A Study of Factors affecting the Rates of Hydrolysis of Some *N*-Aryl-azetidin-2-ones (*N*-Aryl-β-lactams)

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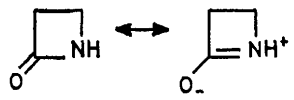
One of the characteristics of the penam system is the ease with which the β-lactam ring undergoes hydrolytic ring opening. From a study of the rates of hydrolysis of various *N*-arylazetidin-2-ones it has been concluded that anchimeric assistance from an amido-group at the 3-position and angle strain imposed by a spiro-group at the 4-position are not important factors in causing this.

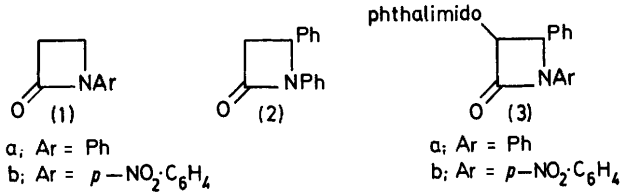
THE β-lactam ring of penicillin readily undergoes alkaline hydrolytic ring opening to give penicilloic acid. In contrast, monocyclic β-lactams are resistant to alkaline hydrolysis. It has been suggested [1] that this is due to resonance stabilisation of the monocyclic β-lactam (Scheme 1), which is not possible in the



SCHEME 1

penicillins owing to enforced tetrahedral geometry [2] at the nitrogen. *X*-Ray analyses show that in active penicillins, which are generally also those most readily hydrolysed, the C–N bond is longer than in β-lactams.[3] The degree of resonance stabilisation, and hence the stability of the β-lactam ring, is also reflected in the frequency and intensity of the β-lactam carbonyl i.r. absorption: [4] monocyclic β-lactams have an absorption in the 1 740 cm^{-1} region; *cf.* 1 770—1 780 cm^{-1} for active penicillins and cephalosporins. There are, however, other factors which may affect the reactivity of the β-lactam ring of penicillin, two of which are (*a*) anchimeric assistance to hydrolysis by the side chain at the 3-position, and (*b*) ring strain imposed by fusion with the thiazolidine ring. By synthesis of suitable β-lactams (azetidin-2-ones) we have sought evidence concerning the efficacy of these two factors; we assume that if they affect the hydrolysis of β-lactams then they will also affect hydrolysis of penicillins.

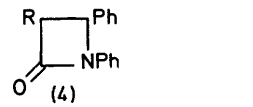
The effect of changing the side chain was examined by a study of the rates of hydrolysis of the β-lactams (1)—(4). In general, standard synthetic methods were used with one exception, the reaction of benzyloxycarbonylglycyl chloride with benzylideneaniline. Sheehan and Corey [5] reported that this reaction gave an imidazolidinone (6), but we found that, under the



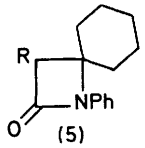
(1) a; Ar = Ph b; Ar = *p*-NO_2·C_6H_4

(2)

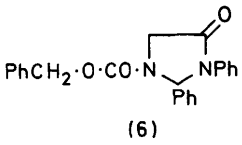
(3) a; Ar = Ph b; Ar = *p*-NO_2·C_6H_4



(4) a; R = NH_2 b; R = PhCO·NH c; R = $PhCH_2$·O·CO·NH d; R = $PhCH_2$·O·CO·NMe e; R = NHMe



(5) a; R = phthalimido b; R = NH_2,HCl c; R = $PhCH_2$·O·CO·NH d; R = NH_2,HBr e; R = $PhCH_2$·O·CO·NMe f; R = MeHN,HBr g; R = PhCO·NMe h; R = PhCO·NH i; R = *p*-MeO·C_6H_4·CO·NH j; R = 2,6-$(MeO)_2C_6H_3$·CO·NH k; R = *p*-BrC_6H_4·CO·NH l; R = *p*-O_2N·C_6H_4·CO·NH m; R = $PhSO_2$·NH



(6)

conditions described here, the β-lactam (4c) was obtained in good yield. Bose *et al.*[6] have briefly reported similar findings.

[1] R. B. Woodward, 'The Chemistry of Penicillin,' Princeton University Press, Princeton, 1949, p. 443.
[2] R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, 1970, **92**, 5489.
[3] S. Abrahamsson, D. C. Hodgkin, and E. N. Maslen, *Biochem. J.*, 1963, **86**, 514; G. J. Pitt, *Acta Cryst.*, 1952, **5**, 770.
[4] R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 1969, **91**, 1401; L. K. Ahern and E. van Heyningen, *J. Medicin. Chem.*, 1968, **11**, 933.
[5] J. C. Sheehan and E. J. Corey, *Org. Reactions*, 1957, **9**, 388.
[6] A. K. Bose, H. P. Chawla, B. Dayal, and M. S. Manhas, *Tetrahedron Letters*, 1973, 2503.

Work by Blackburn and Plackett [7] has demonstrated that β-lactams are more susceptible to alkaline hydrolysis than non-cyclic amides, and these authors conclude that this is due to angular deformation. We have introduced more angular deformation into the ring by attaching a spirocyclohexyl group to the 4-position (5). Some compounds of this type have been prepared previously.[8] The i.r. spectra of these compounds (Table 1) indicate that the ring is perturbed by the

TABLE 1

Relative integrated intensities of the carbonyl i.r. absorption bands of various azetidin-2-ones

Compound	Frequency	Relative intensity
(4a)	1 740	1.16
(4b)	1 740	1.00
(4c)	1 750	1.24
(5e)	1 740	1.98
(5h)	1 740	1.88
(5i)	1 740	1.86
(5j)	1 745	2.33
(5k)	1 740	2.20
(5l)	1 745	2.31
(5m)	1 740	2.31

spirocyclohexyl group. These spiro-lactams are soluble in dioxan but, on addition of this solution to aqueous sodium hydroxide, slow precipitation occurs, accompanied by changes in absorbance that, at first, suggested that hydrolysis was taking place. No variation of the conditions prevented this precipitation. If sufficient dioxan was added to keep the spirolactam in solution then the rate of hydrolysis was too low for convenient study.

It was found possible to prevent precipitation by addition of a surfactant, cetyltrimethylammonium bromide (CTAB). Sodium lauryl sulphate and 'Mulgofen G' (a polyether) had no effect. The general effect of surfactants on reaction rates has been comprehensively reviewed [9] and will not be considered further here. In this study CTAB was employed solely to keep the lactam in solution and not because it was thought that the surfactant would have any special effect on this reaction. In the presence of CTAB the spectral changes expected from the hydrolysis of the spiro-lactam occurred. The effect of different CTAB concentrations was examined, since below a certain concentration, the critical micelle concentration, the surfactant is present mainly as discrete molecules rather than as aggregates or micelles.

The rates of reaction of the β-lactams soluble in aqueous sodium hydroxide were also examined over a range of CTAB concentrations for comparison with the spiro-lactams.

[7] G. M. Blackburn and J. D. Plackett, *J.C.S. Perkin II*, 1972, 1366.
[8] A. K. Bose, Y. H. Chiang, and M. S. Manhas, *Tetrahedron Letters*, 1972, 4091.
[9] H. Morawetz, *Accounts Chem. Res.*, 1970, **3**, 354; E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, 1970, **8**, 271.
[10] A. K. Bose, *Org. Synth.*, 1960, **40**, 82.
[11] J. C. Sheehan and V. S. Frank, *J. Amer. Chem. Soc.*, 1949, **71**, 1856.

EXPERIMENTAL

Materials.—Phthalimidoacetic acid was prepared by a standard procedure [10] and converted into the acid chloride by the method of Sheehan and Frank.[11] *N*-Benzyloxycarbonylglycine was obtained by the reaction of glycine with benzyl chloroformate and converted into *N*-benzyloxycarbonylglycyl chloride by reaction with phosphorus pentachloride.[12] *N*-Aryl-3-bromopropionamides were prepared by the method of Manhas and Jeng.[13] Literature methods were used for the preparation of *N*-benzylideneaniline [14] and *N*-cyclohexylideneaniline.[15] CTAB was recrystallised from ethanol.

The 1-arylazetidin-2-ones (1a and b) were prepared by base-catalysed (sodium methylsulphinylmethanide) cyclisation of the appropriate *N*-aryl-3-bromopropionamides.[13] 1-Phenylazetidin-2-one had m.p. 77° (lit.,[13] 78°) and 1-*p*-nitrophenylazetidin-2-one had m.p. 161° (lit.,[7] 161—162°).

1,4-Diphenylazetidin-2-one (2), prepared by a Reformatsky reaction,[16] had m.p. 154° (lit.,[16] 153—154°).

1,4-Diphenyl-3-phthalimidoazetidin-2-one (3a).—This was prepared by a modification of the method of Sheehan and Ryan.[17] To a stirred and cooled solution of *N*-benzylideneaniline (9 g) and triethylamine (5 g) in dry dichloromethane (100 ml) was added a solution of freshly prepared phthalimidoacetyl chloride (10 g) in dry dichloromethane (200 ml) during 40 min; portions were added as the red colour produced on addition of the previous portion faded. The solution was stirred for 1 h and left overnight. After washing with water (3 ×) and drying ($MgSO_4$), the dichloromethane was evaporated off. Treatment of the orange residue with methanol gave the product as a white powder (10 g, 62%), m.p. 230—231° (lit.,[17] 230—231°).

1-(p-Nitrophenyl)-4-phenyl-3-phthalimidoazetidin-2-one (3b).—This was prepared in a similar manner from *N*-benzylidene-*p*-nitroaniline, and gave yellow *crystals*, m.p. 296° (from methanol) (Found: C, 66.9; H, 3.5; N, 10.0. $C_{23}H_{15}N_3O_5$ requires C, 66.8; H, 3.6; N, 10.2%); M^+ 413.

3-Amino-1,4-diphenylazetidin-2-one (4a).—This was prepared as the hydrochloride from (3a) by reaction with hydrazine; [17] m.p 237—238° (decomp.) [lit.,[17] 237—238° (decomp.)]. Attempts to prepare 3-amino-1-(*p*-nitrophenyl)-4-phenylazetidin-2-one by the same procedure were unsuccessful. The reaction of (4a) with benzoyl chloride and triethylamine in dry dichloromethane gave 3-benzamido-1,4-diphenylazetidin-2-one (4b), m.p. 156—157° (lit.,[18] 157°).

3-(N-Benzyloxycarbonylamino)-1,4-diphenylazetidin-2-one (4c).—To a stirred and cooled solution of *N*-benzylideneaniline (5 g) and triethylamine (2.4 g) in dry dichloromethane (200 ml), portions of freshly prepared *N*-benzyloxycarbonylglycyl chloride (5.8 g) were added. A fresh portion was added after the red colour produced by the previous portion had faded. The solution was stirred for 1 h and left overnight at room temperature. After washing with water (3 ×) the solution was dried ($MgSO_4$) and evaporated. Addition of a small quantity of methanol to the residual gum gave the product as a white *solid* (3.4 g,

[12] M. Bergmann and L. Zervas, *Ber.*, 1932, **65**, 1192.
[13] M. S. Manhas and S. J. Jeng, *J. Org. Chem.*, 1967, **32**, 1246.
[14] L. A. Bigelow and H. Eatnough, *Org. Synth.*, 1928, **8**, 22.
[15] G. Reddelien and O. Meyn, *Ber.*, 1920, **53**, 345.
[16] H. Gilman and M. Speeter, *J. Amer. Chem. Soc.*, 1943, **65**, 2255.
[17] J. C. Sheehan and J. J. Ryan, *J. Amer. Chem. Soc.*, 1951, **73**, 1204.
[18] R. K. Olsen, *J. Org. Chem.*, 1970, **35**, 1912.

30%), m.p. 136—137° (from methanol) (Found: C, 74.4; H, 5.4; N, 7.5. $C_{23}H_{20}N_2O_3$ requires C, 74.2; H, 5.4; N, 7.5%); M^+ 372. This material was *N*-methylated with methyl iodide and silver oxide in dry dimethylformamide.[18] Repeated crystallisation from methanol and finally from ethyl acetate gave 3-(N-*benzyloxycarbonyl*-N-*methylamino*)-1,4-*diphenylazetidin*-2-*one* (4d) as a white powder, m.p. 117° (Found: C, 74.6; H, 5.7; N, 7.3. $C_{24}H_{22}N_2O_3$ requires C, 74.6; H, 5.7; N, 7.3%), M^+ 386. Compound (4d) (0.5 g) was shaken at room temperature with hydrogen bromide in glacial acetic acid (2.5 ml, 37%). Dissolution was complete in 5 min and the mixture was shaken for a further 10 min. After addition of ether 3-*methylamino*-1,4-*diphenylazetidin*-2-*one hydrobromide* (4e) separated as a white powder (0.13 g, 30%), m.p. 228—230° (decomp.) (Found: C, 58.0; H, 5.0; N, 8.4. $C_{16}H_{17}BrN_2O$ requires C, 57.7; H, 5.1; N, 8.4%).

1-*Phenyl*-3-*phthalimido*-1-*azaspiro*[5.3]*nonan*-2-*one* (5a).—The preparation of this spirononan-2-one by the reaction of cyclohexylideneaniline and phthalimidoacetyl chloride has been briefly described by Bose *et al.*[8] Precise conditions were found necessary for a good yield of product, otherwise the main product was phthalimidoacetic anhydride. To a stirred and cooled solution of *N*-cyclohexylideneaniline (5 g) and triethylamine (3.6 g) in dry dichloromethane (200 ml) were added portions of freshly prepared phthalimidoacetyl chloride (6.6 g) over 40 min. As the acid chloride was added a red colour developed. The mixture was stirred for 2 h and left overnight. After filtration the solution was washed with water (3 ×), dried ($MgSO_4$), and evaporated and the residue treated with methanol to give the product, which was crystallised from methanol (yield 3.8 g, 38%); m.p. 278—279° (lit.,[19] 278—279°).

Treatment of (5a) with hydrazine gave 3-*amino*-1-*phenyl*-1-*azaspiro*[5.3]*nonan*-2-*one hydrochloride* (5b) as a white powder, m.p. 236° (decomp.) (Found: C, 63.0; H, 7.1; N, 10.3. $C_{14}H_{19}ClN_2O$ requires C, 63.0; H, 7.2; N, 10.5%).

3-*Benzyloxycarbonylamino*-1-*phenyl*-1-*azaspiro*[5.3]*nonan*-2-*one* (5c) was prepared (65%) from *N*-cyclohexylideneaniline and benzyloxycarbonyl chloride by the method described above for (4c); m.p. 156° (from methanol) (Found: C, 72.4; H, 6.7; N, 7.6. $C_{22}H_{24}N_2O_3$ requires C, 72.5; H, 6.6; N, 7.7%), M^+ 364. The reaction of (5c) with hydrogen bromide in glacial acetic acid gave 3-*amino*-1-*phenyl*-1-*azaspiro*[5.3]*nonan*-2-*one hydrobromide* (5d) as a pink powder. Recrystallisation from methanol afforded a white powder, m.p. 228—230° (decomp.) (Found: C, 54.1; H, 6.2; Br, 25.6; N, 8.9. $C_{14}H_{19}BrN_2O$ requires C, 54.0; H, 6.1; Br, 25.7; N, 9.0%).

[19] M. S. Manhas, J. S. Chib, Y. H. Chiang, and A. K. Bose, *Tetrahedron*, 1969, **25**, 4421.
[20] E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.

Methylation of (5c) with methyl iodide in dimethylformamide, as described for (4d) above, gave 3-(N-*benzyloxycarbonyl*-N-*methylamino*)-1-*phenyl*-1-*azaspiro*[5.3]*nonan*-2-*one* (5e), m.p. 94—95° (Found: C, 73.0; H, 7.0; N, 7.3. $C_{23}H_{26}N_2O_3$ requires C, 73.0; H, 6.9; N, 7.4%), M^+ 378. Reaction of (5e) with hydrogen bromide in glacial acetic acid gave 3-*methylamino*-1-*phenyl*-1-*azaspiro*[5.3]*nonan*-2-*one hydrobromide* (5f), m.p. 231—232° (decomp.) (Found: C, 55.4; H, 6.5; N, 8.7. $C_{15}H_{21}BrN_2O$ requires C, 55.6; H, 6.5; N, 8.6%). Treatment of (5f) in dichloromethane with benzoyl chloride and triethylamine gave 3-(N-*methylbenzamido*)-1-*phenyl*-1-*azaspiro*[5.3]*nonan*-2-*one* (5g), m.p. 87° (Found: C, 75.8; H, 6.9; N, 8.0. $C_{22}H_{24}N_2O_2$ requires C, 75.7; H, 6.9; N, 8.0%), M^+ 348.

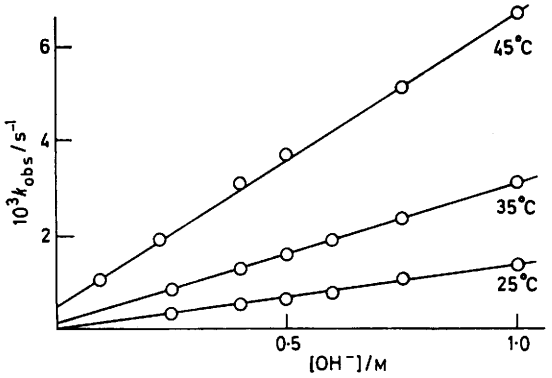
A number of spiro-lactams (5h—m) were prepared from (5b) by reactions in dichloromethane with the appropriate acid chlorides in the presence of triethylamine; analytical data are given in Table 2.

TABLE 2

Analytical data for spiro-lactams

	Found (%)					Required (%)			
	C	H	N	Formula	M^+	C	H	N	M.p. (°C)
(5h)	75.4	6.5	8.2	$C_{21}H_{22}N_2O_2$	334	75.4	6.6	8.5	157
(5i)	72.4	6.8	7.6	$C_{22}H_{24}N_2O_3$	364	72.5	6.6	7.7	184
(5j)	70.2	6.5	6.9	$C_{23}H_{26}N_2O_4$	394	70.0	6.6	7.1	132
(5k)	60.8	5.1	6.7	$C_{21}H_{21}BrN_2O_2$	413	61.0	5.1	6.8	218
(5l)	66.3	5.6	11.1	$C_{21}H_{21}N_3O_4$	379	66.5	5.5	11.1	207
(5m)	65.1	5.8	7.8	$C_{20}H_{22}N_2O_2$		64.9	5.9	7.6	325 (decomp.)

Kinetic Method.—All reactions were run in de-ionised water at an ionic strength of 1.0M maintained by addition of NaCl. One drop of a 10% solution of the azetidinone in dioxan was added to the NaOH solution in a cuvette contained in the thermostatted cell holder of a Unicam SP 500 spectrophotometer and the absorbance at 255 nm was monitored. For those reactants with a 1-*p*-nitrophenyl substituent it was more convenient to follow the absorbance at 400 nm due to product. For the fastest reactions a ' Canterbury ' stopped-flow spectrophotometer was used. All the reactions obeyed good first-order kinetics over three half-lives. With slower reactions the first-order rate constant (k_{obs}) was calculated by the method of Swinbourne.[20] Typical results for the variation of k_{obs} with hydroxide concentration are given in the Figure. Activation parameters were calculated from an Arrhenius plot (Table 3).



Variation of k_{obs} for the hydrolysis of 1-phenylazetidin-2-one with sodium hydroxide concentration

The variation of k_{obs} with CTAB concentration in 1M-NaOH for a number of azetidin-2-ones and azaspirononan-2-ones is shown in Table 4. The critical micelle concentration was found to be 0.003M from a study of the variation of wavelength for maximum absorbance of diethylaniline with CTAB concentration.[21] Lactams (5a, e, and m) were not soluble, even in the presence of the highest concentration of CTAB. Although soluble the rates of hydrolysis of (5j and l) were too slow to be measured.

Further attempts to purify compounds (7) and (8) for analysis resulted in decomposition.

Biological Testing.—Compounds (3a and b) and (5i) were tested for *in vitro* antibacterial activity. A 0.1% solution in propylene glycol was prepared and serial two-fold dilutions were made in a sulphonamide testing broth (usually 100—0.19 μg ml^{-1}). The broth solutions were inoculated with log phase cultures of *Staphylococcus aureus* NCTC 6571A) and *Escherichia coli* (NCTC 4144). After overnight incubation at 37 °C the results were read as the minimal inhibitory concentration according to visible growth in comparison to broth without added drug. None of the compounds tested showed antibacterial activity.

TABLE 3

Kinetic data for the alkaline hydrolysis of azetidin-2-ones

	$10^3k_{OH^-}$/l mol^{-1} s^{-1}					$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
Compound	10 °C	15 °C	25 °C	35 °C	45 °C	kcal mol^{-1}	cal mol^{-1} K^{-1}
(1a)			1.4	3.2	4.6	15.3 (±0.4)	−19 (±1)
(1b)	15.1		50.0	75.2		13.3 (±0.3)	−20 (±1)
(2)			2.1	4.8	9.5	14.1 (±0.3)	−23 (±2)
(3a)	8.6		25.1	55.6		14.1 (±0.3)	−19 (±1)
(3b)		42.2	50.9	101		14.1 (±0.2)	−17 (±1)
(4a)	6.2		20.0	37.4		14.3 (±0.4)	−25 (±2)
(4b)		8.4	21.0	51.9		13.1 (±0.3)	−22 (±1)

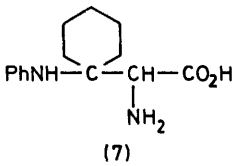
TABLE 4

Effect of CTAB on the rates of hydrolysis of azetidin-2-ones and azaspirononan-2-ones

10^3[CTAB]/M:	0.10	0.50	1.0	2.0	3.0	4.0	5.0	10.0
Substrate	10^3k_{obs}/s^{-1}							
(1a)		0.70	1.7	1.0	1.2	1.1	1.1	1.1
(1b)	23		39	46	54	49	40	34
(2)	1.0	1.0	1.1	1.6	1.6	1.2	1.1	1.0
(3a)	12	19	26	27	28	25	23	21
(3b)				127	164	168	155	111
(4a)	10	12	16	20	34	33	26	19
(4b)	20		21	22	24	24	22	12
(5b)	8.2		12	15	26	26	22	16
(5c)	6.6		21	25	29	29	27	23
(5h)	5.4		10	12	17	17	11	5.1
(5i)	9.6	12	17	20	20	15	12	7.0
(5k)	7.6		8.9	9.3	10.2	9.8	9.2	8.1

Product Analysis.—The product of alkaline hydrolysis of 1-phenylazetidin-2-one is known to be *N*-phenyl-β-alanine, and Blackburn and Plackett [7] found that *N*-(*p*-nitrophenyl)-β-alanine was obtained from 1-(*p*-nitrophenyl)azetidin-2-one.

A mixture of 3-amino-1-phenyl-1-azaspiro[5.3]nonan-2-one hydrobromide (0.20 g), dioxan (20 ml), and 1M-sodium hydroxide (30 ml) was stirred at 25 °C for 1 h. Water (200 ml) was added and the resulting suspension extracted with dichloromethane (3 × 50 ml). After drying ($MgSO_4$) the solvent was removed to leave a brown gum which solidified on trituration with methanol. T.l.c. [benzene–methanol (9 : 1)] showed one spot, R_F 0.78. The mass spectrum exhibited M^+ 248, consistent with 2-(1-anilinocyclohexyl)glycine (7).



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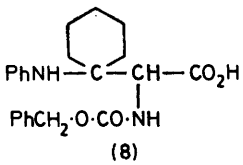


(8)

In a similar manner 3-benzyloxycarbonylamino-1-phenyl-1-azaspiro[5.3]nonan-2-one gave a product with R_F 0.82 and M^+ 382, consistent with 2-(1-anilinocyclohexyl)-*N*-benzyloxycarbonylglycine (8).

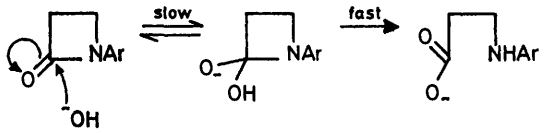
DISCUSSION

The values of k_{OH^-} for (1a and b) at 25 °C (Table 3) are in agreement with the results of Blackburn and Plackett,[7] and the effect of substituents in the *N*-aryl group has been discussed in detail by these authors. The value of k_{OH^-} for (2) does not differ greatly from that for (1a); it is surprising that introduction of a bulky substituent at the 4-position has so little effect, but the same effect was noted by Holley and Holley.[22] On the other hand, the introduction of a 3-amino group (4a) has a substantial effect and it is in the wrong sense to be explained on electronic grounds. Hydrogen bonding cannot be involved as similar enhancements were obtained with (3a and b). Blackburn and Plackett [7] have argued that the slow step in β-lactam hydrolysis is attack of hydroxide on the carbonyl group (Scheme 2). An observed deuterium solvent isotope effect of 1.02 for the alkaline hydrolysis of (5h) is consistent with this proposal. The similarity of the activation parameters

[21] C. G. Swain and J. F. Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2534, 2538.

[22] A. D. Holley and R. W. Holley, *J. Amer. Chem. Soc.*, 1951, **73**, 3172.

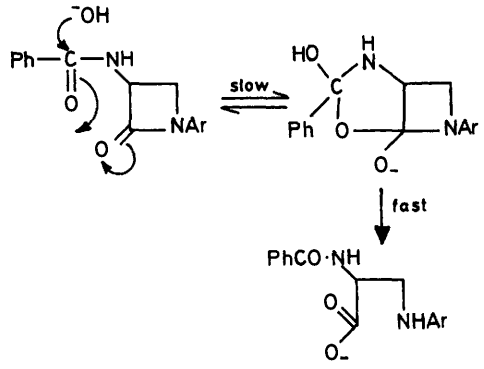
throughout the series of β-lactams indicates that there is no change of mechanism of hydrolysis. It is difficult to see why the presence of a 3-amino-group aids attack



SCHEME 2

of hydroxide ion, but this effect may be one, albeit small, factor in destabilising the β-lactam ring of penicillin.

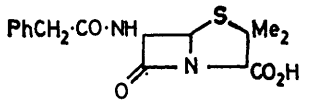
It is possible that the carbonyl group of the benzoyl moiety of (4b) exerts anchimeric assistance in the hydrolysis of the ring (Scheme 3) and this compound is a



SCHEME 3

model for penicillin G (9). This effect has been detected by Burrows and Topping [23] in the hydrolysis of a sterically hindered ester. However, in this instance there is no evidence of such assistance from the rate constants. The similarity of the activation parameters confirms our belief that there is no change of mechanism and anchimeric assistance is not operative here.

The results in Table 4 show that addition of CTAB has little effect on the rate of hydrolysis of β-lactams and spiro-lactams, although there is a maximum in the rate of reaction at the critical micelle concentration (0.003M). For the lactams (1)—(4) there is the same change in reactivity observed in the absence of a surfactant, and this gives us confidence that we can detect



(9)

real changes in the reactivity of the spiro-lactams, the hydrolysis of which can be examined only in the presence of surfactant. The results for the spiro-lactams show that the presence of the spirocyclohexyl group has very little effect on the rate of hydrolysis and there is no change as the side chain in the 3-position is varied.

This study has shown that neither the inclusion of a carbonyl group in the side chain nor the imposition of greater ring strain necessarily leads to more rapid alkaline hydrolysis of β-lactams. These structural features, present in some active penicillins, appear not to be important in determining reactivity. It appears that Woodward's original suggestion [1] of inhibition of resonance stabilisation of the β-lactam ring in penicillin is the factor of importance.

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[6/1794 *Received*, 24*th September*, 1976]

[23] H. D. Burrows and R. M. Topping, *J. Chem. Soc.* (*B*), 1970, 1323.