ANOMALOUS NUCLEOSIDES AND RELATED COMPOUNDS

XVI.* PHENAZINYLPEPTIDES

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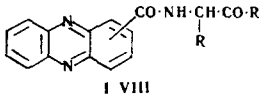
Amino acid and peptide derivatives of phenazinecarboxylic acids (phenazinylpeptides) have been obtained by the reaction of hydrochlorides of esters of amino acids, phosphorus trichloride, and phenazinecarboxylic acids with the subsequent splitting off of the protective ester groups in an acid or an alkaline medium.

In developing work on the synthesis of mono-, di-, and tricyclic analogs of nitrogen-containing bases and nucleosides – components of nucleic acids, nucleotidoenzymes, nucleotidopeptides, and related compounds – amino acid and peptide derivatives of phenazinecarboxylic acids (phenazinylpeptides) have been obtained. As is well known, the phenazine molecule is a structural analog of isoalloxazine, a component of the flavin coenzymes. More than ten natural antibiotics with a broad spectrum of biological activity are also phenazine derivatives.



I VIII

I R = OCH_3, R′ = H
II R = OC_2H_5, R′ = H
III R = OCH_3, R′ = CH_3
IV R = OCH_3, R′ = $CH_2CH(CH_3)_2$
V R = $NHCH_2COOC_2H_5$, R′ = H
VI R = OH, R′ = $CH_2CH(CH_3)_2$
VII R = $NHCH_2COOH$, R′ = H
VIII R = OCH_3, R′ = H

I—VII Phenazine-1-carboxylic acid derivatives
VIII Phenazine-2-carboxylic acid derivative

The synthesis of phenazinylpeptides was effected by "phosphorazo" method [1]. The reaction of hydrochlorides of esters of various amino acids and peptides (glycine, alanine, leucine, glycylglycine, etc.) with phosphorus trichloride in pyridine first gave a "phosphorazo" compound which, without isolation, was

*For Communication XV, see [5].

TABLE 1. Phenazinylpeptides

Compound	mp, °C	R_f[1]	Empirical formula	N, % found	N, % calc.	Yield, %
I	198—200[2]	0,91	$C_{16}H_{13}N_3O_3$	14,10	14,23	50
II	156[3]	0,93	$C_{17}H_{15}N_3O_3$	13,78	13,58	56
III	153—155[4]	0,92	$C_{17}H_{15}N_3O_3$	13,31	13,55	54
IV	134—136[2]	0,97	$C_{20}H_{21}N_3O_3$	12,21	11,96	53
V	216—217[5]	0,72	$C_{19}H_{18}N_4O_4$	15,61	15,29	72
VI	222—223[4]	0,71	$C_{19}H_{19}N_3O_3$	12,60	12,46	77
VII	235—240[2]	0,03	$C_{17}H_{14}N_4O_4$	16,56	16,56	65
VIII	223—225[4]	0,76	$C_{16}H_{13}N_3O_3$	14,09	14,23	33

1. Water-saturated n-butanol system.
2. From methanol.
3. From a mixture of ethyl acetate and petroleum ether.
4. From acetone.
5. From ethanol.

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condensed with phenazine-1- or -2-carboxylic acid [2,3], giving the ester of a phenazinylpeptide. After the elimination of the ester groups in an acid or an alkaline medium, the corresponding unsubstituted phenazinylpeptide was isolated. Examples of the compounds synthesized and some of their characteristics are given in Table 1.

All the substances synthesized are light yellow and crystallize well. The esters of the phenazinylpeptides melt below the melting points of corresponding unsubstituted compounds. They are readily soluble in organic solvents and are insoluble in water. The unsubstituted phenazinylpeptides are soluble in alkali.

EXPERIMENTAL

Methyl Ester of N-(Phenazine-1-carbonyl)glycine (I). With stirring and ice cooling, 0.87 ml (0.01 mole) of freshly distilled phosphorus trichloride in pyridine (10 ml) was added dropwise to 2.52 g (0.02 mole) of the hydrochloride of the methyl ester of glycine in 30 ml of pyridine. After the mixture had been kept at room temperature for 30 min, 4.48 g (0.02 mole) of phenazine-1-carboxylic acid was added and the mixture was heated in the boiling water bath for 3 h. After cooling, the polymetaphosphoric acid was filtered off and the solvent was distilled off in vacuum. The residue was treated alternately with ethyl acetate and dilute hydrochloric acid so that the aqueous layer showed an acid reaction. The ethyl acetate layer was carefully washed with sodium bicarbonate and water and was dried with anhydrous sodium sulfate. After the solvent had been distilled off and the residue had been recrystallized from methanol, 2.9 g (50%) of small yellow needles with mp 198-200°C was obtained. Found %: C 65.10; H 4.53; N 14.10. $C_{16}H_{13}N_3O_3$. Calculated %: C 65.07; H 4.43; N 14.23.

N-(Phenazine-1-carbonyl)glycine. A solution of 0.5 g (0.002 mole) of the ester of N-(phenazine-1-carbonyl)glycine in 10 ml of a mixture of acetone, water, and hydrochloric acid (2 : 2 : 1) was heated at 85°C in the water bath under reflux for 25 min. Vacuum distillation of the solvent yielded 0.4 g (88%) of small light yellow needles (from ethanol) with mp 254-255°C; according to the literature [4], 255°C.

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