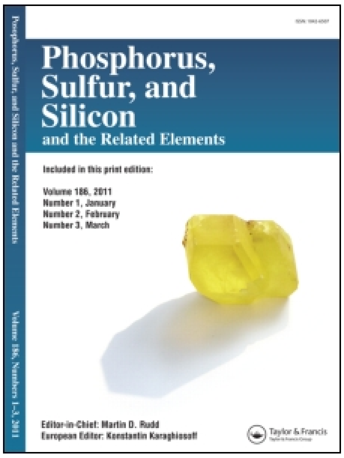

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Phospha-Pharmaca - Antibacterial and Virucidic Compounds

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PHOSPHA-PHARMACA - ANTIBACTERIAL AND VIRUCIDIC COMPOUNDS

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Abstract: Synthetic, antibacterial, and antiviral aspects of the P-glutamic acid type compounds, of phosphonic acids, phospha^{C}-peptides, and of phosphorus derivatives of the formic acid are considered.

Compounds with antibacterial, antibiotic, antineoplastic, and antiviral properties gain in importance in the manifold use of organophosphorus compounds [1]. The general name "phospha-pharmaca" is used for them. Their structure and action mode is characterized by an isosteric principle (replace of O by CH_2) and an antimetabolite concept [2]. In the following, only substances shall be considered, which were of synthetic interest in the Halle group.

The concept of inhibition of many enzymatic reactions by α-aminophosphonic acids lead us to the synthesis of the phosphonic analogue of captopril. It can be obtained conveniently, contrary to the approach of Petrillo [3], via reaction of $(PhO)_2POH$ and 1-pyrroline followed by acylation with S-acetyl-ß-mercapto-propanoylchloride, or from the ester formed from bis-trimethylsilyl-phosphite and an N-benzyl-pyrrolinium salt [4]. The entry to aminophosphonic acids by the benzhydryl approach [5] gets importance because of their analogy with the α-carboxylic acids (cf. phosphanilic acid, alaphosphin, plumbeomycines, phosphono-aminocarboxylic acids and othercompounds). The above mentioned method is based on the interaction of Schiff's bases, formed from Ph_2CHNH_2 and carbonyl compounds, with PH-functionalized compounds, mainly with bis-trimethylphosphite. To this belongs the formation of L-Phosphinotricin from L-vinylglycine and $CH_3P(OSiMe_3)OH$, and the synthesis of the phosphonoglutamic and -aspartic acids respectively. The latter show neuroactivity, e.g. they steer the processing of information in the retina of the eyes [6].

Phosphorus containig peptides can serve as model substances for enzymatic reactions. The tripeptide of a phosphorus analogue amino acid, e.g., is an inhibitor of aspartic peptidases [7]. Peptides with PN-structure are suitable models for the study of enzymatic reaction because of their structural similarity to the tetrahedral intermediate of peptidases. A neat approach to these was realized by the reaction of isocyanato fatty acid esters with the monosilylesters of certain N-protected aminophosphonic acids [8]. In the first step a mixed anhydride is formed, which underlies CO_2 elimination with simultaneous PN-linkage. The free peptides can be obtained after usual deblocking procedures.

The favourite compounds in the chemotherapy of viral diseases are recently nucleoside analogues of the purine and the pyrimidine type, and pyrophosphate analogues [9]. The simple structure of the latter is particular remarkably. Phosphonoacetic acid, phosphono-, thiophosphono-, and phosphonousformic acid, and 1.1-diphosphonic acids respectively inhibit selectively the viral DNA polymerases. They are less selectively then the nucleoside analogues like iodo-, ethyl- or bromovinyldesoxy uridine and acyclovir respectively, and a higher inhibitory concentration is necessary, but they have some advantages as effects against viruses without thymidine kinases, reversible inhibition of cellular DNA polymerases, no incorporation into the DNA because of their enzymatic stability, and last but not least the convenient approach to them. The most effective substances are in the following order phosphonoformic acid, -acetic acid, -hydroxyacetic acid, and carbonyl-1.1-diphosphonic acid which was tested by means of the inhibition of polymerase according to ÖBERG [10].

The trisodium phosphonoformate is the most effective compond against herpes viruses. This was the reason for us to modify the basic structure of the PFA. The result of these efforts was the synthesis of the thiophosphono- and the phosphonousformic acid [11]. Both substances have very good antiviral properties, which are comparable to those of phosphonoformate (PFA) or better respectively, as results of inhibition experiments with HSV-1 and HSV-2 show [12]. Modification of the basic structure to the ethoxycarbonylester or to the phosphane derivative yields very decreased antiherpetical activities.

The synthetic aspects of the above mentioned compounds can be outlined as follows. The classical approach to the PFA according to NYLEN is not acceptable because of only 20% yield, which can be interpreted by PC-bond cleavage in the alkoxycarbonyl-phosphonic acid dialkylester. But the PFA is obtainable in quantitative yield by reaction of chloroformic acid esters and tris- or bis-trimethylsilylphosphite in presence of hexamethyldisilazane in a one-pot-like-reaction [13].

The alkoxycarbonyl-phosphonous-acid-bis-trimethylsilylester, formed from bis-trimethylsilyl-hypophosphite and alkylchloroformates, represents a key substance because after alkaline hydrolysis result the disodium phosphonousformate, and after oxidation with sulfur and following alkaline treatment the trisodium-thiophosphonoformate, which show both antiherpetic activity.

Derivatizations as well as at the carbonyl and at the phosphorus moiety, like transformation of phosphono to phosphino phosphorus, lead to compound with strongly decreased antiviral activity. Single data to the latter and statements to P-derivatives with pharmacological interest are recorded in the cited references.

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