Methods for the introduction of phosphorus-containing groupings into indole and its derivatives and the chemical properties and biological activity of phosphorylated indoles are examined.

If one takes into account the large role that various indole derivatives play in the organism and also the broad spectrum of the biological action of organophosphorus compounds, the interest in compounds that combine indole and phosphorus-containing fragments becomes understandable. Natural, psilocybin, 3-[2-(dimethylamino)ethyl]indol-4-ol dihydrogen phosphate ester—the active principle of "Mexican" fungi—has high psychogenic activity and may serve as an example of this sort of combination.

Since a rather large amount of indole raw material from the coking process has not yet found extensive and intelligent application, the economic factor involved in the development of research in this area is also understandable.

A relatively small number of review papers have been devoted to the phosphorylation of indole [1-8], although the first communication appeared in 1930 [9]. In the present review, material on phosphorylated (phos)indoles is presented with respect to types that differ with respect to the position of the phosphorus-containing substituent in the indole ring and encompasses publications that have appeared prior to the second half of 1975.

1-Phosphorylated Indoles

The methods for the synthesis of 1-phosindoles can be divided into two groups: syntheses based on metal derivatives of indole and the Arbuzov rearrangement from P(III) esters.

Nucleophilic substitution by metal derivatives of indoles of the halogens in compounds with a P-Hal bond opens up possibilities for the synthesis of diverse 1-phosindoles. Diverse 1-bis(dimethylamido)phosphorylated heterocycles, including indoles of the I type, were obtained in 1961 [10]:

\[
\begin{align*}
\text{Indole} + \text{P} \left(\text{OR}\right)_{2} & \rightarrow \text{Phosphorylated Indole}
\end{align*}
\]

Esters (II) of phosphoric and thiophosphoric acids were similarly synthesized [11]:

\[
\begin{align*}
\text{Esters of phosphoric and thiophosphoric acids}
\end{align*}
\]

Indolylmagnesium halides (III) are more convenient than indolylsodium. It is well known, of course, that 3-substituted indoles are more frequently formed when they are used [6]. The authors of the present review were able to obtain both 1- and 3-phosindoles [12]:

\[
\begin{align*}
\text{Indole} + \text{P} \left(\text{OR}\right)_{2} & \rightarrow \text{Phosphorylated Indole}
\end{align*}
\]
An analysis of a series of studies \[6, 13-16\] makes it possible to assume that the degree of ionic character of the N–MgHal bond in indolylmagnesium halides depends on external factors, particularly on the polarity of the medium.

In the examination of the structure of the ambident indole anion IV by means of the principle of soft and hard acids and bases \[17\], the reaction center at the nitrogen atom can be defined as "hard" and the C\(_3\) atom can be defined as "soft." In this case it is completely understandable why "hard" acid chlorides – bis(chloromethyl)phosphine oxide and diphenyl chlorophosphate \[Eq. (2)\] – attack the 1 position of indole.

A second possible method for the synthesis of 1-phosindoles is the classical Arbuzov rearrangement \[18\]. Thus esters \(V\) of P(III) acids underwent rearrangement on reaction with 9-haloacylcarbazoles \[19\]:

\[
\text{O=C(CH}_{2}\text{n)}\text{Hal} \quad \text{O=C(CH}_{2}\text{n)}\text{P(OR)}_{2}
\]

The reaction of phosphites \(V\) with 1-chloroacetylindole also proceeds via a reaction of the (3) type. In this case 1-indolylacyl phosphonates and phosphinates were isolated in 53–67\% yields \[12\]:

\[
\text{O=C(CH}_{2}\text{n)PO\text{R'}}_{2}
\]

\textbf{2-Phosphorylated Indoles}

The number of described compounds of this type is small, and this is probably associated with the lower reactivity of the 2 position with respect to electrophilic reagents as compared with the remaining positions of the indole ring.

The authors of the present review isolated 2-phosindoles \(VI\) instead of the expected 3-substituted compounds in the condensation of phosphorylated acetals with arylhydrazines under the conditions of the Fischer reaction \[20, 21\]:

\[
\text{ROx} \quad \text{H}_2\text{NNH} \quad \text{H}
\]

This fact was explained by intramolecular rearrangement of the initially formed "normal" Fischer reaction products. Intramolecular rearrangement was first observed in the indole series in 1888 \[22\]. The mechanism of rearrangements of this sort has been discussed in detail in the case of alkyl-, aryl-, and acyl-indoles \[23, 24\]. The proposed mechanism also successfully explains reaction \(4\).

Compounds of the \(VI\) type were obtained from the authentic 3 isomers \[25\] by heating the latter with anhydrous zinc chloride in order to prove the possibility of the occurrence of secondary rearrangements in the phosindole series. 2-Phosindoles differ from the 3 derivatives with respect to their higher melting points; the \(\nu\text{NH}\) and \(\nu\text{P=O}\) absorption frequencies in their IR spectra are shifted to the long-wave region, and this is in agreement with the data in \[26\].

Similar isomerization of diphenyl(3-indolyl)phosphine to diphenyl(2-indolyl)phosphine occurs when the former is heated in polyphosphoric acid (PPA) \[12\]. The mechanism of the reaction in this case probably also does not differ from the mechanism proposed in \[23, 24\].

(2-Indolylmethyl)phosphonium iodide \(VII\), (2-tryptopholylmethyl)phosphonium salts \(VIII\), and diethyl (2-2-indolylmethyl)phosphonate \(IX\) were subjected to reaction with aromatic aldehydes and 4-piperidone \(X\) in