[CONTRIBUTION FROM THE LABORATORY OF HIGH MOLECULAR CHEMISTRY,
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THE PREPARATION AND CONDENSATION POLYMERIZATION OF HIGHER ALKYL ESTERS OF α-AMINO ACIDS[1]

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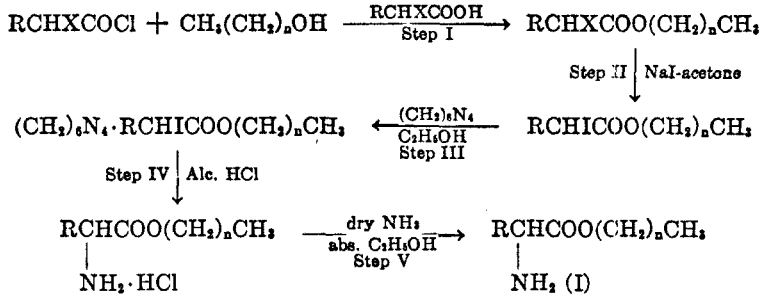
In the course of our general research program on the polymerization of α-amino acid derivatives (1, 2, 3, 4, 4a, 5), we have observed (6, *cf.* refs. 1, 3) that surface forces enhanced the velocity of the condensation polymerization which results in polypeptide chains (1, 7), even with fairly stable amino acid esters. This observation has prompted us to investigate whether the surface activity of higher alkyl esters of α-amino acids would similarly enhance the velocity of polymerization of such esters, in comparison with that of the lower alkyl esters.

The preparation of a series of esters of general formula (I) was carried out according to the following general scheme, advantageously adapting the hexamethylenetetramine method of Delépine (8), Mannich and Drauzburg (9) and Galat and Elion (10).

Synthetic Scheme:—



R = H or CH_3; X = Cl or Br; n = 7, 11, 15 or 17. Yields at each step were 80–90%, with an over-all yield of amino acid esters of about 60%.

The same procedure was sucessfuly applied to the preparation of β-naphthyl α-aminoacetate and the previously known cholesteryl α-aminoacetate (11).

As anticipated, the new esters polymerized readily, with elimination of the free alcohol and formation of polypeptide linkages.

EXPERIMENTAL

Step I. Preparation of RCHXCOO $(CH_2)_nCH_3$. The alcohol to be esterified, mixed with three to four parts by weight of RCHXCOOH, was refluxed with 1.5 equivalents of the corresponding acid chloride until evolution of hydrogen chloride was complete, usually about two hours. The ester was precipitated by pouring the hot reaction mixture, slowly, into a large volume of vigorously stirred ice-water, and was then allowed to stand for 2–3

[1] Abstracted from dissertations for the M. Sc. degree of A. Baniel (1943) and I. Friedrich (1947) at the Hebrew University.

hours to complete hydrolysis of the excess acid chloride and solution of the acid. The crude ester was taken into ether and the ether solution freed of acid by washing with sodium bicarbonate solution, washed to neutrality with water, and dried over sodium sulfate. The ester was isolated by concentration of the ether solution and purified by distillation *in vacuo*. The properties and analytical data for these esters are given in Table I.

Step II. Preparation of $RCHICOO(CH_2)_nCH_3$. The chloro- or bromo-ester was treated for two hours in the dark with an anhydrous acetone solution of 1.25 equivalents of sodium iodide. The solution was freed of the separated salt by filtration and concentrated on the steam-bath. The residue was extracted with peroxide-free ether, the ether solution was washed free of traces of iodine with aqueous sodium bisulfite and then with water. The ether solution, dried over sodium sulfate, was concentrated on the steam-bath and the

TABLE I

$RCHXCOO(CH_2)_nCH_3$

ESTER			FORMULA	ANAL., % X.		M.P., °C.	B.P., °C/MM.
R	X	n		Calc'd	Found		
H	Cl	7	$C_{10}H_{19}ClO_2$	17.2	17.2	Liqu.	110/2
H	Cl	11	$C_{14}H_{27}ClO_2$	13.5	13.6	7	190/25
H	Cl	15	$C_{18}H_{35}ClO_2$	11.1	11.2	28	180/2
H	Cl	17	$C_{20}H_{39}ClO_2$	10.2	10.3	29	Dec.
CH_3	Br	7	$C_{11}H_{21}BrO_2$	30.2	30.1	Liqu.	130/2
CH_3	Br	15	$C_{19}H_{37}BrO_2$	21.2	21.8	11	220/2

TABLE II

$RCHICOO(CH_2)_nCH_3$

ESTER		FORMULA	IODINE, %		M.P., °C.	B.P., °C/2MM.
R	n		Calc'd	Found		
H	7	$C_{10}H_{19}IO_2$	42.7	43.9	Liqu.	122
H	11	$C_{14}H_{27}IO_2$	35.9	36.3	6	173
H	15	$C_{18}H_{35}IO_2$	31.0	30.2	14	201
H	17	$C_{20}H_{39}IO_2$	29.0	28.6	15	Dec.
CH_3	7	$C_{11}H_{21}IO_2$	40.7	39.3	Liqu.	132
CH_3	15	$C_{19}H_{37}IO_2$	29.9	29.2	29	230

iodo-acid ester was purified by distillation *in vacuo*. The properties and analytical data for the iodo-acid esters are given in Table II.

The iodo-acid esters are unstable, undergoing slight decomposition during distillation, as well as on standing for any length of time, as evidenced by the appearance of free iodine. For this reason analyses were always performed immediately on the freshly distilled product.

Step III. Preparation of $(CH_2)_6N_4 \cdot RCHICOO(CH_2)_nCH_3$. The iodo-acid ester (1.5 moles) was added to a warm solution of one mole of hexamethylenetetramine in 500 ml. of alcohol and boiled under reflux for thirty minutes. The mixture was allowed to stand overnight, during which some product separated. The reaction mixture was poured into five liters of vigorously stirred water, completing the precipitation of the product and dissolving the unreacted hexamethylenetetramine. The product was filtered only after it had remained in contact with the aqueous solution for an additional 24 hours, to ensure

complete solution of hexamethylenetetramine and permit the original, finely divided, flaky precipitate to grow into coarser, more easily filterable aggregates. The product was then separated, washed with distilled water, and dried in a desiccator.

For the preparation of the octyl esters (n = 7) the procedure was modified to achieve improved yields by mixing one mole of the iodo-acid ester with 1.25 moles of the tetramine in hot alcohol, and allowing the mixture to stand for a week before working up. The product was isolated, in these cases, by evaporation of the alcohol *in vacuo*, the residue washed with water and dried *in vacuo*. The dried residue was freed of unreacted ester by washing with absolute ether and again drying in a desiccator. The product was then obtained as a white or slightly yellow crystalline powder. The properties and analytical data for these complexes are listed in Table III.

Step IV. Preparation of salts of $RCH(NH_2)_nCH_3$. Two grams of the tetramine complex was suspended in 10 ml. of absolute alcohol. Four equivalents of concentrated hydrochloric acid was added to the mixture which was then boiled gently under reflux for 20–30 minutes.

It was necessary to apply different techniques of isolation for those esters in which n = 7 or 9 than for those in which n = 11, 15, or 17. In the former cases the salts are too water-soluble to be isolated as readily as the corresponding salts of the latter group.

TABLE III

$(CH_2)_6N_4 \cdot RCHICOO(CH_2)_nCH_3$

ESTER		M.P., °C.	FORMULA	IODINE, %		NITROGEN, %	
R	n			Calc'd	Found	Calc'd	Found
H	7	173	$C_{16}H_{31}IN_4O_2$	28.9	28.1	12.8	13.5*
H	11	175	$C_{20}H_{39}IN_4O_2$	25.7	26.0	11.3	11.4
H	15	108	$C_{24}H_{47}IN_4O_2$	23.1	23.1	10.2	10.4
H	17	104	$C_{26}H_{51}IN_4O_2$	22.0	21.3	9.7	9.6
CH_3	7	179	$C_{17}H_{33}IN_4O_2$	28.8	27.5	12.7	12.9
CH_3	15	112	$C_{25}H_{49}IN_4O_2$	22.5	22.4	9.9	10.1

* The material is slightly contaminated by $(CH_2)_6N_4$.

(a) For n = 11, 15, or 17. The hot alcoholic solution of the hydrochloride was poured slowly, with vigorous stirring, into a concentrated solution of sodium bisulfite. The bisulfite salt separated at once as a flaky, white precipitate which was separated by filtration, after standing for two hours, and dried in a desiccator. The salt was recrystallized from absolute ethanol, and was used in this form for the liberation of the free amino acid ester.

(b) For n = 7 or 9. The hydrolysis mixture was concentrated in a desiccator over solid sodium hydroxide to a syrup, which was used in the following step without further purification.

Step V. Liberation of $RCH(NH_2)COO(CH_2)_nCH_3$ *from their salts.* Either salt (IVa or IVb) was suspended in dry ether, the mixture cooled, and then treated with a slow stream of dry gaseous ammonia under strictly anhydrous conditions. A large excess and a rapid stream of ammonia should be avoided to prevent loss of lower esters by volatilization.

After filtration, the ether solution was concentrated in a vacuum desiccator. In this manner the ester was isolated analytically pure. All the esters were colorless liquids or white, soft, waxy solids which tended to polymerize on standing. However, they could be stored as stable hydrochlorides. The properties and analytical data for the esters are given in Table IV.

Preparation of pure hydrochlorides of the two cetyl esters (n = 15, R = H or CH_3) was achieved by treatment of an ether solution of each ester with dry gaseous hydrogen chloride.

The crystalline hydrochlorides, which separate immediately, were filtered and dried for analysis *in vacuo* over sodium hydroxide.

Cetyl α-aminoacetate hydrochloride:

Anal. Calc'd for $C_{18}H_{38}ClNO_2$; Cl, 10.6; N, 4.2.
Found: Cl, 10.4; N, 4.2.

Cetyl α-aminopropionate hydrochloride:

Anal. Calc'd for $C_{19}H_{40}ClNO_2$: Cl, 10.2; N, 4.0.
Found: Cl, 10.3; N, 3.9.

β-Naphthyl α-aminoacetate. The present method has been successfully applied to the synthesis of phenolic esters of α-amino acids by Mannich and Drauzburg (9) and Lakner (12). Using β-naphthyl α-chloroacetate (13) as starting material, and following the modifications of the outlined synthetic scheme for the higher alkyl esters, β-naphthyl α-aminoacetate was produced. The yield at each step was 80–90%. It was obtained as a solid, m.p. 60°.

Anal. Calc'd for $C_{12}H_{11}NO_2$: N, 7.0. Found: N, 6.8.

The hydrochloride was obtained as a solid, m.p. 224° (dec.).

Anal. Calc'd for $C_{12}H_{12}ClNO_2$: Cl, 14.9. Found: Cl, 14.6.

Cholesteryl α-aminoacetate. This ester has been prepared (11) from cholesterol and aminoacetyl chloride. Using cholesteryl α-chloroacetate (14) in our synthetic scheme, cholesteryl α-aminoacetate, identical with that previously reported (11), was obtained.

TABLE IV

$RCH(NH_2)COO(CH_2)_nCH_3$

ESTER		M.P., °C.	FORMULA	NITROGEN, %	
R	n			Calc'd	Found
H	7	Liqu.	$C_{10}H_{21}NO_2$	7.5	7.4
H	15	52	$C_{18}H_{37}NO_2$	4.7	4.4
H	17	60	$C_{20}H_{41}NO_2$	4.3	4.3
CH_3	7	Liqu.	$C_{11}H_{23}NO_2$	7.0	6.9
CH_3	15	57	$C_{19}H_{39}NO_2$	4.5	4.2

Polymerization experiments. (*A*) *Surface polymerization.* We wish to describe only some preliminary observations. Monolayers of the α-aminoacetates, including cetyl and octadecyl, were spread on a water surface and the thus formed films were immediately deposited on a polished metal plate by Blodgett's technique (15). In carrying out similar experiments with the lower alkyl esters of glycine and alanine, it was found that the major part dissolved in water but the remainder formed an insoluble film. The deposit of polylayer was scraped off and submitted to the biuret test. A very distinct violet color, indicative of the presence of polypeptide linkages, was obtained. In contrast, it should be noted, the ester *per se* in bulk, at the same temperature for the same time, underwent no significant polymerization. Even methyl α-aminopropionate, which shows only very slight tendency to polymerize at room temperature, undergoes polymerization when spread and multilayered.

(*B*) *Heat polymerization.* Cetyl α-aminoacetate was heated at 80° in a sealed tube for two hours. The molten mass solidified slowly at the end of the heating period. The contents of the tube was cooled and washed with ether to extract unchanged monomer and cetyl alcohol. Van Slyke manometric analyses for free amino groups proved that condensation-polymerization had occurred. A polyglycine ester with an average of twenty glycine units per polymer was obtained.

In contrast to the polymerization of the lower alkyl esters, the formation of diketopiperazine was not observed in this experiment.

SUMMARY

A method for the preparation of higher alkyl esters of glycine and alanine is described. The preparation and properties of the octyl, dodecyl, hexadecyl, octadecyl, β-naphthyl, and cholesteryl esters of these amino acids, as well as the intermediates are described.

Results of preliminary experiments on the surface enhanced condensation-polymerization of various esters of glycine and alanine are reported.

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