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SOME REACTIONS OF TETRAHEDRAL PHOSPHORUS DERIVATIVES OF GLYCINE RESULTING IN AMIDE OR PEPTIDE BOND FORMATION.

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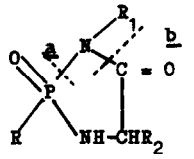
It has been shown by Eberhard and Westheimer that five membered cyclic phosphodiesters, when treated with a nucleophile, are extremely easily opened and that this reaction proceeds by phosphorus oxygen bond fission [1]. The reaction can be rationalised by assuming the formation of an sp^3d phosphorus hybrid [2], and has also been noticed with other five membered cyclic compounds containing a tetrahedral phosphorus atom and various radicals such as aminoalcohol-alcohol [3], acid-alcohol [4], diamine [5], acid-amide [6], amino-alcohol [7]. It was therefore reasonable to assume that the reaction could be extended to five membered cyclic compounds which include $\geq$PO and an α-amino amide radical. Such a cyclic compound, e.g. A

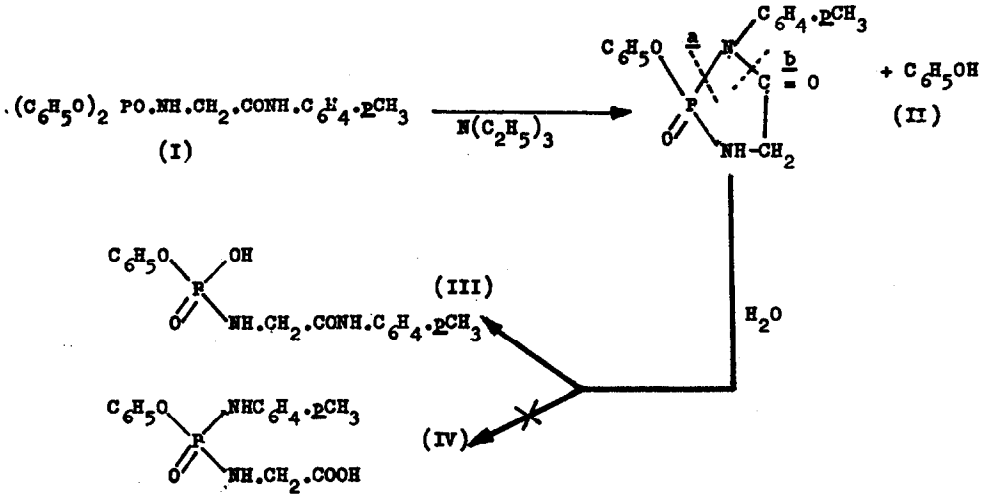


A

when treated with a nucleophile, may be expected to undergo ring opening by phosphorus-nitrogen cleavage (at a) rather than carbon-nitrogen cleavage (at b) (cf N-benzoylphosphoramidic acid is a phosphorylating and not a benzoylating agent [8]).

In an attempt to test this hypothesis, we have prepared the phosphodiesteramide $(C_6H_5O)_2PO.NH.CH_2.CONH.C_6H_4.pCH_3$ (I). Upon treatment with aqueous triethylamine in tetrahydrofuran at room temperature, for a few minutes, this compound lost phenol and gave the

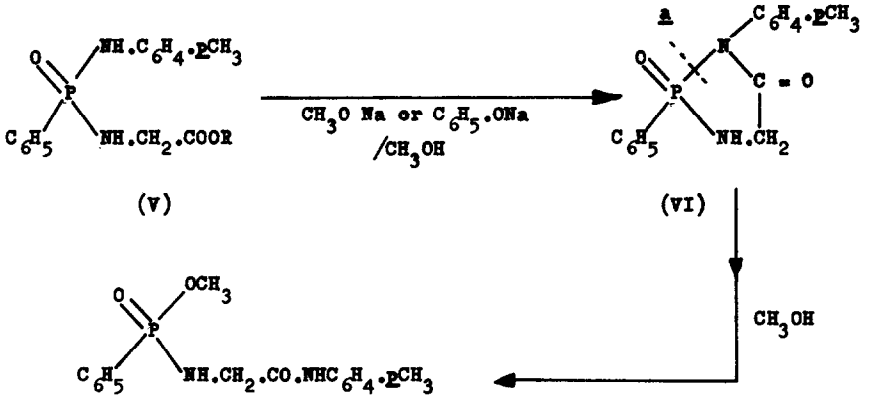
phosphomonoesteramide $C_6H_5O.PO(OH)(NH.CH_2.CONH.C_6H_4.pCH_3)$ (III), isolated as its crystalline dicyclohexylammonium salt in 94% yield. As the analogous phosphodiesteramide $(C_6H_5O)_2 PO.NH.CH_2.C_6H_5$ [9], which, however, unlike compound (I), does not contain an NH group in β position to the phosphorus atom, is not affected by the treatment that transforms (I) into (III), it is most likely that the phosphodiesteramide (I) is first transformed into the five membered cyclic phosphomonoesterdiamide (II), which then, by P-N bond fission at a, yields the acyclic phosphomonoesteramide (III) and not the isomer (IV) which would result from ring opening by C-N bond cleavage at b, and which was independently synthesized by an unambigous route.



The isomers (III) and (IV) can be easily distinguished : while the latter is rapidly destroyed by mild acid treatment, the former remains unchanged. The reaction sequence postulated is analogous to that proposed by Zervas et al. [10] for the transformation of $(C_6H_5O)_2 PO.NH.CH_2.COO.CH_2.C_6H_5$ into $C_6H_5O.PO(OH)(NH.CH_2.COOH)$ isolated as the barium salt.

In another type of experiment, and in analogy with the alkoxide catalysed cyclization of a carbonyl bisaminoacid into a hydantoïn [11], we have applied the same basic treatment (CH_3ONa/CH_3OH) to the phosphonamidates $C_6H_5.PO(NH.C_6H_4.pCH_3)(NH.CH_2.COOR)$,

($R = CH_3$; $CH_2.C_6H_5$; $C(CH_3)_3$), (V). The isolated product was $C_6H_5.PO(OCH_3)(NH.CH_2.CONH-C_6H_4.pCH_3)$, (VII). Its structure was confirmed by the isolation of $H_2N.CH_2.CONH.C_6H_4.pCH_3$ (as hydrochloride) after sequential hydrolysis of (VII) with aqueous sodium hydroxide and citric acid. The formation of compound (VII) can be rationalised, by the methanolysis of the intermediate cyclic product (VI) with P-N bond fission at a :



(V) (VI)

(VII) (85-95% yield)

Similarly, $C_6H_5O.PS(NH.C_6H_4.pCH_3)(NH.CH_2.COO.CH_2.C_6H_5)$ gave with concomitant replacement of C_6H_5O- by CH_3O-, $(CH_3O)_2$ $PS.NH.CH_2.CO.NH-C_6H_4.pCH_3$ in 94% yield and not $CH_3O.PS(NH.C_6H_4.pCH_3)(NH.CH_2.COO.CH_3)$, as shown by the NMR spectrum in which the toluidine amide proton appears as a singlet, unsplit by the phosphorus atom.

Also $pO_2N.C_6H_4.PO$ $(NH.CH_2.COO.CH_2.C_6H_5)_2$ gave $pO_2N.C_6H_4.PO$ $(OCH_3)(NH.CH_2.CO.NH-CH_2.COO.CH_3)$ and, after saponification and acidification, $pNO_2.C_6H_4.PO$ $(OH)_2$ and the dipeptide, $NH_2.CH_2.CO.NH.CH_2.COOH$, in 60% overall yield.

On the basis of these experiments we propose a novel scheme of repetitive and controlled peptide synthesis. The two steps are :

a) formation of the peptide link by cyclization :

B (X= OH, OCH_3, Cl etc.) (Y= O, or S) A

b) displacement of the peptide link by the NH_2 group of the following aminoacid :

(R' = amide, ester, peptide..)
(Y = O, or S) B'

Work is under way to determine the scope and the limitations of this scheme.

All new compounds synthesized in the above experiments gave satisfactory elemental analyses.

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