101. *Palmitoyl- and Stearoyl-glycylglycine and -diglycylglycine.*

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The synthesis of polypeptides bearing long aliphatic chains has been undertaken in order that the surface films of the corresponding amides might be investigated. The stearoyl and palmitoyl derivatives of glycine, glycylglycine and diglycylglycine have been prepared

Long-chain acylamino-acids containing one nitrogen atom have been prepared by Abderhalden and Funk (*Z. physiol. Chem.*, 1910, **65**, 62), Bondi (*Biochem. Z.*, 1909, **17**, 543, 553), and Izar (*Biochem. Z.*, 1912, **40**, 403). Bondi suggested the term " lipopeptide " for this class of compound, but this was unacceptable to Abderhalden because such substances do not contain free amino-groups.

The required derivatives were obtained by the action of the appropriate acid chlorides on an alkaline aqueous solution of glycine or the polyglycine.

The esters of these acids were prepared in two ways. Palmitoyl- and stearoyl-glycine may be esterified by boiling 4% methyl-alcoholic hydrogen chloride. The dipeptides are hydrolysed by such treatment, but survive the action of dry hydrogen chloride passed into a suspension of the acid in anhydrous methyl alcohol. It has not so far been possible to esterify the tripeptides.

The corresponding *amides* were prepared by the action of ammonia on the *methyl* esters of the amino-acids.

Experimental.

Esters of Palmitoylglycine.—The ethyl ester has been obtained by coupling palmitoyl chloride with glycine ethyl ester (Abderhalden and Funk, *loc. cit.*). It was also obtained by refluxing palmitoylglycine (4 g.) with 4% ethyl-alcoholic hydrogen chloride for 2 hours. The ester (3 g.), crystallised from alcohol, had m. p. 80—82° (Abderhalden and Funk give m. p. 80—85°).

The methyl ester, prepared in a similar way and crystallised from alcohol, had m. p. 104—105°.

Palmitoylglycinamide.—Palmitoylglycine methyl ester (3 g.) was dissolved in methyl-alcoholic ammonia (50 g. of 5%). After 24 hours the *amide* began to separate as a white crystalline solid and the separation was complete after about 2 weeks. The solution was cooled in ice, and the product collected and recrystallised from alcohol. It formed large plates with a nacreous lustre (2 g.), m. p. 161—162° (Found: N, 8·8. $C_{18}H_{36}O_2N_2$ requires N, 9·0%).

Stearoylglycine.—This was prepared by the methods of Abderhalden and Funk (*loc. cit.*), Bondi (*loc. cit.*), and Izar (*loc. cit.*). The m. p. given in the literature, 145°, could not, however, be verified. Carefully purified stearic acid was used, and the compound was repeatedly crystallised from alcohol, chloroform, and benzene; it had m. p. 125—126° (Found: C, 70·2; H, 11·3; N, 4·2. Calc. for $C_{20}H_{39}O_3N$: C, 70·3; H, 11·4; N, 4·1%).

Stearoylglycine Methyl Ester.—The acid (5·7 g.) was refluxed with methyl-alcoholic hydrogen chloride (50 g. of 4%) for 3 hours. On cooling, the ester crystallised in needles. After the solution had been cooled in ice, the product was collected and dried over potassium hydroxide; it had m. p. 75—76° (yield, 5·4 g.).

Stearoylglycinamide.—The ester (5·2 g.) was dissolved in methyl-alcoholic ammonia (100 g. of 5%) and kept for 2 weeks; most of the *amide* produced had then separated. The mixture was cooled to 0°, and the product collected and recrystallised from alcohol and from acetic acid; it had m. p. 157—158° (yield, 3·8 g.) (Found: N, 8·5. $C_{20}H_{40}O_2N_2$ requires N, 8·3%).

Palmitoylglycylglycine.—Finely powdered glycine anhydride (Fischer, *Ber.*, 1906, **39**, 2930) (2·5 g.) was stirred with 2N-sodium hydroxide (11 c.c.) until all had dissolved. A solution of palmitoyl chloride (from 5·12 g. of the acid) in ether and 2N-sodium hydroxide (20 c.c.) were added alternately in small portions with vigorous shaking. The product separated as a white emulsion which coagulated to a granular mass. The solution was acidified with dilute hydrochloric acid; *palmitoylglycylglycine*, after being washed with water, crystallised from acetic acid–alcohol in fine needles (5·7 g.), m. p. 171—172° (decomp.) (Found: C, 64·7; H, 10·2; N, 7·6. $C_{20}H_{38}O_4N_2$ requires C, 64·9; H, 10·3; N, 7·6%).

Palmitoylglycylglycine Methyl Ester.—A rapid current of dry hydrogen chloride was passed through a suspension of the above dipeptide (4 g.) in anhydrous methyl alcohol (120 c.c.). As the mixture became hot, the dipeptide went into solution and when this occurred the mixture was cooled in ice. The *ester* soon crystallised; it was collected, washed with a little methyl alcohol and with ether, dried, and recrystallised from methyl alcohol, forming large, rhombic plates (2·85 g.), m. p. 139° (Found: N, 7·4. $C_{21}H_{40}O_4N_2$ requires N, 7·3%).

Palmitoylglycylglycinamide.—The methyl ester (0·9 g.) was heated in a sealed tube for 3 hours with methyl alcohol (15 c.c.) saturated at 0° with ammonia. The product that separated was crystallised from methyl alcohol and acetic acid, being obtained in fine needles. After being dried at 100° in a vacuum for 2 hours, it had m. p. 199—200° (yield, 0·7 g.) (Found: N, 11·5. $C_{20}H_{39}O_3N_3$ requires N, 11·4%).

Stearoylglycylglycine.—This was prepared in the same way as the palmitoyl analogue (glycine anhydride, 2·5 g., 2N-sodium hydroxide, 11 c.c.; stearoyl chloride from 5·7 g. of the acid, 2N-sodium hydroxide, 20 c.c.; time of addition, 45 minutes). The granular precipitate (6·5 g.) obtained on acidification was washed with water and crystallised from aqueous alcohol and from alcoholic acetic acid; it then had m. p. 168°, after softening at 160° (yield, 5·8 g.) (Found: C, 66·0; H, 10·5; N, 7·0. $C_{22}H_{42}O_4N_2$ requires C, 66·3; H, 10·5; N, 7·0%).

Stearoylglycylglycine Methyl Ester.—The dipeptide (4·8 g.) was suspended in anhydrous methyl alcohol (120 c.c.), and a rapid current of dry hydrogen chloride passed through the mixture. When complete solution occurred, the mixture was cooled and kept at room temperature; the product partly crystallised. After cooling in ice, the *ester* was collected, washed with cold methyl alcohol and ether, and recrystallised from methyl alcohol, forming plates or flattened needles (4 g.), m. p. 135—136° (Found: N, 6·6. $C_{23}H_{44}O_4N_2$ requires N, 6·8%).

Stearoylglycylglycinamide.—The methyl ester (2·5 g.) was heated in a sealed tube for 3 hours at 100° with methyl alcohol (15 c.c.) saturated at 0° with ammonia. The white solid obtained was collected, crystallised from acetic acid, and dried for 1 hour in a vacuum at 100°. Yield, almost quantitative; m. p. 196° (Found: N, 10·5. $C_{22}H_{43}O_3N_3$ requires N, 10·6%).

Palmitoyldiglycylglycine.—Palmitoyl chloride (from 5·12 g. of the acid), dissolved in anhydrous ether, and 2N-sodium hydroxide (20 c.c.) were added alternately in small portions with vigorous shaking to a solution of diglycylglycine (4 g.) (Fischer, *loc. cit.*; Abderhalden and Fodor, *Ber.*, 1916, **49**, 516) in 2N-sodium hydroxide (20 c.c.). After acidification, the precipitate was collected, washed with water, and crystallised from alcoholic acetic acid; it had m. p. 207—209° (decomp.) (yield, 5 g.) (Found: C, 62·0; H, 9·8; N, 9·8. $C_{22}H_{41}O_5N_3$ requires C, 61·8; H, 9·6; N, 9·8%).

Stearoyldiglycylglycine.—This was prepared, in the same way as the palmitoyl derivative, from stearoyl chloride (5·7 g. of the acid) and diglycylglycine (4 g.). Crystallised twice from acetic acid and dried at 100° in a vacuum, it had m. p. 210° (yield, 6 g.) (Found: C, 63·5; H, 9·9; N, 9·4. $C_{24}H_{45}O_5N_3$ requires C, 63·3; H, 9·9; N, 9·2%).

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