SYNTHESIS OF α-AMINO ACIDS FROM ETHYL CYANOACETATE[1]

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ABSTRACT

Monosubstituted cyanoacetic esters, obtained by condensation of 1-bromo-3(*s*)-phenoxypropanes (*s* = *o*-Cl, *o*-Br, *o*-I, *o*-, *m*-, and *p*-NO_2) or 1-bromo-2(*s*)-phenoxyethanes (*s* = *o*-Cl, *o*-Br, *o*-I, and *m*-NO_2) with ethyl cyanoacetate by means of potassium carbonate, were transformed through a Curtius degradation into cyanoacetisocyanates. These compounds by hydrolysis in acid or alkaline medium gave α-amino acids. However, hydrolysis of the corresponding carbobenzyloxy- or carbethoxyaminonitriles afforded better yields. The carbobenzyloxyaminonitriles were more readily hydrolyzed in aqueous hydrochloric acid than the carbethoxyaminonitriles. Moreover, the mild action of dry hydrochloric acid on the carbobenzyloxy derivatives yielded the α-amino acids readily whereas similar treatment of the carbethoxy derivatives gave the carbethoxyamino acids.

INTRODUCTION

Synthesis of α-amino acids from ethyl cyanoacetate is possible through the Curtius degradation, $RCO_2Et \rightarrow RCON_3 \rightarrow RNH_2$, as suggested by Darapsky and Hillers in 1915 (3). This method was used many times (4, 5, 6, 7, 8, 9, 10, 11) and was found of wide application even if the yields were occasionally rather low.

The purpose of the present work was to synthesize, from ethyl cyanoacetic ester, new α-amino acids substituted by phenoxyalkyl groups. Modifications of the Darapsky method were also studied in the hope of decreasing the over-all time of reaction and of obtaining better yields in a larger number of cases.

The starting materials, the phenoxyalkylbromides, were prepared with good yields by a process adapted from Marvel and Tanenbaum (12) using sodium phenolates and dibromides in water.

From the halides the monosubstituted cyanoacetic esters were obtained by the use of potassium carbonate (13, 14) instead of sodium ethylate as condensing agent.

The cyanoacethydrazides derived from the cyanoacetic esters were transformed by diazotation into azides. The yields varied from 75 to 85%, as measured by evolution of nitrogen when the azides were decomposed into cyanoacetisocyanates by heat. The temperature of rearrangement was about 50–60°C. These were converted into amino acids or carbamates (urethanes).

Several hydrolytic media were tried with the carbamates. It was found that the original procedure outlined by Darapsky and co-workers could be advantageously modified by using benzyl carbamates. The benzyl carbamates could be hydrolyzed by dry hydrochloric acid in ethyl alcohol, according to the method described by Barkdoll and Ross (2) for carbobenzyloxy groups, and then submitted to a short treatment by aqueous alkali to saponify the orthoester group formed from the nitrile. This process, besides being mild and rapid, is efficient and could be very useful when applied to unstable or slightly soluble carbamates.

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TABLE I

BROMIDES, R-Br

Compound	Time, hr.	B.p., °C./mm.	M.p., °C.	Yield, %	n_D^{25}	Formula	Halogens, %	
							Calc.	Found
o-$ClC_6H_4O(CH_2)_3Br$	5–5½	118–120/5	—	68–70	1.555	$C_9H_{10}BrClO$	46.23	45.8
o-$BrC_6H_4O(CH_2)_3Br$	5½	110–115/1–2	—	73–75	1.575	$C_9H_{10}Br_2O$	54.37	53.3
o-$IC_6H_4O(CH_2)_3Br$	5	150–152/3[1]	21–22	80–82	1.611	$C_9H_{10}BrIO$	60.65	60.2
o-$NO_2C_6H_4O(CH_2)_3Br$	10	138–140/1	37–38	58–60	—	$C_9H_{10}BrNO_3$	30.73	30.5
m-$NO_2C_6H_4O(CH_2)_3Br$	7–9	143–148/1[2]	—	72–74	—	$C_9H_{10}BrNO_3$	30.73	30.3
p-$NO_2C_6H_4O(CH_2)_3Br$	6–8	175–177/2	58–59	67–69	—	$C_9H_{10}BrNO_3$	30.73	30.7
o-$ClC_6H_4O(CH_2)_2Br$	16	138–140/12[3]	10–11	64–66	1.565	C_8H_8BrClO	48.99	48.9
o-$BrC_6H_4O(CH_2)_2Br$	20	110–111/1–2[4]	34–35[5]	72–74	—	$C_8H_8Br_2O$	57.10	57.2
o-$IC_6H_4O(CH_2)_2Br$	18	125–130/1–2	48–49[6]	75–77	—	—	—	—
m-$NO_2C_6H_4O(CH_2)_2Br$	30–35	140–145/1–2	39–40[7]	70–72	—	—	—	—

(1) *B.p.: 154–156°C. at 0.2 mm., yield: 59%, Ref. (16).*
(2) *B.p. 186–188°C. at 7 mm., yield: 75%, n_D^{25}: 1.5700, Ref. (18).*
(3) *B.p.: 140–142°C. at 13 mm., yield: 35%, Ref. (15).*
(4) *B.p.: 160–162°C. at 16 mm., Ref. (15).*
(5) *M.p.: 35–36°C., Ref. (1).*
(6) *M.p.: 50–51°C., yield: 34%, Ref. (16).*
(7) *M.p.: 39°C., Ref. (17).*

EXPERIMENTAL

Substituted Phenoxyalkyl Bromides

(*a*) *Phenoxypropyl Bromides*

Mixtures containing 1,3-dibromopropane (1.0 mole), substituted phenol (0.5 mole), sodium hydroxide (0.5 mole), and water (400 ml.) were heated under reflux with mechanical stirring until neutral. More sodium hydroxide (0.15–0.2 mole) was then added and refluxing was continued. After cooling, the neutral mixtures were made alkaline, decanted and extracted if necessary, and, after rapid drying, they were fractionated by distillation under reduced pressure.

(*b*) *Phenoxyethyl Bromides*

The same method as above mentioned was used except that the 1,2-dibromoethane was substituted for 1,3-dibromopropane. From 0.2–0.25 mole of sodium hydroxide was added to each mixture, after neutralization.

The yield of each preparation was based on the initial quantity of the phenol.

The physical properties and yields of the bromides are listed in Table I.

Monosubstituted Cyanoacetic Esters

(*a*) *From 1-Bromo-3-phenoxypropane*

Anhydrous potassium carbonate (0.12 mole) was added to solutions of the suitable bromides (0.10 mole) in ethyl cyanoacetate (0.5 mole). The mixtures were boiled for two and one-half–three hours under a 15–20 mm. pressure on an oil bath usually kept at 115–120°C. Agitation was ensured by introducing a fine stream of dry air through a capillary. After cooling, the mixtures were poured into water (100–150 ml.), extracted with ether, and the combined extracts dried over sodium sulphate. The monosubstituted esters were separated by distillation under reduced pressure. They could be crystallized from ethanol.

(*b*) *From 1-Bromo-2-phenoxyethanes*

In this case, the procedure was as above except that calcium sulphate (10 gm.) was added to the reaction mixtures (to reduce the saponification) and was filtered off before decanting the ethereal extracts.

The yields and properties of the esters are given in Table II.

TABLE II

MONOSUBSTITUTED CYANOACETIC ESTERS, $RCH(CN)COOC_2H_5$

R	B.p., °C./mm.	M.p., °C.	Yield, %	Formula	Calc., %	Found, %
o-$ClC_6H_4O(CH_2)_3$	128–133/0.05	49–50	89–91	$C_{14}H_{16}ClNO_3$	Cl, 12.59	Cl, 12.3
o-$BrC_6H_4O(CH_2)_3$	140–145/0.05	57–58	87–91	$C_{14}H_{16}BrNO_3$	Br, 24.50	Br, 24.2
o-$IC_6H_4O(CH_2)_3$	150–153/0.05	38–39	89–92	$C_{14}H_{16}INO_3$	I, 34.01	I, 34.2
o-$NO_2C_6H_4O(CH_2)_3$	175–180/0.05	76	81–85	$C_{14}H_{16}N_2O_5$	N, 9.54	N, 9.5
m-$NO_2C_6H_4O(CH_2)_3$	160–165/0.05	64	78–81	$C_{14}H_{16}N_2O_5$	N, 9.54	N, 9.4
p-$NO_2C_6H_4O(CH_2)_3$	185–190/0.05	60	75–80	$C_{14}H_{16}N_2O_5$	N, 9.54	N, 9.5
o-$ClC_6H_4O(CH_2)_2$	118–123/0.05	34–35	75–80	$C_{13}H_{14}ClNO_3$	Cl, 13.25	Cl, 13.1
o-$BrC_6H_4O(CH_2)_2$	130–135/0.05	28–29	77–80	$C_{13}H_{14}BrNO_3$	Br, 25.60	Br, 25.7
o-$IC_6H_4O(CH_2)_2$	135–140/0.05	36–37	77–80	$C_{13}H_{14}INO_3$	I, 35.33	I, 35.6
m-$NO_2C_6H_4O(CH_2)_2$	190–195/1–2	64	61–65	$C_{13}H_{14}N_2O_5$	N, 10.03	N, 10.0

Cyanoacethydrazides

The cyanoacetic esters (0.1 mole), fused and slightly cooled, were mixed with hydrazine hydrate (100%, 5 ml.) and ethanol (2–3 ml.). The solutions obtained were placed in an evacuated desiccator over phosphorus pentoxide and the solid products formed were triturated with ethyl ether and water.

The yields of pure hydrazides recrystallized from dilute ethanol varied from 80 to 90%.

Their properties are shown in Table III.

TABLE III
CYANOACETHYDRAZIDES, RCH(CN)CONHNH$_2$

R	M.p., °C.	Formula	Calc., %	Found, %
o-$ClC_6H_4O(CH_2)_3$	87–88	$C_{12}H_{14}ClN_3O_2$	Cl, 13.25	Cl, 13.1
o-$BrC_6H_4O(CH_2)_3$	99–100	$C_{12}H_{14}BrN_3O_2$	Br, 25.60	Br, 25.7
o-$IC_6H_4O(CH_2)_3$	113–114	$C_{12}H_{14}IN_3O_2$	I, 35.33	I, 35.4
o-$NO_2C_6H_4O(CH_2)_3$	112–113	$C_{12}H_{14}N_4O_4$	N, 20.13	N, 20.0
m-$NO_2C_6H_4O(CH_2)_3$	120	$C_{12}H_{14}N_4O_4$	N, 20.13	N, 20.0
p-$NO_2C_6H_4O(CH_2)_3$	127–128	$C_{12}H_{14}N_4O_4$	N, 20.13	N, 20.2
o-$ClC_6H_4O(CH_2)_2$	88–89	$C_{11}H_{12}ClN_3O_2$	Cl, 13.97	Cl, 14.0
o-$BrC_6H_4O(CH_2)_2$	95–96	$C_{11}H_{12}BrN_3O_2$	Br, 26.80	Br, 26.7
o-$IC_6H_4O(CH_2)_2$	97–98	$C_{11}H_{12}IN_3O_2$	I, 36.77	I, 36.9
m-$NO_2C_6H_4O(CH_2)_2$	101–102	$C_{11}H_{12}N_4O_4$	N, 21.21	N, 20.7

Cyanoacetisocyanates and Carbamates

The hydrazides dissolved in dilute hydrochloric acid (2*N*) were diazotized in the usual way. The azides, on formation, were extracted with ethyl ether or chloroform. The combined extracts were washed with water and dried over sodium sulphate and calcium sulphate. The cyanoacetisocyanates were obtained by heating the azides in the presence of toluene or immediately transformed into the carbamates in the presence of benzyl or ethyl alcohol. When purified by washing with sodium hydroxide (5%) and water, the carbamates could be crys-

TABLE IV
CARBAMATES, RCH(R′)NHCOOR″

R	R′	R″	M.p., °C.	Formula	Calc., %	Found, %
o-$ClC_6H_4O(CH_2)_3$	CN	C_2H_5	46–47	$C_{14}H_{17}ClN_2O_3$	Cl, 11.95	Cl, 11.8
	COOH	C_2H_5	89–90	$C_{14}H_{18}ClNO_5$	Cl, 11.24	Cl, 11.2
o-$BrC_6H_4O(CH_2)_3$	CN	C_2H_5	67–68	$C_{14}H_{17}BrN_2O_3$	Br, 23.45	Br, 23.5
	COOH	C_2H_5	101–102	$C_{14}H_{18}BrNO_5$	Br, 22.20	Br, 21.9
	CN	$CH_2C_6H_5$	84–85	$C_{19}H_{19}BrN_2O_3$	Br, 19.83	Br, 19.8
o-$IC_6H_4O(CH_2)_3$	CN	$CH_2C_6H_5$	90–92	$C_{19}H_{19}IN_2O_3$	I, 28.23	I, 28.3
o-$NO_2C_6H_4O(CH_2)_3$	CN	C_2H_5	66	$C_{14}H_{17}N_3O_5$	N, 13.68	N, 13.6
	COOH	C_2H_5	123–124	$C_{14}H_{18}N_2O_7$	N, 8.60	N, 8.8
m-$NO_2C_6H_4O(CH_2)_3$	CN	C_2H_5	108	$C_{14}H_{17}N_3O_5$	N, 13.68	N, 13.6
p-$NO_2C_6H_4O(CH_2)_3$	CN	C_2H_5	62–63	$C_{14}H_{17}N_3O_5$	N, 13.68	N, 13.5
	CN	$CH_2C_6H_5$	75–76	$C_{19}H_{19}N_3O_5$	N, 11.38	N, 11.4
o-$ClC_6H_4O(CH_2)_2$	CN	C_2H_5	69	$C_{13}H_{15}ClN_2O_3$	Cl, 12.56	Cl, 12.7
o-$BrC_6H_4O(CH_2)_2$	CN	C_2H_5	75	$C_{13}H_{15}BrN_2O_3$	Br, 24.45	Br, 24.2
o-$IC_6H_4O(CH_2)_2$	CN	C_2H_5	74	$C_{13}H_{15}IN_2O_3$	I, 33.95	I, 33.7
	CN	$CH_2C_6H_5$	91–92	$C_{18}H_{17}IN_2O_3$	I, 29.09	I, 28.8
m-$NO_2C_6H_4O(CH_2)_2$	CN	$CH_2C_6H_5$	83–84	$C_{18}H_{17}N_3O_5$	N, 11.83	N, 11.9

TABLE V

AMINO ACIDS AND DERIVATIVES

Amino acids R-CH(NH)$_2$COOH R	Starting materials R-CH(CN)R′ R′	Hydrolyzing method: Agent	Temp., °C.	Time, hr.	Yield, %	Formula	Calc., %	Found, %	Derivatives	M.p., °C.	Formula	Calc., %	Found, %
o-ClC$_6$H$_4$O(CH$_2$)$_3$	NHCOOC$_2$H$_5$	37% HCl	100	2	63–67	$C_{11}H_{14}ClNO_3$	Cl, 14.57	Cl, 14.4	Phenylureido	169–171*	$C_{18}H_{19}ClN_2O_4$	Cl, 9.78	Cl, 9.6
		37% HCl	120	1½	65–69								
o-BrC$_6$H$_4$O(CH$_2$)$_3$	NCO	30% KOH[1]	B.p.	½	43–47	$C_{11}H_{14}BrNO_3$	Br, 27.73	Br, 27.8	Phenylureido	178–180*	$C_{18}H_{19}BrN_2O_4$	Br, 19.65	Br, 19.5
	NHCOOC$_2$H$_5$	16% HCl	B.p.	72	65–69								
		37% HCl	120	1½	65–69								
	NHCOOCH$_2$C$_6$H$_5$	16% HCl	B.p.	9	72–78								
		Dry HCl[2]	B.p.	1–1¼	68–72								
o-IC$_6$H$_4$O(CH$_2$)$_3$	NHCOOCH$_2$C$_6$H$_5$	Dry HCl	B.p.	1–1¼	67–71	$C_{11}H_{14}INO_3$	I, 37.86	I, 37.4	Phenylureido	184–186*	$C_{18}H_{19}IN_2O_4$	I, 27.95	I, 28.0
o-NO$_2$C$_6$H$_4$O(CH$_2$)$_3$	NHCOOC$_2$H$_5$	16% HCl	B.p.	60	76–81	$C_{11}H_{14}N_2O_5$	N, 11.02	N, 11.0	Phenylureido	163–165*	$C_{18}H_{19}N_3O_6$	N, 11.26	N, 11.3
		37% HCl	100	4	76–81								
		37% HCl	120	1½	72–78								
m-NO$_2$C$_6$H$_4$O(CH$_2$)$_3$	NCO	37% HCl[3]	B.p.	1	29–31	$C_{11}H_{14}N_2O_5$	N, 11.02	N, 11.0	Hydantoin	157–158	$C_{12}H_{13}N_3O_5$	N, 15.05	N, 15.2
									Phenylureido	174–176*	$C_{18}H_{19}N_3O_6$	N, 11.26	N, 11.3
	NHCOOC$_2$H$_5$	16% HCl	B.p.	60	72–77								
		37% HCl	100	3	77–83								
		37% HCl	120	1½	75–81								
p-NO$_2$C$_6$H$_4$O(CH$_2$)$_3$	NHCOOC$_2$H$_5$	37% HCl	120	1½	69–73	$C_{11}H_{14}N_2O_5$	N, 11.02	N, 10.7	Phenylureido	190–192*	$C_{18}H_{19}N_3O_6$	N, 11.26	N, 11.4
	NHCOOCH$_2$C$_6$H$_5$	37% HCl	100	1½	66–70								
o-ClC$_6$H$_4$O(CH$_2$)$_2$	NHCOOC$_2$H$_5$	37% HCl	120	1½	60–64	$C_{10}H_{12}ClNO_3$	Cl, 15.45	Cl, 15.5	Phenylureido	167–169*	$C_{17}H_{17}ClN_2O_4$	Cl, 10.18	Cl, 10.1
		Ba(OH)$_2$[4]	160	½	40–46								
o-BrC$_6$H$_4$O(CH$_2$)$_2$	NHCOOC$_2$H$_5$	16% HCl	B.p.	72	48–52	$C_{10}H_{12}BrNO_3$	Br, 29.17	Br, 28.9	*p*-Tolylsulphonamido	147–148	$C_{16}H_{18}BrNO_5S$	Br, 18.66	Br, 18.8
		37% HCl	100	2	57–61								
o-IC$_6$H$_4$O(CH$_2$)$_2$	NHCOOCH$_2$C$_6$H$_5$	Dry HCl	B.p.	1–1¼	59–63	$C_{10}H_{12}INO_3$	I, 39.53	I, 40.0	*p*-Tolylsulphonamido	157–158	$C_{16}H_{18}INO_5S$	I, 26.72	I, 27.0
m-NO$_2$C$_6$H$_4$O(CH$_2$)$_2$	NHCOOCH$_2$C$_6$H$_5$	Dry HCl	B.p.	1–1¼	58–62	$C_{10}H_{12}N_2O_5$	N, 11.67	N, 11.3	Copper salt	—	$C_{20}H_{22}CuN_4O_{10}$	Cu, 11.75	Cu, 11.5

[1] *Aqueous solution. Mixture left standing for 12 hr. at 25°C. after boiling.*
[2] *Treatment followed by a mild hydrolysis with aqueous potassium hydroxide.*
[3] *Heated slowly in an open vessel. Mixture left standing for 8 hr. at 25°C. after boiling.*
[4] *Hot saturated aqueous solution.*
* *Dec. m.p. determined with Dennis & Shelton apparatus.*

tallized from a mixture of petroleum ether (65–110°C.) and ethyl ether. By hydrolysis of the nitrile group in hot alcoholic solution with dry hydrochloric acid, followed by a mild alkaline treatment, the carbethoxyaminonitriles gave rise to carbethoxyamino acids.

The properties of the carbamates are listed in Table IV.

Amino Acids

The crude carbamates or cyanoacetisocyanates were hydrolyzed. The acidified mixtures were evaporated to dryness. Baryta, when used, was first eliminated by sulphuric acid. Water or ethanol was added to the residues. After filtration, the solutions were purified in the usual way. Finally, the amino acids were precipitated with ammonia or sodium hydroxide when in aqueous media, or with piperidine when in alcoholic media. The yields were based on the quantities of cyanoacetisocyanates or carbamates contained in the crude materials.

A summary of the methods of hydrolysis used together with the properties of the derivatives of the amino acids is given in Table V.

REFERENCES

1. AUWERS, K. Ann. 148: 415. 1918.
2. BARKDOLL, A. E. and ROSS, W. F. J. Am. Chem. Soc. 66: 953. 1944.
3. DARAPSKY, A. and HILLERS, D. J. prakt. Chem. 92: 297. 1915.
4. DARAPSKY, A. J. prakt. Chem. 146: 250. 1936.
5. GAGNON, P. E., GAUDRY, R., and KING, F. E. J. Chem. Soc. 13. 1944.
6. GAGNON, P. E., SAVARD, K., GAUDRY, R., and RICHARDSON, E. M. Can. J. Research, B, 25: 28. 1947.
7. GAGNON, P. E. and BOIVIN, J. L. Can. J. Research, B, 26: 503. 1948.
8. GAGNON, P. E. and NOLIN, B. Can. J. Research, B, 27: 742. 1949.
9. GAGNON, P. E., BOIVIN, J. L., and BOIVIN, P. A. Can. J. Research, B, 28: 207. 1950.
10. GAGNON, P. E., BOIVIN, J. L., and GIGUERE, J. Can. J. Research, B, 28: 352. 1950.
11. GAGNON, P. E., BOIVIN, P. A., and CRAIG, H. Can. J. Chem. 29: 70. 1951.
12. MARVEL, C. S. and TANENBAUM, A. L. J. Am. Chem. Soc. 44: 2647. 1922.
13. ROBINSON, G. M. J. Chem. Soc. 125: 226. 1924.
14. ROBINSON, R. and WATT, J. S. J. Chem. Soc. 1539. 1934.
15. STOERMER, R. and GOHL, F. Ber. 36: 2874. 1903.
16. STRAIN, W. H., PLATI, J. T., and WARREN, S. L. J. Am. Chem. Soc. 64: 1436. 1942.
17. WEDDIGE, A. J. prakt. Chem. 24: 241. 1881.
18. WILSON, W. C. and ADAMS, R. J. Am. Chem. Soc. 45: 539. 1923.