Studies on Heterocyclic Chemistry. Part XIII.[1] Cleavage of 5-Benzylamino-oxazoles, Photoproducts of *N*-Benzyl-2*H*-azirine-2-carboxamides, by Dialkyl Phosphite

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N-Benzyl-2*H*-azirine-2-carboxamides were prepared by the photochemical or thermal isomerisation of 5-benzylaminoisoxazoles. Photochemical reaction of the 2*H*-azirines in dialkyl phosphite afforded benzamido-*N*-benzylacetamides *via* 5-benzylamino-oxazoles.

RECENTLY we have reported the reaction of 2*H*-azirines with trialkyl phosphite to give aziridin-2-ylphosphonates.[2] But the yield of the product was not good in some of the reactions, owing to the formation of a large amount of phosphorus-containing tar presumed to be aziridine polymer. In view of the potential insecticidal activity of organophosphorus compounds possessing aziridine ring(s),[3] it was of interest to develop another synthetic route to aziridin-2-ylphosphonates. Addition of dialkyl phosphite to an imino-group is easy,[4] but the reaction of this phosphite with 2*H*-azirine derivatives did not afford the phosphonates. We then briefly examined the possibility of the photochemical addition of dialkyl phosphite to 3-aryl-*N*-benzyl-2*H*-azirine-2-carboxamides. Although the original objective of this work was not achieved, study of the chemistry of 5-benzylamino-oxazoles, photoproducts of *N*-benzyl-2*H*-azirine-2-carboxamides, was of interest.

3-Aryl-5-benzylaminoisoxazoles (2), the required intermediates, were obtained by the reduction of 5-benzylideneaminoisoxazoles (1) with sodium borohydride [5] or sodium bis-(2-methoxyethoxy)aluminium hydride. Both reduction methods afforded the crude amine in comparable yield, but the former procedure is preferable by virtue of simplicity of work-up and the purity of the amine. Nevertheless this reaction shows the wide applicability [6] of the latter reducing agent. New 3-aryl-5-benzylaminoisoxazoles (2) are shown in Table 1.

TABLE 1

5-Benzylamino-3-arylisoxazoles (2) (method a)

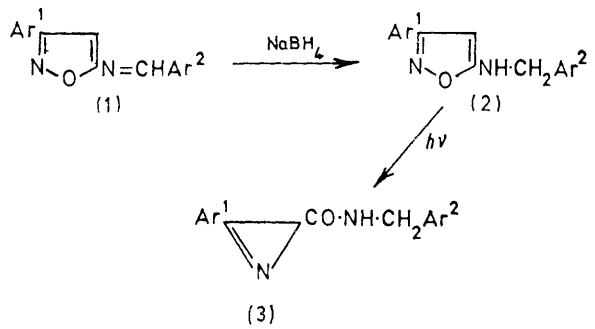
Ar[1]	Ar[2]	Yield (%)	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N	λ_{max}/nm (log ε) [a]
Ph	*p*-MeC_6H_4	67	116	77·4	6·2	10·5	$C_{17}H_{16}N_2O$	77·25	6·1	10·6	234 (4·39) 275 (3·62)
Ph	*p*-ClC_6H_4	86	120—121	67·25	4·5	9·75	$C_{16}H_{13}ClN_2O$	67·5	4·6	9·8	230 (4·65) 277 (4·07)
Ph	2-Furyl	86	73	70·2	5·0	11·7	$C_{14}H_{12}N_2O_2$	70·0	5·0	11·7	232 (4·39) 275 (3·73)
p-MeC_6H_4	Ph	83 [b]	96—97	77·45	6·05	10·6	$C_{17}H_{16}N_2O$	77·25	6·1	10·6	239 (4·51) 273 (4·03)

[a] In EtOH. [b] The crude product after chromatography.

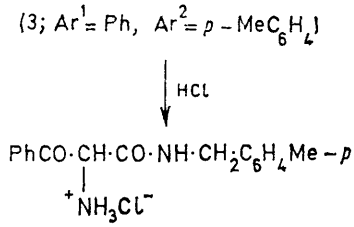
Initially we attempted to prepare the *N*-benzyl-2*H*-azirine-2-carboxamides (3) by the thermally induced isomerisation [7] of the isoxazoles (2), but the yield of the carboxamides (3) was variable (see Experimental section). Photochemical isomerisation [8] of the isoxazoles (2) with radiation with λ >300 nm, however, yielded the 2*H*-azirines (3) in 50—70% yield, except for

[1] Part XII, T. Nishiwaki and K. Kondo, *J.C.S. Perkin I*, 1972, 90.
[2] T. Nishiwaki and T. Saito, *J. Chem. Soc.* (*C*), 1971, 3021.
[3] O. C. Dermer and G. E. Ham, 'Ethyleneimine and Other Related Aziridines,' Academic Press, New York, 1969, p. 407.
[4] D. Redmore, *Chem. Rev.*, 1971, **71**, 315.
[5] H. Kano and Y. Makisumi, *J. Pharm. Soc. Japan*, 1956, **76**, 1311.
[6] M. Čapka, V. Chvalovský, K. Kochloefl, and M. Kraus, *Coll. Czech. Chem. Comm.*, 1969, **34**, 118.
[7] T. Nishiwaki and T. Saito, *J. Chem. Soc.* (*C*), 1971, 2648.
[8] T. Nishiwaki, A. Nakano, and H. Matsuoka, *J. Chem. Soc.* (*C*), 1970, 1825.

the furfuryl compound (3; Ar^1 = Ph, Ar^2 = 2-furyl). Proof of the structure of the 2*H*-azirines obtained was

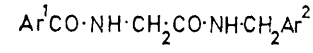


provided by their i.r. spectra and chemical reactions: hydrolysis of the 2*H*-azirine (3; Ar^1 = Ph, Ar^2 = *p*-MeC_6H_4) gave the ammonium chloride (4). The

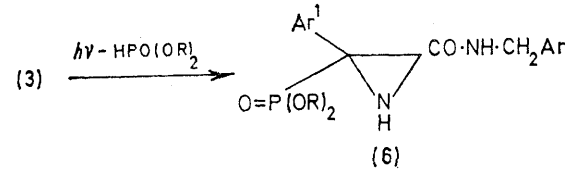


yields, m.p.s, and spectroscopic data of the new 2*H*-azirines obtained are recorded in Table 2. This and our previous observations [7,8] show that photochemical isomerisation of 4-unsubstituted 5-amino-3-arylisoxazoles proceeds more readily than thermal isomerisation, which is more suitable for 5-amino-3,4-diarylisoxazoles.

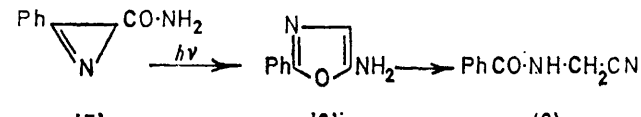
Irradiation of *N*-benzyl-3-phenyl-2*H*-azirine-2-carboxamide (3; Ar^1 = Ar^2 = Ph) in a mixture of ether and diethyl phosphite (12 : 1) at 253·7 nm afforded a crystalline material, $C_{16}H_{16}N_2O_2$, in moderate yield. The reaction of *N*-(*p*-chlorobenzyl)-3-phenyl-2*H*-azirine-2-carboxamide (3; Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4) proceeded similarly, but the yield of the product, $C_{16}H_{15}ClN_2O_2$, was smaller. Elemental analysis of the products indicated that a molecule of water had been incorporated into the starting material. The mass, n.m.r., and i.r. spectral data of the product, $C_{16}H_{16}N_2O_2$, are accounted for by structure (5; Ar^1 = Ar^2 = Ph), and the m.p. is the same as that of benzamido-*N*-benzylacetamide.[9] The structure (5; Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4) was assigned to the product $C_{16}H_{15}ClN_2O_2$ on the basis of



spectral data. The same results were obtained from the reactions in dimethyl phosphite. We could not obtain 2-aryl-3-(*N*-benzylcarbamoyl)aziridin-2-ylphosphonates (6) from these reactions even in a small amount; t.l.c. of the mixture of the 2*H*-azirine (3; Ar^1 = Ar^2 = Ph) and dimethyl phosphite did not show the presence of the aziridine (6; Ar^1 = Ar^2 = Ph, R = Me), which was independently prepared.



Ring expansion of 3-aryl-2-benzoyl-2*H*-azirines to 2-aryl-5-phenyloxazoles by irradiation at 253·7 nm is well known.[10] However, a photochemical product of 3-phenyl-2*H*-azirine-2-carboxamide (7) was benzamidoacetonitrile (9),[8] the formation of which was attributed to the ready isomerisation [11] of 5-amino-2-phenyloxazole (8), an intermediate product. As this type of isomerisation is impossible for 5-benzylamino-oxazole derivatives



(10), they may be isolated from the reaction of the 2*H*-azirines (3) if the acetamides (5) are a secondary

TABLE 2

3-Aryl-*N*-benzyl-2*H*-azirine-2-carboxamides (3)

		Yield		Sol-	Found (%)				Required (%)			$\lambda_{max.}$/nm	$\nu_{max.}$($CHCl_3$)/cm^{-1}		
Ar^1	Ar^2	(%)	M.p. (°C)	vent [a]	C	H	N	Formula	C	H	N	(log ε) [b]	NH	C=N	C=O
Ph	Ph	53	160	A	77·0	5·6	11·3	$C_{16}H_{14}N_2O$	76·8	5·6	11·2	242 (4·18)	3410	1755	1662
Ph	*p*-MeC_6H_4	62	191—193	A	77·5	6·1	10·6	$C_{17}H_{16}N_2O$	77·25	6·1	10·6	241 (4·25)	3420	1758	1665
Ph	*p*-ClC_6H_4	67	168—169	A	67·4	4·6	9·7	$C_{16}H_{13}ClN_2O$	67·5	4·6	9·8	225 (4·21)	3420	1757	1663
												241 (4·13)			
Ph	*p*-$MeOC_6H_4$	71	158—160	B	73·1	6·0	10·0	$C_{17}H_{16}N_2O_2$	72·8	5·75	10·0	229 (4·36)	3410	1758	1665
												240 (sh)			
Ph	2-Furyl	24	140—142	C	70·0	5·0	11·8	$C_{14}H_{12}N_2O_2$	70·0	5·0	11·7	240 (4·12)	3410	1758	1665
p-MeC_6H_4	Ph	50	168—169	A	77·5	6·0	10·6	$C_{17}H_{16}N_2O$	77·25	6·1	10·6	252 (4·35)	3410	1755	1660

[a] A, ethyl acetate–light petroleum; B, benzene; C, ethyl acetate–cyclohexane. [b] In EtOH.

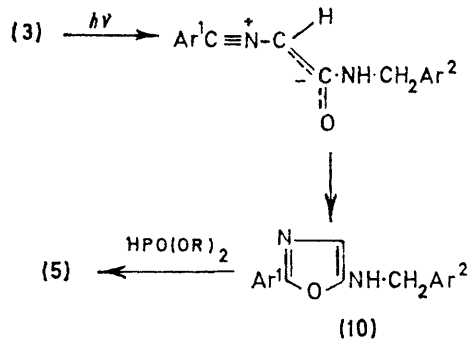
[9] R. Schwyzer, B. Iselin, and N. Feurer, *Helv. Chim. Acta*, 1955, **38**, 69.

[10] B. Singh and E. F. Ullman, *J. Amer. Chem. Soc.*, 1967, **89**, 6911.

[11] G. Killie and J. P. Fleury, *Bull. Soc. chim. France*, 1968, 4631.

product. U.v. spectral examination suggested the formation of the isoxazoles (10); a new absorption at 325 nm appeared within 20 min of irradiation. This absorption did not disappear during irradiation, but it disappeared during the subsequent work-up.

A compound showing $\lambda_{max.}$ 325 nm was indeed isolated in moderate yield from the photochemical reaction of the 2*H*-azirines (3; $Ar^1 = Ar^2 = Ph$) and (3; $Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$), respectively, in ether–methanol (12 : 1) at 253·7 nm. The compound was unstable in solution;



it dissolved in warm common solvents, but the solution produced a yellow colour within a few min. The ether solution of the product derived from the azirine (3; $Ar^1 = Ar^2 = Ph$) was more stable, but the absorption at 325 nm disappeared within a few h and gave a yellow compound of unknown structure. The products, though not analysed, can be regarded as 5-benzylamino-2-aryloxazoles (10; $Ar^1 = Ar^2 = Ph$) and (10; $Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$), respectively, on the basis of spectral data; i.r. spectra of both compounds exhibited an NH absorption at 3200 cm^{-1} but lacked a carbonyl absorption in keeping with the assigned structure (10). Excitation of the singlet $n \longrightarrow \pi^*$ level of the ketimine chromophore of the 2*H*-azirine (3) leads to a nitrile ylide, which gives the oxazole (10) on cyclisation. The oxazoles (10; $Ar^1 = Ar^2 = Ph$) and (10; $Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$) gave the corresponding acetamides (5; $Ar^1 = Ar^2 = Ph$) and (5; $Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$) when treated with warm diethyl phosphite. We conclude that the acetamides (5) isolated from the photochemical reaction of the 2*H*-azirines (3) were produced by the ring-opening of 5-benzylamino-2-aryloxazoles (10) at the C–O bond by neutral [12] dialkyl phosphite. This reaction resembles the ring-opening of 5-amino-oxazole derivatives by aqueous acid [13] and it follows that the C–O bond of 5-amino-oxazoles can be easily cleaved by chemical reagents.

EXPERIMENTAL

^1H N.m.r. spectra (100 Hz) were determined in $(CD_3)_2SO$. Mass spectra were obtained at 70 eV. Commercial dialkyl phosphite was distilled and the purity was checked by g.l.c. Light petroleum had b.p. 30—70° unless otherwise stated.

3-Aryl-5-benzylideneaminoisoxazoles (1).—The 5-amino-3-arylisoxazole (0·025 mol) and the appropriate aldehyde (0·025 mol) were heated under reflux in ethanol (20 ml) for 1·5 h. The solvent was evaporated and the residue was crystallised from ethanol or methanol. The following *isoxazoles* were prepared: 5-p-*methylbenzylideneamino*-3-*phenyl*- (1; $Ar^1 = Ph$, $Ar^2 = p\text{-}MeC_6H_4$) (27%), m.p. 141—143° (Found: C, 77·6; H, 5·5; N, 10·5. $C_{17}H_{14}N_2O$ requires C, 77·8; H, 5·4; N, 10·7%), $\lambda_{max.}$ (EtOH) 230 (log ε 4·23) and 324 nm (4·32); 5-p-*chlorobenzylideneamino*-3-*phenyl*- (1; $Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$) (86%), m.p. 191° (Found: C, 67·7; H, 4·0; N, 9·7. $C_{16}H_{11}ClN_2O$ requires C, 68·0; H, 3·9; N, 9·9%), $\lambda_{max.}$ (EtOH) 230 (log ε 4·39) and 318 nm (4·37); 5-(*furfurylideneamino*)-3-*phenyl*- (1; $Ar^1 =$ Ph, $Ar^2 =$ 2-furyl) (64%), m.p. 140—141° (Found: C, 70·6; H, 4·0; N, 11·7. $C_{14}H_{10}N_2O_2$ requires C, 70·6; H, 4·2; N, 11·8%), $\lambda_{max.}$ (EtOH) 229 (log ε 4·19) and 280 nm (4·40).

5-Benzylamino-3-arylisoxazoles (2).—(*a*) A solution of sodium borohydride (0·013 mol) in methanol (20 ml) was added to a stirred solution of the isoxazole (1) (0·01 mol) in methanol (30 ml) and the mixture was heated at 50° for 2 h. The solvent was evaporated and water was added to the residue. The crude product was filtered off and crystallised from light petroleum (b.p. 100—120°) to give the *isoxazoles* (data are in Table 1).

(*b*) The crude *5-benzylideneamino*-3-p-*tolylisoxazole* (1; $Ar^1 = p\text{-}MeC_6H_4$, $Ar^2 = Ph$) (5·0 g) was reduced as described in (*a*) and the product was chromatographed on silica gel. Elution with ether gave an oil, which was stirred in ether–light petroleum (1 : 1) (20 ml). *5-Benzylamino*-3-p-*tolylisoxazole* (2; $Ar^1 = p\text{-}MeC_6H_4$, $Ar^2 = Ph$) (4·14 g), m.p. 75—87°, was twice recrystallised from light petroleum (b.p. 100—120°) (see Table 1).

(*c*) A benzene solution (70%) of sodium bis-(2-methoxyethoxy)aluminium hydride (4·4 g) was dissolved in benzene (20 ml) and added to a stirred and ice-cooled mixture of the compound (1; $Ar^1 = Ar^2 = Ph$) (2·48 g) in the same solvent (30 ml). The resulting solution was stirred for 15 min and treated with dilute hydrochloric acid. The solution was poured into water and the white precipitate was filtered off. The filtrate was evaporated and crystallisation of the residue from light petroleum (b.p. 100—120°) gave the 5-benzylamino-3-phenylisoxazole (2; $Ar^1 = Ar^2 =$ Ph) (1·59 g, 63%), m.p. 82—85°. An additional crystallisation gave the pure material, m.p. 91—92° (lit.,[5] 91—92°).

3-Aryl-N-benzyl-2H-azirine-2-carboxamides (3).—(*a*) A mixture of the isoxazole (2; $Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$) (0·48 g) and decalin (20 ml) was heated under reflux for 1·5 h. *N*-(*p*-Chlorobenzyl)-3-phenyl-2*H*-azirine-2-carboxamide (3; $Ar^1 = Ph$, $Ar^2 = p\text{-}ClC_6H_4$)(0·08 g, 17%) was obtained. The mother liquor was concentrated *in vacuo* and a residue (0·35 g) was crystallised from light petroleum (b.p. 100—120°). This was identified (m.p. and u.v.) as starting material. When the reaction time was prolonged to 4 h, the yield of the *azirine* was 9%. By heating the isoxazole (2; $Ar^1 = Ph$, $Ar^2 = p\text{-}MeC_6H_4$) (0·24 g) in decalin (15 ml) for 2 h, N-(p-*methylbenzyl*)-3-*phenyl*-2H-*azirine-2-carboxamide* (3; $Ar^1 = Ph$, $Ar^2 = p\text{-}MeC_6H_4$) was obtained (58%). But the *azirine* (3; $Ar^1 = Ph$, $Ar^2 = p\text{-}MeO{\cdot}C_6H_4$) was obtained only in 12% yield by the same procedure.

(*b*) 5-*p*-Methylbenzylamino-3-phenylisoxazole (2; $Ar^1 =$ Ph, $Ar^2 = p\text{-}MeC_6H_4$) (0·81 g) was irradiated in ether (550 ml) with a Pyrex-filtered high-pressure mercury lamp (100 H) for 1 h. The solvent was removed and the residue was washed with cold ether to give the *azirine* (3; $Ar^1 =$ Ph,

[12] G. O. Doak and L. D. Freedman, *Chem. Rev.*, 1961, **61**, 31.
[13] A. R. Martin and R. Ketcham, *J. Org. Chem.*, 1966, **31**, 3612.

Ar^2 = *p*-MeC_6H_4). The washings were combined and chromatographed on silica gel. Elution with ether afforded starting material (0·29 g). The other azirines (3) were obtained in a similar way (see Table 2). However, if the irradiation was carried out with a low-pressure mercury lamp (30 W), the yield of the azirine was poor. For example, irradiation of the 5-*benzylamino*-3-*phenylisoxazole* (2; Ar^1 = Ar^2 = Ph) (0·77 g) in ether (300 ml) for 1 h gave N-*benzyl*-3-*phenyl*-2H-*azirine*-2-*carboxamide* (3; Ar^1 = Ar^2 = Ph) (0·094 g, 13%).

Amino(*benzoyl*)-N-(p-*methylbenzyl*)*acetamide Hydrochloride* (4).—A mixture of the azirine (3; Ar^1 = Ph, Ar^2 = *p*-MeC_6H_4) (0·13 g), ethanol (5 ml), and hydrochloric acid (0·2 ml) was heated under reflux for 30 min. Evaporation of the solvent gave the *acetamide*. This was dissolved in hot ethanol containing a small amount of hydrochloric acid and the solution was concentrated. Addition of ether to this solution afforded needles. The *hydrochloride* turned orange at 210—215° and decomposed at 287° (Found: C, 63·8; H, 6·1; N, 8·5. $C_{17}H_{19}ClN_2O_2$ requires C, 64·0; H, 6·0; N, 8·8%), $\nu_{max.}$ (Nujol) 3280 (NH), 1692 (C=O), and 1655 (C=O) cm^{-1}.

Benzamido-N-*benzylacetamide* (5; Ar^1 = Ar^2 = Ph).—*N*-Benzyl-3-phenyl-2*H*-azirine-2-carboxamide (0·58 g) was irradiated in a mixture of ether (300 ml) and diethyl phosphite (25 ml) for 2·5 h with a low-pressure mercury lamp (30 W). The solvent was removed under reduced pressure and the oil was set aside overnight. The acetamide (0·20 g, 32%) crystallised from benzene–light petroleum as needles, m.p. 158—159° (lit.,[9] 157—158°) (Found: C, 71·7; H, 5·9; N, 10·5; O, 11·3. Calc. for $C_{16}H_{16}N_2O_2$: C, 71·6; 6·0; N, 10·4; O, 11·9%), $\nu_{max.}$ (Nujol) 3290 (NH), 1668 (C=O), and 1640 (C=O) cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 3430 (NH) and 3300 (NH) cm^{-1}, τ 6·08 (CH_2) and 5·70 (CH_2), *m/e* 268 (7%) (M^+), 162 (29) ($PhCO{\cdot}NH{\cdot}CH_2{\cdot}C{\equiv}O^+$), 134 (55) ($PhCH_2{\cdot}NH{\cdot}C{\equiv}O^+$), 106 (60) ($PhCH_2{\cdot}NH^+$), 105 (100) ($PhC{\equiv}O^+$), and 91 (43) ($PhCH_2^+$).

Benzamido-N-(p-*chlorobenzyl*)*acetamide* (5; Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4).—This compound, m.p. 162—163° (from benzene–light petroleum), was obtained in 14% yield as described before (Found: C, 63·2; H, 4·9; Cl, 11·6; N, 9·1. $C_{16}H_{15}ClN_2O_2$ requires C, 63·5; H, 5·0; Cl, 11·7; N, 9·3%), $\nu_{max.}$ (Nujol) 3270 (NH), 1662 (C=O), and 1640 (C=O) cm^{-1}, $\nu_{max.}$ ($CHCl_3$) 3430 (NH) and 3310 (NH) cm^{-1}.

5-*Benzylamino*-2-*phenyloxazole* (10; Ar^1 = Ar^2 = Ph).—*N*-Benzyl-3-phenyl-2*H*-azirine-2-carboxamide (3; Ar^1 = Ar^2 = Ph) (0·32 g) was irradiated in a mixture of ether (300 ml) and methanol (25 ml) for 1·5 h with a low-pressure mercury lamp (30 W). The solvent was removed *in vacuo* and the residue was washed with cold ether (1 ml) to give the oxazole crystals (0·16 g, 50%), m.p. 134°, $\nu_{max.}$ (Nujol) 3200 cm^{-1}, $\lambda_{max.}$ (EtOH) 325 nm (log ε 4·33). This oxazole (0·15 g) was dissolved in diethyl phosphite (2 ml) and the resulting reddish violet solution was heated on a steam-bath for 15 min, during which time the colour faded. Concentration of the solution *in vacuo* gave the acetamide (5; Ar^1 = A^2 = Ph) (0·11 g, 69%).

5-p-*Chlorobenzylamino*-2-*phenyloxazole* (10; Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4).—This compound, m.p. 134—135°, was prepared in 24% yield as before, $\nu_{max.}$ (Nujol) 3220 (NH) cm^{-1}, $\lambda_{max.}$ (EtOH) 325 nm (log ε 4·27). Treatment with diethyl phosphite afforded the acetamide (5; Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4) (37%).

Dimethyl 3-(*N-Benzylcarbamoyl*)-2-*phenylaziridin*-2-*ylphosphonate* (6; Ar^1 = Ar^2 = Ph).—The 2*H*-azirine (3; Ar^1 = Ar^2 = Ph) (0·09 g) and trimethyl phosphite (3 ml) were heated under reflux for 2 h and the solution was mixed with light petroleum (20 ml). The *aziridine* (0·055 g, 42%) crystallised from benzene–light petroleum as needles, m.p. 145—146° (Found: C, 60·1; H, 5·9; N, 7·7. $C_{18}H_{21}N_2O_4P$ requires C, 60·0; H, 5·9; N, 7·8%), $\nu_{max.}$ ($CHCl_3$) 3290 (NH), 1670 (C=O), 1250 (P=O), 1183 (MeO–P), and 1038 (P–O) cm^{-1}.

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