# Reactions of Carbonyl Compounds in Basic Solutions. Part 15.[1] The Alkaline Hydrolysis of *N*-Methyl, *N*-Phenyl and Bicyclo Lactams, Penicillins and *N*-Alkyl-*N*-methylacetamides

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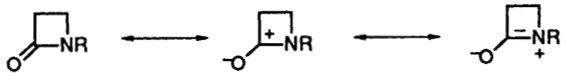
The rate coefficients for the alkaline hydrolysis of a series of *N*-methyl, *N*-phenyl and bicyclo lactams, penicillins and *N*-alkyl-*N*-methylacetamides in water or in aqueous dimethyl sulphoxide have been measured at several temperatures. The reactions were first order in both substrates and base. The reactivities are related to the structures of the substrates, especially *N*-substitution, ring size and fused ring effects. The reactivities, as well as the activation parameters, kinetic solvent and solvent isotope effects, are used to suggest the detailed mechanisms. All the β-lactams appear to react with rate-determining addition of hydroxide anion; while the *N*-alkyl γ- and δ-lactams and *N*-alkyl-*N*-methylacetamides have rate-determining ring fission of the tetrahedral adduct, assisted by water-catalysis. The reactivity of penicillin in alkaline hydrolysis has been analysed by the studies of model compounds. These show that the increased reactivity of the penicillin β-lactam ring arises from the direct action of the fused ring structure and the acylamino side-chain.



The β-lactam ring of penicillins shows remarkable susceptibility towards nucleophilic reagents and, in particular, to base-catalysed ring fission.[2] Woodward[3] in 1949 suggested that this reactivity arose from the inability of the monocyclic β-lactam to receive resonance stabilisation from the canonical structure **3** as shown in Scheme 1 below. This was considered




**1** **2** **3**

**Scheme 1**

to arise from the lack of planarity of the β-lactam ring required for delocalisation of the lone pair on nitrogen. Pracejus[4] suggested that this reactivity arose from the relief of ring strain, both bond-angle and torsional, in the initial state when the tetrahedral intermediate is formed. Other factors that could influence the reactivity of the β-lactam ring in penicillin are further ring strain resulting from fusion of the four-membered lactam with the five-membered thiazolidine ring and neighbouring-group participation of the acylamino side-chain.[5]

Studies by Holley and Holley[6] on a number of model systems gave some preliminary kinetic evidence of the effects of substitution on the base-catalysed hydrolysis of relatively simple β-lactams and these have been extended by others.[7] Later studies[8,9] on fused-ring β-lactams indicated the activating effect of a fused five-membered ring in the 1,4-position compared with a similarly substituted six-membered ring.

Studies[1,5,10] of the alkaline hydrolysis of *N*-phenyl β-lactams have been made. Blackburn and Plackett[10] have shown that *N*-phenyl β-lactams are more susceptible to alkaline hydrolysis than both the *N*-phenyl γ- and δ-lactams, as well as the corresponding acetanilides. They considered the main reason for this was ring strain in the form of angle deformation in the initial state. Butler *et al.*[5] studied a series of 3-substituted *N*,4-diphenyl β-lactams and 4-spiro-*N*-phenyl β-lactams. Their conclusions were that the angle strain induced by the 4-spiro substitution and any neighbouring-group assistance from 3-acylamino groups were not important factors.

The present study is an investigation of the alkaline hydrolysis of a series of model compounds related to penicillin. These models are shown below as **4**–**13**. An attempt is made to relate the reactivity to the detailed mechanisms and separate the factors responsible for reactivity in these reactions.

## Results

The alkaline hydrolysis of all the lactams and amides studied here is of the first order in both the substrate and hydroxide anion, with the exception of **8c** (see below). Rate coefficients for the alkaline hydrolysis of the *N*-methyl and *N*-phenyl lactams and *N*-alkyl-*N*-methylacetamides in water at various temperatures are shown in Table 1. Those for the *N*-phenyl β-lactams in 70% (v/v) aqueous DMSO are shown in Table 2. The effects of various aqueous DMSO compositions on the rates at 60.0 °C for the *N*-phenyl β-lactams are shown in Table 3. Table 4 shows the rate coefficients for the alkaline hydrolysis of several penicillins in water at 30.0 °C. The rates for certain substrates have also been measured in deuterium oxide, as shown in Table 1 and 4. The activation parameters have been derived for several substrates and these are shown in Table 5. Where comparisons are possible by extrapolation or interpolation, the present results agree with literature data.[5,7,8]

The alkaline hydrolysis of **8c** in 70% (v/v) aqueous DMSO was found to be first order in substrate and, at low base concentrations, *i.e.* $<0.01$ mol dm$^{-3}$, first order in hydroxide. However, as the base concentration increased, the apparent second-order rate coefficient decreased. Ionisation of the amide group has been shown[11] to inhibit the alkaline hydrolysis of amides which are themselves ionising, and the hydrolysis of **8c** at higher base concentrations is analysed in part 16 of this series.[12]

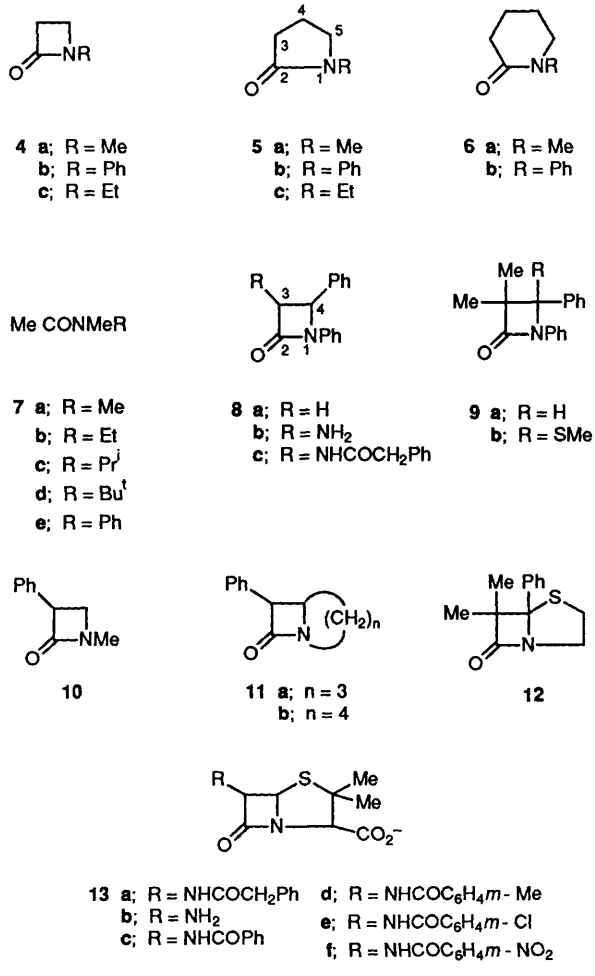
## Discussion

*The Mechanisms of Alkaline Hydrolysis of the Lactams and Amides.*—A generalised mechanism for the alkaline hydrolysis of amides and lactams is shown in Scheme 2.[13,14] In part 14 of this series,[1] it has been shown that *N*-phenyl β-lactams react with rate-determining attack of hydroxide anion ($k'_1$ in Scheme

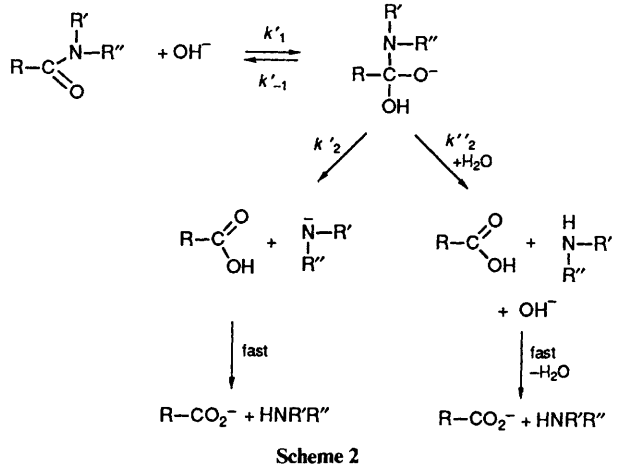
**Table 1** Rate coefficients ($k_2$) for the alkaline hydrolysis of *N*-methyl and -phenyl lactams and *N*-alkyl-*N*-methylacetamides in water at several temperatures[a]

| Substrate | $k_2/10^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ At 66.0 °C | 76.0 °C | 88.0 °C | 100.0 °C | λ/nm |
|---|---|---|---|---|---|
| **4a** | 8.71 | 18.0 | 39.6 | 83.0 (10.7)[b] | 200 |
| **4b** | — | 351 | — | — | 302.5 |
| **4c** | — | — | — | 35.0 | 200 |
| **5a** | 0.354[c] | 0.770 | $1.81_5$ | 3.61 (2.96)[b] | 200 |
| **5b** | — | 1.01 | — | — | 305 |
| **5c** | — | — | — | 1.28 | 200 |
| **6a** | 6.31 | $10.7_5$ | 24.0 | 40.8 (38.4)[b] | 200 |
| **6b** | — | 4.63 | — | — | 300 |
| **7a** | 2.66[c] | 5.85 | 11.4 | 22.8 (23.3)[b] | 200 |
| **7b** | — | — | — | 4.00 | 200 |
| **7c** | — | — | — | 0.721 | 200 |
| **7d** | — | — | — | 0.246 | 200 |
| **7e** | — | 3.22 | — | — | 300 |
| | At 30.0 °C | 40.0 °C | 50.0 °C | 60.0 °C | |
| **10** | 0.449 | 1.06 | 2.30 | 4.91 | 230 |
| **11a** | 26.0 | 46.3 | 79.8 | 134 | 250 |
| **11b** | 1.51 | 3.27 | 6.80 | 13.9 | 240 |
| **12** | — | — | — | $117._5$[d] | 241.5 |

[a] Rate coefficients were reproducible to within ±5%. [b] In deuterium oxide. [c] At 64.0 °C. [d] Rate coefficient was reproducible to within ±12%.




2) and that *N*-phenyl γ- and δ-lactams and acetanilides have the formation of the anion of aniline ($k'_2$ in Scheme 2) as the rate-determining step, which follows equilibrium formation of the tetrahedral adduct. Other related systems, such as formanilides,[1] require catalysis for the breakdown of the adduct by water ($k''_2$ in Scheme 2) or base. In this study all the above reactions are first order in both substrate and base. Thus, it is not necessary to consider any pathways involving catalysis of the breakdown of the tetrahedral complex by base (in contrast with our previous study).[1]




**Scheme 2**

N-*Substituent, Ring Size and Fused Ring Effects.*—The *N*-substituent effects shown in Table 1 are very informative. The ratio of rates, at 76 °C, for the *N*-phenyl: *N*-methyl β-lactam is *ca.* 20. This result can be compared with the ratio of about four or more, observed for the rates of alkaline hydrolysis of phenyl and methyl esters.[15] The later reaction involves rate-determining attack at the carbonyl group. However, the ratio, at 76 °C, for the γ- and δ-lactams and acetanilides is about 1.3, 0.4 and 0.6, respectively. For the pathway shown in Scheme 2 with the formation of the anion of the amine as the rate-determining step, *i.e.* $k'_2$, the relative stability of the leaving group will, in the main, control reactivity. The facility of groups to leave is, for closely related systems, mainly a function of the relative stability of that group as measured by the p$K_a$ of the conjugate acid.[16] The p$K_a$

**Table 2** Rate coefficients ($k_2$) for the alkaline hydrolysis of certain *N*-phenyl β-lactams in 70% (v/v) aqueous DMSO at various temperatures[a]

| Substrate | $k_2/10^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ At 30.0 °C | 40.0 °C | 50.0 °C | 60.0 °C | λ/nm |
|---|---|---|---|---|---|
| (**4b** | 66.3 | 157 | 358 | 715 | 302.5)[b] |
| **8a** | 170 | 383 | 756 | 1 520 | 298 |
| **8b** | 1900 | 3790 | 7 600 | 14 400 | 305 |
| **8c** | 3430 | 7310 | 15 600 | 30 600 | 298 |
| **9a** | 8.81 | 20.3 | 48.3 | 99.5 | 300 |
| **9b**[c] | 2.76 | 6.90 | $15.6_5$ | 39.6 | 300 |

[a] Rate coefficients were reproducible to within ±5%. [b] From ref. 1. [c] Rate coefficients were reproducible to within ±10%.

**Table 3** Rate coefficients ($k_2$) for the alkaline hydrolysis of certain *N*-phenyl β-lactams in aqueous DMSO at 60.0 °C[a]

| Substrate | $k_2/10^{-4}$ dm$^3$ mol$^{-1}$ s$^{-1}$ (v/v) aq. DMSO 10 | 30 | 50 | 70 |
|---|---|---|---|---|
| (**4b** | | 138 | 235 | 715)[b] |
| **8a** | | 335 | 500 | 1520 |
| **9a** | $12.5_5$ | 21.3 | 32.8 | 99.5 |

[a] Rate coefficients were reproducible to within ±5%. [b] From reference 1.

**Table 4** Rate coefficients ($k_2$ for the alkaline hydrolysis of penicillins (**13a**–**f**) in water at constant ionic strength (μ = 0.1 mol dm$^{-3}$) at 30.0 °C[a]

| Substrate | $k_2/10^{-2}$ dm$^3$ mol$^{-1}$ s$^{-1}$ | λ/nm |
|---|---|---|
| **13a** | 15.9 (18.9)[c] | 238, 255 |
| **13b** | 6.41 | 238 |
| **13c** | 17.0 | 255 |
| **13d** | 16.1 | 255 |
| **13e** | 20.7 | 255 |
| **13f** | 25.5 | 310 |

[a] Rate coefficients were reproducible to within ±5%. [b] As sodium salts. [c] In deuterium oxide.

of aniline as an acid in water can be estimated from $H_-$ acidity-function measurements in aqueous DMSO containing base to be about 26.4;[17] while that of aniline in DMSO is about 30.6.[18] No measurements are available for dimethylamine or related amines as acids in these solvents; but estimates of the p$K_a$ of ammonia are *ca.* 35 or 36 relative to water as the solvent[19] and 41 in DMSO.[20] However, the basicities of these amines are in the opposite order, with the p$K_a$ values of the *N*-methylanilinium and dimethylammonium ions being 4.85 and 10.77, respectively.[21] Thus, the rate-determining step for the *N*-methyl γ- and δ-lactams and *N*,*N*-dimethylacetamide cannot be $k'_2$ in Scheme 2 as it would be expected to be very much slower than that for the corresponding *N*-phenyl systems.

The effect of ring-size on reactivity is qualitatively the same for the *N*-methyl as for *N*-phenyl substrates,[1] *i.e.* β-lactam > δ-lactam > acetamide > γ-lactam. However, for *N*-phenyl substrates, the β-lactam is much more reactive than the others.

The effect of varying the *N*-alkyl substitution has also been studied, as shown in Table 1. The decrease in reactivity is in the order, Me < Et < $^i$Pr < $^t$Bu, and the effects are more severe in the order, acetamide > γ-lactam > β-lactam. This appears mainly a function of the increasing steric bulk of the alkyl group which causes crowding in the transition state. This effect is more intense in the less restricted structures, *i.e.* the γ-lactams and acetamides. The effect of *N*-alkyl substitution on the reactivity of the *N*-methylacetamide, R$^1$CONMeR, can be assessed using the Taft steric constants, $E_s$, for RCH$_2$.[15] The use of these constants attempts to allow for the azo link between R and the carbonyl group. Eqn. (1) shown below is rather poor; even

$$\log (k/k_o) = 1.12\,E_s - 2.83 \qquad (1)$$

(Correlation coefficient = 0.954 and standard deviation = 0.25 for four substituents)

**Table 5** Activation parameters for the alkaline hydrolysis of model compounds at 30.0 °C[a]

| Model | Solvent | $\Delta H^‡$/kcal[d] mol$^{-1}$ | $\Delta S^‡$/cal[d] mol$^{-1}$ K$^{-1}$ | $\Delta G^‡$/kcal[d] mol$^{-1}$ |
|---|---|---|---|---|
| **4a** | Water | 16.1 | −25 | 23.6 |
| (**4b** | Water | 15.3 | −19 | 21.1)[b] |
| **5a** | Water | 15.7 | −33 | 25.4 |
| **6a** | Water | 13.5 | −34 | 23.5 |
| **7a** | Water | 14.2 | −33 | 24.2 |
| **10** | Water | 15.4 | −28 | 23.9 |
| **11a** | Water | 10.4 | −36 | 21.3 |
| **11b** | Water | 14.2 | −29 | 23.0 |
| (**4b** | 70% (v/v) aqueous DMSO | 15.4 | −18 | 20.9)[c] |
| **8a** | 70% (v/v) aqueous DMSO | 14.0 | −21 | 20.4 |
| **8b** | 70% (v/v) aqueous DMSO | 13.0 | −19 | 19.4 |
| **8c** | 70% (v/v) aqueous DMSO | 14.1 | −14 | 18.2 |
| **9a** | 70% (v/v) aqueous DMSO | 15.7 | −21 | 22.1 |
| **9b** | 70% (v/v) aqueous DMSO | 17.1 | −19 | 22.9 |

[a] Values of $\Delta H^‡$ ($\Delta G^‡$) are $\Delta S^‡$ are accurate to within ±300 cal mol$^{-1}$ and ±2 cal mol$^{-1}$ K$^{-1}$, respectively. [b] From ref. 5. [c] From ref. 1. [d] 1 cal = 4.184 J.

considering that only four substituents are available and that the substituent constants used are only a first approximation. However, the relation does confirm that it is mainly steric effects that control reactivity as in alkaline ester hydrolysis. This would be expected in a reaction occurring *via* a tetrahedral adduct.

The effect of fused-ring structure is dramatic (see Table 1). A six-membered ring fusion as in **11b** causes only a modest increase in reactivity; but a five-membered fusion as in **11a** increases reactivity strongly. A more difficult comparison involving **12** with **4a** again confirms the significant induction of reactivity by ring fusion, now involving a five-membered thio-containing ring. These effects must arise from the further increase in strain in the β-lactam ring by the increased constraints arising from a five-membered ring fusion.

A comparison of the reactivity of **10** and **4a** (Table 1) indicates the effect of the 3-phenyl substitution to be very small, probably because of cancelling inductive and steric effects.[21] However, the effects on reactivity of the 4-phenyl group, seen in comparing **8a** and **4b** (Table 2), appears to arise from an inductive electron-withdrawing effect activating the *N*-methyl lactams. In the same series, the strongly activating effects of the 3-amino and -acylamino groups in **8b** and **8c** would appear to arise from their powerful inductive electron-withdrawing effect activating nucleophilic attack on the *N*-phenyl lactams. The effect of the methylthio group in **9b**, compared with **9a**, might have been expected to be activating also on the basis of an inductive effect. However, the observed deactivating effect appears to arise from a steric bulk effect caused by buttressing the already highly substituted system, which has both 3,3-dimethyl and 4-phenyl substituents.

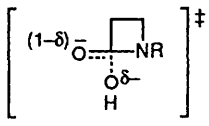
*Activation Parameters.*—The enthalpies and entropies of activation shown in Table 5 all clearly confirm the nature of the bimolecular reactions. In water, a comparison of the *N*-methyl lactams, **4a**, **5a** and **6a**, and *N*,*N*-dimethylacetamide, **7a**, shows that the β-lactam has a larger enthalpy of activation and less negative entropy of activation. The other three substrates have almost the same $\Delta S^{\ddagger}$ value and the relative rates are controlled by the $\Delta H^{\ddagger}$ values. The effect of the fused ring structure in **11a** and **11b**, compared with **10**, is progressively to reduce $\Delta H^{\ddagger}$ and to make $\Delta S^{\ddagger}$ more negative. The first of these effects probably arises from a decrease in ring strain[4] on forming the transition state and the second from the steric hindrance to motion which becomes even more severe in the transition state than in the strained initial state, *cf.* ref. 21 and 22.

In 70% aqueous DMSO, the introduction of a 4-phenyl or 3-amino group appears to decrease the $\Delta H^{\ddagger}$ value, mainly by an electron-withdrawing inductive effect, as would be expected. However, a 3-acylamino group causes a small increase in $\Delta H^{\ddagger}$ and significantly less negative $\Delta S^{\ddagger}$. The introduction of the 4-thiomethoxy group in **9b** appears to increase $\Delta H^{\ddagger}$ severely, presumably by a bulk steric effect buttressing the already crowded structure of **9a**.

*Kinetic Solvent Isotope Effects.*—The values of $k_{H_2O}/k_{D_2O}$ at 100 °C for the hydrolysis of the *N*-methyl β-lactams and acetamide are 0.78, 1.2, 1.1 and 1.0, respectively. The value for the *N*-methyl β-lactam is similar to those previously observed for all the *N*-phenyl lactams and acetanilide[1] and for many ester alkaline hydrolysis reactions.[23] The overall process must be considered in going from initial to transition state. The main reason for these results is the greater nucleophilicity of $OD^-$ in $D_2O$ than $OH^-$ in $H_2O$. The values of unity and above observed for the other *N*-methyl systems must include a small, but definite, primary isotope effect resulting from transfer of hydrogen from water in the rate determining step. This effect is of the same type as that observed for the $k_2$ process for the alkaline hydrolysis of *N*-methylformanilides previously.[1]

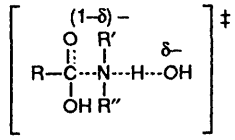
*Solvent Effects.*—The effect of increasing the DMSO content of aqueous DMSO on the alkaline hydrolysis of the *N*-phenyl β-lactams is shown in Table 3. The three substrates show almost parallel behaviour. This appears to confirm the same detailed mechanism occurs for all these lactams, *i.e.* the rate-determining step is $k'_1$ in Scheme 2. The decreasing activity of water and increasing activity of hydroxide as the DMSO content rises are the main factors giving rise to the increasing rates.[24]

*Mechanisms of Hydrolysis.*—All the evidence is in agreement with the rate-determining step for the alkaline hydrolysis of the β-lactams in this study being $k'_1$ in Scheme 2 with the transition state **14** shown below. This appears to be followed by a



**14**

relatively rapid ring-fission step. However, for the *N*-alkyl γ- and δ-lactams and *N*-methylacetamides, the rate-determining step is considered to be $k''_2$ in Scheme 2, preceded by equilibrium formation of the tetrahedral adduct. The fission step for these substrates requires assistance by water. This could be as is shown in the transition state **15** or by water catalysing a transfer of a proton from the hydroxy group below.



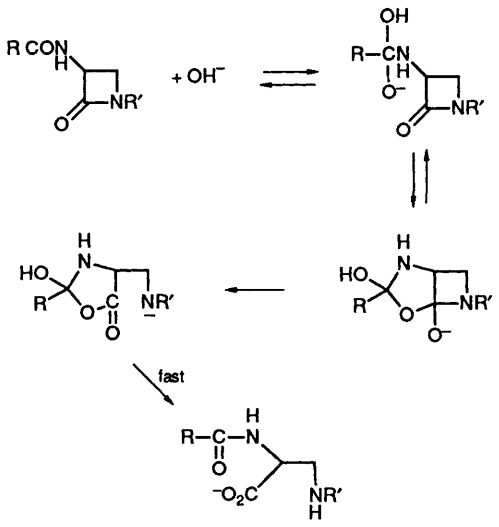
**15**

*Acylamino Side-chains in Penicillins.*—The acylamino side-chain was considered to be a possible source of a neighbouring-group effect in early studies.[25] However, Butler *et al.*[5] considered the specific possibility of neighbouring carbonyl participation as shown in Scheme 3. They dismissed this on the grounds of the activation parameters for the alkaline hydrolysis. However, Bowden *et al.*[27] have characterised such reactions in ester hydrolysis, which involve attack on keto carbonyl groups, by use of substituent effects. The Hammett ρ values for substitution in the benzoyl group, if such effects occur in **13c**–**13f**, would be expected to be comparable to those for benzoate alkaline hydrolysis and related reactions, *i.e. ca.* 2, and would then indicate attack at the neighbouring carbonyl group.[26] An alternative form of neighbouring-group effect is that observed for esters and amides of phthalamic acids.[27] This is formulated in Scheme 4 for 3-acylamino β-lactams. Such a pathway would require ionisation of the amide and a Hammett ρ value of about 1.3 can be predicted for the system **13a**.[12]

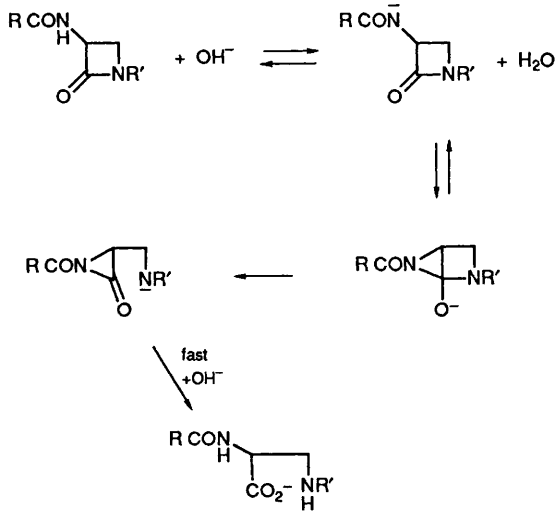
The studies of the effects of *meta*-substitution on the alkaline hydrolysis of phenyl penicillin are shown in Table 4 and the effects are very small. The Hammett equation can be used to assess the effect of substitution and results in the correlation shown in eqn. (2) below, using known σ values.[28] Thus there is no evidence for either of the possible neighbouring-group participation effects and the reaction constant observed is that expected on the basis of the transmission of polar effects[29] from the benzoyl group to the lactam carboxy group.

$$\log (k/k_o) = 0.251\,\sigma - 0.774 \qquad (2)$$

(Correlation coefficient = 0.999 and standard deviation = 0.066 for four substituents)




Scheme 3




Scheme 4

*Reactivity Factors for β-Lactams.*—The difference in reactivity for benzylpenicillin and *N*-methyl β-lactam, $\Delta\Delta G^{\ddagger}$, is about 4.6 kcal mol$^{-1}$ * at 30 °C. Comparison of the models, shown in Tables 1 and 2, allows an estimate of the contributions to reactivity from likely sources, *i.e.* (*i*) the fused five-membered ring, (*ii*) the 3-acylamino side-chain, and (*iii*) the 4-thio substitution. Considerations of models **10** and **11**, as well as of **12**, in Table 1 indicates an increased reactivity of about 2.6 kcal mol$^{-1}$ at 30 °C, resulting from the fusion of the five-membered ring. The effect of the 3-acylamino group can be estimated as 2.1 kcal* mol$^{-1}$ at 30 °C from the models **8a** and **8c** in Table 2. The total estimate of $\Delta\Delta G^{\ddagger}$ equal to 4.7 kcal* at 30.0 °C is in surprisingly good agreement with the observed result. Other factors must be absent or very minor.

Page [30] has considered in detail the mechanism and reactivity of β-lactam antibiotics. He has clearly stated that the biological reactivity is not solely a function of the reactive β-lactam, but a function of transport to and binding at the required enzyme. However, the reactivity of simple penicillins in their alkaline hydrolysis [31] can be almost fully simulated in model systems by a fused ring system and 3-acylamino group.

* 1 cal = 4.184 J.

## Experimental

*Materials.*—*N*-Phenylazetidin-2-one (**4b**), -2-pyrrolidone (**5b**) and -2-piperidone (**6b**), as well as *N*-methylacetanilide (**7e**) were available from our previous study.[1] *N*-Methyl and ethylazetidin-2-one **4a** and **4c** were prepared by reaction of the appropriate ethyl alkylaminopropionate and ethyl magnesium bromide.[6] *N*-Methyl-2-pyrrolidone (**5a**) and -2-piperidone (**6a**) were commercially available. *N*-Ethyl-2-pyrrolidone (**5c**) was prepared by reaction of the anion of 2-pyrrolidone (generated from the lactam and sodium hydride) with ethyl bromide. The *N*-alkyl-*N*-methylacetamides (**7a**)–(**7d**) were prepared by the latter method from the appropriate *N*-alkylacetamide and methyl iodide. 1,4-Diphenylazetidin-2-one (**8a**) was prepared from benzalaniline and ethyl bromoacetate by means of a Reformatsky reaction.[32] Acylation with phenylacetyl chloride of 3-amino-1,4-diphenylazetidin-2-one (**8b**), prepared by Sheehan's method,[33] gave 3-phenylacetamido-1,4-diphenylazetidin-2-one (**8c**).[33] Addition of *N*-benzylideneaniline to dimethylketene gave 3,3-dimethyl-1,4-diphenylazetidin-2-one (**9a**).[34] 3,3-Dimethyl-4-methylthio-1,4-diphenylazetidin-2-one (**9b**) was prepared similarly by the addition of dimethylketene to 5-methylthiobenzanilide.[6] Methylation of 3-phenylazetidin-2-one gave 1-methyl-3-phenylazetidin-2-one (**10**).[7] 6-Phenyl-1-azabicyclo-[3.2.0]heptan-7-one (**11a**) and 7-phenyl-1-azabicyclo[4.2.0]-octan-8-one (**11b**) were prepared by photolysis of 1-(α-diazophenylacetyl)-piperidine and -pyrrolidine, respectively.[8,9] 6,6-Dimethyl-5-phenyl-4-thia-1-azabicyclo[3.2.0]heptan-7-one (**12**) was prepared *via* the lactam formed by the reaction of 2-phenylthiazoline and dimethylketene.[35] Benzylpenicillin sodium salt (**13a**) was available commercially pure. 6β-Aminopenicillanic acid (**13b**) was a generous gift from Beecham Research Laboratories Ltd. The reaction of the appropriate substituted benzoyl chloride with the latter compound gave the substituted phenyl penicillins.[36] The only previously unreported compound was *N*-t-butyl-*N*-methylacetamide **7d**, m.p. 26–28 °C, b.p. 63–64 °C/9 mmHg (Found: C, 64.8; H, 11.9; N, 10.3. $C_7H_{15}NO$ requires C, 65.1; H, 11.6; N, 10.8%). After recrystallisation or distillation, and drying in a vacuum desiccator ($P_2O_5$), all the compounds had m.p.s or b.p.s in good agreement with literature values.[1,6–9,32–39] The purity of the compounds was assessed to be greater than 99% from their $^1$H NMR spectra and from GLC, as applicable. The model compounds **11a**, **11b** and **12** can exist as *cis*- or *trans*-isomers and were found to be *trans* compounds from their $^1$H NMR spectra, *cf.* refs. 8 and 9. Benzylpenicillin sodium salt (**13a**) has been found to have *cis* stereochemistry in the β-lactam ring.[38] Solvents were purified as described previously.[39]

*Kinetic Measurements.*—Rate coefficients for the alkaline hydrolysis of the lactams and amides were determined spectrophotometrically by use of Unicam SP800 and 8000 spectrophotometers. The cell temperature was controlled to within ±0.05 °C from 20 to 60 °C and to within ±0.1 °C from 60 to 90 °C by means of a Churchill thermocirculator. The method used for all the lactams and amides up to 90 °C was that described previously,[1] using the wavelengths shown in Tables 1, 2 and 4. For the measurements at 100.0 °C, the following method was used. Standardised solutions of aqueous sodium hydroxide (5 cm$^3$) were placed in Pyrex tubes and aqueous solutions of the substrate (0.5 cm$^3$) were added. Each was then carefully flame-sealed. The reactions, which were very slow at room temperature, were initiated by simultaneously plunging all tubes of one batch into an oil bath (thermostatted to ±0.1 °C). Tubes were removed at timed intervals (removal of first tube taken as time zero) and rapidly quenched in ice–water. Portions of the contents of the tube (either 0.02 or 0.05 cm$^3$) were added to an excess of acid (0.05 mol dm$^{-3}$ aqueous $H_2SO_4$; 3 cm$^3$) in 1 cm silica cells and, after thorough mixing and

thermal equilibration, absorbance measurements were made at 200 nm. The kinetic solvent isotope effects were studied by simultaneous measurements in $H_2O$ and $D_2O$. The rate coefficients were calculated by means of Guggenheim's method[40] when required. Two well-behaved substrates, **4a** and **7a**, were used to calculate the kinetic activity of concentrated sodium hydroxide from the observed first-order rate coefficients and the calculated second-order rate coefficients obtained from measurements at $[OH^-] < 0.1$ mol dm$^{-3}$. Thus, an activity of $5.5_5$ mol dm$^{-3}$ was found for 3.5 mol dm$^{-3}$ aqueous sodium hydroxide at 100.0 °C. This treatment was only required for **7c** and **7d**.

*Product Analysis*.—The products of the alkaline hydrolysis of the lactams and acetamides studied here are the anions of the *N*-phenyl and *N*-alkyl amino acids or acetic acid with the *N*-alkylmethylamines, (*cf.* refs. 1, 5 and 10). The products of typical *N*-phenyl lactams were studied as previously described.[1] Typical *N*-alkyl lactams were subjected to acid hydrolysis in dilute hydrochloric acid and the products isolated as the hydrochlorides (*cf.* refs. 7–9). Comparison of the latter with and examination of the products of the alkaline hydrolysis by TLC and/or $^1$H NMR spectroscopy indicated their structures to be those expected. Comparison of the UV–VIS spectra of the reaction after ten half-lives with those products isolated or available under the same conditions showed identical or almost identical results, except as discussed below. The hydrolysis of the 4-methylthio β-lactam **9b** is known to proceed beyond ring fission to give aliphatic thiol products.[6] However, the close similarity of the UV spectral changes during the alkaline hydrolysis to that observed for all the other *N*-phenyl derivatives indicates the process followed is the primary reaction giving fission of the β-lactam ring. Similarly the fused thiazolidine β-lactam **12** has similar spectral changes on alkaline hydrolysis to the penicillin derivatives. Both these compounds have further UV–VIS spectral changes indicating secondary hydrolysis. However, the latter reactions are sufficiently slow to enable the primary processes to be studied independently. β-Lactams with reactive side-chains could give other hydrolysis products. Under the conditions of this kinetic study, **8c** and the penicillins, **13a**, **13c–13f** gave the products resulting from β-lactam ring fission (*cf.* ref. 31).

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