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SYNTHESIS AND STUDY OF β-ACRIDYL-α-ALANINES AND THEIR DERIVATIVES

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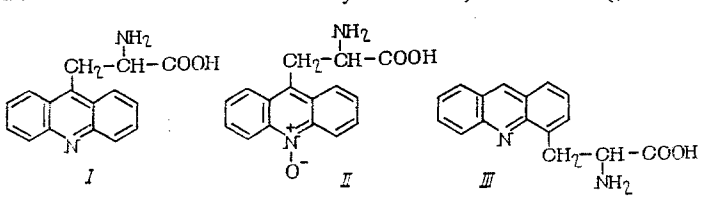
The heterocyclic analogs of natural amino acids (thienylalanines, furylalanines, pyridylalanines) compete with them in metabolic reactions and can profoundly affect both normal and pathological metabolic processes [1-4]; for example, β-(3-thienyl)-α-alanine and β-(2-thienyl)-α-alanine are reported to inhibit the growth of tumors with interwoven cells [5, 6].

Acridylalanines were chosen for the study because acridine derivatives are highly biologically active, and are antineoplastic agents [7]. β-(9-Acridyl)-α-alanine (I) has been synthesized and tested for antitumor activity. It was found to retard the growth of sarcomas which are not susceptible to antimetabolites by 45-72%, and the growth of Ehrlich tumors by 18%.



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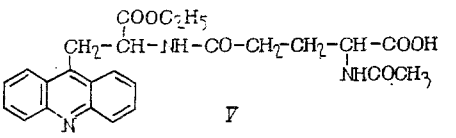
Compound I is known to exhibit antitumor activity; its peptides with natural amino acids, the N oxide (II) and the 4 isomer (III) were therefore synthesized. These compounds were chosen because of reported examples of inclusion in the peptide chain of alkylating metabolites [5], analogs of natural amino acids and their antagonists [8, 9]. Peptides based on compound I, which is known to display antitumor activity, were synthesized. β-(9-Acridyl)-α-alanine N-oxide (II) was synthesized and tested because cancer cells are more sensitive to oxidizing agents than normal cells [10].

The isomers of β-(thienyl)-α-alanine display different biological activities [5, 6] and an isomer of compound I β-(4-acridyl)-β-alanine (III) was therefore synthesized.

Compound III was prepared in the same way as compound I, by the bromination of 4-methylacridine with N-bromosuccinimide followed by condensation of the 4-bromomethylacridine with N-acetylamino malonic ester. The condensation product is then hydrolyzed with hydrochloric acid. Bromination with N-bromosuccinimide in dry carbon tetrachloride proceeds satisfactorily only if the 4-methylacridine is first dried in the melt.

In the synthesis of peptides, compound I was used as a C-terminal amino acid. The carboxyl group was protected by esterification with ethyl alcohol in the presence of sulfuric acid. The ester (IV) was obtained as a colorless, amorphous substance and was used without additional purification in the synthesis of peptides. Compound IV was characterized as the dihydrochloride.

The dipeptides (V-VII) were synthesized by acylation of the amino group of ethyl β-(9-acridyl)-α-alanine (IV) either with the anhydride of N-acetyl glutamic acid [12] (for the synthesis of peptide V), or with the corresponding N-acetyl derivatives of methionine [13] and β-phenylalanine [14].



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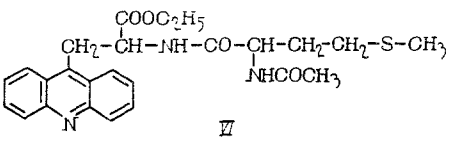

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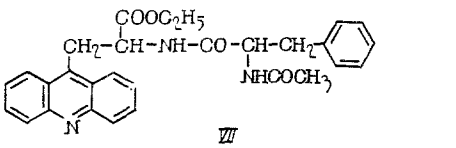

VII

Compound IV was acylated with N-acetylglutamic anhydride in dry dimethylformamide (DMFA) solution at room temperature; the reaction took 24 h.

The product was assigned the structure of a γ peptide of glutamic acid, since it is known acylation of aniline with N-acetylglutamic anhydride gives the γ anilide [12, 15].

The dipeptide VI was obtained by mixing solutions of IV and N-acetylmethionine dissolved in a minimum quantity of DMFA and adding dicyclohexylcarbodiimide (DCC). The dicyclohexylurea was then separated, the DMFA partially distilled, and the dipeptide which separated out was filtered off and repeatedly washed with ether.

The dipeptide VII was synthesized by the azlactone method, i.e., from the previously prepared azlactone of acetylphenylalanine using DCC [16] and subsequent interaction with IV. The peptide VII was isolated in the same way as the dipeptide VI. The compounds I, II, and VII were tested for toxicity and antitumor activity.

Compound I was tested on tumor RS-1 and by its sensitivity to Pliss' lymphosarcoma antimetabolites. The preparation was found to by slightly toxic (LD_{50} 600 mg/kg). When introduced intraperitoneally daily for 6 days at a dose of 100 mg/kg, it retarded the growth of alveolar cancer of the liver RS-1 by 14%, and of Pliss' lymphosarcoma by 35%.

Introduction of the N-oxide group into I to give II led to an increase in activity in tests on Pliss' tumor (62% retardation, using the same method of introduction and the same dose).

The dipeptide VI retarded the growth of Pliss' lymphosarcoma by only 13%.

EXPERIMENTAL

Ethyl Ester of β-(9-Acridyl)-α-alanine (IV). A mixture of compound I (4 g) dissolved in concentrated sulfuric acid (5 ml) and anhydrous ethyl alcohol (36 ml) is refluxed for 8 h and neutralized with a solution of sodium carbonate to weakly alkaline reaction. The ester IV is extracted with chloroform, the extract dried with sodium sulfate, and evaporated to dryness. On rubbing, the oil which remains is readily converted to a colorless powder. Yield 2.5 g of IV (75.5%, mp 91°). This is used without further purification for the preparation of the peptides. To characterize the compound it was converted into the dichloride by twice adding an alcoholic solution of hydrogen chloride to IV and evaporating to dryness. The product was recrystallized from dry ether to give yellow crystals, mp 218-219°. Found, %: C 58.43; H 5.69; N 7.60. $C_{18}H_{18}N_2O_2 \cdot 2HCl$. Calculated, %: C 58.91; H 5.45; N 7.62.

Ethyl Ester of N_α-[N_α-Acetyl-γ-glutamyl]-β-(9-acridyl)-α-alanine (V). N-Acetylglutamic anhydride (oil, 0.32 g) [12] dissolved in a minimum quantity of DMFA is added to a solution of IV (0.5 g) in the same solvent. The reaction mixture is maintained for 48 h at room temperature. The solvent is distilled off in vacuum and the residue recrystallized from distilled water. The yield of V was 0.1 g (12.2% O, mp. 240°). After drying in a vacuum with xylene vapor, it had mp 260-261°. Found, %: C 64.82; H 6.10; N 8.75. $C_{25}H_{27}N_3O_6$. Calculated, %: C 64.50; H 5.85; N 9.03.

Ethyl Ester of N_α-[N_α-Acetylmethionyl]-β-(9-acridyl)-α-alanine (VI). A solution of IV (1 g) in a minimum quantity of DMFA was mixed with a solution of N-acetylmethionine (0.65 g) in the same solvent, DCC (0.7 g) is added, and the mixture is maintained at room temperature for 24 h. The precipitated dicyclohexylurea is filtered off and the volume of the solvent reduced two thirds by distillation in vacuum at room temperature. The dipeptide which precipitates is filtered off and washed with ethyl ether. The yield of VI is 0.95 g (62.8%), mp 201-203°. Found, %: C 64.74; H 6.51; N 9.42; S 6.30. $C_{25}H_{29}N_3O_4$. Calculated, %: C 64.22; H 6.25; N 8.99; S 6.9.

The hydrochloride of the dipeptide is prepared by carefully adding a saturated solution of hydrogen chloride in ethanol to a suspension of VI in dry dioxane. A yellow amorphous powder is obtained, mp 197° (decomp.). Found, %: C 60.09; H 6.67; N 8.53; S 6.35. $C_{25}H_2N_3O_4 \cdot$ HCl. Calculated, %: C 59.6; H 5.96; N 8.34; S 6.34.

Ethyl Ester of N_α-[N_α-Acetyl-β-phenyl-α-alanyl]-β-(9-acridyl)-α-alanine (VII). To a solution of N-acetyl-β-phenyl-α-alanine (0.294 g) dissolved in a minimum quantity of DMFA is added DCC (0.288 g). After 24 h the dicyclohexylurea is filtered off, the filtrate added to a solution of IV (0.4 g) in DMFA. After another 24 h the traces of dicyclohexylurea are filtered off, the solvent distilled off in vacuum at room temperature. The residue is recrystallized from distilled water, and dried in a vacuum over phosphorus pentoxide. The yield of VII was 0.2 g (29.2%), mp 235°. Found, %: C 72.27; H 6.39; N 9.02. $C_{29}H_{29}N_3O_4$. Calculated, %: C 72.0; H 6.05; N 8.7.

4-Bromomethylacridine. A mixture of 4-methylacridine (2.6 g) dried in the melt, N-bromosuccimide (2.28 g), and benzoyl peroxide (0.17 g) in anhydrous carbon tetrachloride (60 ml) is refluxed for 4.5 h. The succinimide is filtered from the hot solution; the filtrate refluxed with activated charcoal and aluminum oxide, filtered, and cooled in the refrigerator. A substance with mp 145° crystallizes out. After two recrystallizations from carbon tetrachloride the mp is 161°. Yield 16.4% (literature mp 159-161° [17]).

Ethyl Ester of β-(4-Aceidyl)-α-carbethoxy-α-acetylaminopropionate. To a solution of sodium alcoholate obtained from dry ethyl alcohol (9 ml) and metallic sodium (0.113 g) is added with mixing N-acetylaminomalonic ester (0.9 g), and after it has dissolved, a solution of 4-bromomethylacridine (0.6 g) in dry benzene (14 ml) is quickly added. The mixture is refluxed for 2 h, the sodium bromide filtered off, and the filtrate concentrated in vacuum. A colorless crystalline precipitate separates and is washed with ether and dried. Yield 0.5 g (57%), mp 144°, mp 154-155° after recrystallization from carbon tetrachloride. Found, %: N 7.11. $C_{23}H_{24}N_2O_5$. Calculated, %: N 6.86.

β-(4-Acridyl)-α-alanine Dihydrochloride. The product of condensation of 4-bromomethylacridine with N-acetylaminomalonic ester (0.15 g) is refluxed for 4 h in diluted hydrochloric acid (0.32 ml, 1:1). A yellow precipitate separates on cooling and is twice recrystallized from a 1:1 mixture of 17.5% hydrochloric acid and ethanol. Yield, 0.1 g (93%), mp 186° (decomp.). Found, %: C 54.07; H 5.31; N 7.86. $C_{16}H_{16}N_2O_6 \cdot 2HCl \cdot H_2O$. Calculated, %: C 53.76; H 6.04; N 7.83.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF ADAMANTANE DERIVATIVES

V. VIRUS-INHIBITING ACTION OF ARYLAMIDES OF ADAMANTANE CARBOXYLIC ACIDS

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It has been shown that 1-(4'-aminophenyl)adamantane-3-carboxylic acid exerts a marked effect on type 3 adenovirus and influenza virus. It was therefore of interest to study the virus-inhibiting activity of the amides of these acids; the amides were obtained according to the scheme shown at the top of the following page.

The starting material 1-(4'-nitrophenyl)adamantane-3-carboxylic acid [1], was converted into the acid chloride using thionyl chloride, and this was condensed with the amines without further purification. Compounds I-XIa (Table 1) were prepared. The acid XIIa was obtained from 1-(4'-nitrophenyl)-3-bromoadamantane [1] and vinylidene chloride by the method described in [2]. The amides XIIIa and XIVa were obtained in the same way as compounds Ia-XIa. The nitro group was reduced with hydrogen and Raney nickel at atmospheric pressure and room temperature, to give the amines Ib-XIVb (see Table 1).

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