SYNTHESIS AND REACTIONS OF N-(3,4,5-TRIMETHOXYBENZOYL)-ε-CAPROLACTAM

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N-(3,4,5-Trimethoxybenzoyl)-ε-caprolactam was prepared and subjected to alkaline alcoholysis to afford the methyl and ethyl ester of N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproic acid. The free N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproic acid was obtained by alkaline hydrolysis of these esters.

Numerous papers have recently appeared on syntheses[1-7] of pharmaceutically interesting compounds for the treatment of the acute phase of myocardium infarction and the treatment of heart ischemia and arrythmia[8-10]. These compounds are of the gallic acid type and also include the N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproic acid (*Va*). The synthesis of the acid *Va* is disclosed in two patents[1,2] which make use of methods known in the field of amino acids, namely, the reaction of ε-aminocaproic acid with the chloride or mixed anhydride of 3,4,5-trimethoxybenzoic acid in alkali and benzene, resp.

We did not meet with success in the attempted preparation of N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproic acid (*Va*) by aminolysis of methyl 3,4,5-trimethoxybenzoate with sodium ε-aminocaproate in various solvents; the unreacted ester was always isolated. A similar failure has been recorded by Schiemenz and Engelhard[11] in the aminolysis of the above ester with aliphatic amines. In another approach, the reaction of 3,4,5-trimethoxybenzoyl chloride (*I*) with ε-caprolactam (*II*) in benzene as solvent and in the presence of triethylamine afforded an 86% yield of the crystalline N-(3,4,5-trimethoxybenzoyl)-ε-caprolactam (*III*), the hydrolysis and alcoholysis of which was then investigated.

In the case of N-acetyl-ε-caprolactam, the ring opening is known[12] to occur readily by the action of 3% aqueous acetic acid and to afford ε-acetylaminocaproic acid. We have therefore treated the lactam *III* with 0·37M-CH_3COOH or 0·01M-HCl in the presence of a little ethanol to increase the solubility. A complex mixture of products was however obtained which was difficult to crystallize or to separate into components. As shown by thin-layer chromatography on silica gel G (Merck), the acidic hydrolysis of the lactam *III* comprises not only the ring opening but also removal of the acyl group from the lactam ring nitrogen atom. We drew therefore our attention to the alkaline hydrolysis.

The alkaline hydrolysis and alcoholysis of N-acyl-ε-caprolactams also may proceed under the ring opening and/or removal of the N-acyl group. Thus as shown by Šebenda and Stehlíček[13]

on the alkaline hydrolysis of various N-acyl-ε-caprolactams of the aliphatic series, the increasing length of acyl groups leads to a decrease of the amount of the opened product and to an increase of the proportion of the deacylated product. A similar effect may be observed with the use of higher temperatures. In the case of N-caproyl-ε-caprolactam, there is obtained only 32% of the opened product, as observed by Coutin and Sekiguchi[14]. After alkaline hydrolysis of 1-benzoyl-5-ethoxycarbonyl-DL-2-pyrrolidone in aqueous 1,4-dioxane, Battersby and Robinson[15] isolated 42% of benzoic acid. None of these reports is encouraging enough for the ring opening of the lactam in compound *III* under the formation of the required N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproic acid. The patent of O'Neill and Tull[16] on the alkaline hydrolysis of N-benzoyl-α-chloro-ε-caprolactam in the presence of methanol claims a 94% yield of the product of the ring-opening. This course may be ascribed to the activation of the lactam carbonyl group by the vicinal halo atom and to the presence of the alcohol (*cf.* the discussion on the alcoholysis).

The hydrolysis of the lactam *III* with an equivalent of 0·5M-NaOH at 0°C and acidification of the reaction mixture afforded an impure product (m.p. 112–156°C) containing a considerable amount of 3,4,5-trimethoxybenzoic acid (*IVa*). When 1,4-dioxane or diethyl ether was added to the hydroxide, the hydrolysis was considerably slower and the product was contaminated with the unreacted starting material.

Subsequent experiments on the hydrolysis of the lactam *III* were performed with the use of a mixture of 0·5M-NaOH and methanol. The results were then considerably better. In the course of the reaction, the temperature was raised from 0°C to 20°C. The starting lactam *III* dissolved in the course of 30 minutes. After acidification of the reaction mixture, there was obtained a crystalline product, m.p. 113–117°C; the infrared spectrum was identical with that of N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproic acid (*Va*). The lower melting point value was due to contamination with the acid *IVa*. Since the attempted purification by crystallisation was fruitless (the melting point range of about 5°C did not change), we made use of the different solubility of triethylammonium salts in benzene (that of the acid *IVa* is soluble, that of the acid *Va* is insoluble). The mixture of acids *IVa* and *Va* was therefore stirred with triethylamine and benzene, the insoluble salt collected with suction, and treated with dilute hydrochloric acid to liberate the acid *Va* (yield, 57·5%) which melted at 121–122°C in accordance with literature[1]. The role of methanol in this hydrolysis may be explained as follows. Methanol and sodium hydroxide form an equilibrium mixture which contains sodium methoxide and water in addition to the original two compounds. Reaction of sodium methoxide with N-acyllactam affords methyl N-acyl-ε-aminocaproate which is hydrolysed by the action of the hydroxide under the formation of the sodium salt of the above N-acyl-ε-aminocaproic acid. This mechanism is supported by results of thin-layer chromatography on silica gel G, *i.e.*, by detection of traces of methyl 3,4,5-trimethoxybenzoate (*IVb*) and methyl N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproate (*Vb*). When 2-propanol is used instead of methanol, a direct hydrolysis obviously takes place without the previous alcoholytical step, since the results are similar to those obtained in the hydrolysis with sodium hydroxide alone. Such a reaction course might be due to a higher bulki-

ness of 2-propanol or to the shift of equilibrium in the first step of the mechanism proposed to the left in favour of the hydroxide and alcohol. In accordance with the proposed mechanism, Battersby and Robinson[15] isolated 26% of the opened product in the form of the ethyl ester in hydrolysis of 1-benzoyl-5-ethoxycarbonyl-DL-2-pyrrolidone with one equivalent of 0·1M-NaOH in ethanol at room temperature. Also in our additional experiments, the alcoholysis of the lactam *III* proved more selective than hydrolysis.

In connection with the potential use of the lactam *III* in the synthesis of esters of the acid *Va*, we drew our attention to the alkaline alcoholysis. The reaction was performed in anhydrous alkanol in the presence of sodium alkoxide (20% molar in respect to the lactam); magnesium alkoxides were not as satisfactory as sodium alkoxides. The alcoholysis proceeds very fastly in both directions; as shown by thin-layer chromatography on silica gel G in 20 : 1 chloroform–methanol solvent system, the starting compound is absent after 30 minutes even at −10°C. The temperature dependence of the ratio *IV* : *V* is shown in Table I (the pure components were separated by chromatography on silica gel). In preparative runs, the contaminants may be removed by extraction with light petroleum because of the insolubility of both methyl (*Vb*) and ethyl (*Vc*) N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproate in this solvent. It may be seen from Table I that the yield of the ethyl ester *Vc* is good and moderately dependent on temperature (optimum, about 30°C). The presence of water has an unfavourable effect on the course of the reaction as shown by hydrolysis of the lactam *III* with an equivalent of sodium hydroxide in methanol at room temperature: there was isolated 43% of the methyl ester *IVb* (by chromatography).

With the aim to increase the selectivity of the alcoholysis, the diazomethane-catalysed alcoholysis of the lactam *III* was investigated. Thus, Schönberg and Mustafa[19] observed the quantitative

TABLE I

Chromatographic Yields of Esters *IV* and *V* after Alcoholysis of the Lactam *III*

Temperature °C	Methanolysis		Temperature °C	Ethanolysis	
	IVb, %	*Vb*, %[a]		*IVc*, %	*Vc*, %[a]
			0	33	66·8 (56·7)
−10	33	61·8 (51·3)	10	31	68 (62)
0	29	65 (51)	30	25	71 (65·5)
17[b]	29	69 (61)	30[c]	31·5	66 (61)
			70	31·4	64 (56·4)

[a] Yields after crystallisation are given in parentheses. [b] Catalysis with diazomethane. [c] Saturated ethanolic magnesium ethoxide was used.

removal of one acetyl group when N,N-diacetyl-1-naphthylamine was treated with alcohol and diazomethane. The role of diazomethane in alcoholysis of esters and N-acyl derivatives was investigated in detail by Bredereck and coworkers[20]. According to these authors, the diazomethane acts as a basic catalyst and the N-acyl group is removed in that case when the resulting product is not of a basic character. To our knowledge, the diazomethane-catalysed reaction has not been so far applied to N-acyllactams. Two types of intermediary complexes may be formed by reaction of diazomethane with N-acyllactam and alcohol; each of them affords different products. Consequently, some selectivity could be expected. As shown, however, by experiments, the diazomethane-catalysed alcoholysis of the lactam *III* does not considerably differ from the alcoholysis with an alkali metal alkoxide (see Table I). Some other effects than steric ones are obviously involved. Moreover, the reaction time is much longer.

Conclusively, the alkaline alcoholysis of the lactam *III* is more selective than the alkaline hydrolysis. A fair yield of the corresponding alkyl N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproate is obtained which may be hydrolysed to the free acid.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and are uncorrected. Analytical samples were dried at 45°C/0·1 Torr for 8 h. Thin-layer chromatography was performed on silica gel G (Merck, Darmstadt; non-activated). Infrared spectra were measured on a Perkin-Elmer 247 apparatus. NMR spectra were taken on a Varian Anaspect EM 300 apparatus with the use of chloroform as internal standard; the δ values are recalculated to TMS on the basis of the 7·27 p.p.m. value for chloroform.

N-(3,4,5-Trimethoxybenzoyl)-ε-caprolactam (*III*)

A solution of ε-caprolactam (*II*; 1·13 g; 0·01 mol) and 3,4,5-trimethoxybenzoyl chloride (*I*; 2·31 g; 0·01 mol) in anhydrous benzene (20 ml) was treated with anhydrous triethylamine (1·54 ml; 10% excess), the mixture kept at room temperature for one hour and then at 80°C for additional one hour, filtered, and the salt on the filter washed with a little benzene. The filtrate and washings were combined, filtered with active charcoal, and evaporated to dryness under diminished pressure. The residue was crystallised from methanol (8 ml) to afford 2·20 g (71·7%) of compound *III*, white crystals, m.p. 100–102°C. An additional crop (m.p. 97·5–101·5°C) was obtained (0·44 g; 14·5%) from mother liquors. Overall yield, 86%. Infrared spectrum (tetrachloromethane): $\tilde{\nu}$ 1 680 and 1 700 cm^{-1} (C=O). For $C_{16}H_{21}NO_5$ (307·3) calculated: 62·53% C, 6·89% H, 4·56% N; found: 62·84% C, 7·06% H, 4·55% N.

N-(3,4,5-Trimethoxybenzoyl)-ε-aminocaproic Acid (*Va*)

The lactam *III* (1·00 g) was added into a precooled (0°C) mixture of 0·46M-NaOH (7·08 ml; 1 equivalent) and methanol (4 ml). The mixture was stirred without cooling until the lactam dissolved (for about 35 min). After additional two hours, the mixture was acidified with 1M-HCl (3·5 ml) and set aside for several hours to deposit crystals which were collected with suction and dried. Yield 0·83 g of the crude compound *Va*, m.p. 113–117°C. The infrared spectrum was identical with that of authentic N-(3,4,5-trimethoxybenzoyl)-ε-aminocaproic acid (*Va*), prepared by the known procedure[1]; the lower m.p. value was obviously due to contamination with 3,4,5-trimethoxybenzoic acid (*Va*). A mixture of the crude product (0·50 g), benzene (5 ml), and anhydrous triethylamine (0·2 ml) was stirred at room temperature for 30 min, the insoluble crystals collected with suction, dried, and then stirred on 0·14M-HCl for 15 min. The insoluble

solid was collected with suction, washed with water, and dried to afford 0·37 g (73·8%) of the acid *Va*, m.p. 121—122°C in accordance with literature[1]; yield, 57·5% when based on compound *III*. For $C_{16}H_{23}NO_6$ (325·3) calculated: 59·07% C, 7·12% H, 4·30% N; found: 59·24% C, 7·18% H, 4·24% N.

Methyl N-(3,4,5-Trimethoxybenzoyl)-ε-aminocaproate (*Vb*)

A. Methanolic sodium methoxide (1 ml; from 7·5 mg of sodium) was added at 0°C to a suspension of the lactam *III* (0·50 g) in methanol (10 ml) and the mixture kept at 0°C for one hour. After 10 min, a clear solution was obtained lacking the starting lactam *III* as shown (after 30 min) by thin-layer chromatography on silica gel G in 20 : 1 chloroform–methanol solvent system. The solution was neutralised to phenolphthalein with 1M-HCl, evaporated under diminished pressure, and the crystalline residue chromatographed on a column of silica gel CH (Spolana, Neratovice, Czechoslovakia; 15 g; 10% of water; particle size, 70—200 micron). Elution with benzene (110 ml) afforded 0·106 g (29%) of methyl 3,4,5-trimethoxybenzoate (*IVb*), m.p. 82·0 to 82·7°C (1 : 10 ethanol–light petroleum); infrared spectrum was identical with that of the specimen prepared according to Späth[17] (reported m.p. value, 82—83°C). The subsequent elution with 100 : 1 benzene–ethanol solvent mixture (300 ml) afforded 0·36 g (65%) of the methyl ester *Vb*, m.p. 83—83·5°C (1 : 6 ethanol–light petroleum); overall yield, 51%. Infrared spectrum (methylene chloride): $\tilde{\nu}$ 1650 and 1730 cm^{-1} (C=O) and 3450 cm^{-1} (NH). For $C_{17}H_{25}NO_6$ (339·4) calculated: 60·16% C, 7·42% H, 4·13% N; found: 60·06% C, 7·60% H, 4·13% N.

B. Ethereal diazomethane (prepared from 1·5 g of nitrosomethylurea[21]; not distilled, only dried over potassium hydroxide pellets for 3 h) was added to a solution of the lactam *III* (500 mg) in methanol (5 ml), the reaction mixture kept at room temperature for 45 h (after 17 h, thin-layer chromatography on silica gel G indicated the presence of the starting lactam *III*), and evaporated to dryness under diminished pressure. The crystalline residue was chromatographed as above on 15 g of silica gel CH. Elution of the column with benzene (100 ml) afforded 0·108 g (29%) of the ester *IVb*, m.p. 82—83°C (light petroleum) in accordance with literature[17]; infrared spectrum identical with that of an authentic specimen. The subsequent elution with 100 : 1 benzene–ethanol solvent mixture (190 ml) afforded 0·38 g (69%) of the ester *Vb*, m.p. 83·0—83·7°C (1 : 6 ethanol–light petroleum); yield, 61%; infrared spectrum identical with that of the specimen obtained in paragraph *A*.

Ethyl N-(3,4,5-Trimethoxybenzol)-ε-aminocaproate (*Vc*)

A. Ethanolic sodium ethoxide (1 ml; corresponding to 7·5 mg of sodium) was added at 30°C to a solution of the lactam *III* (0·50 g) in absolute ethanol (10 ml), the reaction mixture kept at the same temperature for one hour, cooled down, neutralised to phenolphthalein with 1M-HCl, and evaporated to dryness under diminished pressure. The crystalline residue was chromatographed on a column of silica gel CH (15 g; 10% of water; particle size, 70—200 micron). Elution with benzene (80 ml) afforded 0·098 g (25%) of ethyl 3,4,5-trimethoxybenzoate (*IVc*), m.p. 50—53°C (ligroin, b.p. 60—70°C; reported[18], m.p. 53—57°C. Infrared spectrum (tetrachloromethane) $\tilde{\nu}$ 1715 cm^{-1} (C=O) NMR spectrum (tetrachloromethane): 1·23 p.p.m. (CH_3, triplet, *J* 6·7 Hz, 3 H), 3·61 p.p.m. (CH_3O, singlet), 3·71 p.p.m. (2 × CH_3O, singlet), 3·91 p.p.m. (CH_2, quartet, superposition with CH_3O, *J* 6·7 Hz), 7·06 p.p.m. (H arom, singlet, 2 H). The subsequent elution with 100 : 1 benzene–ethanol solvent mixture (190 ml) afforded 0·407 g (71%) of the ester *Vc*, m.p. 83·0—84·5°C (1 : 7 ethanol–light petroleum); yield, 65·5%. Infrared spectrum (tetrachloromethane): $\tilde{\nu}$ 1640 cm^{-1} (C=O) and 3300 cm^{-1} (NH). For $C_{18}H_{27}NO_6$ (353·4) calculated: 61·17% C, 7·70% H, 3·96% N; found: 61·23% C, 7·86% H, 3·88% N.

B. Instead of 1M-HCl, the reaction mixture (prepared as above) was neutralised with Dowex 50 W X 8 (H^+) ion exchange resin, filtered, and the resin washed with ethanol. The filtrate and washings were combined, evaporated to dryness under diminished pressure, and the crystalline residue extracted at 60°C with 5 ml of ligroin (b.p. 60—70°C). The insoluble portion was collected with suction and recrystallised, m.p. 82·5—83·5°C (1 : 7 ethanol–light petroleum). Yield of the ester *Vc*, 65%.

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