PHOSPHORYLATION OF INDOLES (REVIEW)

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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.

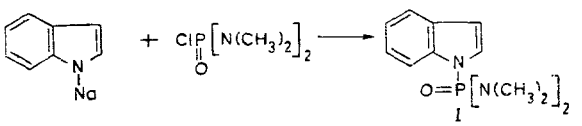
Since a rather large amount of indole raw material from the coking process has not yet found extensive and intelligent application, the economic factor involved in the development of research in this area is also understandable.

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

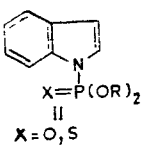
The methods for the synthesis of 1-phosindoles can be divided into two groups: syntheses based on metal derivatives of indole and the Arbuzov rearrangement from P(III) esters.

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]:

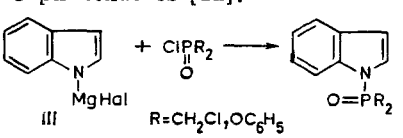


(1)

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



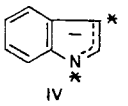
Indolylmagnesium halides (III) are more convenient than indolylsodium. It is well known, of course, that 3-substituted indoles are more frequently formed when they are used [6]. The authors of the present review were able to obtain both 1- and 3-phosindoles [12]:



(2)

S. M. Kirov Kazan Chemical-Engineering Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 867-878, July, 1976. Original article submitted January 12, 1976.

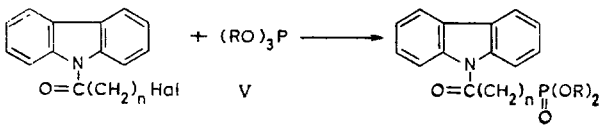
An analysis of a series of studies [6, 13-16] makes it possible to assume that the degree of ionic character of the N–MgHal bond in indolylmagnesium halides depends on external factors, particularly on the polarity of the medium.



IV

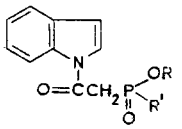
In the examination of the structure of the ambident indole anion IV by means of the principle of soft and hard acids and bases [17], the reaction center at the nitrogen atom can be defined as "hard" and the C_3 atom can be defined as "soft." In this case it is completely understandable why "hard" acid 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]:



(3)

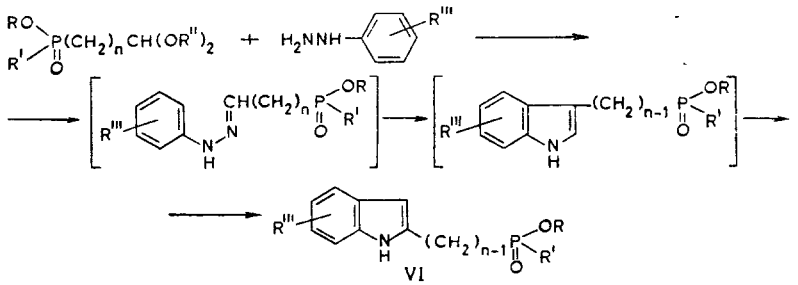
The reaction of phosphites V with 1-chloroacetylindole also proceeds via a reaction of the (3) type. In this case 1-indolylacyl phosphonates and phosphinates were isolated in 53-67% yields [12]:



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]:



(4)

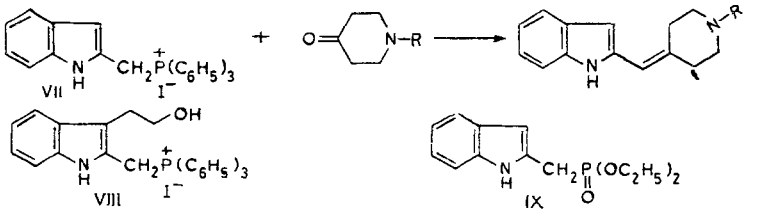
This fact was explained by intramolecular rearrangement of the initially formed "normal" Fischer reaction products. Intramolecular rearrangement was first observed in the indole series in 1888 [22]. The mechanism of rearrangements of this sort has been discussed in detail in the case of alkyl-, aryl-, and acylindoles [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 ν_{NH} and $\nu_{P=O}$ 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-indolylmethyl)phosphonate (IX) were subjected to reaction with aromatic aldehydes and 4-piperidone (X) in

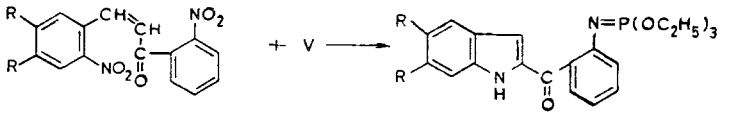
order to study the behavior of phosphinomethylenes containing indole fragments in Wittig reactions [27, 28]. In this case it was observed that phosphonium salts (for example, VII) react with ketone X to give adducts:



(5)

A reaction of the (5) type was not observed in the case of phosphonate IX. The reason for this, as Eenkhoorn and co-workers validly assume [27, 28], consists in an increase in the acidity of the NH group and a decrease in the C–H acidity of the methylene protons of phosphonate IX as compared with phosphonium salts VII and VIII.

An interesting method for the preparation of indoles with a phosphonimide grouping consists in the reduction of substituted β-(2-nitrobenzoyl)-2-nitrostyrenes with triethyl phosphite (V) [29]:

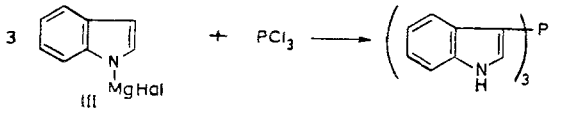


3-Phosphorylated Indoles

Calculations of the electron density distribution in the indole molecule [30, 31] show that the 3 position is the most reactive with respect to electrophilic reagents. Most of the synthesized indoles, including also the phosphorus-containing compounds, are the 3 derivatives.

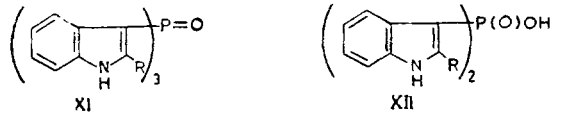
3-Phosindoles can be divided into three types with respect to the position of the phosphorus-containing substituent relative to the indole ring: compounds with a $P-C_3$ (indole) bond, phosskatoles, and others. The material in this section is presented in this order.

A convenient and promising method for the synthesis of compounds of the first type is nucleophilic substitution at the phosphorus atom by means of indolylmagnesium halides (III). This sort of reaction was the first example of the synthesis of phosindoles [9]:



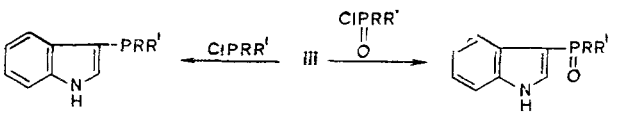
(6)

Tri(3-indolyl)phosphine oxide (XI) was similarly obtained subsequently by the use of phosphorus oxychloride in place of phosphorus trichloride [32]:



Di(3-indolyl)phosphinic acid (XII) was detected along with phosphine oxide XI. Its formation was explained by the initial generation of di(3-indolyl)chlorophosphinate, which was hydrolyzed to acid XII during isolation.

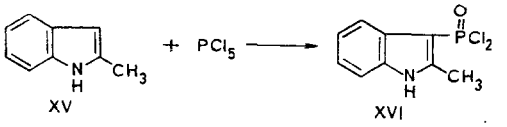
Diverse 3-phosindoles – phosphines XIIIa, phosphinites XIIIb, phosphonites XIIIc, phosphine oxides XIVa, phosphinates XIVb, and phosphonates XIVc – can be obtained by reaction of the products of indolylmagnesium halides III with tri- and tetracoordinated phosphorus acid chlorides [33]:



(7)

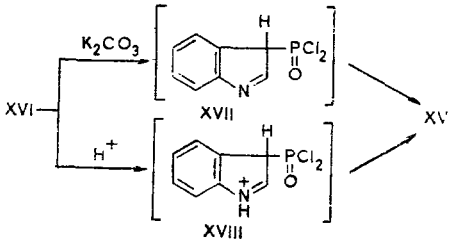
The C_3 atom – the "soft" center of the indolylmagnesium halide – is attacked by the relatively "soft" chlorides of P(III) and P(IV) acids. This is probably an acceptable explanation of the occurrence of reactions (7) in the indicated direction.

A relatively simple method for the preparation of (2-methyl-3-indolyl)phosphonic acid dichloride (XVI), which consists in the reaction of 2-methylindole (XV) with phosphorus pentachloride, has been proposed [34]:



Powers [34] assumes that dichloride XVI is formed as a result of electrophilic attack of PCl_4^+ on indole XV. However, the method of isolation of XVI is rather "peculiar," since it includes a step involving treatment of the acid chloride with potassium carbonate and aqueous alkali. This "peculiarity" is augmented to an even greater extent when one examines another paper by the same author [35], in which hydrolysis of XVI with aqueous potassium carbonate solution led to cleavage of the phosphorus-containing fragment from the 3 position of indole and isolation of starting indole XV. Of course, it is well known that the calculated amount of water [38] or ice-cooled hydrochloric acid [39] is used in the preparation of organodichlorophosphonates by the Kinnear–Perren–Clay method [36, 37] to decompose the complex consisting of phosphorus trihalide, alkyl halide, and anhydrous aluminum halide. However, it is well known that the chlorides of phosphorus acids are extremely sensitive to traces of moisture [40].

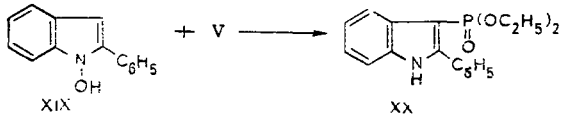
Powers [35] feels that the above-indicated loss of a substituent from the 3 position is a general reaction for 3-phosindoles. He has proposed a hydrolysis mechanism consisting in the conversion of dichloride XVI to tautomeric indolenine XVII in alkaline media or to indolenine salt XVIII in acidic media; XVII and XVIII then lose phosphorus:



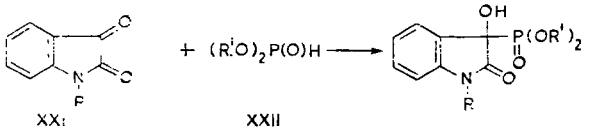
It should be noted that cleavage of a substituent from the 3 position of phosindoles has not been observed in a number of studies [41-43].

In all likelihood, the production of phosindoles by means of PCl_5 can hardly be classified, in general, with convenient methods for the phosphorylation of indole. The formation of only the (2-indolyl)acyl chloride was observed in the reaction of indole-2-carboxylic acid with PCl_5 [44]. Ethyl indole-2-carboxylate was converted to corresponding 3- and 6-chloro derivatives on treatment with PCl_5 [45].

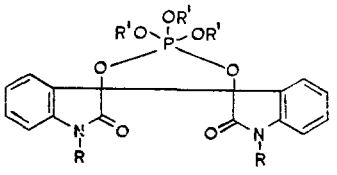
The preparation of diethyl (2-phenyl-3-indolyl)phosphonate (XX) from 1-hydroxy-2-phenylindole (XIX) and triethyl phosphite (V), which presumably proceeds via a homolytic mechanism, has been described [46]:



Isatin (XXI) adds dialkyl phosphites (XXII) to the carbonyl oxygen atom in the 3 position to give 2-oxo-3-hydroxyindolyl phosphonates [47].

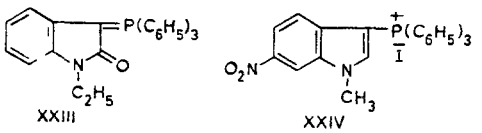


The oxygen in the 2 position does not undergo reaction, since it has amide character. In the case of triethyl phosphite, isatin (XXI) underwent reaction to the extent of a ratio of 1 : 2 to give a compound with an oxyphosphorane structure:



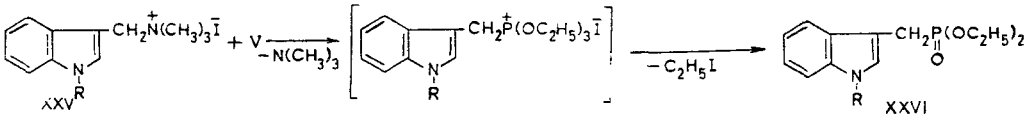
The product (XXIII) of the reaction of 1-ethyl-2-oxo-3-methyleneindole with triphenylphosphine dihalide is a 3-phosindole [48].

The nitration of a triphenyl(1-methyl-3-indolyl)phosphonium salt with nitric acid at 0° led to the corresponding 6-nitro derivative (XXIV) [49]:



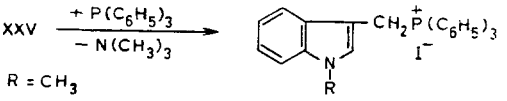
XXIII XXIV

Skatole derivatives occupy a significant position among 3-phosindoles. The reaction of quaternarized Mannich bases with P(III) derivatives was found to be a convenient method for the preparation of phosskatoles. Transfer of the onium function from nitrogen to phosphorus presumably occurs in these reactions [50]. For example, skatyltrimethylammonium iodide (XXV) forms skatyl phosphate XXVI when it is heated with triethyl phosphite (V) [25]:

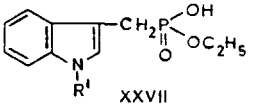


XXV XXVI (8)

N-Methylskatyltriphenylphosphonium iodide is obtained via a mechanism similar to that of reaction (8) [50]:

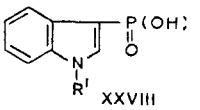


One ester group was saponified to give acid ester XXVII in the course of several transformations of phosphonate XXVI, particularly in the case of hydrolysis with aqueous alkali:



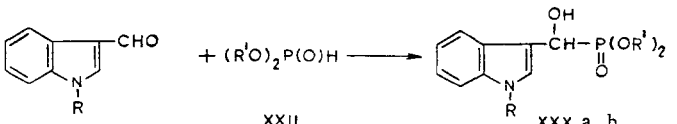
XXVII

The hydrolysis of diester XXVI in acidic media led to destruction of the molecule. Saponification of both ester groups of XXVI to give skatylphosphonic acid XXVIII occurs during alkaline hydrolysis under pressure at high temperature [41]. Veldstra and van der Westeringh [41] were unable to effect acid hydrolysis of phosphonate XXVI, since, in their opinion, it is unstable in acidic media. It has been reported in a patent [51] that acid XXVIII is obtained when diester XXVI is heated in a mixture of acetic and hydrochloric acids:



XXVIII

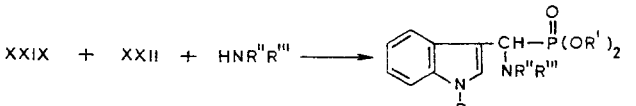
Convenient methods for the synthesis of hydroxy- and aminoskatyl phosphonates have been developed on the basis of formylindoles XXIX. Thus hydroxyskatyl phosphonates XXX were formed in 60-65% yields in the reaction of the latter with dialkyl phosphites XXII in the presence of catalytic amounts of triethylamine in acetonitrile [52] or dimethylformamide (DMF) [53]:



XXX a, b; a R=H; b R=COCH$_3$ XXII XXX a, b (9)

The alkaline hydrolysis of diester XXX under mild conditions made it possible to obtain a hydroxyskatylphosphonic acid monoester. Phosphonate XXX readily forms alkoxides. The latter were converted to the corresponding ethers and esters by reaction with alkyl and acyl halides [53].

Aminoskatyl phosphonates XXXI were obtained in 50-60% yields via the scheme [54, 55]

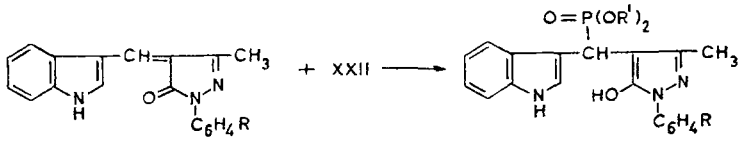


XXX a-c XXXI (10)

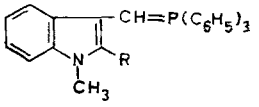
XXX a $R''=R'''=H$; b $R''=H, R'''=Alk$; c $R''=R'''=Alk$

The corresponding imines or products of the addition of the amine to the aldehyde group, which on subsequent reaction with phosphite XXII are converted to phosphonates XXXI. are initially formed, depending on the nature of the amine.

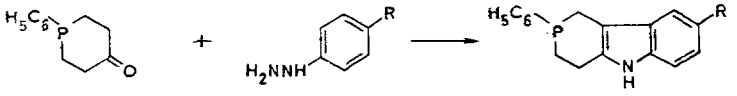
Pyrazolyl-substituted skatyl phosphonates were obtained as a result of the addition of phosphite XXII to a conjugated system [56]:



One can also include 3-indolylmethylenephosphine [57]

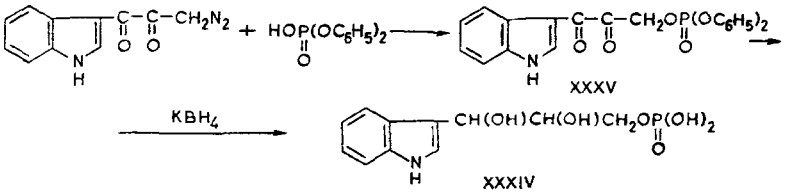


and products of Fischer cyclization (XXXIII) of 1-phenyl-2,3-benzophosphorinan-4-one [58] and 1-phenylphosphorinan-4-one (XXXII) among the phosskatoles [59]:



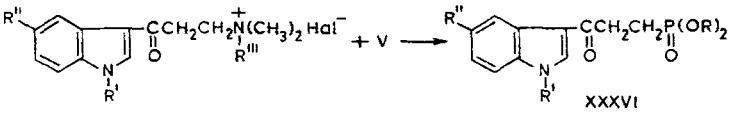
XXXII XXXIII

It has been shown in a number of papers [60-62] that the biosynthesis of tryptophan occurs in many microorganisms through (3-indolyl)glyceryl phosphate (XXXIV). The synthesis of phosphate XXXIV has been worked out by reduction of diphenyl[2,3-dioxo-3-(3-indolyl)propyl] phosphate (XXXV), obtained in turn from 3-diazopyruvolylindole [63], with potassium borohydride:



XXXV XXXIV

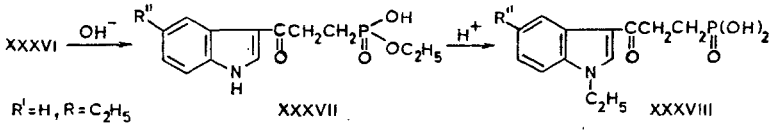
The alkylating ability of quaternized Mannich bases has been used for the preparation of [3-keto-3-(3-indolyl)propyl] phosphonates (XXXVI) [42]:



(11)

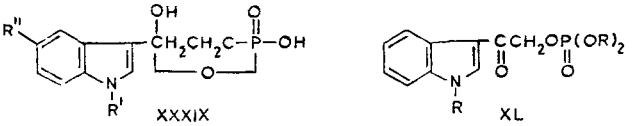
XXXVI

The mechanism of reaction (11) is similar to that presented in Eq. (8). Acid ester XXXVII is formed by alkaline hydrolysis of diester XXXVI and is converted to dibasic acid XXXVIII by acid hydrolysis. In this case it was noted that alcohol ROH, which is liberated during the hydrolysis, alkylates the nitrogen atom when R' = H:



R'=H, R=C_2H_5 XXXVII XXXVIII

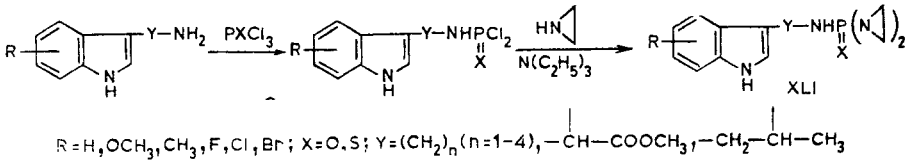
Acid XXXVIII exists in lactol form XXXIX in the solid state.



XXXIX XL

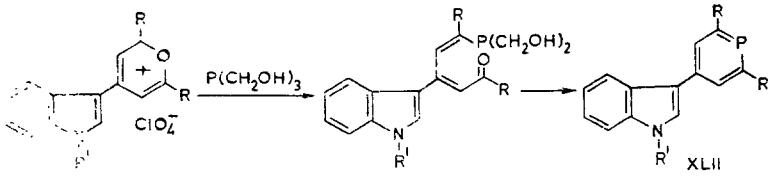
Keto phosphates XL, obtained by reaction of 3-hydroxyacetylindoles with phosphorus acid chlorides, have been described [64].

The synthesis of diethyleneimides (XLI) of phosphoric and thiophosphoric acids was realized during a search for substances that have radiation-protection [65] and cytostatic [66] activity [67, 68]:



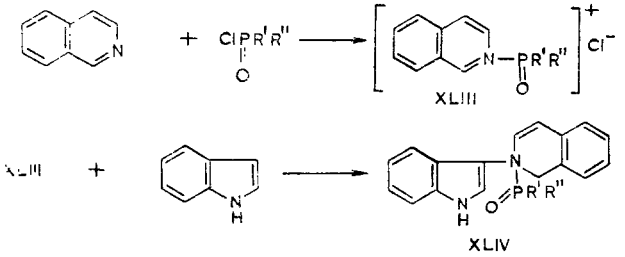
R = H, OCH_3, CH_3, F, Cl, Br; X = O, S; Y = $(CH_2)_n$ (n = 1-4), $-CH(COOCH_3)-$, $-CH_2-CH(CH_3)-$

The preparation of phosphorus-containing formylindole acylhydrazones has been reported [69]. Replacement of the oxygen atom by a phosphorus atom, as a result of which 4-(3-indolyl)phosphorines (XLII) are formed, occurs when 3-indolylpyrylium salts are treated with tris(hydroxymethyl)phosphine in absolute pyridine in a nitrogen atmosphere [70]:



Sheinkman and co-workers have developed methods for the introduction of six-membered nitrogen-containing heterocycles in the indole ring in the presence of phosphorus acid chlorides [71-74].

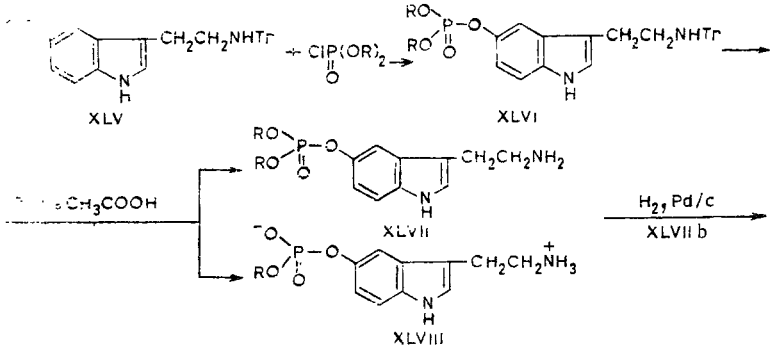
N-Phosphorylisoquinolinium salts, which hetarylated indole even at room temperature, were found to be the most active compounds. Pyridine and, particularly, quinoline were found to be considerably less active.

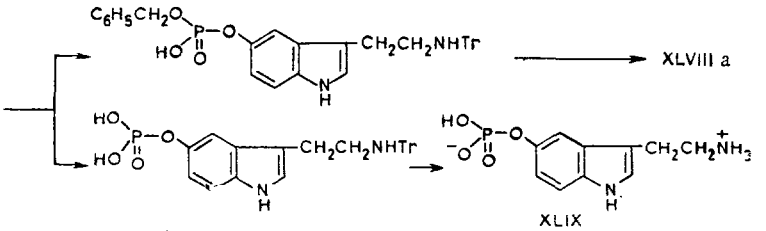


Derivatives with Phosphorus-Containing Substituents in the Benzene Ring of Indole

In connection with the high physiological activity of psilocybin [75-78], it was natural to anticipate the synthesis of substances with a similar structure.

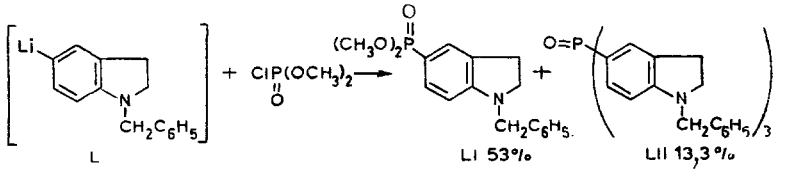
A number of studies in this direction were made by Suvorov and co-workers [79-84]. Thus the development of a method for the protection of the amino group of serotonin (XLV) [80] made it possible to selectively introduce a phosphorus-containing substituent in the 5 position of indole [79]. The trityl protective group was removed by treatment of phosphorylation product XLVI with 50% acetic acid, as a result of which O-substituted and unsubstituted serotonin phosphates (XLVII-XLIX) were formed:





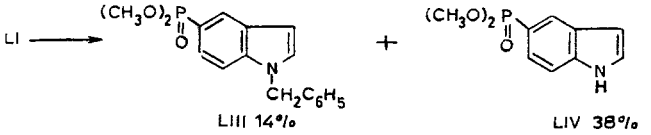
XLV a R'=H; b R'=Na XLVI a R=C_2H_5; b R=$CH_2C_6H_5$; c R=$C_6H_4NO_2$-4
XLVII a R=C_6H_5; b R=$C_6H_4NO_2$-4 XLVIII a R=$CH_2C_6H_5$; b R=$C_6H_4NO_2$-4

5-Phosindolines and 5-phosindoles were obtained when 1-benzyl-5-lithioindoline (L) was used [81-84]. In addition to the principal reaction products – dimethyl 1-benzyl-5-indolinylphosphonate (LI) – tris(1-benzyl-5-indolyl)phosphine oxide (LII) was isolated from the reaction of indoline L with dimethyl chlorophosphate. The formation of LII was explained by reaction of indoline L with the ester groups of the chlorophosphate; this probably requires more detailed proof.



L LI 53% LII 13,3%

The indoline system was converted to the indole system by refluxing LI in xylene over 10% palladium on carbon in a stream of hydrogen:



LIII 14% LIV 38%

The yield of indole LIII was raised to 33% by dehydrogenation of indoline LI with chloranil.

Biological Activity of Phosindoles

Most of the literature on this topic has been devoted to the problem associated with the affect of psilocybin, which, in doses of 0.08 mg/kg, produces, in humans, lively hallucinations usually of a pleasant (more rarely frightening) character [77, 78].

The fungicidal, insecticidal, and ascaricidal activity of 1-indolyl amidophosphonates I is inferior to that of many compounds used for these purposes [10].

Data on the toxicity of phoscarbazoles with respect to warm-blooded animals have been presented [19].

Dialkyl skatylphosphonates XXVI have been studied as analogs of natural metabolites [41]. There is an indication that acid XXVIII and its salts have been found to be antagonists of heteroauxins [51].

The antimicrobial activity of hydroxyskatyl phosphonates XXX has been reported [53].

Dialkyl(5-indolyl)phosphonates [81] have extremely low serotoninlike activity (they are inferior to serotonins by a factor of more than 10,000 with respect to their spasmogenic activity) and antiserotonin properties, but they do not have a cholinomimetic effect.

Problems involving the phosphatase activity of 3-indolyl and 5-bromo-3-indolyl phosphates in tissue were elucidated in [85].

4-Chloro-5-bromo-3-indolyl phosphate has been detected in biochemical substrates [86].

The structure of a streptomycin metabolite, which includes tryptophan and a phosphate grouping, was recently established [87].

LITERATURE CITED

1. R. J. Sundberg, The Chemistry of Indoles, Academic Press, New York–London (1970).
2. F. G. Mann, in: Progress in Organic Chemistry, Vol. 4, London (1958), p. 217.
3. R. S. Edmundson, Indian J. Chem., 41, 1770 (1962).

4. G. Märkl, Angew. Chem., 77, 1109 (1965).
5. G. Märkl, F. Lieb, and A. Mess, Angew. Chem., 79, 947 (1967).
6. R. A. Heacock and S. Kasparek, Advances in Heterocyclic Chemistry, Vol. 10, (1969), p. 43.
7. F. G. Mann, The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony, and Bismuth, Vol. 2, New York–London (1970).
8. D. Redmore, Chem. Rev., 71, 316 (1971).
9. Q. Mingoia, Gazz. Chim. Ital., 60, 144 (1930).
10. B. G. van den Boss, C. J. Schoot, M. J. Koopmans, and J. Meltzer, Rec. Trav. Chim., 80, 1040 (1961).
11. J. Meltzer, K. Wellinga, and B. G. van den Boss, US Patent No. 3111525 (1963); Chem. Abstr., 60, 9285 (1964).
12. A. I. Razumov, Material from the Fourth All-Union Colloquium on the Chemistry and Pharmacology of Indole Compounds [in Russian], Shtiintsa, Kishinev (1975), p. 7.
13. A. Katritzy and J. Lagowski, The Chemistry of Heterocyclic Compounds [Russian translation], Inostr. Lit., Moscow (1963), p. 179.
14. G. M. Badger, The Chemistry of Heterocyclic Compounds, Academic Press, New York (1961), p. 64.
15. M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, Tetrahedron Lett., 1183 (1963).
16. J. C. Powers, W. P. Meyer, and T. G. Parsons, J. Am Chem. Soc., 89, 5812 (1967).
17. R. G. Pearson, Usp. Khim., 11, 1259 (1971).
18. B. A. Arbuzov, in: Reactions and Methods for the Study of Organic Compounds [in Russian], Moscow (1954), p. 3.
19. D. Kh. Yarmukhametova, B. V. Kudryavtsev, and L. I. Ampilova, Izv. Akad. Nauk SSSR. Ser. Khim., 435 (1974).
20. A. I. Razumov and P. A. Gurevich, Zh. Obshch. Khim., 37, 1615 (1967).
21. A. I. Razumov and P. A. Gurevich, Trudy Kazansk. Khim.-Tekhnol. Institimeni S. M. Kirova 36, 480 (1967).
22. E. Fischer and T. Schmidt, Ber., 21, 1811 (1888).
23. V. A. Budylin, A. N. Kost, and E. D. Matveeva, Khim. Geterotsikl. Soedin., No. 1, 55 (1972).
24. V. A. Budylin, A. N. Kost, E. D. Matveeva, and V. I. Minkin, Khim. Geterotsikl. Soedin., No. 1, 68 (1972).
25. A. E. Torralba and T. C. Myers, J. Org. Chem., 22, 972 (1957).
26. F. Millich and E. J. Becker, J. Org. Chem., 23, 1096 (1958).
27. J. A. Eenkhoorn, O. S. de Silva, and V. Snieckus, Chem. Commun., 1095 (1970).
28. J. A. Eenkhoorn, O. S. de Silva, and V. Snieckus, Can. J. Chem., 51, 792 (1973).
29. T. Kametani, T. Yamanaka, K. Nyu, and S. Takano, Yakugaku Zasshi, 91, 1033 (1971); Chem. Abstr., 75, 151626 (1971).
30. A. N. Kost, L. G. Yudin, V. A. Budylin, and V. I. Minkin, Dokl. Akad. Nauk SSSR, 176, 1096 (1967).
31. J. E. Bloor and D. L. Breen, J. Am. Chem. Soc., 89, 6835 (1967).
32. Q. Mingoia, Gazz. Chim. Ital., 62, 333 (1932).
33. A. I. Razumov, P. A. Gurevich, S. Yu. Baigil'dina, T. V. Zykova, and R. A. Salakhutdinov, Zh. Obshch. Khim., 44, 2587 (1974).
34. J. C. Powers, J. Org. Chem., 31, 2627 (1966).
35. J. C. Powers, Tetrahedron Lett., 655 (1965).
36. A. M. Kinnear and E. A. Perren, J. Chem. Soc., 3437 (1952).
37. J. P. Clay, J. Org. Chem., 16, 852 (1951).
38. J. B. Conant, J. Amer. Chem. Soc., 39, 2679 (1917).
39. P. C. Crofts and G. M. Kosolapoff, J. Am. Chem. Soc., 75, 3379 (1953).
40. É. E Nifant'ev, The Chemistry of Organophosphorus Compounds [in Russian], MGU, Moscow (1971), p. 255.
41. C. van der Westeringh and H. Veldstra, Rec. Trav. Chim., 77, 1096 (1958).
42. J. Szmuszkovicz, J. Amer. Chem. Soc., 80, 3782 (1958).
43. P. A. Gurevich, Master's Dissertation, Kazan (1967).
44. J. Sato and J. Matsumoto, Takamine Kenkyusho Nempo, 11, 33 (1959).
45. M. Kunori, Nippon Kagaku Zasshi, 81, 1431 (1960).
46. R. J. Sundberg, J. Org. Chem., 30, 3604 (1965).
47. A. Mustafa, M. M. Sidky, and F. M. Soliman, Tetrahedron, 22, 393 (1966).
48. J. J. Pappas and E. Gancher, J. Heterocycl. Chem., 6, 265 (1969).
49. E. Zbiral and L. Berner-Fenz, Monatsh., 98, 666 (1967).
50. D. Purdela and R. Vilceanu, The Chemistry of Organic Phosphorus Compounds [in Russian], Moscow (1972), pp. 228, 229.

51. N. F. Albertson, US Patent No. 2980692 (1961); Chem. Abstr., 56, 457 (1962).
52. A. I. Razumov, P. A. Gurevich, and S. Yu. Baigil'dina, USSR Author's Certificate No. 422740 (1972); Byul. Izobr., No. 13, 93 (1974).
53. A. I. Razumov, P. A. Gurevich, and S. Yu. Baigil'dina, Zh. Obshch. Khim., 44, 2586 (1974).
54. A. I. Razumov, P. A. Gurevich, S. Yu. Baigil'dina, and M. V. Alparova, Zh. Obshch. Khim., 44, 2585 (1974).
55. A. I. Razumov, P. A. Gurevich, R. I. Tarasova, and S. Yu. Baigil'dina, Zh. Obhsch. Khim., 46, 33 (1976).
56. B. P. Lugovkin, Zh. Obhsch. Khim., 43, 1261 (1973).
57. S. Hünig and H.-C. Steinmetzer, Tetrahedron Lett., 643 (1972).
58. M. J. Gallagher and F. G. Mann, J. Chem. Soc., 4855 (1963).
59. K. C. Srivastava and K. D. Berlin, J. Org. Chem., 37, 4487 (1972).
60. C. Janofsky and M. Rachmeler, Biophys. Acta, 28, 640 (1958).
61. O. Smith and C. Janofsky, J. Biol. Chem., 235, 2051 (1960).
62. C. Lingens and W. Lück, Z. Physiol. Chem., 333, 190 (1963).
63. A. A. P. G. Archer and J. Harley-Mason, Proc. Chem. Soc., 285 (1958).
64. M. N. Preobrazhenskaya, K. V. Kholodkovskaya, E. G. Balashova, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 1, 28 (1967).
65. P. G. Zherebchenko, N. N. Suvorov, and V. S. Murashova, Med. Radiol., 27 (1961).
66. V. A. Chernov, S. M. Volodarskaya, and L. G. Lytkina, Vopr. Onkol., 10, 76 (1964).
67. N. N. Suvorov, V. A. Chernov, L. M. Morozovskaya, and S. M. Volodarskaya, USSR Author's Certificate No. 168294 (1963); Byul. Izobr., No. 4, 27 (1965).
68. L. M. Morozovskaya, N. N. Suvorov, M. A. Kolesnikova, V. A. Chernov, and S. M. Volodarskaya, in: The Chemistry of Organic Phosphorus Compounds [in Russian], Nauka, Leningrad (1967), p. 223.
69. A. I. Razumov, P. A. Gurevich, R. L. Yafarova, and L. A. Monakhova, USSR Author's Certificate No. 362025 (1971); Byul. Izobr., No. 2, 54 (1973).
70. G. I. Zhungietu, F. N. Chukhrii, and A. I. Tolmachev, Zh. Vese. Khim. O-va, 15, 590 (1970).
71. A. K. Sheinkman, G. V. Samoilenko, S. N. Baranov, and P. A. Gurevich, USSR Author's Certificate No. 407900 (1971); Byul. Izobr., No. 47, 83 (1973).
72. A. K. Sheinkman, G. V. Samoilenko, and N. A. Klyuev, Zh. Obshch. Khim., 44, 1472 (1974).
73. A. K. Sheinkman, Khim. Geterotsikl. Soedin., No. 1, 3 (1974).
74. A. K. Sheinkman, G. V. Samoilenko, and S. N. Baranov, The Chemistry and Applications of Organophosphorus Compounds [in Russian], Nauka, Moscow (1974), p. 366.
75. A. Hofmann, Experientia, 14, 397 (1958).
76. A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, T. Potrzilka, and F. Trohler, Helv. Chim. Acta, 42, 1557 (1959).
77. D. F. Downing, Quart. Rev., 16, 144 (1962).
78. N. N. Yarovenko, Zh. Vses. Khim. O-va, 4, 448 (1964).
79. L. M. Morozovskaya, M. A. Kolesnikova, and N. N. Suvorov, Zh. Obshch. Khim., 38, 2788 (1968).
80. N. N. Suvorov, L. M. Morozovskaya, and G. N. Tsvetkova, USSR Author's Certificate No. 191564 (1966); Byul. Izobr., No. 4, 35 (1967).
81. V. P. Shamshin, V. F. Shner, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 4, 498 (1972).
82. V. P. Shamshin, V. F. Shner, and N. N. Suvorov, Zh. Obshch. Khim., 41, 537 (1971).
83. V. P. Shamshin, V. F. Shner, and N. N. Suvorov, Zh. Vses. Khim. O-va, 4, 474 (1969).
84. V. P. Shamshin, V. F. Shner, and N. N. Suvorov, The Chemistry and Applications of Organophosphorus Compounds [in Russian], Nauka, Moscow (1974), p. 363.
85. K. S. Tsou, H. C. F. Su, D. J. R. Heymann, and A. M. Seligman, J. Med. Chem., 10, 662 (1967).
86. J. P. Horwitz, C. V. Easwaran, and P. L. Wolf, Biochem. Biophys. Acta, 276, 206 (1972).
87. S. Umezawa, K. Tatsuta, O. Izawz, and T. Tsuchiya, Tetrahedron Lett. 97 (1972).