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THE SYNTHESIS OF γ-FLUOROGLUTAMIC ACID

M. Hudlický

Research Institute for Pharmacy and Biochemistry

Prague, Czechoslovakia

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SOME of the organic monofluorides show interesting properties as antimetalbolites. Thus fluorocitric acid has been recognized as an antimetabolite of citric acid in the Krebs cycle[1] and 5-fluorouracil as an antimetabolite for uracil in the synthesis of nucleic acids.[2] It was interesting to find out what an effect would produce the introduction of fluorine into the molecules of some amino acids. After some unsuccessful attempts to synthesize fluoroaspartic acid,[3] γ-fluoroglutamic acid has been prepared by the following sequence of reactions:

Ethyl α,α,β-tribromopropionate was converted by heating with mercurous fluoride and iodine to ethyl α,β-dibromo-α-fluoropropionate[4](I),b.p. 67-67.5°/ 3.2 mm, n_D^{20} 1.4810; (Found: C, 21.60%, H, 2.59%. Calc. for $C_5H_7Br_2FO_2$: C, 21.6%, H, 2.54%). Dehalogenation with zinc of ethyl α,β-dibromo-α-fluoro-

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[1] R.H. Peters, Endeavour 13, 147 (1954).

[2] M.P. Gordon and M. Staehelin, J. Amer. Chem. Soc. 80, 2340 (1958).

[3] M. Hudlický, Unpublished results.

[4] A.L. Henne, J. Amer. Chem. Soc. 76, 479 (1954).

propionate afforded 70% yield of ethyl α-fluoroacrylate (II), b.p. 110°/728 mm, n_D^{20} 1.3940; (Found: C, 50.68%, H, 6.12%. Calc. for $C_5H_7FO_2$: C, 50.85%, H, 5.98%). Michael addition of ethyl acetamidomalonate to ethyl α-fluoroacrylate in the presence of sodium ethoxide yielded 58-68% of ethyl 1-fluoro-3-acetamido-1,3,3-propanetricarboxylate (III), m.p. 103-104° (from ethanol); (Found: C, 50.51%, H, 6.57%, F, 5.95%, N, 4.05%. Calc. for $C_{14}H_{22}FNO_7$: C, 50.15%, H, 6.58%, F, 5.67%, N, 4.18%). Hydrolysis of the ester III by boiling with concentrated hydrochloric acid followed by the removal of chloride ions with silver oxide gave, after evaporation in vacuo, γ-fluoroglutamic acid (IV) in 50-60% yield.

γ-Fluoroglutamic acid separated from the aqueous solution as a white microcrystalline substance, melting at 184-186° with a slight decomposition. After crystallization from water the m.p. rose to 191-192° (when heating the sample in a sealed capillary starting at 150°). (Found: C, 35.97%, H, 4.99%. F, 11.71%, N, 8.64%. Calc. for $C_5H_8FNO_4$: C, 36.37%, H, 4.89%, F, 11.51%, N, 8.48%). R_F for the system butanol-acetic acid-water (4:1:5) was 0.05, for the system isopropanol - ammonium hydroxide - water (9:1:2) 0.14. (Glutamic acid had the respective R_F values 0.16 and 0.14). The reaction of γ-fluoroglutamic acid with ninhydrin produced a yellow color.

$CH_2BrCBrFCO_2Et$ (I)

$CH_2{=}CFCO_2Et$ (II)

$(EtO_2C)_2CCH_2CHFCO_2Et$, NHAc (III)

$HO_2CCHCH_2CHFCO_2H$, NH_2 (IV)

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