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MONOFLUORINATED ANALOGUES OF AMINO ACIDS

Vladimír Tolman

Institute of Microbiology, Czechoslovak Academy of Sciences, Prague

Karel Vereš

Isotope Laboratory of the Institutes for Biological Research, Czechoslovak Academy of Sciences, Prague

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Some fluorinated analogues of natural metabolites are known to be highly active antimetabolites. A classical example is the blocking of the Krebs cycle by fluoroacetic acid[1]. As to the amino acids antimetabolic activity has been observed recently by γ-fluoroglutamic acid I[2,3]. In order to facilitate more extensive investigations in this field other substances were now synthesized which are structurally related to γ-fluoroglutamic acid.

For synthesis of γ-fluoroglutamine II acid I was first phthaloylated according to Nefkens[4], however, it was not possible to cyclize the N-phthaloyl-γ-fluoroglutamic acid III (yield 38%; m.p. 202°, for m.w. 295.23 calculated 4.74% N, found 4.46% N) to the anhydride required for the synthesis of the amide II.

By esterification of acid I with excess dimethyl carbonate in the presence of 2.4 mol of perchloric acid the γ-methylester of γ-fluoroglutamic acid IV (m.p. 153.5° decomp., for m.w. 179.15 calculated 7.82% N, found 7.71% N) was obtained in 32.5% yield after standing for 7 days at

room temperature. By esterification of acid I with methanolic hydrochloric acid compound IV was obtained in 41.5% yield. When this compound was treated by ammonia, the amino group being temporarily protected by carbon disulphide in analogy to the preparation of glutamine[5], γ-fluoroglutamine II was prepared in 28% yield (unsharp decomposition between 144-8°, for m.w. 164.14 calculated 17.07% N, 11.57% F, found 17.21% N, 11,26% F).

The ethylester of 2-fluorocrotonic acid[6] on bromination with N-bromosuccinimide catalyzed by traces of benzoyl peroxide yielded 72% of the theoretical quantity of ethyl-2--fluoro-4-bromocrotonate V (b.p. 95-97.5°/15 mm, n_D^{20} 1.4733; for m.w. 211.04 calculated 9.00% F; 37.86% Br, found 8.64% F, 37.91% Br).

This compound easily reacted with potassium phthalimide in dimethyl formamide giving rise to 79% of ethyl-2-fluoro--4-phthalimidocrotonate VI (m.p. 97-100°; for m.w. 277.25 calculated 5.08% N, found 5.05% N). Hydrolysis of compound VI by boiling concentrated hydrochloric acid yielded 55% of 2-fluoro-4-aminocrotonic acid hydrochloride VII (unsharp decomp. 172-8°; for m.w. 155.57 calculated 9.00% N, 12.21% F, 22.79% Cl, found 9.18% N, 11.70% F, 23.05% Cl. The ester V was also condensed with the sodium salt of ethyl acetamidomalonate in dimethyl formamide solution. From the reaction mixture were isolated 94% of oily ethyl 2-acetamino-2-carbethoxy-5-fluoro-Δ^4-dehydroadipate VIII, which was hydrolysed directly by hydrochloric acid and yielded 46% of 2-amino-5-

-fluoro- Δ^4-dehydroadipic acid IX (decomp. 253-5° after preceding slow darkening from 200°; for m.w. 177.13 calculated 7.91% N, 10.73% F, found 7.62% N, 10.42% F).

With substances VI-IX experiments were carried out to reduce the olefinic bond by catalytic hydrogenation on an Adams catalyst or by heating with hydroiodic acid and red phosphorus. However, reductive removal of fluorine occured simultaneously in all cases and in the resulting mixture (in the case of substances VI and VIII after hydrolysis) γ-aminobutyric acid or α-aminoadipic acid were identified chromatographically besides the not-reduced amino acids, no traces of fluoro derivatives being observed.

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