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Studies on Heterocyclic Chemistry. Part X.[1] Synthesis of Aziridin-2-ylphosphonates by the Thermally Induced Isomerization of Isoxazoles in Trialkyl Phosphites. A Related Reaction of 2*H*-Azirine

By **Tarozaemon Nishiwaki** * and (in part) **Toshinori Saito**, Department of Chemistry, Yamaguchi University, Yamaguchi City 753, Japan

The reactions of isoxazoles and of 2*H*-azirines with trialkyl phosphite have been studied. 5-Amino-3-arylisoxazoles and 3-aryl-2*H*-azirine-2-carboxamides afford aziridin-2-ylphosphonates whereas 5-methoxy-3-phenylisoxazole gives an aziridine dimer which has a phosphonyl group at C-2. 5-Amino-3,4-diphenylisoxazole, 2,3-diphenyl-2*H*-azirine-2-carboxamide, and related compounds produce Δ^4-oxazolin-2-ylphosphonates *via* aziridin-2-ylphosphonates. The mechanism of these reactions is accounted for in terms of the nucleophilic attack on the C=N bond of 2*H*-azirine by trialkyl phosphite.

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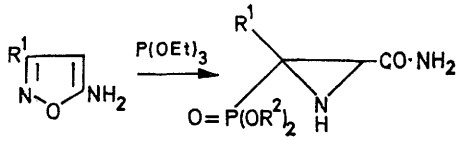
In relation to our study of the thermally induced valence-bond isomerization of isoxazoles to 2*H*-azirines,[2] we were interested in the thermal behaviour of 5-alkylamino-isoxazoles, and attempted to prepare these compounds by the procedure of Amos and Gillis.[3] These workers reported that aniline gave *N*-ethyl- and *NN*-diethyl-anilines when treated with boiling triethyl phosphite. Unexpectedly, the product from 5-amino-3-phenyl-isoxazole (1; R^1 = Ph) and this phosphite contained phosphorus. The reaction proceeded slowly, as shown by the u.v. spectrum, and yielded a crystalline material, $C_{13}H_{19}N_2O_4P$, in 11% yield, together with a large amount of unidentifiable tar. The i.r. spectrum ($CHCl_3$) of the solid indicated that it was a primary amide (1685, 3500, and 3380 cm^{-1}) and had a secondary amino-group (3290 cm^{-1}), presumed to be that of an aziridine,[4] and a diethyl phosphonate group {1243 (P=O), 1162 [Et–O–(P)], and 1020 [P–O–(C)] cm^{-1}}.[5] The u.v. spectrum showed the presence of an isolated phenyl group, and the n.m.r. spectrum had signals at τ 2·79 (5H, s, Ph), 8·90 (6H, m, 2 × Me), 6·10 (4H, m, 2 × CH_2), and 3·20 and 3·70 ($CO{\cdot}NH_2$). There were three peaks (2H) at higher field, one (τ 7·00) of which was removed by D_2O. The other two (centre at τ 6·99) corresponded to one proton and could be ascribed to a P–C–CH group ($J_{P,OH}$ 11 Hz). A proton on an aziridine nitrogen atom tends to have a very high τ value;[6] hence we formulate the product as diethyl 3-carbamoyl-2-phenylaziridin-2-ylphosphonate (2; R^1 = Ph, R^2 = Et), of unspecified stereochemistry.†

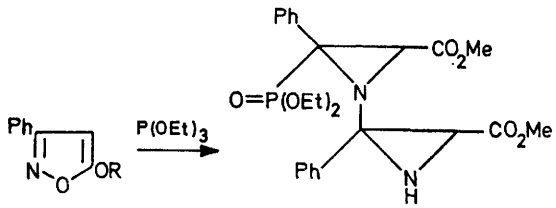
The reactions of the analogous *p*-tolyl- (1; R^1 = *p*-MeC_6H_4) and *p*-chlorophenyl- (1; R^1 = *p*-ClC_6H_4) isoxazoles with triethyl phosphite proceeded more rapidly and gave crystalline aziridin-2-ylphosphonates (2; R^1 = *p*-MeC_6H_4 or *p*-ClC_6H_4, R^2 = Et), again in low yield; no rigorously characterized material was obtained from the corresponding reaction of the 2-furyl analogue (1; R^1 = 2-furyl).

5-Alkoxyisoxazoles behaved differently. Although the reaction of 5-methoxy-3-phenylisoxazole (3; R = Me) with neat boiling triethyl phosphite yielded only tar, a crystalline material, $C_{24}H_{29}N_2O_7P$, was isolated in 19%



(1) (2)

yield when the reactants were heated in the presence of ethanol. This compound must also have an aziridine structure possessing a diethyl phosphonate group and at least one methoxycarbonyl group (i.r. and u.v. spectra). Its n.m.r. spectrum showed signals at τ 6·37 and 6·63 (2 × OMe) and 2·1—3·4 (10H, m, 2 × Ph). We therefore assign structure (4) to this product and eliminate those in which one of the aziridine rings is replaced by a Δ^4-isoxazoline or a Δ^4-oxazoline ring (the ring expansion of aziridine is discussed later). The $O{\cdot}CH_2{\cdot}CH_3$ signals appeared as two triplets (τ 8·80 and 8·98), probably because of hindered rotation[7] around the P–C bond, which could lead to preferred conformations of the aziridine ring with respect to the phosphorus atom. The reaction of 5-ethoxy-3-phenylisoxazole (3; R = Et) with triethyl phosphite yielded only tar, even in the presence of ethanol. The i.r. spectra of the tars obtained from the isoxazoles (3; R = Me) and (3; R = Et)



(3) (4)

† All phosphates obtained were homogeneous (t.l.c.) and no other crystalline materials were isolated. This suggests that the phosphite approaches the least hindered side of the 2*H*-azirine, but the available evidence does not unequivocally determine the stereochemistry of the product.

[1] Part IX, T. Nishiwaki and T. Saito, *J. Chem. Soc.* (*C*), 1971, 2648.

[2] (*a*) T. Nishiwaki, *Tetrahedron Letters*, 1969, 2049; (*b*) T. Nishiwaki, T. Kitamura, and A. Nakano, *Tetrahedron*, 1970, **26**, 453; (*c*) T. Nishiwaki, A. Nakano, and H. Matsuoka, *J. Chem. Soc.* (*C*), 1970, 1825; (*d*) T. Nishiwaki, *Chem. Comm.*, 1970, 945.

[3] D. Amos and R. G. Gillis, *Austral. J. Chem.*, 1969, **22**, 1555.

[4] R. W. Mitchell, J. C. Burr, jun., and J. A. Merritt, *Spectrochim. Acta*, 1967, *A***23**, 195.

[5] L. C. Thomas and R. A. Chittenden, *Spectrochim. Acta*, 1964, **20**, 467, 489.

[6] O. C. Dermer and G. E. Ham, 'Ethyleneimine and Other Related Aziridines,' Academic Press, New York, 1969, p. 99.

[7] T. H. Siddall, tert., and C. A. Prohaska, *J. Amer. Chem. Soc.*, 1962, **84**, 3467.

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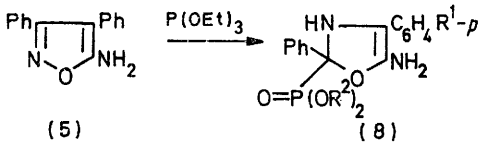
indicated the presence of ester(s) and diethyl phosphonate groups, but lacked an NH band.

When 5-amino-3,4-diphenylisoxazole (5) was heated with triethyl phosphite, a crystalline material, $C_{19}H_{23}N_2O_4P$, was isolated in 14% yield. This was not the expected aziridine (6), but one of its valence-bond isomers incorporating an oxygen atom in the ring, since its i.r. spectrum lacked an amide carbonyl absorption. The i.r. spectrum showed the presence of NH_2, NH, and $P(O)(OEt)_2$ groups and the u.v. spectrum indicated that one of the phenyl groups was conjugated. The n.m.r. spectrum had a sharp doublet centred at τ −1·90 (1H, J 12 Hz), removed by D_2O, and ascribed to NH. Splitting into a doublet must be due to the proximity of a phosphorus atom. Other signals were at τ 9·00 (t, 2 × Me), 6·32 (quintet, 2 × CH_2), 4·42br (NH_2), and 3·05 (2 × Ph). The presence of the quintet is ascribed to the similarity of $J_{CH_2,Me}$ and J_{P,CH_2}.[8] The only structures which satisfy these spectral data are (7) and (8; R^1 = H, R^2 = Et). The latter is preferred on the basis of the thermal stability of the product; Δ^4-isoxazolines are known to be unstable to heat and readily isomerize into Δ^4-oxazolines [9a] or enol betaines,[9b] or decompose into pyrroles,[10] but the product from (5) was recovered almost quantitatively after prolonged heating in heptane. Further confirmation by chemical methods was impossible, since this and related compounds derived from the 2,3-diaryl-2*H*-azirine-2-carboxamides described later were available in poor yield only.



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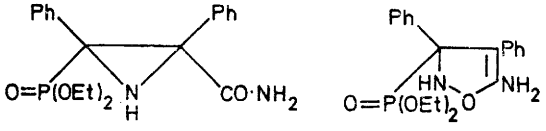
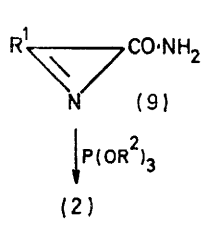


(6) (7)

It was expected that the 2*H*-azirines isomeric with the foregoing isoxazoles would behave similarly. The reactions of 3-phenyl-2*H*-azirine-2-carboxamide (9; R^1 = Ph) and the 3-*p*-tolyl analogue (9; R^1 = *p*-MeC_6H_4) with triethyl phosphite produced the aziridin-2-ylphosphonates (2; R^1 = Ph or *p*-MeC_6H_4, R^2 = Et), again in low yield, together with a large amount of tar. The yield could be raised to 50—60% by carrying out the reaction in ethanol. The 2*H*-azirine-2-carboxamides (9; R^1 = Ph, *p*-MeC_6H_4, or *p*-ClC_6H_4) reacted smoothly with boiling trimethyl phosphite, producing the corresponding dimethyl aziridin-2-ylphosphonates in fair yield even in the absence of a hydrogen donor, although the reaction of the corresponding isoxazoles with this phosphite failed. We had hoped to obtain the aziridin-2-ylphosphonate (6) by the reaction of 2,3-diphenyl-2*H*-azirine-2-carboxamide (10; R^1 = H) with triethyl phosphite, but the sole product characterized was the oxazoline (8; R^1 = H, R^2 = Et). Similarly, this azirine and its derivative (10; R^1 = Cl) produced the Δ^4-oxazolin-2-ylphosphonates (8; R^1 = H, R^2 = Me), (8; R^1 = Cl, R^2 = Et), and (8; R^1 = Cl, R^2 = Me) when treated with boiling trialkyl phosphite.



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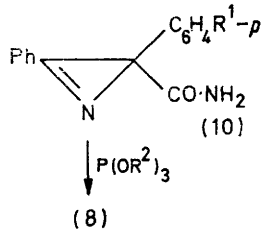
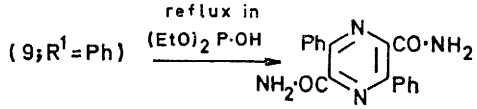


(10) (8)

We suggest that a 2*H*-azirine is an intermediate in the transformation of isoxazoles into aziridin-2-ylphosphonates. The b.p. of triethyl phosphite is sufficiently high to bring about the isomerization [2c] of isoxazoles into 2*H*-azirines. The successful conversion of some of the 2*H*-azirine-2-carboxamides into aziridin-2-ylphosphonates strongly supports this idea, though in no case was the intermediate azirine isolated (*cf.* the reaction of isoxazoles with arylamines [2d]). Failure to isolate the aziridin-2-ylphosphonate from the reaction of the 5-aminoisoxazole (1) with the much lower boiling trimethyl phosphite lends further support to this suggestion.

Fields [11a] and Tyka [11b] have reported the addition of diethyl phosphite to Schiff's bases. The formula of our product (2; R^1 = Ph, R^2 = Et) is equivalent to a 1 : 1 adduct of the azirine (9; R^1 = Ph) and diethyl phosphite, and the latter is often present as an impurity in triethyl phosphite. In fact, the trialkyl phosphite employed by us contained less than 2% of dialkyl phosphite and was used without further purification. However, this possibility can be eliminated; the reaction of the azirine (9; R^1 = Ph) in boiling diethyl phosphite gave 3,6-diphenylpyrazine-2,5-dicarboxamide (11) as the only isolable product, and the azirine (10; R^1 = H) did



(11)

not react with diethyl phosphite even in the presence of a small amount of sodium at 100°.

[8] J. D. Baldeschwieler and E. W. Randall, *Chem. Rev.*, 1963, **63**, 81.

[9] (*a*) J. E. Baldwin, R. G. Pudussery, A. K. Qureshi, and B. Sklartz, *J. Amer. Chem. Soc.*, 1968, **90**, 5325; (*b*) H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.*, 1969, **102**, 904.

[10] I. Adachi, K. Harada, and H. Kano, *Tetrahedron Letters*, 1969, 4875.

[11] (*a*) E. K. Fields, *J. Amer. Chem. Soc.*, 1952, **74**, 1528; (*b*) R. Tyka, *Tetrahedron Letters*, 1970, 677.

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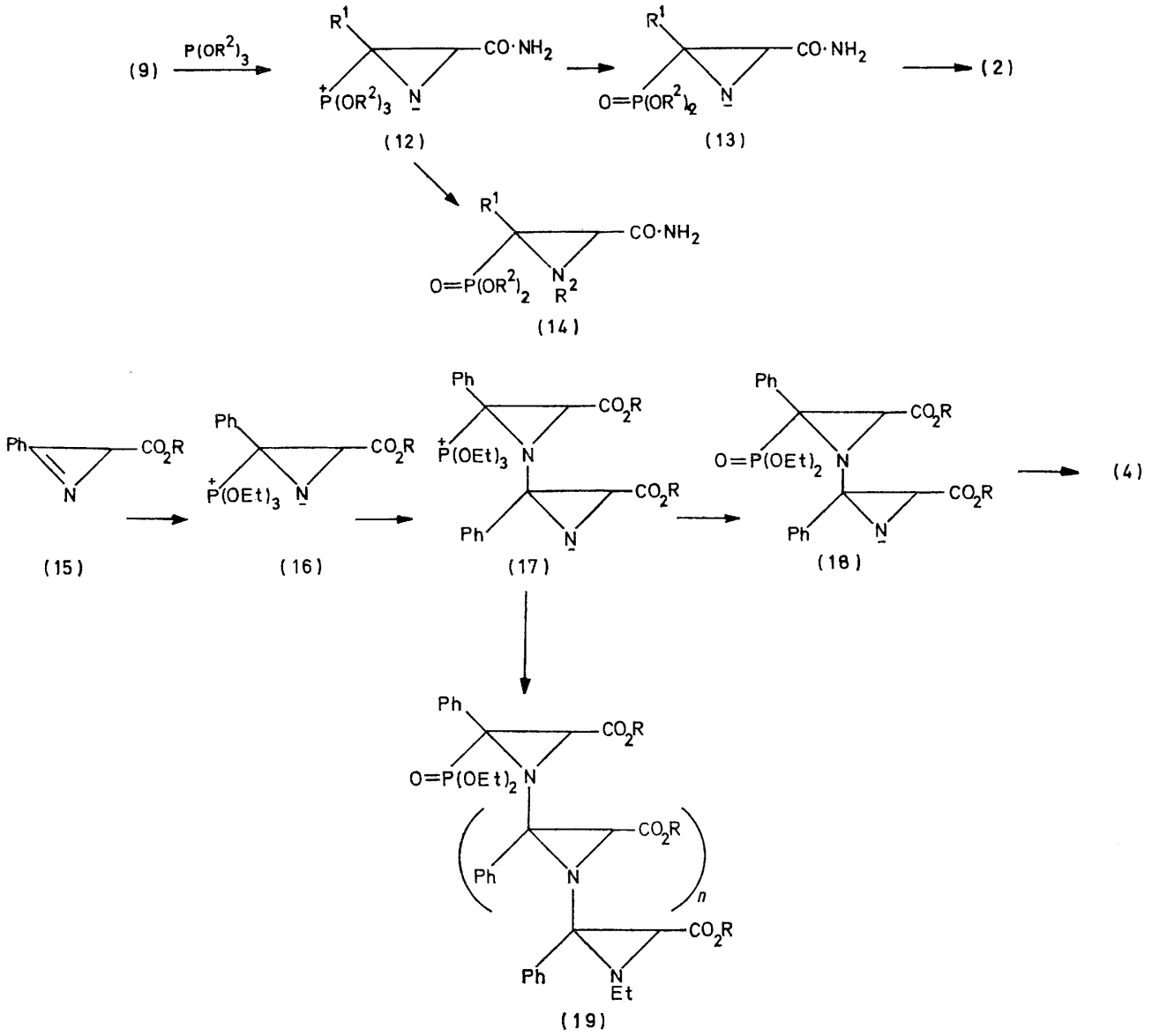
We postulate nucleophilic attack on the C=N bond of the 2*H*-azirine [1,12] by trialkyl phosphite as an initial reaction step. The resulting betaine (12) could then undergo valence-shell expansion of phosphorus to give a phosphonate anion (13), which can afford compound (2) by proton abstraction from an amino-group or from an added proton donor. By analogy with the reactions of carbonyl compounds with trialkyl phosphite,[13] the betaine (12) might be expected to give an *N*-alkylaziridine (14) by intramolecular alkyl migration, but the aziridine (14) was not detected. The observed appreciable increase of yields of the aziridin-2-ylphosphonates (2; R^1 = Ph or *p*-MeC_6H_4, R^2 = Et) in the reactions of the 2*H*-azirines (9; R^1 = Ph or *p*-MeC_6H_4) in the presence of ethanol indicates that the amino-group is a less efficient proton source for the stabilization of the anion (13).

The reaction of the isoxazole (3; R = Me) presumably proceeds *via* the betaine (16), produced from the 2*H*-azirine ester (15), which then makes a nucleophilic attack on the C=N bond of (15) and produces a new betaine (17); this would then yield compound (4) after proton abstraction by the anion (18). However, if a proton donor is absent, polymerization must proceed and afford structures of the type (19). An alkyl leaving group may enter the terminus of the developing polymer; the absence of



[12] (*a*) R. M. Carlson and Sin Yen Lee, *Tetrahedron Letters*, 1969, 4001; (*b*) A. Hassner, J. O. Currie, jun., A. S. Steinfeld, and R. F. Atkinson, *Angew. Chem. Internat. Edn.*, 1970, **9**, 731; (*c*) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, 1968, **33**, 3418; (*d*) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, 1968, **90**, 2869.

[13] (*a*) R. F. Hudson, 'Structure and Mechanism in Organophosphorus Chemistry,' Academic Press, New York, 1965, p. 164; (*b*) B. A. Arbuzow, *Pure Appl. Chem.*, 1964, **9**, 307.

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an NH band in the i.r. spectra of the tars obtained from the isoxazoles (3; R = Me) (in the absence of ethanol) or (3; R = Et) supports this postulate. We cannot explain the different behaviour of the isoxazoles (3; R = Me) and (3; R = Et) at present. But, as 2*H*-azirines readily undergo an anion-initiated polymerization,[12d,14] and an alkyl 2*H*-azirine-2-carboxylate [2b] has a greater tendency to polymerize on heating than 2*H*-azirine-2-carboxamide, termination at the dimer stage seems exceptional.

We have tried to isolate the aziridin-2-ylphosphonate from the reaction of 2,3-diphenyl-2*H*-azirine-2-carboxamide (10; R^1 = H) with trimethyl phosphite by lowering the reaction temperature, but the substrate did not dissolve in this phosphite at room temperature, and it was recovered quantitatively after reaction in refluxing methylene chloride. But the reactions already described suggest the intermediacy of the aziridine (20) in the formation of the Δ^4-oxazolin-2-ylphosphonate (8). Some thermal equilibration is known to occur between aziridines and the azomethine ylides generated by C–C bond cleavage,[15] and thermal reactions of aziridines have been explained in therms of such ylides.[9a,16,17] Padwa and Eisenhardt [17] suggested the intermediacy of ylides in the formation of oxazole and Δ^4-oxazoline derivatives on heating 2-acylaziridines. As the dipolar species (21) generated from the intermediate (20) is resonance-stabilized, ir could cyclize into the Δ^4-oxazolin-2-ylphosphonate (8). The tendency of an aryl group to conjugate will assist this cyclization [the aziridine (2; R^1 = Ph, R^2 = Me) did not undergo any change on heating in dioxan].

Kotera *et al.*[18] have recently reported the formation of aziridines from Δ^2-isoxazolines, but not from isoxazoles, by reduction with lithium aluminium hydride and Baldwin *et al.*[9a] have carried out the thermally induced isomerization of Δ^4-isoxazolines to give aziridines. Our results show that isoxazoles, too, are directly transformed into aziridines having an unique structure. These new aziridin-2-ylphosphonates are of potential pharmacological interest, since aziridin-1-ylphosphonates show insecticidal activity.[19]

EXPERIMENTAL

Molecular weights were determined by the Rast method. N.m.r. spectra were run at 60 Hz for solutions in $(CD_3)_2SO$. Analyses were performed at the Department of Pharmacy, Kyoto University. Trialkyl phosphites were commercial products and their purity was checked by g.l.c. T.l.c. was performed on silica gel using methanol as eluant. Light petroleum had b.p. 30—70°.

Diethyl 3-Carbamoyl-2-phenylaziridin-2-ylphosphonate (2; R^1 = Ph, R^2 = Et).—(*a*) The isoxazole (1; R^1 = Ph) (1·00 g) and triethyl phosphite (15 ml) were heated under reflux for 5 h. Concentration of the yellow solution *in vacuo* and addition of ether to the residual oil gave the *aziridine* (0·21 g, 11%), which crystallized from benzene–hexane as needles, m.p. 183—184°, $\lambda_{max.}$ (EtOH) 259 nm (log ε 2·48) (Found: C, 52·6; H, 6·7; N, 9·6; P, 9·9%; *M*, 300. $C_{13}H_{19}N_2O_4P$ requires C, 52·3; H, 6·4; N, 9·4; P, 10·4%; *M*, 298). When the reaction was carried out by heating the isoxazole (0·30 g) in the phosphite (5 ml) and ethanol (0·5 ml) for 3·5 h, the yield of aziridine was 26%.

(*b*) 3-Phenyl-2*H*-azirine-2-carboxamide (9; R^1 = Ph) (0·66 g) and triethyl phosphite (10 ml) were heated for 90 min, the u.v. absorption of the azirine beginning to disappear after about 20 min. Work-up as before gave the aziridine in 13% yield. When the reaction was carried out by heating the azirine (0·27 g) and the phosphite (5 ml) in the presence of ethanol (0·5 ml) for 1 h, the yield was 60%.

Dimethyl 3-Carbamoyl-2-phenylaziridin-2-ylphosphonate (2; R^1 = Ph, R^2 = Me).—This compound was prepared in 57% yield by heating the azirine (9; R^1 = Ph) (0·67 g) and trimethyl phosphite (10 ml) for 1 h. Recrystallization from benzene–hexane gave *needles*, m.p. 155—156° (Found: C, 49·2; H, 5·6; N, 10·3%; *M*, 269. $C_{11}H_{15}N_2O_4P$ requires C, 48·9; H, 5·6; N, 10·4%; *M*, 270), $\lambda_{max.}$ (EtOH) 259 nm (log ε 2·40), $\nu_{max.}$ ($CHCl_3$) 3500, 3380 (NH_2), 3290 (NH), 1684 (C=O), 1250 (P=O), 1184 [Me–O–(P)], and 1035 [P–O–(C)] cm^{-1}. When the isoxazole (1; R^1 = Ph) (0·60 g) and trimethyl phosphite (8 ml) were heated for 10 h, the aziridine was not obtained.

Diethyl 3-Carbamoyl-2-p-tolylaziridin-2-ylphosphonate (2; R^1 = *p*-MeC_6H_4, R^2 = Et).—(*a*) The isoxazole (1; R^1 = *p*-MeC_6H_4) (0·62 g) and triethyl phosphite (7 ml) were heated for 1 h. On cooling, the *aziridine* (0·183 g, 16%) precipitated and crystallized from benzene as needles, m.p. 177—178° (Found: C, 56·1; H, 6·8; N, 8·7; P, 9·2. $C_{14}H_{21}N_2O_4P,0{\cdot}33C_6H_6$ requires C, 56·8; H, 6·85; N, 8·3; P, 9·2%), $\lambda_{max.}$ (EtOH) 261 nm (log ε 2·42), $\nu_{max.}$ ($CHCl_3$) 3500, 3380 (NH_2), 3280 (NH), 1684 (C=O), 1240 (P=O), 1164 [Et–O–(P)], and 1020 [P–O–(C)] cm^{-1}, τ 2·82 (2H, s), 3·04 (4H, s), 3·35 (1H, exchangeable), 3·90 (1H, exchange-

[14] C. S. Cleaver and C. G. Krespan, *J. Amer. Chem. Soc.*, 1965, **87**, 3716.
[15] R. Huisgen, W. Sheer, and H. Hubert, *J. Amer. Chem. Soc.*, 1967, **89**, 1753.
[16] G. Dallas, J. W. Lown, and J. P. Moser, *J. Chem. Soc.* (*C*), 1970, 2383, and references cited therein.
[17] A. Padwa and W. Eisenhardt, *Chem. Comm.*, 1968, 380.
[18] K. Kotera, Y. Takano, A. Matsuura, and K. Kitahonoki, *Tetrahedron*, 1970, **26**, 539.
[19] A. Hassner and J. E. Galle, *J. Amer. Chem. Soc.*, 1970, **92**, 3733; ref. 6, pp. 172, 407.

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able), 4·5—5·8 (4H, m), 7·10 (1H, d, $J_{P,OH}$ 12 Hz), 7·09 (1H, exchangeable), 7·83 (3H, s), and 8·65—9·1 (6H, m). Recrystallization from heptane gave the unsolvated *compound* (Found: C, 54·0; H, 7·0; N, 9·2. $C_{14}H_{21}N_2O_4P$ requires C, 53·8; H, 6·8; N, 9·0%).

(*b*) The azirine (9; R^1 = *p*-MeC_6H_4) (0·47 g), triethyl phosphite (10 ml), and ethanol (1 ml), heated under reflux for 1 h gave the aziridine (0·39 g, 45%).

Dimethyl 3-*Carbamoyl*-2-p-*tolylaziridin*-2-*ylphosphonate* (2; R^1 = *p*-MeC_6H_4, R^2 = Me).—The azirine (9; R^1 = *p*-MeC_6H_4) (0·38 g) and trimethyl phosphite (7 ml), heated for 1·5 h, gave the *aziridine* (0·31 g, 50%) as needles, m.p. 159° (from benzene–hexane) (Found: C, 50·8; H, 5·9; N, 10·0. $C_{12}H_{17}N_2O_4P$ requires C, 50·7; H, 6·0; N, 9·9%), $\lambda_{max.}$ 263 nm (log ε 2·43), $\nu_{max.}$ ($CHCl_3$) 3500, 3390 (NH_2), 3290 (NH), 1684 (C=O), 1250 (P=O), 1182 [Me–O–(P)], and 1035 [P–O–(C)] cm^{-1}.

5-*Amino*-3-p-*chlorophenylisoxazole* (1; R^1 = *p*-ClC_6H_4).—To a stirred refluxing mixture of sodium hydride (50% in mineral oil; 4·4 g) and dry tetrahydrofuran (50 ml) a solution of ethyl *p*-chlorobenzoate (14·2 g), acetonitrile (3·2 g), and tetrahydrofuran (10 ml) was added during 10 min, and the mixture was further heated until the evolution of hydrogen ceased (*ca.* 1 h). After cooling, ether (100 ml) was added, and the solid obtained was filtered off and dissolved in water. Acidification yielded a precipitate (11·4 g, 83%) and two recrystallizations from benzene–hexane gave p-*chlorobenzoylacetonitrile* as needles, m.p. 128—130° (Found: C, 60·1; H, 3·6. C_9H_6ClNO requires C, 60·2; H, 3·4%). A solution of this nitrile (0·73 g) in ethanol (20 ml) was mixed with a solution of sodium acetate (2·0 g) and hydroxylamine hydrochloride (1·5 g) in water (20 ml) and the mixture was heated under reflux for 1·5 h. Concentration afforded the *isoxazole* (1; R^1 = *p*-ClC_6H_4) (0·67 g, 85%), as needles, m.p. 165—167° (from water) (Found: C, 55·8; H, 3·9; N, 14·5. $C_9H_7ClN_2O$ requires C, 55·5; H, 3·6; N, 14·4%), $\lambda_{max.}$ (EtOH) 240 (log ε 4·31) and 277 nm (3·48). An extremely low yield was obtained by the procedure of Obrégia.[20]

3-p-*Chlorophenyl*-2H-*azirine*-2-*carboxamide* (9; R^1 = *p*-ClC_6H_4).—The isoxazole (1; R^1 = *p*-ClC_6H_4) (0·585 g) in ether (550 ml) was irradiated with a Pyrex-filtered high-pressure mercury lamp (100 W) for 1·5 h. The solvent was removed and the residue was washed with ether, leaving the *azirine* (0·166 g, 28%). Recrystallization from ethyl acetate–hexane gave needles, m.p. 162—163° (Found: C, 55·5; H, 3·9; N, 14·4. $C_9H_7ClN_2O$ requires C, 55·5; H, 3·6; N, 14·4%), $\lambda_{max.}$ (EtOH) 253 nm (log ε 4·34), $\nu_{max.}$ ($CHCl_3$) 3520, 3400 (NH_2), 1763 (C=N), and 1682 (C=O) cm^{-1}. That no rearrangement took place on the benzene ring during irradiation was shown by an i.r. band of medium intensity at 836 cm^{-1} (Nujol).

Dimethyl 3-*Carbamoyl*-2-p-*chlorophenylaziridin*-2-*ylphosphonate* (2; R^1 = *p*-ClC_6H_4, R^2 = Me).—The azirine (9; R^1 = *p*-ClC_6H_4) (0·20 g) and trimethyl phosphite (6 ml) were heated under reflux for 30 min. Concentration of the solution *in vacuo* gave a tar, which was dissolved in methylene chloride (2 ml) and mixed with light petroleum (10 ml). The *aziridine* (0·18 g, 57%) slowly precipitated and crystallized from tetrahydrofuran–hexane as needles, m.p. 137—138° (Found: C, 43·5; H, 4·7; N, 9·0. $C_{11}H_{14}ClN_2O_4P$ requires C, 43·4; H, 4·6; N, 9·2%), $\lambda_{max.}$ (EtOH) 225 (log ε 4·02) and 266 nm (2·45), $\nu_{max.}$ ($CHCl_3$) 3510, 3890 (NH_2), 3290 (NH), 1685 (C=O), 1252 (P=O), 1183 [Me–O–(P)], and 1036 [P–O–(C)] cm^{-1}.

Diethyl 3-*Carbamoyl*-2-p-*chlorophenylaziridin*-2-*ylphosphonate* (2; R^1 = *p*-ClC_6H_4, R^2 = Et).—The isoxazole (1; R^1 = *p*-ClC_6H_4) (0·78 g) and triethyl phosphite (10 ml) were heated under reflux for 2 h. The mixture was concentrated *in vacuo* and chromatographed on silica gel with ether and ether–methanol (2 : 1) as successive eluants. The latter eluant afforded an oil, which was triturated with ether–hexane. The *aziridine* (0·045 g, 3%) crystallized from ethyl acetate–hexane as needles, m.p. 149—150° (Found: C, 47·0; H, 5·7; N, 8·2; P, 9·4. $C_{13}H_{18}ClN_2O_4P$ requires C, 46·9; H, 5·45; N, 8·4; P, 9·3%), $\lambda_{max.}$ (EtOH) 225 (log ε 4·10) and 265 nm (2·36), $\nu_{max.}$ ($CHCl_3$) 3510, 3390 (NH_2), 3290 (NH), 1687 (C=O), 1245 (P=O), 1165 [Et–O–(P)], and 1020 [P–O–(C)] cm^{-1}.

5-*Amino*-3-(2-*furyl*)*isoxazole* (1; R^1 = 2-furyl).—By the procedure already described, 2-*furoylacetonitrile* was prepared in 42% yield; m.p. 81—82° (from benzene–light petroleum) (Found: C, 62·3; H, 3·95. $C_7H_5NO_2$ requires C, 62·2; H, 3·7%). Condensation of this nitrile with hydroxylamine hydrochloride according to the procedure of Obrégia [20] gave the *isoxazole* in 38% yield, as rods, m.p. 98—99° (from carbon tetrachloride) (Found: C, 56·1; H, 4·2; N, 18·5. $C_7H_6N_2O_2$ requires C, 56·0; H, 4·0; N, 18·7%), $\lambda_{max.}$ (EtOH) 215 (log ε 3·96) and 256 nm (4·20).

Diethyl N-(2-*Phenyl*-3-*methoxycarbonylaziridinyl*)-2-*phenyl*-3-*methoxycarbonylaziridin*-2-*ylphosphonate* (4).—A mixture of the isoxazole (3; R = Me) (0·62 g), triethyl phosphite (8 ml), and ethanol (1 ml) was heated under reflux for 10 h and concentrated *in vacuo*. The residual oil was dissolved in ether (1 ml) and light petroleum was slowly added until a precipitate was obtained (0·33 g, 19%). Recrystallization from cyclohexane gave rods, m.p. 124—125° (Found: C, 59·2; H, 6·2; N, 5·9; P, 6·3. $C_{24}H_{29}N_2O_7P$ requires C, 59·0; H, 6·0; N, 5·7; P, 6·3%), $\lambda_{max.}$ (EtOH) 258 nm (log ε 2·75), $\nu_{max.}$ (Nujol) 3250 (NH), 1743 (C=O), 1237 (P=O), 1210 (C–O–C), 1162 [Et–O–(P)], and 1020 [P–O–(C)] cm^{-1}.

5-*Amino*-4-p-*chlorophenyl*-3-*phenylisoxazole*.— p-*Chlorophenylbenzoylacetonitrile* was prepared as described for phenyl-*p*-toluoylacetonitrile [1] in 24% yield as rods, m.p. 100—101° (from aqueous ethanol) (Found: C, 70·7; H, 4·2. $C_{15}H_{10}ClNO$ requires C, 70·45; H, 3·9%). It was condensed with hydroxylamine hydrochloride as described for 5-amino-3,4-diphenylisoxazole,[1] and 5-*amino*-4-p-*chlorophenyl*-3-*phenylisoxazole* was obtained (60%), m.p. 185—186° (from ethanol) (Found: C, 66·8; H, 3·9; N, 10·4. $C_{15}H_{11}ClN_2O$ requires C, 66·55; H, 4·1; N, 10·35%), $\lambda_{max.}$ 271 nm (log ε 4·14).

2-p-*Chlorophenyl*-3-*phenyl*-2H-*azirine*-2-*carboxamide* (10; R^1 = Cl).—The foregoing isoxazole (1·00 g) was heated under reflux in decalin (50 ml) for 1·5 h. Next day, the precipitate was collected and washed with a small amount of ether, giving the *azirine* (0·71 g, 71%). Two recrystallizations from cyclohexane gave needles, m.p. 163—165° (Found: C, 66·25; H, 3·9; N, 10·2. $C_{15}H_{11}ClN_2O$ requires C, 66·55; H, 4·1; N, 10·35%), $\lambda_{max.}$ (EtOH) 242 nm (log ε 4·48), $\nu_{max.}$ ($CHCl_3$) 3510, 3400 (NH_2), 1750 (C=N), and 1680 (C=O) cm^{-1}.

Diethyl 5-*Amino*-2,4-*diphenyl*-Δ⁴-*oxazolin*-2-*ylphosphonate* (8; R^1 = H, R^2 = Et).—(*a*) The isoxazole (5) (1·00 g) and triethyl phosphite (15 ml) were heated under reflux for 3 h. Concentration *in vacuo* and addition of light petroleum to the residue afforded the compound, which crystallized from

[20] A. Obrégia, *Annalen*, 1891, **266**, 324.

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heptane as *needles*, m.p. 188—189° (0·215 g, 14%) (Found: C, 60·9; H, 6·3; N, 7·5; P, 8·1%; *M*, 371. $C_{19}H_{23}N_2O_4P$ requires C, 60·95; H, 6·2; N, 7·5; P, 8·3%; *M*, 374), $\lambda_{max.}$ (EtOH) 274br nm (log ε 4·13), $\nu_{max.}$ (Nujol) 3460, 3280 (NH_2), 3150 (NH), 1247 (P=O), 1164 [Et–O–(P)], and 1020 [P–O–(C)] cm^{-1}, δ_{NH_2} 1642 (1640 in $CHCl_3$) cm^{-1}. This compound was recovered (97%) after being heated in heptane for 24 h.

(*b*) The azirine (10; R^1 = H) (0·48 g) and triethyl phosphite (10 ml) were heated for 3 h and the Δ^4-oxazoline was obtained in 23% yield.

Dimethyl 5-*Amino*-2,4-*diphenyl*-Δ^4-*oxazolin*-2-*ylphosphonate* (8; R^1 = H, R^2 = Me).—This compound was obtained (23%) by heating the azirine (10; R^1 = H) (0·50 g) and trimethyl phosphite (10 ml) for 5 h, and crystallized from benzene–heptane as *needles*, m.p. 167—168° (decomp.) (Found: C, 58·7; H, 5·5; N, 7·9. $C_{17}H_{19}N_2O_4P$ requires C, 58·95; H, 5·5; N, 8·1%), $\lambda_{max.}$ (EtOH) 274br nm (log ε 4·10), $\nu_{max.}$ (Nujol) 3450, 3280 (NH_2), 3160 (NH), 1260 (P=O), 1188 [Me–O–(P)], and 1020 [P–O–(C)] cm^{-1}, δ_{NH_2} 1642 (1640 in $CHCl_3$) cm^{-1}.

Diethyl 5-*Amino*-4-p-*chlorophenyl*-2-*phenyl*-Δ^4-*oxazolin*-2-*ylphosphonate* (8; R^1 = Cl, R^2 = Et).—This compound was prepared (22%) by heating the azirine (10; R^1 = Cl) (0·43 g) and triethyl phosphite (10 ml) for 1·5 h and crystallized from heptane as *needles*, m.p. 177—178° (Found: C, 55·9; H, 5·3; N, 6·7%; *M*, 413. $C_{19}H_{22}ClN_2O_4P$ requires C, 55·8; H, 5·4; N, 6·85%; *M*, 408·5), $\lambda_{max.}$ (EtOH) 270 nm (log ε 4·32), $\nu_{max.}$ ($CHCl_3$) 3510, 3400 (NH_2), 3160 (NH), 1256 (P=O), 1167 [Et–O–(P)], and 1028 [P–O–(C)] cm^{-1}, δ_{NH_2} 1640 cm^{-1}.

Dimethyl 5-*Amino*-4-p-*chlorophenyl*-2-*phenyl*-Δ^4-*oxazolin*-2-*ylphosphonate* (8; R^1 = Cl, R^2 = Me).—This compound was obtained (11%) by heating the azirine (10; R^1 = Cl) (1·00 g) and trimethyl phosphite (10 ml) for 1·5 h and crystallized from ethyl acetate–hexane as *needles*, m.p. 185° (decomp.) (Found: C, 53·7; H, 4·9; N, 7·6. $C_{17}H_{13}ClN_2O_4P$ requires C, 53·6; H, 4·8; N, 7·4%), $\lambda_{max.}$ (EtOH) 270 nm (log ε 4·18), $\nu_{max.}$ (Nujol) 3460, 3300 (NH_2), 3130 (NH), 1250 (P=O), 1188 [Me–O–(P)], and 1027 [P–O–(C)] cm^{-1}, δ_{NH_2} 1643 cm^{-1}.

Reaction of the Azirine (9; R^1 = Ph) *with Diethyl Phosphite*.—A mixture of the azirine (0·51 g) and diethyl phosphite (10 ml) was heated under reflux for 1 h and concentrated *in vacuo*. Solid (0·078 g, 15%) separated and was recrystallized from dimethylformamide; m.p. >300°. This was identified as the pyrazine (11) by comparison (i.r.) with an authentic sample.[2c]

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