Academician of the Academy of Sciences of the Tajik SSR K. T. POROSHIN, S. B. DAVIDYANTS, V. K. BURICHENKO, L. V. BULGAKOVA

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Abstract

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Academician of the Academy of Sciences of the Tajik SSR K. T. POROSHIN, S. B. DAVIDYANTS, V. K. BURICHENKO, L. V. BULGAKOVA

SYNTHESIS OF ALKALOID-PEPTIDE COMPOUNDS

The preparation of complexes of medicinal preparations with peptides and amino acids is of interest. They may possess a number of important properties, such as enhancement and prolongation of the action of the medicinal preparation, reduction of toxicity, etc.

We have obtained such complexes on the basis of certain alkaloids, amino acids, and peptides. In obtaining them, an amino- or imino-acyl bond is formed, in contrast to the usual salt-like type of bond with various acids. In the case of the use of pharmacologically active heterocyclic acids, ordinary amidation is observed. Compounds of this type have already been encountered in the literature, in particular amino-acid and peptide derivatives of nicotinic acid, which were used to study the hydrolytic activity of chymotrypsin ([1–3]), as well as derivatives of isonicotinic acid possessing high pharmacological activity ([4]).

The combination of alkaloids and heterocyclic acids with amino acids and peptides was carried out by the "mixed anhydride" method ([6]) using "protecting" and "activating" groups ([5–9]). The first components in the syntheses were "protected" amino acids and dipeptides: glycine, *DL*-alanine, *L*-alanine, *DL*-serine, glycylglycine, glycyl-*DL*-alanine, and also the heterocyclic acid α-phenylcinchoninic acid (atophan). The carbobenzoxy group ($Z = C_6H_5CH_2OCO—$) was used as the "protection" ([10,11]). As the second component, hydrochlorides of methyl esters of glycine and *DL*-serine and the alkaloids cytisine and salsolidine (hydrochloride) were used. In the case of condensation of *DL*-alanine with optically active cytisine ($[\alpha]_D^{17} = -119°$, in water), separation of *DL*-alanine into the *L*- and *D*-forms was observed. Thus, in contrast to the known method of separating racemates into *L*- and *D*-forms, based on the formation of salts with optically active bases (for example, *DL*-alanine with the aid of brucine and strychnine), in the present case another type of resolution takes place: by introduction of an asymmetric atom upon formation of a chemical compound with an iminoacyl bond between the amino acid and an alkaloid possessing sufficient stability.

Experimental Part

Z-Glycylcytisine. To 2.1 g (0.01 mole) of carbobenzoxyglycine in 25-30 ml of chloroform with 1.5 ml of triethylamine at −10-−15°, 1.14 g (0.0105 mole) of

ethyl chloroformate was added. After 1.5 hours, a solution of 2 g (0.0105 mole) of cytisine in 25 ml of chloroform, cooled to −15°, was poured into the mixture. The mixture was left overnight, after which it was washed with water, 0.5 *N* $NaHCO_3$, dried over ignited Na_2SO_4, filtered, and the chloroform was distilled off in vacuo. The oily residue was dissolved in ethyl acetate and, upon addition of dry ether, a white precipitate separated, which was washed once more with ether. The product is soluble in water, ethyl and methyl alcohol, chloroform, acetone; insoluble in sulfuric and petroleum ether. Yield 38.5%, m.p. 138°.

Found, %: C 65.94, 65.91; H 6.12, 6.14; N 10.85, 10.85
$C_{21}H_{23}O_4N_3$. Calculated, %: C 66.1; H 6.04; N 11.02

Z-Alanylcytisine. The first component used was *Z*-DL-alanine. The reaction conditions were analogous to those for the preparation of *Z*-glycylcytisine. On treatment of the oily residue with ethyl acetate, two products were obtained: one immediately precipitated and, after recrystallization from aqueous methanol, had m.p. 199°; the other was precipitated from ethyl acetate and had m.p. 155°. It was supposed that, with the aid of optically active cytisine ($[\alpha]_D^{17} = -119^\circ$, in water), resolution of *DL*-alanine into the *L*- and *D*-forms had occurred. To verify this supposition, condensation of cytisine with *Z*-*L*-alanine was carried out. The product obtained as a result melted at 199°; $[\alpha]_D^{20} = -208^\circ$, in chloroform. A mixed sample with the corresponding product obtained on resolution gave no depression. Consequently, one of the products of resolution of *Z*-DL-alanine (m.p. 198–199°) is the *L*-form ($[\alpha]_D^{20} = -200^\circ$, in chloroform).

Z-*L*-alanylcytisine is a white product, readily soluble in methyl alcohol, chloroform, and dioxane, moderately soluble in water, ethyl alcohol, acetone, and carbon tetrachloride, and insoluble in ethyl acetate, sulfur ether, and petroleum ether.

$C_{22}H_{25}O_4N_3$. Found, %: C 66.79, 66.68; H 6.33, 6.35; N 10.61, 10.62
Calculated, %: C 66.85; H 6.32; N 10.63

Z-*D*-alanylcytisine is a white product, m.p. 155°, readily soluble in chloroform, acetone, dioxane, and ethyl alcohol, moderately soluble in water, methyl alcohol, and carbon tetrachloride, and insoluble in sulfur and petroleum ether.

Found, %: N 10.60, 10.40
Calculated, %: N 10.63

Hydrobromides of *L*- and *D*-alanylcytisine, obtained by removal of the *Z*-protection with 40% HBr in glacial acetic acid [12], had $R_f = 0.23$.

Z-Glycylglycylcytisine. This was obtained by two methods. In one case the protected dipeptide was taken and the reaction was carried out by method [6]. *Z*-glycylglycylcytisine was obtained in 41% yield, m.p. 96°.

$C_{23}H_{26}O_5N_4$. Found, %: N 12.5, 12.5
Calculated, %: N 12.77

In another case, the synthesized *Z*-glycylcytisine was used, from which the *Z*-protection was first removed with HBr in glacial acetic acid (glycylcytisine hydrobromide had m.p. 340° (decomp.), $R_f = 0.33$). The reaction product was analogous to that obtained by the first method; yield 43%, m.p. 96°; a mixed sample gave no depression. *Z*-glycylglycylcytisine is soluble in ethyl and methyl alcohol, chloroform, and acetone; insoluble in ether.

Glycylglycylcytisine hydrobromide is a white product, m.p. 350° (decomp.), $R_f = 0.24$.

Z-Glycylalanylcytisine. Obtained by condensation of *Z*-glycylalanine with cytisine. Yield 35%, m.p. 145°. Soluble in chloroform and ethyl acetate; insoluble in ether.

$C_{24}H_{28}O_5N_4$. Found, %: N 12.4, 12.5
Calculated, %: N 12.3

Z-Cytisinyl-Z-salsolidine. Prepared according to Bergmann-Zervas [10]. Yield of *Z*-cytisine 50%. M.p. 129°, $R_f = 0.93$.

$C_{19}H_{20}O_3N_2$. Found, %: N 8.89, 8.89
Calculated, %: N 8.64

Analogously, *Z*-salsolidine was obtained. Yield 73%, m.p. 98–100°, $R_f = 0.90$.

$C_{20}H_{23}O_4N$. Found, %: N 3.99, 3.98
Calculated, %: N 4.1

Z-glycylsalsolidine. The synthesis was carried out by the known method ([6]). The product was obtained as an oil, which could not be crystallized. Yield 68%, $R_f = 0.75$.

Found, %: 6.78, 6.79
$C_{22}H_{26}O_5N_2$. Calculated, %: 7.03

Glycylsalsolidine hydrobromide—a product with a yellowish tint, yield 84%, m.p. 165°, $R_f = 0.5$.

Found, %: N 7.98, 7.99
$C_{14}H_{21}O_3N_2$. Calculated, %: N 8.11

Z-serylsalsolidine. Obtained in the same way as Z-glycylsalsolidine. The oil was crystallized from an acetone–ether mixture, yield 57%, m.p. 65–67°, $R_f = 0.8$.

Found, %: N 6.42, 6.42
$C_{23}H_{29}O_6N_2$. Calculated, %: N 6.54

O-acetylserylsalsolidine hydrobromide, which is formed on treatment of Z-serylsalsolidine with HBr/CH_3COOH, had m.p. 135°, yield 64%.

Found, %: N 6.76, 6.65
$C_{17}H_{25}O_5N_2Br$. Calculated, %: N 6.71

Z-glycylglycylsalsolidine. Obtained by condensation of Z-glycine with glycylsalsolidine hydrobromide. Yield 57%, m.p. 80°, $R_f = 0.94$.

Found, %: N 8.92, 9.01
$C_{24}H_{29}O_6N_3$. Calculated, %: N 9.23

Z-glycyl-(O-acetyl)-serylsalsolidine. Obtained as a result of condensation of Z-glycine with (O-acetyl)-serylsalsolidine hydrobromide. Yield 57.8%, m.p. 85–87°, $R_f = 0.93$. $C_{27}H_{33}O_8N_3$.

Methyl ester of α-phenylcinchoninylglycine. The first component used was α-phenylcinchoninic acid. The second was glycine methyl ester hydrochloride. By the Bausson reaction a cream-colored product was obtained in 32% yield, m.p. 145–146° (crystallized from a methanol–water mixture).

Found, %: N 9.00, 9.08
$C_{19}H_{16}O_3N_2$. Calculated, %: N 8.75

The product is readily soluble in methanol, ethanol, chloroform, sulfuric ether, acetone, benzene, toluene, and dioxane. It is insoluble in petroleum ether and water.

Methyl ester of α-phenylcinchoninylserine. Obtained analogously to the preceding compound. Yield 35%, m.p. 151–155°.

Found, %: N 8.07, 8.05
$C_{20}H_{18}O_4N_2$. Calculated, %: N 8.00

Chromatographic determinations were carried out in the system butanol–water–acetic acid (4 : 5 : 1) on "Leningrad" paper of type "M"; developers: ninhydrin

(in the case of compounds with cytisine) and Dragendorff' s reagent (in the case of compounds with salsolidine and in the case of Z-cytisine).

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Institute of Chemistry
Academy of Sciences of the Tajik SSR

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Note: Figure translations are in progress. See original paper for figures.