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POTENTIAL ANTIMETABOLITES DERIVED FROM 4-FLUOROGLUTAMIC ACID

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For studies of biological effects we have recently prepared and described (1) some compounds structurally related to 4-fluoroglutamic acid I. Starting from this compound we have synthesized a number of further derivatives derived from it by modifying the carboxylic groups.

Besides previously published synthetic methods (2,3) we obtained substance I from tetramethyl ester of 2-acetamino-2,4-dicarboxyglutaric acid (4). This compound when treated with perchloryl fluoride was transformed to 2-acetamino-2,4-dicarboxy-4-fluoroglutaric acid-tetramethyl ester II in 46% yield (m.p. 141-144°; for $C_{13}H_{18}FNO_9$ calculated 44,44% C, 5,17% H, 3,98% N, found 44,29% C, 5,19% H, 4,08% N). Hydrolysis of this substance yielded 60% of acid I identical with the previously synthesized preparations (2,3).

4-Fluoroglutamic acid I was transformed by boiling with ethanolic hydrogen chloride into its diethylester-hydrochloride III (yield 47%, m.p. 143°; for $C_9H_{17}ClFNO_4$ calculated 5,43% N, 13,71% Cl, found 5,45% N, 13,55% Cl). Moreover, 20% of the theoretical quantity of ethylester of 3-fluoro-2-pyrrolidone-5-carboxylic acid IV were isolated from mother liquors (m.p.90-1°,

b.p. 114°/0,01 mm, 137°/0,5 mm; for $C_7H_{10}FNO_3$ calculated 47,99% C, 5,75% H, 7,99% N, found 48,10% C, 5,81% H, 8,03% N). Ester IV was also prepared from acid I in 68-72% yield without isolation of primarily formed compound III. Compound IV was converted with ethanolic ammonia to the corresponding amide V (97% yield, m.p. 198-200°; for $C_5H_7FN_2O_2$ calculated 41,09% C, 4,83% H, 19,45% N, found 41,30% C, 4,75% H, 19,50% N). By alkaline hydrolysis of ester IV the free 3-fluoro-2-pyrrolidone-5-carboxylic acid VI was prepared in 80-3% yield. Acid VI exists in two forms: A, m.p. 198-202°, and B, m.p. 179-180°(for $C_5H_6FNO_3$ calculated 40,82% C, 4,11% H, 9,52% N; A-found 41,04% C, 4,29% H, 9,83% N; B-found 40,55% C, 4,06% H, 9,72% N).

By boiling with ethanolic hydrogen chloride the lactame ring in amide V was opened giving ethylester of 2-fluoro-4-aminoglutaramic acid isolated as its hydrochloride VII (70% yield, m.p. 177-8° dec.; for $C_7H_{14}ClFN_2O_3$ calculated 36,77% C, 6,17% H, 12,25% N; found 37,01% C, 6,20% H, 12,19% N). Mild hydrolysis of this compound in cold aqueous hydrochloric acid led to hydrochloride of 2-fluoro-4-aminoglutaramic acid (2-fluoroisoglutamine) VIII (67% yield, m.p. 180-1° dec.; for $C_5H_{10}ClFN_2O_3$ calculated 29,93% C, 5,02% H, 17,67% Cl, 13,97% N; found 30,06% C, 5,22% H, 17,29% Cl, 13,79% N).

Diethylester of N-benzyloxycarbonyl-4-fluoroglutamic acid IX, obtained from compound III by usual way was transformed without purification to N^2-benzyloxycarbonyl-4-fluoroglutamamide X in total yield 83% (m.p. 213-4° dec.; for $C_{13}H_{16}FN_3O_4$ calculated 52,52% C, 5,40% H, 14,13% N; found 52,84% C, 5,50% H, 14,31% N). Protecting group was split off from nitrogen by hydrogen chloride in acetic acid under formation of 4-fluoro-

glutamamide -hydrochloride XI (76% yield, m.p. 199-200,5° dec.; for $C_5H_{11}ClFN_3O_2$ calculated 30,08% C, 5,56% H, 17,76% Cl, 21,05% N; found 30,44% C, 5,67% H, 17,32% Cl, 20,79% N).

In comparison with our preceding communication (1) 4-fluoroglutamic acid-5-methylester XII was better prepared by application of method after Boissonas et al. (5). The product obtained in this way melts higher than that originally prepared (1)(56,5% yield, m.p. 164-6°; for $C_6H_{10}FNO_4$ calculated 40,22% C, 5,59% H, 7,82% N; found 40,20% C, 5,76% H, 7,96% N). In another experiment ester XII was isolated in the form of its hydrochloride (52,5% yield, m.p. 164-5°; for $C_6H_{11}ClFNO_4$ calculated 16,44% Cl, 6,96% N; found 15,95% Cl, 6,66% N). Decomposition of this hydrochloride was carried out by pyridine in methanol, and the resulting yield of compound XII was quite quantitative. This compound was reduced with sodium borohydride in aqueous solution at 0-3°; after demineralization 2-amino-4-fluoro-5-hydroxyvaleric acid XIII was isolated (44% yield, m.p. 217-225° dec.; for $C_5H_{10}FNO_3$ calculated 39,73% C, 6,68% H, 9,27% N; found 39,95% C, 6,45% H, 9,33% N). Lithium borohydride was found less suitable for this reduction due to considerable hydrolysis of the ester function, this fact being proved by paper chromatography.

The final compounds of the syntheses described were passed on biological tests which have not yet been finished.

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