NEW METHOD FOR THE SYNTHESIS OF 1-AMINOALKYL-PHOSPHONIC AND -PHOSPHINIC ACIDS

COMMUNICATION 4. SYNTHESIS OF (1-AMINOALKYL)PHENYLPHOSPHINIC ACIDS

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In previous communications [1] we have shown that a dialkyl hydrogen phosphite, an aldehyde or ketone, and ammonia will react together and yield a 1-aminoalkylphosphonic ester:

\[ R'\text{H} + \text{NH}_3 + \text{C}=\text{O} \rightarrow \text{C} = \text{O} + \text{NH}_3 + \text{R}'\text{H} \]

We treated the mechanism of this reaction as follows. We considered that the dialkyl phosphate ionizes in presence of ammonia, with transfer of reaction center and formation of a phosphite anion containing tervalent phosphorus:

\[ \text{NH}_3 + \text{OR} \rightarrow \text{NH}_4^+ + \text{O} - \text{POR} \]

and this then adds to the carbonyl compound:

\[ \text{R'}\text{C}=\text{O} + \text{NH}_4^+ \rightarrow \text{R'}\text{C}=\text{O} + \text{NH}_4^+ \]

after which hydroxyl is replaced by amino:

\[ \text{R'}\text{C}(\text{O})\text{POR} + \text{NH}_3 \rightarrow \text{R'}\text{C}(\text{O})\text{NH}_3 + \text{H}_2\text{O} \]

We then suggested that reactions of this type should be possible for the ammonium salts of all acids capable of diad or triad tautomerism [2]. For example, dialkyl phosphorothioites are acids of this type [3]. For this reason, these substances, as we have shown in our laboratory [4], react with carbonyl compounds and ammonia with formation of the corresponding esters of 1-aminoalkylphosphonothionic acids:

\[ \text{R'}\text{C}(\text{S})\text{POR} + \text{NH}_3 \rightarrow \text{R'}\text{C}(\text{S})\text{NH}_3 + \text{H}_2\text{O} \]

Monoesters of aryl (or alkyl)phosphonous acids are of the same type:

\[ \text{R} = \text{POH}(\text{OR}) \text{ or } \text{C}_6\text{H}_5 = \text{POH}(\text{OR}). \]

These substances are able to form metal derivatives, which react with alkyl halides by a reaction of the Michaelis-Becker type [5]:

\[ \text{R'}\text{PO}(\text{OR}) + \text{ROH} + \text{NaOH} \rightarrow \text{R'}\text{PO}(\text{OR})(\text{OH}) + \text{NaOH} \]
In presence of alkaline catalysts they add to an activated double bond, for example that of an acrylate ester [6]:

\[
\text{RO} \quad \text{P} \quad \text{O} / \quad \text{H} / \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{COOR} + \text{RONa} \quad \rightarrow \quad \text{RO} \quad \text{P} \quad \text{O} / \quad \text{H} / \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{COOR}
\]

and they add also to carbonyl compounds with formation of alkyl(1-hydroxyalkyl)phosphinic esters:

\[
\text{RO} \quad \text{P} \quad \text{O} / \quad \text{H} / \quad \text{C} \quad \text{R}'' \quad \text{R}''' \quad \text{RONa} \quad \rightarrow \quad \text{RO} \quad \text{P} \quad \text{O} / \quad \text{H} / \quad \text{C} \quad \text{OR} \quad \text{R}'' \quad \text{R}'''
\]

and they show all the other properties of diad-tautomeric substances:

\[
\text{RO} \quad \text{P} \quad \text{O} / \quad \text{H} / \quad \text{R} \quad \rightarrow \quad \text{R} \quad \text{P} \quad \text{OH}.
\]

There was every reason to expect, therefore, that monoesters of phenylphosphonous acid would react with carbonyl compounds in presence of ammonia with formation of the corresponding esters of (1-aminoalkyl)phenylphosphinic acids:

\[
\text{RO} \quad \text{P} \quad \text{O} / \quad \text{H} / \quad \text{C} \quad \text{NH}_2 + \text{R}'' \quad \text{R}''' \quad \text{H}_2\text{O}
\]

It was in fact found that, when a mixture of acetone, ethyl hydrogen phenylphosphonite, and alcoholic ammonia was heated in a sealed tube in a boiling water bath for three hours, reaction occurred in accordance with the foregoing scheme, and the product was undoubtedly ethyl (1-amino-1-methylethyl)phenylphosphinate. If, however, alcohol and (under reduced pressure) unchanged ethyl phenylphosphonite were distilled from the reaction mixture, only a very small amount of this ester could be isolated (as its hydrochloride II). The main product isolated was the acid (I') (internal salt).

The same free acid is obtained when butyl phenylphosphonite is used instead of the ethyl ester. Reduction in the duration of heating results in only a slight increase in the yield of ester. It may be supposed that the ester formed in the reaction is decomposed by heat:

\[
\text{CH}_3 \quad \text{PO(O})^+\text{C}_6\text{H}_5 \quad \text{CH}_3 \quad \text{PO(O})^+\text{C}_6\text{H}_5
\]

\[
(\text{I}) \quad (\text{II})
\]

The low yield of ester may be explained also by partial hydrolysis of the original phosphonous ester.

It is in fact found that the ammonium salt of free phenylphosphonous acid (III) can always be found in the reaction products; it is formed by the hydrolysis of the original ester:

\[
\text{H} \quad \text{P} \quad \text{O} / \quad \text{C}_6\text{H}_5 / \quad \text{O} / \quad \text{C}_6\text{H}_5 + \text{H}_2\text{O} + \text{NH}_3 \quad \rightarrow \quad \text{H} \quad \text{P} \quad \text{O} / \quad \text{C}_6\text{H}_5 / \quad \text{O} / \quad \text{C}_6\text{H}_5 + \text{C}_2\text{H}_5\text{OH}
\]

(III')