Studies concerning the Antibiotic Actinonin. Part III.[1] Synthesis of Structural Analogues of Actinonin by the Anhydride–Imide Method †

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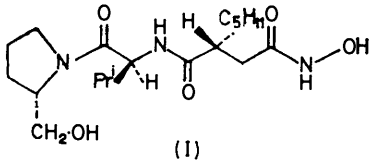
A synthetic route, associated with a high degree of stereoselectivity, has been developed for the synthesis of structural analogues (XIII) of actinonin (I). The anhydride–imide method involves the sequence (IIIb) + (V) ⟶ [(VI) + (VII)] ⟶ (XI) ⟶ (XIII). (±)-Amino-amides (IIIb) yielded the (±)-hydroxamic acids with the relative configuration (XIII) and L-amino-amides (X) yielded single enantiomers with the absolute configuration (XIII).

THE determination of the constitution [2,3] of the antibiotic actinonin (I) and its total synthesis [1] have been described. We now report the synthesis of some structural analogues (II) of actinonin.

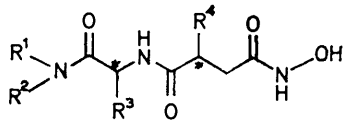
Actinonin shows an interesting but low-level spectrum of antibacterial activity [4] but this is unfortunately associated with a rapid emergence of resistant strains.



(I)

These limitations upon its possible use encouraged the syntheses of structural analogues (II). There was also the possibility that such studies might produce useful information about structure–activity relationships. The pseudo-L-polypeptide [5] nature of actinonin follows from the topological analogy between the D-pentylsuccinic acid residue of actinonin with a corresponding L-amino-acid residue in a polypeptide.[2,3] This topological relationship [6] might well be related to the antibiotic activity of actinonin and the mechanism of its action.[7]

The structural analogues (II) selected for synthesis were those in which the L-prolinol residue of actinonin (I) was replaced by a variety of amine residues [R^1 and R^2 in (XIII)] (Table 4). Systematic modification of the L-valyl residue of actinonin (I) included its replacement by, for example, glycyl, alanyl, phenylalanyl, leucyl, *o*-aminobenzoyl, and *p*-aminobenzoyl groupings [R^3 in (II)].



(II)

The side-chain of the D-pentylsuccinic acid residue of actinonin (I) was variously replaced by hydrogen, methyl, ethyl, propyl, butyl, 3-methylbutyl, hexyl, decyl, cyclopentyl, phenyl, benzyl, *p*-chlorobenzyl, *p*-nitrobenzyl, and *p*-aminobenzyl [R^4 in (II)].

A possible synthetic route to the analogues (II) involving the reaction between the amino-amides (IIIb) (Table 2) and the anhydrides (V) was investigated. The amino-amides (IIIb) were prepared by standard methods from the amines R^1R^2NH and *N*-benzyloxycarbonyl-

† Preliminary communication, J. P. Devlin, W. D. Ollis, J. E. Thorpe, R. J. Wood, B. J. Broughton, P. J. Warren, K. R. H. Wooldridge, and D. E. Wright, *J.C.S. Chem. Comm.*, 1974, 421.

[1] Part II, N. H. Anderson, W. D. Ollis, J. E. Thorpe, and A. D. Ward, preceding paper.

[2] W. D. Ollis, A. J. East, J. J. Gordon, and I. O. Sutherland in 'Chemistry of Microbial Products,' Institute of Applied Microbiology Symposium No. 6, University of Tokyo, 1964, p. 204.

[3] Part I, J. J. Gordon, J. P. Devlin, A. J. East, W. D. Ollis, I. O. Sutherland, D. E. Wright, and L. Ninet, *J.C.S. Perkin I*, 1975, 819.

[4] J. J. Gordon, B. K. Kelly, and G. A. Miller, *Nature*, 1962, **195**, 701.

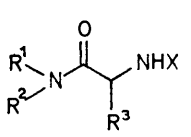
[5] R. O. Studer, *Progr. Medicin. Chem.*, 1967, **5**, 1.

[6] M. M. Shemyakin, Yu. A. Ovchinnikov, and V. T. Ivanov, *Angew. Chem. Internat. Edn.*, 1969, **8**, 492.

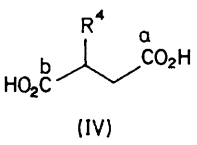
[7] M. M. Atwood, *J. Gen. Microbiol.*, 1969, **55**, 209.

amino-acid *p*-nitrophenyl esters, with hydrogenolysis of the intermediate *N*-benzyloxycarbonyl-amides (IIIa) (Table 1). The succinic acids (IV) prepared by a malonate route gave the anhydrides (V) with acetyl chloride.

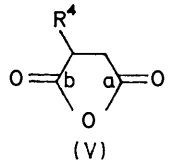
We then required a synthetic method which would lead to actinonin analogues (II) in which the alkyl substituent, R^4, was located in a β-relation to the hydroxamic acid grouping. Our experience [1] with the reaction



(III) a; X=CO_2·CH_2Ph
b; X=H



(IV)



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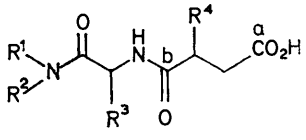

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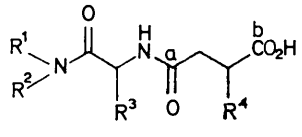
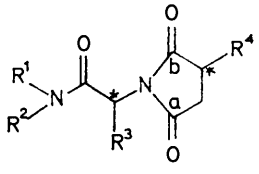
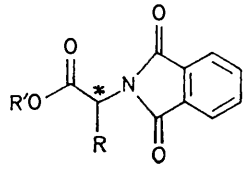


(VII)



(VIII)



(IX)

between primary amines and monoalkylmaleic anhydrides persuaded us that the reaction between amines (IIIb) and monoalkylsuccinic anhydrides (V) would lead to a mixture of isomeric products (VI) and (VII). The unwanted isomer (VII) would be expected to be formed preferentially for steric reasons [see (V); C_a is less sterically protected than C_b]. In order to surmount this difficulty, the mixtures [(VI) and (VII)] were directly dehydrated to the succinimides (VIII) (Table 3). For similar steric reasons (C_a is less sterically protected than C_b), it was expected with the imides (VIII) that a selective reaction with hydroxylamine might occur in the desired manner. In the event it was found that base-catalysed reaction of the imides (VIII) (Table 3) with methanolic alkaline solutions of hydroxylamine [8] was positionally selective and gave the hydroxamic acids (II) (Table 4). The sequence (IIIb) + (V) ⟶ [(VI) + (VII)] ⟶ (VIII) may be carried out without separation or isolation of intermediates.

Configuration of the Structural Analogues (II).—When R^3 and R^4 are substituents, then the imides (VIII) and the desired hydroxamic acids (II) contain two centres of chirality (*). It follows that the imides (VIII) and the hydroxamic acids (II) could, in principle, exist in four diastereoisomeric forms related as two racemates. However, the reaction sequence (IIIb) + (V) ⟶ [(VI) + (VII)] ⟶ (VIII) ⟶ (II) was shown to be associated not only with a high degree of regiospecificity in the final step [(VIII) ⟶ (II)], but also with a remarkable degree of stereoselectivity. Even when racemic precursors (IIIb) and (V) were used, the imides (VIII) and the hydroxamic acids (II) were almost invariably obtained as crystalline compounds with sharp m.p.s indicating that the intermediate (VIII) and the final products (II) were being obtained as single racemates. This posed the question of the determination of the relative configuration of the racemates (II) and (VIII).

For example, DL-valylmorpholine (IIIb; R^1R^2 = $[CH_2]_2$·O·$[CH_2]_2$, R^3 = Pr^i) and DL-pentylsuccinic anhydride (V; R^4 = C_5H_{11}) yielded a mixture of carbamoyl-acids [(VI) + (VII)] which with boiling acetyl chloride gave the (±)-imide (VIII; R^1R^2 = $[CH_2]_2$·O·$[CH_2]_2$, R^3 = Pr^i, R^4 = n-C_5H_{11}), m.p. 79—81°. This (±)-imide with methanolic alkaline hydroxylamine at room temperature gave a (±)-hydroxamic acid (II; R^1R^2 = $[CH_2]_2$·O·$[CH_2]_2$, R^3 = Pr^i, R^4 = n-C_5H_{11}), m.p. 162—163°. Lossen degradation of this racemic hydroxamic acid, by using methylketen diethyl acetal,[3] yielded the β-amino-acid C_5H_{11}·CH(CH_2·NH_2)·CO_2H. This result firmly established the constitution (II; R^1R^2 = $[CH_2]_2$·O·$[CH_2]_2$, R^3 = Pr^i, R^4 = n-C_5H_{11}) for the racemic hydroxamic acid, m.p. 162—163°. In order to determine the relative configurations of the (±)-imide, m.p. 79—81°, and the (±)-hydroxamic acid, m.p. 162—163°,

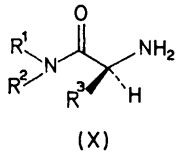
[8] C. D. Hurd and D. G. Botteron, *J. Org. Chem.*, 1946, **11**, 207; C. D. Hurd, C. M. Buess, and L. Bauer, *J. Amer. Chem. Soc.*, 1951, **73**, 2409 and 4387; W. B. Renfrow and C. R. Hauser, *ibid.*, 1937, **59**, 2312; C. R. Hauser and W. B. Renfrow, *Org. Synth.*, Coll. Vol. 2, 1943, 67; R. Deghenghi, *Org. Synth.*, 1960, **40**, 60.

the synthesis was repeated using L-valylmorpholine (X; $R^3 = Pr^i$) and DL-n-pentylsuccinic anhydride (V; $R^4 = n\text{-}C_5H_{11}$). This yielded a laevorotatory imide (VIII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), m.p. 99—101°, $[\alpha]_D$ −91°. Its reaction with methanolic alkaline hydroxylamine yielded the corresponding laevorotatory hydroxamic acid (II), m.p. 134—135°, $[\alpha]_D$ −25°, which on mild acidic hydrolysis [3] gave L-valylmorpholine (X; $R^3 = Pr^i$) and D-pentylsuccinic acid (XII; $R^4 = n\text{-}C_5H_{11}$) previously obtained from natural actinonin.[3] This established (i) the absolute configuration (XIII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) for the (−)-hydroxamic acid, m.p. 134—135°, and (ii) the absolute configuration (XI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) for the (−)-imide, m.p. 99—101°. From these results two conclusions may be drawn concerning the high degree of stereoselectivity associated with the sequence: (X) + (V) ⟶ [(VI) + (VII)] ⟶ (XI) ⟶ (XIII). First the formation of *one* enantiomer of the imide (XI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) from L-valylmorpholine and DL-pentylsuccinic anhydride must involve an equilibration, requiring acid-catalysed enolisation or its equivalent, associated with the chiral centre of the pentylsuccinic acid residue; this takes place during the dehydrative formation of the imide (XI) with hot acetyl chloride. Secondly, the fact that the transformation (XI) ⟶ (XIII) by methanolic alkaline hydroxylamine occurs with retention of configuration at both chiral centres could be ascribed to the high nucleophilicity of hydroxylamine and inhibition of carbanion formation in the derived hydroxamic acid (XIII).

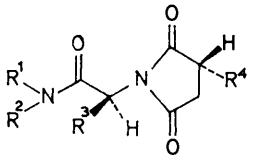
The determination of the relative configuration of the (±)-imides (VIII) and (±)-hydroxamic acids (II) obtained from racemic precursors [IIIb) and (V)] was now possible. The very high degree of stereoselection in the formation of the (±)-imides (VIII) and the (±)-hydroxamic acids (II) was inferred from their sharp m.p.s and was clearly supported by their n.m.r. spectra which gave no evidence of the presence of diastereoisomers. Furthermore, the n.m.r. spectra and i.r. spectra (solution) of the following pairs (a) and (b) were identical: (pair a) the (−)-imide, m.p. 99—101°, and (±)-imide, m.p. 79—81° (VIII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), and (pair b) the (−)-hydroxamic acid, m.p. 134—135°, and the (±)-hydroxamic acid, m.p. 162—163° (II; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$). The deduction of the absolute configuration (XIII) of the (−)-hydroxamic acid, m.p. 134—135°, has already been presented and we believe that all the (±)-hydroxamic acids (II) prepared by base-catalysed reaction between the imides (VIII) and methanolic alkaline solutions of hydroxylamine have the relative configuration (XIII). This leads to the proposal that the (±)-imides (VIII) have the relative configuration (XI). These results with the morpholino-derivatives (XI and XIII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$) are fully confirmed by the following results in the pyrrolidino-series (XI and XIII; $R^1R^2 = [CH_2]_4$).

Hydrolysis with aqueous alkali of the (±)-imide (XI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) gave a mixture of two carbamoyl-acids, m.p.s 135—136° and 153—154°. Under identical conditions, the corresponding (−)-imide (XI) gave the same two *racemic* carbamoyl acids, m.p. 135—136°, $[\alpha]_D$ 0, and m.p. 153—154°, $[\alpha]_D$ 0. The establishment that the formation of these two (±)-carbamoyl-acids did not involve two sites for cleavage (a or b) of the imide (VIII) but that they were related only as diastereoisomers [(XV) and (XVI)] with the same constitution [VI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$] rests upon the following evidence.

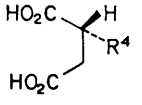
In this series ($R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), the (±)-carbamoyl-acid (XV) or (XVI), m.p. 135—136°, gave *via* its mixed anhydride [9] [(XVII) or (XVIII)] a (±)-*O*-benzylhydroxamic acid [(XIX) or (XX)], m.p. 137—138°, which by catalytic debenzylation gave a (±)-hydroxamic acid [(XIII) or (XIV)], m.p. 153—154°.



(X)



(XI)†



(XII)

† These formulae depict either the established absolute configuration of single enantiomers or the relative configuration of single racemates.

The decision that this (±)-hydroxamic acid had the relative configuration (XIII) was made possible by its direct synthesis from the corresponding imide (XI) and methanolic alkaline hydroxylamine: the relative configurations (XV) and (XIX) for its precursors follow. The other (±)-carbamoyl-acid, m.p. 153—154°, could then be assigned the diastereoisomeric relative configuration (XVI) because its derived *O*-benzylhydroxamic acid (XX), m.p. 167—168°, and the *O*-benzylhydroxamic acid (XIX), m.p. 137—138°, were shown [9] by independent synthesis to have the same constitution. Catalytic debenzylation of the *O*-benzylhydroxamic acid (XX), m.p. 167—168°, gave the (±)-hydroxamic acid (XIV), m.p. 159—160°. Comparison of the n.m.r. spectra of the (±)-hydroxamic acids (XIII), m.p. 153—154°, and (XIV), m.p. 159—160°, with that of actinonin (I) provided alternative support for these configurational assignments.

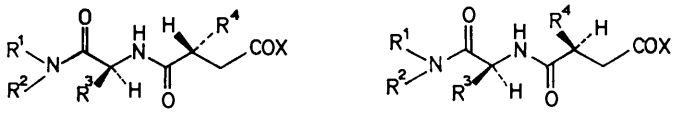
In our studies we have compared the n.m.r. spectra of

[9] Part IV, B. J. Broughton, P. J. Warren, K. R. H. Wooldridge, D. E. Wright, W. D. Ollis, and R. J. Wood, following paper.

a number of pairs of diastereoisomerically related hydroxamic acids [(XIII) and (XIV)] with that of actinonin (I): in all cases there is a close correspondence between one of the diastereoisomers (XIII) and actinonin in the region τ 7·0—8·0. The spectrum of actinonin in [$^2H_5$]pyridine shows highly characteristic signals (ABX system: τ_A 7·07, τ_B 7·43, τ_X *ca.* 7·8; J_{AB} 14, J_{AX} 8, J_{BX} 6 Hz by first-order analysis; H_X shows additional coupling with the adjacent methylene of n-C_5H_{11}) which are assigned to the indicated protons of the pentylsuccinic acid residue, -NH·CO·CH_X(n-C_5H_{11})·CH_AH_B·CO·NH·OH. The n.m.r. spectrum of the (±)-hydroxamic acid, m.p. 153—154°, shows signals identical with those of actinonin (I) in the region τ 7·0—8·0 compatible with the relative configuration (XIII; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = n-C_5H_{11}). The diastereoisomeric (±)-hydroxamic acid, m.p. 159—160°, has an obviously different pattern of n.m.r. signals in the range τ 7·0—8·0 pointing towards the relative configuration (XIV; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = n-C_5H_{11}). Although comparison of n.m.r. spectra of diastereoisomers in this way is not conclusive, it is reassuring that the conclusions drawn are identical with opinions based upon iron-clad chemical evidence.

ported for the (±)-hydroxamic acid, m.p. 165—166°. The n.m.r. spectrum of the (±)-hydroxamic acid, m.p. 169—170°, in the region τ 7·0—8·0 indicates that it has the relative configuration (XIV; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = Bu^n).

In summary, the (±)-imides (XI) with methanolic alkaline hydroxylamine yield the (±)-hydroxamic acid (XIII) alone, whereas the (±)-imides (XI) with aqueous alkali yield mixtures of the (±)-carbamoyl-acids (XV) and (XVI). This difference may be explained by postulating that the (±)-hydroxamic acids (XIII) are formed directly from the (±)-imides (XI) without equilibration when methanolic alkaline hydroxylamine is used. However, when the (±)-imides (XI) are treated with aqueous alkali equilibration does occur *via* carbanionic intermediates giving the diastereoisomerically related (±)-carbamoyl-acids (XV) and (XVI). This equilibration involves both chiral centres; carbanion formation from



(XIII)† X = NH·OH (XIV)†
(XV)† X = OH (XVI)†
(XVII)† X = O·CO_2Et (XVIII)†
(XIX)† X = NH·O·CH_2Ph (XX)†

Exactly corresponding results were obtained in the n-butylsuccinimide series (XI; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = Bu^n). Mild alkaline hydrolysis of the (−)-imide and the corresponding (±)-imide each gave an identical mixture of two racemic pairs, (XV) and (XVI). The two (±)-carbamoyl-acids (XV and XVI; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = Bu^n) gave, *via* their mixed anhydrides (XVII) and (XVIII), the (±)-*O*-benzylhydroxamic acids (XIX) and (XX), which on catalytic hydrogenolysis gave two (±)-hydroxamic acids (XIII) and (XIV). The identity of constitution of these two (±)-hydroxamic acids (XIII and XIV; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = Bu^n) was established by Lossen degradation with methylketen diethyl acetal [3] followed by acidic hydrolysis. Both (±)-hydroxamic acids gave the same β-amino-acid, BuCH(CH_2·NH_2)·CO_2H, characterised by its thermal transformation into 2-methylenehexanoic acid and by its mass spectrum. This showed a highly characteristic fragmentation pattern (*m/e* 145, 102, 89, and 73) which corresponded exactly with that of 2-(aminomethyl)-heptanoic acid.[3] The n.m.r. spectrum of the (±)-hydroxamic acid, m.p. 165—166°, in the region τ 7·0—8·0 was identical with those of actinonin (I) and the (±)-hydroxamic acid (XIII; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = n-C_5H_{11}). On this basis, the relative configuration (XIII; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = Bu^n) is supported for the (±)-hydroxamic acid, m.p. 165—166°. The n.m.r. spectrum of the (±)-hydroxamic acid, m.p. 169—170°, in the region τ 7·0—8·0 indicates that it has the relative configuration (XIV; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = Bu^n).

In summary, the (±)-imides (XI) with methanolic alkaline hydroxylamine yield the (±)-hydroxamic acid (XIII) alone, whereas the (±)-imides (XI) with aqueous alkali yield mixtures of the (±)-carbamoyl-acids (XV) and (XVI). This difference may be explained by postulating that the (±)-hydroxamic acids (XIII) are formed directly from the (±)-imides (XI) without equilibration when methanolic alkaline hydroxylamine is used. However, when the (±)-imides (XI) are treated with aqueous alkali equilibration does occur *via* carbanionic intermediates giving the diastereoisomerically related (±)-carbamoyl-acids (XV) and (XVI). This equilibration involves both chiral centres; carbanion formation from the imide (VIII) (as an α-succinimido-amino-acid derivative) is entirely analogous to the base-catalysed racemisation [10] of α-phthalimido-derivatives (IX) (at the asterisked position). This proposal is also compatible with the observation that the (−)-imide (XI; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i, R^4 = H) shows partial racemisation under alkaline cleavage conditions.

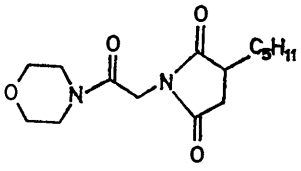
Selectivity of Ring Cleavage of Imides (XI).—The reaction of imides (XI) either with methanolic alkaline hydroxylamine to give the hydroxamic acids (XIII), or with aqueous alkali to give the carboxylic acids (XV) and (XVI), is in general regiospecific giving only those products where the substituent R^4 is in a β-relation to the hydroxamic acid or carboxy-groupings. We have encountered only one exception to this general circumstance for imides of the type (XI).

The imide (XXI) (with a glycyl residue) and methanolic alkaline hydroxylamine gave two hydroxamic acids, m.p.s 157—158° and 126—128°, in approximately equal yields which must be the constitutional isomers (XXII) and (XXIII). Structural allocation rests on the following evidence.

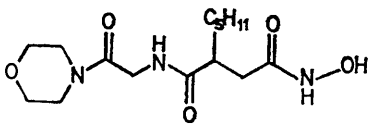
Lossen degradation of the (±)-hydroxamic acid, m.p. 157—158°, with methylketen diethyl acetal [3] followed by acidic hydrolysis gave the β-amino-acid C_5H_{11}·CH(CH_2·NH_2)·CO_2H, thus settling its constitution (XXII): this was subsequently confirmed by synthesis.[9] The other (±)-hydroxamic acid, m.p. 126—128°, behaved quite differently in that the isocyanate from the Lossen degradation cyclised easily giving the dihydrouracil

[10] B. Liberek, *Tetrahedron Letters*, 1963, 925, 1103.

(XXIV), which with acid gave the stable hydrolysis product (XXV). The n.m.r. spectrum of compound (XXV) showed an ABX system [τ(CD_3OD) 7·20 (H_A), 7·54 (H_B), and 6·57 (H_X, broad m); J_{AB} 16, J_{AX} 4, J_{BX} 7·5 Hz] which located the n-pentyl substituent and established the constitution (XXIII) of the hydroxamic acid, m.p. 126—128°.



(XXI)



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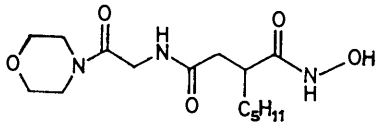

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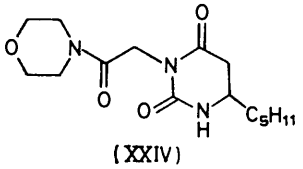
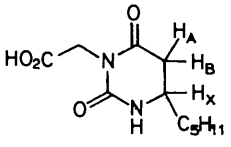


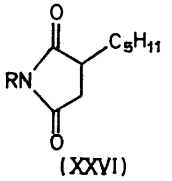
(XXIV)



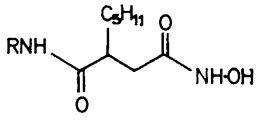
(XXV)

The formation of two hydroxamic acids (XXII) and (XXIII) from the imide (XXI) was unexpected. When the synthesis of structural analogues (II) by the transformation (VIII) ⟶ (II) was first considered a possibly useful directive influence of the group R^4 [see (VIII)] was recognised. It now appears that selectivity in the ring cleavage of the imides (VIII) operates more obviously when R^3 is a substituent than when R^3 = H in glycyl derivatives [*e.g.* (XXI)].

The possibility of substituent effects in the base-catalysed ring cleavage of similar imides (XXVI) with hydroxylamine was also examined. Whereas the imides (XXVI; R = Pr^i or Bu^t) gave the hydroxamic acids (XXVII; R = Pr^i or Bu^t, respectively), the *N*-phenylimide (XXVI; R = Ph) gave a mixture of hydroxamic acids (XXVII; R = Ph) and (XVIII; R = Ph) from which (XXVII; R = Ph) was isolated by fractional crystallisation. The approximate composition of this mixture [(XXVII; R = Ph) *ca.* 70%; (XXVIII; R = Ph) *ca.* 30%] was obtained by reaction of the mixture with methylketen diethyl acetal directly and n.m.r. analysis of the derived mixture of dihydrouracils (XXIX; R = Ph) and (XXX; R = Ph). The n.m.r. spectra of these dihydrouracils showed highly characteristic ABX systems after deuteriation, which were useful models for the structural definition of other Lossen degradation products [*e.g.* (XXV)]. The ABX systems of the dihydrouracils (XXIX; R = Ph) [τ 6·60 (H_A), 6·92 (H_B),



(XXVI)



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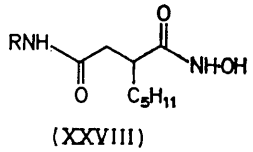
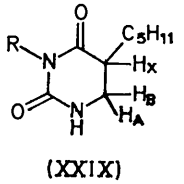
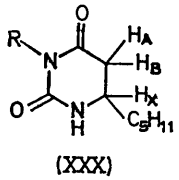


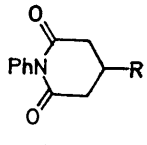
(XXVIII)



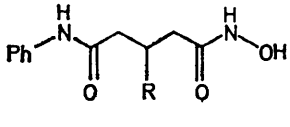
(XXIX)



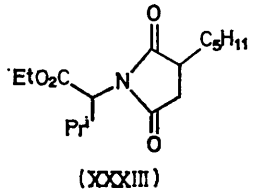
(XXX)



(XXXI)



(XXXII)



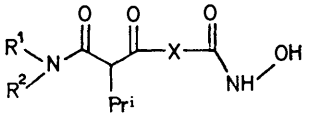
(XXXIII)

and *ca.* 7·3 (H_X, broad m); J_{AB} 12, J_{AX} 5·9, J_{BX} 8·3 Hz] and (XXX; R = Ph) [τ 7·15 (H_A), 7·51 (H_B), and *ca.* 6·7 (H_X, broad m); J_{AB} 16·2, J_{AX} 4·9, J_{BX} 9 Hz] are amenable to first-order analysis. Lossen degradation of the hydroxamic acid (XXVII; R = Ph) gave the dihydrouracil (XXIX). The glutarimides (XXXI; R = H or Me) yielded the corresponding hydroxamic acids (XXXII; R = H or Me) with methanolic alkaline hydroxylamine.

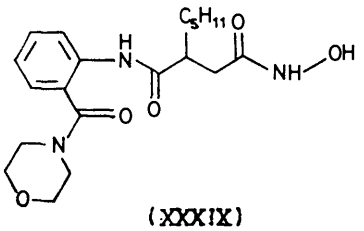
Miscellaneous Actinonin Analogues.—The bis-hydroxamic acid (II; R^1 = OH, R^2 = H, R^3 = Pr^i, R^4 = n-C_5H_{11}) was prepared from the imide ester (XXXIII) and methanolic alkaline hydroxylamine.

In connection with structure–activity studies [11] the hydroxamic acids (XXXIV)—(XL) were similarly prepared from various succinimides or glutarimides.

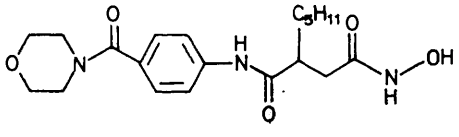
Advantages of the Anhydride–Imide Method for the Synthesis of Actinonin Analogues.—The anhydride–imide method involves the general sequence: (IIIb) + (V) ⟶ [(VI) + (VII)] ⟶ (VIII) ⟶ (II). The major advantage of this method is that the product (II) is almost invariably obtained as a single compound. It follows that the cleavage of the imide (VIII) is associated with a very high degree of regiospecificity and stereochemical selectivity. Thus the (±)-amino-amide (IIIb) and the (±)-anhydride (V) yield a single racemate (XIII) which is topologically equivalent to natural actinonin (I). Other synthetic methods leading mainly to the diastereoisomeric racemate (XIV) are discussed in subsequent Parts of this series. The synthesis by the anhydride–imide route of structural analogues of actinonin either as racemates (XIII) or as single enantiomers (XIII) was of particular interest in relation to structure–activity studies.[11]



	R^1 — R^2	X
(XXXIV)	$[CH_2]_4$	
(XXXV)	$[CH_2]_2O[CH_2]_2$	CHMe·CHMe
(XXXVI)	$[CH_2]_2O[CH_2]_2$	CMeEt·CH_2
(XXXVII)	$[CH_2]_2O[CH_2]_2$	$CH_2CH(C_5H_{11})\cdot CH_2$
(XXXVIII)	$[CH_2]_2O[CH_2]_2$	$CH(C_5H_{11})\ CH_2CH_2$



(XXXIX)



(XL)

EXPERIMENTAL

General experimental procedures are described in Part I.[3]

N-Benzyloxycarbonyl Derivatives (IIIa).—Compounds prepared with yields, analytical data, and physical constants are shown in Table 1. Most were isolated as solids which were purified by crystallisation. Where this was not possible, the crude product was directly converted into the amine (IIIb) (Table 2) by hydrogenolysis. The following examples illustrate the general methods of synthesis.

Method A. N-(N-*Benzyloxycarbonyl*-L-*alanyl*)*diethylamine* (IIIa; R^1 = R^2 = Et, R^3 = Me).—Diethylamine (0·8 g) was treated with a solution of *N*-benzyloxycarbonyl-L-alanine *p*-nitrophenyl ester (3·44 g) in ethyl acetate (20 ml; anhydrous) and kept (24 h) at room temperature. Chloroform (200 ml) was added to the mixture, and the solution was successively washed with 2N-hydrochloric acid (2 × 20 ml), 2N-ammonium hydroxide (in 50 ml portions until the yellow colour which developed in the aqueous layer no longer persisted), and water (2 × 20 ml), then dried (Na_2SO_4) and evaporated. Crystallisation of the residue from

[11] B. J. Broughton, P. Chaplen, W. A. Freeman, P. J. Warren, K. R. H. Wooldridge, and D. E. Wright, *J.C.S. Perkin I*, 1975, 857.

ether–light petroleum gave N-(N-*benzyloxycarbonyl*-L-*alanyl*)-*diethylamine* as needles (2·41 g, 86%), m.p. 62—63°, $\nu_{max.}$ 1700 and 1630 cm^{-1}.

Method B. N-(N-*Benzyloxycarbonyl*-DL-*valyl*)*piperidine* (IIIa; $R^1R^2 = [CH_2]_5$, $R^3 = Pr^i$).—To a cooled (−15°) (1·48 ml). The mixture was kept at 0° for 0·5 h and at room temperature overnight. Chloroform (25 ml) was added, and the mixture was successively washed with hydrochloric acid (N; 50 ml), aqueous sodium hydrogen carbonate (5% w/v; 50 ml), and water (50 ml). The organic layer was dried

TABLE 1

N-Benzyloxycarbonyl (Z) derivatives (IIIa)

Reactants: Amine *	Reactants: Z-Amino-acid	Method of coupling	Product (IIIa): R^1	R^2	R^3	Yield (%)	Cryst. solvent.†	M.p. (°C)	Found (%): C	H	N	Formula	Calc. (%): C	H	N	$[\alpha]_D^{25}$ k (°)
Et_2NH	Z-L-Ala-ONp a	A	Et	Et	Me	86	Et_2O-LP	62—63	65·0	7·9	9·8	$C_{14}H_{22}N_2O_3$	64·7	8·0	10·1	−1·1
Et_2NH	Z-L-Val-ONp a	A	Et	Et	Pr^i	90		Oil	67·0	8·5	9·4	$C_{17}H_{26}N_2O_3$	66·6	8·6	9·1	−4·8
$[CH_2]_4NH$	Z-Gly b	B	$[CH_2]_4$		H	18	EtOAc-LP	87—90	59·9	7·1	10·0	$C_{14}H_{18}N_2O_3,H_2O$ h	60·0	7·2	10·0	
$[CH_2]_4NH$	Z-L-Leu-ONp c	A	$[CH_2]_4$		Bu^i	89	Et_2O-LP	44—45	68·2	8·3	8·7	$C_{18}H_{26}N_2O_3$	67·9	8·2	8·8	−6·5
$[CH_2]_4NH$	Z-L-Phe-ONp b	A	$[CH_2]_4$		CH_2Ph	93	Et_2O-LP	74—75	71·9	7·1	7·9	$C_{21}H_{24}N_2O_3$	71·6	6·9	8·0	+21·6
$[CH_2]_4NH$	Z-L-Val-ONp a	A	$[CH_2]_4$		Pr^i	90		Oil i				$C_{17}H_{24}N_2O_3$				+8·6
$[CH_2]_4NH$	Z-D-Val-ONp d	A	$[CH_2]_4$		Pr^i	94		Oil i	66·8	7·9	8·9	$C_{17}H_{24}N_2O_3$	67·1	8·0	9·2	−8·4
$[CH_2]_4NH$	Z-DL-Val-ONp e	A	$[CH_2]_4$		Pr^i	70	Ch	65—67 i	66·9	8·1	9·2	$C_{17}H_{24}N_2O_3$	67·1	8·0	9·2	
$[CH_2]_4NH$	Z-DL-Val f	B	$[CH_2]_4$		Pr^i	64	EtOAc-LP	84—86	67·9	8·3	8·7	$C_{18}H_{26}N_2O_3$	67·9	8·2	8·8	
2-Me·$[CH_2]_4NH$	Z-L-Ala-ONp a	A	Me·$[CH_2]_4$		Me	90	Et_2O-LP	62—63	66·9	7·7	9·0	$C_{17}H_{24}N_2O_3$	67·1	8·0	9·2	+37·9
2-Me·$[CH_2]_4NH$	Z-DL-Val-ONp e	A	Me·$[CH_2]_4$		Pr^i	49	EtOAc-LP	91—92	68·4	8·5	8·4	$C_{19}H_{28}N_2O_3$	68·6	8·5	8·4	
2-$(HOCH_2)[CH_2]_4NH$	Z-DL-Val-ONp e	A	$(CH_2OH)·CH[CH_2]_4$		Pr^i			Oil				$C_{19}H_{28}N_2O_4$				
Thpy	Z-DL-Val-ONp e	A	$CH_2·CH:CH·[CH_2]_2$		Pr^i	74	EtOAc-LP	82—84	68·3	7·6	8·8	$C_{18}H_{26}N_2O_3$	68·3	7·7	8·9	
$[CH_2]_6NH$	Z-DL-Val-ONp e	A	$[CH_2]_6$		Pr^i	61	Ch-LP	74—76	68·8	8·4	8·5	$C_{19}H_{28}N_2O_3$	68·6	8·5	8·4	
Morph	Z-Gly-ONp e	A	$[CH_2]_2·O·[CH_2]_2$		H	77	EtOAc	142—144 j	60·3	6·5	10·2	$C_{14}H_{18}N_2O_4$	60·4	6·5	10·1	
Morph	Z-DL-Ala-ONp b	A	$[CH_2]_2·O·[CH_2]_2$		Me	77	EtOH	136—137	61·8	6·8	9·6	$C_{15}H_{20}N_2O_4$	61·6	6·9	9·6	
Morph	Z-DL-Val-ONp e	A	$[CH_2]_2·O·[CH_2]_2$		Pr^i	84	EtOAc-LP	87—88	63·4	7·5	8·6	$C_{17}H_{24}N_2O_4$	63·7	7·6	8·7	
Morph	Z-L-Val-ONp a	A	$[CH_2]_2·O·[CH_2]_2$		Pr^i	90		Oil				$C_{17}H_{24}N_2O_4$				
Morph	Z-DL-Phe-ONp g	A	$[CH_2]_2·O·[CH_2]_2$		CH_2Ph	69	EtOH	152—153	68·3	6·6	7·4	$C_{21}H_{24}N_2O_4$	68·5	6·6	7·6	
Morph	Z-DL-Leu-ONp e	A	$[CH_2]_2·O·[CH_2]_2$		Bu^i	70	EtOAc-LP	80—81	64·7	7·8	8·3	$C_{18}H_{26}N_2O_4$	64·7	7·8	8·4	
2-Me-Morph	Z-DL-Val-ONp e	A	$CH_3·CHMe·O·[CH_2]_2$		Pr^i	76		77—80	64·4	7·9	8·3	$C_{18}H_{26}N_2O_4$	64·7	7·8	8·4	
2,6-Me_2-Morph	Z-DL-Val-ONp e	A	$CH_3·CHMe·O·$-$CHMe·CH_2$		Pr^i	40	EtOAc	62—63	65·7	8·2	7·9	$C_{19}H_{28}N_2O_4$	65·5	8·1	8·0	
3-NH_2·Thtd	Z-DL-Val-ONp e	A	$CH[CH_2]_2·S(O_2)·CH_2$	H	Pr^i	39	EtOAc	154—156	55·7	6·9	7·8	$C_{17}H_{24}N_2O_5S$	55·4	6·6	7·6	
2-NH_2·Py	Z-DL-Val b	B	2-pyridyl	H	Pr^i	15	EtOH–H_2O	103—105	66·2	6·3	12·8	$C_{13}H_{21}N_3O_2$	66·0	6·5	12·8	
2-NH_2·Tz	Z-DL-Val b	C	2-thiazolyl	H	Pr^i	34	PhH	165—167	58·0	5·5	12·4	$C_{16}H_{19}N_3O_3S$	57·6	5·7	12·6	

Method C: coupling of the amine and amino-acid by using dicyclohexylcarbodi-imide with ethyl acetate as solvent.

a Ref. 1. b T. Wieland, B. Heinke, and K. Vogeler, *Annalen*, 1962, **655** 189. c B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, *Helv. Chim. Acta*, 1957, **40** 373. d M. Botvinik, I. Kuranova, and L. Ivanov, *Khim. prirod. Soedinenii Akad. Nauk Uzbek. S.S.R.*, 1966, **2(2)**, 134 (*Chem. Abs.* 1966, **65** 10,655h). e T. Wieland and B. Heinke, *Annalen*, 1958, **615**, 184. f S. W. Fox, M. Fling, H. Wax, and C. W. Pettinga, *J. Amer. Chem. Soc.*, 1950, **72**, 1862. g Yu. I. Khurgin and M. G Dmitrieva, *Tetrahedron*, 1965, **21**, 2305. h Found: H_2O, 5·7. $C_{14}H_{18}N_2O_3,H_2O$ requires H_2O, 6·4%. i The i.r. spectra of these compounds were identical. j J. Vaughan (*J. Amer. Chem. Soc.*, 1951, **73**, 1389) prepared this compound, m.p. 144—145°, by a mixed anhydride method using diethyl chloroarsenite. k Optical rotation measurements were determined for solutions in chloroform.

* Thpy = 1,2,3,6-tetrahydropyridine; Morph = morpholine; Thtd = tetrahydrothiophen *SS*-dioxide; Py = pyridine; Tz = thiazole. † LP = light petroleum; Ch = cyclohexane.

TABLE 2

Amino-amides (IIIb)

Configuration	R^1	R^2	R^3	Yield (%)	Derivative	Cryst. solvent †	M.p. (°C)	Found (%): C	H	N	Cl	Formula	Calc. (%): C	H	N	Cl
L	Et	Et	Me		2,4-DNP a	EtOH	117—118	50·5	5·7	18·1		$C_{13}H_{18}N_4O_5$	50·3	5·9	18·1	
L	Et	Et	Pr^i		2,4-DNP a	EtOH	94—95	53·0	6·9	16·7		$C_{15}H_{22}N_4O_5$	53·2	6·6	16·6	
	$[CH_2]_4$	H		68	Picrate b	EtOH–H_2O	210—213	40·3	4·2	19·5		$C_{12}H_{15}N_3O_8$	40·3	4·2	19·6	
L	$[CH_2]_4$	Pr^i			2,4-DNP a	EtOH	165—166	53·9	5·9	17·0		$C_{15}H_{20}N_4O_5$	53·6	6·0	16·7	
D	$[CH_2]_4$	Pr^i			2,4-DNP a	EtOH	165—166	53·7	5·8	16·5		$C_{15}H_{20}N_4O_5$	53·6	6·0	16·7	
DL	$[CH_2]_4$	Pr^i		80			Oil					$C_{15}H_{20}N_4O_5$				
L	$[CH_2]_4$	Bu^i			2,4-DNP a	EtOH	152—153	55·0	6·4	16·2		$C_{16}H_{22}N_4O_5$	54·9	6·3	16·0	
L	$[CH_2]_4$	CH_2Ph			2,4-DNP a	EtOH	89—90	59·4	5·3	14·4		$C_{19}H_{20}N_4O_5$	59·4	5·2	14·6	
L	CHMe·$[CH_2]_4$	Me			2,4-DNP a	EtOH	74—75	53·8	6·2	16·5		$C_{15}H_{20}N_4O_5$	53·6	6·0	16·7	
DL	CHMe·$[CH_2]_4$	Pr^i					Oil					$C_{11}H_{23}N_3O$				
DL	$(CH_2OH)·CH·[CH_2]_4$	Pr^i			Picrate	AcOH	210—212	46·2	6·0	15·6		$C_{17}H_{25}N_5O_9$	46·1	5·7	15·8	
	$[CH_2]_5$	H		97	Picrate b,c	EtOH	206—207	41·7	4·6	18·7		$C_{13}H_{17}N_5O_8$	42·1	4·6	18·9	
DL	$[CH_2]_5$	Pr^i		65	Hydrochloride d	EtOH–PhH-LP	193—194			12·5	16·0	$C_{10}H_{20}N_2O,HCl$			12·7	16·1
DL	$CH_3·CH:CH·[CH_2]_2$	Pr^i		72	Hydrochloride	EtOH–Et_2O	157—159					$C_{10}H_{20}N_2O,HCl$				
DL	$[CH_2]_5$	Pr^i					Oil					$C_{11}H_{23}N_2O$				
	$[CH_2]_2·O·[CH_2]_2$	H		66	Hydrochloride	EtOH	243—245 (lit.,b 239—244)	40·0	7·2	15·2	18·7	$C_6H_{13}N_2O_2,HCl$	39·9	7·3	15·5	19·6
DL	$[CH_2]_2·O·[CH_2]_2$	Pr^i		72	Hydrochloride	Pr^{i}OH–Et_2O	266—267 (decomp.)			12·6	16·0	$C_9H_{18}N_2O_2,HCl$			12·6	15·9
L	$[CH_2]_2·O·[CH_2]_2$	Pr^i		66	Picrate e	EtOH	195—196	43·7	5·1	16·8		$C_{15}H_{21}N_5O_9$	43·4	5·1	16·9	
DL	$[CH_2]_2·O·[CH_2]_2$	Me		b			Oil					$C_7H_{14}N_2O_2$				
DL	$[CH_2]_2·O·[CH_2]_2$	Bu^i					Oil					$C_{10}H_{20}N_2O_2$				
DL	$[CH_2]_2·O·[CH_2]_2$	CH_2Ph					Oil					$C_{13}H_{18}N_2O_2$				
DL	$CH_2·CHMe·O·[CH_2]_2$	Pr^i					Oil					$C_{10}H_{20}N_2O_2$				
DL	$CH_3·CHMe·O·CHMe·CH_2$	Pr^i					Oil					$C_{11}H_{22}N_2O_2$				
DL	$CH[CH_2]_2·S(O_2)·CH_2$	H	Pr^i				Oil					$C_8H_{15}N_2O_2S$				
DL	2-pyridyl	H	Pr^i	34		Ch	101—102	62·1	7·7	21·8		$C_{10}H_{14}N_2O$	62·2	7·8	21·9	
DL	2-thiazolyl	H	Pr^i	49		Ch	109—110			20·8		$C_8H_{12}N_2OS$ f			21·1	

a Prepared by the general method of K. R. Rao and H. A. Sober, (*J. Amer. Chem. Soc.*, 1954, **76** 1328). b Previously prepared, either as the free base or as the hydrochloride, from the corresponding chloro-amide and ammonia by R. H. Earle, D. T. Hurst, and M. Viney (*J. Chem. Soc.*, 1969, 2093). c The *N*-benzyloxycarbonyl precursor was prepared by the method of F. Weygand and W. Steglich (*Ber.*, 1960, **93** 2983). d Mentioned but not described by T. Wieland and W. Schäfer (*Annalen*, 1952, **576**, 104). e $[\alpha]_D^{20}$ + 46·3° (*c* 1·71 in $Me_2N·CHO$). f Found: S, 16·4. $C_8H_{12}N_2OS$ requires S, 16·1%.

† For abbreviations see Table 1.

solution of *N*-benzyloxycarbonyl-DL-valine (3·6 g) in chloroform (15 ml; anhydrous) were added triethylamine (2 ml; anhydrous) and ethyl chlorocarbonate (1·37 ml). The mixture was kept at −15° for 0·5 h, then at 0° for 5 min, and stirred at −15° during the slow addition of piperidine ($MgSO_4$) and evaporated. Trituration of the residual oil with light petroleum gave the *piperidine derivative* as a solid (3·1 g), m.p. 82—84° (raised to 84—86° by crystallisation from ethyl acetate–light petroleum).

Amino-amides (IIIb) (*Table* 2).—These were prepared in

high yield by hydrogenolysis of the corresponding *N*-benzyloxycarbonyl derivatives, according to the general method described for L-alanyldiethylamine. Most of these amines were characterised either as salts, or as their *N*-2,4-dinitrophenyl derivatives.

N-(L-*Alanyl*)*diethylamine* (IIIb; $R^1 = R^2 = Et$, $R^3 = Me$). A solution of *N*-(*N*-benzyloxycarbonyl-L-alanyl)-diethylamine (1·4 g) in ethanol (30 ml) containing palladised charcoal (0·5 g; 10%) was shaken with hydrogen at room temperature and atmospheric pressure until uptake ceased. The catalyst was removed; evaporation gave L-*alanyldiethylamine* (0·69 g) as an oil, $\nu_{max.}$ 1630 cm^{-1}. The *N*-2,4-dinitrophenyl derivative, prepared by treatment of the amine with 2,4-dinitrofluorobenzene, was obtained as yellow needles (from ethanol), m.p. 117—118°.

Triethyl 1-p-*Nitrobenzylethane*-1,1,2-*tricarboxylate*.—To a solution of sodium (11·5 g) in ethanol (700 ml; anhydrous) was added triethylethane-1,1,2-tricarboxylate (123·1 g), followed by *p*-nitrobenzyl chloride (85·8 g). The mixture was stirred and refluxed for 18 h then the filtered solution was evaporated and the residue treated with water (100 ml). The oil which separated was extracted into ether; the extract was dried and evaporated to leave the crude product (190 g, 100%) as a brown oil. A sample of the oil was triturated at −70° with light petroleum and the solid which separated was crystallised from ethyl acetate–light petroleum giving the p-*nitrobenzyl derivative* as yellow crystals, m.p. 47—49° (Found: C, 57·0; H, 6·1; N, 3·7. $C_{18}H_{23}NO_8$ requires C, 56·7; H, 6·1; N, 3·7%).

Triethyl 1-p-*Chlorobenzylethane*-1,1,2-*tricarboxylate*.—Similarly *p*-chlorobenzyl chloride and triethylethane-1,1,2-tricarboxylate yielded the p-*chlorobenzyl derivative* (51%) as an oil, b.p. 159° at 0·3 mmHg (Found: C, 58·0; H, 5·9; Cl, 9·6. $C_{18}H_{23}ClO_6$ requires C, 58·3; H, 6·3; Cl, 9·6%).

p-*Nitrobenzylsuccinic Acid* (IV; $R^4 = p\text{-}NO_2{\cdot}C_6H_4{\cdot}CH_2$). —Triethyl 1-*p*-nitrobenzylethane-1,1,2-tricarboxylate (100 g) was stirred and refluxed with concentrated hydrochloric acid (1 l) for 45 h. The mixture was extracted with chloroform (3 × 500 ml) and the extract shaken with potassium hydroxide solution (2N; 2 × 300 ml). The alkaline solution was acidified with hydrochloric acid to give *p*-nitrobenzylsuccinic acid as a solid (33 g, 62%), m.p. 144—146° (148—150° after crystallisation from ethyl acetate–light petroleum) (Found: C, 51·9; H, 4·4; N, 5·2. Calc. for $C_{11}H_{11}NO_6$; C, 52·2; H, 4·4; N, 5·5%) (lit.,[12] m.p. 153° for this compound prepared in 35% yield by nitration of benzylsuccinic acid).

p-*Chlorobenzylsuccinic Acid* (IV; $R^4 = p\text{-}ClC_6H_4{\cdot}CH_2$).—Similarly triethyl 1-*p*-chlorobenzylethane-1,1,2-tricarboxylate yielded (48%) *p*-chlorobenzylsuccinic acid, m.p. 120—

[12] H. Le Moal, A. Foucard, R. Carrie, J. Hamelin, and C. Sévellec, *Bull. Soc. chim. France*, 1964, 578.

TABLE 3

Imides (XI) from the amino-amides (IIIb) and the succinic anhydrides (V)

(IIIb) R^1	R^2	R^3	(V) R_4	Yield (%)	Cryst. Solvent †	M.p. (°C)	Found C (%)	Found H (%)	Found N (%)	Found *M*	Formula	Calc. C (%)	Calc. H (%)	Calc. N (%)	Calc. *M*
Et	Et	Me [a]	n-C_5H_{11} [d]	40		Oil				296	$C_{18}H_{28}N_2O_3$				296
Et	Et	Pr^i	n-C_5H_{11}	36		Oil				324	$C_{19}H_{32}N_2O_3$				324
CHMe·[CH_2]$_4$		Me [a]	n-C_5H_{11}	73		Oil				322	$C_{18}H_{30}N_2O_3$				322
[CH_2]$_4$		H	H	80	$CHCl_3$–LP	139—142	57·3	6·7	13·2	210	$C_{10}H_{14}N_2O_3$	57·1	6·7	13·3	210
[CH_2]$_4$		Pr^i [b]	Bu^n [e]	91		Oil				308	$C_{17}H_{28}N_2O_3$				308
[CH_2]$_4$		Pr^i [a]	Bu^n [e]	87		Oil [f]				308	$C_{17}H_{28}N_2O_3$				308
[CH_2]$_4$		Me [a,b]	n-C_5H_{11}	86		Oil				294	$C_{18}H_{26}N_2O_3$				294
[CH_2]$_4$		Pr^i [a]	n-C_5H_{11}	80		Oil [g]				322	$C_{18}H_{30}N_2O_3$				322
[CH_2]$_4$		Pr^i [c]	n-C_5H_{11}	74		Oil [g]				322	$C_{18}H_{30}N_2O_3$				322
[CH_2]$_4$		Pr^i [a]	n-C_5H_{11}	90		Oil [g]				322	$C_{18}H_{30}N_2O_3$				322
[CH_2]$_4$		Bu^i [a]	n-C_5H_{11}	83		Oil				336	$C_{19}H_{32}N_2O_3$				336
[CH_2]$_4$		CH_2Ph [a]	n-C_5H_{11}	70	Et_2O–LP	85—86	71·2	8·2	7·4	370	$C_{22}H_{30}N_2O_3$	71·3	8·2	7·6	370
[CH_2]$_4$		Pr^i [a]	n-C_6H_{13} [h]	63		Oil				336	$C_{19}H_{32}N_2O_3$				336
[CH_2]$_5$		Pr^i	n-C_5H_{11}			Oil					$C_{19}H_{32}N_2O_3$				
[CH_2]$_5$		Pr^i	iso-C_5H_{11} [i]			Oil					$C_{19}H_{32}N_2O_3$				
CHMe·[CH_2]$_4$		Pr^i	iso-C_5H_{11}			Oil					$C_{20}H_{34}N_2O_3$				
CH(CH_2OH)·[CH_2]$_4$		Pr^i	n-C_5H_{11}			Oil [j]					$C_{20}H_{34}N_2O_4$				
CH_2·CH:CH·[CH_2]$_2$		Pr^i	n-C_5H_{11}			Oil					$C_{19}H_{30}N_2O_3$				
[CH_2]$_6$		Pr^i	n-C_5H_{11}			Oil					$C_{20}H_{34}N_2O_3$				
[CH_2]$_2$·O·[CH_2]$_2$		H	n-C_5H_{11}	46	Ch	96—98	60·4	8·2	9·1		$C_{15}H_{24}N_2O_4$	60·8	8·2	9·5	
[CH_2]$_2$·O·[CH_2]$_2$		Me	n-C_5H_{11}	89		Oil					$C_{16}H_{26}N_2O_4$				
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Me [k]	22	PhH–LP	89—91	59·5	7·7	10·1		$C_{14}H_{22}N_2O_4$	59·6	7·9	9·9	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Et [l]	19	Ch	88—90	61·2	8·2	9·3		$C_{15}H_{24}N_2O_4$	60·8	8·2	9·5	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Pr^n [m]	29	PhH–LP	75—77	62·2	8·4	8·8		$C_{15}H_{26}N_2O_4$	61·9	8·4	9·0	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Bu^n	85		Oil					$C_{17}H_{28}N_2O_4$				
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	n-C_5H_{11}	35	LP	79—81	63·5	8·9	8·1		$C_{18}H_{30}N_2O_4$	63·9	8·9	8·3	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i [a]	n-C_6H_{11}	19	Ch	99—101 [l]	64·1	8·9	8·3		$C_{18}H_{30}N_2O_4$	63·9	8·9	8·3	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	iso-C_5H_{11}	31	Ch	84—85	63·9	9·0	8·4		$C_{18}H_{30}N_2O_4$	63·9	8·9	8·3	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	[CH_2]$_2$CH [n]	57	PhH–LP	92—94	64·6	8·3	8·0		$C_{18}H_{28}N_2O_4$	64·3	8·4	8·3	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	n-C_6H_{13}	33	LP	57—58	64·9	9·2	7·8		$C_{19}H_{32}N_2O_4$	64·7	9·2	8·0	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	n-$C_{10}H_{21}$ [d]	98		Oil					$C_{23}H_{40}N_2O_4$				
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	CH_2Ph [p]	14	LP	108—110	66·6	7·2	7·8		$C_{20}H_{26}N_2O_4$	67·0	7·3	7·8	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	p-$ClC_6H_4{\cdot}CH_2$ [q]	22	PhH	157—159	61·4	6·4	6·9		$C_{20}H_{25}ClN_2O_4$ [r]	61·1	6·4	7·1	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	p-$O_2N{\cdot}C_6H_4{\cdot}CH_2$	64	EtOAc	148—149	59·7	6·3	10·2		$C_{20}H_{25}N_3O_6$	59·5	6·3	10·4	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Ph [s]	90		Oil					$C_{18}H_{24}N_2O_4$				
[CH_2]$_2$·O·[CH_2]$_2$		Bu^i	n-C_5H_{11}	90		Oil					$C_{19}H_{32}N_2O_4$				
[CH]$_2$·O·[CH_2]$_3$		CH_2Ph	n-C_5H_{11}			Oil					$C_{23}H_{30}N_2O_4$				
CH_2·CHMe·O·[CH_2]$_2$		Pr^i	n-C_5H_{11}			Oil					$C_{19}H_{32}N_2O_4$				
CH_2·CHMe·O·CHMe·CH_2		Pr^i	n-C_5H_{11}	87		Oil					$C_{20}H_{34}N_2O_4$				
CH_2·CHMe·O·CHMe·CH_2		Pr^i	iso-C_5H_{11}	87		Oil					$C_{18}H_{30}N_2O_5S$				
CH[CH_2]$_2$·S(O_2)·CH_2	H	Pr^i	n-C_5H_{11}			Oil					$C_{19}H_{37}N_3O_3$				
2-pyridyl	H	Pr^i	n-C_5H_{11}	88		Oil					$C_{17}H_{25}N_3O_3S$				
2-thiazolyl	H	Pr^i	n-C_5H_{11}												

[a] Derived from the L-amino-acid. [b] The preparation of the parent amino-amide (IIIb) has been described.[1] [c] Derived from the D-amino-acid. [d] S. U. Mehta and K. S. Nargund, *J. Univ. Bombay*, 1942—1944, 11, 134 (*Chem. Abs.*, 1943, **37**, 2349). [e] E. Stöcklmayer and T. Meinhard, *Scientia Pharm.*, 1955, **23**, 212 (*Chem. Abs.*, 1956, **50**, 11,312). [f] $[\alpha]_D^{27}$ −7·9° (*c* 1·79 in $CHCl_3$). [g] The i.r. spectra of these compounds were identical. [h] A. Higson and J. F. Thorpe, *J. Chem. Soc.* 1906, 1455. [i] N. A. Babiyan, G. A. Mednikyan, A. A. Gamburyan, Zh. A. Shakaryan, and O. L. Mndzhoyan, *Armyan. khim. Zhur.*, 1966, **19** 434 (*Chem. Abs.*, 1967, **66**, 10,528g). [j] Cyclisation of the intermediate carbamoyl-acid [(VI) + (VII)] to the imide (VIII) was effected by dicyclohexylcarbodi-imide in ethyl acetate. [k] W. H. Perkin, *J. Chem. Soc.*, 1888, 561. [l] G. Polko, *Annalen*, 1887, **242**, 113. [m] P. W. Clutterbuck, H. Raistrick, and F. Reuter, *Biochem. J.*, 1937, **31**, 987. [n] S. K. Ranganathan, *J. Indian Chem. Soc.*, 1939, **16**, 107 (*Chem. Abs.*, 1939, **33**, 5815). [p] R. Fittig and P. Röders, *Annalen*, 1890, **256**, 87. [q] A. Seiglitz, W. Müller, and K. Pomper, *Annalen*, 1965, **682**, 159. [r] Found: Cl, 8·9. $C_{20}H_{25}ClN_2O_4$ requires Cl, 9·0%. [s] H. Alexander, *Annalen*, 1890, **258** 67. [t] $[\alpha]_D^{28}$ −91° (*c* 1·67 in EtOH).

† For abbreviations see Table 1.

125° (Found: C, 54·9; H, 4·9; Cl, 14·4. Calc. for $C_{11}H_{11}ClO_4$; C, 54·5; H, 4·6; Cl, 14·6%) (lit.,[13] m.p. 131·5—132·5 for this acid prepared from *p*-chlorotoluene and maleic anhydride).

p-*Nitrobenzylsuccinic Anhydride* (V; $R^4 = p\text{-}NO_2\cdot C_6H_4\cdot CH_2$).—A mixture of *p*-nitrobenzylsuccinic acid (28 g) and acetyl chloride (50 ml) was heated under reflux for 3 h and the solution evaporated. The residue was triturated with light petroleum to give p-*nitrobenzylsuccinic anhydride* as a solid (21·9, 84%), m.p. 128—130° (from benzene) (Found: C, 56·6; H, 4·0; N, 5·8. $C_{11}H_9NO_5$ requires C, 56·2; H, 3·9; N, 6·0%).

Reaction of Amino-amides (IIIb) *with Succinic Anhydrides* (V); *Formation of the Carbamoyl-acids* (VI) *and* (VII) *and their Dehydration to the Imides* (XI) (*Table* 3).—A solution of the amino-amide (IIIb) (0·1 mol) and the succinic anhydride (V) (0·1 mol) in dichloromethane (50 ml) was heated under reflux for 1 h, then evaporated, and the mixture of carbamoyl-acids (VI) and (VII) was heated under reflux with acetyl chloride (0·5 mol) for 2·5 h. The residue obtained after evaporating the solution was treated with aqueous sodium hydrogen carbonate (100 ml; 5% w/v) and extracted with ether (3 × 100 ml). The extract was successively washed with aqueous sodium hydrogen carbonate (5 × 100 ml; 5% w/v), hydrochloric acid (2N; 100 ml), and water (100 ml), dried, and evaporated giving the *imide* (XI) (Table 3). In some cases the imide was not characterised but was converted directly into the hydroxamic acid (XIII).

Reaction of the Imides (VIII) *with Hydroxylamine; Formation of the Hydroxamic Acids* (XIII) (*Table* 4).—A stirred solution of hydroxylamine hydrochloride (0·2 mol) in methanol (100 ml) at 0° was treated with a solution of potassium hydroxide (0·3 mol) in methanol (50 ml). The mixture was kept at 0° for 15 min, and the filtered solution was added immediately to the imide (VIII) (0·1 mol). The mixture was kept at room temperature for 24 h and brought to pH 6·0 by addition of Dowex 50W-X8 resin (H^+ form). The resin was filtered off, and the filtrate was evaporated giving the *hydroxamic acid* (XIII) as a syrup. Trituration of the syrup with ether–light petroleum gave a solid which was recrystallised from the appropriate solvent. In those cases where solids were not obtained, initial purification was carried out by chromatography on either a polyamide or a silica column, as indicated in Table 4. The emergence of the required eluates from the column was detected by the purple colouration developed by a sample when treated with ethanolic iron(III) chloride.

TABLE 4

Hydroxamic acids (XIII) (data refer to single racemates unless otherwise indicated)

R^1	R^2	R_3	R_4	Yield (%)	Cryst. solvent †	M.p. (°C)	Found C(%)	Found H(%)	Found N(%)	Found *M*	Formula	Calc. C(%)	Calc. H(%)	Calc. N(%)	Calc. *M*
Et	Et	Me [a]	n-C_6H_{11}	48	Et_2O [h]	68—70 [g]	58·3	9·2	12·9	329	$C_{14}H_{31}N_3O_4$	58·3	9·5	12·8	329
Et	Et	Pr^i [a]	n-C_6H_{11}	39	Et_2O [h]	131—133 [g]	60·6	10·2	12·1	357	$C_{15}H_{33}N_3O_4$	60·5	9·9	11·8	357
[CH_2]$_4$		H	H	25	$CHCl_3$ [h]	130—133	49·2	6·9	17·2		$C_{10}H_{17}N_3O_4$	49·4	7·0	17·3	
[CH_2]$_4$		Me [a]	n-C_6H_{11}	32	Et_2O [h]	72—75 [g]			12·6	327	$C_{16}H_{29}N_3O_4$			12·8	327
[CH_2]$_4$		Pr^i [a]	Bu^n	30	Et_2O [h]	116—120 [g]			12·1	341	$C_{17}H_{31}N_3O_4$			12·3	341
[CH_2]$_4$		Pr^i [b]	n-C_6H_{11}	32	Et_2O [h]	148—150 [g]				355	$C_{18}H_{33}N_3O_4$				355
[CH_2]$_4$		Pr^i [a]	n-C_6H_{11}	40	Et_2O [h]	150—151				355	$C_{18}H_{33}N_3O_4$				355
[CH_2]$_4$		Pr^i [a]	n-C_6H_{11}	21	EtOAc	153—154	60·8	9·6	11·8		$C_{13}H_{23}N_3O_4$	60·8	9·4	11·8	
[CH_2]$_4$		Pr^i [a]	n-C_5H_{13}	29	Et_2O [h]	86—90 [g]	62·0	9·4		369	$C_{19}H_{35}N_3O_4$	61·8	9·6		369
[CH_2]$_4$		Bu^i [a]	n-C_6H_{11}	26	Et_2O [h]	86—91 [g]	61·7	9·8	11·4	369	$C_{19}H_{35}N_3O_4$	61·8	9·6	11·4	369
[CH_2]$_4$		CH_2Ph [a]	n-C_6H_{11}	35	Et_2O [h]	137—140 [g]	65·2	8·4	10·8	403	$C_{23}H_{33}N_3O_4$	65·5	8·2	10·4	403
[CH_2]$_5$		Pr^i	n-C_6H_{11}	13	EtOAc	177—178	62·1	9·5	11·3		$C_{19}H_{35}N_3O_4$	61·8	9·6	11·4	
[CH_2]$_5$		Pr^i	iso-C_6H_{11}	16	EtOAc–LP [e]	173—175	61·7	9·6	11·2		$C_{19}H_{35}N_3O_4$	61·8	9·6	11·4	
CHMe·[CH_2]$_4$		Me [a]	n-C_6H_{11}	29	[h]	Oil [g]	61·0	9·6		355	$C_{13}H_{25}N_3O_4$	60·8	9·4		355
CHMe·[CH_2]$_4$		Pr^i	iso-C_6H_{11}	16	EtOAc–LP	170—172	62·9	9·3	10·8		$C_{20}H_{37}N_3O_4$	62·6	9·7	11·0	
CH(CH_2OH)·[CH_2]$_4$		Pr^i	n-C_6H_{11}	6	EtOH–LP [e]	182—184	59·5	9·3	10·5		$C_{20}H_{37}N_3O_5$	60·1	9·3	10·5	
CH_2·CH:CH·[CH_2]$_2$		Pr^i	n-C_6H_{11}	10	EtOAc	147—149	62·1	8·7	11·3		$C_{20}H_{35}N_3O_4$	62·1	9·1	11·4	
[CH_2]$_6$		Pr^i	n-C_6H_{11}	25	PhH–EtOH–LP	185—188	62·8	9·7	10·6		$C_{20}H_{37}N_3O_4$	62·6	9·7	11·4	
[CH_2]$_2$·O·[CH_2]$_2$		Me	n-C_6H_{11}	10	EtOAc	137—138	55·8	8·4	12·0		$C_{13}H_{25}N_3O_5$	56·0	8·5	12·2	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Me	19	EtOH	177—179	52·0	7·8	12·8		$C_{14}H_{28}N_3O_6$,0·4H_2O	52·1	8·1	13·0	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Et	15	Me_2CO [e]	163—165	54·3	8·3	12·6		$C_{14}H_{27}N_3O_5$	54·7	8·3	12·8	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Pr^n	8	EtOH	179—180	55·8	8·3	12·4		$C_{14}H_{29}N_3O_5$	56·0	8·5	12·2	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Bu^n	21	EtOAc	155—157	57·0	8·6	11·7		$C_{17}H_{31}N_3O_5$	57·1	8·7	11·8	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i [a]	n-C_6H_{11}	25	EtOAc	134—135 [d,g]	58·5	8·7	11·2		$C_{18}H_{33}N_3O_5$	58·2	9·0	11·3	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	n-C_6H_{11}	34	EtOAc	162—163	58·1	9·0	11·2		$C_{18}H_{33}N_3O_5$	58·2	9·0	11·3	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	iso-C_6H_{11}	31	EtOAc	169—170	58·2	9·1	11·3		$C_{18}H_{33}N_3O_5$	58·2	9·0	11·3	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	[CH_2]$_2$CH	28	Me_2CO	170—172	58·5	8·3	11·0		$C_{19}H_{35}N_3O_5$	58·5	8·5	11·4	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	n-C_6H_{13}	28	EtOAc	150—151	59·0	9·1	10·7		$C_{19}H_{35}N_3O_5$	59·2	9·2	10·9	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	n-$C_{10}H_{21}$	6	EtOAc [e]	131—132	62·5	9·9	9·8		$C_{23}H_{43}N_3O_4$	62·6	9·8	9·5	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	CH_2Ph	10	EtOAc [e]	168—170	61·6	7·4	10·9		$C_{20}H_{29}N_3O_4$	61·4	7·5	10·7	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	*p*-$ClC_6H_4\cdot CH_2$	28	EtOAc	113—116	56·5	6·7	9·8		$C_{20}H_{28}ClN_3O_5$ [e]	56·4	6·6	9·9	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	*p*-$O_2N\cdot C_6H_4\cdot CH_2$	10	Me_2CO [e]	116—118	54·8	6·5	12·4		$C_{20}H_{28}N_4O_7$	55·0	6·5	12·8	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	*p*-$H_2N\cdot C_6H_4\cdot CH_2$ [f]	51	Me_2CO	108—110	59·3	7·4	13·5		$C_{20}H_{30}N_4O_5$	59·1	7·4	13·8	
[CH_2]$_2$·O·[CH_2]$_2$		Pr^i	Ph	20	Me_2CO	174—175	60·3	7·3	10·8		$C_{19}H_{27}N_3O_5$	60·5	7·2	11·1	
[CH_2]$_2$·O·[CH_2]$_2$		Bu^i	n-C_6H_{11}	16	EtOH	188—190	58·8	9·0	10·6		$C_{19}H_{35}N_3O_5$	59·2	9·2	10·9	
[CH_2]$_2$·O·[CH_2]$_2$		CH_2Ph	n-C_6H_{11}	10	EtOAc	167—168	61·9	7·9	9·5		$C_{23}H_{33}N_3O_5$,0·5H_2O	61·7	8·0	9·8	
CH_2CHMe·O·[CH_2]$_2$		Pr^i	n-C_6H_{11}	20	EtOAc–LP [e]	115—117	59·2	9·4	10·7		$C_{19}H_{35}N_3O_5$	59·2	9·2	10·9	
CH_2·CHMe·O·CHMe·CH_2		Pr^i	n-C_6H_{11}	2	EtOAc	145—146	60·0	9·5	10·7		$C_{20}H_{37}N_3O_5$	60·1	9·3	10·5	
CH_2·CHMe·O·CHMe·CH_2		Pr^i	iso-C_6H_{11}	19	EtOAc	147—148	60·3	9·4	10·5		$C_{20}H_{37}N_3O_5$	60·1	9·3	10·5	
CH[CH_2]$_2$·S(O_2)·CH_2	H	Pr^i	n-C_6H_{11}	36	EtOAc–LP	175—177 (decomp.)	51·6	7·9	10·0		$C_{19}H_{35}N_3O_5S$	51·3	8·4	10·0	
2-pyridyl	H	Pr^i	n-C_6H_{11}	10	Me_2CO [e]	183—184	60·1	8·0	14·6		$C_{19}H_{30}N_4O_4$	60·3	8·0	14·8	
2-thiazolyl	H	Pr^i	n-C_6H_{11}	12	EtOAc–LP [e]	174—176	53·5	7·5	14·4		$C_{17}H_{28}N_4O_4S$	53·1	7·3	14·6	

[a] Derived from the corresponding L-amino-acid. [b] Derived from the corresponding D-amino-acid. [e] Initial purification by column chromatography on silica gel. [d] $[\alpha]_D^{25}$ −25° (*c* 1·52 in EtOH). [e] Found: Cl, 8·3. $C_{20}H_{28}ClN_3O_5$ requires Cl, 8·3%. [f] Prepared by reduction of the corresponding nitro-derivative. [g] Single enantiomer. [h] Initial purification on polyamide columns with benzene–propan-2-ol as eluant.

† For abbreviations see Table 1.

Lossen Degradation of the (±)-*Hydroxamic Acid of M.p.* 162—163° (XIII; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$).—Methylketen diethyl acetal [3] (4·0 g) was added to a suspension of the (±)-hydroxamic acid (2·0 g) in anhydrous ether (60 ml). The mixture was stirred and refluxed for 24 h to afford a clear solution, a sample of which gave no colouration with ethanolic iron(III) chloride. The ether was then evaporated off and the residue dissolved in anhydrous benzene (60 ml) and heated (4 h) under reflux. The benzene was evaporated off and the residual oil [$\nu_{max.}$

[13] H. Shechter and H. Barker, *J. Org. Chem.*, 1956, **21**, 1473.

(film) 2280 cm^{-1} (isocyanate)] was heated (3 h) under reflux with hydrochloric acid (6N; 180 ml). After shaking with ether (3 × 50 ml), the aqueous layer was evaporated giving a yellow syrup. T.l.c. (silica) of this material with n-butanol–acetic acid–water (4 : 1 : 5; upper layer) as solvent, and development of the chromatogram with ninhydrin revealed the presence of two amino-acid components at R_F 0·56 [2-(aminomethyl)heptanoic acid] and 0·26 (valine). The product was chromatographed (silica gel column) with n-butanol–acetic acid–water (4 : 1 : 5; upper layer) as eluting solvent. Fractions (6 × 50 ml) were collected, and each examined by t.l.c. (silica gel) with ethanol–ammonia–water (40 : 2 : 8) as solvent, valine as reference, and ninhydrin as developer. Those fractions containing the β-amino-acid were pooled, and evaporated and the residue was further purified by column chromatography (silica gel) with ethanol–ammonia–water (40 : 2 : 8) as eluant. Fractions (5 × 50 ml) were collected and examined by t.l.c. (silica gel) with n-butanol–acetic acid–water (4 : 1 : 5; upper layer) as solvent (development with ninhydrin). Those fractions containing the β-amino-acid were pooled and evaporated, and the residue was crystallised from methanol giving 2-(aminomethyl)heptanoic acid, as microprisms, m.p. 227—228° (decomp) (Found: C, 60·4; H, 10·7; N, 8·6. Calc. for $C_8H_{17}NO_2$: C, 60·3; H, 10·8; N, 8·8%), identical (mass spectra and mixed m.p.) with an authentic specimen.[3]

Acidic Hydrolysis of the (−)-Hydroxamic Acid of M.p. 134—135° (XIII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$).—The hydroxamic acid (200 mg) was treated with hydrochloric acid (N; 5 ml), and heated at 100° for 3 h. The acidic solution was shaken with ether (3 × 5 ml) and the aqueous layer made alkaline (pH 10·0) with aqueous sodium hydroxide (50% w/v). The aqueous solution was saturated with sodium chloride and continuously (18 h) extracted with ether. The extract was dried ($MgSO_4$) and evaporated to leave L-valylmorpholine (X; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$) as an oil. This material was converted directly into the *picrate*, obtained as yellow needles (106 mg, 45%) from ethanol (Found: C, 43·3; H, 5·1; N, 16·4. $C_{15}H_{21}N_5O_9$ requires C, 43·4; H, 5·1; N, 16·9%), m.p. 193—195°, $[\alpha]_D^{21}$ +43·3° (*c* 1·39 in $Me_2N{\cdot}CHO$).

The ethereal extract from the initial extraction of the reaction mixture was shaken with water (10 ml) and dried ($MgSO_4$). Evaporation left an oily residue (100 mg) which on recrystallisation from light petroleum gave crystals of (+)-D-pentylsuccinic acid, m.p. 79°, $[\alpha]_D^{29}$ +28° (*c* 0·85 in EtOH), identical with the acid {m.p. 82·5—83·5°, $[\alpha]_D^{25}$ +24° (EtOH)} obtained from the acidic hydrolysis of natural actinonin.[3]

Alkaline Hydrolysis of the (±)-Imide (XI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$).—A solution of the imide (20 g) in ethanol (50 ml) was treated with sodium hydroxide solution (2·5N; 25 ml, 1·2 equiv.) and the mixture was stirred overnight at room temperature. The solution was evaporated to half volume, diluted with water (40 ml), and shaken with chloroform (2 × 60 ml) and with ether (50 ml). The aqueous solution was acidified (pH 1·0) with 2N-hydrochloric acid and extracted with chloroform (4 × 50 ml) and ether (50 ml), and the combined extracts were dried and evaporated. The residual gum (17·7 g, 82%) was dissolved in the minimum quantity of anhydrous ether and refrigerated (8 days); colourless micro-crystals (5 g, 24%) were obtained, m.p. 117—125°. Recrystallisation of this material from benzene–n-hexane (1 : 1) gave two crystalline forms: small prisms (2·9 g), m.p. 135—136°, and large elongated plates (1·64 g), m.p. 155—156°, which were separated manually. These two fractions were recrystallised from benzene–n-hexane (1 : 1) giving small prisms (2·2 g) of the *carbamoyl-acid* (XV; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), m.p. 135—136° (Found: C, 63·1; H, 9·4; N, 8·0. $C_{18}H_{32}N_2O_4$ requires C, 63·5; H, 9·5; N, 8·2%), and elongated plates (1·4 g) of the *carbamoyl-acid* (XVI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), m.p. 153—154° (Found: C, 63·5; H, 9·0; N, 8·2%).

Alkaline Hydrolysis of the (−)-Imide (XI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$).—The hydrolysis was carried out exactly as in the preceding experiment giving the carbamoyl-acids (XV; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), m.p. 135—136° (Found: C, 63·2; H, 9·4; N, 8·1. Calc. for $C_{18}H_{32}N_2O_4$: C, 63·5; H, 9·5; N, 8·2%), $[\alpha]_D^{25}$ 0, and (XVI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), m.p. 153—154° (Found: C, 63·4; H, 9·1; N, 8·1%), $[\alpha]_D^{26}$ 0, each identical (mixed m.p.) with the corresponding carbamoyl acid obtained from the hydrolysis of the (±)-imide in the preceding experiment.

Conversion of the (±)-Carbamoyl-acid of M.p. 135—136° (XV; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) *into the* (±)-O-*Benzylhydroxamic Acid of M.p.* 137—138° (XIX; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$).—To a stirred and cooled (0°) solution of the (±)-carbamoyl-acid (2 g) in tetrahydrofuran (100 ml; anhydrous) was added triethylamine (0·85 ml). The mixture was stirred at 0° for 5 min, and ethyl chlorocarbonate (0·59 ml) was added. Stirring was continued at 0° for 50 min; then *O*-benzylhydroxylamine [1] (0·75 g) was added and the mixture was further stirred at 0° for 2 h and kept at 0° overnight. Triethylamine hydrochloride was collected and the filtrate evaporated. The residual solid was dissolved in chloroform (65 ml) and the solution successively washed with hydrochloric acid (2N; 25 ml), saturated aqueous sodium hydrogen carbonate (2 × 20 ml), and water (20 ml), dried, and evaporated giving a solid (2·14 g, 82%), m.p. 137—139° on trituration with n-pentane–ether. Crystallisation from benzene–n-hexane gave the (±)-O-*benzylhydroxamic acid*, m.p. 137—138° (Found: C, 67·0; H, 8·9; N, 9·4. $C_{25}H_{39}N_3O_4$ requires C, 67·4; H, 8·8; N, 9·5%), identical with that described in Part IV.[9]

Conversion of the (±)-Carbamoyl-acid of M.p. 153—154° (XVI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) *into the* (±)-O-*Benzylhydroxamic Acid of M.p.* 167—168° (XX; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$).—Similarly, the (±)-carbamoyl-acid was converted into the corresponding (±)-O-*benzylhydroxamic acid* (XX; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) (70%), m.p. 167—168° (Found: C, 67·3; H, 8·8; N, 9·3%), identical with that described in Part IV.[9]

Hydrogenolysis of the (±)-O-Benzylhydroxamic Acid of M.p. 137—138° (XIX; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) *to the Corresponding* (±)-*Hydroxamic Acid of M.p.* 153—154° (XIII).—A solution of the (±)-*O*-benzylhydroxamic acid in methanol was shaken with hydrogen at room temperature and 1 atm over palladised charcoal (10%) until the theoretical uptake was obtained. The catalyst was removed; evaporation gave the (±)-*hydroxamic acid* as prisms (from ethyl acetate), m.p. 153—154° (Found: C, 60·7; H, 9·2; N, 11·7. $C_{18}H_{33}N_3O_4$ requires C, 60·8; H, 9·4; N, 11·8%).

Hydrogenolysis of the (±)-O-*Benzylhydroxamic Acid of M.p.* 167—168° (XX; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$) *to the Corresponding* (±)-*Hydroxamic Acid of M.p.* 159—160°

(XIV).—Similarly, hydrogenolysis of this (±)-*O*-benzylhydroxamic acid gave the (±)-*hydroxamic acid* as prisms (from ethyl acetate), m.p. 159—160° (Found: C, 60·9; H, 9·3; N, 12·0%).

Alkaline Hydrolysis of the (−)- *and* (±)-*Imides* (XI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = Bu^n$).—Both the (−)-imide and the (±)-imide when treated with 2·5N-sodium hydroxide as described above for the alkaline hydrolysis of the n-pentyl analogue yielded the (±)-*carbamoyl-acids* (XV; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = Bu^n$) as plates, m.p. 131—132° (from benzene–n-hexane) (Found: C, 62·5; H, 9·2; N, 8·2%; M^+, 326. $C_{17}H_{30}N_2O_4$ requires C, 62·8; H, 9·2; N, 8·6%; *M*, 326) and (XVI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = Bu^n$) as needles, m.p. 137—143° (from benzene–n-hexane), *m/e* 326 (M^+, $C_{17}H_{30}N_2O_4$).

Conversion of the (±)-*Carbamoyl-acid of M.p.* 131—132° (XV; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = Bu^n$) *into the Corresponding* (±)-O-*Benzylhydroxamic Acid of M.p.* 129—130° (XIX) *and the Corresponding* (±)-*Hydroxamic Acid of M.p.* 165—166° (XIII).—By the method described above for the preparation of the n-pentyl-analogue, this (±)-carbamoyl-acid gave the (±)-*O-benzylhydroxamic acid* (63%) as prisms, m.p 129—130° (from ether–n-pentane) (Found: C, 67·5; H, 8·6; N, 9·7%; M^+, 431. $C_{24}H_{37}N_3O_4$ requires C, 67·1; H, 8·6; N, 9·7%; *M*, 431). Hydrogenolysis of this compound gave the (±)-*hydroxamic acid* as a microcrystalline solid (70%), m.p. 165—166°, (from chlorform–n-pentane) (Found: C, 59·8; H, 9·1; N, 12·2%; M^+, 341. $C_{17}H_{31}N_3O_4$ requires C, 59·9; H, 9·1; N, 12·2%; *M*, 341).

Conversion of the (±)-*Carbamoyl-acid of M.p.* 137—143° (XVI; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = Bu^n$) *into the Corresponding* (±)-O-*Benzylhydroxamic Acid of M.p.* 156—157° (XX) *and the Corresponding* (±)-*Hydroxamic Acid of M.p.* 169—170° (XIV).—Similarly, this (±)-carbamoyl-acid gave the (±)-*O-benzylhydroxamic acid*, needles, m.p. 156—157° (from benzene–n-hexane) (Found: C, 66·7; H, 8·2; N, 9·4%). Hydrogenolysis of this compound gave the (±)-hydroxamic acid (78%) as prisms, m.p. 169—170° (from chloroform–n-pentane) (Found: C, 59·5; H, 9·0; N, 12·1%).

2-*Methylenehexanoic Acid*.—This compound was prepared from monoethyl n-butylmalonate by the method described,[14] and was obtained (74%) as an oil, b.p. 64—68° at 6 mmHg (Found: C, 65·1; H, 9·1. Calc. for $C_7H_{12}O_2$: C, 65·5; H, 9·4%).

Lossen Degradation of the (±)-*Hydroxamic Acids of M.p.* 165—166° (XIII) *and* 169—170° (XIV) ($R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = Bu^n$).—These transformations were carried out as described for the Lossen degradation of actinonin [3] yielding 2-(aminomethyl)hexanoic acid, characterised by its mass spectrum (*m/e* 145, 102, 89, and 73). Pyrolysis of 2-(aminomethyl)hexanoic acid yielded 2-methylenehexanoic acid.

Reaction of the (±)-*Imide* (XXI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = H$, $R^4 = n\text{-}C_5H_{11}$) *with Hydroxylamine; Formation of the* (±)-*Hydroxamic Acids* (XXII) *and* (XXIII).—The product obtained from the imide (19·55 g) and methanolic alkaline hydroxylamine (4 h; room temperature) by the method described above was chromatographed (silica column). Elution with chloroform gave unchanged imide (4·5 g). Further elution with ethyl acetate–acetone (1 : 1) gave the crude (±)-*hydroxamic acid* (XXII) as crystals (1·5 g), m.p. 147—149°, when the eluate was kept at room temperature for 2 days. Recrystallisation from acetone gave prisms (1·35 g), m.p. 157—158° (Found: C, 55·0; H, 8·3; N, 12·7. $C_{15}H_{27}N_3O_5$ requires C, 54·7; H, 8·3; N, 12·8%).

The filtrate was evaporated giving a residue (4·1 g), m.p. 117—120°, which was crystallised from acetone and then from ethyl acetate giving the (±)-*hydroxamic acid* (XXIII) as prisms (2·15 g), m.p. 126—128° (Found: C, 54·6; H, 8·5; N, 12·8. $C_{15}H_{27}N_3O_5$ requires C, 54·7; H, 8·3; N, 12·8%).

Lossen Degradation of the (±)-*Hydroxamic Acid* (XXII).—This was carried out as described above for the (±)-hydroxamic acid (XIII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$). Acidic hydrolysis of the intermediate isocyanate and chromatography (silica column) gave 2-(aminomethyl)heptanoic acid, m.p. 231—232°, identical with an authentic specimen.[3]

Lossen Degradation of the (±)-*Hydroxamic Acid* (XXIII); *Formation of the Dihydrouracils* (XXIV) *and* (XXV).—A mixture of methylketen diethyl acetal (4·2 g) and the hydroxamic acid (XXIII) (1·85 g) in anhydrous ether (55 ml) was heated under reflux with stirring (22 h). The ether was then evaporated off and the residue boiled (3 h) in anhydrous benzene (65 ml). Evaporation gave a residue (no isocyanate i.r. absorption at 2280 cm^{-1}) which was triturated with light petroleum and ethyl acetate giving the *dihydrouracil* (XXIV) (0·8 g, 46%), m.p. 134—135° (from ethyl acetate) (Found: C, 57·9; H, 8·1; N, 13·5. $C_{15}H_{25}N_3O_4$ requires C, 57·9; H, 8·1; N, 13·5%), $\nu_{max.}$ (KBr) 1720, 1680, and 1630 cm^{-1}.

A solution of the dihydrouracil (XXIV) (0·2 g) in 6N-hydrochloric acid was heated (3 h) under reflux and evaporated, and water (10 ml) was added to the residue. The insoluble solid was crystallised from ethyl acetate giving the *dihydrouracil* (XXV) (40 mg, 26%) as prisms, m.p. 154—156° (Found: C, 54·6; H, 7·6; N, 11·6. $C_{11}H_{18}N_2O_4$ requires C, 54·5; H, 7·5; N, 11·6%), $\nu_{max.}$ (KBr) 1720, 1700, and 1680 cm^{-1}.

Preparation of the Imides (XXVI; R = Pr^i, Bu^t, *or* Ph) *and* (XXXI; R = H *or* Me).—Treatment of the corresponding succinic or glutaric anhydrides with the appropriate amines and cyclisation of the resulting carbamoyl-acids with acetyl chloride by the method described above gave the following imides: (XXVI; R = Pr^i) (78%), an oil, *m/e* 211 (M^+, $C_{12}H_{21}NO_2$); (XXVI; R = Bu^t) (75%), an oil (Found: C, 68·9; H, 10·1; N, 6·0%; M^+, 225. $C_{13}H_{23}NO_2$ requires C, 69·3; H, 10·3; N, 6·2%; *M*, 225); (XXVI; R = Ph) (84%), m.p. 74—75° (from light petroleum) (Found: C, 73·7; H, 7·7; N, 5·5%; M^+, 245. $C_{15}H_{19}NO_2$ requires C, 73·5; H, 7·8; N, 5·7%; *M*, 245); (XXXI; R = H) (55%), m.p. 151—152° (lit.,[15] 145°); (XXXI; R = Me) (25%), m.p. 124—126° (from chloroform) *m/e* 203 (M^+, $C_{12}H_{13}NO_2$).

Preparation of the Hydroxamic Acids (XXVII; R = Pr^i, Bu^t, *or* Ph) *and* (XXXII; R = H or Me).—Treatment of the above imides with methanolic alkaline hydroxylamine according to the general method described above gave the following hydroxamic acids: (XXVII; R = Pr^i) (23%), m.p. 145—155° (from chloroform–methanol) (Found: C, 58·9; H, 9·9; N, 11·4%; M^+, 244. $C_{12}H_{24}N_2O_3$ requires C, 59·0; H, 9·9; N, 11·5%; *M*, 244); (XXVII; R = Bu^t) (58%), m.p. 133—136° (from carbon tetrachloride) (Found: C, 60·2; H, 9·9; N, 10·9%; M^+, 258. $C_{13}H_{26}N_2O_3$ requires C, 60·5; H, 10·1; N, 10·9%; *M*, 258); (XXVII; R = Ph) (12%), m.p. 137—138° (from chloroform) (Found: C, 64·5; H, 7·9; N, 10·1%; M^+, 278. $C_{15}H_{22}N_2O_3$ requires

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C, 64·7; H, 8·0; N, 10·1%; *M*, 278), and N-*hydroxy-n-pentylsuccinimide* (50%), m.p. 54—57° [from benzene–light petroleum (b.p. 80—100°)] (Found: C, 58·5; H, 8·1; N, 7·6%; M^+, 185. $C_9H_{15}NO_3$ requires C, 58·4; H, 8·2; N, 7·6%; *M*, 185), $\nu_{max.}$ (Nujol) 3150, 1775, 1760, and 1695 cm^{-1}; (XXXII; R = H) (50%), m.p. 137—138° (from chloroform–methanol) (Found: C, 59·3; H, 6·6; N, 12·8%; M^+, 222. $C_{11}H_{14}N_2O_3$ requires C, 59·5; H, 6·3; N, 12·6%; *M*, 222); (XXXII; R = Me) (85%), m.p. 145—148° (from chloroform–methanol) (Found: C, 60·8; H, 7·0; N, 12·0%; M^+, 236. $C_{12}H_{16}N_2O_3$ requires C, 61·0; H, 6·8; N, 11·9%; *M*, 236).

Lossen Degradation of the Hydroxamic Acid (XXVII; R = Ph); *Formation of 5,6-Dihydro-5-n-pentyl-3-phenyluracil* (XXIX; R = Ph).—The hydroxamic acid (XXVII; R = Ph) (230 mg) was heated under reflux with methylketen diethyl acetal (1 g) in chloroform (30 ml). The reaction was monitored by i.r. spectroscopy: isocyanate absorption ($\nu_{max.}$ 2280 cm^{-1}) was observed after 5 min, and reached maximum intensity after 30 min. After heating for 15 h no isocyanate absorption was detectable and the mixture was evaporated. The residue was triturated with light petroleum, and the solid was crystallised from chloroform–light petroleum giving the *dihydrouracil* (130 mg, 60%), m.p. 140—143° (Found: C, 69·2; H, 7·9; N, 10·5%; M^+, 260. $C_{15}H_{20}N_2O_2$ requires C, 69·2; H, 7·7; N, 10·8%; *M*, 260), $\nu_{max.}$ (Nujol) 3280, 3150, 1720, and 1688 cm^{-1}.

Miscellaneous Actinonin Analogues (II; R^1 = OH, R^2 = H, R^3 = Pr^i, R^4 = n-C_5H_{11}) *and* (XXIV—(XL).—*The bis-hydroxamic acid* (II; R^1 = OH, R^2 = H, R^3 = Pr^i, R^4 = n-C_5H_{11}). L-Valine ethyl ester [16] was treated with n-pentylsuccinic anhydride, and the crude carbamoyl-acid was converted with boiling acetyl chloride into the *imide* (XXXIII), an oil, b.p. 90—92° at 0·02 mmHg (Found: C, 64·7; H, 9·4; N, 4·9%; M^+, 297. $C_{16}H_{27}NO_4$ requires C, 64·6; H, 9·2; N, 4·7%; *M*, 297), $\nu_{max.}$ (film) 1778, 1742, and 1708 cm^{-1}.

The imide (XXXIII) was treated with methanolic alkaline hydroxylamine according to the general method for the conversion of the imides (VIII) into the hydroxamic acids (XIII) but with two-fold quantities of reagents. The crude product was purified by chromatography (polyamide column) giving the bis-hydroxamic acid as crystals (52%), m.p. 150° (from chloroform–light petroleum), *m/e* 317 (M^+, $C_{14}H_{27}N_3O_5$).

The hydroxamic acid (XXXIV). This was prepared from L-valylpyrrolidine (IIIb; R^1R^2 = $[CH_2]_4$, R^3 = Pr^i) (Table 2) and *cis*-hexahydrophthalic anhydride.[17] The intermediate phthalimido-derivative (60%), *m/e* 306 (M^+, $C_{12}H_{21}NO_2$) was treated with methanolic alkaline hydroxylamine by the general method described above giving the *hydroxamic acid* (XXXIV) (34%), m.p. 155—160° (from ether) (Found: C, 60·0; H, 8·6; N, 12·2%; M^+, 339. $C_{17}H_{29}N_3O_4$ requires C, 60·2; H, 8·6; N, 12·4%; *M*, 339).

The hydroxamic acid (XXXV). This was prepared from DL-valylmorpholine and 2,3-dimethylsuccinic anhydride.[18] The intermediate *succinimide* was isolated (28%); m.p. 95—97° (from carbon tetrachloride–light petroleum) (Found: C, 60·5; H, 8·1; N, 9·1. $C_{15}H_{24}N_2O_4$ requires C, 60·8; H, 8·2; N, 9·5%). Treatment of this imide with methanolic alkaline hydroxylamine gave the *hydroxamic acid* (XXXV) (10%), m.p. 180—181° (from ethanol) (Found: C, 54·8; H, 8·4; N, 12·8. $C_{15}H_{27}N_3O_5$ requires C, 54·7; H, 8·3; N, 12·8%).

The hydroxamic acid (XXXVI). This was prepared from DL-valylmorpholine and 2-ethyl-2-methylsuccinic anhydride.[19] The intermediate imide gave the *hydroxamic acid*, m.p. 141—143° (from ethyl acetate) (Found: C, 56·3; H, 8·8; N, 12·1. $C_{16}H_{29}N_3O_5$ requires C, 56·0; H, 8·5; N, 12·2%).

The hydroxamic acid (XXXVII). This was prepared from DL-valylmorpholine and 3-n-pentylglutaric anhydride.[20] The intermediate imide gave the *hydroxamic acid*, m.p. 113—114° (from ethyl acetate) (Found: C, 59·4; H, 9·1; N, 10·8. $C_{19}H_{35}N_3O_5$ requires C, 59·2; H, 9·2; N, 10·9%).

The hydroxamic acid (XXXVIII). This was prepared from DL-valylmorpholine and 2-n-pentylglutaric anhydride.[21] The intermediate glutarimide was isolated (22%); m.p. 77—79° (from light petroleum) (Found: C, 65·0; H, 9·0; N, 7·8. $C_{19}H_{32}N_2O_4$ requires C, 64·7; H, 9·2; N, 8·0%). This imide with methanolic alkaline hydroxylamine gave the *hydroxamic acid*, m.p. 128—130° (from ethyl acetate–light petroleum) (Found: C, 59·0; H, 8·8; N, 10·6. $C_{19}H_{35}N_3O_5$ requires C, 59·2; H, 9·2; N, 10·9%).

The hydroxamic acid (XXXIX). This *product*, m.p. 129—131° (from acetone), was prepared from *o*-aminobenzoylmorpholine [22] and n-pentylsuccinic anhydride (Found: C, 61·4; H, 7·6; N, 10·4. $C_{20}H_{29}N_3O_5$ requires C, 61·4; H, 7·5; N, 10·7%).

The hydroxamic acid (XL). This was prepared from *p*-aminobenzoylmorpholine (see below) and n-pentylsuccinic anhydride. The intermediate *succinimide* was isolated (65%); m.p. 105—106° (from cyclohexane) (Found: C, 67·3; H, 7·4; N, 7·6. $C_{20}H_{26}N_2O_4$ requires C, 67·0; H, 7·3; N, 7·8%). This imide gave the *hydroxamic acid* (XL) (24%), m.p. 120—122° (from acetone) (Found: C, 61·2; H, 7·5; N, 10·4. $C_{20}H_{29}N_3O_5$ requires C, 61·4; H, 7·5; N, 10·7%).

p-*Aminobenzoylmorpholine*.—Reduction of the correspond-nitro-derivative [22] by the method described [23] for *o*-aminobenzoylmorpholine gave the *amino-amide* as crystals, m.p. 132—134° (from ethyl acetate) (Found: C, 63·9; H, 6·9; N, 13·3. $C_{11}H_{14}N_2O_4$ requires C, 64·1; H, 6·8; N, 13·6%).

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