Studies on Heterocyclic Chemistry. Part XVI.[1] Reaction of 4-*o*-Nitrobenzylidene-Δ^2-pyrazolin-5-ones with Trialkyl Phosphites: Synthesis of Phosphorus-substituted Pyrazolo[3,4-*b*]quinoline Derivatives

By **Tarozaemon Nishiwaki,* Genji Fukuhara,** and **Tamiyoshi Takahashi,** Department of Chemistry, Yamaguchi University, Yamaguchi City 753, Japan

The reaction of 4-*o*-nitrobenzylidene-Δ^2-pyrazolin-5-ones with trialkyl phosphites is much more complicated than that of the related 4-*o*-nitrobenzylidene-Δ^2-oxazolin-5-ones, affording dialkyl 9a-alkoxy-9,9a-dihydropyrazolo-[3,4-*b*]quinolin-4-ylphosphonates as the major products (7—25% yield).

DEOXYGENATION of aromatic nitro-compounds by triethyl phosphite is a versatile method for synthesising nitrogen-containing heterocyclic compounds,[2] and works best when a five-membered ring is produced. The reaction of *o*-nitrobenzylidene-substituted heterocyclic compounds with trialkyl phosphites has received little attention despite its potential usefulness in the synthesis of condensed quinoline derivatives; Kametani *et al.* have reported that the deoxygenation of 4-*o*-nitrobenzylidene-Δ^2-oxazolin-5-ones by triethyl phosphite gives oxazolo-[5,4-*b*]quinoline derivatives as the sole type of product.[3] We have found that the deoxygenation of 4-*o*-nitrobenzylidene-Δ^2-pyrazolin-5-ones by trialkyl phosphites is much more complicated than that of the related oxazolinones, and affords at least four types of product, three of which have a phosphorus-containing substituent.

Heating a mixture of 3-methyl-4-*o*-nitrobenzylidene-1-phenyl-Δ^2-pyrazolin-5-one (1; Ar = Ph, R^1 = Me) and an excess of triethyl phosphite under reflux, and column chromatography of the reaction mixture, resulted in the separation of three components. The major compound, a yellow crystalline material, $C_{23}H_{28}N_3O_4P$, has NH and $PO(OEt)_2$ groups as revealed from its i.r. spectrum. Its n.m.r. spectrum consists of signals for three ethoxy-groups, one methyl, one NH group, and nine aromatic protons (see Table 1) and reveals the absence of the α-hydrogen atom on the benzylidene group in the starting material. The absence of the carbonyl group and the presence of an additional ethoxy-group in this product implies that the latter has replaced the former. The high resolution mass spectrum displays, besides the molecular ion at *m/e* 441·184 and an abundant ion at *m/e* 304·141 $[M - PO(OEt)_2]^+$, an $(M - EtOH)^{+\cdot}$ ion at *m/e* 395·137, suggesting that the ethoxy-group is near to the NH

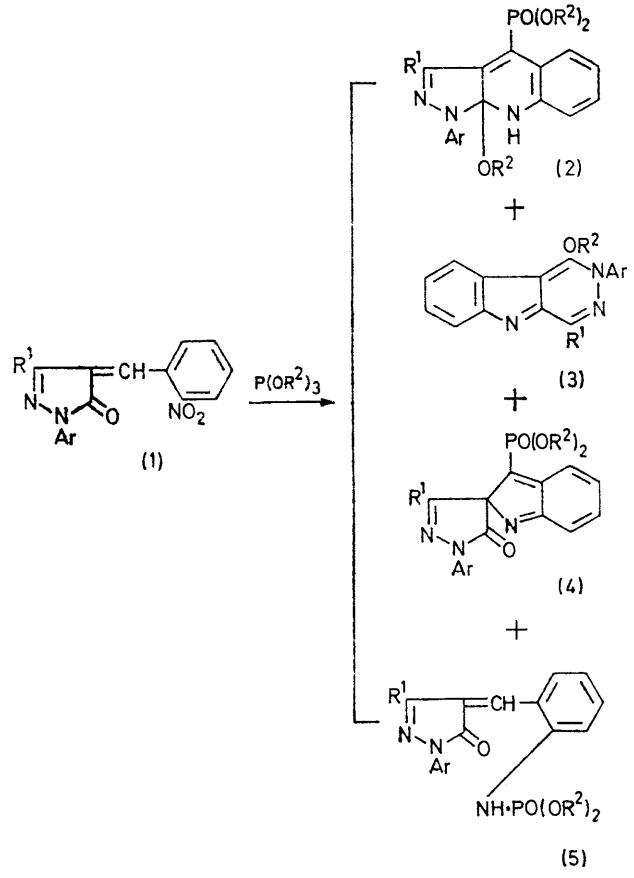
[1] Part XV, T. Nishiwaki and F. Fujiyama, *J.C.S. Perkin I*, 1973, 817.

[2] J. I. G. Cadogan, (*a*) *Quart. Rev.*, 1968, **22**, 222; (*b*) *Synthesis*, 1969, 11; (*c*) *Accounts Chem. Res.*, 1972, **5**, 303.

[3] T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Chem. Soc.* (*C*), 1969, 385.

group. These data indicate that this compound is diethyl 9a-ethoxy-9,9a-dihydropyrazolo[3,4-*b*]quinolin-4-ylphosphonate (2; Ar = Ph, R^1 = Me, R^2 = Et).

The appearance of the NH signal as a doublet and the relatively large J_{PH} value made us suspect that the product under consideration might have the phosphoramidate structure [*cf.* diethyl *N*-(2',4',6'-trimethylbiphenyl-2-yl)phosphoramidate,[4a] $J_{P,NH}$ 9 Hz]. This would be possible only if the pyrazoline ring had lost its identity. However, the CMe signal of the product appears in a normal region (τ 7·7) (*cf.* τ 7·73 for 3,5-dimethylpyrazole), whereas the τ value of the NH proton is too low for *ortho*-substituted phenylphosphoramidates (*cf.* ref. 4), even though it must be to some extent concentration-dependent. For these reasons we rule out any phosphoramidate structure in favour of structure (2).



Two further products were obtained in smaller quantities. One of them was a colourless crystalline material, $C_{19}H_{17}N_3O$, $\nu_{max.}$ 1615 cm^{-1} (C=N) (in the region reported for the 3*H*-indole C=N absorption [5]). Its n.m.r. spectrum consists of signals for one ethoxy [τ 8·47 (t) and 5·30 (q)], one methyl [τ 7·25 (s)], and one phenyl group [τ 2·42 (s)], and four aromatic protons [τ 2·0—3·0 (m)]. The methyl signal occurs at lower field than that of the pyrazolo[3,4-*b*]quinoline (2; Ar = Ph, R^1 = Me, R^2 = Et), suggesting that this compound does not possess the Δ^2-pyrazoline ring. Its high resolution mass spectrum shows the abundant molecular ion at *m/e* 303·140 and the $(M - C_2H_4)^{+\cdot}$ ion as the base peak. Such a ready loss of ethylene indicates that the ethoxy-group is attached to an unsaturated bond. From these data, this product is inferred to be the 2*H*-pyridazino[4,5-*b*]indole derivative (3; Ar = Ph, R^1 = Me, R^2 = Et).

Another minor crystalline product was obtained in a trace amount. High resolution mass spectrometry established the molecular formula [$C_{21}H_{22}N_3O_4P$ (*m/e* 411·131)]. An intense peak at *m/e* 274·101 ($C_{17}H_{12}N_3O$) showed the presence of a $PO(OEt)_2$ group. The pyrazoline ring is inferred to be intact, since the PhN_2^+ ion (found in the mass spectrum of 3-methyl-1-phenyl-Δ^2-pyrazolin-5-one [6]) is present at *m/e* 105·041 in high abundance and an intense peak at *m/e* 120·042 is regarded as a protonated phenyl isocyanate ion. Abundant ions at *m/e* 223·003 ($C_9H_6NO_4P$) and 183·005 ($C_7H_6NO_3P$) must be produced by the elimination of two molecules of ethylene plus MeC=N–NPh and two molecules of ethylene plus MeC=N–NPh–CO–C, respectively, from the molecular ion. These data, coupled with the presence of a strong i.r. absorption at 1680 cm^{-1} (C=O) and the absence of an NH stretching band, suggest that this product has to have the spiro-structure (4; Ar = Ph, R^1 = Me, R^2 = Et).

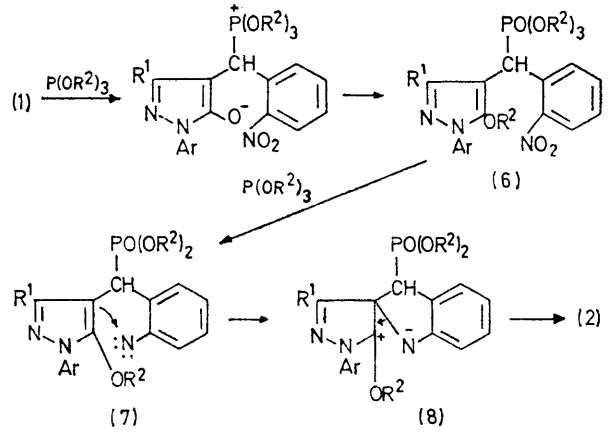
To discover the scope of this reaction, several 1-aryl-3-methyl- and 1,3-diphenyl-4-*o*-nitrobenzylidene-Δ^2-pyrazolin-5-ones (1) were treated with triethyl, trimethyl, and tri-isopropyl phosphites. The reactions of the pyrazolines (1; Ar = Ph, R^1 = Me), (1; Ar = *p*-MeC_6H_4, R^1 = Me), and (1; Ar = *m*-MeC_6H_4, R^1 = Me) with trimethyl and triethyl phosphites afforded the corresponding dialkyl 9a-alkoxy-9,9a-dihydropyrazolo[3,4-*b*]quinolin-4-ylphosphonates (2) as the major products (see Table). Isolation and identification of the minor products from these reactions was difficult on account of their small quantities and/or their reluctance to crystallise. The reaction of the pyrazoline (1; Ar = *p*-MeC_6H_4, R^1 = Me) with triethyl phosphite was the only one which yielded the 2*H*-pyridazino[4,5-*b*]indole derivative (3; Ar = *p*-MeC_6H_4, R^1 = Me, R^2 = Et). The reaction of the pyrazoline (1; Ar = Ph, R^1 = Me) with trimethyl phosphite afforded a fourth type of product in trace amount. This was identified as the phosphoramidate (5; Ar = Ph, R^1 = R^2 = Me). The reaction of the pyrazoline (1; Ar = Ph, R^1 = Me) with tri-isopropyl phosphite and that the pyrazoline (1; Ar = R^1 = Ph) with triethyl phosphite, on the other hand, instead of giving the pyrazolo[3,4-*b*]quinolines (2; Ar = Ph, R^1 = Me, R^2 = Pr^i) and (2; Ar = R^1 = Ph, R^2 = Et), afforded the phosphoramidates (5; Ar = Ph, R^1 = Me, R^2 = Pr^i) and (5; Ar = R^1 = Ph, R^2 = Et), respectively, as the only identified products in moderate yields. These were characterised by elemental analyses and i.r. and n.m.r. spectrometry.

[4] (*a*) J. I. G. Cadogan and M. J. Todd, *J. Chem. Soc.* (*C*), 1969, 2808; (*b*) R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604.

[5] A. R. Katritzky and A. P. Ambler, 'Physical Methods in Heterocyclic Chemistry,' ed. A. R. Katritzky, vol. II, Academic Press, New York, 1963, p. 187.

[6] T. Nishiwaki, *J. Chem. Soc.* (*B*), 1967, 885.

The pyrazolo[3,4-*b*]quinolines (2) are presumably produced *via* the phosphonates (6), formed by nucleophilic attack of trialkyl phosphite on the benzylidene group of the pyrazoline (1) followed by alkyl migration. An analogous reaction has been reported by Arbuzov *et al.*,[7] who obtained dimethyl α-(5-methoxy-3-methyl-1-phenylpyrazol-4-yl)benzylphosphonate by the reaction of 4-benzylidene-3-methyl-1-phenyl-Δ²-pyrazolin-5-one with trimethyl phosphite. A related reaction is reported for 4-benzylidene-Δ²-isoxazolin-5-one derivatives.[8] The reaction leading to compounds (2) from the phosphonates (6) can be explained in terms of nitrene participation.[2] The nitrene in structure (7) could attack C-4 of the pyrazole ring to give a five-membered, spiro-intermediate (8) which then undergoes sigmatropic and protropic shifts to give the observed compound (2). Reactions which proceed through spiro-intermediates are widely known.[2c,9]



Pyrazolo[3,4-*b*]quinoline derivatives have hitherto been prepared by two methods, namely hydrogenation of 4-*o*-nitrobenzylidene-Δ²-pyrazolin-5-ones [10a] and cyclisation of 5-(*o*-carboxyanilino)pyrazoles with polyphosphoric acid.[10b] The present reaction provides a third method, and also represents a further synthesis of heterocyclic phosphonates.[11]

Failure of the pyrazolines (1) to give the pyrazolo-[3,4-*b*]quinoline derivatives free of phosphorus may be due to the fact that the carbonyl group is *trans* to the *o*-nitrophenyl group and/or because nucleophilic attack of the phosphite proceeds much faster than the deoxygenation of the *cis*- or *trans*-pyrazoline (1).* Isolation of the phosphoramidate (5; Ar = R¹ = Ph, R² = Et) as the sole product from the pyrazoline (1; Ar = R¹ = Ph) may be explained on the former grounds. Although the isolation of the phosphoramidate (5; Ar = Ph, R¹ = Me, R² = Pr^i) may also be explained similarly, the bulk of the phosphite group must prevent the formation of the phosphonate (6; Ar = Ph, R¹ = Me, R² = Pr^i); this will be partly responsible for the failure to produce the pyrazolo[3,4-*b*]quinoline (2; Ar = Ph, R¹ = Me, R² = Pr^i).

Dialkyl 9a-alkoxy-9,9a-dihydropyrazolo[3,4-*b*]quinolin-4-ylphosphonates (2)

Ar	R¹	R²	Yield (%)	M.p. (°C)	Form [a]	Solvent	Found (%) / Required (%) C	H	N	P	λmax./nm (log ε)	νmax./cm⁻¹ NH	P=O	τ (CDCl₃)
Ph	Me	Me	18	199—200	Plates	MeOH	60·4 60·1	5·9 5·55	10·2 10·5	7·65 7·8	248(4·28), 276(4·30), 338(3·78), 365(3·64)	3270 [b]	1228	1·46 (d, *J* 7 Hz) (NH), 2·1—3·2 (9H), 5·89 (Me), 6·25 (d, *J* 12 Hz) (2Me), 7·70 (Me)
Ph	Me	Et	12	188—189	Plates	EtOH	62·6 62·6	6·5 6·4	9·55 9·5	6·7 7·0	249(4·36), 276(4·36), 337(3·85), 365(3·71)	3270 [b]	1228	1·48 (d, *J* 7 Hz) (NH), 2·0—3·2 (9H), 5·20—6·07 (6H), 7·73 (Me), 8·46—8·88 (9H)
p-MeC₆H₄	Me	Me	25	188—190	Needles	Me₂CO	61·3 61·0	6·0 5·85	10·1 10·2	7·4 7·5	248(4·34), 277(4·35), 338(3·84), 375(3·74)	3360 [c]	1234	1·48 (d, *J* 7 Hz) (NH), 2·0—2·75 (4H), 3·02 (4H), 5·90 (Me), 6·28 (d, *J* 12 Hz) (2Me), 7·72 (2Me)
p-MeC₆H₄	Me	Et	14	191—193	Plates	EtOH	63·1 63·3	6·5 6·6	9·2 9·2	6·8 6·8	248(4·51), 275(4·47), 338(3·87), 374(3·76)	3260 [b]	1225	1·48 (d, *J* 7 Hz), (NH), 2·0—2·7 (4H), 3·03 (4H), 5·28—6·10 (6H), 7·72 (2Me), 8·45—8·88 (9H)
m-MeC₆H₄	Me	Me	7	207—208	Prisms	AcOEt	60·6 61·0	5·8 5·85	10·3 10·2	6·9 7·5	248(4·41), 276(4·38) 338(3·78), 370(3·72)	3250 [b]	1230	1·53 (d, *J* 8 Hz), (NH), 2·1—3·4 (8H), 5·90 (Me), 6·30 (α, *J* 12 Hz) (2Me), 7·73 (2Me)
m-MeC₆H₄	Me	Et	7	165—167	Needles	AcOEt-LP †	62·8 63·3	6·6 6·6	9·2 9·2	6·4 6·8	248(4·23), 277(4·23), 338(3·70), 370(3·60)	3350 [c]	1230	1·53 (d, *J* 8 Hz) (NH), 2·05—3·40 (8H), 5·28—6·10 (6H), 7·74 2Me), 8·46—8·88 (9H)

[a] Yellow crystals. [b] In Nujol. [c] In $CHCl_3$. [d] In $(CD_3)_2SO$.
† Light petroleum.

EXPERIMENTAL

Light petroleum used had b.p. 30—70°. N.m.r. spectra were run at 60 Hz. High resolution mass spectra were registered by ' element map ' technique.

3-Methyl-4-o-nitrobenzylidene-1-p-tolyl-Δ²-pyrazoline-5-one (1; Ar = *p*-MeC_6H_4, R¹ = Me), m.p. 193—195° (from ethanol) (Found: C, 67·0; H, 4·8; N, 12·8. $C_{18}H_{15}N_3O_3$ requires C, 67·3; H, 4·7; N, 13·1%), and *3-methyl-4-o-nitrobenzylidene-1-m-tolyl-Δ²-pyrazolin-5-one* (1; Ar = *m*-MeC_6H_4, R¹ = Me), m.p. 148—149° (from ethanol) (Found: C, 67·4; H, 4·6; N, 13·1%), were prepared by the method described in ref. 10*a*.

Reaction of 1-Aryl-3-methyl-4-o-nitrobenzylidene-Δ²-pyrazolin-5-ones with Trialkyl Phosphite.—(*a*) A mixture of the pyrazoline (1; Ar = Ph, R¹ = Me) (4·20 g) and triethyl

* The stereochemistry of the pyrazolines (1) is unknown.

[7] B. A. Arbuzov, E. N. Dianova, V. S. Vinogradova, and A. A. Musina, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1969, 1530 (*Chem. Abs.*, 1969, **71**, 113052c).

[8] B. A. Arbuzov, E. N. Dianova, V. S. Vinogradova, and Yu. Yu. Samitov, *Doklady Akad. Nauk S.S.S.R.*, 1967, **173**, 1321.

[9] M. S. Newman, *Accounts Chem. Res.*, 1972, **5**, 354.

[10] (*a*) R. T. Coutts and J. B. Edwards, *Canad. J. Chem.*, 1966, **44**, 2009; (*b*) R. G. Stein, J. H. Biel, and T. Singh, *J. Medicin. Chem.*, 1970, **13**, 153.

[11] J. I. G. Cadogan, D. J. Sears, D. M. Smith, and M. J. Todd, *J. Chem. Soc.* (*C*), 1969, 2813; D. Redmore, *Chem. Rev.*, 1971, **71**, 315.

phosphite (25 ml) was heated at 160° for 16 h in nitrogen. The excess of the phosphite was removed under reduced pressure and the reddish-black residue was chromatographed on alumina with benzene–ether (1 : 1). 1-*Ethoxy*-4-*methyl*-2-*phenyl*-2H-*pyridazino*[4,5-b]*indole* (3; Ar = Ph, R^1 = Me, R^2 = Et) (0·13 g, 3%) was eluted first and crystallised from a small amount of ethanol as needles, m.p. 135—136° (Found: C, 75·5; H, 5·6; N, 13·8; O, 5·4. $C_{19}H_{17}N_3O$ requires C, 75·2; H, 5·65; N, 13·85; O, 5·3%). *Compound* (2; Ar = Ph, R^1 = Me, R^2 = Et) was eluted next (see Table). *Diethyl* 3′-*methyl*-5′-*oxo*-1′-*phenyl*-2H-*indole*-2-*spiro*-4′-Δ^2-*pyrazoline*-3-*phosphonate* (4; Ar = Ph, R^1 = Me, R^2 = Et) was then eluted. Repeated crystallisations from ethanol gave needles (0·007 g), m.p. 163—164° (Found: M^+, 411·131. $C_{21}H_{22}N_3O_4P$ requires M, 411·135).

(*b*) A mixture of the pyrazoline (1; Ar = *p*-MeC_6H_4, R^1 = Me) (2·27 g) and triethyl phosphite (40 ml) was heated at 160° for 10 h in nitrogen. The excess of phosphite was removed under reduced pressure and the residue was chromatographed on alumina. Benzene–ether (1 : 1) eluted yellow crystals which on recrystallisation gave *compound* (2; Ar = *p*-MeC_6H_4, R^1 = Me, R^2 = Et) (see Table). Concentration of the mother liquor gave the *pyridazinoindole* (3; Ar = *p*-MeC_6H_4, R^1 = Me, R^2 = Et) (0·09 g, 4%), which formed needles, m.p. 159—160° (from cyclohexane) (Found: C, 75·4; H, 6·0; N, 13·1%; M^+, 317. $C_{20}H_{19}N_3O$ requires C, 75·7; H, 6·0; N, 13·2%; M, 317), $\nu_{max.}$ ($CHCl_3$) 1615 cm^{-1} (C=N), τ ($CDCl_3$) 8·47 (Me, t), 7·50 (Me, s), 7·27 (Me, s), 5·30 (2H, q), 2·60 (4H, s), and 2·0—3·0 (4H, m).

(*c*) A mixture of the pyrazoline (1; Ar = Ph, R^1 = Me) (1·42 g) and trimethyl phosphite (25 ml) was heated at 120° for 10 h in nitrogen. The excess of phosphite was removed under reduced pressure and the residue was chromatographed with benzene–ether (1 : 1). The eluate was evaporated leaving a light yellow solid. Recrystallisation from methanol gave *compound* (2; Ar = Ph, R^1 = R^2 = Me) (see Table). Evaporation of the filtrate and crystallisation of the residue from acetone gave *dimethyl* N-[o-(3-*methyl*-5-*oxo*-1-*phenyl*-Δ^2-*pyrazolin*-4-*ylidenemethyl*)*phenyl*]-*phosphoramidate* (5; Ar = Ph, R^1 = R^2 = Me), m.p. 224—227°, as needles (0·013 g) (Found: C, 58·9; H, 5·2; N, 10·8. $C_{19}H_{20}N_3O_4P$ requires C, 59·2; H, 5·2; N, 10·9%), $\nu_{max.}$ (Nujol) 3150 (NH) and 1710 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 243 and 295 nm (log ε 4·57 and 3·95).

(*d*) The reactions of the pyrazoline (1; Ar = *p*-MeC_6H_4, R^1 = Me) with trimethyl phosphite, of the pyrazoline (1; Ar = *m*-MeC_6H_4, R^1 = Me) with trimethyl phosphite, and of the pyrazoline (1; Ar = *m*-MeC_6H_4, R^1 = Me) with triethyl phosphite were carried out in a similar way. Properties of the products (2; Ar = *p*-MeC_6H_4, R^1 = R^2 = Me), (2; Ar = *m*-MeC_6H_4, R^1 = Me, R^2 = Et), and (2; Ar = *m*-MeC_6H_4, R^1 = R^2 = Me) are collected in the Table.

(*e*) A mixture of the pyrazoline (1; Ar = R^1 = Ph) (0·21 g) and triethyl phosphite (25 ml) was heated at 150° for 30 h in nitrogen. The excess of phosphite was removed under reduced pressure and the residue was set aside for several days. The *phosphoramidate* (5; Ar = R^1 = Ph, R^2 = Et) slowly crystallised (0·123 g, 48%). Recrystallisation from ethanol gave needles, m.p. 207—208° (Found: C, 65·2; H, 6·0; N, 8·6; P, 6·2. $C_{26}H_{26}N_3O_4P$ requires C, 65·7; H, 5·5; N, 8·8; P, 6·5%), $\nu_{max.}$ (Nujol) 3240 (NH) and 1720 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 257 and 314 nm (log ε 4·54 and 3·98). The filtrate was carefully chromatographed on alumina, but compound (2; Ar = R^1 = Ph, R^2 = Et) was not isolated.

(*f*) A mixture of the pyrazoline (1; Ar = Ph, R^1 = Me) (1·00 g) and tri-isopropyl phosphite (11 ml) was heated at 170° for 13 h in nitrogen. The excess of phosphite was removed under reduced pressure and the residue was chromatographed on alumina with benzene–ether (1 : 1) and ether–ethyl acetate (3 : 1), successively. The *phosphoramidate* (5; Ar = Ph, R^1 = Me, R^2 = Pr^i) (0·45 g, 31%) was obtained by evaporation of the eluates, and two recrystallisations from benzene–light petroleum gave needles, m.p. 178—180° (Found: C, 63·05; H, 64·; N, 9·6; P, 7·0. $C_{23}H_{28}N_3O_4P$ requires C, 62·6; H, 6·4; N, 9·5; P, 6·8%), $\nu_{max.}$ ($CHCl_3$) 3380 (NH) and 1720 cm^{-1} (C=O), $\lambda_{max.}$ (EtOH) 243 and 294 nm (log ε 4·40 and 3·80), τ ($CDCl_3$) 8·7—8·9 (4Me, m), 7·86 (Me, s), 6·0 (NH, d, J 11 Hz), 5·0—5·5 (2H, m), 2·5—3·4 (9H, m), and 2·1 (1H, s).

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