4] The properties of the esters, their hydrochlorides and acyl derivatives are given in Table I.[5]

TABLE I

PROPERTIES OF N-2-CARBETHOXYETHYL DERIVATIVES OF AMINO ACID ETHYL ESTERS AND ACYLATED AMINO ACID ETHYL ESTERS

N-(CH₂-CH₂-COOEt) derivatives of the ethyl esters of	Yield, %[a]	Sp. gr. 30/30	$n^{25}D$	Boiling point, °C. Atm.[b]	1–2 mm.	Molecular formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Glycine[c]	75	1.0533	1.4365	253	97–100	$C_9H_{17}O_4N$	..	..	..	..	6.89	6.82
Alanine[d]	70	1.0222	1.4325	245	89–91	$C_{10}H_{19}O_4N$	..	..	..	..	6.44	6.37
Leucine	88	0.9794	1.4358	270	119–120	$C_{13}H_{25}O_4N$	60.2	59.7	9.72	9.72	5.40	5.35
Methionine	70		1.4720	Dec.	145–150	$C_{12}H_{23}O_4NS$	..	..	..	..	5.05	5.05
Aspartic acid	60		1.4440	Dec.	138–140	$C_{13}H_{23}O_6N$	53.9	53.4	8.01	8.00	4.79	4.84
Pyroglutamic acid	73	1.1403	1.4650	337	144–145	$C_{12}H_{19}O_5N$	56.0	55.4	7.44	7.47	5.44	5.44
Tyrosine	80			Dec.	Dec.	$C_{16}H_{23}O_5N$	62.1	59.9	7.49	7.33	4.53	4.45
Acetylglycine	94	1.1117	1.4551	310	134–135	$C_{11}H_{19}O_5N$	53.9	53.3	7.81	7.91	5.71	5.69
Acetylalanine	97	1.0914	1.4549	315	142–145	$C_{12}H_{21}O_5N$	55.6	55.0	8.16	8.07	5.40	5.39
Acetylleucine	97	1.0457	1.4548	318	142–143	$C_{15}H_{27}O_5N$	59.8	59.5	9.03	8.76	4.65	4.60
Acetylmethionine	85	1.1250	1.4845	330	166–170	$C_{14}H_{25}O_5N$	52.6	52.4	7.89	7.88	4.39	4.42
Acetylphenylalanine[e]	73	1.1122	1.5003	333	175–177	$C_{18}H_{25}O_5N$	64.5	64.2	7.51	7.51	4.18	4.15
Acetylaspartic acid	95	1.1308	1.4571	319	180–185	$C_{15}H_{25}O_7N$	54.4	54.2	7.60	7.59	4.23	4.26
Benzoylalanine	80	1.1203	1.5003	327	167–168	$C_{17}H_{23}O_5N$	63.5	63.2	7.21	7.19	4.36	4.32
Benzoylleucine	80	1.0769	1.4950	337	175–178	$C_{20}H_{29}O_5N$	66.1	66.1	8.04	8.00	3.85	3.81

[a] Yields for amino acid derivatives based on N-2-cyanoethyl derivatives. Yields for acylated amino acid derivatives based on ethyl N-2-carbethoxyethyl derivatives. [b] Distillation accompanied by some decomposition. [c] Hydrochloride, yield 87%, m.p. 85–87°. *Anal.* Calcd. N, 5.85. Found: N, 5.86. [d] Hydrochloride, yield 71%, m.p. 74–76°. *Anal.* Calcd.: N, 5.55. Found: N, 5.55. [e] Ethyl N-(2-carbethoxyethyl)-phenylalaninate hydrochloride was prepared, yield 73%, m.p. 101–103°. *Anal.* Calcd. for $C_{16}H_{23}O_4NCl$: C, 58.2; H, 7.40; N, 4.25. Found: C, 57.9; H, 7.33; N, 4.19.

N-Bis-(2-carbethoxyethyl)-glycine ethyl ester was prepared in 50% yield by treating N-bis-(2-cyanoethyl)-glycine with ethanolic hydrogen chloride. This ester was relatively unstable and the odor of ethyl acrylate was present in the distilled product. Attempts to prepare these bis-ester derivatives from the dicyanoethyl derivatives of higher molecular weight amino acids gave decomposition products from which ethanol and ethyl acrylate were isolated. When N-bis-(2-cyanoethyl)-aspartic acid was treated with methanolic hydrogen chloride, the reaction mixture decomposed on heating to yield a mixture of dimethyl fumarate and methyl acrylate.

The N-2-carbalkoxyethyl derivatives of amino

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(2) L. L. McKinney, *et al.*, THIS JOURNAL, **72**, 2599 (1950); **73**, 1641 (1951).

(3) A. Pinner, "Die Imido Ather und ihre Derivative," Berlin, 1892; R. L. Shriner and F. W. Neuman, *Chem. Revs.*, **35**, 351 (1944).

(4) L. L. McKinney, *et al.*, U. S. Patent 2,607,797.

(5) All melting points by capillary method, corrected.

acid esters were also unstable. When attempts were made to distil these esters at atmospheric pressure, they decomposed to acrylic acid esters, alcohol and other substances. On vacuum distillation of these esters at 1 mm., an odor of acrylate escaped from the vacuum pump with all except the leucine derivative. The stability of the leucine derivative was also evident when purified samples were stored. All other samples had a strong odor of acrylate after one year. These esters were stabilized by acetylation and benzoylation. The acyl derivatives were distilled under reduced pressure and stored for two years without decomposition. The acylated esters were compatible with polymethylmethacrylate, polyvinyl chloride and polystyrene.

Although we had previously been unable to acylate the N-2-carboxyethyl derivatives of amino acids,[6] we were able to isolate in good yields N-(2-carboxyethyl)-acetyl- and -benzoyl-α-alanine. The acylated esters were converted to the acylated acids by a combination of saponification and neutralization. The crude acids were then purified by crystallization.

Condensation of ethyl N-(2-carbethoxyethyl)-acetylglycinate with *p*-phenylenediamine at 250° gave fusible, brown, brittle polymers. With ethylene- and hexamethylenediamine, similar polymers were obtained at lower temperatures.

Experimental

Alcoholysis and Esterification.—The general method applicable to the ethyl N-2-carbethoxyethyl derivatives of the amino acid esters is illustrated by the following example. A solution of 142.1 g. (1 mole) of N-(2-cyanoethyl)-α-alanine in 750 ml. of absolute ethanol (99%) was placed in a three-necked, round-bottomed flask fitted with stirrer, thermometer and inlet tube from a hydrogen chloride generator. A total of 220 g. of dry hydrogen chloride was added with stirring to the solution. The reaction mixture became clear after 100 g. of hydrogen chloride was added. The temperature of the reaction mixture was maintained at approximately 10° by partial immersion of the reaction flask in an ice-bath. After the reaction was complete, as shown by testing an aliquot, the mixture was refluxed on a steam-bath for 1 hour. The volume of the reaction mixture was reduced to 600 ml. by removing alcohol under reduced pressure. Ammonium chloride which precipitated during the reflux was removed by filtration. The yield of ammonium chloride was 52.0 g. (97%). The filtrate was divided into two parts, 1/4 for the isolation of the ester hydrochloride and 3/4 for the isolation of the ester.

The reaction was followed by testing an aliquot for ammonium chloride. Excess magnesium oxide was added to each aliquot and the ammonia distilled and titrated.

Isolation of Ester Hydrochlorides.—The 1/4 portion of the above-mentioned filtrate was concentrated to dryness under reduced pressure. Traces of moisture were removed by adding benzene to this residue and then distilling the benzene from it. The semi-solid residue was dissolved in 200 ml. of chloroform, then 100 ml. of ether was added. The solution was warmed and allowed to stand at room temperature. A yield of 45 g. (71%) of crystals was obtained.

Isolation of Esters.—The 3/4 portion of the above-mentioned filtrate was neutralized by two successive treatments with 126 g. (1.5 moles) of sodium bicarbonate. The salt was removed by filtration. The alcohol was removed by distillation, leaving a residue of 147 g. On distilling the crude ester under reduced pressure at 1–2 mm., a main fraction of 114 g., boiling at 89–92° was obtained. On redistillation, a yield of 111 g. (68%) of a product boiling at 89–91° was obtained. For other properties of this ester and the properties of others, see Table I.

n-Butyl N-(2-carbobutoxyethyl)-α-alaninate was prepared by replacing ethanol with *n*-butanol in the above procedure. A yield of 192 g. (69%) of the ester distilling at 120–125° and 1 mm., $n^{25}D$ 1.4384, was obtained.

Anal. Calcd. for $C_{13}H_{25}O_4N$: N, 5.22. Found: N, 5.19.

Acetylation.—A general method applicable to the acetyl derivatives is illustrated by the following example. A solution of 43 g. (0.2 mole) of ethyl N-(2-carbethoxyethyl)-α-alaninate in a mixture of 0.2 mole of glacial acetic acid and 0.4 mole of acetic anhydride was warmed at 50° for 1 hour. The acetic acid and excess anhydride were removed by distillation under reduced pressure. On distilling the residue at 1 mm., a main fraction of 51 g. boiling at 140–145° was obtained. On redistilling, a yield of 50 g. (97%) of a product boiling at 142–145° at 1 mm. was obtained.

n-Butyl N-(2-carbobutoxyethyl)-acetylalaninate was prepared according to the above procedure. It distilled at 156–157° at 1 mm. with a yield of 81% based on the cyanoethyl derivative, $n^{25}D$ 1.4384.

Anal. Calcd. for $C_{16}H_{29}O_5N$: C, 60.9; H, 9.26; N, 4.44. Found: C, 60.6; H, 9.11; N, 4.39.

Films were cast from solutions of polymethylmethacrylate, polyvinyl chloride and polystyrene to which 30 and 40% (based on polymer weight) of ethyl N-(2-carbethoxyethyl)-acetylalaninate and of ethyl N-(2-carbethoxyethyl)-acetylleucinate had been added. The films remained flexible and did not discolor on standing in the laboratory for 2 years. These compounds were incompatible with zein and the cellulose esters.

Benzoylation.—The general method applicable to the preparation of benzoyl derivatives is illustrated by the following example. To a solution of 64.8 g. (0.25 mole) of ethyl N-(2-carbethoxyethyl)-leucinate in 100 ml. of benzene in a 1-liter beaker was added with stirring 37 g. (0.265 mole) of benzoyl chloride. The temperature rose to 60° and 22 g. of sodium bicarbonate was added. The mixture was held at 50–60° for about 30 minutes until the evolution of carbon dioxide ceased. The reaction mixture was filtered, and the benzene removed by distillation. On vacuum distillation at 1 mm., a yield of 71 g. (80%) of a product distilling at 175–178° was obtained.

Ethyl N-Bis-(2-carbethoxyethyl)-glycinate.—To a solution of 90.5 g. (0.5 mole) of N-bis-(2-cyanoethyl)-glycine in 500 ml. of 96% ethanol was added 143 g. of hydrogen chloride. The solution was refluxed 2 hours on a steam-bath, and 50 g. (94.5%) of ammonium chloride was separated by filtration. The excess hydrogen chloride was neutralized by two successive treatments of sodium bicarbonate; salts were removed by filtration. The alcohol was removed under reduced pressure, and the residue distilled to give two fractions boiling at 95–100° and 137–150° at 1 mm. The higher boiling fraction, redistilled, yielded 76 g. (50%) of a product distilling at 130–135° at 1 mm. Some decomposition occurred and ethanol and ethyl acrylate were isolated from the contents of the Dry Ice trap. The odor of ethyl acrylate, present in the final product, was removed by washing the product with water and drying over anhydrous calcium sulfate. A product free of acrylate odor was analyzed for nitrogen.

Anal. Calcd. for $C_{14}H_{25}O_6N$: N, 4.62. Found: N, 4.60.

After 3 months storage at room temperature in a glass bottle, the liquid was cloudy and an acrylate odor was present.

N-(2-Carboxyethyl)-acetyl-α-alanine.—A mixture of 35 g. (0.111 mole) of *n*-butyl N-(2-carbobutoxyethyl)-acetylalaninate and 13.4 g. (0.335 mole) of sodium hydroxide dissolved in 150 ml. of water was shaken mechanically for 2 hours at room temperature. The reaction mixture, neutralized by adding 27.94 ml. (0.335 mole) hydrochloric acid, was evaporated to dryness under reduced pressure. The residue was extracted with 100 ml. of acetone. The acetone was filtered to remove occluded salt and the solution evaporated to dryness. The residue was crystallized from 150 ml. of aqueous dioxane (95%). The product contained 1/2 molecule of dioxane of crystallization. On heating in a vacuum oven at 100° for 3 hours, a yield of 18 g. (80%) of a product melting at 140–141° (capillary) and discoloring at 170° was obtained. The solubility in g. per 100 g. of solvent at room temperature was: dioxane, 2.6; acetone, 4.5; water, 60; and ethanol, 22.

Anal. Calcd. for $C_{13}H_{13}O_5N$: N, 6.86; neut. equiv., 203.3. Found: N, 6.85; neut. equiv., 202.5.

(6) L. L. McKinney, *et al.*, THIS JOURNAL, **74**, 1942 (1952).

N-(2-Carboxyethyl)-benzoyl-α-alanine.—A mixture of 16.05 g. (0.05 mole) of ethyl N-2-carbethoxyethyl)-benzoyl-alaninate and 4 g. of sodium hydroxide dissolved in 100 ml. of water was shaken mechanically for 2 hours at room temperature. The reaction mixture was treated in the same manner as described in the preparation of N-(2-carboxyethyl)-acetylalanine to obtain the crude product for crystallization, *i.e.*, residue from acetone distillation. This residue was crystallized twice from water to give a yield of 11.5 g. (87%) of a product melting at 126–128° (capillary) and discoloring at 170°. The solubility in g. per 100 g. of solvent at room temperature was: water, 7.2; acetone, 2.7; and ethanol, 65.

Anal. Calcd. for $C_{13}H_{15}O_5N$: N, 5.28; neut. equiv., 265. Found: N, 5.21; neut. equiv., 266.

Condensations with Diamines.—The ethyl N-(2-carbethoxyethyl)-glycinate, alaninate, leucinate, methioninate, pyroglutamate, and the corresponding acetyl derivatives of the first four were condensed with ethylene, hexamethylene and *p*-phenylenediamine. The following example illustrates the results obtained. A mixture of 8.18 g. (0.0333 mole) of ethyl N-(2-carbethoxyethyl)-acetylglycinate and 3.61 g. (0.333 mole) of *p*-phenylenediamine was placed in a thick-walled test-tube into which a capillary tube was inserted for bubbling nitrogen through the reaction mixture. The tube was heated with a silicone-bath equipped with a thermometer. The temperature of the bath was raised to 200° over a period of 2 hours and held at 200° for 6 hours. A vacuum was applied and the temperature raised to 250° over a period of 2 hours and held at 250° for 6 hours. The brown resin weighed 7.5 g. (calcd. 8.73 g.), and contained 15.4% nitrogen (calcd. 16.1, disregarding end groups). It had a soft point of 160° and was insoluble in water, acetone and alcohol but soluble in methyl cellosolve. A film cast from solution was brittle and disintegrated when soaked in water. Similar results were obtained with ethylenediamine and hexamethylenediamine when the temperature was held at 180–200°. With prolonged heating at 250°, decomposition occurred with the formation of infusible polymers.

With the unacetylated derivatives, it was necessary to keep the temperature under 200° during the condensation reaction to avoid excessive decomposition. These polymers were water soluble, brown, brittle and had softening points from 130 to 190°.

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Preparation of Primary Amines by Reduction of Oximes with Lithium Aluminum Hydride and by the Leuckart Reaction

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A variety of carbonyl compounds have been converted to the corresponding primary amines by reduction of their oximes with lithium aluminum hydride. Other reducible groups in the molecule are generally not affected. The procedure is compared with an alternate one for obtaining primary amines, *viz.*, the Leuckart Reaction. Several new amines are described.

In the conversion of ketones of various types, the Leuckart reaction, while in general superior to the method involving formation and reduction of oximes by metal combinations or by catalytic means, nevertheless fails in many instances.[1,2] Thus Ingersoll notes that the Leuckart reaction appears to be inapplicable to α,β-unsaturated ketones.[2] Furthermore it has been shown that compounds such as benzoin do not give the normal hydroxyamine in the Leuckart reaction.[3,4] On the other hand, the Leuckart method has often proved to be successful with compounds in which functional groups are present that are easily reduced by many reducing agents which are ordinarily used to reduce oximes.[1]

A study was therefore initiated to investigate the reduction of oximes to primary amines by means of lithium aluminum hydride, and to compare this method of amine formation with the Leuckart method. The results of this work indicate that the method of oxime formation followed by lithium aluminum hydride reduction provides in most cases a satisfactory alternate to the Leuckart procedure for the preparation of primary amines from carbonyl compounds and often supplements the Leuckart method where the latter fails.

Only few instances of reductions of oximes with $LiAlH_4$ have been reported.[5–10] We have studied the reduction of eleven oximes using lithium aluminum hydride and compared the results to those obtained using the Leuckart method on the original carbonyl compounds. The results are given in Table I.

TABLE I

CONVERSION OF CARBONYL COMPOUNDS TO PRIMARY AMINES

Compound	Primary amine	Yield, %[a] $LiAlH_4$ reduction of oxime	Yield, % Leuckart method
Cyclohexanone	Cyclohexylamine	42	26[b]
2,2-Tetramethylenecyclohexanone	2,2-Tetramethylenecyclohexylamine	65.8	44.6
2,2-Pentamethylenecycloheptanone	2,2-Pentamethylenecycloheptylamine	40	52.5
$CH_3COC_6H_5$	$CH_3CH(NH_2)C_6H_5$	43	50–81[b]
$(CH_3)_2CHCOCH(CH_3)_2$	$(CH_3)_2CH(NH_2)CH(CH_3)_2$	46.8	48.2
p-$ClC_6H_4COCH_3$	*p*-$ClC_6H_4CH(NH_2)CH_3$	56.6	65, 82[b]
p-$BrC_6H_4COCH_3$	*p*-$BrC_6H_4CH(NH_2)CH_3$	65.4	63, 79[b]
m-$NO_2C_6H_4COCH_3$	*m*-$NO_2C_6H_4CH(NH_2)CH_3$	0	56[b]
$C_6H_5CH{=}CHCHO$	$C_6H_5CH{=}CHCH_2NH_2$	53.3	0
$C_6H_5CH{=}CHCOCH_3$	$C_6H_5CH{=}CHCH(NH_2)CH_3$	55	0[c]
$C_6H_5CHOHCOC_6H_5$	$C_6H_5CHOHCH(NH_2)C_6H_5$	12.7	0

[a] Based on oxime. [b] These figures refer to yields taken from tables, pp. 325–330 in ref. 1. [c] Ref. 2.

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