# The Chemistry of Heteroarylphosphorus Compounds. Part 10.[1] Synthesis and Kinetics of Alkaline Hydrolysis of Heteroarylphosphinate Esters and Hydrolysis of Heteroarylphosphine Oxides

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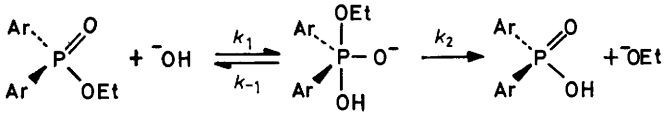
The rates of alkaline hydrolysis in aqueous dioxan of the ethyl esters of di-(2-furyl)-, di-(2-thienyl)-, and diphenylphosphinic acids have been determined. At 30 °C, second-order rate constants are respectively $2.76 \times 10^{-2}$, $1.02 \times 10^{-3}$, and $2.57 \times 10^{-4}$ l mol$^{-1}$ s$^{-1}$ The variation in rate with the nature of the *P*-substituent is discussed, and it is concluded that the heteroaryl substituents interact with phosphorus mainly by a σ-electron-withdrawing effect.

The alkaline hydrolysis of tri-(2-furyl)- and tri-(2-thienyl)-phosphine oxides affords a convenient route to the above phosphinic acids. The corresponding bis-(1-methylpyrrol-2-yl)phosphinic acid could not be prepared by this procedure; other routes to this compound have been explored, without success, owing to the capacity of the 1-methylpyrrol-2-yl substituent to inhibit nucleophilic attack at phosphorus.

We have previously reported the effects of heteroaryl *P*-substituents on the rate and course of nucleophilic displacement reactions at phosphorus in the alkaline hydrolysis of phosphonium salts,[2-5] in the decomposition of phosphonium betaines,[6] and in the alkaline hydrolysis of phosphonate esters.[7] We have now extended our studies to include the rates of nucleophilic displacement at phosphorus in ethyl phosphinates



Scheme

derived from furan and thiophen, and a comparison of these with corresponding rate data for ethyl diphenylphosphinate. As for the hydrolysis of the heteroarylphosphonate esters, it seems reasonable to assume the involvement of unstable pentacovalent intermediates, especially in view of recent work by Haake *et al.*,[8] and the rate data will be discussed in terms of the Scheme shown. The observed second-order rate constants can be expressed as in equation (i).

$$k_{obs.} = k_1/(1 + k_{-1}/k_2) \quad \text{(i)}$$

## RESULTS

The kinetics of alkaline hydrolysis of ethyl di-(2-furyl)- and di-(2-thienyl)phosphinate (1; X = O or S) and diphenylphosphinate (2) in 50% aqueous dioxan (0.1M in potassium chloride) were studied by a titrimetric procedure. The esters undergo hydrolysis on treatment with 1 mol. equiv. of sodium hydroxide to give the sodium phosphinate, and second-order behaviour is observed. The rate data are presented in the Table, together with $^{31}$P n.m.r. data for the esters.

## DISCUSSION

*Rate Data.*—The rates of alkaline hydrolysis of the heteroarylphosphinates (1; X = O or S) and ethyl

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[5] D. W. Allen, B. G. Hutley, and M. T. J. Mellor, *J.C.S. Perkin II*, 1974, 1690.
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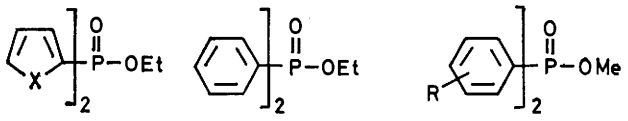
[8] R. D. Cook, C. E. Diebert, W. Schwarz, P. C. Turley, and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8088.

diphenylphosphinate (2) are in the order 2-furyl > 2-thienyl > phenyl (90 : 4 : 1). In this series, electron-withdrawing groups should increase the rate constant $k_1$ by stabilising the electron-rich transition state for



(1) (2) (3)

phosphorane formation. In contrast, such substituents should decrease the rate constants $k_{-1}$ and $k_2$ because their effect on the stability of the phosphorane with its full negative charge should be greater than their effect on the stability of the transition states (having partial negative charge) leading back to reactants and forward to products.

Because of the similarity of the two potential leaving groups ($^-$OH and $^-$OEt) in the decomposition of the phosphorane, the effect of *P*-substituents on $k_{-1}$ and $k_2$ will be partly compensatory, and therefore $k_1$ will be the dominant factor in the rate equation. The relative rate data therefore indicate that both 2-furyl and 2-thienyl substituents are more electron-withdrawing than phenyl in this situation, and that 2-furyl is more strongly electron-withdrawing than 2-thienyl. Thus in the above phosphinate series, these heteroaryl substituents are behaving in the same way as in the phosphonate ester series.[7]

There is no indication of any $p_\pi \rightarrow d_\pi$ interaction between these ' π-excessive ' heterocycles and the phosphorus atom, which would be expected to result in a decrease in $k_1$ and a reduction in the rate of hydrolysis. Consistent with earlier studies of $P^V$ ester hydrolysis,[9] the heteroarylphosphinates are hydrolysed significantly faster than the corresponding phosphonate esters under the same conditions. Thus ethyl di-(2-furyl)phosphinate (1; X = O) is hydrolysed **35** times faster than diethyl (2-furyl)phosphonate, and the di-(2-thienyl)- and diphenyl-phosphinates are hydrolysed respectively 9 and 3 times more rapidly than the phosphonate analogues.[7]

The above conclusions on the electronic effects of the 2-furyl and 2-thienyl substituents are of interest in view of other reports on the electronic effects of *P*-substituents in phosphinate ester hydrolysis. Thus Haake *et al.*,[10] in the light of kinetic studies of the hydrolysis of a series of esters of substituted arylphosphinic acids, suggest that resonance interactions are involved between the π-system of the aromatic ring and the phosphorus atom. Thus a plot of $\log_{10}k$ (hydrolysis) for compounds of type (3) gave a linear correlation with the Hammett σ constants, in which data for the *p*-methoxy- and *p*-dimethylamino-substituents were included. The rate data for the alkaline hydrolysis of ethyl benzoates was also shown to correlate with those for arylphosphinate ester hydrolysis, and thus it was concluded that interactions between aryl rings and phosphorus in phosphinate esters are similar to aryl–carbonyl interactions and that there are electronic effects of the resonance type ($p_\pi \rightarrow d_\pi$) in arylphosphinates.

Second-order rate constants and activation parameters for the alkaline hydrolysis of phosphinate esters [$R_2P(O)OEt$] in aqueous 50% (v/v) dioxan (0.1M in KCl); $^{31}P$ n.m.r. data for the esters in $CHCl_3$

| R | Temp. (°C) | $k_{obs}$ / l mol$^{-1}$ s$^{-1}$ | $E_A$ / kJ mol$^{-1}$ | $\Delta S^\ddagger$ / J K$^{-1}$ mol$^{-1}$ | δ $^{31}P$ (p.p.m. rel. to 85% $H_3PO_4$) * |
|---|---|---|---|---|---|
| 2-Furyl | 30 | $(2.76 \pm 0.04) \times 10^{-2}$ | 47.7 | −118.2 | −4.25 |
| | 40 | $(4.89 \pm 0.05) \times 10^{-2}$ | | | |
| 2-Thienyl | 30 | $(1.02 \pm 0.02) \times 10^{-3}$ | 62.0 | −98.1 | −16.0 |
| | 40 | $(2.19 \pm 0.02) \times 10^{-3}$ | | | |
| Phenyl | 30 | $(2.57 \pm 0.03) \times 10^{-4}$ | 70.5 | −81.7 | −27.2 |
| | 40 | $(5.98 \pm 0.06) \times 10^{-4}$ | | | |

* Negative shifts to low field.

However, as we have similarly argued earlier,[7] it is more probable that the fit of electron-donating *para*-substituents to such Hammett correlations for phosphinate esters results simply from a π-inductive effect which places electron density adjacent to phosphorus and thereby reduces $k_1$ for phosphorane formation. In the case of the 2-furyl and 2-thienyl substituents, the inductive electron-withdrawing effect of the heteroatom is clearly of paramount importance.

Consistent with this conclusion are the observed $^{31}P$ n.m.r. chemical shifts of the heteroarylphosphinates (Table). As observed for the related heteroarylphosphonates,[7] the shielding at phosphorus increases on going from the phenyl- to the 2-thienyl- to the 2-furylphosphinate, indicating, on the basis of earlier work,[11,12] that the apparent electron-withdrawing nature of the substituents increases in this order.

*Preparative Aspects.*—Griffin has reported that tri-(2-thienyl)phosphine oxide (4; X = S) decomposes on heating with aqueous sodium hydroxide to give a mixture of the phosphinic acid (5; X = S), thiophen, and sodium metaphosphate, whereas triphenylphosphine oxide and tris-(1-methylpyrrol-2-yl)phosphine oxide (4; X = NMe) are not affected under the same conditions.[13,14] We have investigated the alkaline hydrolysis of heteroarylphosphine oxides further with a view

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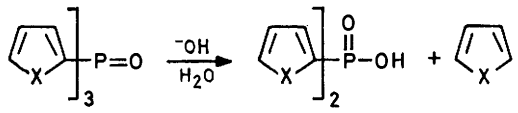
to using it as a preparative route to heteroarylphosphinic acids, since heteroarylphosphine oxides are readily available either by direct synthesis from an organometallic derivative with phosphoryl chloride [15] or *via* oxidation of tertiary phosphines.[6]



(4) (5)

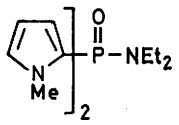
The alkaline hydrolysis of the phosphine oxides (4; X = O, S, or NMe) gave contrasting results. Prolonged reflux (72 h) of equimolar quantities of tri-(2-furyl)-phosphine oxide (4; X = O) and sodium hydroxide in 50% aqueous dioxan gave, after acidification, the phosphinic acid (5; X = O) in 72% yield with an 8% recovery of the phosphine oxide. In contrast, when equimolar quantities of tri-(2-thienyl)phosphine oxide (4; X = S) and sodium hydroxide were heated together under the same conditions for 120 h, the phosphinic acid (5; X = S) was isolated in only 37% yield, with a 60% recovery of phosphine oxide. Attempts to obtain bis-(1-methylpyrrol-2-yl)phosphinic acid (5; X = NMe) from an excess of sodium hydroxide and the phosphine oxide under reflux in aqueous dimethyl sulphoxide (30 : 70 v/v) (in which the activity of the hydroxide ion is much increased) [16] resulted in quantitative recovery of phosphine oxide.

Thus the reactivity of the triheteroarylphosphine oxides to hydrolysis decreases in the order 2-furyl > 2-thienyl > 1-methylpyrrol-2-yl. Our studies of phosphonium salt hydrolysis [5] have shown that the electron-withdrawing ability of the heteroaryl groups decreases in the order 2-furyl > 2-thienyl > 1-methylpyrrol-2-yl, while the stabilities of the carbanions ejected in the rate-determining step are in the order 2-thienyl > 2-furyl > 1-methylpyrrol-2-yl. It appears that the relative reactivities of the above heteroarylphosphine oxides are determined primarily by the electron-withdrawing effects of the substituents, which aid the approach of the nucleophile. The reaction closely resembles the analogous alkaline hydrolysis of phosphonium salts in that reactivity is dependent on both the electron-withdrawing abilities of the substituents and the relative stabilities of the carbanions formed, although the inductive effects of substituents have a predominant effect on the overall rate of the reaction because of the equilibrium between phosphonium and hydroxide ions which precedes the rate-determining step in which a carbanionic group is cleaved from phosphorus.

The heteroarylphosphinic acids (5; X = O or S) were converted into the ethyl esters (1; X = O or S) in high yield with diazoethane [17] in ethanol.

The lack of P–C bond cleavage in the alkaline hydrolysis of tris-(1-methylpyrrol-2-yl)phosphine oxide prompted exploration of other routes to the phosphinic acid (5; X = NMe). The reaction of equimolar quantities of 1-methylpyrrol-2-yl-lithium and phosphoryl chloride in ether (as in the procedure [18] for the preparation of diarylphosphinic acids), followed by hydrolysis and alkaline extraction, gave after acidification an intractable tar.

The ready hydrolysis of diphenylphosphinamides to the corresponding phosphinic acids under mildly acidic conditions had been reported by Haake *et al.*[19] The bis-(1-methylpyrrol-2-yl)phosphinamide (6) was therefore prepared by addition of *NN*-diethylphosphoramidic dichloride to a gently refluxing solution of 1-methylpyrrol-2-yl-lithium in ether. Hydrolytic work-up followed by distillation and recrystallisation gave (6) in



(6)

28% yield. Attempted removal of the diethylamino-group in dilute aqueous hydrochloric acid led to resinous material, reflecting the sensitivity of pyrrole derivatives to protic acids even when bound to the electron-withdrawing phosphoryl group. Although phosphinamidates undergo alkaline hydrolysis only slowly, Haake [19] has reported kinetic studies of the hydrolysis of diphenylphosphinamides, and accordingly we attempted the alkaline hydrolysis of (6). However, prolonged reflux in aqueous alkaline dimethyl sulphoxide resulted in no change.

Thus as was established in phosphonium salt hydrolysis, the 1-methylpyrrol-2-yl derivatives in the phosphine oxide (and phosphinamide) series show a much lower tendency to undergo alkaline hydrolysis than the 2-furyl and 2-thienyl (and phenyl) analogues. These results are fully consistent with our earlier findings on the differences in electronic character amongst the above heteroaryl substituents. Thus the 1-methylpyrrol-2-yl group is much less electron-withdrawing than either 2-furyl or 2-thienyl.

## EXPERIMENTAL

$^1$H N.m.r. spectra were recorded at 60 MHz with a JEOL spectrometer. $^{31}$P N.m.r. data were recorded at 24 MHz with the same instrument, with phosphoric acid (85%) as external standard (positive shifts to high field). M.p.s were determined with a Kofler hot-stage apparatus.

(A) *Preparation of Phosphinate Esters.—Ethyl di-(2-furyl)-phosphinate* (1; X = O). A mixture of tri-(2-furyl)-phosphine oxide [15] (5 g, 0.02 mol) and sodium hydroxide (0.81 g, 0.02 mol) in aqueous dioxan (50% v/v; 60 cm$^3$) was heated under reflux for 72 h; then cooled and extracted with chloroform. Evaporation of the dried extract gave unchanged phosphine oxide (0.4 g, 8%). The aqueous phase

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[17] C. W. Stanley, *J. Agric. Food Chem.*, 1966, **14**, 321.
[18] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 1949, **71**, 369.
[19] T. Koizumi and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8073.

was acidified with concentrated hydrochloric acid to precipitate *di-(2-furyl)phosphinic acid* as a white solid (2.8 g, 71%), m.p. 149° (from n-hexane–ethanol) (Found: C, 48.7; H, 3.5. $C_8H_7O_4P$ requires C, 48.5; H, 3.55%); τ [$(CD_3)_2CO$] 2.0—2.15 (2 H, m), 2.7—2.85 (2 H, m), 3.3—3.45 (2 H, m), and 4.55 (1 H, s, removed by $D_2O$). Diazoethane (0.02 mol) [prepared [17] from *N*-ethyl-*N'*-nitro-*N*-nitrosoguanidine (3.2 g, 0.02 mol) and potassium hydroxide (4.6 g, 0.08 mol)] in ether (50 cm³) was added slowly to a chilled solution of di-(2-furyl)phosphinic acid (2 g, 0.01 mol) in absolute ethanol (30 cm³). The mixture was then set aside for 1 h before removal of the excess of diazoethane by passage of nitrogen through the solution. The mixture was then dried ($Na_2SO_4$) and evaporated to give a yellow oil which solidified. Recrystallisation from hexane gave the *ester* (1.3 g, 57%), m.p. 76° (Found: C, 53.15; H, 5.0. $C_{10}H_{11}O_4P$ requires C, 53.1; H, 4.9%); τ ($CDCl_3$) 2.2—2.35 (2 H, m), 2.65—2.82 (2 H, m), 3.38—3.55 (2 H, m), 5.55—6.08 (2 H, m), and 8.62 (3 H, t); δ $^{31}P$($CHCl_3$) −4.25 p.p.m.

*Ethyl di-(2-thienyl)phosphinate* (1; X = S). A mixture of tri-(2-thienyl)phosphine oxide [15] (4.2 g, 0.014 mol) and sodium hydroxide (0.57 g, 0.014 mol) in aqueous dioxan was heated under reflux for 120 h and then treated as above to give di-(2-thienyl)phosphinic acid (1.2 g, 37%), m.p. 193° (from hexane–ethanol) (lit.,[13] 193°), together with unchanged phosphine oxide (2.5 g, 60%). The phosphinic acid (2.0 g, 0.009 mol) was treated with diazoethane (0.02 mol) as above to give the *ester* (1.4 g, 62%), m.p. 61° (from n-hexane) (Found: C, 46.55; H, 4.2. $C_{10}H_{11}O_2PS$ requires C, 46.5; H, 4.25%); τ ($CDCl_3$) 2.15—2.5 (4 H, m), 2.65—3.0 (2 H, m), 5.58—6.08 (2 H, m), and 8.63 (3 H, t); δ $^{31}P$($CHCl_3$) −16.0 p.p.m.

Ethyl diphenylphosphinate was prepared by the reaction of diphenylphosphinyl chloride with absolute ethanol in benzene in the presence of pyridine; [20] b.p. 170—172° at 1.5 mmHg (lit.,[20] 173—175° at 15 mmHg); τ ($CDCl_3$) 1.8—2.8 (10 H, m), 5.66—6.15 (2 H, m), and 8.67 (3 H, t); δ $^{31}P$($CHCl_3$) −27.2 p.p.m.; >99% pure (by g.l.c.).

(B) *Preparation of* NN-*Diethylbis-(1-methylpyrrol-2-yl)-phosphinamide* (6).—*NN*-Diethylphosphoramidic dichloride (26.0 g, 0.14 mol) in ether (100 cm³) was added over 1 h to a gently refluxing solution of 1-methylpyrrol-2-yllithium (0.44 mol) [from n-butyl-lithium (0.44 mol) and 1-methylpyrrole (36.0 g, 0.44 mol)] in ether (300 cm³). The mixture was heated under reflux for a further 4 h, cooled in ice, and hydrolysed by the addition of ammonium chloride solution (10% w/v; 200 cm³). The organic layer was separated, and the aqueous phase extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated, and the residue distilled to give the *phosphinamide* (11 g, 28%), b.p. 140—160° at 0.35 mmHg, which crystallised; m.p. 94° [from petroleum (b.p. 40—60°)] (Found: C, 60.05; H, 8.0; N, 14.9. $C_{14}H_{22}N_3OP$ requires C, 60.2; H, 7.95; N, 15.05%); τ ($CDCl_3$) 3.0—3.2 (2 H, m), 3.6—3.95 (4 H, m), 6.12 (6 H, s), 6.45—7.12 (4 H, m), and 8.95 (6 H, t).

(C) *Alkaline Hydrolysis of Phosphinate Esters.*—The esters were heated under reflux in sodium hydroxide solution (10% w/v) until homogeneous solutions were formed. These were then cooled, acidified with hydrochloric acid, and extracted with chloroform. After drying ($Na_2SO_4$), the extracts were evaporated to give the appropriate phosphinic acid: di-(2-furyl)phosphinic acid, m.p. 149°, identical with authentic material prepared as above; di-(2-thienyl)phosphinic acid, m.p. 193° (lit.,[13] 193°), identical with an authentic sample; and diphenylphosphinic acid, m.p. 195° (lit.,[13] 195—196°).

*Kinetic Studies.*—The hydrolyses were carried out in aqueous dioxan (50% v/v; 0.1M in KCl) at equal initial concentrations (0.01M) of phosphinate and sodium hydroxide, and were followed by a conventional back-titration procedure in which the decrease in the concentration of sodium hydroxide was determined. The solutions were held in a thermostatted bath controlled to within ±0.1 °C. The data were evaluated by the method of integration using the least-squares programme of an I.M.E. 120 electronic desk calculator, and in all cases a plot of $1/[OH^-]$ *versus* time was linear, confirming second-order behaviour.

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