Chemistry of 2-Bromo-2-methylpropanamides. Synthesis and Solvolytic Behaviour of Oxazolidinones and Spiro-oxazolidinones

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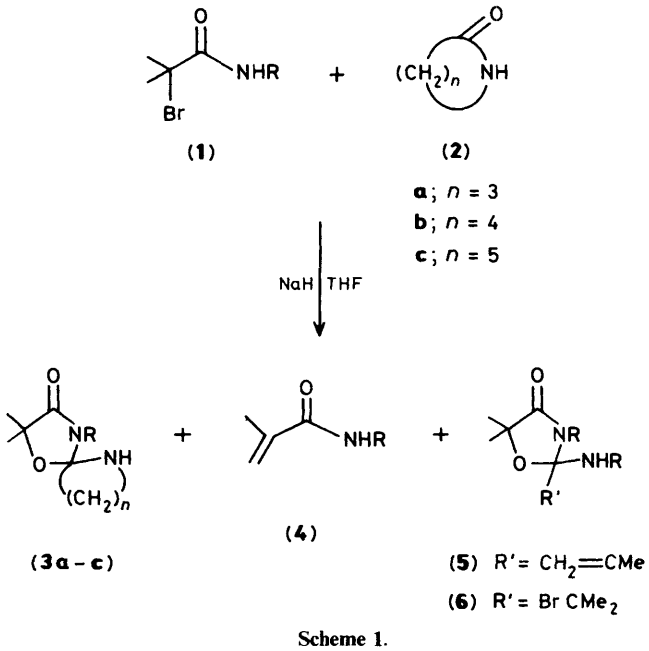
The base-promoted reaction of 2-bromo-2-methylpropanamides (**1**) with 5-, 6-, and 7-membered lactams (**2**) affords spiro-oxazolidinones (**3**). The latter compounds are hydrolysed under acidic conditions to yield the ω-aminoester amides (**7**). The solvolytic behaviour of some monocyclic oxazolidinones obtained upon reaction of common amides with 2-bromoamides (**1**) is also reported.

Amides carrying a suitably positioned halide atom are known precursors of common-ring lactams, as well as of the small-ring α- and β-lactams.[1] In previous studies of base-promoted reactions of 2-bromocarboxamides, α-lactams were obtained.[2] As a more general trend, however, we observed self-condensation reactions affording five- or six-membered heterocyclic derivatives. The observed chemoselectivity depends upon the character of the halide (1°, 2°, 3°), and the group linked to the nitrogen atom.[3] Cross-condensations of 2-bromo-2-methylpropanamides with common amides or a thioamide[4] were also observed and, in the presence of an exogeneous or electrogenerated base, with the common dipolar aprotic amide solvents *N*,*N*-dimethylformamide[5,6] and *N*,*N*-dimethylacetamide,[7] to afford the pertinent oxazolidinone derivatives. Finally, cyclohexanespiro-2-oxazolidinones arise in cross-condensations of 2-bromo-2-methylpropanamides with cyclic enaminones such as 3-aminocyclohex-2-enones.[8]

In the present paper, we report further examples of cyclocondensations of 2-bromoisobutyramides, and the solvolytic behaviour of representative products including the novel spiro-heterocycles and some oxazolidinones reported in a preliminary communication.[4] *N*-Benzyl-2-bromo-2-methylpropanamide (**1**) was used as representative starting material in most experiments, since the ^{1}H n.m.r. non-equivalence of the benzyl protons in the oxazolidinones, spiro-oxazolidinones, and solvolytic derivatives is expedient to the diagnosis of the chiral centre at the C(2), when the oxazolidine ring is present.



Scheme 1.

Unless otherwise stated, R = Benzyl throughout the paper

Results and Discussion

Base-promoted Reactions of N-*Benzyl-2-bromo-2-methylpropanamide* (**1**) *with Lactams* (**2a**—**c**).—*N*-Benzyl-2-bromo-2-methylpropanamide (**1**) reacts with lactams pyrrolidin-2-one, piperidin-2-one and perhydroazepin-2-one (**2a**—**c**) in the presence of sodium hydride in tetrahydrofuran (THF), to afford the corresponding pyrrolidino-, piperidino-, and azepino-spiro-oxazolidin-4-ones (**3a**—**c**) (Scheme 1). Not unexpectedly, the geometries of the lactam rings affect the reaction yields, which averaged 30, 60, and 50%, respectively. The *X*-ray analysis of the two crystalline spiro-heterocycles (**3b**, **c**) confirms the proposed structures.[9] The spiro-heterocycles (**3**), as well as the monocyclic oxazolidinones (**5**) and (**6**), are cyclic orthoester aminals,[10] formally derived through cyclocondensation of the unrearranged 2-bromo-2-methylpropanamide onto an amide carbonyl. The mechanism of the cyclocondensation reaction of 2-bromoamides with different reagents contributing the carbonyl group is currently under investigation through theoretical calculations and electrochemical detection of the relevant intermediates.[11] In the reactions of the bromoamide (**1**) with the three lactams (**2a**—**c**), some co-products were isolated with the following yields: the unsaturated amide (**4**): 10, 7, 15%; the condensation product (**5**) of (**1**) with (**4**): 30, 20, 10%; the self-condensation product (**6**)[12] from (**1**): *ca.* 5%.

An analogous reaction between 2-bromo-2-methyl-*N*-phenylpropanamide (**1**; R = Ph) and pyrrolidin-2-one (**2a**) afforded the pyrrolidino-spiro-oxazolidinone (**3a**; R = Ph), in low yield. Competitive formation of base-promoted reaction products from the 2-bromo-2-methyl-*N*-phenylpropanamide,[13] is dominant and makes the isolation of the spiro-derivative impractical.

Solvolysis Studies.—The spiro-heterocycles (**3a**—**c**) in which atom C(2) is linked to three heteroatoms, undergo mild acid-

catalysed hydrolysis with opening of both rings at the C(2)–N bond, to yield the ω-aminoalkanoate esters of *N*-benzyl-2-hydroxy-2-methylpropanamide (**7a—c**) (Scheme 2). The

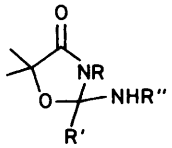
$$(\mathbf{3a—c}) \xrightarrow[H_2O]{HCl} Cl^- \; H_3\overset{+}{N}(CH_2)_nCO_2CMe_2CONHR \quad (\mathbf{7a—c})$$

Scheme 2.

$$(\mathbf{7a}) \longrightarrow (\mathbf{2a}) + HOCMe_2CONHR \quad (\mathbf{8})$$

Scheme 3.

relative ease of hydrolysis follows the order: (**3a**) > (**3c**) > (**3b**). The resulting aminoester amides (**7a—c**), in turn, are rather unstable; for example, (**7a**) decomposes spontaneously, to afford the 2-hydroxyamide (**8**) and the parent lactam (**2a**) (Scheme 3), possibly due to recyclization through intramolecular ester aminolysis.



(**9**)

	R	R′	R″
a;	$PhCH_2$	Ph	Me
b;	$PhCH_2$	Ph	Ph
c;	$PhCH_2$	*p*-BrC_6H_4	Me
d;	$PhCH_2$	Me	$PhCH_2$
e;	Bu^t	Me	$PhCH_2$

$$(\mathbf{9a—e}) \xrightarrow{H_3O^+} R'CO_2CMe_2CONHR + R''NH_3^+$$

(**10**)

	R′	R
a;	Ph	$PhCH_2$
b;	*p*-BrC_6H_4	$PhCH_2$
c;	Me	$PhCH_2$
d;	Me	Bu^t
e;	$BrCMe_2$	Me
f;	CH_2=CMe	Ph

Scheme 4.

Acid hydrolysis of representative members of the monocyclic 2-amino-oxazolidin-4-ones (**9**) gives the corresponding amide ester (**10**) and amine (Scheme 4);[4] oxazolidinones (**5**; R = Ph), (**6**; R = Me) show similar behaviour. However, in different solvolytic conditions (see Experimental section), the open-chain amide ester (**10**), its cyclic tautomer, *i.e.*, a 2-hydroxy-oxazolidinone derivative (**11**), and a 2-ethoxyoxazolidinone (**12**) were obtained. The chirality at C-2 causes a variable chemical-shift difference at the N-3 benzyl protons in the oxazolidinone and spiro-oxazolidinone derivatives, smaller than reported for four- and five-membered ring lactams.[14] Further, in the solvolysis products (**11**) and (**12**), a chemical-shift difference was observed for the geminal methylene protons of a 2-benzylamino or 2-ethoxy group. Finally, the two methyl groups at C-5 were non-equivalent in all cyclic derivatives, except the two spiro-oxazolidin-4-ones (**3a**, **c**).

Preliminary kinetic experiments on the conversion of the representative oxazolidinone (**9a**) into the amide ester (**10a**) indicated that the rate of hydrolysis in water at 25 °C was independent of the acidity at pH 1.2—3.5, increased from pH 3.5 to 5.5, and then decreased. The bell-shaped pattern of the logarithm of the observed rate constant *vs.* pH (see Figure) is similar to the one observed in the hydrolysis of some amide acetals.[15a] The related amide acetal (**12**) is hydrolysed to (**10**) at rates identical with the ones observed for (**9a**) at the two pH values investigated, *i.e.*, 2.5 and 5.5. The rate-determining step must follow the formation of the carbocation (**13**) that may be

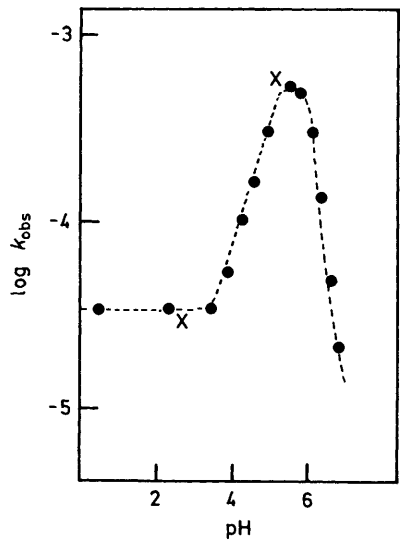
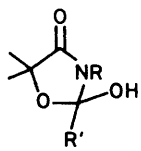


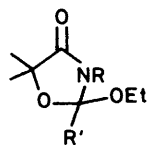
Figure. Logarithm of the observed rate constant, k_{obs}, for the hydrolysis of oxazolidinones (**9a**), (●), and (**12**), (×), as a function of pH. The dotted line has been arbitrarily drawn

envisaged as the common intermediate in the hydrolytic process.[15] Intermediate (**13**) could subsequently react with water affording an amide hemiacetal and finally the ester (**10**) could be isolated. In the hydrolysis of (**9d**), the amide hemiacetal intermediate (**11**) was isolated and fully characterized (see Experimental section). It is interesting to note that ring opening involves exclusively the cleavage of the C(2)–N bond.* No product such as (**14**) related to a C(2)–O opening mode was



(**11**)

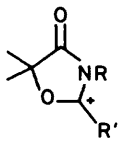
R′ = Me



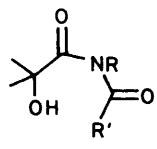
(**12**)

a; R′ = Ph

b; R′ = Me



(**13**)



(**14**)

observed.[15a,c] In view of the interest in tetrahedral intermediates in solvolysis reactions,[15] the present relatively stable compounds look particularly suitable for detailed kinetic analysis.

Experimental

M.p.s were determined with a Reichert-Kofler hot stage microscope and are uncorrected. ^{1}H N.m.r. spectra were

* The hydrolytic behaviour at pH > 7 was not examined in the present study. Different opening modes could take place under basic conditions.[15a]

measured with a Perkin-Elmer R32 spectrometer operating at 90 MHz, in $CDCl_3$: chemical shifts are in δ p.p.m. downfield from $SiMe_4$ as internal standard. I.r. spectra were measured with a Perkin-Elmer 157 G. All samples were purified until they gave a single spot in t.l.c., using 0.25 mm SiO_2 plates (Merck) and ethyl acetate–toluene (1:4) as eluant. Column chromatography was performed using columns of SiO_2 (Merck, KG-60) or Al_2O_3 (Fluka). Unsatisfactory elemental analysis were obtained for the aminoester amide hydrochlorides (**7**) and some other products, possibly due to strong association of amide-like compounds. Sodium hydride (50% in mineral oil, Fluka) was washed free from the oil, with light petroleum (b.p. 30—50 °C), immediately before use. Pyrrolidin-2-one, piperidin-2-one, and perhydroazepin-2-one (**2a**—**c**) from Fluka AG were dried over NaOH pellets. Tetrahydrofuran (THF) was dried over $CaCl_2$ and redistilled from $LiAlH_4$. Samples were dried over P_2O_5 under vacuum to a constant weight.

Synthesis of Spiro-oxazolidinones.—(a) 4-*Benzyl*-2,2-*dimethyl*-1-*oxa*-4,6-*diazaspiro*[4,4]*nonan*-3-*one* (**3a**). Pyrrolidin-2-one (**2a**) (0.85 g, 10 mmol) in THF (10 ml), was added to a suspension of sodium hydride (0.58 g, 12 mmol) in THF (8 ml), and the mixture was stirred for a few hours or overnight at room temperature. *N*-Benzyl-2-bromo-2-methylpropanamide (**1**)[12] (2.56 g, 10 mmol) in THF (50 ml) was added during 1 h, stirring was continued for 30 min, and then the mixture was centrifuged and the solution evaporated to dryness. The crude oil was chromatographed using a column of Al_2O_3, to yield compound (**3a**) (0.82 g, 32%) as an oil; R_F 0.3; $\nu_{max.}$(neat) 3 360 (NH) and 1 710 cm^{-1} (CO); δ($CDCl_3$) 1.4 (6 H, s, Me_2), 1.6—1.9 (5 H, m, 2 × CH_2, NH), 2.9—3.2 (2 H, m, H_2CN), 4.36 and 4.63 (2 H, AB, *J* 15.3 Hz, CH_2Ph), and 7.25 (5 H, s, Ph) (Found: C, 69.15; H, 7.75; N, 10.6. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.74; N, 10.76%). Subsequent fractions yielded the following co-products: (**4**) 10%; (**5**) (see below) 20—30%; (**6**) 5%.

(b) 4-*Benzyl*-2,2-*dimethyl*-1-*oxa*-4,6-*diazaspiro*[4,5]*decan*-3-*one* (**3b**). Piperidin-2-one (**2b**) was allowed to react with compound (**1**) in a similar manner as for compound (**2a**), but at 50 °C, due to the low solubility of the sodium salt of piperidin-2-one in THF. Chromatography on Al_2O_3 yielded compound (**3b**) as colourless prisms (52—60%), m.p. 133—135 °C; R_F 0.5; $\nu_{max.}$(KBr) 3 310 (NH) and 1 695 cm^{-1} (CO); δ($CDCl_3$) 1.38 and 1.4 (6 H, 2 × s, Me_2), 1.25—1.8 (7 H, m, 3 × CH_2, NH), 2.7—3.3 (2 H, m, H_2CN), 4.3 and 4.7 (2 H, AB, *J* 15.3 Hz, CH_2Ph), and 7.3 (5 H, s, Ph) (Found: C, 70.35; H, 8.15; N, 10.35. $C_{16}H_{22}N_2O_2$ requires C, 70.07; H, 8.08; N, 10.21%). Subsequent fractions yielded the following co-products: (**4**) 7%; (**5**) 20%; (**6**) 1%.

(c) 4-*Benzyl*-2,2-*dimethyl*-1-*oxa*-4,6-*diazaspiro*[4,6]*undecan*-3-*one* (**3c**). Compound (**3c**) was obtained in a similar way to compounds (**3a**, **b**) from perhydroazepin-2-one (**2c**) and (**1**) as colourless prisms (49%), m.p. 72—75 °C; R_F 0.6; $\nu_{max.}$($CHCl_3$) 3 380 (NH) and 1 695 cm^{-1} (CO); δ($CDCl_3$) 1.42 (6 H, s, Me_2), 1.3—2.0 (9 H, m, 4 × CH_2, NH), 2.8—3.0 (2 H, m, H_2CN), 4.46 and 4.58 (2 H, AB, *J* 18 Hz, CH_2Ph), and 7.3 (5 H, s, Ph) (Found: C, 69.4; H, 8.5; N, 9.65. $C_{17}H_{24}N_2O_2$ requires C, 70.80; H, 8.39; N, 9.71%). The following co-products were also obtained: (**4**) 15%; (**5**) 10%; (**6**) 5%.

Synthesis of Oxazolidinones.—(a) 3-Benzyl-5,5-dimethyl-2-methylamino-2-phenyloxazolidin-4-one (**9a**).[4] A sample of *N*-methylbenzamide (Aldrich, m.p. 76—78 °C) (0.68 g, 5 mmol) in THF (10 ml) was added during 10 min with stirring to sodium hydride (0.22 g, 9 mmol) suspended in THF (5 ml). When the evolution of hydrogen had subsided, *N*-benzyl-2-bromo-2-methylpropanamide (**1**) (1.02 g, 4 mmol) in THF (10 ml) was added during 2 h with continuous stirring. The mixture was centrifuged, the solution was concentrated to dryness, and the residue chromatographed on a column of SiO_2. The title product (**9a**) was obtained as colourless prisms (0.78 g, 65%), m.p. 97—99 °C; $\nu_{max.}$($CHCl_3$) 3 395 (NH) and 1 695 cm^{-1} (CO); δ($CDCl_3$) 1.54 and 1.56 (6 H, 2 × s, Me_2), 2.15 (3 H, s, MeN), 4.28 and 4.6 (2 H, AB, *J* 15 Hz, CH_2), and 6.7—7.7 (10 H, m, 2 × Ph) (Found: C, 73.1; H, 7.2; N, 8.85. $C_{19}H_{22}N_2O_2$ requires C, 73.52; H, 7.14; N, 9.02%). Separate fractions yielded compound (**5**), m.p. 73—75 °C[4] (43 mg, 6%); $\nu_{max.}$(KBr) 3 340 (NH) and 1 715 cm^{-1} (CO); $\nu_{max.}$($CHCl_3$) 3 460 (br, NH) and 1 705 cm^{-1} (CO); δ($CDCl_3$) 1.45 and 1.53 (6 H, 2 × s, Me_2), 1.69 (3 H, s, MeC=), 2.47 (1 H, s, NH, exchanges with D_2O in few min), 3.37 and 3.79 (2 H, AB of ABX, CH_2NH, J_{AX} 13 Hz, J_{BX} 12 Hz, J_{AB} 1.8 Hz), 4.26 and 4.65 (2 H, AB, *J* 14 Hz, CH_2N), 5.1 and 5.4 (2 H, 2 × s, H_2C=), and 7.3 (10 H, m, 2 × Ph) (Found: C, 75.25; H, 7.35; N, 7.80. $C_{22}H_{26}N_2O_2$ requires C, 75.4; H, 7.47; N, 7.98%). Compound (**5**) was also obtained (in 58% yield) upon reaction of (**1**) with *N*-benzylmethacrylamide (**4**), in the same way as for (**9a**).

(b) 2-Anilino-3-benzyl-5,5-dimethyl-2-phenyloxazolidin-4-one (**9b**) was obtained as was (**9a**) from benzanilide, sodium hydride, and compound (**1**) as prisms from ethanol–water, m.p. 103—105 °C (66%);[4] $\nu_{max.}$(KBr) 3 325 (NH) and 1 700 cm^{-1} (CO); δ($CDCl_3$) 1.4 and 1.6 (6 H, 2 × s, Me_2), 3.94 and 4.78 (2 H, AB, *J* 15.4 Hz, CH_2), 4.2 (1 H, s, NH, exchanges with D_2O in 3 min), and 7.0—7.6 (15 H, m, 3 × Ph) (Found: C, 77.55; H, 6.5; N, 7.4. $C_{24}H_{24}N_2O_2$ requires C, 77.39; H, 6.49; N, 7.51%).

(c) 3-*Benzyl*-2-p-*bromophenyl*-5,5-*dimethyl*-2-*methylamino*-*oxazolidin*-4-*one* (**9c**). A sample of *N*-methyl-*p*-bromobenzamide (1.07 g, 5 mmol) in THF (10 ml) was added to sodium hydride (0.43 g, 9 mmol) suspended in THF (10 ml). Compound (**1**) (1.02 g, 4 mmol) in THF (10 ml) was added with stirring during 1 h. After being stirred for a further 0.5 h, the mixture was centrifuged and the solution was taken to dryness. The crude residue (1.1 g) was chromatographed on alumina, to yield prisms (0.8 g, 40%), m.p. 134 °C from diethyl ether–light petroleum; $\nu_{max.}$(KBr) 3 330 (NH) and 1 700 cm^{-1} (CO); δ($CDCl_3$) 1.54 and 1.55 (6 H, 2 × s, Me_2), 2.18 (3 H, s, MeN), 4.3 and 4.54 (2 H, AB, *J* 17 Hz, CH_2), and 6.8—7.8 (9 H, m, Ar) (Found: C, 59.1; H, 5.35; Br, 21.95; N, 6.9. $C_{19}H_{21}BrN_2O_2$ requires C, 58.79; H, 5.44; Br, 21.08; N, 7.2%).

(d) 3-Benzyl-2-benzylamino-2,5,5-trimethyloxazolidin-4-one (**9d**).[4] *N*-Benzylacetamide (3 g, 0.02 mol), sodium hydride (0.48 g, 0.02 mol), and compound (**1**) (5.12 g, 0.02 mol), were allowed to react and the mixture was worked up according to the above procedure. Chromatography on Al_2O_3 gave an oil that was recrystallized from ethyl acetate–light petroleum (40—70 °C) or from hexane as prisms (25%), m.p. 100—102 °C;[4] $\nu_{max.}$(KBr) 3 340 (NH) and 1 695 cm^{-1} (CO); δ($CDCl_3$) 1.37, 1.49, and 1.53 (9 H, 3 × s, 3 × Me), 3.25 and 3.7, after exchange with D_2O of NH for 10 min (2 H, AB, *J* 12 Hz, CH_2NH), 3.3 (1 H, br m, NH), 4.31 and 4.69 (2 H, AB, *J* 14.5 Hz, CH_2N), and 7.3 and 7.4 (10 H, 2 × s, 2 × Ph) (Found: C, 72.35; H, 7.4; N, 8.4. $C_{20}H_{24}N_2O_2$ requires C, 74.04; H, 7.45; N, 8.63%).

(e) 2-Benzylamino-2,5,5-trimethyl-3-t-butyloxazolidin-4-one (**9e**) was obtained from *N*-benzylacetamide, sodium hydride and 2-bromo-2-methyl-*N*-t-butylpropanamide (**1**; R = Bu^t) as prisms from light petroleum (b.p. 40—60 °C), m.p. 50—52 °C[4] (Found: C, 70.3; H, 8.9; N, 9.65. $C_{17}H_{26}N_2O_2$ requires C, 70.31; H, 9.02; N, 9.65%).

Hydrolysis of Spiro-oxazolidinones.—(a) 1-(N-*Benzyl*-*carbamoyl*)-1-*methylethyl* 4′-*aminobutanoate* (**7a**) *hydrochloride and* N′-*benzoyl derivative.* Hydrochloric acid (5M, 0.8 ml, 4 equiv.) was added with stirring to a solution of the spiro-oxazolidinone (**3a**) (1.04 g, 4 mmol) in absolute ethanol, and stirring was continued overnight. The mixture was evaporated to dryness and the residue was triturated with diethyl ether and dried. Hygroscopic oil (0.8 g, 69%), $\nu_{max.}$($CHCl_3$) 3 450br (NH),

1 740 (ester, CO), and 1 665 cm^{-1} (amide CO); δ($CDCl_3$) 1.4 (6 H, s, Me_2), 1.5—2.0 (4 H, m, 2 × CH_2), 2.9—3.2 (2 H, m, H_2CN), and 4.4 (2 H, d, or unresolved m, CH_2Ph). Elemental data for $C_{15}H_{23}ClN_2O_3$ were unsatisfactory. Accordingly, a sample of the oil (0.8 g, 2.6 mmol) was benzoylated under Schotten-Bauman conditions in water (10 ml) with benzoyl chloride (0.38 g, 2.7 mmol) and 1M NaOH (5.5 ml) (or in chloroform in the presence of triethylamine). The mixture was extracted with diethyl ether (10 ml), the extract was dried (Na_2SO_4) and concentrated, and the oil was purified by chromatography on a column of SiO_2 (R_F 0.4) and recrystallized from diethyl ether–light petroleum to give colourless prisms (70%), m.p. 118—120 °C; $\nu_{max.}$($CHCl_3$) 3 300 (br, NH), 1 735 (ester CO), and 1 655 cm^{-1} (amide CO); δ($CDCl_3$) 1.4—1.8 (12 H, m, Me_2, 3 × CH_2), 4.4 (2 H, d, *J* 7 Hz, CH_2Ph), 7.2—7.7 and 8.0—8.3 (10 H, 2 × m, 2 × Ph) (Found: C, 67.8; H, 6.75; N, 7.25. $C_{22}H_{26}N_2O_4$ requires C, 69.09; H, 6.85; N, 7.32%).

A sample of (**7a**) hydrochloride (0.16 g, 0.54 mmol) was dissolved in ethyl acetate, and allowed to stand a few days, after which colourless prisms of the 2-hydroxyamide (**8**) (0.04 g, 0.2 mmol) identical with an authentic specimen were obtained: R_F 0.15, m.p. 133—135 °C; pyrrolidin-2-one (**2a**) (0.1 g, 0.12 mmol) was also obtained from the mother liquor.

(b) 1-(N-*Benzylcarbamoyl*)-1-*methylethyl* 5′-*aminopentanoate* (**7b**) *hydrochloride* (80%) was obtained in a similar way to (**7a**) from (**3b**), as a hygroscopic oil; $\nu_{max.}$($CHCl_3$) 3 420 (br, NH), 1 735 (ester CO), and 1 655 cm^{-1} (amide CO); δ($CDCl_3$) 1.6 (6 H, s, Me_2), 1.5—3.8 (8 H, unresolved m, 4 × CH_2), 4.5 (2 H, unresolved d, CH_2Ph), 7.3 (5 H, s, Ph), and 8.3 (1 H, br m, NH_3^+). Elemental data required for $C_{16}H_{25}ClN_2O_3$ were satisfactory only for Cl (Found: 11.01. Calc.: 10.78%).

A sample of the (**7b**) hydrochloride (0.16 g, 0.5 mmol) in chloroform (10 ml) was treated with triethylamine (0.1 g, 1 mmol) and benzoyl chloride (70 mg, 0.5 mmol) at room temperature. Work up gave the N′-*benzoyl* derivative of (**7b**), m.p. 105—106 °C (Found: C, 69.35; H, 7.25; N, 6.9. $C_{23}H_{28}N_2O_4$ requires C, 69.67; H, 7.12; N, 7.06%).

A sample of (**7b**) hydrochloride (0.16 g, 0.5 mmol) in methanol (1 ml) was shaken with saturated sodium hydrogencarbonate (1 ml). The resulting mixture was extracted with methylene dichloride, to yield (**7b**) free amine, as a hygroscopic oil (Found: C, 64.3; H, 8.15; N, 9.9. $C_{16}H_{24}N_2O_3$ requires C, 65.73; H, 8.27; N, 9.58%).

(c) 1-(N-*Benzylcarbamoyl*)-1-*methylethyl* 6′-*aminohexanoate* (**7c**) *hydrochloride*. Hygroscopic oil, obtained in a similar way to (**7a**, **b**); $\nu_{max.}$($CHCl_3$) 3 450 (br, NH), 1 735 (ester CO), and 1 660 cm^{-1} (br, amide CO); δ($CDCl_3$) 1.6 (6 H, s, Me_2), 1.5—3.7 (10 H, m, 5 × CH_2), 4.45 (2 H, d, *J* 7 Hz, CH_2Ph), and 7.3 (5 H, m, Ph) (Found: C, 57.85; H, 8.0; N, 7.75; Cl, 10.65. $C_{17}H_{27}ClN_2O_3$ requires C, 59.55; H, 7.94; N, 8.16; Cl, 10.34%).

Solvolysis of 2-*Amino-oxazolidinone Derivatives*.—(a) A sample of compound (**9a**) (236 mg, 0.76 mmol) was dissolved in anhydrous ethanol (25 ml) and treated with 1M HCl (0.76 ml). The solution was stirred at room temperature and the reaction followed by t.l.c. until (**9a**) had disappeared; after being left overnight, the solution was concentrated under reduced pressure. The residue was triturated with diethyl ether. Some methylamine hydrochloride remained undissolved. The solution was again concentrated to yield an oil. Column chromatography (SiO_2) gave the following: (i) 3-*Benzyl*-2-*ethoxy*-5,5-*dimethyl*-2-*phenyloxazolidin*-4-*one* (**12a**) (132 mg, 53%), oil, b.p. 215 °C (1.5 mmHg); R_F 0.54; $\nu_{max.}$($CHCl_3$) 1 715 cm^{-1} (CO); δ($CDCl_3$) 1.0 (3 H, t, *J* 7 Hz, CH_2Me), 1.53 and 1.56 (6 H, 2 × s, Me_2), 3.3 (2 H, m, collapsing to AB on irradiation at 1.0 p.p.m., CH_2O), 4.14 and 4.54 (2 H, AB, *J* 14.6 Hz, CH_2Ph), and 7.0—7.8 (10 H, m, 2 × Ph) (Found: C, 73.7; H, 7.05; N, 4.4. $C_{20}H_{23}NO_3$ requires C, 73.82; H, 7.12; N, 4.30%); (ii) 1-(N-*Benzylcarbamoyl*)-1-*methylethylbenzoate* (**10a**) (102 mg, 44%), colourless prisms, m.p. 78—80 °C; R_F 0.34; $\nu_{max.}$($CHCl_3$) 3 450 (NH), 1 750 (ester CO), and 1 680 cm^{-1} (amide CO); δ($CDCl_3$) 1.75 (6 H, s, Me_2), 4.47 (2 H, d, *J* 7 Hz, CH_2Ph), 6.37 (1 H, br t, NH), and 7.1—8 (10 H, m, 2 × Ph) (Found: C, 72.8; H, 6.55; N, 4.75. $C_{18}H_{19}NO_3$ requires: C, 72.71; H, 6.44; N, 4.71%).

(b) A sample of compound (**9b**)[4] (171 mg, 0.46 mmol) suspended in anhydrous ethanol (10 ml) was treated with a solution of HCl (0.17M) in anhydrous chloroform (2.7 ml) and the mixture was stirred overnight. The solution was taken to dryness, the residue was extracted with diethyl ether, and the extract washed with HCl (0.5M; 3 × 5 ml) and with water until neutral (3 × 5 ml), then dried and concentrated. The oil was extracted with light petroleum (40—70 °C) and the solution was concentrated to give an oil (113 mg, 78%) consisting of the oxazolidinone (**12a**) (see above).

(c) A sample of oxazolidinone (**9c**) (195 mg, 0.5 mmol) in dioxane (5 ml) was treated with 1M HCl (0.6 ml); the mixture was kept for 30 min at 20 °C, then taken to dryness and chromatographed on alumina using dichloromethane–toluene (1 : 1) as eluant. Pertinent fractions gave 1-(*N*-benzylcarbamoyl)-1-methylethyl *p*-bromobenzoate (**10b**), m.p. 76 °C; $\nu_{max.}$($CHCl_3$) 3 500 br (NH), 1 730 (ester CO), and 1 660 cm^{-1} (amide CO); δ($CDCl_3$) 1.8 (6 H, s, Me_2), 4.55 (2 H, d, *J* 7 Hz, CH_2), 6.3 (1 H, br , NH), 7.3 (5 H, s, Ph), and 7.7 and 7.85 (4 H, AB, m, C_6H_4) (Found: C, 57.75; H, 4.7; N, 3.95; Br, 21.25. $C_{18}H_{18}BrNO_3$ requires C, 57.46; H, 4.82; N, 3.72; Br, 21.24%).

(d) A sample of the oxazolidinone derivative (**9d**) (162 mg, 0.5 mmol) in absolute ethanol (6 ml) was treated with 5M HCl (0.1 ml) and the solution was allowed to stand for 4 h at 20 °C. The mixture was taken to dryness and the residue was extracted with diethyl ether, leaving some undissolved benzylamine hydrochloride; concentration of the extract gave an oil that was recrystallized from cyclohexane to give colourless prisms (97 mg, 83%) of 3-*benzyl*-2-*hydroxy*-2,5,5-*trimethyloxazolidin*-4-*one* (**11**), m.p. 94—97 °C; $\nu_{max.}$(KBr) 3 400 (NH) and 1 700 cm^{-1} (CO); $\nu_{max.}$(CCl_4) 3 600 (OH) and 1 730 (CO) cm^{-1}; δ($CDCl_3$) 1.41, 1.42, and 1.47 (9 H, 3 × s, 3 × Me), 4.5 (2 H, AB, *J* 16 Hz, CH_2Ph), and 7.38 (5 H, s, Ph) (Found: C, 66.5; H, 7.25; N, 5.9. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.28; N, 5.95%).

An identical run, as well as an experiment where (**9d**) (324 mg, 1 mmol) was treated in absolute ethanol (6 ml) with 0.17M HCl in chloroform (7.5 ml), followed by identical work-up and column chromatography on SiO_2, gave the following: (i) an oil (24 mg, 9%) of 1-(N-*benzylcarbamoyl*)-1-*methylethyl acetate* (**10c**); R_F 0.12; $\nu_{max.}$($CHCl_3$) 3 450 (NH), 1 740 (ester CO), and 1 675 cm^{-1} (amide CO); δ($CDCl_3$) 1.65 (6 H, s, Me_2), 2.03 (3 H, s, MeCO), 4.46 (2 H, d, *J* 7 Hz, CH_2), 6.34 (1 H, br, NH), and 7.3 (5 H, s, Ph) (Found: C, 65.8; H, 7.4; N, 5.9. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.28; N, 5.95%); (ii) an oil, R_F 0.42; $\nu_{max.}$ and ^1H n.m.r. spectra with decoupling similar to those of the analogous (**12a**), and analytical data, suggested 3-*benzyl*-2-*ethoxy*-2,5,5-*trimethyloxazolidin*-4-*one* (**12b**), which spontaneously decomposed into the above amide ester (**10c**).

(e) A sample of the oxazolidinone (**9e**) (117 mg, 0.4 mmol) in ethanol (3 ml) was treated with 1M HCl (0.5 ml) with stirring (1 h). The solvent was evaporated off and the oil was extracted with diethyl ether. Evaporation gave colourless prisms of (**10d**) (45 mg, 59%), m.p. 79—80 °C; $\nu_{max.}$($CHCl_3$) 3 440 (NH), 1 735 (ester CO), and 1 650 cm^{-1} (amide CO); δ($CDCl_3$) 1.44 (9 H, s, Me_3), 1.58 (6 H, s, Me_2), 2.04 (3 H, s, MeCO), and 5.8 (1 H, s, NH) (Found: C, 59.65; H, 9.65; N, 6.95. $C_{10}H_{19}NO_3$ requires C, 59.68; H, 9.51; N, 6.96%).

(f) A sample of 2-(1-bromo-1-methylethyl)-3,5,5-trimethyl-2-oxazolidin-4-one (**6**; R = Me)[3] was treated with ethanolic HCl as (**9e**) under reflux for 1.5 h; similar work up gave colourless prisms (73%) of 1-(N-*methylcarbamoyl*)-1-*methylethyl* 2-*bromo*-

2-*methylpropanoate* (**10e**), m.p. 56—58 °C; $\nu_{max.}$($CHCl_3$) 3 450 (NH), 1 745 (ester CO), and 1 680 cm^{-1} (amide CO) (Found: C, 40.8; H, 6.15; Br, 30.15; N, 5.05. $C_9H_{16}BrNO_3$ requires C, 40.62; H, 6.06; Br, 30.02; N, 5.26%).

(g) A sample of (**5**; R = Ph)[12] was dissolved in toluene and poured onto a column of SiO_2. Concentration of the pertinent fractions gave colourless prisms (80%) of 1-(N-*phenylcarbamoyl*)-1-*methylethyl* 2-*methylprop*-2-*enoate* (**10f**), m.p. 98—100 °C; $\nu_{max.}$($CHCl_3$) 3 440 (NH), 1 750 (ester CO), and 1 695 cm^{-1} (amide CO); δ($CDCl_3$) 1.73 (6 H, s, Me_2), 1.95 (3 H, s, MeC=), 5.65 and 6.15 (2 H, 2 × m, H_2C=), 7.0—7.7 (5 H, m, Ph), and 8.0 (1 H, s, NH) (Found: C, 68.1; H, 7.0; N, 5.55. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.93; N, 5.66%).

Kinetics of Hydrolysis.—Buffer solutions (acetic acid, 1M sodium hydroxide, pH 3.5—6.1; phosphate, pH 6.9; hydrochloric acid, pH 1.1—2.3) of ionic strength 0.1 were used throughout. Reaction mixtures were prepared by adding in the cuvette 2 ml of buffer solution followed by 20 μl of a 2.9 × 10^{-3}M solution of the oxazolidinone in anhydrous dioxane. Kinetics were followed at 25 °C by measuring the increase of the absorbance of the ester-amide produced, at the wavelength of 231 nm.

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References

1 B. C. Challis and J. A. Challis, in J. Zabicky, 'The Chemistry of Amides,' Interscience Publ., London, 1970, p. 750.
2 P. Scrimin, F. D'Angeli, and A. C. Veronese, *Synthesis*, 1982, 586.
3 P. Scrimin, F. D'Angeli, V. Baioni, and G. Cavicchioni, *J. Chem. Res.*, 1983, (*M*), 2237, and references therein.
4 G. Cavicchioni, P. Scrimin, A. C. Veronese, and F. D'Angeli, *J. Chem. Soc., Chem. Commun.*, 1981, 416.
5 P. Scrimin, F. D'Angeli, A. C. Veronese, and V. Baioni, *Tetrahedron Lett.*, 1983, 4473.
6 F. Maran, E. Vianello, G. Cavicchioni, and F. D'Angeli, *J. Chem. Soc., Chem. Commun.*, 1985, 660.
7 F. Maran, E. Vianello, F. D'Angeli, G. Cavicchioni, and G. Vecchiati, *J. Chem. Soc., Perkin Trans. 2*, 1987, 33.
8 A. C. Veronese, P. Scrimin, G. Vecchiati, S. Sferra, and F. D'Angeli, *J. Chem. Soc., Perkin Trans. 1*, 1984, 781.
9 V. Bertolasi *et al.*, to be published.
10 R. H. De Wolfe, 'Carboxylic Ortho Acid Derivatives,' Academic Press, New York, 1970, p. 441.
11 F. D'Angeli, A. Goldblum, F. Maran, and E. Vianello, to be published.
12 G. Zanotti, F. Filira, A. Del Pra, G. Cavicchioni, A. C. Veronese, and F. D'Angeli, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2249.
13 G. Cavicchioni, P. Scrimin, A. C. Veronese, G. Balboni, and F. D'Angeli, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2969.
14 K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 1965, 3325, and references therein.
15 (*a*) R. A. McLelland and M. Ahmad, *J. Org. Chem.*, 1979, **44**, 1855; (*b*) R. A. McLelland and G. Patel, *J. Am. Chem. Soc.*, 1981, **103**, 6908; (*c*) B. Capon, A. S. Ghosh, and D.Mc L. A. Grieve, *Acc. Chem. Res.*, 1981, **14**, 306.

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