Synthesis of Long Chain Fatty Acid Amides of Amino Acids[1]

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The preparation of long chain fatty acid amides of sphingosine and dihydrosphingosine in a nonaqueous medium was reported in an earlier communication.[2] This procedure has been successfully extended to the synthesis of several long chain fatty acid amides of serine and its methyl ester. *N*-palmitoylserine has been made previously, but no information was given concerning its preparation and physical properties.[3] In the present method, the amino acid was converted to the methyl ester which was allowed to react with the acyl chloride in dimethylformamide in the presence of pyridine as acid acceptor. The resulting *N*-acylamino acid methyl ester yielded the free acid after mild saponification. The difficulties encountered in the long chain acylation of monoamino polycarboxylic acids by Jungermann *et al.*[4] were obviated in this system as illustrated in the preparation of *N*-palmitoylglutamate. Advantages of the present nonaqueous procedure are (1) reasonable yields, (2) avoidance of emulsions, (3) ease of isolation of the product, particularly with increasing chain length of the fatty acid moiety, and (4) elimination of the necessity for *p*H regulation of the reaction mixture.[4]

TABLE I

Compound	Yield, %	M.P.	Analysis					
			Carbon		Hydrogen		Nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
N-*trans*-2-hexadecenoyl-DL-serine methyl ester	51	79–80	67.55	67.55	10.50	10.54	3.94	3.82
N-palmitoyl-DL-serine methyl ester	67	86–87	67.17	67.44	11.00	11.08	3.92	3.82
N-stearoyl-DL-serine methyl ester	70	90–91	68.51	68.34	11.25	11.31	3.63	3.66
N-palmitoyl-L-glutamic acid dimethyl ester	47[a]	73–74	66.77	67.03	10.49	10.64	3.39	3.40
N-*trans*-2-hexadecenoyl-DL-serine	88	122–123	66.81	66.79	10.34	10.38	4.10	4.00
N-palmitoyl-DL-serine	91	108–109	66.42	67.13	10.86	11.03	4.08	3.97
N-stearoyl-DL-serine	94	110–111	67.86	67.91	11.13	11.30	3.77	3.68
N-palmitoyl-L-glutamic acid	87	104–106	65.40	66.09	10.20	10.20	3.63	3.67

[a] Calculated on the basis of the L-glutamic acid employed in the preparation of the dimethyl ester; see text.

EXPERIMENTAL

N-Acylamino acid methyl ester. DL-Serine methyl ester hydrochloride, m.p., 133–135°, was prepared according to the method of Fischer and Suzuki.[5] The stoichiometric amount of sodium methoxide in methanol[5] was added to 4.0 g. (25.7 mM) of DL-serine methyl ester hydrochloride and, after the addition of one-sixth volume of ether, the reaction mixture was successively chilled, filtered and concentrated to a sirup. To the resulting free base in 35 ml. of dimethylformamide and 2 ml. of pyridine were added 23.1 mM of the acyl chloride[2] (*trans*-2-hexadecenoyl chloride was prepared from the corresponding acid according to the procedure of Shapiro *et al.*[6]) in 15 ml. of dimethylformamide. After standing at room temperature for 1 hr., the reaction mixture was chilled overnight at 5°. The precipitate was removed by suction filtration and crystallized successively from petroleum ether, b.p., 60–70°, and methanol (Table I).

The L-glutamic acid dimethyl ester hydrochloride was prepared in essentially the same manner as was the serine compound by saturating 70 ml. of anhydrous methanol containing 5.0 g. of L-glutamic acid with dry HCl. After concentrating the reaction mixture below 50°, the residue was reconcentrated upon the addition of 50 ml. of methanol and dried *in vacuo* over phosphorus pentoxide and potassium hydroxide. The free base was liberated from the hydrochloride and reacted with the acyl chloride in exactly the manner as was described for the corresponding serine methyl ester (Table I).

N-acylamino acid. One g. of the *N*-acylamino acid methyl ester was dissolved in 100 ml. of methanol followed by the addition of 10 ml. of *N* NaOH. A precipitate formed after several minutes and the reaction mixture was allowed to stand overnight at room temperature. After acidification with 6*N* HCl, the solution was chilled and the precipitate, removed by suction filtration, was crystallized from 95 ml. of 85% ethanol containing 2 ml. of 6*N* HCl and then from 100 ml. of 95% ethanol; *N*-palmitoyl-L-glutamic acid was crystallized from 50% ethanol (Table I.). All of the *N*-acylamino acids gave negative ester[7] and ninhydrin (conducted in 95% ethanol) reactions.

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Preparation of Chenodeoxycholic Acid

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During the course of our work on the isolation of bile acids, it became necessary for us to obtain

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