Reactions of Carbonyl Compounds in Basic Solutions. Part 27.[1] Alkaline Hydrolysis of Bridged Benz[*de*]isoquinolin-1-ones: Torsionally Distorted Lactams†

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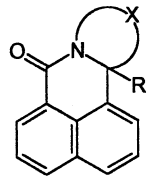
Keith Bowden* and Simon P. Hiscocks

Department of Biological and Chemical Sciences, Central Campus, University of Essex, Wivenhoe Park, Colchester, Essex CO4 3SQ, UK

Rate coefficients have been measured for the alkaline hydrolysis of 2,3-ethanoxy- and 2,3-propanamino-2,3-dihydro-1*H*-benz[*de*]isoquinolin-1-ones‡ in 70% (v/v) dimethyl sulfoxide–water at several temperatures and of *N*,*N*-dimethyl-1-naphthamide in water: the relative rates of hydrolysis, activation parameters and other studies indicate the importance of the torsional distortion of the lactam nitrogen and steric 'bulk' factors in controlling reactivity.

There have been a number of studies of the alkaline hydrolysis of strained lactams[2–4] and amides.[5] Structural distortion of an amide or lactam group from planarity has been demonstrated to increase the reactivity towards alkaline hydrolysis. Several bicyclic lactams have been used to establish a relationship between the degree of distortion and the susceptibility towards hydrolysis.[3,4] However, these lactams all involve alkyl–carbonyl and aryl–amine linkages.

The present study is an investigation of the alkaline hydrolysis of the torsionally distorted lactams, the 2,3-bridged 2,3-dihydro-1*H*-benz[*de*]isoquinolin-1-ones **1**, in which the lactams have aryl–carbonyl and alkyl–amine linkages, while being locked by a 1,8-naphthalene template. The effects of structure and substitution on the rates of reaction, as well as the activation parameters, are considered to enable an analysis of the reactivity and reaction mechanism.



R—CONMe$_2$

1a R = H, X = –[CH$_2$]$_2$O–
b R = H, X = –[CH$_2$]$_3$NH–
c R = Ph, X = –[CH$_2$]$_2$O–
d R = Ph, X = –[CH$_2$]$_3$NH–

2a R = Ph
b R = 1-Naphthyl

Experimental

Materials.—*N*,*N*-Dimethyl-1-naphthamide (**2b**) was prepared by the reaction of 1-naphthoyl chloride with dimethylamine.[6] The 2,3-bridged 2,3-dihydro-1*H*-benz[*de*]isoquinolin-1-ones **1a–d** were prepared by the reaction of 8-formyl- or 8-benzoyl-1-naphthoyl chloride in chloroform with an excess of ethanolamine or 1,3-diaminopropane. The reaction products were purified by use of a Chromatotron (dichloromethane–ethyl acetate). **1a** and **2b** are known compounds[6,7] and were recrystallised from ethyl acetate.

Melting points are uncorrected. IR spectra were recorded on a Zeiss Specord M-80 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL EX270 FT spectrometer with Me$_4$Si as internal reference. Chemical shifts are expressed as δ/ppm. The purity of the lactams and amide was monitored by IR and ^{1}H and ^{13}C NMR spectroscopy, as well as mass spectroscopy. The mps of the compounds, after repeated recrystallisation and drying under reduced pressure (P_2O_5), were either in agreement with literature values[6,7] or are shown below, together with their spectral details and elemental analysis.

10,11,12,12a-*Tetrahydro*-9H-*benzo*[de]*pyrimidino*[1,2-b]*isoquinolin*-7-*one* (**1b**) (32%), mp 155–158 °C (colourless needles from ethyl acetetate); ν_{max}/cm^{-1} ($CHCl_3$) 1649 (C=O); ([$^2H_6$]Me$_2$SO) 3.51–4.20 (m, 6 H, CH_2), 4.88 (1 H, NH), 6.11 (s, 1 H, CH), 7.63–8.21 (m, 6 H, arom.); *m*/*z* (70 eV) 238 (M^+) (Found: C, 75.2; H, 6.2; N, 11.65%). $C_{15}H_{14}N_2O$ requires C, 75.6; H, 5.9; N, 11.75%).

11a-*Phenyl*-9,10-*dihydro*-11aH-*benzo*[de][1,3]*oxazolo*[3,2-b]*isoquinolin*-7-*one* (**1c**) (13%), mp 151–153 °C (colourless needles from ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$) 1648 (C=O); δ_H ($CDCl_3$) 3.28–4.60 (m, 4 H, CH_2), 7.13–8.52 (m, 11 H, arom.); *m*/*z* (70 eV) 301 (M^+) (Found: C, 79.4; H, 4.95; N, 4.55. $C_{20}H_{15}NO_2$ requires C, 79.7; H, 5.0; N, 4.65%).

12a-*Phenyl*-10,11,12,12a-*tetrahydro*-9H-*benzo*[de]*pyrimidino*[1,2-b]*isoquinolin*-7-*one* (**1d**) (5%), mp 255–256 °C (colourless needles from ethyl acetate); ν_{max}/cm^{-1} ($CDCl_3$) 1647 (C=O); δ_H ($CDCl_3$) 1.58–2.96 (m, 6 H, CH_2), 7.14–8.53 (m, 11 H, arom.); 5.05 (1 H, NH); *m*/*z* (70 eV) 314 (M^+) (Found: C, 80.25; H, 5.75;l N, 8.9. $C_{21}H_{18}N_2O$ requires C, 80.25; H, 5.75; N, 8.9%).

The solvents were purified as described previously.[8]

Measurements.—Rate coefficients for the alkaline hydrolysis of the lactams and amide were determined by use of a Perkin-Elmer Lambda 5 or 16 UV–VIS spectrometer. The cell temperature was controlled to within ±0.05 °C by means of a Haake DC3 circulator. The reactions were followed at the wavelengths shown in Table 1. The procedure used as that described previously.[9] The alkaline hydrolysis of **1a**, **1b** and **2b** is of first order in both substrate and hydroxide anion. The rate coefficient in 70% (v/v) aqueous dimethyl sulfoxide (DMSO) and other solvent systems are shown in Table 1. The activation parameters are shown in Table 2. The products of the alkaline hydrolysis of **2b** are the anion of 1-naphthoic acid and dimethylamine, that of **1a** is the anion of 8-(1,3-oxazolidin-2-yl)-1-naphthoic acid **3a** and that of **1b** is the anion of 8-(hexahydropyrimidin-2-yl)-1-naphthoic acid **3b**. Both the structures of **3a** and **3b** were determined by ^{1}H NMR spectroscopy of the solution of the product in 70% (v/v) [$^2H_6$]DMSO–D_2O. The corresponding acids could not be obtained pure on acidification, as cyclisation occurred. Both **1c** and **1d** were *very* resistant to alkaline hydrolysis. No significant reaction could be observed for either substrate after 12 h at 60 °C in 70% (v/v) aqueous DMSO and 0.3 mol dm^{-3} base.

Discussion

A mechanistic pathway for the alkaline hydrolysis of lactams under present study is shown in Scheme 1.[2,4] The first step is the addition of base to form the adduct **4**, which collapses to form **5**. The latter rapidly transforms to the final product **3**.

The lactams **1a** and **1b** are relatively reactive in their alkaline hydrolysis, *cf*. ref. 2. The relative rate of hydrolysis in water of **1a** (extrapolated) to **2b** at 60.0 °C is *ca*. 60. This is considerably less than the factor of *ca*. 10^7 noted by Brown's group[4] in passing from *N*-methylacetanilide to their most distorted lactam, 3,4-dihydro-1,4-ethanoquinolin-2(1*H*)-one (**6**).

The torsional distortions in **1a** and **1b** are not as great as that in **6**, but the effect on the rates appears to persist in systems with aryl–carbonyl and alkyl–amino linkages. The lactam **1a** has a fused ring consisting of a five-membered ring containing nitrogen and oxygen, whereas **1b** has a six-membered ring containing nitrogen and nitrogen. The small difference in their rates of hydrolysis, a factor of *ca*. 2, indicates that the effect is achieved by ring fusion itself and does not depend on ring size. A comparison of the activation parameters for the hydrolysis of **1a** and **1b** with those for related systems indicates that the hydrolysis of the latter shows rather large $\Delta H^{\ddagger}$

*To receive any correspondence (*email*: keithb@essex.ac.uk).

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‡9,10-Dihydro-11a*H*-benzo[*de*]oxazolo[3,2-*b*]- and 10,11,12,12a-tetrahydro-9*H*-benzo[*de*]pyrimidino[1,2-*b*]-isoquinolin-7-ones respectively.

Table 1 Rate coefficients (k_2) for the alkaline hydrolysis of the lactams **1a** and **1b** in 70% (v/v) aqueous DMSO[a]

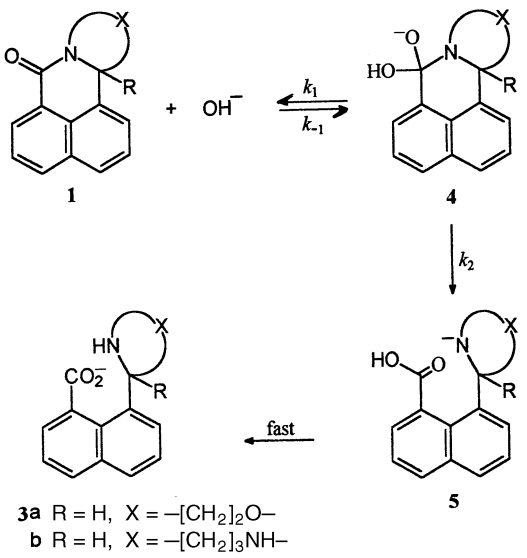
	$10^3 k_2$/dm^3 mol^{-1} s^{-1}				
Compound	At 30.0 °C	At 40.0 °C	At 50.0 °C	At 60.0 °C	λ/nm[b]
1a	0.920	2.58	6.74	16.0 (5.27)[c] (3.25)[d]	325
1b	1.87	5.63	14.6	38.3	350
2b				(0.0360)[e]	240

[a]Rate coefficients were reproducible to ±3%. [b]Wavelengths used to monitor alkaline hydrolysis. [c]In 50% (v/v) aqueous DMSO. [d]In 30% (v/v) aqueous DMSO. [e]In water, *i.e.* 1.5% (v/v) aqueous DMSO.

Table 2 Activation parameters for the alkaline hydrolysis of the lactams **1a** *and* **1b** in 70% (v/v) aqueous DMSO at 30.0 °C[a]

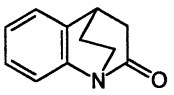
Compound	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
1a	18.5	−11
1b	19.5	−7
2a[b]	15.6	−30

[a]Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are accurate to ±300 cal mol^{-1} and ±1 cal mol^{-1} K^{-1}, respectively. [b]In water (k_2 equal to 6.0×10^{-6} and 15.2×10^{-4} dm^3 mol^{-1} s^{-1} at 25.0 and 100.4 °C, respectively).[5,10]



Scheme 1

values and *very* small negative values of $\Delta S^{\ddagger}$. This would be in accord with partial fission of the carbon–nitrogen bond in the rate-determining step releasing ring strain angle and torsional effects in the fused ring system[11] and indicates the rate determining step to be k_2 in Scheme 1, *cf.* refs. 2 and 4. The resistance to hydrolysis of **1c** and **1d** apparently arises from a steric 'bulk' effect. Dunitz *et al.*[12] have shown that nucleophilic attack at the carbonyl group of an amide occurs with stereoelectronic control at a preferred angle. This is when the nucleophile approaches the carbonyl bond along a line that forms an angle of about 107° to the plane of the bond. The lactams **1** were modelled.[13] These results show that the carbonyl carbon, nitrogen and acyl carbon are almost coplanar with the naphthalene ring and that the nitrogen is disposed towards an sp^3 pyramidal geometry by the ethanoxy or propanamino link which is itself out of this plane. The links will sterically inhibit hydroxide anion attack from that face of the plane. However, for **1a** and **1b** the face of the plane having the acyl hydrogen substituent is free for attack at the preferred angle, whereas for **1c** and **1d** this face of the plane contains the acyl phenyl substituent which almost



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completely blocks such a preferred attack by its steric 'bulk'. All the ring (pseudo) esters of 8-acyl-1-naphthoic acids previously studied[14] have at least one comparatively free face for nucleophilic attack and are relatively reactive.

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