SYNTHESIS OF N-[4-(2-NAPHTHYL)]- AND N-[4-(2-THIENYL)METHYLAMINO-BENZOYL]-dl-GLUTAMIC ACIDS

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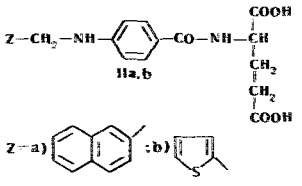
N-[4-(2-Naphthyl)]- (IIa) and N-[4-(2-thienyl)methylaminobenzoyl]-dl-glutamic acids (IIb) have been synthesized for biological tests by the reaction of the corresponding halogen derivatives with diethyl p-aminobenzoyl-dl-glutamate (III) with subsequent hydrolysis of the esters obtained.

In view of the fact that pteroylglutamic (folic) acid (I) and its derivatives possess an exceptionally varied function in biological processes and that antimetabolites of folic acid include known effective antitumoral agents, in recent years a large number of analogs and antagonists of folic acid have been synthesized using various methods for modifying the chemical structure of the metabolite.

The best known analogs of folic acid are those in which the pteridine part is replaced by another cyclic grouping. Among the investigations on the synthesis of compounds of this type must be mentioned those published in the last few years [1–4].

The object of the present work was to synthesize analogs of pteroylglutamic acid II in which a change was made to that part of the structure of I that is responsible for the participation of folic acid in the metabolism of the monocarbon compounds from which the purine and pyrimidine bases and, consequently, nucleic acids, amino acids, and other compounds are constructed [5].



In one of the compounds synthesized (IIa), the heterocycle in pteroylglutamic acid has been replaced by a purely hydrocarbon residue, with the complete retention of the geometry of the molecule. The second, heterocyclic, analog of folic acid, in contrast to the first, distorts the geometry of the heterocyclic part of the molecule and contains a thienyl residue in place of a pteridine residue (IIb).

By analogy with one of the well-known methods for the synthesis of the acid I, compounds IIa and b were obtained by the reaction of the corresponding halomethyl derivatives (2-bromomethylnaphthalene [6] and 2-chloromethylthiophene [7]) with the ester III, which was obtained by the condensation of p-nitrobenzoyl chloride with diethyl dl-glutamate with subsequent catalytic reduction of the nitro group [8]. The esters formed, without being isolated from the reaction mixture, were saponified with aqueous alkali at room temperature to the corresponding acids.

Both the naphthalene IIa and the thienyl IIb analogs of pteroylglutamic acid consist of amorphous yellow substances readily resinifying in the air. They are readily soluble in ethanol and aqueous solutions of alkalies and are insoluble in ether and water.

EXPERIMENTAL

N-[4-(2-Naphthyl)methylaminobenzoyl]-dl-glumatic acid (IIa). A mixture of 1.1 g (0.005 mole) of 2-bromomethylnaphthalene, 1.65 g (0.005 mole) of III, 0.05 g of sodium bicarbonate, a few crystals of NaI, and 15 ml of ethanol was boiled in the water bath for 10 hr. The ethanolic solution was filtered, the ethanol was driven off in vacuum, and the residual viscous liquid was dissolved in 10 ml of ethanol. This solution was treated with 1.5 ml of 30% NaOH solution, and the mixture was left at room temperature for 3 hr. After the neutralization of the solution with hydrochloric acid, a flocculent precipitate deposited which rapidly resinifed and darkened in the air. The precipitate was filtered off, carefully washed with water, and dried over P_2O_5. The mass, which solidified after some time, was ground into a yellow powder. For analysis, the substance was reprecipitated 2–3 times from an aqueous solution of sodium bicarbonate with hydrochloric acid. Yield 0.72 g (48.7%). Mp 93–97° C. Found, %: C 68.67, 68.96; H 5.35, 5.53; N 6.92, 6.21. Calculated for $C_{23}H_{22}N_2O_5$, %: C 68.00; H 5.41; N 6.65.

N-[4-(2-Thienyl)methylaminobenzoyl]-dl-glutamic acid (IIb). A mixture of 1.32 g (0.01 mole) of 2-chloromethylthiophene, 3.2 g (0.01 mole) of III, 1 g of triethylamine, and 25 ml of dry benzene was heated for 5 hours. The precipitate was filtered off and the solvent was driven off in vacuum. The residual viscous liquid was dissolved in 20 ml of ethanol and the solution was treated with 2 ml of 40% NaOH. The subsequent treatment was as described above. Yield 1.85 g (51.2%). The product melted in the range from 70 to 95° C. Found, %: C 56.88, 56.56; H 5.05, 5.11; N 7.85, 7.41. Calculated for $C_{17}H_{18}N_2O_5S$, %: C56.32; H 4.97; N 7.73.

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