Amino-acids and Peptides. Part IX.[1] Some Neighbouring-group Amino–Amide and Hydroxy–Amide Interactions

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Base-catalysed hydrolysis studies have provided evidence of neighbouring-group amino–amide interactions in compounds with the formulae $H_2N{\cdot}[CH_2]_x{\cdot}CO{\cdot}NHMe$ (x = 3, 4, or 5), and in 6-aminodecane-10-lactam. Acid-catalysed hydrolysis studies have indicated that transannular hydroxy-amide interactions occur with 4-hydroxyhexane-6-lactam, 5-hydroxyoctane-8-lactam, and 6-hydroxydecane-10-lactam. The mechanisms of these reactions and the significance of such processes in peptide chemistry is discussed.

THERE is a long-standing suggestion that α-amino-acids may occasionally be combined in proteins through linkages other than amide and disulphide.[2] More recently, experimental support has been obtained for the existence of ester,[3] diphenyl,[4] and other [5] linkages in proteins. However, there is very limited evidence relating to a proposal made over 40 years ago [6] that unusual bonding of amino-acids in natural products may also arise through intramolecular reactions involving amide groups. If such bonding occurred, even occasionally, it could be important in determining the structures, chemical reactivity, and physical properties of particular peptides and proteins. In this connection we have undertaken the investigation of hydroxy–amide and of amino–amide interactions in some simple model systems.

Amino–Amide Interactions.—It has been proposed that the isolation of both phenylalanylhistidine and phenylalanylisoleucine from hydrolysates of the antibiotic bacitracin-A (I) arises from the interaction of the amino-group of the chain-terminating isoleucine residue with the amide function linking the single phenylalanine residue to histidine.[7,8] The 'cyclol' structure of the alkaloid ergotamine (II) is well established [9] and evidently results from what may be regarded as a related hydroxy–amide interaction. Moreover, there is some support from studies on simple synthetic products for the suggestion that amino–amide interactions may occur. The reactions of *N*-*o*-aminophenyl derivatives of peptides,[10] the remarkably ready cleavage of the peptide link in *N*-tosylornithylglycine,[11] the aminoacyl insertion reactions of Brenner [12] and of Wieland,[13] and the behaviour of peptides of diaminobutyric acid,[14] all appear to result from intramolecular amino–amide interactions. Related amide–amide interactions [(III) → (IV)] have been observed.[15]

We have investigated the rates of hydrolysis at several pH values, of amino-*N*-methylamides of the general formula (V). It was to be expected that, if intramolecular amino–amide interactions were involved, there would be differences in rate through the series of compounds. The rate coefficients for alkali-catalysed hydrolysis at 75° were obtained through the estimation, by the Conway diffusion technique,[16] of the amounts of methylamine liberated at predetermined time intervals. The plots $[\ln (a_o/a_o - a_t)]/t$ † which were straight lines passing through the origin for each of the compounds, were used to calculate pseudounimolecular rate constants (Figure, Table 1). The results in Table 1 agree with the

† a_o, is the initial concentration and a_t the concentration at time t.

[1] Part VIII, C. H. Hassall, J. O. Thomas, and D. G. Sanger, 'Peptides,' ed. E. Bricas, North Holland Publishing Co., Amsterdam, 1968, p. 70.

[2] E. Fischer, 'Untersuchungen uber Aminosauren, Polypeptide, und Proteine,' vol. I, p. 80; vol. II, p. 39 (quoted in ref. 8).

[3] O. O. Blumenfield, M. Rojkind, and P. M. Gallop, *Biochemistry*, 1965, **4**, 1780.

[4] S. O. Anderson, *Nature*, 1967, **216**, 1029; F. S. Labella, F. Keeley, S. Vivian, and D. Thornhill, *Biochem. Biophys. Res. Comm.*, 1965, **21**, 575.

[5] J. S. Fruton, *J. Polymer Sci.*, 1961, **49**, 69; J. J. Harding, *Adv. Protein Chem.*, 1965, **20**, 109.

[6] D. Wrinch, *Nature*, 1936, **137**, 411; 1937, **139**, 972.

[7] D. Wrinch, 'Chemical Aspects of Polypeptide Chain Structures, and the Cyclol Theory,' Munksgaard, Copenhagen, 1956.

[8] E. P. Abraham and G. F. Newton, 'Ciba Foundation Symposium on Amino-acids and Peptides with Antimetabolic Activity,' Churchill, London, 1958, p. 205.

[9] A. Stoll, *Fortschr. Chem. org. Naturstoffe*, 1959, **9**, 114; A. Hofmann, A. J. Frey, and H. Ott, *Experentia*, 1961, **17**, 206.

[10] R. W. Holley and A. D. Holley, *J. Amer. Chem. Soc.*, 1952, **74**, 3069, 5445.

[11] B. C. Barrass and D. T. Elmore, *J. Chem. Soc.*, 1957, 4830.

[12] M. Brenner, J. P. Zimmerman, J. Wehrmüller, P. Quitt, and I. Photaki, *Experentia*, 1955, **11**, 397.

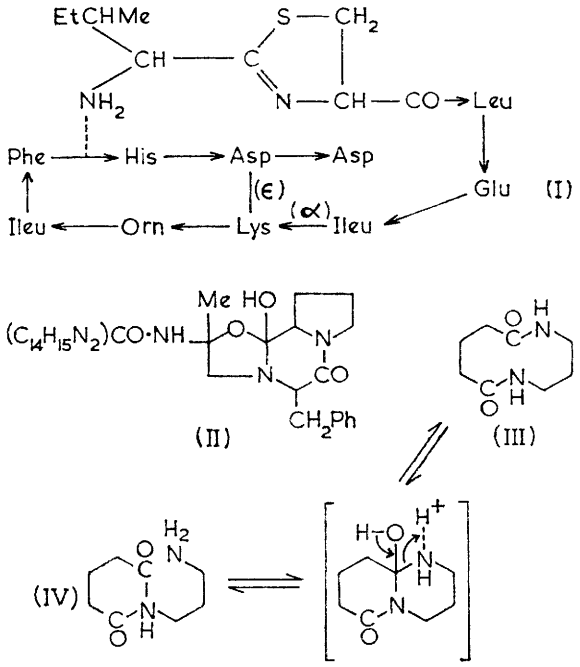
[13] T. Wieland and H. Urbach, *Annalen*, 1958, **613**, 84; M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, V. I. Shchelokov, and Z. E. Agadzhanyan, *Tetrahedron*, 1965, **21**, 3537.

[14] W. J. LeQuesne and G. T. Young, *J. Chem. Soc.*, 1952, 594; K. Poduska, G. S. Katrukha, A. B. Silaev, and J. Rudinger, *Coll. Czech. Chem. Comm.*, 1965, **30**, 2410.

[15] G. I. Glover, R. B. Smith, and H. Rapoport, *J. Amer. Chem. Soc.*, 1965, **87**, 2003.

[16] E. J. Conway and A. Byrne, *Biochem. J.*, 1933, **27**, 419.

full rate law, $v = k_2$[amide][OH^-]. T.l.c. of the hydrolysis mixtures obtained from compounds (VI), (VII), (XI), and (XII) showed the presence of the corresponding



amino-acids (XVIII) alone, whereas each of the compounds (VIII), (IX), and (X) gave two products; in each case one was identified as the appropriate amino-acid (XVIII) and the other as the related cyclic amide, (XV)—(XVII).

Comparison of the rate constants for the hydrolysis of the amides (VI)—(XII) in M-sodium hydroxide (Figure) indicated a significant enhancement of rate in the case

TABLE 1

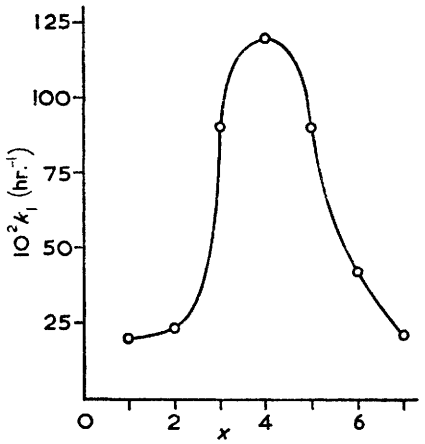
Pseudounimolecular rate constants for alkali-catalysed hydrolyses at 75°

	10^2k_1 (hr.$^{-1}$)			
NH_2·[CH_2]$_x$·CO·NHMe	M-NaOH	0·75M-NaOH	0·5M-NaOH	0·2M-NaOH
(VI) $x = 1$	20·0	14·0	9·6	4·2
(VII) $x = 2$	23·4	17·0	12·0	4·8
(VIII) $x = 3$	90·0	60·0	44·0	18·0
(IX) $x = 4$	120·0	90·0	60·0	23·0
(X) $x = 5$	90·0	66·0	45·0	18·5
(XI) $x = 6$	42·0	31·2	20·4	8·4
(XII) $x = 7$	21·0	15·6	10·8	4·6
MeN·[CH_2]$_4$·CO·NHMe	24·0			

of compounds (VIII), (IX), and (X). The results for different concentrations of sodium hydroxide are summarised in Table 1. There were no significant differences in the rates of hydrolysis of the amides (VI)—(XII) in the presence of M-hydrochloric acid.

[17] M. Vinnik and Y. V. Moiseyev, *Tetrahedron*, 1963, **19**, 1441.
[18] R. B. Martin, R. Hedrick, and A. Parcel, *J. Org. Chem.*, 1964, **29**, 158.
[19] T. C. Bruice and S. Benkovic, 'Bio-organic Mechanisms,' vol. I, Benjamin, New York, 1966, p. 134.

We attribute the faster rates of hydrolysis of the compounds (VIII), (IX), and (X) to amino–amide interactions. Of several alternatives, we favour a mechanism which proceeds through the carbinolamine (XIII) [mechanism (A)]. The formation of this intermediate, by analogy with the case of Vinnik and Moiseyev,[17] may involve the participation of a molecule of water at the stage of proton transfer. An alternative mechanism (B) is similar to that suggested by Martin and his co-workers [18] for the alkali-catalysed hydrolysis of the ethyl esters of 4- and 5-aminobutyrates. Mechanism (C), involving intramolecular nucleophilic catalysis, is excluded. It is not in accord with the formation of the cyclic amide (XIV). Furthermore, it is significant that



Pseudounimolecular rate constants for the hydrolysis of H_2N·[CH_2]$_x$·CO·NHMe in M-sodium hydroxide

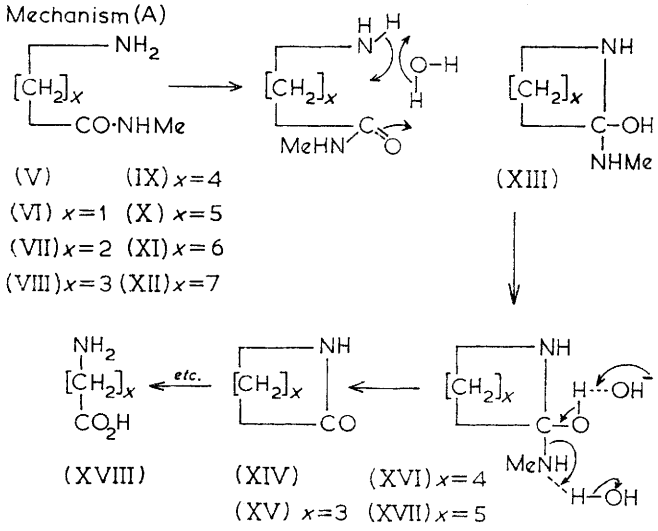
hydrolysis of 5-dimethylamino-*N*-methylvaleramide in M-sodium hydroxide proceeded at a rate similar to that of the unassisted amides (VI), (VII), (XI), and (XII). By analogy with a related case,[19] the difference in rates of 5-amino-*N*-methylvaleramide (IX) and 5-dimethylamino-*N*-methylvaleramide is not likely to arise from the difference in size between the amino- and dimethylamino-groups. The results in Table 1 suggested that a transannular amino–amide interaction would be likely in such a compound as 6-aminodecane-10-lactam (XX). This has been synthesised from the readily available keto-amide (XIX) by reduction of the oxime. It was converted by a transannular amino–amide interaction in the presence of M-sodium hydroxide, to 6-(4-aminobutyl)-hexane-6-lactam (XXI). The structure of this product was established by the mass spectrum and the observation that the i.r. spectrum included an amide I band (at 1665 cm.$^{-1}$) but no amide II band. This was unlike the case of the cyclic amides (XIX) and (XX) which, as expected for 11-membered rings [20] had both amide I and amide II bands.

Hydroxy–Amide Interactions.—The limited evidence for the existence of these intramolecular interactions has been reviewed by Wrinch [7] and by Bruice and Benkovic.[21]

[20] R. Huisgen, H. Brade, H. Walz, and J. Glogger, *Chem. Ber.*, 1957, **90**, 1137.
[21] See ref. 19, p. 146.

Recently an insertion reaction which utilises an hydroxy–amide interaction has been used in an elegant way by Shemyakin and his co-workers to synthesise cyclodepsipeptides such as serratamolide.[22]

Mechanism (A)

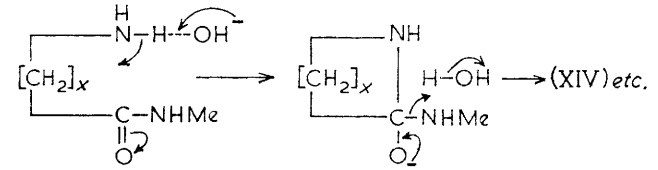


(V) (IX) $x=4$
(VI) $x=1$ (X) $x=5$
(VII) $x=2$ (XI) $x=6$
(VIII) $x=3$ (XII) $x=7$

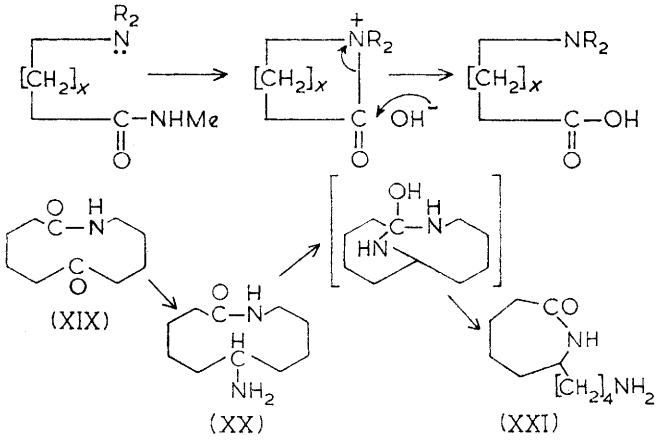
(XIII)

(XVIII) (XIV) (XVI) $x=4$
(XV) $x=3$ (XVII) $x=5$

Mechanism (B)



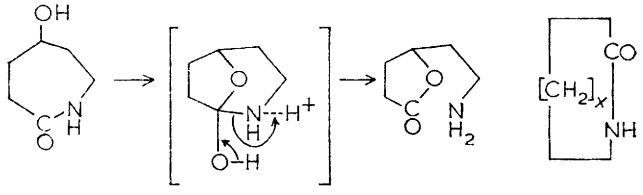
Mechanism (C)



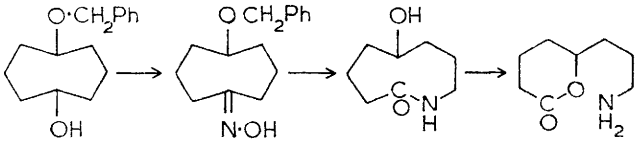
(XIX) (XX) (XXI)

The indication that an amino–amide interaction occurred in the compound 6-aminodecane-10-lactam (XX) led us to study the possibility of similar transannular interactions in related hydroxyamides. 4-Hydroxyhexane-6-lactam (XXII), a known compound,[23] 5-hydroxyoctane-8-lactam (XXVII), prepared from 5-benzyloxycyclo-octanol (XXVI), and 6-hydroxydecane-10-lactam (XXX), prepared from 6-benzyloxycyclodecanone (XXIX), were investigated. The hydrolysis of 0·1M-solutions of the hydroxy-lactams (XXII) and (XXVII) proceeded readily in 0·2M-hydrochloric acid at 25°. There was no significant hydrolysis of the compound (XXX) under these conditions but cleavage occurred with 2M-hydrochloric acid at 60°. Similar treatment of the corresponding unsubstituted lactams (XXV) led to no measurable hydrolysis. In the case of the hydroxy-lactams (XXII) and (XXX), crystalline hydrochlorides of the amino-lactones (XXIV) and (XXXI), respectively, were isolated from the hydrolysates. The corresponding product from (XXVII) could not be obtained crystalline.

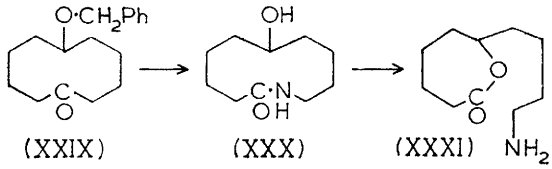
Evidently a transannular interaction, presumably involving a carbinolamine intermediate such as (XXIII), has taken place in the case of each of the hydroxy-lactams (XXII), (XXVII), and (XXX). The distinctly slower rate of reaction of (XXX) may be attributed to the less favourable stereochemistry of the bicyclic intermediate (7,8-membered rather than 5,6- and 6,7-membered rings).



(XXII) (XXIII) (XXIV) (XXV)



(XXVI) (XXVII) (XXVIII)



(XXIX) (XXX) (XXXI)

The evidence which we have obtained of amino– and hydroxy–amide interactions in these model systems makes it more reasonable to expect cases in which similar processes involving the side-chains of amino-acid residues take place in natural peptides and proteins.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. U.v. absorption spectra were measured with Unicam SP 500 and SP 800 spectrophotometers for ethanolic solutions, except where stated otherwise. I.r. spectra, unless specified, were measured for potassium bromide discs with a Perkin-Elmer 237 spectrophotometer. Mass spectra were determined with an A.E.I. MS9 double-focussing mass

[22] V. K. Antonov, V. I. Shchelokov, M. M. Shemyakin, I. I. Tovarova, and O. A. Kiseleva, *Antibiotiki*, 1965, 387; M. M. Shemyakin, V. K. Antonov, A. M. Shkrob, V. I. Shchelokov, and Z. E. Agadzhanyan, *Tetrahedron*, 1965, **21**, 3537; V. K. Antonov, A. M. Shkrob, V. I. Shchelokov, and M. M. Shemyakin, *Tetrahedron Letters*, 1963, 1353.

[23] G. Boffa, *Gazzetta*, 1956, **86**, 646.

spectrometer. Inlet temperatures of *ca.* 200° with an electron beam energy of 70 ev were used. Ions with an abundance of 10% or more are noted; ions of lesser abundance are included if they are of diagnostic value.

The Amides $H_2N{\cdot}[CH_2]_xCO{\cdot}NHMe$ (x = 1—6).—These amides were prepared by the action of methylamine in ethanol on the appropriate ethyl ester. In the case of glycine and 3-aminopropionic acid the corresponding amino-esters were used for the solvolysis but, with the higher homologues the terminal amino-function was protected by a benzyloxycarbonyl group which was later removed with hydrogen bromide–acetic acid. In a typical synthesis, 4-aminobutyric acid (10·3 g.) was converted into 4-benzyloxycarbonylaminobutyric acid (21 g., 89%) by the procedure of Zervas and Bergman.[24] Ethyl 4-benzyloxycarbonylaminobutyrate (10 g.), prepared by esterification of the acid with ethanol–sulphuric acid, was treated with a 33% solution of methylamine in ethanol (300 ml.) at room temperature for 38 hr. The product, 4-*benzyloxycarbonylamino*-N-*methylbutyramide* (8 g., 85%) was recrystallised from ethyl acetate–light petroleum (b.p. 60—80°). 4-*Amino*-N-*methylbutyramide hydrobromide* (3·2 g., 77%) was prepared from the benzyloxycarbonyl derivative (5·0 g.) by the action of 2N-hydrogen bromide in anhydrous acetic acid (50 ml.). The product was recrystallised from ethanol–ether. Table 2 summarises the properties of the new compounds prepared in this way.

5-(NN′-*Dimethylamino*)-N-*methylvaleramide*.— 5-Amino-*N*-methylvaleramide (5 g.), palladium–charcoal (10%; 5 g.), aqueous formaldehyde (40%; 6 ml.), and water (2 ml.) were shaken under hydrogen until reduction was complete. The mixture was worked up in the usual way to give 5-(NN′-*dimethylamino*)-N-*methylvaleramide* (4 g., 60%), b.p. 110°/0·5 mm. (Found: C, 61·2; H, 11·25; N, 17·3. $C_9H_{20}N_2O$ requires C, 60·7; H, 11·5; N, 17·7%).

Rate Studies on the Hydrolysis of the Compounds $H_2N{\cdot}[CH_2]_xCO{\cdot}NHMe$ (x = 1—6).—(a) *With sodium hydroxide.* The hydrochloride, or hydrobromide, of the methylamide of the amino-acid (350 mg.) was dissolved in water (10 ml.) to which sufficient sodium perchlorate had been added to ensure that the hydrolysis solution was unimolar with respect to sodium ion. Samples of this solution (1 ml.) were mixed with the sodium hydroxide solution (1 ml.) at −10°. The reaction tubes were sealed, heated quickly to 75° in a thermostat, and removed at intervals. The tubes were broken in M-hydrochloric acid (10 ml.) and a sample of the solution (1 ml.) was used in the Conway determination [16] of the liberated methylamine. The inner chamber of the Conway dish contained 0·0125M-sulphuric acid (1 ml.). The sample in the outer chamber was neutralised with M-sodium hydroxide (1 ml.) and methylamine was then liberated by further addition of potassium carbonate (20 mg.). After 38 hr. at room temperature the solution in the inner chamber was back-titrated. First-order rate constants were obtained by determining the slopes of plots of $[\ln (a_o/a_o - a_t)]/t$ where a_o is the initial concentration and a the concentration at time t. The amides were hydrolysed in 1·00M-, 0·75M-, 0·50M-, and 0·20M-sodium hydroxide.

(b) *With hydrochloric acid.* The Conway method was used in a similar manner to estimate the hydrolysis of the amides (VI)—(IX) (x = 1—4), in M-hydrochloric acid at 50°. Rate constants were determined on the assumption that methylamine was the only base liberated. An estimation which was specific for methylamine [25] confirmed that this was so and that no ammonia was released in this acid-catalysed hydrolysis. These studies established that there was no significant difference in the rates for the four compounds [k = 11·8 (±0·4) × 10^{-2} hr.$^{-1}$) and that, as might be expected for a protonated amino-group, there was no anchimeric assistance of amide hydrolysis.

6-*Benzyloxycyclodecanone Oxime*.— *trans*-9-Decalyl hydroperoxide (39 g.) [26] was heated at 50° for 25 min. in benzyl alcohol (90 ml.) saturated with anhydrous hydrogen chloride. After removal of excess of reagents, the crude product was distilled. The material which distilled above 240°/0·04 mm. (19·8 g.) was converted into the *oxime* (12·6 g.), m.p. 86—90° [from light petroleum (b.p. 60—80°)] (Found: C, 74·4; H, 9·5; N, 5·0. $C_{17}H_{25}NO_2$ requires C, 74·1; H, 9·15; N, 5·1%).

6-*Hydroxydecane*-10-*lactam* (XXX).—6-Benzyloxycyclodecanone oxime (12·5 g.), toluene-*p*-sulphonyl chloride (17·5 g.), and pyridine (65 ml.) were set aside at 0° for 18 hr. The crude product obtained by working up the neutralised reaction mixture was dissolved in acetone (590 ml.) and

TABLE 2

x	$H_2N{\cdot}[CH_2]_x{\cdot}CO_2H$	$ZNH{\cdot}CH_2]_x{\cdot}CO_2H$ *						$ZNH{\cdot}[CH_2]_x{\cdot}CO{\cdot}NHMe$						$H_2N{\cdot}[CH_2]_x{\cdot}CO{\cdot}NHMe$					
		Found (%)			Required (%)			Found (%)			Required (%)			Found (%)			Required (%)		
		C	H	N	C	H	N	C	H	N	C	H	N	C	H	N	C	H	N
1														Hydrochloride, m.p. 148° (lit.,[a] 144°)					
2														34·5	7·4	19·9	34·7	7·9	20·1
					M.p. 68°						M.p. 90°			M.p. 140°, hydrobromide					
3		60·5	6·4	5·8	60·8	6·3	5·9	62·3	7·4	11·1	62·4	7·2	11·2	30·9	7·0	13·8	30·9	7·0	14·2
					M.p. 106°						M.p. 160°			M.p. 124°, hydrobromide					
4	Ref. *b*	61·9	6·7	5·3	62·1	6·8	5·6	63·5	8·0	10·6	63·5	7·6	10·6	34·0	7·6	13·7	34·1	7·1	13·3
					M.p. 55—57°						M.p. 90°			M.p. 140°, hydrobromide					
5	Ref. *c*	63·2	7·5	5·4	63·4	7·2	5·3	65·0	8·2	10·1	64·7	8·0	10·1	35·7	7·7	11·6	35·8	7·3	11·9
					M.p. 90°						M.p. 104°			M.p. 96—98°, hydrobromide					
6	Ref. *d*	64·7	7·9	5·3	64·5	7·6	5·0	64·9	8·7	10·1	64·5	8·5	9·9	40·6	8·3	11·6	40·2	8·0	11·7
					M.p. 58—60°						M.p. 122°			M.p. 122—124°, hydrobromide					
7	Ref. *d*	65·7	7·9	5·2	65·6	7·9	4·7	66·8	8·4	9·1	66·7	8·5	8·9	42·7	8·7	11·2	42·7	8·3	11·1

* Z = benzyloxycarbonyl.

[a] C. S. Marvel, J. R. Elliot, F. E. Boettner, and M. Yuskov, *J. Amer. Chem. Soc.*, 1946, **68**, 1684. [b] L. E. Schniepp and C. S. Marvel, *J. Amer. Chem. Soc.*, 1939, **57**, 1557. [c] A. F. McKay, E. J. Tarlton, S. I. Petri, L. R. Steyermark, and M. A. Mosley, *J. Amer. Chem. Soc.*, 1958, **80**, 1570. [d] H. Treibs and S. Hamptmann, *Chem. Ber.*, 1956, **99**, 117.

[24] M. Zervas and L. Bergmann, *Ber.*, 1932, **65**, 1192.
[25] A. A. Ormsley and S. Johnson, *J. Biol. Chem.*, 1950, **71**, 187.
[26] A. C. Cope, P. J. Cotter, and G. G. Roller, *J. Amer. Chem. Soc.*, 1955, **77**, 3590.

treated with sodium hydrogen carbonate (12·0 g.) in water (580 ml.) and dioxan (40 ml.) at room temperature for 48 hr. After the removal of solvents the ether extract of the residue was dried and evaporated to give 6-*benzyloxydecane*-10-*lactam* (6·0 g.), m.p. 81—84° (from cyclohexane) (Found: C, 74·5; H, 9·4; N, 5·05. $C_{17}H_{25}NO_2$ requires C, 74·1; H, 9·15; N, 5·1%).

Hydrogenolysis of the benzyloxy-derivative (1·37 g.) in methanol (25 ml.) over palladium–charcoal gave 6-*hydroxydecane*-10-*lactam* (XXX) which was purified by sublimation at 120°/0·01 mm.; m.p. 188—190° (Found: C, 64·8; H, 10·4; N, 7·2. $C_{10}H_{19}NO_2$ requires C, 64·8; H, 10·3; N, 7·6%), $\nu_{max.}$ (Nujol) 3250, 3200sh, 3090, 1645 (amide I), and 1570 (amide II) cm.$^{-1}$, $\lambda_{max.}$ (water) 192 mμ (log ε 3·87), the mass spectrum (M^+ 185) included:

m/e	30	41	42	43	44	45	54	55	56	59
I	100	46	12	25	25	18	11	41	35	12
m/e	67	68	69	70	71	72	73	81	82	83
I	30	25	21	45	12	41	27	13	11	25
m/e	84	85	86	87	97	98	99	100	101	111
I	41	28	20	37	12	19	15	59	14	19
m/e	112	113	114	115	128	156	157	167	185	
I	12	12	20	40	37	23	26	19	4	

(*m** 167/185, loss of H_2O)

6-*Aminodecane*-10-*lactam* (XX).—6-Oxodecane-10-lactam (2 g.), b.p. 60—64°/0·01 mm., prepared from the alcohol (XXX) by oxidation with chromium trioxide in pyridine [27] was converted into the *oxime*, m.p. 212—214 (Found: C, 60·6; H, 8·7; N, 14·5. $C_{10}H_{18}N_2O_2$ requires C, 60·6; H, 9·1; N, 14·1%). When this oxime (1·0 g.) in methanol (10 ml.) was hydrogenated at 60 lb./in.^{2} at room temperature for 12 hr. in the presence of Raney nickel (1·5 g.), 6-*aminodecane*-10-*lactam* (0·5 g.), m.p. 196—199° was formed (Found: C, 64·7; H, 10·8; N, 15·0. $C_{10}H_{20}N_2O$ requires C, 65·2; H, 10·9; N, 15·2%), $\nu_{max.}$ 1665 (amide I) and 1520 (amide II) cm.$^{-1}$.

6-(4-*Aminobutyl*)*hexane*-6-*lactam* (XXI).— 6-Aminodecane-10-lactam (200 mg.) was dissolved in N-sodium hydroxide (10 ml.) and set aside at 50° for 6 hr. The mixture was concentrated *in vacuo*, acidified, and evaporated to dryness. Evaporation of the ether extract of the residue gave a mixture of starting material and 6-(4-*aminobutyl*)-*hexane*-6-*lactamhydrochloride*, which was obtained pure (30 mg.) only after extensive recrystallisation from ethanol–ether and chloroform–ether; m.p. 198—202° (Found: C, 54·1; H, 9·8; N, 13·0. $C_{10}H_{21}N_2OCl$ requires C, 54·4; H, 9·5; N, 12·7%), $\nu_{max.}$ 1660 cm.$^{-1}$ (amide I), no amide II. The mass spectrum (M^+ 184 for the free base, $C_{10}H_{20}N_2O$) included:

m/e	79	86	87	91	107	108	115	125	139	153
I	11	100	11	44	10	16	10	3	5	4
m/e	167	184								
I	3	2								

5-*Benzyloxycyclo-octanol*.—The transannular hydroxy–carbonyl interaction of 5-hydroxycyclo-octanone necessitated an indirect synthesis of the *O*-benzyl derivative. 5-Hydroxycyclo-octanone (25 g.) [28] (Badische Anilin und Soda-Fabrik A.G.) was hydrogenated in ethanol (500 ml.) at 75—80°/80 atmos. in the presence of Raney nickel (W-2; 3·6 g.) for 17 hr. The product (23·9 g.) had n_D^{21} 1·5009.

This cyclo-octane-1,5-diol (47·7 g.) in anhydrous dioxan (270 ml.) was treated with sodium (7·75 g.) for 15 min. at room temperature, heated under reflux for 4 hr., then cooled. Benzyl bromide (56·5 g.) in dioxan (40 ml.) was added during 10 min., and the mixture was heated under reflux for 18 hr. The crude product (52·5 g.) obtained by filtration, removal of the solvent, extraction of the residue with ether, washing the ether extract with water, and evaporating the dried extract, was shown by t.l.c. (benzene and Kieselgel G) to contain at least four components. This mixture (20·0 g.) was applied to a column of silica gel (1000 g.; 51 × 6·5 cm.) and eluted with benzene to remove impurities. Subsequent elution with ether gave 5-*benzyloxycyclo-octanol* as an oil (13·2 g.), b.p. 126—127°/0·05 mm. (Found: C, 76·3; H, 9·6; $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

5-*Benzyloxycyclo-octanone Oxime*.— 5-Benzyloxycyclo-octanone (7·3 g.), prepared crude by the oxidation of the corresponding alcohol with chromium trioxide–pyridine [27] was treated with hydroxylamine hydrochloride (8·1 g.) and pyridine (8 ml.) in ethanol (85 ml.) under reflux for 1 hr. The *oxime* (4·0 g.) had m.p. 63—66° (from benzene) (Found: C, 72·8; H, 8·5; N, 5·5. $C_{15}H_{21}NO_2$ requires C, 72·8; H, 8·6; N, 5·7%).

5-*Hydroxyoctane*-8-*lactam*.—The oxime of 5-benzyloxy-cyclo-octanone (2·47 g.), toluene-*p*-sulphonyl chloride (3·81 g.), and pyridine (13 ml.) were set aside at 0° for 17 hr. The ether extract of the product obtained by pouring the reaction mixture into water was washed with 5N-sulphuric acid (40 ml.), dried, and evaporated. The residue was dissolved in acetone–water (1 : 1; 600 ml.) containing sodium–hydrogen carbonate (4·73 g.). The solution was left overnight at room temperature, and the solvent was then removed under reduced pressure. The gum obtained by extraction with ether followed by evaporation solidified after several days and was identified as the *cis*-amide by its i.r. spectrum. 5-*Benzyloxyoctane*-cis-8-*lactam* had m.p. 73—76° [from benzene–light petroleum (b.p. 40—60°)] (Found: C, 72·7; H, 8·7; N, 5·7. $C_{15}H_{21}NO_2$ requires C, 72·8; H, 8·6; N, 5·7%).

Hydrogenolysis of the benzyloxylactam (395 mg.) over 10% palladium–charcoal gave 5-*hydroxyoctane*-8-*lactam* (118 mg.) as a microcrystalline solid, m.p. 104—120° (Found: C, 60·5; H, 9·5; N, 8·8. $C_8H_{15}NO_2$ requires C, 61·1; H, 9·6; N, 8·9%), $\nu_{max.}$ (chloroform) 3617 (OH), 3460sh, 3441, 3408, 3396sh, and 1654 (amide I) cm.$^{-1}$, $\nu_{max.}$ (Nujol) 3320, 3210sh, 3095, 1660 (amide I), and 1555 (amide II) cm.$^{-1}$, $\lambda_{max.}$ (water) 196·5 mμ (log ε 3·89); the mass spectrum (M^+ 157) included:

m/e	30	39	41	42	43	44	55	56	68	69
I	100	10	23	11	44	11	14	13	25	14
m/e	70	72	73	101	139	140	157	(*m** 139^2/157,		
I	12	15	14	14	13	3	3	lsss of H_2O)		

Acid-catalysed Hydrolysis of 4-*Hydroxyhexane*-6-*lactam* (XXII), 5-*Hydroxyoctane*-8-*lactam* (XXVII), *and* 6-*Hydroxydecane*-10-*lactam* (XXX).—Rates of hydrolysis of each hydroxylactam were investigated by measuring the decrease in u.v. absorption at 205 mμ (amide function). 0·01 Molar solutions of the lactams were employed in all cases but the concentrations of hydrochloric acid and the temperatures were chosen so as to differentiate the rates of hydrolysis of the hydroxylactams and of the correspond-

[27] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarrett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.

[28] H. Moell and F. Urbanek, G.P. 1,029,368/1958; B.P. 823,007/1959 (*Chem. Abs.*, 1960, **54**, 8675).

ing lactams. It was confirmed, for each case, that Beer's Law applied.

A measurable rate of hydrolysis was obtained for the compounds (XII) and (XXVII) in 0·1M-hydrochloric acid at 25°. More than 50% of the lactam was hydrolysed during 20 hr. However, it was necessary to use 2M-hydrochloric acid at 60° during 30 hr. for a comparable degree of hydrolysis of the compound (XXX). No measurable hydrolysis of (XXX) occurred during 48 hr. in 0·1M-hydrochloric acid at 25°.

No hydrolysis of hexane-6-lactam, octane-8-lactam, or decane-10-lactam (XXV; $x = 5$, 7, or 9) was observed for 0·1M-solutions in 0·1M-hydrochloric acid at 25° during 28 hr., or for decane-10-lactam (XXV; $x = 9$) as a 0·2M-solution in 2M-hydrochloric acid at 60° during 22 hr.

The products of the acid-catalysed hydrolysis of the hydroxylactams were isolated from the reaction mixtures by removal of solvent and recrystallisation of the resulting hydrochloride. In agreement with Boffa,[23] we found that 4-hydroxyhexane-6-lactam was converted into the hydrochloride of 4-(2-aminoethyl)butane-4-lactone (XXIV), m.p. 163—167° (decomp.), identified by comparison of the i.r. spectrum with that of authentic material. The product of hydrolysis of 5-hydroxyoctane-8-lactam with hydrochloric acid was a gum that could not be purified by crystallisation. The product formed on hydrolysis of 6-hydroxydecane-10-lactam was identified as the hydrochloride of 6-(4-*aminobutyl*)*hexane*-6-*lactam*, m.p. 133—137° (from ethanol–water) (Found: C, 54·5; H, 8·9; N, 6·4. $C_{10}H_{20}ClNO_2$ requires C, 54·2; H, 9·1; N, 6·3%), $\nu_{max.}$ 1755 cm.$^{-1}$ (ester CO), no hydroxy-band.

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