EM 360 (Me_4Si). All solvents were dried and used without further purification. The 1,3-dialkanoylglycerols were prepared by literature procedures.[6] TLC's were performed on fluorescent silica gel GF plates; the spots were detected by UV or with a potassium permanganate solution. The purity of the products was also checked by high-performance LC.

1,3-Didecanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2-yl)-glyceride (2b). Method A. A solution of 1,3-didecanoylglyceride (10.0 g, 0.025 mol), acetylsalicyloyl chloride (4.96 g, 0.025 mol), and pyridine (2.2 mL, 0.028 mol) in dry ethanol-free $CHCl_3$ was refluxed for 24 h. The reaction mixture was treated with 100 mL of H_2O. The $CHCl_3$ layer was decanted, washed with 100 mL of 1% HCl, 100 mL of 1% aqueous $NaHCO_3$, and 2 × 100 mL of H_2O, and dried over $MgSO_4$, and the solvent was removed in vacuo. The oily product was chromatographed on 500 g of silica gel (previously deactivated with wet ether) with petroleum ether–ether (85:15). This procedure gave 4.8 g (31%) of **2b**: ^1H NMR ($CDCl_3$) δ 1.85 (s, 3 H, $OOOCCH_3$), 4.1 (m, 4 H, 2 × CH_2O), 4.4 (m, 1 H, CH). Compounds **2a** and **2c** were prepared in a similar manner except that they were purified by crystallization.

Method B. Trifluoroacetic anhydride (10.5 g, 0.05 mol) was added to a stirred suspension of acetylsalicylic acid (8.94 g, 0.045 mol) in dry C_6H_6 (60 mL). The reaction mixture was heated at 45 °C until a clear solution was obtained (1–2 min). The stirring was continued at room temperature for 30 min and 1,3-didecanoylglycerol (18.03 g, 0.045 mol) was added. The reaction mixture was stirred for 1 h at room temperature and cooled in an ice bath. To the cold solution was added 5% $NaHCO_3$ (about 150 mL), until the medium was neutral or slightly basic. The organic layer was decanted, washed with water (2 × 100 mL) and brine (100 mL), and dried over $MgSO_4$. Removal of C_6H_6 yielded crude 1,3-didecanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2-yl)-glyceride (23.0 g, 92%). The clear oil was purified by chromatography as described in method A (19 g, 76% yield).

2-Hexadecyl-1,3-benzodioxan-4-one. *O*-Acetylsalicyloyl chloride (993 mg, 5 mmol) was added to a solution of cetyl alcohol (1.21 mg, 5 mmol) in 50 mL of dry $CHCl_3$ (ethanol free), and the solution was refluxed for 17 h. The reaction product was isolated as described for compound **2b**. The oily product was chromatographed on silica gel with petroleum ether–ether (95:5): yield 700 mg (35%); mp 36–38 °C (MeOH); ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H, $OOOCCH_3$), 3.65 (m, 2 H, OCH_2); MS m/e 404 (M^+).

Acknowledgment. The authors are most grateful to Dr. S. Huckin and Mr. G. Nettleship for high-performance LC and ^1H NMR spectra. We also thank Dr. R. Egan, Ms. R. Stanaszek and Dr. M. Levenberg, and Ms. S. Mueller of Abbott Laboratories, North Chicago, for ^{13}C NMR and mass spectra, respectively, and to the staff of the Analytical Research Department of Abbott Laboratories for elemental analysis.

Cholecystokinin (Pancreozymin). 5.[1] Hormonally Active Desamino Derivative of Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2

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Acylation of the 6-peptide derivative L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide with the *N*-hydroxysuccinimide ester of desaminotryosine afforded 3-(4-hydroxyphenyl)propionyl-L-methionyl-glycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide. The phenolic hydroxyl group in this compound was esterified by treatment with SO_3–pyridine complex in dimethylformamide–pyridine. The sulfate ester was purified by chromatography and by countercurrent distribution. The desamino analogue of the C-terminal 7-peptide segment of cholecystokinin (DA-CCK-7) was tested for its abilities to stimulate amylase secretion from dispersed pancreatic acini in vitro, to increase protein secretion from cat pancreas in vivo, and to cause contraction of guinea pig gall bladder in situ. In increasing amylase secretion in vitro, the desamino heptapeptide was equal in efficacy with but approximately one-tenth as potent as the unaltered heptapeptide, whereas when tested in vivo or in situ, these two peptides were approximately equal in biological activity. It is evident that the N-terminal amino group of the C-terminal heptapeptide of CCK is not essential for its biological activities. The difference between the biological activity of the desamino compound and the unaltered heptapeptide seen in vitro and the absence of a substantial difference in vivo or in situ may indicate that the N-terminal amino group of CCK-7 is important in influencing its rate of disposition from the circulation. Additional evidence for this possibility is our finding that the desamino 7-peptide had a longer duration of action on gall bladder contraction in situ than did the unaltered peptide.

In our earlier studies[1,3] on the biologically active C-terminal 7-peptide segment of cholecystokinin (pancreozymin),[4] we observed that the partially protected intermediate in which the N-terminal *tert*-butyloxycarbonyl group was still present (Boc-CCK-7) showed somewhat

Boc–Tyr(SO_3H)–Met–Gly–Trp–Met–Asp–Phe–NH_2
Boc–CCK–7

more activity than the free 7-peptide (CCK-7). In fact,

(1) For the preceding paper in this series, which also summarizes the discovery, structure determination, and biological activities of cholecystokinin (pancreozymin), cf. M. Bodanszky, J. Martinez, G. P. Priestley, J. D. Gardner, and V. Mutt, *J. Med. Chem.*, **21**, 1030 (1978).

(2) Visiting scientist on leave from Equipe de Recherche No. 195 du Centre National de la Recherche Scientifique, Ecole Nationale Superieur de Chimie, Montpellier, France.

(3) M. Bodanszky, S. Natarajan, W. Hahne, and J. D. Gardner, *J. Med. Chem.*, **20**, 1047 (1977).

(4) V. Mutt and J. E. Jorpes, *Biochem. Biophys. Res. Commun.*, **26**, 392 (1967); *Eur. J. Biochem.*, **6**, 156 (1968); *Proc. Int. Union Physiol. Sci.*, **6**, 193 (1968); J. W. Jorpes, *Gastroenterology*, **55**, 157 (1968); V. Mutt and J. E. Jorpes, *Biochem. J.*, **125**, 57 (1971).

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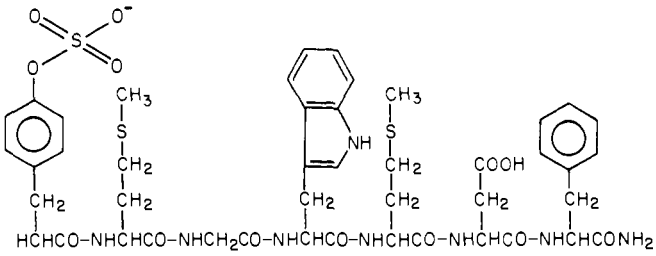

Figure 1. The structure of desamino-CCK-7 (DA-CCK-7, II).

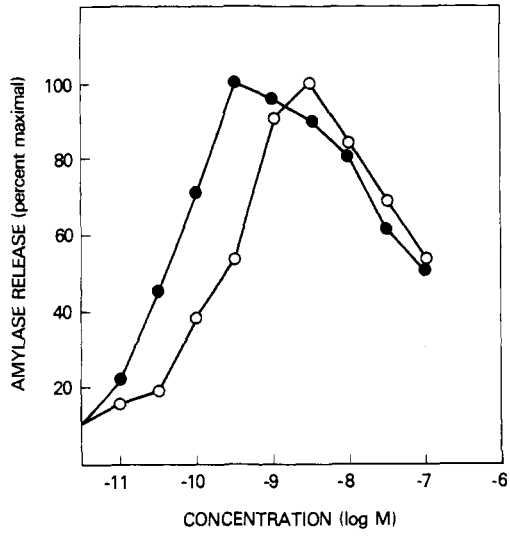

Figure 2. Amylase secretion by dispersed acini prepared from guinea pig pancreas. Closed circles represent results with CCK-7; open circles represent results with desamino-CCK-7. Results are means from four separate experiments.

the potency of Boc-CCK-7 in the release of amylase from pancreatic acinar cells of guinea pigs was equal[5] to that of the C-terminal 8-peptide[6] used as a diagnostic agent in medicine.[7] The similar potency-enhancing effect of a *tert*-butyloxycarbonyl group and of an L-aspartyl residue suggested that the amino group of the N-terminal tyrosine sulfate residue of CCK-7 may not participate in the interaction between hormone and its specific receptors. This possibility was examined in the study here reported. For this purpose, desamino-CCK-7 (Figure 1) was synthesized.

Synthesis. The 6-peptide amide, L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine amide (compound Va in ref 1) was acylated with the *N*-hydroxy-succinimide ester of 3-(4-hydroxyphenyl)propionic acid (deaminotyrosine). The product was purified by chromatography and then treated with SO_3–pyridine complex in a mixture of dimethylformamide and pyridine to afford the desired desamino-7-peptide derivative. This was purified by chromatography on a column of silica gel or by countercurrent distribution. The chromatographically homogeneous product, which gave a correct amino acid analysis after hydrolysis, was tested for biological activity.

Amylase Secretion from Pancreatic Acinar Cells. With CCK-7 or the desamino peptide, the configurations of the dose–response curves for stimulation of amylase secretion were similar to those for native CCK as well as other C-terminal fragments and analogues of CCK.[1,8]

Table I. Light Absorbance of the Pancreatic Juice

peptide injected[a]	$OD_{280\,nm}$ [1 cm] of pancreatic juice[b]
1 cu of secretin	0.22
1 cu of secretin + 125 ng of Boc-CCK-7	0.74
1 cu of secretin + 125 ng of CCK-7	0.86
1 cu of secretin + 125 ng of DA-CCK-7	1.13
1 cu of secretin + 250 ng of Boc-CCK-7	0.90
1 cu of secretin + 250 ng of CCK-7	1.25
1 cu of secretin + 250 ng of DA-CCK-7	1.36
1 cu of secretin	0.19
1 cu of secretin + 2 idu of CCK	0.77

[a] cu = clinical unit; idu = Ivy dog unit. [b] Diluted to 10 mL with physiological saline.

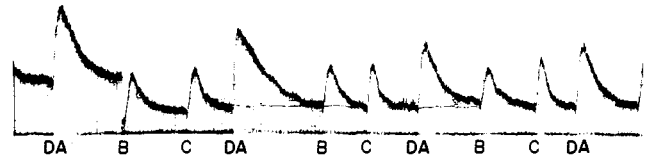

Figure 3. Contractile activities (guinea pig gall bladder): DA = DA-CCK-7; B = Boc-CCK-7; C = CCK-7. All were applied in equal volumes (0.02 mL) of solutions of equal concentrations (125 ng/mL).

Significant stimulation of amylase secretion could be detected with 10^{-11} M CCK-7, and maximal stimulation occurred when the peptide concentration was 3×10^{-10} M (Figure 2). Increasing the concentration of CCK-7 above 3×10^{-10} M caused a progressive decrease in amylase secretion. In terms of the lowest concentration that would cause half-maximal stimulation of enzyme secretion, the desamino peptide was approximately one-tenth as potent as CCK-7 (Figure 2). In terms of the maximal stimulation of enzyme secretion, deamino-CCK-7 was equal in efficacy to the unaltered peptide (Figure 2).

Protein Secretion from the Anesthetized Cat Pancreas. The C-terminal 7-peptide amide of cholecystokinin (CCK-7), its *tert*-butyloxycarbonyl derivative (Boc-CCK-7), and its desamino analogue (DA-CCK-7) were compared with each other and also with CCK according to the procedure of Jorpes and Mutt.[9] The light absorbance of the pancreatic juice, diluted with physiological saline (cf. Experimental Section for details), was determined and the results are shown in Table I. Although only two concentrations of each peptide were tested, the desamino heptapeptide (DA-CCK-7) was at least as potent as CCK-7 or Boc-CCK-7.

Contractile Activity of the Guinea Pig Gall Bladder in Situ. This assay was carried out according to Ljungberg.[10] The desamino compound (DA-CCK-7) was clearly stronger than CCK-7 or Boc-CCK-7. Furthermore, its effect was distinctly of longer duration than the action of the unaltered heptapeptide CCK-7 (Figure 3). In previous studies of the action of C-terminal fragments of CCK on gall bladder contraction, Rubin and his associates[11] found that CCK (the 33-residue form) had a longer duration of action than did the C-terminal octapeptide of CCK, even

(5) Cf. Figure 2 in ref 1.
(6) M. A. Ondetti, J. Pluscec, E. F. Sabo, J. T. Sheehan, and N. Williams, *J. Am. Chem. Soc.*, **92**, 195 (1970).
(7) Kinevac (Squibb); generic name Sincalide.
(8) S. R. Peikin, A. J. Rottman, S. Batzri, and J. D. Gardner, *Am. J. Physiol.*, **235**, E743 (1978).
(9) J. E. Jorpes and V. Mutt, *Acta Physiol. Scand.*, **66**, 196 (1966).
(10) S. Ljungberg, *Acta Pharm. Suec.*, 6, 599 (1969).
(11) B. Rubin, S. L. Engel, A. M. Drungis, M. Dzelkalns, E. O. Grigas, M. H. Waugh, and E. Yiacas, *J. Pharm. Sci.*, **58**, 955 (1969).

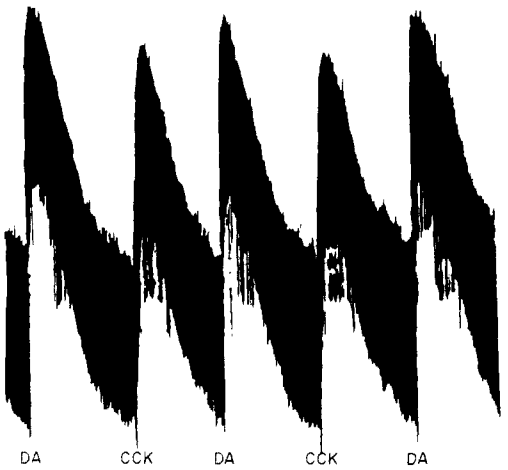

Figure 4. Contractile activities (guinea pig gall bladder): DA = DA-CCK-7, CCK = cholecystokinin (33-residue form). Equal volumes (0.025 mL) of a CCK solution (1 Ivy dog unit/mL) and of a DA-CCK-7 solution (125 ng/mL) were applied.

though CCK was less potent than the octapeptide.

Conclusion

The difference between the biological activity of the desamino peptide and the unaltered 7-peptide seen in vitro and the absence of a substantial difference in vivo or in situ may indicate that the N-terminal amino group of CCK-7 is important in influencing its rate of disposition from the circulation. Our finding that the desamino heptapeptide had a longer duration of action on gall bladder contraction in situ than did the unaltered heptapeptide further supports this possibility. It is clear, however, that the amino group of the tyrosine sulfate residue, the N-terminal amino acid of the C-terminal 7-peptide of cholecystokinin, is not necessary for the characteristic biological activities of this fragment. In fact, without this amino group the 7-peptide is quite similar to CCK both in potency and the duration of action (Figure 4).

Experimental Section

Capillary melting points are reported uncorrected. Thin-layer chromatography (TLC) was performed on precoated (Merck) silica gel plates in the following solvent systems (ratios by volume): A, EtOAc–pyridine–AcOH–H_2O (60:20:6:11); B, *n*-BuOH–AcOH–H_2O (4:1:1). Spots were revealed with iodine vapor, ninhydrin, fluorescamine, Ehrlich's reagent, charring, and by their absorption in the UV. For amino acid analysis, samples were hydrolyzed with constant-boiling HCl in evacuated sealed ampules at 110 °C for 16 h and analyzed by the Stein–Moore–Spackman method on a Beckman-Spinco instrument.

β-(4-Hydroxyphenyl)propionyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalanine Amide (I). To a solution of the 6-peptide amide Met-Gly-Trp-Met-Asp-Phe-NH_2·$2H_2O$ (compound Va in ref 1; 205 mg, 0.25 mmol) in DMF (1 mL) was added β-(4-hydroxyphenyl)propionic acid *N*-hydroxysuccinimide ester[12] (75 mg, 0.28 mmol, Aldrich) in three portions, within 30 min. After 5 h, a negative spot test with fluorescamine indicated completion of the acylation reaction. The mixture was diluted with EtOAc (60 mL), and the precipitate was collected by centrifugation, washed thoroughly with EtOAc (60 mL), and dried in vacuo. The crude product (220 mg) was purified by chromatography on a column (40 × 3 cm) of silica gel (Baker) with a 60:20:6:11 mixture of EtOAc–pyridine–AcOH–H_2O as eluent. For dissolution of the sample, this mixture was used without EtOAc, which was added only after dissolution occurred. The elution was monitored by TLC run in the same system. The fractions containing the main compound were pooled. The purified product (I, 180 mg, 77%) was obtained by evaporation with a stream of N_2. It was chromatographically homogeneous: TLC R_f (A) 0.45; R_f (B) 0.65; mp 211–215 °C dec; $[\alpha]^{24}_D$ −27° (c 1, DMF). Anal. ($C_{45}H_{56}N_8O_{10}S_2$) C, H, N.

Desamino-CCK-7 (II). A sample of compound I (125 mg, 0.13 mmol) was dissolved in a mixture of DMF (4 mL) and pyridine (2 mL), and SO_3–pyridine complex (750 mg, Aldrich) was added. The mixture was stirred at room temperature overnight. At this time, no more starting material could be detected by TLC (system A). The solvents were removed in vacuo, and H_2O (6 mL) was added to the residue. The resulting suspension was cooled in an ice–water bath while it was adjusted to about pH 7 with the gradual addition of 1 N Na_2CO_3.[13] After about 0.5 h, the reaction remained neutral. The precipitate was collected by centrifugation, washed several times with H_2O, and dried in vacuo over P_2O_5. Additional product was obtained by extraction of the aqueous solution with *n*-BuOH. The two crops were combined (125 mg) and chromatographed on a column (40 × 1 cm) of silica gel in the solvent system described in the previous paragraph. Elution was monitored by TLC. The sulfated material (II) was obtained by combining the fractions which showed only one spot with R_f (A) 0.20, R_f (B) 0.50, revealed by charring and with Ehrlich's reagent. The solvents were removed with a stream of N_2; the residue was dissolved, with warming to about 40 °C, in 0.5 M NH_4OH and lyophilized: yield 80 mg; $[\alpha]^{24}_D$ −17.4 (c 0.7, DMF). Amino acid analysis: Asp, 1.01; Gly, 1.01; Met, 1.97; Phe, 1.00 (98% recovery). In the IR spectrum, a strong, sharp band at 1040 cm^{-1} is characteristic for the sulfate ester group. The UV spectrum (in H_2O) is close to that of tryptophan: ϵ (λ_{max} 280 nm) 5700 with a second peak at 228 nm (ϵ 4800).

Amylase Secretion from Pancreatic Acinar Cells. Amylase secretion by dispersed acini prepared from guinea pig pancreas was determined using the techniques described previously.[1,9] Acini from the pancreas of one animal were suspended in 200 mL of solution composed of 24.5 mM Hepes (pH 7.4); 98 mM NaCl; 6 mM KCl; 2.5 mM KH_2PO_4; 1.2 mM $MgCl_2$; 0.5 mM $CaCl_2$; 5 mM sodium fumarate, sodium glutamate, and sodium pyruvate; 2 mM glutamine; 5 mM theophylline; 11.5 mM glucose; 1% (w/v) bovine plasma albumin; 0.01% (w/v) soybean trypsin inhibitor; 1% (v/v) essential vitamin mixture; and 1% (v/v) Eagle's amino acid mixture. One milliliter of cell suspension was gassed with 100% O_2 and incubated with the appropriate agent for 30 min at 37 °C. Amylase secretion was measured as the percentage of total cellular amylase released into the incubation medium during the 30-min incubation. In each experiment, each value was determined in triplicate incubations. The results are shown in Figure 2.

Protein Secretion from the Anesthetized Cat Pancreas.[9] The peptides were dissolved in "physiological saline" which contained 0.1 mg of L-cysteine and 0.1 mg of $NaHCO_3$ per milliliter, and all dilutions were made using this solvent. Injections of one clinical unit of secretin and of the CCK peptides (in the amounts shown in the introduction) were made every 15 min. The pancreatic juice was collected for these periods and then diluted with physiological saline to 10 mL. The light absorbance of the solution in a 1-cm path (quartz cuvettes) was determined in a Zeiss PMQ II spectrophotometer.

(12) J. Rudinger and U. Rüegg, *Biochem. J.*, **133**, 538 (1973).

(13) In previous experiments (cf. ref 1), ammonium hydroxide was used to neutralize the sulfuric acid which gradually formed from the unreacted SO_3–pyridine complex in the reaction mixture. This time, however, in addition to the desired material with R_f (A) 0.20, a second product with R_f (A) 0.25 could also be observed in the mixture after neutralization. Separation of the two compounds was achieved by countercurrent distribution in a Craig apparatus (3-mL phases) in the solvent system *n*-BuOH–EtOH–H_2O (5:1:8) [cf. A. Anastasi, V. Erspamer, and R. Endean, *Experentia*, **23**, 699 (1967)]. After 19 transfers, starting from 60 mg, compound II (30 mg) was recovered from fractions 5–9, the byproduct (8 mg) from fractions 13–18. Amino acid analysis of the byproduct gave the same results as that of II, except that the NH_3 content was 1 mol higher. Therefore, tentatively we assume that the byproduct is the asparagine analogue of compound II, formed via a sulfuric acid mixed anhydride [G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2069 (1952)]. The potency of this material in the release of amylase from pancreatic acinar cells of guinea pigs was about 20 times less than that of compound II.

Contractile Activity of the Guinea Pig Gall Bladder. Solutions were prepared as described in the previous paragraph. The contractile activities were compared according to the procedure in ref 10.

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Potential Carcinostatics. 4.[1] Synthesis and Biological Properties of *erythro*- and *threo*-β-Fluoroaspartic Acid and *erythro*-β-Fluoroasparagine[2]

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Received November 9, 1978

(*E*)- and (*Z*)-Di-*tert*-butyl 2-amino-3-fluoro-2-butene-1,4-dioate [(*E*)- and (*Z*)-**2**] were synthesized in two ways: (a) by elimination of hydrogen fluoride from di-*tert*-butyl β,β-difluoroaspartate under the influence of 1,5-diazabicyclo[4.3.0]non-5-ene and (b) by amination with the ammonium acetate of di-*tert*-butyl monofluorooxaloacetate (**3**), obtained via condensation of *tert*-butyl monofluoroacetate with di-*tert*-butyl oxalate. Reduction of **2** with sodium cyanoborohydride yielded a mixture of di-*tert*-butyl monofluoroaspartates in which the erythro isomer constituted the major product. The structure of this isomer (**4a**) was established by X-ray crystallographic analysis of the corresponding acid **5a**. Esterification of **5a** to the β-methyl ester **6**, followed by aminolysis, yielded *erythro*-β-fluoroasparagine (**7**). Tests with **5a** and **7** in the L-5178Y test system showed that the compounds exhibited toxicity at levels at which no antitumor activity was observed.

The major pathway for the biosynthesis of adenosine monophosphate (AMP)—a nucleotide essential for nucleic acid anabolism—involves the condensation of inosine monophosphate (IMP) with aspartate, to form adenylosuccinate, and subsequent loss of fumarate from the latter intermediate. We have recently directed our attention to the development of nucleoside analogues[3,4] which could act as inhibitors of adenylosuccinate synthetase (EC 6.3.4.4) and adenylosuccinate lyase (EC 4.3.2.2). An important target compound for this study is the adenylosuccinate analogue containing a stereospecifically located fluorine atom at the β position of the succinate moiety. Such an analogue could act as an inhibitor, especially of the lyase, if the elimination of fumarate from the adenylosuccinate proceeds via a stereospecific deprotonation step. For the synthesis of the aforementioned modified nucleotide, it is necessary to have convenient access to β-fluoroaspartic acids, which have been quoted to be unavailable on account of their instability.[5] This paper describes the synthesis of *threo*- and *erythro*-β-fluoroaspartic acid (**5a** and **5b**) and the conversion of **5a** to *erythro*-β-fluoroasparagine (**7**). The results of the preliminary biological investigation of **5a** and **7** are reported.

Chemistry. A practical approach to the synthesis of β-fluoroaspartic acid was conceived via the hydrogenation of β-fluoro-α-aminomaleic/fumaric acids (**2**). The latter precursor could be conveniently obtained by two routes (Scheme I). In one case, *tert*-butyl β,β-difluoroaspartate (**1**),[3] described by us recently, was subjected to dehydrohalogenation. While several bases could bring about the elimination of the elements of hydrogen fluoride, the best results were obtained by treating **1** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[6] in THF, whereupon a mixture of the *Z* and *E* isomers of **2** (*Z*/*E* = 20:1; NMR) was obtained in 96% yield. In the second procedure, *tert*-butyl monofluoroacetate was condensed with di-*tert*-butyl oxalate, to yield monofluorooxaloacetate **3**,[7] which upon treatment with an excess of ammonium acetate (CH_3OH, room temperature, 4 days) gave an isomeric mixture of **2** (*E*/*Z* = 1:1, NMR) in a total yield of 85%. Attempts to catalytically hydrogenate **2** (isomeric mixture), however, led, in all cases, to the formation of di-*tert*-butyl aspartate. Presumably, the initially formed (desired) reduction product eliminates HF to give amino fumarate/maleate, which is reduced in a further hydrogenation reaction to the aspartate system.

The reduction of **2** with metal hydride reagents was investigated with a view to circumvent the problems associated with the catalytic reduction reaction. The use of cyanoborohydride in methanol/acetic acid, at room temperature, gave an isomeric mixture (**4a** + **4b**) of the expected di-*tert*-butyl β-fluoroaspartate contaminated with 5% of its cyanoborohydride complex and 5–10% of di-*tert*-butyl aspartate (the complex could be converted into a mixture of amino fumarate/maleate and *tert*-butyl β-fluoroaspartate upon heating in morpholine). The major isomer could be readily obtained in the pure form by crystallization. The minor product was isolated by laborious chromatography of the reaction mixture of a large-scale reduction of **2**. Since protonation of (*Z*)- and (*E*)-**2** leads to the same iminium salt (or its mirror image), the product distribution of **4a**/**4b** is independent of the composition of the starting mixture. NMR spectra of the individual isomers were insufficiently characteristic to allow their structural assignments (threo or erythro). The *tert*-butyl ester **4a** was conveniently converted into the

(1) For part 3, see W. M. Odijk, M. J. Wanner, G. J. Koomen, and U. K. Pandit, *Heterocycles*, **9**, 1403 (1978).
(2) Part of the forthcoming thesis of J. J. M. Hageman.
(3) J. J. M. Hageman, M. J. Wanner, G. J. Koomen, and U. K. Pandit, *J. Med. Chem.*, **20**, 1677 (1977).
(4) M. J. Wanner, J. J. M. Hageman, G. J. Koomen, and U. K. Pandit, *Recl. Trav. Chim. Pays-Bas*, **97**, 211 (1978).
(5) **Note added in proof**: Since the submission of this paper, the synthesis of DL-*threo*- and DL-*erythro*-β-fluoroaspartic acid without configurational assignment has been reported via a different synthetic route. [J. Kollonitsch, S. Marburg, and L. M. Perkins, *J. Org. Chem.*, **44**, 771 (1979)]. There has also been a comment on the presumed instability of β-fluoroaspartic acid [E. Kun, D. W. Fanshier, and D. R. Grasetti, *J. Biol. Chem.*, **235** 416 (1960)].
(6) H. Oediger, *Chem. Ber.*, 2012 (1966).
(7) D. E. A. Rivett, *J. Chem. Soc.*, 3710 (1953).

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