SYNTHESIS OF AMINO ACIDS FROM SUBSTITUTED CYANOACETIC ESTERS¹

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Abstract

The Darapsky degradation, by which a carbethoxy group is replaced by an amino group, has been applied successfully to substituted cyanoacetic esters for the preparation of 10 amino acids. The esters were formed by condensation of ethyl cyanoacetate with alkyl or arylalkyl halides. The hydrazides were obtained by treatment of the esters with hydrazine hydrate and identified by their anisal derivatives. Diazotization of the hydrazides gave rise to azides. These were transformed into carbethoxyaminonitriles by refluxing with absolute ethanol. The urethanes, on acid hydrolysis, yielded the amino acids. The following amino acids were synthesized: DL- β -methylleucine, DL- α -amino- β -methylisheptanoic acid, DL- α -amino- β -cyclohexylpropionic acid, DL-C-*o*-methylcyclohexylglycine, DL-C-*m*-methylcyclohexylglycine, DL-C-*p*-methylcyclohexylglycine, DL-C-*o*-xylylglycine, DL-C-*m*-xylylglycine, DL-C-*p*-xylylglycine, DL-*p*-ethylalanine.

Introduction

The Curtius reaction, whereby acid azides break down on heating into isocyanates and nitrogen, was applied in 1915 to the preparation of an amino acid from cyanoacetic ester by Darapsky and Hillers (4), who obtained glycine. Since that time a considerable number of amino acids (3, 6, 7, 8, 9, 10, 11) have been synthesized from substituted cyanoacetic esters by application of the Darapsky degradation. The aim of the present work was to extend the limits of this synthesis to 10 other amino acids and to observe the effect of the various substituents on the properties of the new compounds.

The starting materials, the alkyl or arylalkyl halides, were prepared in three different ways. By chloromethylation (2) of toluene and ethylbenzene, *p*-xylyl chloride and ethylbenzyl chloride respectively were obtained. The bromides were prepared by the action of phosphorus tribromide on the carbinols (17). The iodide was obtained by the reaction of iodine on a mixture of cyclohexylcarbinol and red phosphorus (5). The yields varied from 26 to 90%.

By refluxing the halides with ethyl cyanoacetate in sodium ethylate solution, the esters (I) were obtained in yields varying from 18 to 60%.

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R = 2-methyl-3-butyl, C_5H_{11} -; 2-methyl-4-pentyl, C_6H_{13} -; cyclohexylmethyl, $C_6H_{11}-CH_2$ -; *o*-methylcyclohexyl, $CH_3-C_6H_{10}$ -; *m*-methylcyclohexyl, $CH_3-C_6H_{10}$ -; *p*-methylcyclohexyl, $CH_3-C_6H_{10}$ -; *o*-xylyl, $CH_3-C_6H_4-CH_2$ -; *m*-xylyl, $CH_3-C_6H_4-CH_2$ -; *p*-xylyl, $CH_3-C_6H_4-CH_2$ -; *p*-ethylbenzyl, $C_2H_5-C_6H_4-CH_2$ -.

Hydrazine hydrate mixed with the esters (I) at room temperature gave rise to the hydrazides (II). These were identified by their condensation products with anisaldehyde.

The conversion of the hydrazides into the corresponding azides (III) took place by treatment with nitrous acid, the azides being extracted with ether. On boiling the alcoholic solutions of the azides under reflux, the ethyl urethanes (IV) were formed.

The hydrolysis of the urethanes to amino acids (V) was effected by refluxing in hydrochloric acid (20%). A mixture of equal volumes of concentrated hydrochloric acid, formic acid (85%), and water did not increase the yield whenever it was used.

The following α -amino acids were synthesized: DL- β -methylleucine, DL- α -amino- β -methylisheptanoic acid, DL- α -amino- β -cyclohexylpropionic acid, DL-C-*o*-methylcyclohexylglycine, DL-C-*m*-methylcyclohexylglycine, DL-C-*p*-methylcyclohexylglycine, DL-C-*o*-xylylglycine, DL-C-*m*-xylylglycine, DL-C-*p*-xylylglycine, and DL-*p*-ethylalanine.

Experimental*

Starting Materials

The halides, R-X, were prepared by three different methods.

(a) Chloromethylation of Aromatic Hydrocarbons

A mixture of aromatic hydrocarbon (2.5 moles), trioxymethylene (1.0 mole), and pulverized zinc chloride (20 gm.) was treated with a rapid current of moist hydrochloric acid while stirring. The reaction was exothermic. The mixture was cooled to 60°C. and maintained at this temperature until the reaction was complete. The mixture was placed in a separatory funnel, the aqueous portion discarded, and the upper layer washed repeatedly with water and dilute sodium carbonate, dried over anhydrous sodium sulphate, and filtered. By fractional distillation of the filtrate at reduced pressure the aromatic chloride was obtained.

(b) Alkyl Bromides

Phosphorus tribromide (1.0 mole) was placed in a round bottomed flask with a condenser attached, and the alcohol (1.0 mole) was slowly added. The reaction proceeded with evolution of heat. The reaction mixture was allowed to stand overnight at room temperature, after which it was refluxed gently for two hours, cooled, and poured into cold water (500 ml.), and placed in a

*All melting points are uncorrected.

separatory funnel. The aqueous layer was discarded. The upper layer was dried over anhydrous sodium sulphate and, by fractional distillation at reduced pressures, the bromide obtained.

(c) *Cyclohexylmethyl Iodide*

Iodine (20 gm.) was added to a mixture of cyclohexylcarbinol (161 gm., 1.5 moles) and dry red phosphorus (20 gm.). The mixture was heated on a water bath until the iodine had dissolved. After cooling, another portion of iodine (20 gm.) was added. The same procedure was repeated until sufficient iodine (170 gm.) had been added. The reaction mixture was heated for five minutes at 120°C., cooled, poured into ice-water and diluted sodium hydroxide, and extracted with ether. The ether was evaporated and the iodide obtained by fractional distillation at reduced pressure.

The properties and yields of the organic halides are given in Table I.

TABLE I
SUBSTITUTED HALIDES, R-X

Compound	B.p., °C.	Yield, %	Formula	Halogen, %	
				Calc.	Found
2-Methyl-3-butyl bromide*	60 (25 mm.)	80	C ₅ H ₁₁ Br	53.0	52.5
2-Methyl-4-pentyl bromide**	68 (25 mm.)	60	C ₆ H ₁₃ Br	48.5	48.0
Cyclohexylmethyl iodide†	99 (17 mm.)	55	C ₆ H ₁₁ CH ₂ I	56.7	56.4
<i>o</i> -Methylcyclohexyl bromide††	86 (30 mm.)	75	C ₇ H ₁₃ Br	45.2	45.0
<i>m</i> -Methylcyclohexyl bromide†††	78 (20 mm.)	80	C ₇ H ₁₃ Br	45.2	44.7
<i>p</i> -Methylcyclohexyl bromide†	92 (30 mm.)	90	C ₇ H ₁₃ Br	45.2	44.6
<i>p</i> -Xylyl chloride††	96-97 (25 mm.)	75	C ₈ H ₉ Cl	25.3	24.8
<i>p</i> -Ethylbenzyl chloride†††	92 (12 mm.)	26	C ₉ H ₁₁ Cl	23.0	22.6

*Ref. (19)

**Ref. (18)

†Ref. (13)

††Ref. (15)

†††Ref. (14)

†Ref. (12)

††Ref. (16)

†††Ref. (2)

Substituted Cyanoacetic Esters (I)

Ethyl cyanoacetate (113 gm., 1.0 mole) was added to a clear solution of sodium ethoxide (11.5 gm., 0.5 mole; 250 ml. of absolute ethanol) and the suspension heated to the boiling point. After cooling, the substituted halides (0.5 mole) were slowly added, and the reaction mixture refluxed until neutral to wet litmus paper. The alcohol was distilled off under reduced pressure and the remainder poured into cold water (500 ml.) and acidified with hydrochloric acid. The aqueous solutions were extracted three times with ether and the combined extracts dried over anhydrous sodium sulphate. The ether was evaporated and the esters obtained by fractional distillation under reduced pressure.

The properties and yields are summarized in Table II.

Substituted Cyanoacethydrazides (II)

The monosubstituted cyanoacetic esters (0.05 mole) were vigorously stirred with 100% hydrazine hydrate (2.5 gm., 0.05 mole). There was evolution of heat and the two layers passed into solution from which the white hydrazide pre-

TABLE II
 ETHYL α -SUBSTITUTED CYANOACETATES, $\text{RCH}(\text{CN})\text{COOC}_2\text{H}_5$

R	Starting material	Yield, %	B.p., °C.	Formula	Nitrogen, %		n_D^{25}
					Calc.	Found	
2-Methyl-3-butyl	$\text{C}_6\text{H}_{11}\text{Br}$	45	123 (17 mm.)	$\text{C}_{10}\text{H}_{17}\text{O}_2\text{N}$	7.65	7.52	1.4280
2-Methyl-4-pentyl	$\text{C}_6\text{H}_{11}\text{Br}$	60	181 (19 mm.)	$\text{C}_{11}\text{H}_{19}\text{O}_2\text{N}$	7.11	7.34	1.4303
Cyclohexylmethyl	$\text{C}_6\text{H}_{11}\text{CH}_2\text{I}$	51	166 (19 mm.)	$\text{C}_{12}\text{H}_{19}\text{O}_2\text{N}$	6.69	6.32	1.4570
<i>o</i> -Methylcyclohexyl	$\text{CH}_3\text{C}_6\text{H}_{10}\text{Br}$	18	149 (15 mm.)	$\text{C}_{12}\text{H}_{19}\text{O}_2\text{N}$	6.69	6.44	1.4488
<i>m</i> -Methylcyclohexyl	$\text{CH}_3\text{C}_6\text{H}_{10}\text{Br}$	32	180 (20 mm.)	$\text{C}_{12}\text{H}_{19}\text{O}_2\text{N}$	6.69	6.47	1.4501
<i>p</i> -Methylcyclohexyl	$\text{CH}_3\text{C}_6\text{H}_{10}\text{Br}$	32	154 (2 mm.)	$\text{C}_{12}\text{H}_{19}\text{O}_2\text{N}$	6.69	6.63	1.4485
<i>o</i> -Xylyl	$\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{Br}$	55	175 (19 mm.)	$\text{C}_{13}\text{H}_{15}\text{O}_2\text{N}$	6.45	6.38	1.5052
<i>m</i> -Xylyl	$\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{Br}$	55	180 (19 mm.)	$\text{C}_{13}\text{H}_{15}\text{O}_2\text{N}$	6.45	6.38	1.5101
<i>p</i> -Xylyl	$\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{Cl}$	48	178 (19 mm.)	$\text{C}_{13}\text{H}_{15}\text{O}_2\text{N}$	6.45	6.32	1.5023
<i>p</i> -Ethylbenzyl	$\text{C}_2\text{H}_5\text{C}_6\text{H}_4\text{CH}_2\text{Cl}$	50	116 (17 mm.)	$\text{C}_{14}\text{H}_{17}\text{O}_2\text{N}$	6.06	6.03	1.5001

precipitate appeared after a few minutes. The products were recrystallized from ethanol. On occasion it was found necessary to place the solution in a desiccator, where on standing the precipitate formed.

The properties are listed in Table III.

 TABLE III
 α -SUBSTITUTED CYANOACETHYDRAZIDES, $\text{RCH}(\text{CN})\text{CONHNH}_2$

R	M.p., °C.	Formula	Nitrogen, %	
			Calc.	Found
2-Methyl-3-butyl	101	$\text{C}_8\text{H}_{15}\text{ON}_3$	24.9	24.8
2-Methyl-4-pentyl	144	$\text{C}_9\text{H}_{17}\text{ON}_3$	23.0	23.2
Cyclohexylmethyl	246	$\text{C}_{10}\text{H}_{17}\text{ON}_3$	21.5	21.5
<i>o</i> -Methylcyclohexyl	174	$\text{C}_{10}\text{H}_{17}\text{ON}_3$	21.5	21.5
<i>m</i> -Methylcyclohexyl	207	$\text{C}_{10}\text{H}_{17}\text{ON}_3$	21.5	21.8
<i>p</i> -Methylcyclohexyl	148	$\text{C}_{10}\text{H}_{17}\text{ON}_3$	21.5	21.4
<i>o</i> -Xylyl	116	$\text{C}_{11}\text{H}_{15}\text{ON}_3$	20.7	20.5
<i>m</i> -Xylyl	107	$\text{C}_{11}\text{H}_{15}\text{ON}_3$	20.7	20.6
<i>p</i> -Xylyl	128	$\text{C}_{11}\text{H}_{15}\text{ON}_3$	20.7	20.6
<i>p</i> -Ethylbenzyl	88	$\text{C}_{12}\text{H}_{15}\text{ON}_3$	19.4	19.5

Anisal Derivatives of Substituted Cyanoacethydrazides

The hydrazides were dissolved in ethanol and anisaldehyde added to the hot solutions. If precipitation did not take place immediately, one drop of concentrated hydrochloric acid was added and the solutions let stand until precipitation occurred. The products were purified by recrystallization from ethanol.

The properties are listed in Table IV.

Amino Acids (V)

The hydrazides (0.05 mole) were dissolved in aqueous hydrochloric acid (15%, 100 ml.), cooled to 0°C., and covered with a layer of ether (75 ml.). Sodium nitrite (10 gm.) dissolved in water (30 ml.) was added dropwise to the

TABLE IV
ANISAL DERIVATIVES

Compound	M.p., °C.	Formula	Nitrogen, %	
			Calc.	Found
2-Methyl-3-butyl	219	C ₁₆ H ₂₁ O ₂ N ₃	14.6	14.7
2-Methyl-4-pentyl	196	C ₁₇ H ₂₃ O ₂ N ₃	14.0	13.9
Cyclohexylmethyl	109	C ₁₈ H ₂₃ O ₂ N ₃	13.4	13.3
<i>o</i> -Methylcyclohexyl	213	C ₁₈ H ₂₃ O ₂ N ₃	13.4	13.3
<i>m</i> -Methylcyclohexyl	183	C ₁₈ H ₂₃ O ₂ N ₃	13.4	13.6
<i>p</i> -Methylcyclohexyl	139	C ₁₈ H ₂₃ O ₂ N ₃	13.4	13.4
<i>o</i> -Xylyl	147	C ₁₉ H ₁₉ O ₂ N ₃	13.1	13.4
<i>m</i> -Xylyl	172	C ₁₉ H ₁₉ O ₂ N ₃	13.1	12.7
<i>p</i> -Xylyl	162	C ₁₉ H ₁₉ O ₂ N ₃	13.1	12.8
<i>p</i> -Ethylbenzyl	152	C ₂₀ H ₂₁ O ₂ N ₃	12.5	12.7

mechanically stirred mixtures. The azides, on formation, passed into the ether layer. On completion of the reaction, the ether was decanted and the aqueous layers rapidly extracted with two fresh portions of ether. The extracts were combined, dried over anhydrous sodium sulphate, and filtered into absolute ethanol (75 ml.). The ether was evaporated and the azides (III) refluxed on a water bath for one hour to complete the transformation to the urethanes (IV). The alcohol was removed by distillation at reduced pressure. The urethanes were hydrolyzed to the amino acids by refluxing in aqueous hydrochloric acid (20%, 200 ml.) for 48 hr. at 140°C. The mixtures were evaporated to dryness, dissolved in water, boiled with charcoal, and filtered several times. The filtrates were neutralized, concentrated to a small volume, and cooled. On the addition of acetone (2.5 liters) the amino acids precipitated. These were purified by reprecipitation in the same manner and dried in the oven at 100°C.

Table V summarized the physical constants as well as the derivatives formed.

TABLE V
AMINO ACIDS AND DERIVATIVES

Compound	Yield, %	Derivative	M.p., °C.	Formula	Nitrogen, %	
					Calc.	Found
DL- β -Methylleucine	50	Ureido	168	C ₁₄ H ₂₀ O ₃ N ₂	10.6	10.3
DL- α -Amino- β -methylisoheptanoic acid	58	Hydantoin	145	C ₉ H ₁₆ O ₃ N ₂	15.2	14.8
DL- α -Amino- β -cyclohexylpropionic acid*	39	Copper salt	—	(C ₉ H ₁₆ O ₂ N) ₂ Cu	6.94	6.68
DL-C- <i>o</i> -Methylcyclohexylglycine	39	Copper salt	—	(C ₉ H ₁₆ O ₂ N) ₂ Cu	6.94	6.84
DL-C- <i>m</i> -Methylcyclohexylglycine	35	Hydantoin	180	C ₁₀ H ₁₆ O ₂ N ₂	14.2	14.2
DL-C- <i>p</i> -Methylcyclohexylglycine	78	Hydantoin	210	C ₁₀ H ₁₆ O ₂ N ₂	14.2	14.7
DL-C- <i>o</i> -Xylylglycine	54	Hydantoin	215	C ₁₁ H ₁₂ O ₂ N ₂	13.7	14.0
DL-C- <i>m</i> -Xylylglycine	80	Ureido	172	C ₁₇ H ₁₈ O ₃ N ₂	9.40	9.71
DL-C- <i>p</i> -Xylylglycine	75	Hydantoin	190	C ₁₁ H ₁₂ O ₂ N ₂	13.7	13.9
DL- <i>p</i> -Ethylalanine	17	Hydantoin	182	C ₁₂ H ₁₄ O ₂ N ₂	12.8	13.0

*Ref. (1).

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