HETEROCYCLIC SYSTEMS BEARING PHOSPHORUS SUBSTITUENTS. SYNTHESIS AND CHEMISTRY

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Contents

I. Introduction

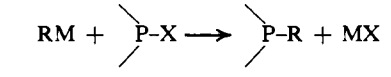
This review is limited to those compounds in which the phosphorus substituent is attached to a carbon atom of the heterocyclic ring, so that compounds such as tris-1-arizidinyl phosphoramide (commonly incorrectly called tris-aziridinyl phosphine) are excluded from consideration. Numerous heterocyclic systems are represented and several phosphorus groupings, including phosphines, phosphine oxides, sulfides, and selenides, phosphoranes, and phosphinic and phosphonic acid derivatives. The coverage is comprehensive through September 1970. Particular emphasis has been placed on synthetic methods, chemistry, and properties which are peculiar to the heterocyclic phosphorus derivatives.

II. General Methods of Synthesis

A. NUCLEOPHILIC DISPLACEMENT REACTIONS ON PHOSPHORUS BY HETEROCYCLIC ORGANOMETALLIC REAGENTS

1. Preparation of Phosphines, Phosphine Oxides, and Phosphine Sulfides

Nucleophilic displacement on phosphorus esters and halides by organometallic reagents is a very facile process leading to tertiary phosphines or phosphine oxides.[1] The results obtained



using heterocyclic Grignard or lithium reagents do not differ from those obtained with aliphatic or aryl derivatives except that yields tend to be lower. This is due to the susceptibility of the heterocyclic organometallics to side reactions, such as self-condensation. The addition of phenyllithium to pyridine, for example, is a well-known reaction.

Phosphine oxides can be prepared by the reaction of a Grignard reagent on phosphorus trichloride or bromide followed by oxidation or, alternatively, from the nucleophilic displacement by the same reagent on phosphoryl chloride or a dialkyl phosphorochloridate. It appears that the single-stage procedure gives superior yields. Table I[2-12] summarizes the heterocyclic phosphines and phosphine oxides prepared by nucleophilic displacement on phosphorus. It should be noted that in the reaction of indolyl Grignard reagents on phos-

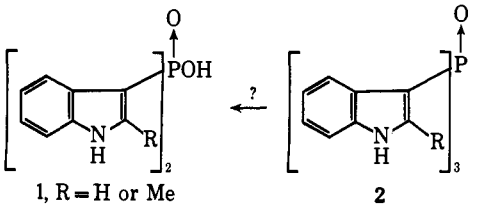
(1) K. D. Berlin, T. H. Austin, M. Peterson, and M. Nagabhushanam, *Top. Phosphorus Chem.*, **1**, 17 (1964).
(2) K. Issleib and A. Brock, *Z. Anorg. Allg. Chem.*, **292**, 245 (1957).
(3) C. E. Griffin, R. P. Peller, K. R. Martin, and J. A. Peters, *J. Org. Chem.*, 30, 97 (1965).
(4) E. Niwa, H. Aoki, H. Tanaka, and K. Munakata, *Chem. Ber.*, **99**, 712 (1966).
(5) A. Burger and N. D. Dawson, *J. Org. Chem.*, **16**, 1250 (1951).
(6) H. J. Jakobsen and J. Nielsen, *Acta Chem. Scand.*, **23**, 1070 (1969).
(7) M. D. Rausch, T. R. Criswell, and A. K. Ignatowicz, *J. Organometal. Chem.*, **13**, 419 (1968).
(8) Q. Mingoia, *Gazz. Chim. Ital.*, 60, 144 (1930).
(9) Q. Mingoia, *ibid.*, **62**, 333 (1932).
(10) W. C. Davies and F. G. Mann, *J. Chem. Soc.*, 279 (1944).
(11) E. Plazek and R. Tyka, *Zesz. Nauk. Politech. Wroclaw. Chem.*, 79(1957); *Chem. Abstr.*, **52**, 20156 (1958).
(12) F. G. Mann and J. Watson, *J. Org. Chem.*, **13**, 502 (1948).

Table I

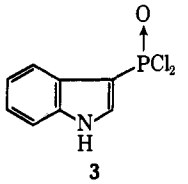
Phosphines and Phosphine Oxides by Nucleophilic Displacement on Phosphorus

Heterocyclic organometallic deriv	*Phosphorus reagent*	*Product (yield, %)*	*Ref*
Pyrrylpotassium	PCl_3	Tri-2-pyrrylphosphine (40)	2
Pyrrylmagnesium bromide	$POCl_3$	Tri-2-pyrrylphosphine oxide (42)	3
1-Methyl-2-pyrryllithium	$(EtO)_2POCl$	Tri-2(1-methylpyrryl)-phosphine oxide (28)	3
2-Furyllithium	PBr_3	Tri-2-furylphosphine (33)	4
2-Furyllithium	$POCl_3$	Tri-2-furylphosphine oxide (68)	3, 4
2-Thienylmagnesium bromide	PCl_3	Tri-2-thienylphosphine (70)	2
2-Thienylmagnesium bromide	$(EtO)_2POCl$	Tri-2-thienylphosphine oxide (75)	3, 5
3-Thienyllithium	PBr_3	Tri-3-thienylphosphine (50)	6
3,4,5-Trichloro-2-thienyllithium	Ph_2PCl	Diphenyl(3,4,5-trichloro-2-thienyl)phosphine (34)	7
Indolylmagnesium bromide	PCl_3	Tri-3-indolylphosphine	8
2-Methylindolylmagnesium bromide	PCl_3	Tri-3-(2-methylindolyl)-phosphine	8
3-Methylindolylmagnesium	PCl_3	Tri-2-(3-methylindolyl)-phosphine	8
Indolylmagnesium bromide	$POCl_3$	Tri-3-indolylphosphine oxide	9
2-Methylindolylmagnesium bromide	$POCl_3$	Tri-3-(2-methylindolyl)-phosphine oxide	9
2-Pyridylmagnesium bromide	PCl_3	Tri-2-pyridylphosphine	10
2-Pyridyllithium	PCl_3	Tri-2-pyridylphosphine (38)	11
2-Pyridylmagnesium bromide	$PhPCl_2$	Phenyldi(2-pyridyl)-phosphine	12
2-Pyridylmagnesium bromide	Ph_2PCl	Diphenyl(2-pyridyl)-phosphine (16)	12
3-Pyridylmagnesium bromide	*p*-$BrC_6H_4(Ph)PCl$	Phenyl-*p*-bromophenyl-3-pyridylphosphine	10

phoryl chloride the bis(indolyl)phosphinic acids **1** are reported



1, R = H or Me 2



3

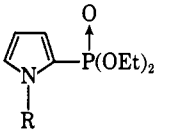
as by-products along with the product phosphine oxide **2**.[9] The origin of the phosphinic acids **1** is not clear but most probably arises from degradation of the phosphine oxide **2** upon work-up in view of the reported facile C–P bond cleavage in **3**.[18] The alternative genesis of **1** by displacement of two chloride ions from phosphoryl chloride by the indolyl Grignard followed by hydrolysis of the remaining chlorine seems unlikely.[1] Repetition of these syntheses would be worthwhile in view of the sketchy characterization in the original work.

(13) J. C. Powers, *Tetrahedron Lett.*, 655 (1965).

2. *Preparation of Phosphinates, Phosphonates, and Phosphoranes*

In principle, reaction of phosphoryl chloride or dialkyl phosphorochloridates with one equivalent of heterocyclic Grignard or lithium reagent should yield a phosphonic acid dihalide or diester. In practice this is not readily achieved; the product phosphonic acid derivative competes with the starting halide for reaction with the organometallic reagent, so that a complex product mixture results.

Addition of pyrrylmagnesium bromide to diethyl phosphorochloridate in refluxing ether has allowed the preparation of diethyl pyrryl-2-phosphonate (**4**) in 30% yield.[14] By a similar technique 1-methyl-2-pyrryllithium reacts with diethyl phosphorochloridate with the formation of diethyl 1-methylpyrryl-2-phosphonate (**5**).[14] The reaction of 2,5-dimethyl-

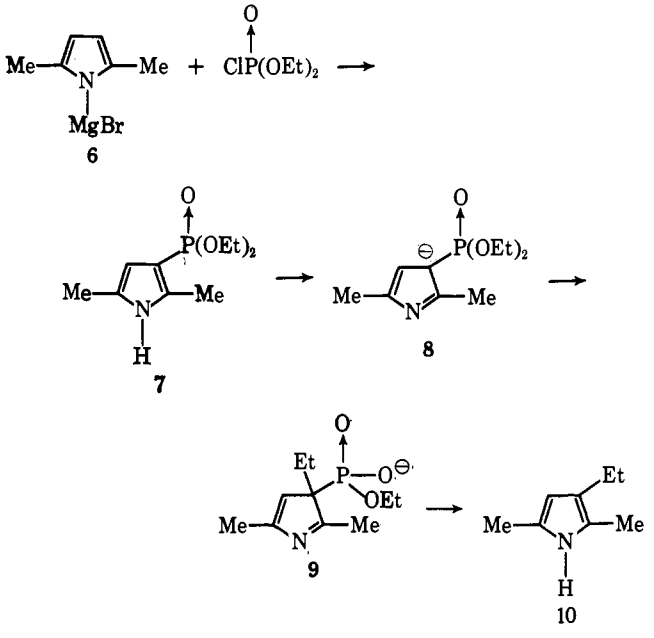


4, R = H
5, R = Me

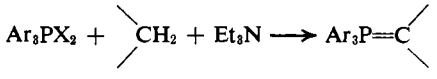
pyrrylmagnesium bromide (**6**) with diethyl phosphorochloridate yields 3-ethyl-2,5-dimethylpyrrole (**10**) rather than the desired phosphonate **7**. This phosphonate **7** is postulated as

(14) C. E. Griffin, R. P. Peller, and J. A. Peters, *J. Org. Chem.*, 30, 91 (1965).

the initial product but forms anion **8** which undergoes rearrangement to **9** and C–P cleavage to **10**[14] (see section III.B for further discussion).



A series of stable heterocyclic phosphorus ylides has been prepared by an extension of the well-known ylide-forming reaction in which a triarylphosphine dihalide is reacted with an activated methylene group in presence of a base. The products obtained by this procedure are shown in Table II.[15]



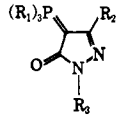
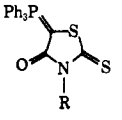
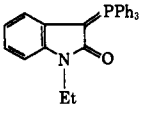
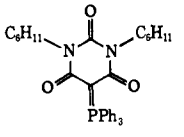
B. NUCLEOPHILIC DISPLACEMENT REACTIONS BY PHOSPHORUS NUCLEOPHILES

1. Arbuzov and Michaelis–Becker Reactions on Heterocyclic Halides

The Arbuzov and Michaelis–Becker reactions are among the most widely used procedures for forming carbon–phosphorus bonds[16] and have been successfully applied in the synthesis of heterocyclic phosphorus derivatives. Nucleophilic displacements on heterocyclic halides have been well studied for alkoxides, amines, etc., and a general order of reactivity has been recognized for these nucleophiles. Thus, at one extreme 1-halo-2,4,6-triazines have a high susceptibility to displacement of halide, whereas 2-halopyridines are relatively unreactive.[17] For the case of displacements by trialkyl phosphites (Arbuzov) or dialkyl alkali metal phosphonates (Michaelis–Becker), a similar order of reactivity appears to exist although no kinetic measurements have been reported. Table III[18–29]

Table II

Heterocyclic Phosphoranes[15]

Compound		Yield, %
	R_1 = Ph; R_2 = Me; R_3 = Ph	98
	$R_1 = R_2 = R_3$ = Ph	78
	R_1 = Ph; R_2 = Me; R_3 = *p*-$NO_2C_6H_4$	49
	R_1 = *p*-$MeOC_6H_4$; R_2 = Me; R_3 = Ph	67
	R_1 = *p*-$MeOC_6H_4$; R_2 = Me; R_3 = *p*-$NO_2C_6H_4$	52
	$(R_1)_3$ = $(Ph)_2$(*p*-$Me_2NC_6H_4$); R_2 = Me; R_3 = Ph	57
	R = Ph	22
	R = Et	92
		73
		95

summarizes the derivatives of heterocycles prepared by these reactions. It appears that 2-chloroquinoline[19] and 2-chloropyrimidine[22] are the least reactive substrates successfully reacted. It has been reported that 2-bromo- or 2-chloropyridine[19] and 5-halopyrimidines[22] fail to react in either the Arbuzov or Michaelis–Becker reactions. It would seem that these unreactive halides could be made more susceptible to displacement by protonation or quaternization. An alternative to this approach is the use of nickel salts as catalysts which apparently enhances the nucleophilicity of the trialkyl phosphites.[29a] In this way aryl halides can be converted into aryl phosphonates in high yield (70–90%); for example, 2-bromothiophene is converted into diethyl 2-thienylphosphonate by reaction with triethyl phosphite in the presence of nickel bromide.[29a]

The reaction of diphenylphosphinous chloride with 2-ethoxy-1,3-dioxane (**11**) (R = H) appears to proceed by a pathway related to the Arbuzov reaction in yielding the

(15) J. J. Pappas and E. Gancher, *J. Heterocycl. Chem.*, 6, 265 (1969).
(16) R. G. Harvey and E. DeSombre, *Top. Phosphorus Chem.*, 1, 57 (1964).
(17) R. G. Shepherd and J. L. Fedrick, *Advan. Heterocycl. Chem.*, 4, 262 (1965).
(18) Y. N. Ivashchenko, L. S. Sologub, S. D. Moshchitsbii, and A. V. Kirsanov, *Zh. Obshch. Khim.*, 39, 1695 (1969); *Chem. Abstr.*, 71, 124600 (1969).
(19) A. Burger, J. B. Clements, N. D. Dawson, and R. B. Henderson, *J. Org. Chem.*, 20, 1383 (1955).
(20) W. Lorenz, German Patent 930212 (1955); *Chem. Abstr.*, 52, 14700 (1958).
(21) V. L. Narayanan, J. Bernstein, and J. Williams, *J. Pharm. Sci.*, 55, 217 (1966).
(22) G. M. Kosolapoff and C. H. Roy, *J. Org. Chem.*, 26, 1895 (1961).
(23) R. M. Ismail, *Justug Liebigs Ann. Chem.*, 732, 107 (1970).
(24) W. Hewertson, R. A. Shaw, and B. C. Smith, *J. Chem. Soc.*, 1670 (1963).
(25) Y. F. Shealy, R. F. Struck, J. D. Clayton, and J. A. Montgomery, *J. Org. Chem.*, 26, 4433 (1961).
(26) B. A. Arbuzov and B. P. Lugovkin, *Zh. Obshch. Khim.*, 22, 1193 (1952); *Chem. Abstr.*, 47, 4871 (1953).
(27) A. Mustafa, M. M. Sidky, and F. M. Soliman, *Justus Liebigs Ann. Chem.*, 698, 109 (1966).
(28) H. Gross, G. Englehardt, J. Freiberg, W. Buerger, and B. Costisella, *ibid.*, 707, 35 (1967).
(29) H. Gross, J. Freiberg, and B. Costisella, *Chem. Ber.*, 101, 1250 (1968).
(29a) P. Tavs, *ibid.*, 103, 2428 (1970).

Table III

Phosphonates by Arbuzov and Michaelis–Becker Reactions

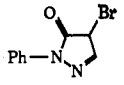
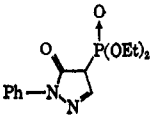
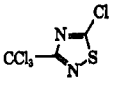
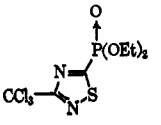
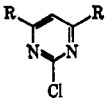
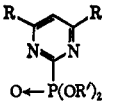
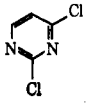
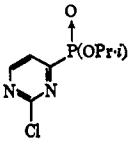
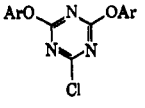
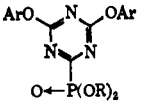
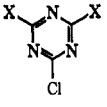
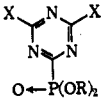
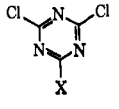
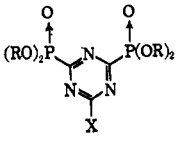
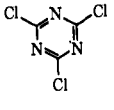
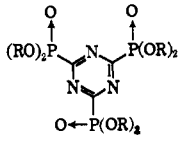
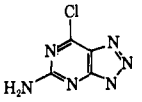
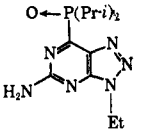
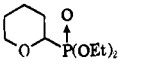
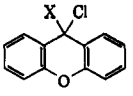
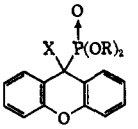
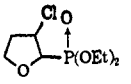
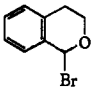
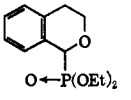
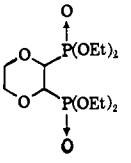
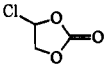
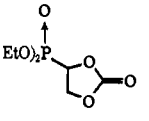
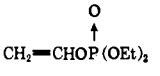
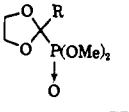
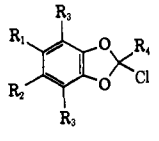
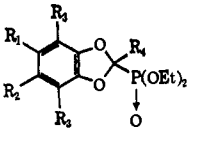
Halide	*Nucleophile*	*Product*	*Yield, %*	*Ref*
Pentachloropyridine	$(EtO)_3P$	Diethyl 2,3,5,6-tetrachloropyridyl-4-phosphonate		18
2-Chloroquinoline	$NaPO(OEt)_2$	Diethyl quinolyl-2-phosphonate	29	19
2-Chloro-4-methylquinoline	$NaPO(OEt)_2$	Diethyl 4-methylquinolyl-2-phosphonate	25	19
	$(EtO)_3P$			20
	$(EtO)_3P$			21
				
R = Me	$NaPO(OEt)_2$	R′ = Et	28	22
R = H	$P(OPr\text{-}i)_3$	R′ = *i*-Pr	71.5	22
	$P(OPr\text{-}i)_3$		70	22
				
Ar = C_6Cl_5	$P(OEt)_3$	R = Et	88	23
Ar = 2,3,4,6-tetrachlorophenyl	$P(OCH_2CH_2Cl)_3$	R = CH_2CH_2Cl	92	23
Ar = 2,4,5-trichlorophenyl	$P(OEt)_3$	R = Et	93	23
Ar = 2,4,6-tribromophenyl	$P(OEt)_3$	R = Et	90	23
				
X = Ph	$P(OMe)_3$	R = Me	81	24
X = Ph	$P(OEt)_3$	R = Et	78	24
X = $C_5H_{10}N$	$P(OEt)_3$	R = Et	66	24
				
X = Ph	$P(OEt)_3$	R = Et	72	24
X = Ph	$P(OMe)_3$	R = Me	76	24
X = $C_5H_{10}N$	$P(OEt)_3$	R = Et	67	24
	$P(OR)_3$			
		R = Me, Et, Pr, Bu, Bz	68–94	24
	$MeOP(OPh)_2$	R = Ph	70	24
	$EtOP(OPh)_2$	R = Ph	57	24
	$EtOPPh_2$	OR = Ph	65	24

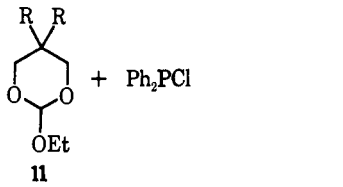
Table III (Continued)

Halide	*Nucleophile*	*Product*	*Yield, %*	*Ref*
	$P(OPr\text{-}i)_3$		64	25
	$NaPO(OEt)_2$		46	26
	$(RO)_3P$			
X = H		X = H; R = Me	81	27
X = Cl		X = PO(OR)$_2$; R = Et	83	27
X = Cl		X = PO(OR)$_2$; R = Pr	70	27
	$(EtO)_3P$		57	28
	$(EtO)_3P$		66	28
	$(EtO)_3P$		24	28
	$(EtO)_3P$	 + 	45 34	28
	$(MeO)_3P$			
		R = Me, CH_2Cl, $CHCl_2$, CCl_3	36–61	29
	$P(OEt)_3$			
		$R_1 = CO_2Me$; $R_2 = R_3 = R_4 = H$	71	28
		$R_1 = R_2 = Cl$; $R_3 = R_4 = H$	86	
		$R_4 = Ph$; $R_1 = R_2 = R_3 = H$	70	
		$R_4 = CO_2Me$; $R_1 = R_2 = R_3 = H$	50	
		$R_1 = R_2 = R_3 = Cl$; $R_4 = H$	50	

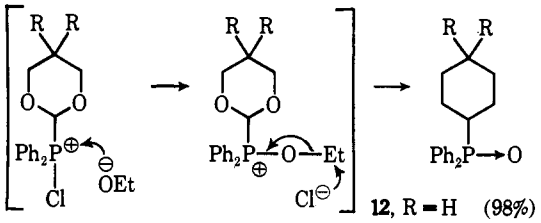
phosphine oxide **12** (R = H). The 5,5-dimethyl derivative **11** (R = Me) reacts similarly.[30]

Although diisopropyl 2-chloropyrimidyl-4-phosphonate (**14**) is readily formed from 2,4-dichloropyrimidine (**13**) and triisopropyl phosphite, displacement of the second chlorine in an Arbuzov reaction with the same phosphite to give **15a** was not successful.[22] In view of the fact that this chlorine is readily displaced by a variety of nucleophiles to produce **15b–f**,[22] it would seem that less vigorous conditions or a different phosphite would yield a pyrimidyl-2,4-diphosphonate (such as **15a**). This view is reinforced by the results of the reactions of cyanuric chloride (**16**) with trialkyl phosphites.[24] When cyanuric chloride (**16**) is allowed to react with 2 equiv of tri-

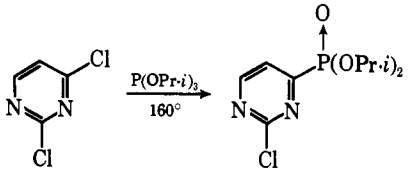
(30) W. Dietsche, *Justus Liebigs Ann. Chem.*, 712, 21 (1968).



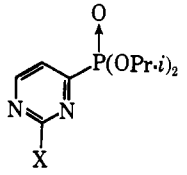
11



12, R = H (98%)
R = Me (80%)

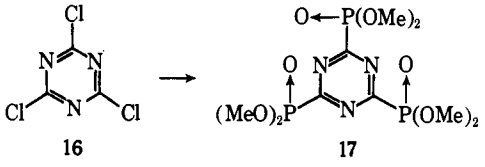


13 14

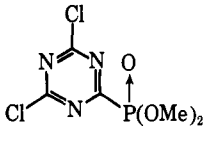


15

a, X = PO(OPr-*i*)$_2$ d, X = NH$_2$
b, X = NHMe$_2$ e, X = OEt
c, X = NHEt$_2$ f, X = H



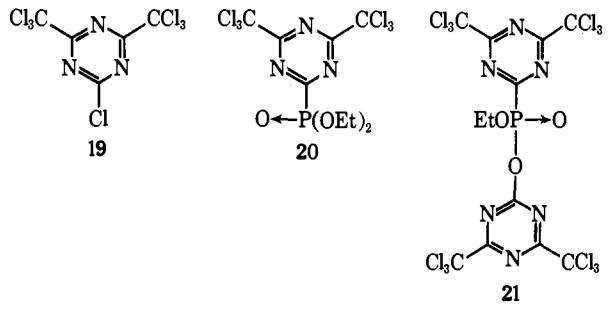
16 17



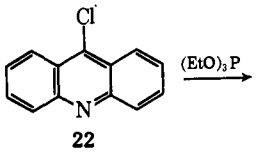
18

methyl phosphite, only trisubstituted triazine **17** (64%) and unreacted chloride (32%) are isolated, which suggests that the phosphonate group may in fact enhance the reactivity of the remaining chlorine to nucleophilic displacement. The reaction of cyanuric chloride (10 mol) with triethyl phosphite (1 mol) did result in monosubstitution product **18** (77%).[24] The reaction of 2-chloro-4,6-bistrichloromethyltriazine (**19**) with triethyl phosphite at 145° is reported to yield the phosphonate **21** rather than the expected phosphonate **20**.[31] It is not worthwhile to speculate on a mechanism of formation of **21**, in view of the lack of a rigorous structure proof. It is possible that **20** could be obtained by the use of less vigorous conditions as, for example, in a solvent.[24]

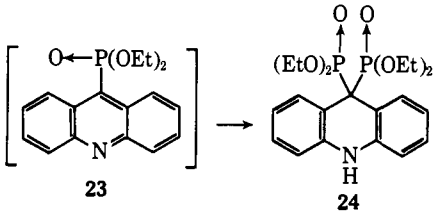
9-Chloroacridine (**22**) is reported to yield diethyl acridyl-9-phosphonate (**23**) upon reaction with triethyl phosphite,[32] but



19 20 21



22

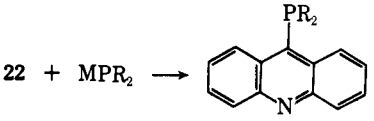


23 24

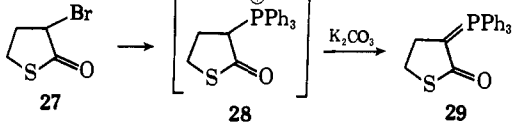
recent attempts to repeat this work gave the diphosphonate **24** as the only characterizable product.[33] This diphosphonate **24** is the product of the reaction of **22** and of **23** with diethyl sodiophosphonate.[33] These results suggest that diethyl acridyl-9-phosphonate (**23**) is the initial product of Arbuzov and Michaelis–Becker reactions of 9-chloroacridine but undergoes facile nucleophilic addition reactions (see section II.C).

2. *Other Nucleophilic Displacements by Phosphorus*

The displacement of chloride ion from 9-chloroacridine (**22**) by the anion of dicyclohexyl- or diphenylphosphine provides a synthesis of the tertiary phosphines **25** and **26** in yields of 16 and 48%, respectively.[34] Triphenylphosphine displaces bromide from tetrahydrothiophenone (**27**), and the resulting phosphonium salt **28** can be converted, without isolation, into the phosphorane **29**.[35]



25, R = *c*-C$_6$H$_{11}$
26, R = Ph

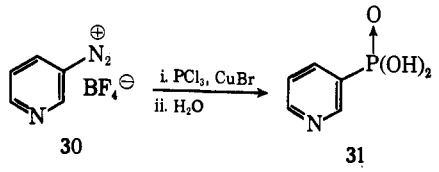


27 28 29

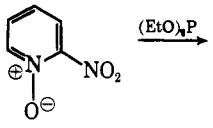
All the syntheses of pyridine phosphonic acid derivatives recorded to date have involved nucleophilic displacements by phosphorus. Pyridyl-3-phosphonic acid (**31**) is formed by the

(31) H. Schroeder, *J. Amer. Chem. Soc.*, 81, 5658 (1959).
(32) G. M. Kosolapoff, *ibid.*, 69, 1002 (1947).
(33) D. Redmore, *J. Org. Chem.*, 34, 1420 (1969).
(34) K. Issleib and L. Bruesehaber, *Z. Naturforsch.*, 20b, 181 (1965).
(35) H. Zimmer, F. Haupter, S. P. Kharidia, H. Pauling, R. G. Gailey, T. Pampalone, T. C. Purcell, and R. Walter, *Tetrahedron Lett.*, 5435 (1968).

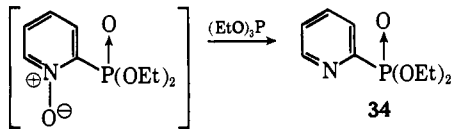
treatment of 3-pyridyldiazonium fluoroborate (**30**) with phosphorus trichloride in presence of cuprous bromide followed by work-up with water.[36] 2-Nitropyridine *N*-oxide (**32**) when heated with triethyl phosphite yields diethyl pyridyl-2-phosphonate (**34**) presumably *via* the *N*-oxide **33**.[37] 4-Nitropyridine *N*-oxide fails to undergo this reaction.[37] A series of pyridines **35a–d** have been converted into the pyridyl-2-phosphonate esters (**36a–d**), respectively, by the reaction sequence, oxidation, O-alkylation, and treatment with an alkali metal derivative of diethyl phosphonate.[38] The unsymmetrical pyr-



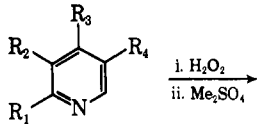
30 31



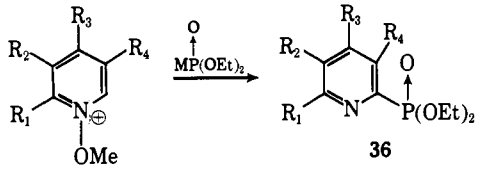
32



33 34



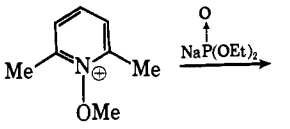
35



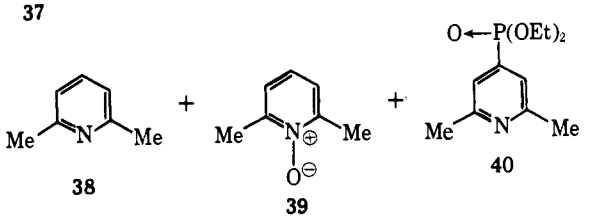
36

a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = Me$; $R_2 = R_3 = R_4 = H$
c, $R_3 = Me$; $R_1 = R_2 = R_4 = H$
d, $R_2 = R_4 = Me$; $R_1 = R_3 = H$
e, $R_2 = Me$; $R_1 = R_3 = R_4 = H$
f, $R_2 = R_3 = Me$; $R_1 = R_4 = H$
g, $R_4 = Me$; $R_1 = R_2 = R_3 = H$
h, $R_3 = R_4 = Me$; $R_1 = R_2 = H$

idine (**35e**) yields a mixture of 3-methylpyridyl-2-phosphonate **36g** and the 5-methyl compound **36e** in the ratio 6:1 and **35f** yields a mixture of **36h** and **36f** in a 3:1 ratio in the same reaction sequence. The predominance of substitution adjacent to the 3-alkyl substituent is reminiscent of the reaction of phenyllithium with 3-methylpyridine.[39] Only in the case of *N*-methoxy-2,6-dimethylpyridinium methosulfate (**37**) was 4 substitution observed. In this case attack on the methoxy group was a major reaction yielding, by attack at hydrogen, **38** (47%) and, by attack at carbon, **39** (6%). The 4-phosphonate **40** was obtained in 24% yield.[38]

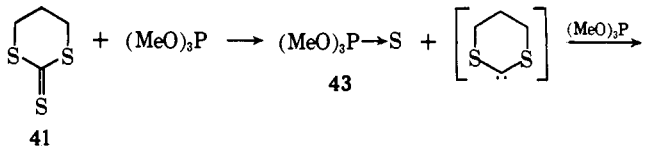


37

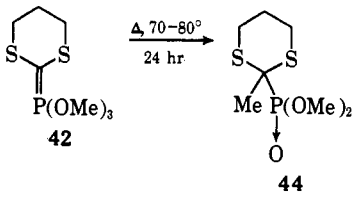


38 39 40

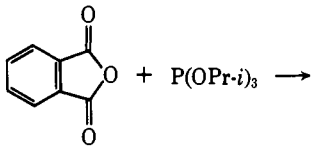
Reaction of 1,3-dithiacyclohexane-2-thione (**41**) with excess trimethyl phosphite leads to the formation of ylide **42**, together with trimethyl thionophosphate (**43**).[40] Although a reaction sequence has not been specified, a possible pathway is shown. The ylide **42** upon heating at 70–80° for 24 hr is isomerized into phosphonate **44**.[40] The reaction of phthalic anhydride (**45**) with triisopropyl phosphite which yields phosphonate **47** is proposed to involve carbene **46** as an intermediate.[41]



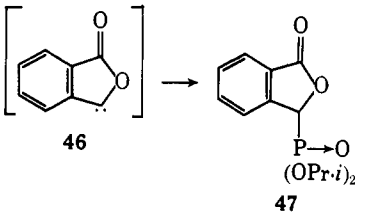
41 43



42 44



45



46 47

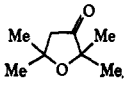
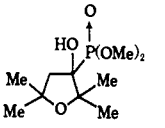
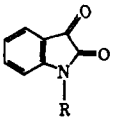
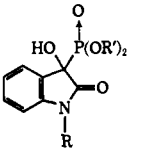
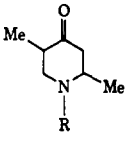
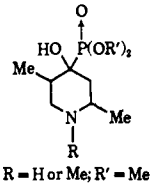
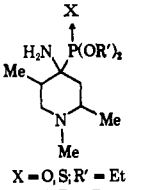
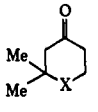
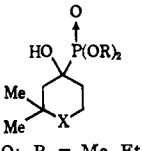
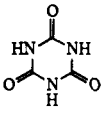
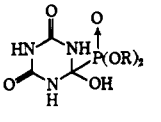
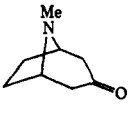
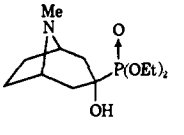
C. NUCLEOPHILIC ADDITION REACTIONS

Carbon–phosphorus bonds can readily be formed by the addition of an anion (phosphonate or phosphine, for example) to a multiple bond, such as carbonyl, imine, or activated carbon–carbon double bond. The addition of dialkyl phosphonates to a carbonyl function is typically carried out under anhydrous conditions in the presence of a catalytic amount of base, such as

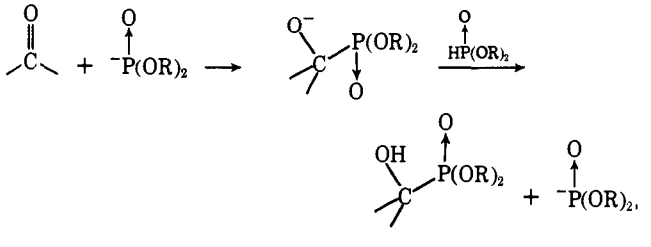
(36) R. D. Bennett, A. Burger, and W. A. Volk, *J. Org. Chem.*, 23, 940 (1958).
(37) J. I. G. Cadogan, D. J. Sears, and D. M. Smith, *J. Chem. Soc. C*, 1314 (1969).
(38) D. Redmore, *J. Org. Chem.*, 35, 4114 (1970).
(39) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, 6, 280 (1966).
(40) E. J. Corey and G. Markl, *Tetrahedron Lett.*, 3201 (1967).
(41) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Amer. Chem. Soc.*, 83, 173 (1961).

Table IV

Nucleophilic Addition Reactions

Carbonyl compound	*Nucleophile*	*Product*	*Yield, %*	*Ref*
	$HPO(OMe)_2$			44
 R = H, Me, $COCH_3$	$HPO(OR')_2$ R′ = Me, Et, *i*-Pr		62–85	45
	$HPO(OR')_2$			
		R = H or Me; R′ = Me	75–80	46
		R = Me; R′ = Et	32	47
	NH_3, $HPX(OR')_2$			
		X = O, S; R′ = Et	42–43	47
		X = O; R′ = Bu	52	47
	$HPO(OR)_2$			
		X = O; R = Me, Et, Pr	48–87	48
		X = S; R = Me, Et, Pr	53–80	48
	$(RO)_2POH$			
		R = Me, Et, *i*-Pr, Pr, Bu, *i*-Bu	50–65	49
	$(EtO)_2POH$			50

tertiary amine or alkoxide.[42] In strong aqueous base the reaction is reversed readily. The reaction of a carbonyl compound



with a dialkyl phosphonate and a primary amine or ammonia yields an α-amino phosphonate most probably *via* an imine since α-hydroxy phosphonates are not readily converted into α-amino phosphonates by treatment with amines.[43] Table IV[44–50] summarizes the preparation of heterocyclic phos-

(42) K. Sasse, in Houben-Weyl, "Organophosphorus Compounds," Part I, Georg Thieme Verlag, Stuttgart, 1963, pp 475–482.

(43) E. K. Fields, *J. Amer. Chem. Soc.*, **74**, 1528 (1952); N. S. Kozlov, V. D. Pak, and E. S. Elin, *Zh. Obshch. Khim.*, **39**, 2407 (1969); *Chem. Abstr.*, **72**, 79156 (1970). Ammonia can apparently convert α-hydroxy phosphonates into α-amino phosphonates: M. I. Kabachnik and T. Y. Medved, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 868 (1953); *Chem. Abstr.*, **49**, 840 (1955).

(44) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1825 (1966).

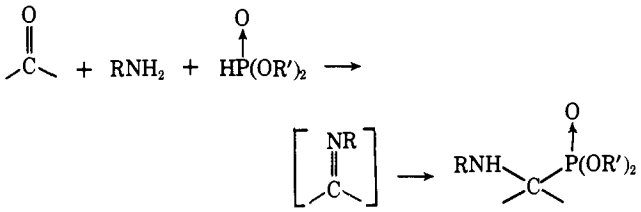
(45) A. Mustafa, M. M. Sidky, and F. M. Soliman, *Tetrahedron*, **22**, 393 (1966).

(46) I. N. Azerbaev, T. G. Sarbaev, E. U. Gafurov, A. M. Aleshin, B. D. Abiyurov, and K. B. Erzhanov, *Tr. Inst. Khim. Nauk, Akad. Nauk Kaz. SSR*, **19**, 49 (1967); *Chem. Abstr.*, **68**, 95894 (1968).

(47) T. Y. Medved and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1357 (1957); *Chem. Abstr.*, **52**, 7316 (1958).

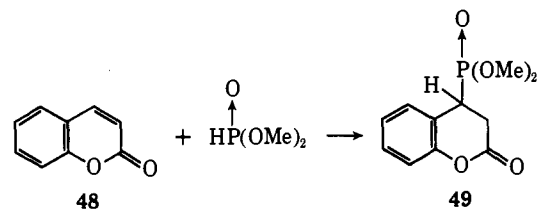
(48) I. N. Azerbaev, T. G. Sarbaev, B. D. Abiyurov, and V. S. Basalitskaya, *Izv. Akad. Nauk Kaz. SSR, Ser. Khim.*, **18**, 56 (1968); *Chem. Abstr.*, **70**, 57948 (1969).

(49) B. P. Lugovkin, *Zh. Obshch. Khim.*, **31**, 3408 (1961); *Chem. Abstr.*, **57**, 3478 (1962).



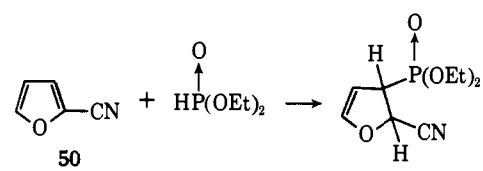
phonates by addition to heterocyclic carbonyl and exocyclic imine groups.

Michael-type additions of dialkyl phosphonates to activated carbon–carbon double bonds yield heterocyclic phosphonates when this moiety is part of a heterocyclic ring. The addition of dimethyl phosphonate to coumarin (**48**) yields the dihydrocoumarylphosphonate **49** (20%) without reaction at the carbonyl carbon.[51] The reported addition of diethyl phosphonate

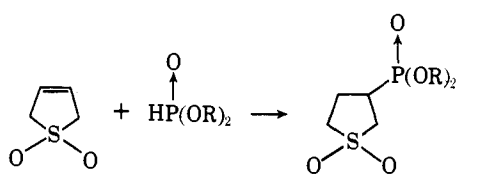


48 **49**

to 2-cyanofuran (**50**) to yield diethyl 2-cyano-2,3-dihydrofuryl-3-phosphonate (**51**) is surprising in view of loss of resonance energy.[52] The addition of diethyl phosphonate to Δ^3-sulfolene dioxide (**52**) to yield the sulfolane dioxide (**53**) is to be expected in view of the reported addition of many other nucleophiles to this double bond.[53] The addition of phosphorus nucleophiles to acyclic imines is a well-known re-



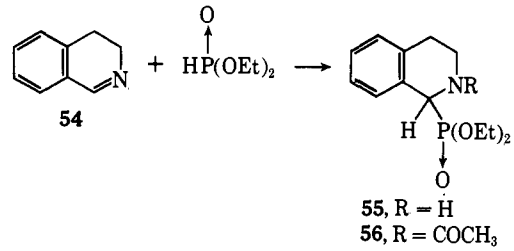
50 **51**



52

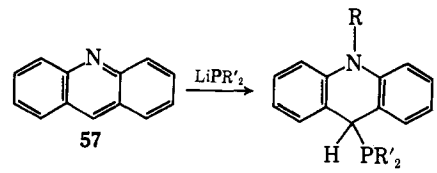
53, R = Et, Bu, C_6H_{11}

action[54] which has recently been applied to cyclic imines. 3,4-Dihydroisoquinoline (**54**) adds diethyl phosphonate to yield the tetrahydroisoquinolylphosphonate **55** which has been characterized as its crystalline acetyl derivative **56**.[55] Acridine (**57**) undergoes 1,4 addition of phosphorus nucleophiles; thus the lithium salts of diethyl-, diphenyl-, and dicyclo-



54

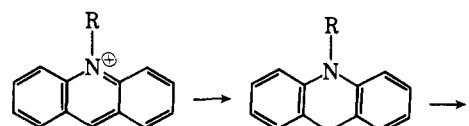
55, R = H
56, R = $COCH_3$



57

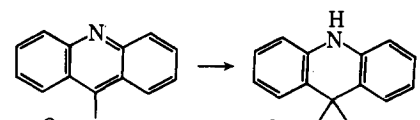
58, R = H; R′ = Et
59, R = H; R′ = Ph
60, R = H; R′ = c-C_6H_{11}

hexylphosphines yield the 9,10-dihydroacridines **58**, **59**, and **60** (~30%).[34] Similarly, the dihydroacridylphosphonate **63** is formed in quantitative yield by the addition of diethyl phosphonate in presence of catalytic amounts of base to acridine (**57**). This same phosphonate **63** and homolog **64** are the products of the addition of diethyl sodiophosphonate to the salts **61** and **62**.[33] The dihydroacridylphosphonate **63** can be de-



61, R = H
62, R = Me

63, R = H
64, R = Me
65, R = $COCH_3$



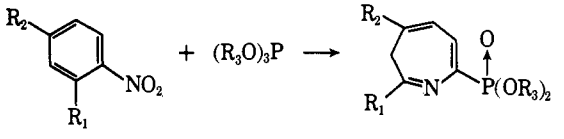
66, R = Et
67, R = H

68

hydrogenated to **66** which itself will add diethyl phosphonate to yield the diphosphonate **68**.[33] A recent report, without experimental details, discloses the reaction of acridine, quinoline, and pyridine with a trialkyl phosphite and acetyl chloride in a Reissert-type reaction.[56] In the case of acridine, the initial product is the dihydroacridine **65** which is hydrolyzed to acridyl-9-phosphonic acid (**67**). Similar sequences are reported to give quinolyl-2-phosphonic acid and pyridyl-2-phosphonic acid.[56] The melting points of these three acids do not correspond to previously reported values[33,19,38] and, further, other attempts to carry out this type of reaction have been unsuccessful,[57] suggesting that the above reactions have not taken place as claimed.[56]

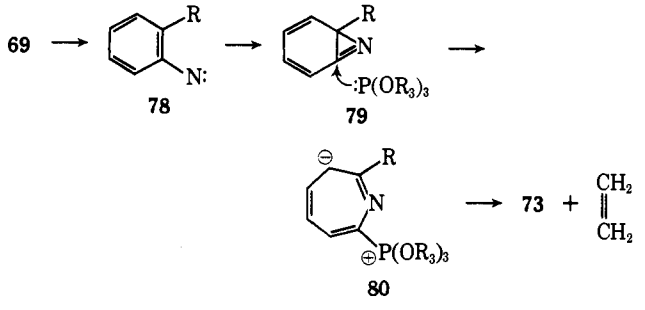
(50) G. M. Kosolapoff, K. H. Bloss, and D. K. Myers, *Zh. Obshch. Khim.*, 38, 1517 (1968); *Chem. Abstr.*, 70, 11860 (1969).
(51) B. A. Arbusov and V. M. Soroastrova, *Izv. Akad. Nauk SSSR*, 681 (1955); *Chem. Abstr.*, 50, 7109 (1956).
(52) A. N. Pudovik and N. I. Plakatina, *Sb. Statei Obshch. Khim.*, 2, 831 (1953); *Chem. Abstr.*, 49, 62814 (1955).
(53) R. L. McConnell and N. H. Shearer, U. S. Patent 2882278 (1959); *Chem. Abstr.*, 53, 17149 (1959).
(54) E. K. Fields, *J. Amer. Chem. Soc.*, 74, 1528 (1952); R. W. Layer *Chem. Rev.*, 63, 489 (1963).
(55) D. Redmore, unpublished work.
(56) A. K. Sheinkman, G. V. Samoilenko, and S. N. Baranov, *Zh. Obshch. Khim.*, 40, 700 (1970); *Chem. Abstr.*, 73, 14931 (1970).
(57) D. Redmore, unpublished work.

Among the products of deoxygenation of a series of nitrobenzenes **69–72** are the 3*H*-azepinyl-7-phosphonates **73–77**[58,59] in the yields shown. The pathway postulated for the reaction involves deoxygenation of **69** to nitrene **78** and rearrangement

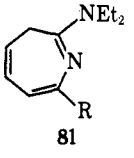


69, R_1 = Me; R_2 = H
70, R_1 = Et; R_2 = H
71, R_1 = H; R_2 = Me
72, R_1 = H; R_2 = OMe

73, R_1 = Me; R_2 = H; R_3 = Me (18%)
74, R_1 = Me; R_2 = H; R_3 = Et (8.5%)
75, R_1 = Et; R_2 = H; R_3 = Et (7%)
76, R_1 = H; R_2 = Me; R_3 = Me (9%)
77, R_1 = H; R_2 = OMe; R_3 = Me (15%)



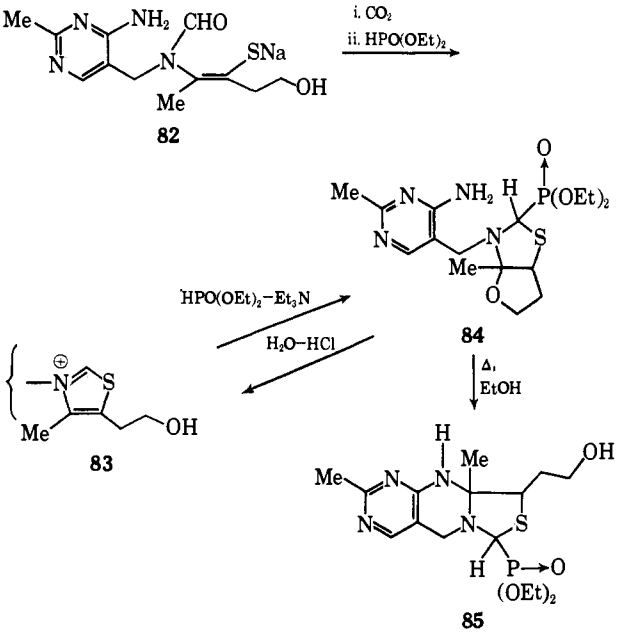
to imine **79** which is attacked by phosphite with ring opening to dipolar intermediate **80** and then to azepine **73** with ethylene liberation.[58] 2-Diethylaminoazepine (**81**) results from the trapping of **79** when the deoxygenation is carried out in presence of diethylamine[59] which suggests that higher yields of azepinylphosphonates (*e.g.*, **73**) could be obtained by deoxy-



81

genation in the presence of diethyl phosphonate, since diethyl phosphonate should add more readily to **79** than triethyl phosphite. Generation of nitrenes (*e.g.*, **78**) by other means, such as from azides, in the presence of dialkyl phosphonates might provide alternative routes to azepinylphosphonates.

Two routes to the phosphonate **84** have been described; one a nucleophilic addition to **83** and the second from **82** which could involve **83** as an intermediate.[60,61] A facile isomerization of **84** to **85** is observed upon heating in ethanol. Several other dialkyl phosphonates and phosphorous acid esters were found to undergo this addition to yield products analogous to **84** and **85**, all of which reverted to thiamine hydrochloride in aqueous HCl.[60,61]



82

83

84

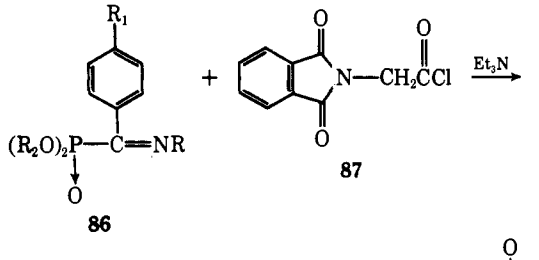
85

D. CYCLOADDITION REACTIONS

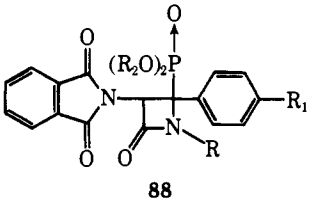
A series of azetidone phosphonates **88** has been prepared by the cycloaddition of the imine phosphonates **86** to the ketene derived from the acid chloride **87** in the presence of triethylamine[62] in an extension of a well-known reaction.[63]

The 1,3-dipolar cycloaddition reaction of 1,3 dipoles with alkenes has been used in the synthesis of heterocyclic phosphorus derivatives in two different ways: the first in which the phosphorus substituent is present in the alkene (or alkyne) and the second in which it is attached to the 1,3 dipole. Diisopropyl ethynylphosphonate (**89**) upon reaction with diazomethane is converted into the pyrazolyl phosphonate **90** in 28% yield.[64] The ethynyldiphosphonate **91** is converted into the pyrazole **92** in 95% yield in a similar reaction with diazomethane.[65] At low temperatures diphenyldiazomethane adds to diethyl vinylphosphonate (**93**) to yield dihydropyrazolylphosphonate **94** (73%), although at higher temperatures the cyclopropylphosphonate **95** is the product.[66] Triphenylvinylphosphonium bromide (**96**) can also be used as a dipolarophile with diazoalkanes. Thus, with diphenyldiazomethane the product in quantitative yield is 5,5-diphenyl-2-pyrazolin-3-yltriphenylphosphonium bromide (**97**), while with diazomethane the product is reported to be 2-pyrazolin-3-yltriphenylphosphonium bromide (**98**).[67] 1,2,5-Triphenylphosphole oxide (**99**) serves as a dipolarophile for ethyl diazoacetate or diazomethane in which case the products are dihydropyrazole compounds **100** and **101**, respectively.[68] An alternative route to dihydropyrazole phosphorus compounds **104** has been provided in the addition of the nitrile imine **103** to vinylphosphorus compounds **102**.[69]

(58) J. I. G. Cadogan, D. J. Sears, D. M. Smith, and M. J. Todd, *J. Chem. Soc. C*, 2813 (1969).
(59) R. J. Sundberg, B. P. Das, and R. H. Smith, *J. Amer. Chem. Soc.*, **91**, 658 (1969).
(60) A. Takamizawa, K. Hirai, and Y. Hamashima, *Tetrahedron Lett.*, 5081 (1967).
(61) A. Takamizowa, K. Hirai, Y. Hamashima, Y. Matsumoto, and S. Tanaka, *Chem. Pharm. Bull.*, **16**, 1761 (1968).
(62) L. Paul and K. Zieloff, *Chem. Ber.*, **99**, 1431 (1966).
(63) R. Huisgen, R. Grashey, and J. Sauer, "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, pp 802–805.
(64) B. C. Saunders and P. Simpson, *J. Chem. Soc.*, 3351 (1963).
(65) D. Seyferth and J. D. H. Paetsch, *J. Org. Chem.*, **34**, 1483 (1969).
(66) A. N. Pudovik, R. D. Gareev, and L. I. Kuznetsova, *Zh. Obshch. Khim.*, **39**, 1536 (1969); *Chem. Abstr.*, **71**, 113049 (1969).
(67) E. E. Schweizer, C. S. Khim, and R. A. Jones, *Chem. Commun.*, 39, 1584 (1970).
(68) I. G. M. Campbell, R. C. Cookson, M. B. Hocking, and A. N. Hughes, *J. Chem. Soc.*, 2184 (1965).
(69) I. G. Kolokol'tseva, V. N. Chistoketov, B. I. Ionin, and A. A. Petrov, *Zh. Obshch. Khim.*, **38**, 1248 (1968); *Chem. Abstr.*, **69**, 96834 (1968).

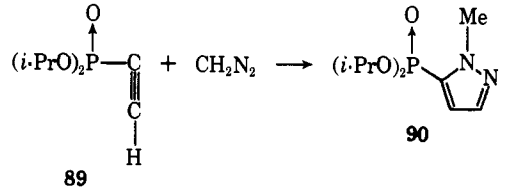


86 87

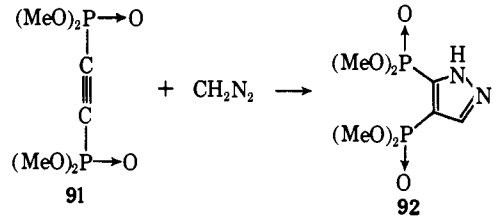


88

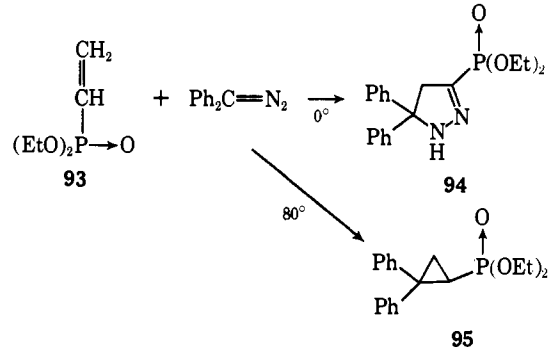
R	R_1	R_2	Yield, %
Ph	H	Me, Et	18, 46
Ph	Me	Me, Et	29, 32
Ph	Cl	Me, Et	17, 28
Ph	Br	Me, Et	22, 27
Ph	OMe	Me, Et	36, 40
Me	H	Et	24



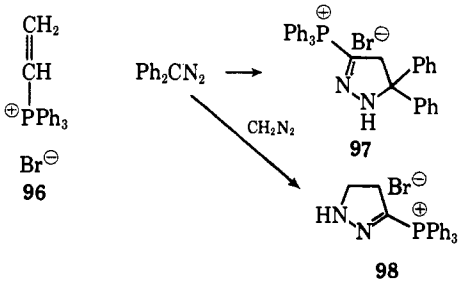
89 90



91 92

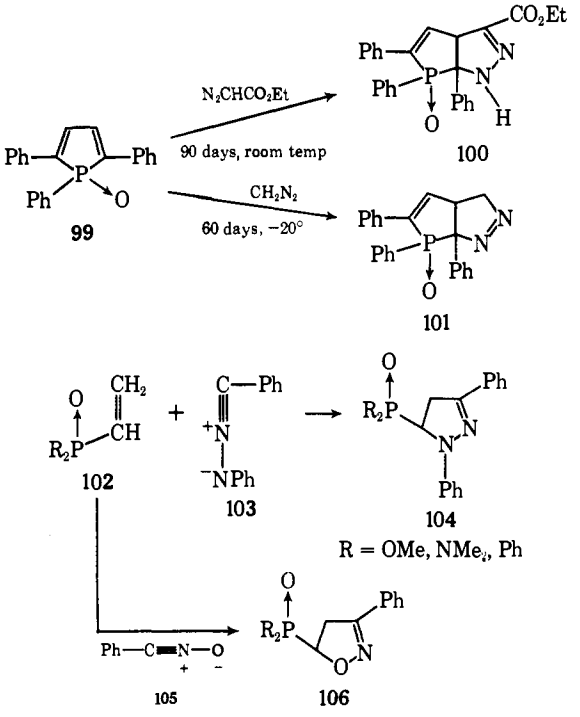


93 94 95



96 97 98

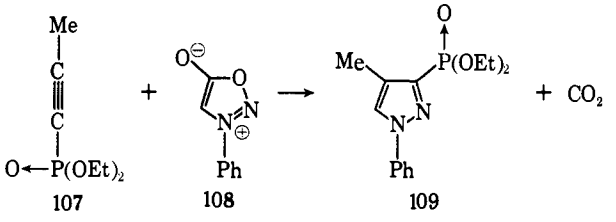
Dihydroisoxazoles **106** result when nitrile oxide **105** is substituted as the 1,3 dipole.[69]



99 100 101 102 103 104 105 106

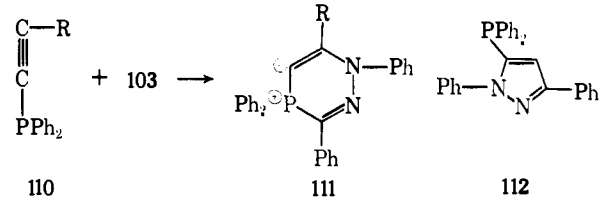
R = OMe, NMe_2, Ph

N-Phenylsydnone (**108**) can be used as a 1,3-dipolar compound in reaction with propynylphosphonate **107** yielding pyrazoylphosphonate **109** (53%) with extrusion of carbon dioxide.[70] The reaction between diphenylethynylphosphine



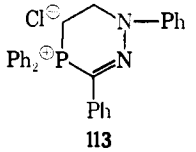
107 108 109

(**110a**) and diphenylnitrilimine (**103**) does not yield the expected pyrazole **112**, but rather the phosphonia diazacyclohexadiene (**111**) (98%).[71] Additional acetylenes **110b** and **110c** yield **111b** and **111c** in the reaction and, further, diphenylvinylphosphine undergoes a similar reaction yielding **113**.[71] This unexpected reaction of the unsaturated phosphines merits fur-



110 111 112

a, R = H; b, R = Me; c, R = Ph



113

ther investigation, and, in particular, a rigorous structure proof of the products is warranted. The potential of the 1,3-dipolar

(70) A. N. Pudovik and N. G. Khusainova, *Zh. Obshch. Khim.*, 40, 697 (1970); *Chem. Absir.*, 73, 14923 (1970).

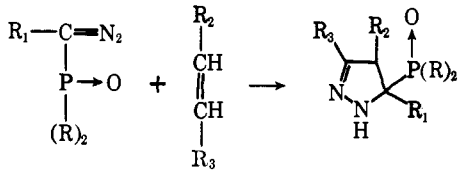
(71) I. G. Kolokoltseva, V. N. Chistokletov, and A. A. Petrov, *Zh. Obshch. Khim.*, 40, 574 (1970); *Chem. Absir.*, 73, 25582 (1970).

cycloaddition reaction using vinylphosphorus compounds as dipolarophiles as a method to heterocyclic phosphorus compounds seems to offer possibilities, many as yet unexamined.[72]

The preparation of heterocyclic phosphorus compounds by the cycloadditions of phosphorus-containing dipoles to olefins has been described for a series of α-diazophosphorus compounds and activated olefins as shown in Table V,[73-75]

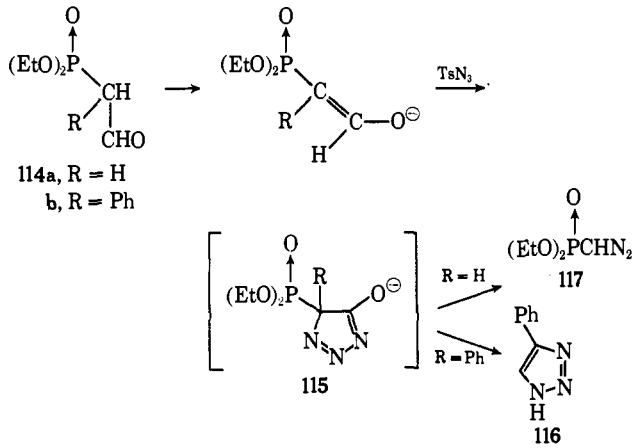
Table V

Addition of Phosphorus-Containing Dipoles to Activated Olefins



R	R_1	R_2	R_3	Yield, %	Ref
OMe	Ph	H	$COCH_3$	92	73
OMe	Ph	CO_2Et	CO_2Et	46	73
OMe	Me	H	$COCH_3$, CN, CO_2Et	90–98	73
Ph	Ph	H	$COCH_3$	89	74
OEt	*p*-$NO_2C_6H_4$	H	$COCH_3$	42	75
OEt	Ph	H	$COCH_3$	55	75

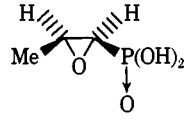
The addition of tosylazide to the phosphonates **114a** and **114b** almost certainly yields the triazolines **115a** and **115b** which, under the reaction conditions, yield diazophosphonate **117** and triazole **116**, respectively.[75,76]



E. CONDENSATION REACTIONS

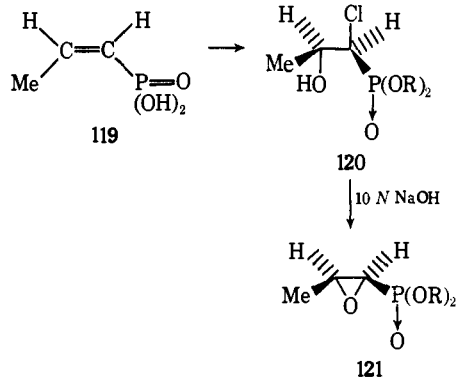
1. Epoxyethylphosphorus Compounds

Many of the classical condensation methods of heterocyclic synthesis have been carried out with phosphorus-bearing reactants to provide syntheses of heterocyclic phosphorus derivatives. Oxirane phosphorus derivatives figure particularly prominently in this section. Interest in these structures has been stimulated by the recent discovery of the antibiotic phosphonomycin, (−1*R*,2*S*)-1,2-epoxypropylphosphonic acid (**118**).[77] The numerous syntheses disclosed in recent patents attest to the potential of this phosphonic acid.[78] Although little experimental detail is available on these syntheses, some of them are discussed below because of current interest.



118

The treatment of halohydrins with base is a well-known method for the formation of epoxides[79] and has been exploited in the synthesis of epoxy phosphonates. The halohydrin **120a** derived from the treatment of *cis*-1-propenylphosphonic acid (**119**) with sodium hypochlorite is converted into phosphonomycin (**118**) with sodium hydroxide.[80]



a, R = H; **b**, R = Me

Similarly, the dimethyl ester **120b** is converted into the phosphonomycin ester **121b** which is demethylated by reaction with trimethylchlorosilane to the acid **118**.[81] Halohydrins **124** formed by heating a dialkyl phosphonate **123** with an α-chlorocarbonyl compound **122** are converted by treatment with potassium hydroxide into epoxy phosphonates **125** as summarized in Table VI.[82-84] In the steroid field the cholestane deriva-

(72) Reference 63, pp 806–874.

(73) D. Seyferth, P. Hilbert, and R. S. Marmor, *J. Amer. Chem. Soc.*, 89, 4811 (1967).

(74) M. Regitz and W. Anschutz, *Chem. Ber.*, 102, 2216 (1969).

(75) M. Regitz, W. Anschutz, and A. Liedhegener, *ibid.*, 101, 3734 (1968).

(76) M. Regitz and W. Anschutz, *Justus Liebigs Ann. Chem.*, 730, 194 (1969).

(77) B. G. Christensen, W. J. Leanza, T. R. Beattie, A. A. Patchett, B. H. Arison, R. E. Ormond, F. A. Kuehl, G. Albers-Schonberg, and O. Jardetzky, *Science*, 166, 123 (1969).

(78) B. Christensen, German Offen. 1924104 (1970); *Chem. Abstr.*, 72, 90630 (1970); J. M. Chemerda and E. J. Glamkowski, German Offen. 1924118 (1970); *Chem. Abstr.*, 72, 132953 (1970); R. A. Firestone and E. J. Glamkowski, German Offen. 1924105 (1970); *Chem. Abstr.*, 72, 132952 (1970); E. F. Shoenewaldt, German Offen. 1924231 (1970); *Chem. Abstr.*, 72, 132972 (1970); M. Sletzinger and S. Karady, German Offen. 1924149 (1970); *Chem. Abstr.*, 72, 90628 (1970); R. A. Firestone, German Offen. 1924098 (1970); *Chem. Abstr.*, 72, 90629 (1970); J. M. Chemerda and E. J. Glamkowski, German Offen. 1924173 (1970); *Chem. Abstr.*, 72, 43871 (1970).

(79) A. Rosowsky in "Heterocyclic Compounds with Three and Four Member Rings," A. Weissberger, Ed., Interscience, New York, N. Y., 1964, pp 94–106.

(80) N. N. Girotra and N. L. Wendler, *Tetrahedron Lett.*, 4647 (1969).

(81) P. I. Pollak, B. G. Christensen, and N. L. Wendler, German Offen. 1924169 (1970); *Chem. Abstr.*, 72, 100882 (1970).

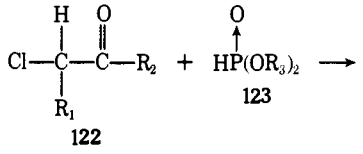
(82) V. S. Abramov and R. N. Savintseva, *Khim. Org. Soedin. Fosfora*, 129 (1967); *Chem. Abstr.*, 69, 67465 (1968).

(83) B. A. Arbuzov, V. S. Vinogradova, and N. A. Polezhaeva, *Dokl. Akad Nauk SSSR*, 111, 107 (1956); *Chem. Abstr.*, 51, 8001 (1957).

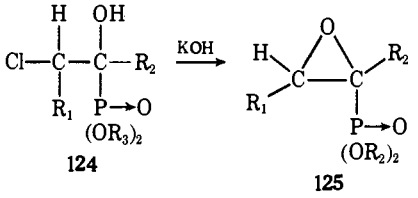
(84) P. A. Kirpichnikov, A. S. Kapustina, and G. N. Tokareva, *Tr. Kazan. Khim.-Tekhnol. Inst.*, 33, 188 (1964); *Chem. Abstr.*, 66, 2619 (1967).

Table VI

Structure of halohydrin **124**	*Yield of* **125**, %	*Ref*
$R_1 = R_2 = H$; R_3 = Me, Et, *i*-Pr, Bu	25–34	82
$R_1 = H$; R_2 = Me; R_3 = Et	...	83
$R_1 + R_2 = -(CH_2)_4-$; R_3 = Me, Et, Pr, Bu	30–65	84

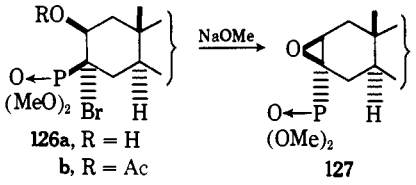


122 **123**



124 **125**

tives **126a** or **126b** are readily converted into the epoxide **127** with sodium methoxide in high yields (85 and 75%, respectively).[85]



126a, R = H
b, R = Ac **127**

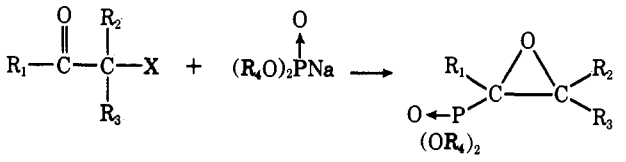
Reaction of α-halo ketones with certain nucleophiles is a standard epoxide synthesis[86] which can be used with appropriate phosphorus nucleophiles. Alkali metal derivatives of dialkyl phosphonates attack α-halo ketones primarily at the carbonyl carbon atom forming an alkoxide anion which displaces the α-halogen. In some cases, however, attack at carbonyl oxygen can be a competitive reaction which results in formation of an enol phosphate ester.[87–89] Syntheses by this route are summarized in Table VII.[90–93]

A variation of this procedure is exemplified in the conversion of the steroidal α-tosyloxy ketone **128** to epoxy phosphonate **129** in 69% yield by treatment with diethyl sodiophosphonate.[94] The reaction of diethyl ethylsodium phosphinate (**130**) on α-halo ketones is reported to take different courses

(85) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 624 (1967).
(86) Reference 79, pp 119–147.
(87) A. Meisters and J. M. Swan, *Aust. J. Chem.*, 18, 168 (1965).
(88) B. A. Arbuzov, V. S. Vinogradova, N. A. Polezhaeva, and A. V. Shamsutdinova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1380 (1963); *Chem. Abstr.*, **59**, 15306 (1963).
(89) T. Y. Medved and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1357 (1957); *Chem. Abstr.*, **52**, 7316 (1958).
(90) G. Sturtz, *Bull. Soc. Chim. Fr.*, 2333 (1964).
(91) B. A. Arbuzov, V. S. Vinogradova, and N. A. Polezhaeva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 41 (1959); *Chem. Abstr.*, **53**, 15035 (1959).
(92) M. Sprecher and D. Kost, *Tetrahedron Lett.*, 703 (1969).
(93) D. Redmore, unpublished.
(94) S. Hirai, R. G. Harvey, and E. V. Jensen, *Tetrahedron*, **22**, 1625 (1966).
(95) B. A. Arbuzov, V. S. Vinogradova, and M. A. Zvereva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1772 (1960); *Chem. Abstr.*, **55**, 16398 (1961).

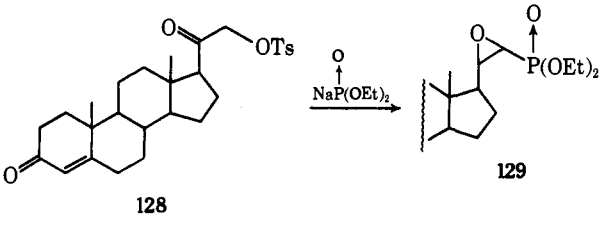
Table VII

Epoxyethylphosphonates from α-Halo Ketones



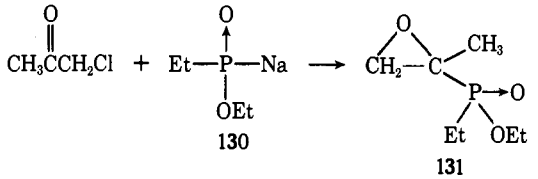
α-Halo ketone	*Phosphonate*	*Yield*, %	*Ref*
R_1 = Me; $R_2 = R_3 = H$	R_4 = Et	65	83, 90, 91
R_1 = Me; $R_2 = R_3 = H$	R_4 = Bu	69	90
R_1 = Et; $R_2 = R_3 = H$	R_4 = Et	71	90
R_1 = Ph; $R_2 = R_3 = H$	R_4 = Et[a]	55	87, 88
R_1 = Ph; R_2 = Me; $R_3 = H$	R_4 = Et	...	88, 92
R_1 = Ph; $R_2 = R_3$ = Me	R_4 = Et	...[b]	88
$R_1 + R_3 = -(CH_2)_4-$; $R_2 = H$	R_4 = Et	79	93
$R_1 = R_2$ = Ph; $R_3 = H$	R_4 = Me		92
R_1 = *t*-Bu; R_2 = Ph; $R_3 = H$	R_4 = Et		92
R_1 = *p*-$MeOC_6H_4$; R_2 = Ph; $R_3 = H$	R_4 = Me		92

[a] In liquid ammonia also gives CH_2=C(Ph)OPO(OEt)$_2$. [b] No epoxide, only Me_2C=C(Ph)OPO(OEt)$_2$.

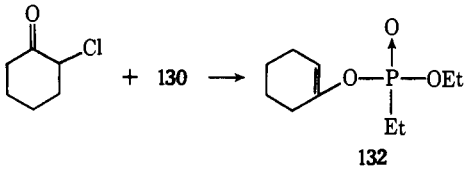


128 **129**

depending on the ketone structure.[95,96] This nucleophile with α-chloroacetone gives epoxyphosphinate **131**,[96] but with α-chlorocyclohexanone the product is enol phosphonate, ethyl cyclohexenyl ethylphosphonate (**132**).[96] The dependence of the reaction course upon the structure of the α-halo ketone requires more examples for clarification.



130 **131**



132

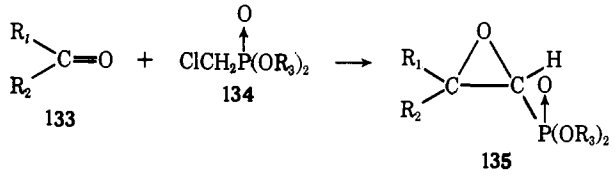
Although the reaction of α-halocarbonyl compounds with phosphorus nucleophiles has been satisfactorily applied in the synthesis of epoxyphosphonates, side reactions leading to unsaturated products can intervene as seen above. The Darzens procedure of reaction of halomethylphosphorus compounds **134** with carbonyl compounds yields epoxyphosphorus deriva-

(96) B. A. Arbuzov, V. S. Vinogradova, and M. A. Zvereva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1981 (1960); *Chem. Abstr.*, **55**, 16398 (1961).

tives **135** without side reactions. The halomethylphosphorus reactant used has been exclusively the readily available chloromethylphosphonic acid methyl or ethyl ester (**134**), while the carbonyl compound **133** is limited to ketones and arylaldehydes.[97] Table VIII summarizes the results.[98-100]

Table VIII

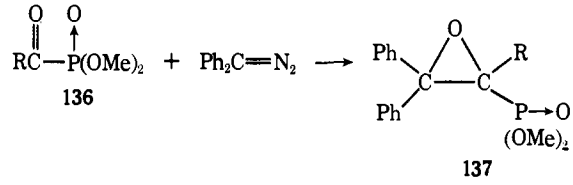
Epoxyphosphonates by Darzens Reaction



Carbonyl compound	*Phosphonate*	*Yield, %*	*Ref*
$R_1 = CH_2CH_2CHMe_2$; $R_2 = Me$	$R_3 = Me$	37	98
$R_1 = c\text{-}C_6H_{11}$; $R_2 = H$	$R_3 = Et$	43	98
$R_1 = Ph$; $R_2 = Me$	$R_3 = Me$	36	98, 99
$R_1 = Ph$; $R_2 = H$	$R_3 = Me$, Et	61-65	98, 99
$R_1 = p\text{-}MeC_6H_4$; $R_2 = H$	$R_3 = Me$	68	98
$R_1 = p\text{-}MeOC_6H_4$; $R_2 = H$	$R_3 = Me$	10	98
$R_1 = R_2 = Me$	$R_3 = Me$	...	99
$R_1 = R_2 = Ph$	$R_3 = Me$, Et	...	99
$R_1 = R_2 = -(CH_2)_5-$	$R_3 = Et$	31	99, 100

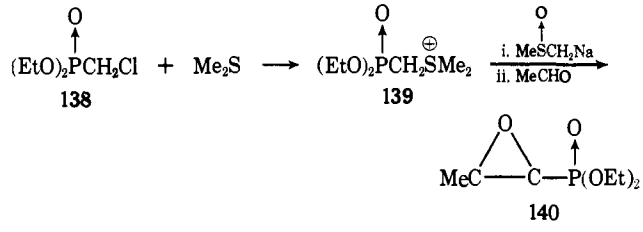
Direct epoxidation of α,β-unsaturated phosphonates with either acidic or basic reagents has been successful in the synthesis of epoxyphosphonates. With trifluoroperacetic acid, the initially formed epoxide may be ring opened unless mild conditions are employed.[101] In the case of epoxidation with *tert*-butyl peroxide Michael addition of butoxide to olefin may be a significant side reaction.[102] The epoxyphosphonates synthesized by epoxidation reactions are summarized in Table IX.[103,104]

An additional procedure used in the preparation of epoxyphosphonates is the reaction of diphenyldiazomethane with dimethyl acetylphosphonate (**136a**) or dimethyl benzoylphosphonate (**136b**) which yields **137a** or **137b**, respectively.[105] A useful supplement to the Darzens condensation, applicable to aliphatic aldehydes, has been used to convert diethyl chloromethylphosphonate (**138**) into phosphonomycin (**118**).[106] Reaction of **138** with dimethyl sulfide yields sulfonium salt



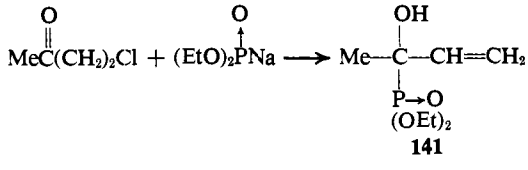
a, R = Me; b, R = Ph

139 which *via* its ylide is converted into epoxyphosphonate **140** by reaction with acetaldehyde and thence to phosphonomycin (**118**).

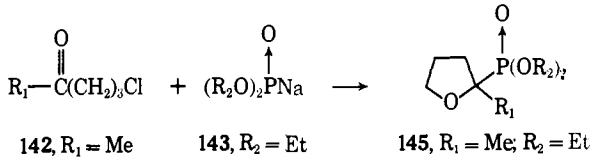


2. Five-Membered Ring Compounds

Although the reaction of dialkyl sodiophosphonates with α-halo and γ-halo ketones yields cyclic phosphonates (epoxyethylphosphonates and tetrahydrofurylphosphonates, respectively), the reaction with β-halo ketones yields only unsaturated acyclic products such as **141**.[90] A γ-chloro ketone, 1-chloropentan-4-one (**142**), upon reaction with alkali metal phosphonates **143** and **144** gives good yields of 2-methyltetra-

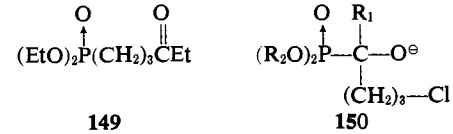


hydrofurylphosphonates **145** and **146** (79 and 66%, respectively).[90,91] In the case of 1-chlorohexanone-4 (**147**), the ex-



142, $R_1 = Me$	**143**, $R_2 = Et$	**145**, $R_1 = Me$; $R_2 = Et$
147, $R_1 = Et$	**144**, $R_2 = Bu$	**146**, $R_1 = Me$; $R_2 = Bu$
		148, $R_1 = Et$; $R_2 = Et$

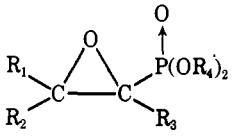
pected 2-ethyltetrahydrofurylphosphonate **148** is formed in only 14% yield, and phosphonate **149** is formed in significant amounts (17%).[90] In order to form the tetrahydrofuran, the phosphorus nucleophile must attack the carbonyl carbon to generate the alkoxide ion **150** which intramolecularly displaces chloride ion. It is surprising that sufficiently greater steric hindrance is introduced in **147** over **142** that direct halide displacement now competes favorably with attack at the carbonyl carbon.



(97) *Cf.* M. S. Newman and B. J. Magerlein, *Org. React.*, **5**, 413 (1949).
(98) V. F. Martynov and V. E. Timofeev, *Zh. Obshch. Khim.*, **34**, 3890 (1964); *Chem. Abstr.*, **62**, 19457 (1965).
(99) R. H. Churi and C. E. Griffin, *J. Amer. Chem. Soc.*, 88, 1824 (1966).
(100) V. F. Martynov and V. E. Timofeev, *Zh. Obshch. Khim.*, **32**, 3449 (1962); *Chem. Abstr.*, **58**, 9121 (1963).
(101) K. Hunger, *Chem. Ber.*, **101**, 3530 (1968).
(102) C. E. Griffin and S. K. Kundu, *J. Org. Chem.*, **34**, 1532 (1969).
(103) E. J. Glamkowski, G. Gal, R. Purick, A. J. Davidson, and M. Sletzinger, *ibid.*, **35**, 3510 (1970).
(104) J. M. Chemerda and M. Sletzinger, German Offen. 1924172 (1970); *Chem. Abstr.*, **72**, 90631 (1970).
(105) A. N. Pudovik, R. D. Gareev, and L. A. Stabrovskaya, *Zh. Obshch. Khim.*, 40, 698 (1970); *Chem. Abstr.*, **73**, 14933 (1970).
(106) B. G. Christensen and R. A. Firestone, German Offen. 1924135 (1969); *Chem. Abstr.*, **72**, 43870 (1970).

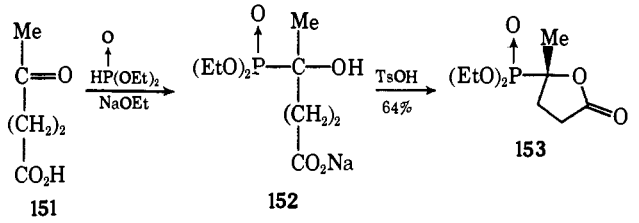
Table IX

Epoxyethylphosphonates by Oxidation of Olefins

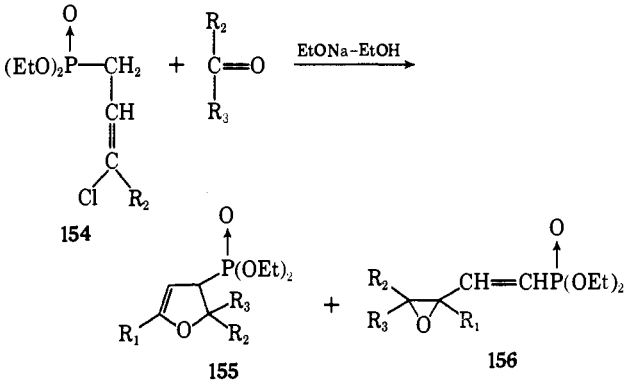


Reagent	*Epoxide*	*Yield, %*	*Ref*
CF_3CO_3H	$R_1 = H$; $R_2 + R_3 = -(CH_2)_4-$; $R_4 = Me$	73	101
CF_3CO_3H	$R_1 = R_2 = R_3 = H$; $R_4 = Et$	67	101
$MeOH-H_2O_2$, pH 9.5–10	$R_1 = R_2 = R_3 = H$; $R_4 = Et$	10	102
t-BuOOH–Triton B	$R_1 = R_2 = R_3 = H$; $R_4 = Et$	62	102
t-BuOOH–Triton B	$R_1 = R_2 = R_3 = H$; $R_4 = Me$	18	102
CF_3CO_3H	$R_1 = R_2 = Me$; $R_3 = H$; $R_4 = Et$	76	101
CF_3CO_3H	$R_1 = R_2 = Me$; $R_3 = H$; $R_4 = Et$	65	101
m-$ClC_6H_4CO_3H$	$R_1 = R_3 = Ph$; $R_2 = H$; $R_4 = Me$	..	92
m-$ClC_6H_4CO_3H$	$R_1 = Me$; $R_2 + R_3 = -(CH_2)_4-$; $R_4 = Me$	..	92
H_2O_2–$NaWO_4$, pH 5.0	$R_1 = Me$; $R_2 = R_3 = H$; $R_4 = H$	64	77, 103
CF_3CO_3H	$R_1 = Me$; $R_2 = R_3 = Cl$; $R_4 = PhCH_2$	..	104

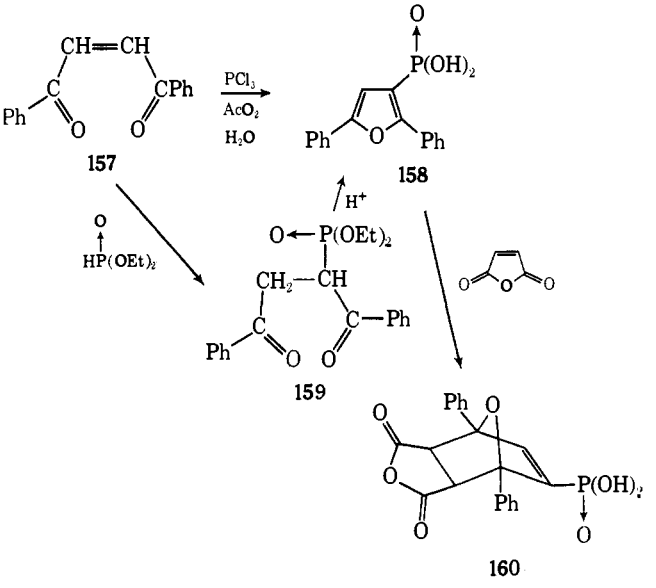
Levulinic acid (**151**) reacts with diethyl phosphonate to form a rather unstable adduct **152** which can be cyclized with *p*-toluenesulfonic acid to furanone **153**.[107]



Generation of the anion from allylphosphonate **154** in a protic solvent in presence of carbonyl compounds yields mixtures of 2,3-dihydrofuryl-3-phosphonates **155** and epoxides **156**.[108] In aprotic solvent the Wadsworth–Emmons reaction is the major pathway leading to butadienes.[108]



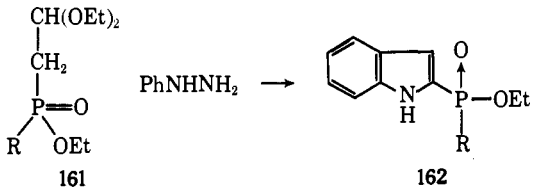
2,5-Diphenylfuryl-3-phosphonic acid (**158**) is conveniently obtained by reaction of phosphorus trichloride with dibenzoylethylene (**157**) in the presence of acetic anhydride followed by careful hydrolytic work-up.[109] A less efficient alternative is radical-induced[109] or base-catalyzed addition[110] of diethyl phosphonate to **157** yielding phosphonate **159** which with strong acid is cyclized to the acid **158**. The furylphosphonic



acid **158** undergoes a Diels–Alder addition with maleic anhydride to yield phosphonic acid **160**.[109] Subjecting phosphonate **161a** or phosphinate **161b** to reaction with phenylhydrazine under Fisher indole synthesis conditions affords the indolyl-2-phosphonate **162a** or -2-phosphinate **162b**, respectively, in low yield.[111,112] One would have anticipated the corresponding 3-substituted indole as the product;[113] thus the structure assignment may be incorrect (see section III.B).

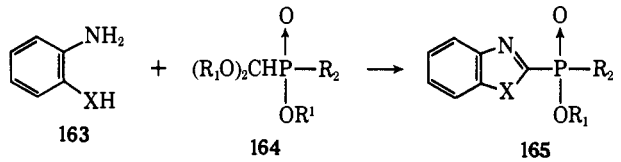
Acetals of formyl phosphonates or phosphinates **164** have been utilized in condensations with amino, hydroxy, or mercapto 1,2-disubstituted benzene derivatives **163** to yield a

(107) J. A. Cade, *J. Org. Chem.*, **23**, 1372 (1958).
(108) G. Lavielle and H. Normant, *C. R. Acad. Sci., Ser. B*, 270, 86 (1970).
(109) C. E. Griffin and J. T. Brown, *J. Org. Chem.*, **26**, 853 (1961).
(110) N. Kreutzkamp and W. Mengel, *Arch. Pharm. (Weinheim)*, **300**, 389 (1967).
(111) A. I. Razumov and P. A. Gurevich, *Zh. Obshch. Khim.*, 37, 1615 (1967); *Chem. Abstr.*, 68, 39730 (1968).
(112) A. I. Razumov and P. A. Gurevich, *Tr. Kazan. Khim. Tekhnol. Inst.*, 480 (1967); *Chem. Abstr.*, 70, 20160 (1969).
(113) B. Robinson, *Chem. Rev.*, **63**, 373 (1963); **69**, 227 (1969).



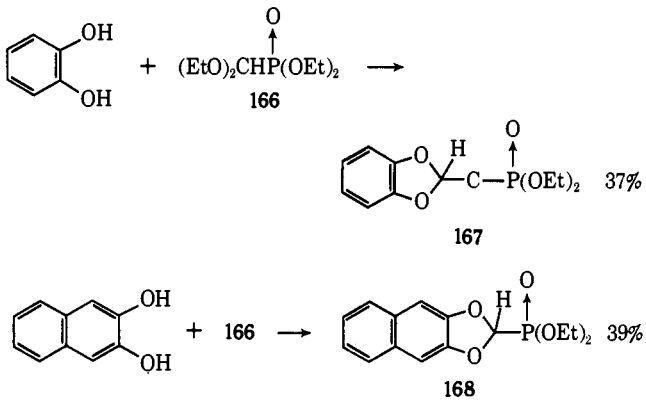
a, R = OEt; b, R = Ph

series of benzoheterocyclic phosphorus compounds **165**.[114-118] The yields of benzoxazole and benzothiazole derivatives are acceptable, but very poor yields of benzimidazoles are obtained. The source of oxidant in these reactions is not apparent, and in fact the reactions are carried out under a nitrogen blanket. Catechol and naphthalene-2,3-diol upon reaction



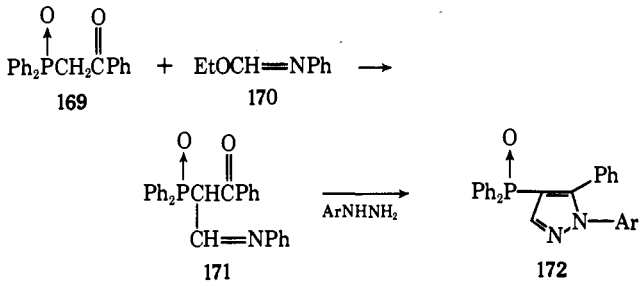
	Phosphorus reactant (**164**)	*Yield*, %	*Ref*
X = O	$R_1 = R_2$ = Et	68	114, 115
X = S	$R_1 = R_2$ = Et	30	116
X = NH	$R_1 = R_2$ = Me	7.5	117
X = NH	R_1 = Et; R_2 = *p*-Cl-C_6H_4	6.5	117

with formyl phosphonate **166** are converted into dioxolane phosphonates **167** and **168**, respectively, in a similar reac-

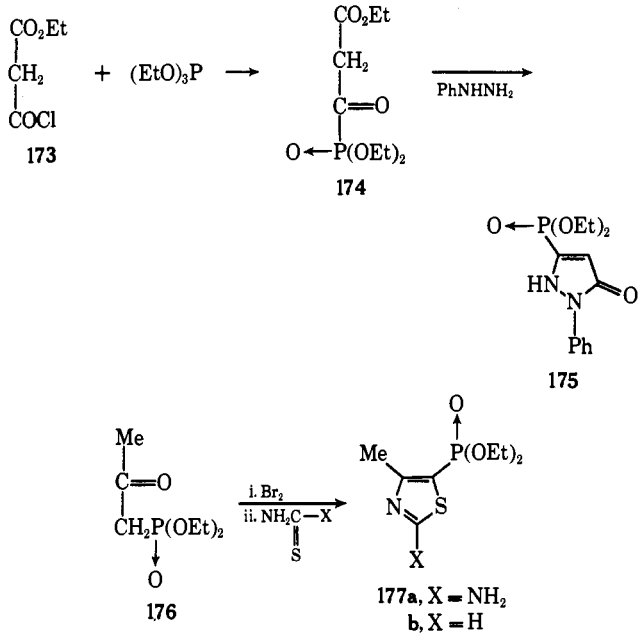


tion.[118] Phenacyldiphenylphosphine oxide (**169**) condenses with imine **170** to form ketoimine **171** which upon reaction with phenyl- or *p*-nitrophenylhydrazine yields the diphenylpyrazolylphosphine oxides **172a** and **172b**.[119]

The Arbuzov reaction of triethyl phosphite and malonic acid derivatives **173** yields phosphonate **174** which upon condensation with phenylhydrazine is converted into pyrazolone phosphonate **175** in low yield.[120]



a, Ar = Ph (56%); b, Ar = p-$NO_2C_6H_4$ (55%)



Diethyl acetonylphosphonate (**176**), readily obtained from chloroacetone and triethyl phosphite by an Arbuzov reaction, after bromination, condenses with thiourea or thioformamide to thiazole phosphonates **177a** and **177b**. Both are rather unstable unless converted into salts.[121]

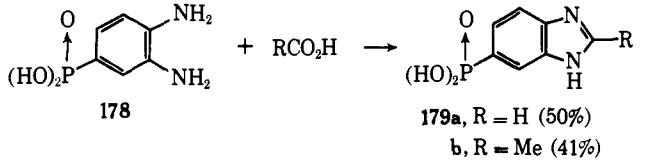
Conventional condensations of 3,4-diaminophenylphosphonic acid (**178**) with formic or acetic acid provides syntheses of benzimidazolyl-5-phosphonic acids **179a** and **179b**.[122]

Upon reaction with tosyl azide, acetamides **180a** and **180b** are converted into triazolyl phosphonate **181a**[75] and triazolyldiphenylphosphine oxide **181b**,[74] respectively, in a reaction involving diazo intermediates. The pyridyltriazolylphosphine oxide **183** is formed from **182** by a similar sequence.[74]

3. *Six-Membered Ring Compounds*

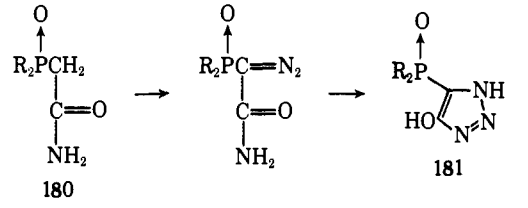
A few phosphonic acid derivatives of six-membered rings have been prepared, mostly by straightforward condensation procedures. Diethyl 4-phenyltetrahydropyranyl-4-phosphonate (**184**) is the product from the reaction of diethyl benzylphosphonate and bis(β-chloroethyl) ether in the presence of sodamide.[123] Magnesium ethoxide brings about cyclization of the

(114) A. I. Razumov, B. G. Liorber, and P. A. Gurevich, *Zh. Obshch. Khim.*, 37, 2782 (1967); *Chem. Abstr.*, 69, 43977 (1968).
(115) A. I. Razumov, P. A. Gurevich, B. G. Liorber, and T. B. Borisova, *Zh. Obshch. Khim.*, **39**, 392 (1969); *Chem. Abstr.*, 71, 115230 (1969).
(116) A. I. Razumov, B. G. Liorber, and P. A. Gurevich, *Zh. Obshch. Khim.*, 38, 199 (1968); *Chem. Abstr.*, 69, 52216 (1968).
(117) A. I. Razumov and P. A. Gurevich, *Zh. Obshch. Khim.*, 37, 1620 (1967); *Chem. Abstr.*, 68, 39731 (1968).
(118) A. I. Razumov and P. A. Gurevich, *Zh. Obshch. Khim.*, 38, 944 (1968); *Chem. Abstr.*, 69, 67467 (1968).
(119) H. G. Henning, G. Petzold, and G. Busse, *Z. Chem.*, 8, 302 (1968).
(120) M. H. Maguire, R. K. Ralph, and G. Shaw, *J. Chem. Soc.*, 2299 (1958).
(121) N. D. Dawson and A. Burger, *J. Amer. Chem. Soc.*, 74, 5312 (1952).
(122) R. W. Bost and L. D. Quin, *J. Org. Chem.*, 18, 358 (1953).
(123) P. Malatesta and A. Ciaramella, *Ann. Chim. (Rome)*, 51, 230 (1961).



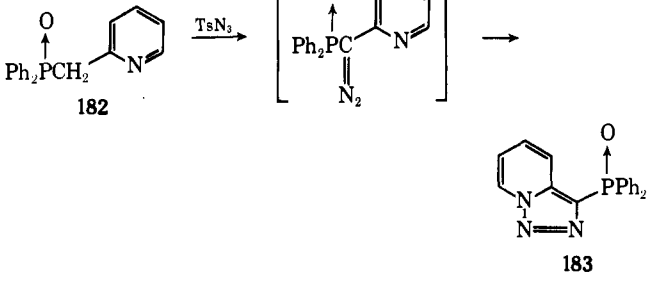
178

179a, R = H (50%)
b, R = Me (41%)



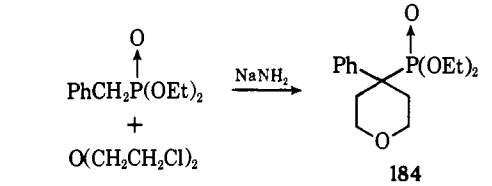
180 181

a, R = OEt; b, R = Ph



182 183

ester **185** into the tetrahydrothiopyranylphosphonate **186** in 56% yield.[124]



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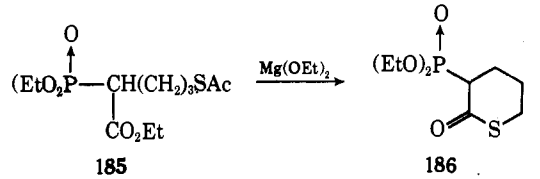
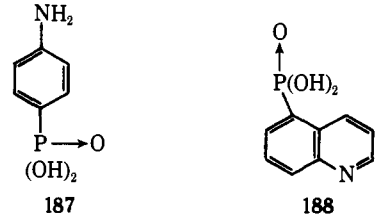
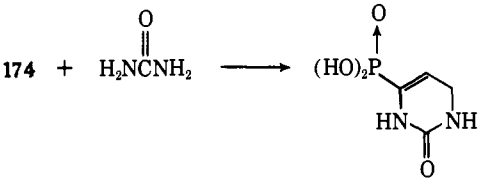


185 186



187 188

The Skraup quinoline synthesis has successfully been applied to quinolyl-6-phosphonic acid (**188**) from *p*-aminophenylphosphonic acid (**187**).[125] Two rather low yield preparations of pyrimidylphosphonic acid derivatives have been reported: uracil-6-phosphonic acid (**189**) is obtained by condensing **174** with urea[120] while pentane-2,4-dione 3-phosphonate (**190**) with urea yields the pyrimidyl-5-phosphonate (**191**).[126] Tetraethyl 1,4-dioxane-2,6-phosphonate (**194**) reportedly is formed by condensing diphosphonate **192** and chloro ether **193**.[127]



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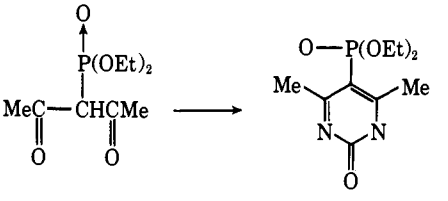
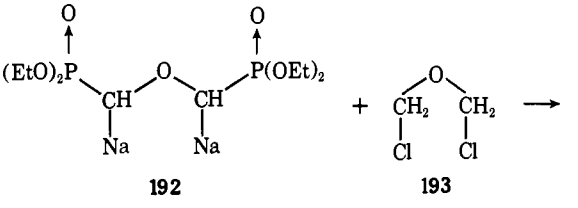
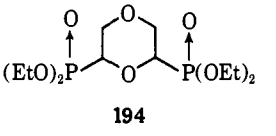


190 191



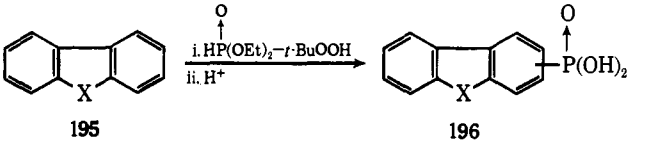
192 193



194

F. RADICAL REACTIONS[127a]

Syntheses of phosphorus derivatives of heterocyclic systems by reactions involving radical intermediates are very few and of little importance. However, dibenzofuran (**195a**) and carbazole (**195b**) undergo phosphonation in good yield when heated with diethyl phosphonate in the presence of *tert*-butyl peroxide. After work-up by hydrolysis the products in each case are a mixture of isomeric phosphonic acids **196a** and **196b** not readily separable.[128] The formation of diethyl 2-

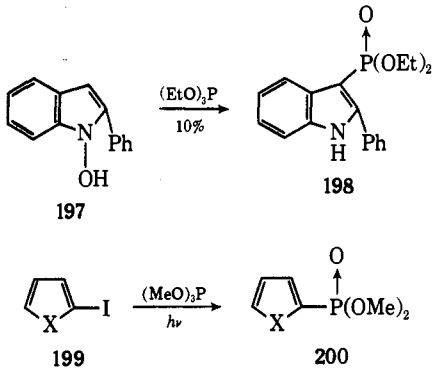


195 196

a, X = O; b, X = NH

phenylindolyl-3-phosphonate (**198**) by deoxygenation of 1-hydroxy-2-phenylindole (**197**) with triethyl phosphite is postulated to proceed by radical intermediates.[129] The generation of aryl radicals by photolysis of aryl iodides in the presence of trimethyl or triethyl phosphite gives good yields of aryl phosphonates.[130] In the case of 2-iodofuran (**199a**) and 2-iodothiophene (**199b**), however, rather low yields of the corresponding

(124) F. Korte and F. F. Wiese, *Chem. Ber.*, 97, 1963 (1964).
(125) G. M. Kosolapoff, *J. Org. Chem.*, 21, 1046 (1956).
(126) A. N. Pudovik and T. M. Moshkina, *Zh. Obshch. Khim.*, 27, 1611 (1957); *Chem. Abstr.*, 52, 3713 (1958).
(127) A. N. Pudovik, E. A. Ishmaeva, and I. V. Shergina, USSR Patent 253804 (1969); *Chem. Abstr.*, 72, 90618 (1970).
(127a) For a review of radical reactions of organophosphorus compounds see C. Walling and M. S. Pearson, *Top. Phosphorus Chem.*, 3, 1 (1966).
(128) E. F. Jason and E. K. Fields, *J. Org. Chem.*, 27, 1402 (1962).
(129) R. J. Sundberg, *ibid.*, 30, 3604 (1965).
(130) R. Obrycki and C. E. Griffin, *ibid.*, 33, 632 (1968).



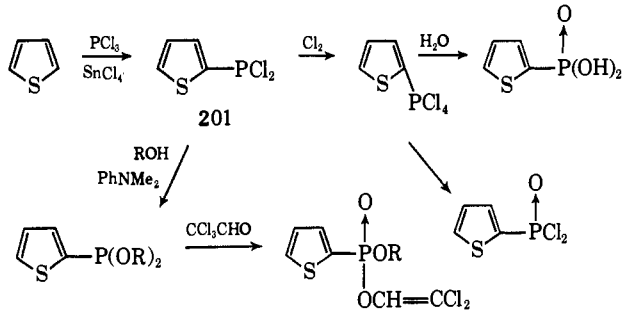
a, X = O; b, X = S

phosphonates **200a** and **200b**, respectively, are obtained owing to difficulty in obtaining pure iodides, and also owing to instability of the product phosphonates **200** under the photolysis conditions.[130] A superior method of preparation of these phosphonates is the nickel salt catalyzed Arbuzov reaction[29a] (section II.B).

G. ELECTROPHILIC SUBSTITUTION BY PHOSPHORUS

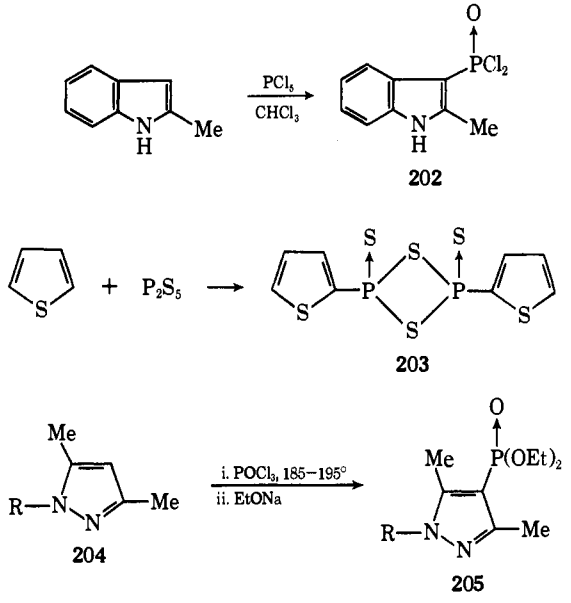
Although many heterocyclic rings, *e.g.*, pyridine, are rather inert to electrophilic attack, the more electron-rich systems, *e.g.*, thiophene, readily undergo electrophilic substitution. For example, the Friedel–Crafts reaction of phosphorus trichloride and thiophene in the presence of stannic chloride yields 2-thienylphosphonous dichloride (**201**) in 50% yield.[131] This procedure is a modification of that described by Sachs in 1892.[132] The phosphonous dichloride **201** can be converted by standard transformations into a series of derivatives (Scheme I).[131,132]

Scheme I



2-Methylindolyl-3-phosphonic dichloride (**202**) has been prepared by reaction of phosphorus pentachloride with 2-methylindole followed by mild hydrolytic work-up.[132a]

The following preparations are discussed in this section, although no strong evidence is available to define the mechanism. The reaction of phosphorus pentasulfide with excess thiophene is reported, without supporting physical data, to yield 2-thienylthiophosphonic anhydride (**203**).[133] A similar type of substitution reaction results from the treatment of pyrazole **204** with phosphoryl chloride in which the product after esterification is the ester **205**.[134]

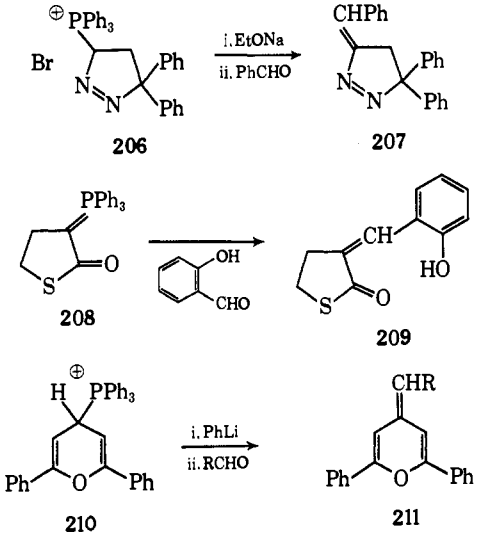


III. Chemistry

A. CARBON–PHOSPHORUS BOND CLEAVAGE

1. *Wittig and Wadsworth–Emmons Reactions*

Appropriate heterocyclic phosphorus compounds undergo the title reactions in a manner similar to the corresponding acyclic and alicyclic compounds.[135] Thus, pyrazoline **206** with base



a, R = Ph; b, R = Me

(131) M. Ventov, L. David, and E. D. Bergmann, *J. Chem. Soc.*, 4750 (1964).

(132) H. Sachs, *Chem. Ber.*, **25**, 1514 (1892).

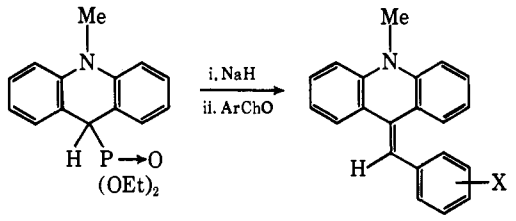
(132a) J. C. Powers, *J. Org. Chem.*, **31**, 2627 (1966).

(133) H. Hirai and H. Yoshiska, German Offen. 1896105 (1969); *Chem. Abstr.*, **71**, 50213 (1969).

(134) I. I. Grandberg and A. N. Kost, *Zh. Obshch. Khim.*, **31**, 129 (1961); *Chem. Abstr.*, **55**, 22292 (1961).

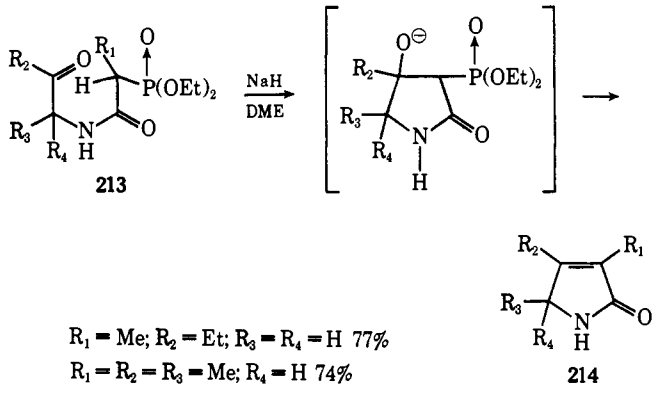
(135) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 132–215.

and treatment of the resulting ylide with benzaldehyde gives benzylidene compound **207** in 65% yield,[67] and ylide **208** with salicylaldehyde is converted to **209**.[35] Similarly, the phosphonium salt **210** upon treatment with base yields an ylide which with benzaldehyde or acetaldehyde is converted into pyran derivatives **211a** and **211b** in 40 and 42% yields, respectively.[136] The anion generated from dihydroacridinylphosphonate **64** is converted into a series of benzylidene dihydroacridines **212a–c** by treatment with the appropriate aldehyde in yields of 40–



64 **212a**, X = H; **b**, X = *p*-MeO; **c**, X = *m*-NO_2

70%.[33] A useful synthesis of pyrrolinones is presumed to involve a heterocyclic phosphonate intermediate, derived from **213**, which undergoes elimination of diethyl phosphate to give good yields of **214**.[137]



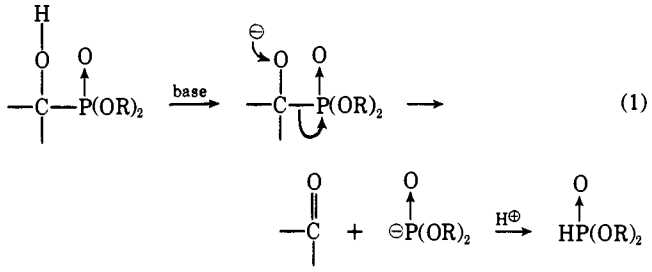
213

214

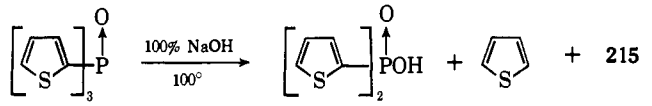
R_1 = Me; R_2 = Et; R_3 = R_4 = H 77%
R_1 = R_2 = R_3 = Me; R_4 = H 74%

2. *Other C–P Bond Cleavages*

Carbon–phosphorus bonds in heterocyclic systems seem to be much more susceptible to cleavage upon treatment with base than C–P bonds in aliphatic or most aromatic derivatives. Thus, triphenylphosphine oxide can withstand vigorous base treatment without much C–P cleavage, although certain aminophenylphosphonic acids undergo C–P bond cleavage with nucleophiles.[138] The α-hydroxyphosphonic acid esters are particularly susceptible to C–P bond cleavage upon treatment with aqueous base. Thus, the addition reaction of phosphorus anions to carbonyl groups (see section II.C) can be easily reversed. It is thought that the base removes a proton and the resulting anion expels a phosphonate anion (eq 1). It should be noted that the α-hydroxy acids are quite stable to base. Tri-2-thienylphosphine oxide (**215**) undergoes significant C–P bond cleavage upon heating with aqueous sodium hydroxide to a mixture of di-2-thienylphosphinic acid (**216**) and thiophene together with sodium meta-



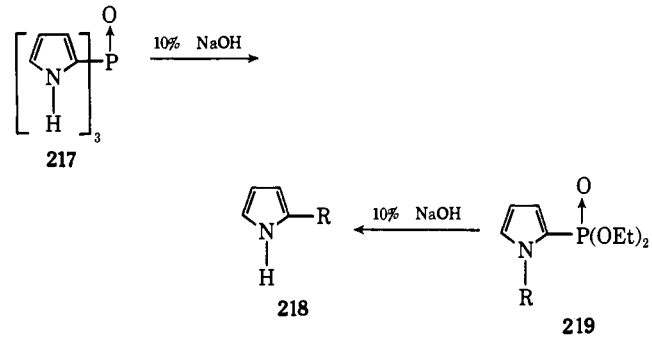
phosphate.[139] The greater degree of cleavage in **215** compared with triphenylphosphine oxide is thought to be a reflection of the greater stability of the 2-thienyl anion in comparison with the phenyl anion.[139] Anions of the aryl group are thought to be involved in these cleavages. Tri-2-pyrrylphosphine oxide (**217**)



215 **216**

24 hours	22%	65%	12%
48 hours	27%	73%	—

is similarly cleaved in high yield (87%) by aqueous sodium hydroxide to yield pyrrole (**218a**).[14] Diethyl pyrrolyl-2-phosphonate (**219a**) suffers C–P bond cleavage under these conditions to pyrrole (**218a**) (70%) and 2-ethylpyrrole (**218b**) (28%).[14] Other bases, such as sodium hydride, ethylmagnesium bromide, or pyrrylmagnesium bromide also serve to



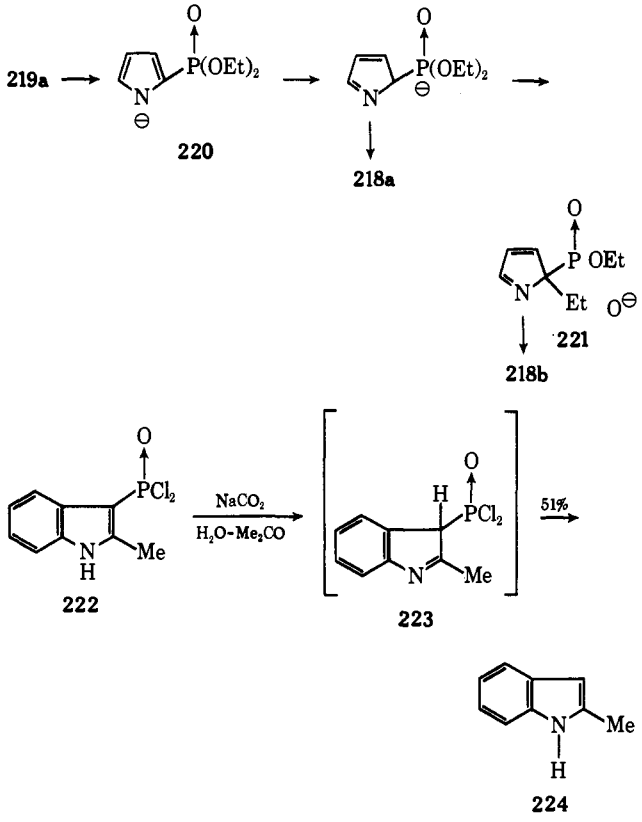
217 **218** **219**

a, R = H; **b**, R = Et; **c**, R = Me

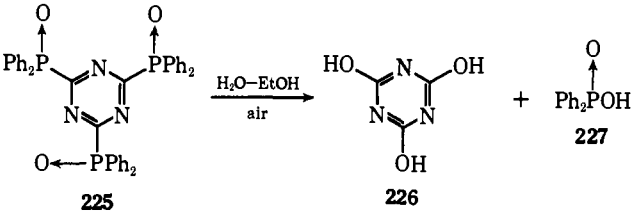
convert the phosphonate **219a** into the cleavage products **218a** and **218b**.[14,140] An attractive reaction pathway is as shown in which the base forms anion **220** which may or may not be intramolecularly alkylated before cleavage of the C–P bond. Nmr suggests the presence of **221**[140] (see section III.B). Supporting evidence for this pathway is provided by the observation that diethyl 1-methylpyrrolyl-2-phosphonate (**219c**) undergoes normal hydrolysis to its monoethyl ester with aqueous base.[14] In common with several other 3-substituted indoles, 2-methyl-3-indolylphosphonic dichloride (**222**) is cleaved of its 3 substituent with aqueous base to yield, in this case, 2-methylindole (**224**). It is thought that indolenine intermediates, such as **223**, are involved.[13]

Triazine derivative **225** is particularly susceptible to hydrolytic cleavage so that attempted recrystallization from aqueous ethanol in air results in the formation of cyanuric acid (**226**) (93%) and diphenylphosphinic acid (**227**) (80%).[24] It is not

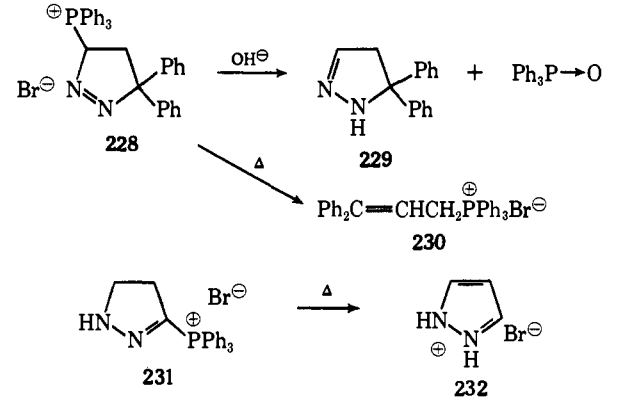
(136) S. V. Krivun, *Dokl. Akad. Nauk SSSR*, 182, 347 (1968); *Chem. Abstr.*, 70, 29009 (1969).
(137) G. Stork and R. Matthews, *Chem. Commun.*, 445 (1970).
(138) L. D. Freedman and G. O. Doak, *Chem. Rev.*, 57, 479 (1957).
(139) K. R. Martin and C. E. Griffin, *J. Heterocycl. Chem.*, 3, 92 (1966).
(140) C. E. Griffin, private communication.



clear whether air is essential for this cleavage. There are no reports regarding the hydrolytic stability of other phosphorus-substituted triazines.[140a] 3,3-Diphenyl-5-triphenylphosphonia-Δ^1-pyrazoline bromide (**228**) yields 5,5-diphenyl-3*H*-pyrazo-



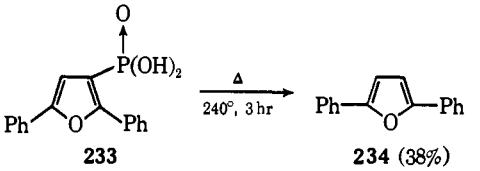
line (**229**) in 87% as expected when treated with 10% sodium hydroxide.[67] This same phosphonium salt **228** undergoes ring



opening with extrusion of nitrogen upon heating to yield **230**, whereas the related pyrazoline **231** yields pyrazolium hydro-

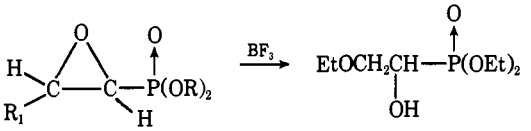
(140a) Recently it has been reported [J. P. Moreau and L. H. Chance, *J. Chem. Eng. Data*, 15, 581 (1970)] that ammonia readily displaces one or two phosphonate groups from trisubstituted triazines such as 17.

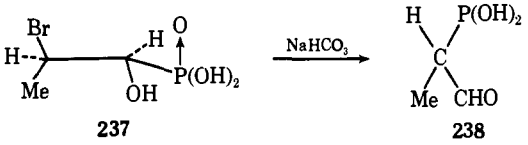
bromide (**232**) quantitatively upon heating.[67] Thermal C–P bond cleavage in phosphonic acids has been observed in some cases,[138] so that the thermal conversion of 2,5-diphenylfuryl-3-phosphonic acid (**233**) to 2,5-diphenylfuran (**234**) is not exceptional.[109]



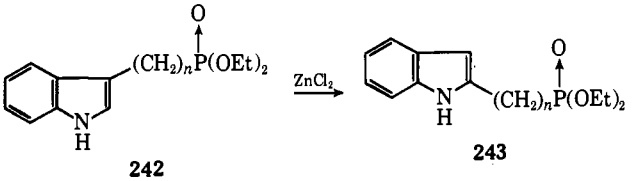
B. REARRANGEMENTS

The rearrangement of epoxides to carbonyl compounds, usually induced by Lewis acids, is a well-established reaction.[141] 1,2-Epoxyalkylphosphonates have been found to readily undergo rearrangement, with migration of the phosphonyl group, to β-carbonyl-containing phosphonates.[92,99,102,142] Although in some cases an efficient thermal rearrangement has been observed, the use of boron trifluoride at room temperature is much more generally useful.[92,99] In fact, the rearrangement products themselves can be thermally labile undergoing dephosphonation.[99] From the results of the rearrangement studies summarized in Table X, the following order of migratory aptitudes has been established: Ph > PO(OR)$_2$ > H > alkyl. It has been found that there are limitations in this rearrangement; for example, the less substituted members can undergo ring opening without rearrangement. Thus, diethyl 1,2-epoxyethylphosphonate (**235a**) upon treatment with boron trifluoride ethereate yields hydroxy ether **236**,[102] and phosphonomycin dimethyl ester (**235b**) gave no characterizable product with this reagent.[80] It is interesting to note, however, that mild base treatment of bromohydrin **237** induces a rearrangement with apparent phosphorus migration yielding alde-





hyde **238** (90%).[80] In the synthesis of indolyl-2-phosphonates **243a** and **243b**, it is postulated that the initially formed prod-

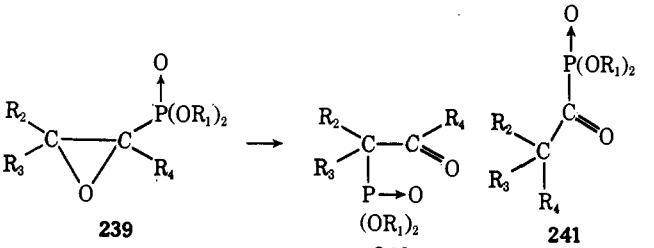


(141) Reference 79, pp 230–261.

(142) B. A. Arbuzov, N. A. Polezhaeva, and V. S. Vinogradova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1146 (1967); *Chem. Abstr.*, 68, 13092 (1968).

Table X

Rearrangement of 1,2-Epoxyethylphosphonates



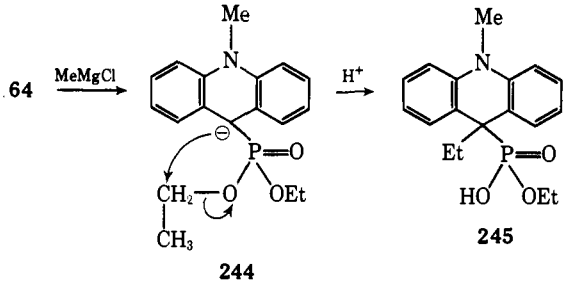
239 240 241

Epoxide **239**	*Conditions*	*Product*	*Yield, %*	*Ref*
R_1 = Et; R_2 = Ph; R_3 = Me; R_4 = H	Δ, 170°	**240**	86	99
R_1 = Me; R_2 = R_3 = Me; R_4 = H	Δ, 170°	**240**	...	99
R_1 = Me or Et; R_2 = R_3 = Ph; R_4 = H	Δ, 170°	**240**	...	99
R_1 = Me or Et; R_2 + R_3 = $-(CH_2)_5-$; R_4 = G	BF_3, rt[b]	**240**	100	92, 99
R_1 = Et; R_2 = Ph; R_3 = R_4 = H	BF_3, rt	**240**	100	99
R_1 = Et; R_2 = H; R_3 = Ph; R_4 = Me	BF_3, rt	**240**	100	92
R_1 = Et; R_2 = H; R_3 = Ph; R_4 = *t*-Bu	BF_3, rt	**240**	33	92
R_1 = Me; R_2 = Me; R_3 + R_4 = $-(CH_2)_4-$	BF_3, rt	**240**	100	92
R_1 = Me; R_2 = H; R_3 = Ph; R_4 = *p*-MeC_6H_4	BF_3, rt	**241**	100	92
R_1 = Me; R_2 = H; R_3 = R_4 = Ph[a]	BF_3, rt	**240**, 11% **241**	66	92
R_1 = Et; R_2 = R_3 = H; R_4 = Me	$ZnCl_2$, 160–170°	**240**	...	142
R_1 = Et; R_2 = H; R_3 = R_4 = Me	$ZnCl_2$, 160–170°	**240**	...	142
R_1 = Et; R_2 = H; R_3 + R_4 = $-(CH_2)_3-$	$ZnCl_2$, 160–170°	**240**	...	142

[a] This result is for (*E*)-stilbene oxide. The *Z* isomer gives **249** (34%) and $HCOC(Ph)_2PO(OMe)_2$ (66%) under similar conditions. The mode of formation of this latter product remains to be clarified. [b] rt = room temperature.

ucts are the 3-phosphonates **242a** and **242b**, which rearrange under the reaction conditions.[111] Although this rearrangement appears to be established for the indolylmethylphosphonate **242b**, conclusive characterization is lacking in the case of the lower homolog where the product of the synthesis could be **242a** and not **243a** as claimed.[111]

Diethyl 1-methyl-9,10-dihydroacridinyl-9-phosphonate (**64**) undergoes an isomerization reaction upon treatment with methyl- (or phenyl-) magnesium chloride yielding the 9-ethyl compound **245**.[33] The Grignard reagent functions as a base to form anion **244** which undergoes intramolecular alkylation to yield **245**. These results lend strong support for the postulated mechanism of the dephosphonation of diethyl pyrrolyl-2-phosphonate (**219a**) with base resulting in the formation of 2-ethylpyrrole[14,140] (see section III.A.2).



64 MeMgCl → H+ → 244 245

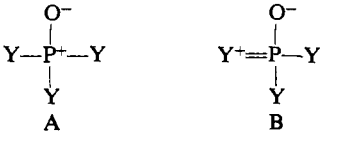
C. OTHER REACTIONS

Much of the chemistry of heterocyclic phosphorus compounds is unexceptional and follows the behavior of the parent heterocycle or for manipulations on the phosphorus group, the behavior of that group in simple systems. Thus, for example, diethyl 1,2-epoxyethylphosphonate undergoes ring opening of the epoxide upon treatment with nucleophiles,[102] and the phosphonate ester, diethyl pyridyl-2-phosphonate, is readily hydrolyzed to the corresponding acid with aqueous acid.[38] Although this acid hydrolysis could not be applied to epoxyphosphonates without affecting the epoxide function, gentle methods are available for the conversion of phosphonate esters to phosphonic acids such as reaction with chlorotrimethylsilane followed by water.[143] This procedure has not been widely exploited, but its potential is demonstrated in the conversion of diethyl *cis*-1,2-epoxypropylphosphonate to the acid, phosphonomycin, leaving the epoxide ring intact.[80]

IV. Properties

A. SPECTRA

Spectral measurements, particularly ultraviolet and nuclear magnetic resonance spectra, provide a means for determining the extent of π bonding involving the overlap of a phosphorus d orbital with a p orbital of an adjacent carbon of an aryl or vinyl group. Since certain aromatic heterocyclic systems are more effective electron donors than unsubstituted phenyl rings, heteroaryl phosphorus derivatives are particularly important systems in the study of $d\pi$–$p\pi$ bonding in organophosphorus compounds. This bonding is expressed in terms of canonical structures, such as B, and is reflected in bathochromic shifts in



A B

(143) R. Rabinowitz, *J. Org. Chem.*, 28, 2975 (1963).

Table XI

Ultraviolet Spectra of Heterocyclic Phosphorus Derivatives

Compound	λ_{max}, *nm*	$\epsilon_{max} \times 10^3$	$\Delta\lambda$, *nm*	*Ref*
Pyrrole	208	7.3	...	3
Tri-2-pyrrylphosphine oxide	237.5	11.6	39.5	3
Diethyl pyrryl-2-phosphonate	211	6.5	3	14
1-Methylpyrrole	213	6.7	...	3
Tri-2-(1-methylpyrryl)phosphine oxide	243	12.9	30	3
Diethyl 1-methylpyrryl-2-phosphonate	218	6.4	5	14
Furan	205	6.4	...	3
Tri-2-furylphosphine oxide	238	33.6	33	3
	245	38.9	40	4
Tri-2-furylphosphine	243	21.8	38	4
Tri-2-furylphosphine sulfide	241	30.2	36	4
Tri-2-furylphosphine selenide	239	24.0	34	4
2,5-Diphenylfuran	324	29.2	...	109
2,5-Diphenylfuryl-3-phosphonic acid	318	36.4	−6	109
Thiophene	231	7.1	...	3
Tri-2-thienylphosphine oxide	238	33.0	7	3
Pyridine	251, 270	2.0, 0.45	...	144
Diethyl pyridyl-2-phosphonate	259, 267	2.79, 1.97	8, −4	38
2,6-Dimethylpyridine	266	4.5	...	145
Diethyl 2,6-dimethylpyridyl-4-phosphonate	279	3.2	13	
Acridine	359	10	...	146
Diethyl acridyl-9-phosphonate	369	11.48	10	33
2-Phenylindole	309	24.6	...	147
Diethyl 2-phenylindolyl-3-phosphonate	293	17.8	−16	129

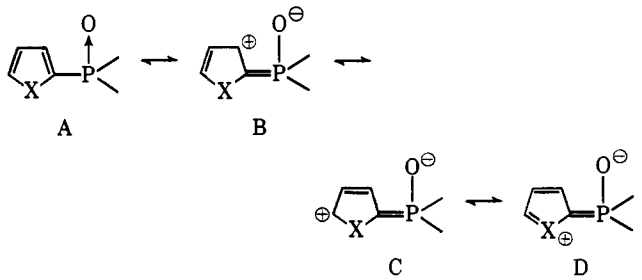
the ultraviolet spectrum and, in the nmr spectra, by deshielding of certain ring protons in the heterocyclic ring. These measurements do not necessarily give identical results but are, in fact, complementary, since uv spectra are excited-state measurements and nmr spectra are ground-state measurements.

1. Ultraviolet Adsorption Spectra

Table XI summarizes the uv spectral data and shows the shift from the parent heterocyclic system ($\Delta\lambda$).[144-147] Several trends are apparent from the data: those heterocyclic rings which are strongest electron donors show largest interaction and phosphine oxides conjugate more effectively than phosphonates. The 2-pyrryl- and 2-furylphosphine oxides show appreciable shifts from the parent heterocycle and a significant amount of $d\pi$–$p\pi$ bonding, but this is smaller than the shift observed for the formyl derivatives. In the case of tri-2-furylphosphine oxide there is a discrepancy in position of the maximum adsorption reported by two groups of workers.[3,4] Thiophene and pyridine phosphorus derivatives show virtually no $d\pi$–$p\pi$ interaction from the measurements of the uv spectra. It should be noted, however, there is a much larger effect from a phosphonate in the 4 position than in the 2 position of pyridine. Thus, relative to the appropriate pyridine, diethyl pyridyl-2-phosphonate has $\Delta\lambda$ = 4 nm and diethyl 2,6-dimethylpyridyl-4-phosphonate has $\Delta\lambda$ = 13 nm.[38] The uv spectrum of the unknown tri-4-pyridylphosphine oxide *vs.* that of the 2-pyridyl isomer would be informative in determining the relative extent of $d\pi$–$p\pi$ bonding in 2- and 4-pyridyl systems. It should be noted that 4-trimethylsilylpyridine is less basic than its 2 isomer, suggesting that $d\pi$–$p\pi$ interaction is stronger for 4-substituted pyridines.[148]

2. Nuclear Magnetic Resonance Spectra

Detailed analysis has been made of the nmr spectra of a number of heteroarylphosphines and phosphine oxides and sulfides. In addition to chemical shift data, ^1H–^{31}P spin coupling data have been obtained for coupling through three, four, and five bonds. The chemical shift data, which for selected compounds are summarized in Table XII, have been used to determine the presence of $d\pi$–$p\pi$ bonding in the heteroaryl phosphorus compounds. For the five-membered heterocycles substantial deshielding of H(5) may be a reflection of $d\pi$–$p\pi$ interactions represented by the contribution of canonical form C. The interaction is much greater in tetracoordinate phosphorus



derivatives as can be seen by a comparison of the chemical shifts of tri-2-furylphosphine and its oxide (Table XII). The magnitude of the ^1H–^{31}P coupling strongly supports this conclusion in both five- and six-membered heteroaryl phosphorus

(144) A. I. Scott, "Interpretation of Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, p 179.
(145) H. C. Brown and X. R. Mihn, *J. Amer. Chem. Soc.*, 77, 1723 (1955).
(146) A. Albert, "The Acridines," 2nd ed, Edward Arnold, London, 1966, p 176.
(147) M. J. Kamlet and J. C. Dacons, *J. Org. Chem.*, **26**, 220 (1961).
(148) D. G. Anderson, J. R. Chipperfield, and D. E. Webster, *J. Organometal. Chem.*, **12**, 323 (1968).

Table XII

Nmr Spectra for Heteroaryl Phosphine Derivatives and Model Compounds

	Solvent	Chemical shift, δ H(3)	H(4)	H(5)	H(6)	Ref
Furan	$CDCl_3$	6.37	6.37	7.42		149
2-Formylfuran	$CDCl_3$	7.28	6.63	7.72		149
Tri-2-furylphosphine	$CDCl_3$	6.63	6.26	7.45		151
Tri-2-furylphosphine oxide	$CDCl_3$	7.14	6.53	7.71		149, 151
Tri-2-furylphosphine sulfide	$CDCl_3$	7.15	6.50	7.69		151
Tri-2-furylphosphine selenide	$CDCl_3$	7.19	6.50	7.71		151
Diethyl 2-furylphosphonate	$(CH_3)_2CO$	7.10	6.62	7.88		149
2-Formylpyrrole	$CDCl_3$	7.17	6.30	6.98		149
Tri-2-pyrrylphosphine oxide	$CDCl_3$	6.33	6.33	6.82		149
Thiophene	$CDCl_3$	7.20	7.20	7.30		149
2-Formylthiophene	$CDCl_3$	7.78	7.22	7.78		149
Tri-2-thienylphosphine oxide	$CDCl_3$	7.58	7.17	7.74		149, 151
Diethyl 2-thienylphosphonate	$(CH_3)_2CO$	7.64	7.27	7.94		149
		H(3)	H(4)	H(5)	H(6)	
2-Formylpyridine	$(CH_3)_2SO$	8.36	8.17	7.88	9.03	150
Tri-2-pyridylphosphine oxide	$CDCl_3$	8.19	7.78	7.35	8.75	150, 152
Diethyl 2-pyridylphosphonate	CCl_4	8.10	8.02	7.65	8.88	38

compounds.[149-152] For example, in tri-2-thienylphosphine oxide the coupling between phosphorus and hydrogens at C_3, C_4, and C_5 is 7.98, 2.00, and 4.48 Hz, while in tri-2-thienylphosphine these values are 6.17, 1.33, and 0.19 Hz, respectively.[151] The increased deshielding of H(5) with increasing solvent polarity, Table XIII, argues in favor of an important contribution from resonance hybrid C and hence to the existence of $d\pi$-$p\pi$ interaction. The general conclusions from Table XII are that in furan and thiophene phosphorus derivatives $d\pi$-$p\pi$ interaction is present, whereas in pyrrole and pyridine derivatives there is little or no evidence for interaction.

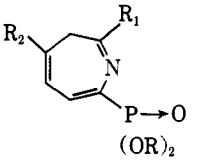
Table XIII

Solvent Effect on Chemical Shift of Tri-2-thienylphosphine[151]

Solvent	Chemical shift, δ H(3)	H(4)	H(5)
Carbon tetrachloride	7.26	6.96	7.41
Deuteriochloroform	7.32	7.02	7.50
Deuterioacetone	7.35	7.09	7.70
Deuterioacetonitrile	7.33	7.06	7.62
Deuteriodimethyl sulfoxide	7.35	7.10	7.79

Studies on other derivatives not summarized in Table XII include tri-2-thienylphosphine sulfide and selenide,[151] tri-2-(5-methylfuryl)phosphine and its sulfide,[153] tri-3-thienylphosphine and its oxide, sulfide, and selenide,[151] and tri-2-pyridylphosphine and its sulfide and selenide.[150,152] Analysis of the spectrum of the pyridylphosphines has given the first values of ^1H-^{31}P coupling through five bonds.[150,152] These coupling constants range from 1.18 to 3.10 Hz [for ^{31}P with H(5)] for tri-2-pyridylphosphine to tri-2-pyridylphosphine selenide.

The nmr spectra of a series of azepine phosphonates **246** have been studied and, in fact, formed part of the structure proof.[154] This analysis also disclosed a five-bond ^1H-^{31}P spin coupling (J = 2 Hz).



246a, R = Et; R_1 = Me; R_2 = H
b, R = Et; R_1 = Et; R_2 = H
c, R = Me; R_1 = H; R_2 = Me
d, R = Me; R_1 = Me; R_2 = H
e, R = Et; R_1 = R_2 = H

B. BIOLOGICAL ACTIVITY

Although the stated purpose of many of the syntheses of heterocyclic phosphorus compounds, particularly phosphonic acids, was to determine biological activity, very few positive results are reported. From this class of compounds, phosphonomycin appears to stand alone in its biological activity.[77] It is reported to be a bactericidal antibiotic effective against a wide range of organisms comparable to tetracycline or chloramphenicol in its activity. This antibiotic, which has low toxicity, functions by inhibiting bacterial cell-wall synthesis.[77] Among compounds reported to have weak or no biological activity are quinolinephosphonic acids,[19] 3-pyridylphosphonic acid,[36] thiazolephosphonate ethyl ester,[121] and pyrimidinephosphonate esters.[22] It would seem that many of the phosphonates tested only as esters should be reexamined as the corresponding acids which may well be more readily assimilated by organisms.

(149) R. H. Kemp, W. A. Thomas, M. Gordon, and C. E. Griffin, *J. Chem. Soc. B*, 527 (1969).
(150) G. E. Griffin and W. A. Thomas, *ibid.*, 477 (1970).
(151) H. J. Jakobsen and J. A. Nielsen, *J. Mol. Spectrosc.*, **33**, 474 (1970).
(152) H. J. Jakobsen, *ibid.*, **34**, 245 (1970).
(153) H. J. Jakobsen and M. Begrup, *ibid.*, **35**, 158 (1970).
(154) J. I. G. Cadogan and R. K. Mackie, *J. Chem. Soc. C*, 2819 (1969).