Studies concerning the Antibiotic Actinonin. Part IV.[1] Synthesis of Structural Analogues of Actinonin by the Mixed Anhydride Method †

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The reaction between alkylsuccinic anhydrides (III) and *O*-benzylhydroxylamine yields the acids (VI). These acids (VI) may be coupled with amino-amides (II) by the mixed anhydride procedure, giving a mixture of the racemates (VIII) and (IX). Hydrogenolysis of the *O*-benzylhydroxamic acids (VIII) and (IX) yields structural analogues [(X) and (XI)] of the natural antibiotic actinonin (I).

THE n-pentylsuccinic acid residue in actinonin[2] (I) is connected to the rest of the molecule by two amide bonds (a and b). In the anhydride–imide route[1] [(II) + (III) ⟶ (IV) ⟶ (V)] leading to structural analogues (V) of actinonin, bond a is created before bond b. We now report an alternative route to structural analogues (V) in which bond b is created before bond a: this has interesting stereochemical consequences.

In the anhydride–imide route,[1] bond a is created by forming the imide (IV) from the amino-amide (II) and then bond b is generated by the transformation (IV) ⟶ (V) with hydroxylamine. In the alternative now examined, bond b is created first by reaction between the succinic anhydride (III) and *O*-benzylhydroxylamine. This yields the *N*-(benzyloxy)succinamic acid (VI), which is then coupled, *via* its mixed anhydride[3] prepared by using ethyl chlorocarbonate, with the amine (II), yielding the *O*-benzylhydroxamic acid (VII). Hydrogenolysis of the hydroxamic acid (VII) gives the structural analogue (V).

The synthesis was first examined in the succinoyl series ($R^4 = H$). Succinic anhydride and *O*-benzylhydroxylamine yielded the acid (VI; $R^4 = H$), which was coupled with DL-valylmorpholine (II; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$) giving the *O*-benzylhydroxamic acid (VII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R_3 = Pr^i$, $R^4 = H$). Hydrogenolysis gave the corresponding hydroxamic acid (V). The corresponding sequence of reactions was then carried out with n-pentylsuccinic anhydride (III; $R^4 = n\text{-}C_5H_{11}$), which with *O*-benzylhydroxylamine gave a single product. On the basis of steric direction by the pentyl substituent in the anhydride (III; $R^4 = n\text{-}C_5H_{11}$) this product was assumed to have the constitution (VI; $R^4 = n\text{-}C_5H_{11}$), which was confirmed by coupling with DL-valylmorpholine (II; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$). Two isomeric compounds were obtained: a minor product, m.p. 132—133°, and a major product, m.p. 167—168°. These were regarded as diastereoisomerically related racemates with the constitution (VII). Assignment of their relative configurations [(VIII) and (IX)] was based on the following evidence.

In the series ($R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), hydrogenolysis of the minor product (VII), m.p. 132—133°, gave a hydroxamic acid, m.p. 162—163°, which was identical with the racemate (X) prepared by the anhydride–imide route.[3] This settled the relative configuration of the minor product, m.p. 132—133°, as (VIII), and thus the major product, m.p. 167—168°, was the racemate (IX).

Hydrogenolysis of the (±)-*O*-benzylhydroxamic acid, m.p. 167—168° (IX; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), gave the corresponding (±)-hydroxamic acid, m.p. 132—133° (XI). The argument that the two products from the mixed anhydride coupling reaction [(II) + (VI)] are the diastereoisomerically related racemates (VIII) and (IX) clearly rests upon the proof that (VIII) and (IX) both have the constitution (VII). This was placed beyond doubt by Lossen degradation of the corresponding (±)-hydroxamic acids (X) and (XI) with methylketen dimethyl acetal.[1,2] The Lossen degradation of the (±)-hydroxamic acid, m.p. 162—163° (X; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), followed by acidic hydrolysis yielding the β-amino-acid (XII), has already been reported.[1] The diastereoisomeric (±)-hydroxamic acid (XI), m.p. 132—133°, on Lossen degradation gave, surprisingly, the isocyanate (XIII) as a stable crystalline solid; its acidic hydrolysis also yielded the β-amino-acid (XII).

The stereochemical characteristics of the mixed anhydride route were settled by repeating the above sequence of reactions with L-valylmorpholine (XIV) and the mixed anhydride derived from the DL-acid (VI; $R^4 = n\text{-}C_5H_{11}$). This gave a mixture of the diastereoisomers (VIII and IX; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$). These unfortunately could not be separated and neither could the mixture of derived hydroxamic acids [(X) and (XI)]. However, mild acidic hydrolysis of this mixture of hydroxamic acids yielded only L-valylmorpholine (XIV), thus establishing that the mixed anhydride coupling and subsequent reaction were not associated with racemisation at the chiral centre of the L-valyl residue.

In Part III,[1] the unexpected result was reported that the reaction of the imide (IV; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = H$, $R^4 = n\text{-}C_5H_{11}$) with methanolic alkaline hydroxylamine gave two products, (XV) and (XVI).

† 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.

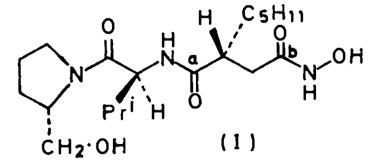
[1] Part III, B. J. Broughton, P. J. Warren, K. R. H. Wooldridge, D. E. Wright, J. P. Devlin, W. D. Ollis, J. E. Thorpe, and R. J. Wood, preceding paper.

[2] 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.

[3] J. P. Greenstein and M. Winitz, 'Chemistry of the Amino Acids,' Wiley, New York, 1961, vol. 2, p. 978.

The reaction between *N*-glycylmorpholine (II; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = H$) and the mixed anhydride of the acid (VI; $R^4 = n\text{-}C_5H_{11}$) gave the ($\pm$)-*O*-benzylhydroxamic acid (VII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = H$, $R^4 = n\text{-}C_5H_{11}$), which on hydrogenolysis gave the ($\pm$)-hydroxamic acid (XV), m.p. 157—158°, described previously.[1]

Mixed anhydride coupling of DL-valylpyrrolidine (II; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$) and the acid (VI; $R^4 = n\text{-}C_5H_{11}$) gave a minor product (VIII), m.p. 137—138°, and a major product (IX; $R^1R^2 = [CH_2]_4$, $R^3 = Pr^i$, $R^4 = n\text{-}C_5H_{11}$), m.p. 167—168°. The relative configurations of these two ($\pm$)-*O*-benzylhydroxamic acids were established in Part III.[1]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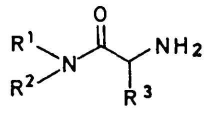
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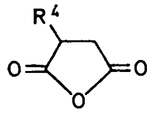
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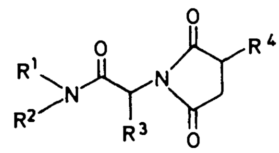
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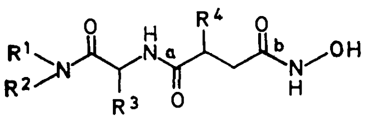
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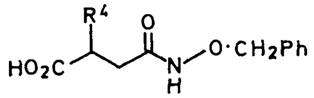
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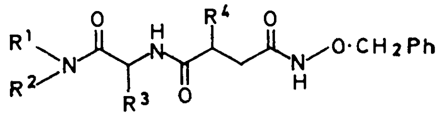
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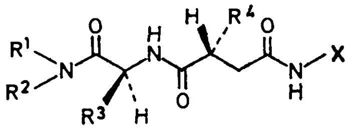
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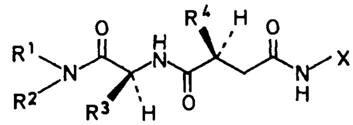
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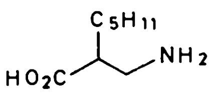
(XI) X = OH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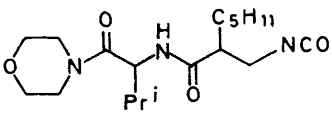
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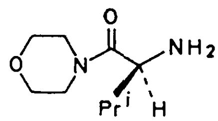
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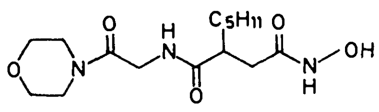
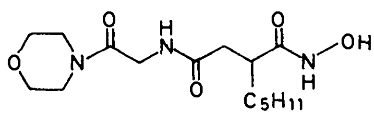

(XV)


(XVI)

The mixed anhydride coupling reaction [(II) + (VI)] has been used to synthesise a variety of structural analogues (V) of actinonin (I). Variants include cases (V) in which R^1R^2 is derived from morpholine, piperidine, and 2-methylpiperidine and R^3 from DL-valine, and R^4 is Pr^n, Bu^n, $n\text{-}C_5H_{11}$, $iso\text{-}C_5H_{11}$, or $[CH_2]_4CH{\cdot}$. In all the coupling reactions two products were obtained, assumed to have the relative configurations (VIII) (minor product) and (IX) (major product).

The two synthetic routes to structural analogues of actinonin described in Part III [1] and in this paper are complementary. With racemic reactants, the anhydride–imide route gives one racemate (X) whereas the mixed anhydride route gives a minor (X) and a major product (XI). There are therefore two synthetic routes leading by suitable choice of starting materials either to the enantiomer or racemate (X) or to the enantiomer or racemate (XI). Information concerning the biological activity of these four configurational types will be considered in a forthcoming publication.[4]

EXPERIMENTAL

General experimental procedures will be found in Part I.[2]

N-Benzyloxy-3-n-pentylsuccinamic Acid (VI; $R = n\text{-}C_5H_{11}$).—A suspension of *O*-benzylhydroxylamine hydrochloride [5] (32 g) in water (150 ml) was treated with an excess of potassium carbonate, and the mixture extracted with

[4] Part VIII, 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.

[5] Part II, N. H. Anderson, W. D. Ollis, J. E. Thorpe, and A. D. Ward, *J.C.S. Perkin I*, 1975, 825.

ether (2 × 150 ml). The combined extracts were dried and concentrated to 100 ml. The concentrate was slowly added (15 min) to a stirred and cooled (−15°) solution of n-pentylsuccinic anhydride [1] (34 g) in ether (200 ml; anhydrous). The mixture was stirred at −15° for 1 h, and the *succinamic acid* (20 g, 34%) was obtained, m.p. 95—96° (from ether) (Found: C, 65·8; H, 8·0; N, 4·7. $C_{16}H_{23}NO_4$ requires C, 65·5; H, 7·9; N, 4·8%).

N-*Benzyloxy*-3-(3-*methylbutyl*)*succinamic Acid* (VI; R = iso-C_5H_{11}) was similarly prepared from isopentylsuccinic anhydride [1] (37% yield); m.p. 103—105° (from ether) (Found: C, 65·7; H, 7·9; N, 4·9. $C_{16}H_{23}NO_4$ requires C, 65·5; H, 7·9; N, 4·8%). N-*Benzyloxy*-3-n-*propylsuccinamic acid* (VI; R = Pr^n) was prepared from n-propylsuccinic anhydride [1] (16% yield); m.p. 84—85° (from ether) (Found: C, 63·3; H, 7·1; N, 5·6. $C_{14}H_{19}NO_4$ requires C, 63·4; H, 7·2; N, 5·3%). N-*Benzyloxy*-3-n-*butylsuccinamic acid* (VI; R = Bu^n) was prepared from n-butylsuccinic anhydride [1] (21% yield); m.p. 89—90° (from ether) (Found: C, 64·7; H, 7·4; N, 4·9. $C_{15}H_{21}NO_4$ requires C, 64·5; H, 7·6; N, 5·0%). N-*Benzyloxy*-3-n-*hexylsuccinamic acid* (VI; R = n-C_6H_{13}) was prepared from n-hexylsuccinic anhydride [1] (20% yield); m.p. 104—105° (from ether) (Found: C, 66·2; H, 8·2; N, 4·2. $C_{17}H_{25}NO_4$ requires C, 66·4; H, 8·2; N, 4·6%). N-*Benzyloxy*-3-*cyclopentylsuccinamic acid* (VI; R = $[CH_2]_4CH\cdot$) was prepared from cyclopentylsuccinic anhydride [1] (60% yield); m.p. 141—142° (from ether) (Found: C, 65·7; H, 7·5; N, 4·6. $C_{16}H_{21}NO_4$ requires C, 66·0; H, 7·3; N, 4·8%).

General Method of Preparation of the Hydroxamic Acids (X) *and* (XI) via *the* O-*Benzyl Derivatives* (VIII) *and* (IX).—The general method of preparation of the *O*-benzylhydroxamic acids (VIII) and (IX) by the mixed anhydride route, either as single racemates or as mixtures of diastereoisomers, together with the separation of these isomers and their separate conversion into the corresponding hydroxamic acids, is exemplified by the synthesis described below.

Preparation of the Diastereoisomeric (±)-O-*Benzylhydroxamic Acids of M.p.s* 132—133 *and* 167—168° (VIII *and* IX; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}).—To a stirred and cooled (−15°) solution of *N*-benzyloxy-3-n-pentylsuccinamic acid (2·75 g) and ethyl chlorocarbonate (0·88 ml) in anhydrous chloroform (20 ml) was added anhydrous triethylamine (1·26 ml). The mixture was stirred at −15° for 0·5 h, then at 0° for 5 min, and cooled to −15°; a solution of DL-valylmorpholine [1] (1·7 g) in anhydrous chloroform (20 ml) was then added slowly with stirring. The mixture was kept at 0° for 0·5 h and at room temperature for 3 days. The solution was diluted with chloroform (50 ml) and successively washed with hydrochloric acid (N; 2 × 25 ml), aqueous sodium carbonate (5%; 2 × 25 ml), and water (2 × 25 ml), dried, and evaporated. Crystallisation of the resulting solid from ethyl acetate gave needles (2 g, 46%) of the (±)-O-*benzylhydroxamic acid* (IX; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}), m.p. 167—168° (Found: C, 64·9; H, 8·7; N, 9·0. $C_{23}H_{29}N_3O_5$ requires C, 65·1; H, 8·5; N, 9·1%).

The filtrate from the above crystallisation was allowed to evaporate slowly at room temperature to half volume and the solid which separated was crystallised from benzene–light petroleum to give the (±)-O-*benzylhydroxamic acid* (VIII; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}) as prisms (0·58 g, 14%), m.p. 132—133° (Found: C, 64·7; H, 8·3; N, 9·3%).

Preparation of the (±)-*Hydroxamic Acid of M.p.* 162—163° (X; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}).—A solution of the (±)-*O*-benzylhydroxamic acid of m.p. 132—133° (VIII; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}) in methanol (10 ml) containing palladised charcoal (5%; 50 mg) was hydrogenated at room temperature and 1 atm. Filtration, evaporation, and trituration of the residue with ether gave a solid (0·3 g), crystallisation of which from ethyl acetate gave prisms (0·19 g, 53%) of the (±)-hydroxamic acid, m.p. 162—163° (Found: C, 58·1; H, 9·1; N, 11·1. Calc. for $C_{18}H_{33}N_3O_5$: C, 58·2; H, 9·0; N, 11·3%), identical with that prepared in Part III.[1]

Preparation of the (±)-*Hydroxamic Acid of M.p.* 132—133° (XI; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}).—Catalytic hydrogenolysis of the (±)-*O*-benzylhydroxamic acid of m.p. 167—168° (IX; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}) as described above gave the (±)-*hydroxamic acid* (76%) as prisms (from ethyl acetate), m.p. 132—133° (Found: C, 58·0; H, 8·9; N, 11·0%).

The (±)-*Hydroxamic Acid* (V; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = H).—Treatment of DL-valylmorpholine with *N*-benzyloxysuccinamic acid [6] under the conditions described above gave the (±)-O-*benzylhydroxamic acid* (VII; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = H) (66%), m.p. 120—121° (from ethyl acetate) (Found: C, 61·1; H 7·3; N, 10·6. $C_{20}H_{29}N_3O_5$ requires C, 61·4; H, 7·5; N, 10·7%). Subsequent hydrogenolysis gave the (±)-*hydroxamic acid* (26%), m.p. 145—146° (from ethyl acetate) (Found: C, 51·9; H, 7·5; N, 14·2. $C_{13}H_{23}N_3O_5$ requires C, 51·8; H, 7·7; N, 14·0%).

Lossen Degradation of the (±)-*Hydroxamic Acid of M.p.* 132—133° (XI; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}).—This degradation was carried out as described [1] for the corresponding (±)-hydroxamic acid of m.p. 162—163° (X; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}). The intermediate (±)-*isocyanate* (XIII) was obtained as a crystalline solid (from light petroleum), m.p. 102—103° (Found: C, 61·5; H, 8·9; N, 11·8. $C_{18}H_{31}N_3O_4$ requires C, 61·2; H, 8·8; N, 11·9%), $\nu_{max.}$ (KBr) 2280 cm^{-1} (isocyanate). Acidic hydrolysis of the isocyanate gave 2-(aminomethyl)heptanoic acid (XII) as prisms (from methanol), m.p. and mixed m.p. 227—228°.

Preparation of the (−)-*Hydroxamic Acids* (X *and* XI; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}).—This preparation, from L-valylmorpholine,[1] was carried out as described above for the corresponding (±)-hydroxamic acids obtained from DL-valylmorpholine. The intermediate (−)-O-*benzylhydroxamic acids* (VIII and IX; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}) were obtained as a mixture of diastereoisomers (55%), m.p. 77—83° (Found: C, 65·3; H, 8·5; N, 9·1. $C_{25}H_{39}N_3O_5$ requires C, 65·1; H, 8·5; N, 9·1%), $[\alpha]_D^{26}$ −27° (*c* 1·40 in EtOH), which could not be separated by fractional crystallisation. Hydrogenolysis of this mixture gave the corresponding (−)-*hydroxamic acids* as a mixture of diastereoisomers (89%), m.p. 108—115° (Found: C, 58·5; H, 8·9; N, 11·2. $C_{18}H_{33}N_3O_5$ requires C, 58·2; H, 9·0; N, 11·3%), $[\alpha]_D^{26}$ −31·5° (*c* 1·44 in EtOH), which could not be separated.

Acidic Hydrolysis of the Mixture of (−)-*Hydroxamic acids of M.p.* 108—115° (X *and* XI; $R^1R^2 = [CH_2]_2\cdot O\cdot[CH_2]_2$, $R^3 = Pr^i$, R^4 = n-C_5H_{11}).—The mixture of (−)-hydroxamic acids (500 mg) described above was heated with dilute hydrochloric acid (N; 10 ml) at 100° for 3 h and extracted with ether (3 × 10 ml). The aqueous layer was made alkaline with aqueous sodium hydroxide (50% w/v), then saturated

[6] D. E. Ames and T. F. Gray, *J. Chem. Soc.*, 1955, 631.

with sodium chloride and continuously extracted with ether (16 h). The extract was dried and evaporated to leave L-valylmorpholine (XIV) as an oil. This material was converted into the picrate, obtained as yellow needles (340 mg, 56%), m.p. 195—196°, $[\alpha]_D^{28}$ +43·8° (*c* 1·77 in $Me_2N{\cdot}CHO$), identical with the material obtained previously.[1]

Preparation of the Hydroxamic Acid (XV).—Treatment of glycylmorpholine [1] with *N*-benzyloxy-3-n-pentylsuccinamic acid as described above gave the intermediate O-*benzylhydroxamic acid* (VII; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = H, R^4 = n-C_5H_{11}) (63%), m.p. 119—120° (from ethyl acetate) (Found: C, 63·0; H, 7·7; N, 9·9. $C_{22}H_{33}N_3O_5$ requires C, 63·0; H, 7·9; N, 10·0%). Hydrogenolysis of this material gave the (±)-hydroxamic acid (91%), m.p. 157—158° (from acetone) (Found: C, 54·5; H, 8·3; N, 12·7. Calc. for $C_{15}H_{27}N_3O_5$: C, 54·7; H, 8·3; N, 12·8), identical with that obtained previously.[1]

The (±)-O-*Benzylhydroxamic Acids of M.p.s* 137—138 *and* 167—168° (VIII *and* IX; $R^1R^2 = [CH_2]_4$, R^3 = Pr^i, R^4 = n-C_5H_{11}).—The crude mixture of (±)-*O*-benzylhydroxamic acids which was obtained from the mixed anhydride coupling of DL-valylpyrrolidine [1] with *N*-benzyloxy-3-n-pentylsuccinamic acid was separated by fractional crystallisation from ethyl acetate. The minor (±)-*O*-benzylhydroxamic acid (VIII; $R^1R^2 = [CH_2]_4$, R^3 = Pr^i, R^4 = n-C_5H_{11}) was isolated (12%) as prisms, m.p. 137—138° (Found: C, 67·3; H, 8·7; N, 9·2. Calc. for $C_{25}H_{39}N_3O_4$: C, 67·4; H, 8·8; N, 9·4%) and the major (±)-*O*-benzylhydroxamic acid (IX) (28%) as crystals, m.p. 167—168° (Found: C, 67·4; H, 9·0; N, 9·2%). These hydroxamic acids are identical with those previously prepared.[1]

The (±)-*Hydroxamic Acids* (X *and* XI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = iso-C_5H_{11}).—The crude mixture of (±)-*O*-benzylhydroxamic acids (VIII) and (IX) obtained from DL-valylmorpholine [1] and *N*-benzyloxy-3-(3-methylbutyl)succinamic acid was separated by fractional crystallisation from ethyl acetate and from ethanol. The major (±)-O-*benzylhydroxamic acid* (IX; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = iso-C_5H_{11}) was obtained in 35% yield; m.p. 185—186° (Found: C, 65·4; H, 8·7; N, 9·0. $C_{25}H_{39}N_3O_5$ requires C, 65·1; H, 8·5; N, 9·1%). Hydrogenolysis of this isomer gave the (±)-*hydroxamic acid* (XI) (37%), m.p. 157—158° (from ethyl acetate) (Found: C, 58·3; H, 8·8; N, 11·4. $C_{18}H_{33}N_3O_5$ requires C, 58·2; H, 9·0; N, 11·3%). The minor (±)-*O*-benzylhydroxamic acid (VIII) was isolated in 3% yield; m.p. 139—140°. This isomer was not characterised but was hydrogenolysed directly to the (±)-*hydroxamic acid* (X) (67%), m.p. 162—164° (from ethyl acetate) (Found: C, 58·2; H, 9·0; N, 11·2%).

The (±)-*Hydroxamic Acids* (X *and* XI; $R^1R^2 = [CH_2]_5$, R^3 = Pr^i, R^4 = iso-C_5H_{11}).—Treatment of DL-valylpiperidine [1] with *N*-benzyloxy-3-(3-methylbutyl)succinamic acid and fractional crystallisation of the product from ethyl acetate gave the minor (±)-O-*benzylhydroxamic acid* (VIII; $R^1R^2 = [CH_2]_5$, R^3 = Pr^i, R^4 = iso-C_5H_{11}) (33%), m.p. 142—143° (from ethyl acetate–light petroleum) (Found: C, 68·2; H, 9·0; N, 9·2. $C_{26}H_{41}N_3O_4$ requires C, 67·9; H, 9·0; N, 9·1%). Hydrogenolysis of this compound gave the corresponding (±)-*hydroxamic acid* (X) (79%), m.p. 178—180° (from ethyl acetate) (Found: C, 61·9; H, 9·5; N, 11·5. $C_{19}H_{35}N_3O_4$ requires C, 61·8; H, 9·6; N, 11·4%). The major (±)-O-*benzylhydroxamic acid* (IX) was obtained in 45% yield; m.p. 163—165° (from ethyl acetate) (Found: C, 67·6; H, 8·9; N, 8·9%). Hydrogenolysis of this isomer gave the (±)-*hydroxamic acid* (XI) (78%), m.p. 124—126° (from ethyl acetate) (Found: C, 61·7; H, 9·5; N, 11·3. $C_{19}H_{35}N_3O_4$ requires C, 61·8; H, 9·6; N, 11·4%).

The (±)-*Hydroxamic Acids* (X *and* XI; $R^1R^2 = CHMe{\cdot}[CH_2]_4$, R^3 = Pr^i, R^4 = iso-C_5H_{11}).—Treatment of DL-valyl-DL-2-methylpiperidine with *N*-benzyloxy-3-(3-methylbutyl)-succinamic acid and fractional crystallisation of the mixture of (±)-*O*-benzylhydroxamic acids from ethyl acetate gave the minor (±)-O-*benzylhydroxamic acid* (VIII; $R^1R^2 = CHMe{\cdot}[CH_2]_4$, R^3 = Pr^i, R^4 = iso-C_5H_{11}) (38%), m.p. 117—119° (Found: C, 68·5; H, 9·1; N, 8·7. $C_{27}H_{43}N_3O_4$ requires C, 68·5; H, 9·2; N, 8·9%). Hydrogenolysis of this isomer gave the (±)-*hydroxamic acid* (X) (65%), m.p. 168—170° (from ethyl acetate) (Found: C, 62·2; H, 9·7; N, 11·0. $C_{20}H_{37}N_3O_4$ requires C, 62·6; H, 9·7; N, 11·0%). The major (±)-O-*benzylhydroxamic acid* (IX) was obtained in 52% yield; m.p. 164—166° (from ethyl acetate) (Found: C, 68·1; H, 9·0; N, 8·9. $C_{27}H_{43}N_3O_4$ requires C, 68·5; H, 9·2; N, 8·9%). Hydrogenolysis of this isomer gave the (±)-*hydroxamic acid* (XI) (82%), m.p. 145—147° (from ethyl acetate) (Found: C, 62·4; H, 9·6; N, 10·6. $C_{20}H_{37}N_3O_4$ requires C, 62·6; H, 9·7; N, 11·0%).

(±)-*Hydroxamic Acids* (XI) *derived from* DL-*Valylmorpholine*.—The following additional (±)-hydroxamic acids (XI), derived from DL-valylmorpholine,[1] were obtained from the corresponding (±)-*O*-benzylhydroxamic acid precursor (IX), the major diastereoisomer, which was isolated from the mixture of (±)-*O*-benzylhydroxamic acids (VIII) and (IX). The separation and characterisation of the minor (±)-*O*-benzylhydroxamic acid precursor (VIII) were not carried out.

(i) *The* (±)-*hydroxamic acid* (XI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = Pr^n). DL-Valylmorpholine [1] and *N*-benzyloxy-3-n-propylsuccinamic acid gave the (±)-O-*benzylhydroxamic acid* (IX; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = Pr^n) (50%), m.p. 198—199° (from ethanol) (Found: C, 63·8; H, 8·0; N, 9·5. $C_{23}H_{35}N_3O_5$ requires C, 63·7; H, 8·1; N, 9·7%). Hydrogenolysis gave the (±)-*hydroxamic acid* (48%), m.p. 142—145° (from acetone) (Found: C, 56·2; H, 8·6; N, 12·1. $C_{16}H_{29}N_3O_5$ requires C, 56·0; H, 8·5; N, 12·2%).

(ii) *The* (±)-*hydroxamic acid* (XI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = Bu^n). DL-Valylmorpholine and *N*-benzyloxy-3-n-butylsuccinamic acid gave the (±)-O-*benzylhydroxamic acid* (IX; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = Bu^n) (27%), m.p. 196—197° (from ethanol) (Found: C, 64·3; H, 8·3; N, 9·4. $C_{24}H_{37}N_3O_5$ requires C, 64·4; H, 8·3; N, 9·4%). Hydrogenolysis gave the (±)-*hydroxamic acid* (60%), m.p. 137—138° (from ethyl acetate) (Found: C, 57·1; H, 8·7; N, 11·6. $C_{17}H_{31}N_3O_5$ requires C, 57·1; H, 8·7; N, 11·8%).

(iii) *The* (±)-*hydroxamic acid* (XI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, $R^4 = [CH_2]_4CH{\cdot}$). DL-Valylmorpholine and *N*-benzyloxy-3-cyclopentylsuccinamic acid gave the (±)-O-*benzylhydroxamic acid* (IX; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, $R^4 = [CH_2]_4CH{\cdot}$) (44%), m.p. 207—208° (from ethanol) (Found: C, 65·3; H, 7·9; N, 9·1. $C_{25}H_{37}N_3O_5$ requires C, 65·3; H, 8·1; N, 9·2%). Hydrogenolysis gave the (±)-*hydroxamic acid* (44%), m.p. 177—179° (from ethyl acetate) (Found: C, 58·7; H, 8·4; N, 11·6. $C_{18}H_{31}N_3O_5$ requires C, 58·5; H, 8·5; N, 11·4%).

(iv) *The* (±)-*hydroxamic acid* (XI; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = n-C_6H_{13}). DL-Valylmorpholine and *N*-benzyloxy-3-n-hexylsuccinamic acid gave the (±)-O-*benzylhydroxamic acid* (IX; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, R^3 = Pr^i, R^4 = n-C_6H_{13}) (43%), m.p. 162—163° (from ethyl acetate) (Found: C, 65·7; H, 8·8; N, 8·8. $C_{26}H_{41}N_3O_5$ requires C, 65·7; H, 8·7; N, 8·8%). Hydrogenolysis gave the (±)-*hydroxamic acid* (74%), m.p. 88—89° (from ethyl acetate–light petroleum) (Found: C, 59·2; H, 9·1; N, 10·8. $C_{19}H_{35}N_3O_5$ requires C, 59·2; H, 9·2; N, 10·9%).

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