Studies concerning the Antibiotic Actinonin. Part VI.[1] Synthesis of Structural Analogues of Actinonin by Dicyclohexylcarbodi-imide Coupling Reactions

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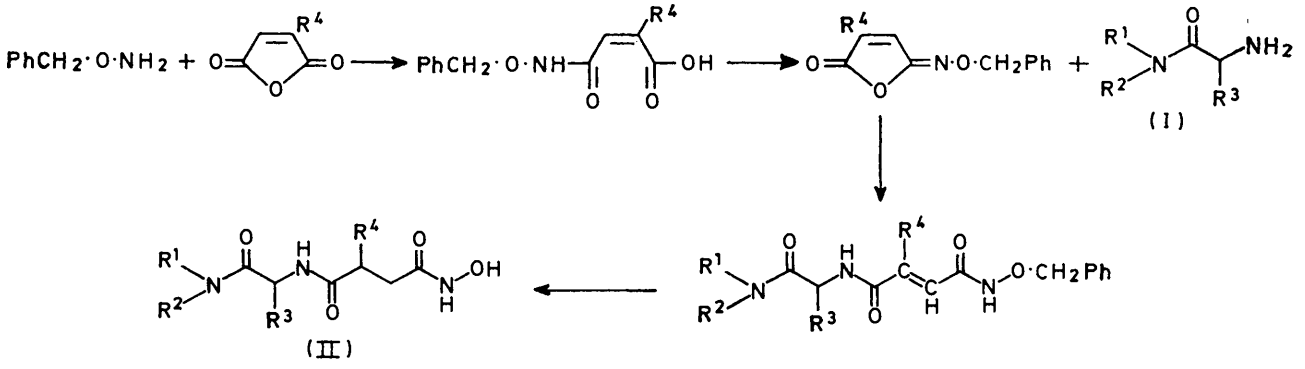
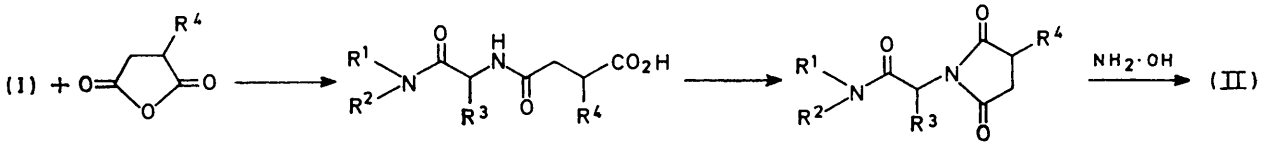
The coupling of amino-amides (I) with monoalkyl esters (V) of dicarboxylic acids has been investigated as a route for the specific synthesis of structural analogues (II) and (III) of actinonin (XVII). Methods for the synthesis of the isomers (X) and (XI) have been developed, but their coupling with amino-amides (I) by use of dicyclohexylcarbodi-imide is not specific.

In Parts II, III, and V [1-3] methods have been described for the syntheses of structural analogues of actinonin. These three methods are summarised in Schemes 1—3. possibility of specifically creating a new amide linkage by a dehydrative reaction between amino-amides (I) and monoalkyl esters of dicarboxylic acids.



SCHEME 1 Isomaleimide method (Part II) [2]



SCHEME 2 Anhydride–imide method (Part III) [3]

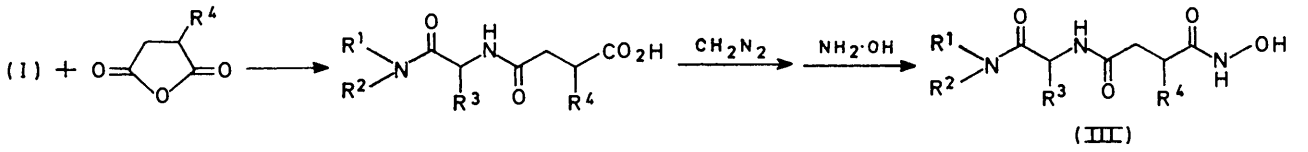
They all involve ring cleavage reactions involving nucleophilic attack by amino-amides (I) upon various cyclic anhydro-derivatives. Although these three methods are generally useful they do have some shortcomings. We were therefore encouraged to explore the

DL-Valylmorpholine (I; $R^1R^2 = [CH_2]_2{\cdot}O{\cdot}[CH_2]_2$, $R^3 = Pr^i$) and monoethyl pentylmalonate (Vb; X = n-C_5H_{11}·CH) with dicyclohexylcarbodi-imide in dichloromethane gave the corresponding dicarbamoyl-ester (VIa) (Table 1). By a similar process, DL-valylmorpholine

[1] Part V, J. P. Devlin, W. D. Ollis, and J. E. Thorpe, preceding paper.
[2] Part II, N. H. Anderson, W. D. Ollis, J. E. Thorpe, and A. D. Ward, *J.C.S. Perkin I*, 1975, 825.
[3] Part III, 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. Perkin I*, 1975, 830.

and monoethyl 3-methylbutylmalonate (Vb; X = iso-C_5H_{11}·CH) gave the dicarbamoyl-ester (VIb) (Table 1). These esters (VIa and b) were converted into the corresponding hydroxamic acids (VIc and d) with methanolic alkaline hydroxylamine (Table 2).

The isomeric monomethyl esters (X) and (XI) of pentylsuccinic acid had similar but distinct i.r. and n.m.r. spectra. Their respective constitutions were clearly supported by their mass spectra, which were very similar but showed an important difference. The acid (X)



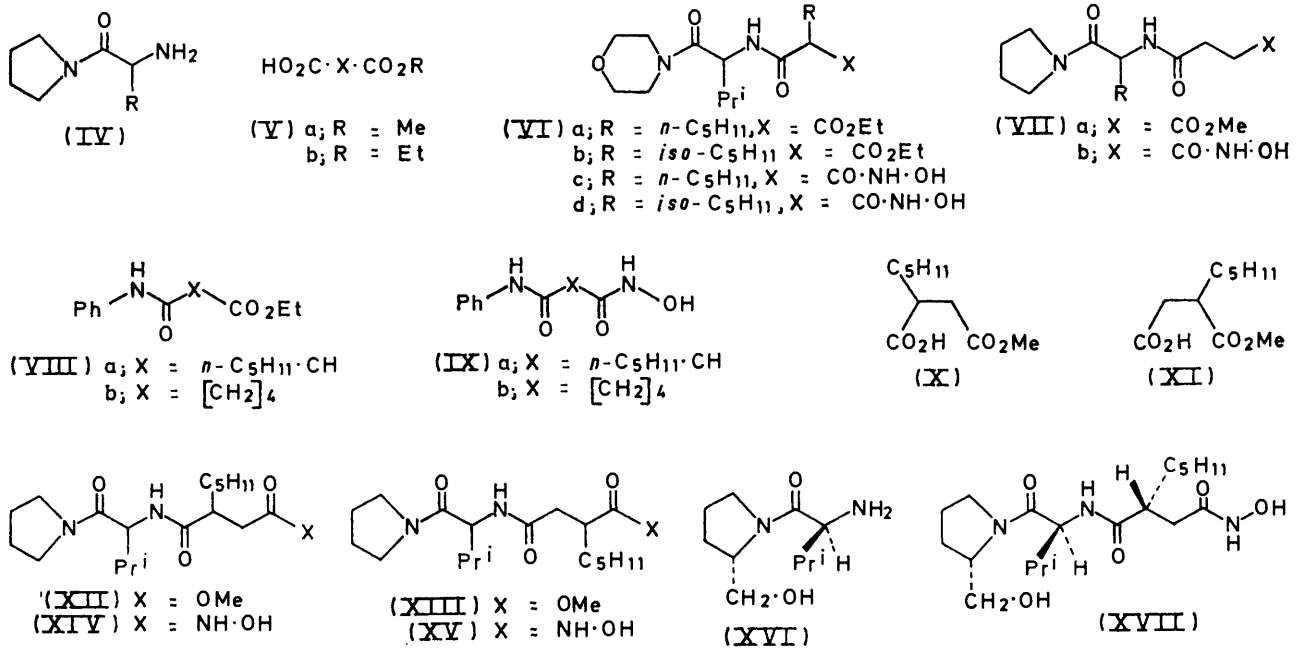
(III)

SCHEME 3 Anhydride–ester method (Part V) [1]

L-Valylpyrrolidine (IV; R = Pr^i) and monomethyl succinate [4] (Va; X = $[CH_2]_2$) with dicyclohexylcarbodi-imide in dichloromethane yielded the corresponding dicarbamoyl-ester (VIIa; R = Pr^i) (Table 1). The DL- and L-alanyl derivatives (VIIa; R = Me) were similarly prepared (Table 1). These esters (VIIa; R = Pr^i or

showed a fragment ion at *m/e* 129 (C_5H_{11}·CH·$CO_2H^{+\cdot}$) and no significant fragment ion at *m/e* 143. In contrast, the isomer (XI) showed a fragment ion at *m/e* 143 (C_5H_{11}·CH·$CO_2Me^{+\cdot}$) and no significant fragment ion at *m/e* 129.

With the existence of the isomeric acids (X) and (XI)



Me) were identical with those previously prepared during the study of the anhydride–ester method.[1] Their conversion into the actinonin analogues (VIIb; R = Pr^i or Me) has been previously described.[1]

In view of our interest in the biological activity shown by phenylcarbamoylhydroxamic acid analogues of actinonin, the hydroxamic acids (IXa and b) were similarly prepared from the carbamoyl-esters (VIIIa and b).

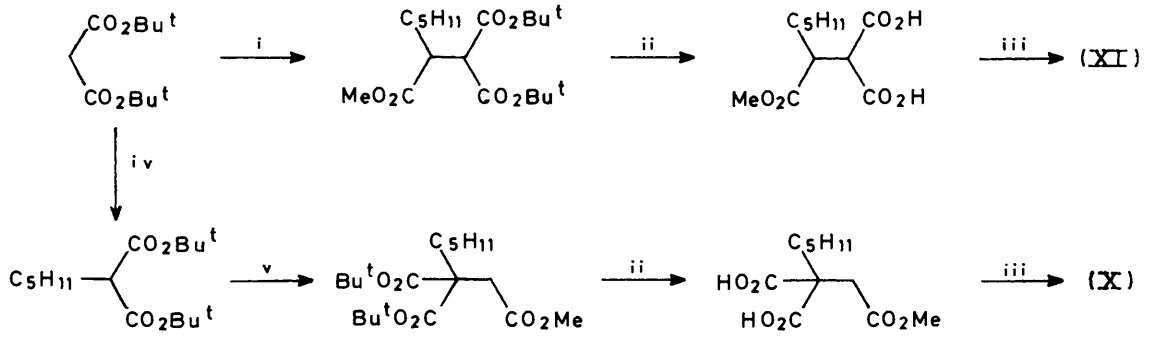
In order to examine the specificity associated with the dicyclohexylcarbodi-imide coupling reaction between amino-amides (I) and monomethyl esters of dicarboxylic acids (Va), it was decided to prepare the isomers (X) and (XI). The methods of synthesis are summarised in Scheme 4.

demonstrated, it was now possible to examine the specificity and selectivity of their coupling with amino-amides (I), with dicyclohexylcarbodi-imide as the dehydrating agent. The acid (X) and L-valylpyrrolidine (IV; R = Pr^i) with dicyclohexylcarbodi-imide yielded a mixture of two esters that were separated by chromatography. It was not established whether these two esters were related as diastereoisomers (XII) or whether they were constitutional isomers, (XII) and (XIII). Their n.m.r. spectra were similar but there were differences which could be regarded as significant. However, these differences were not directly interpretable. The methyl esters [(XII) and/or (XIII)] were separately treated with

[4] W. A. Bone, J. J. Sudborough, and C. H. G. Sprankling, *J. Chem. Soc.*, 1904, **85**, 534.

methanolic alkaline hydroxylamine to give the corresponding hydroxamic acids. The constitutions of these hydroxamic acids [(XIV) and/or (XV)] were not established.

In view of the uncertainty about the actual constitution of the products formed in the dicyclohexylcarbodiimide coupling reaction with monoalkyl succinic acid derivatives, the reaction between L-valyl-L-prolinol [2] (XVI) and the acid (X) was examined. Reaction of the intermediate mixture of esters with methanolic alkaline hydroxylamine gave a mixture of hydroxamic acids from



SCHEME 4 Reagents: i, K–C_6H_6–C_5H_{11}·CHBr·CO_2Me; ii, HCO_3H; iii, heat (xylene); iv, K–Bu^tOH–$C_5H_{11}Br$; v, K–C_6H_6–$BrCH_2$·CO_2Me

which actinonin (XVII) was eventually isolated (*ca.* 20% yield). In view of this comparatively low overall yield it was concluded that the coupling of the ester-acid (X) was not very selective: the synthesis of actinonin analogues by the dicyclohexylcarbodi-imide coupling reaction was not pursued further. Various mechanisms involving cyclic intermediates may be written for the lack of selectivity shown in this coupling rection with dicyclohexylcarbodi-imide. These results are related to the established ring–chain tautomerism of acid halides of half esters of dibasic acids.[5]

EXPERIMENTAL

General experimental procedures are described in Part I.[6]

Ethyl Hydrogen Pentylmalonate (Vb; X = n-C_5H_{11}·CH). —Diethyl pentylmalonate [7] (34·5 g) was mixed with a solution of potassium hydroxide (8·4 g) in ethanol (100 ml) and the solution kept at room temperature for 48 h. After addition of benzene (200 ml) the mixture was heated under reflux for 10 min and acidified (pH 6·0) with Dowex 50W-X8 ion-exchange resin. The resin was removed and the residue from evaporation of the filtrate was dissolved in saturated aqueous sodium hydrogen carbonate (300 ml). The solution was washed with chloroform (3 × 100 ml) and, after acidification, extracted with ether (3 × 100 ml). The dried extract was evaporated and distilled giving *ethyl hydrogen pentylmalonate* (27 g, 89%) as a liquid, b.p. 110—115° at 0·4 mmHg (Found: C, 59·6; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%); $\nu_{max.}$ (film) 1740 and 1715 cm^{-1}; τ (CCl_4) −1·48 (1H, s, CO_2H), 5·81 (2H, q, *J* 7 Hz, CH_2·CH_3), and 8·72 (3H, t, *J* 7 Hz, CH_2·CH_3).

Ethyl Hydrogen 3-Methylbutylmalonate (Vb; X = iso-C_5H_{11}·CH).—This compound was prepared from diethyl 3-methylbutylmalonate [8] by the method described above for ethyl hydrogen pentylmalonate and was obtained as a *liquid* (66%), b.p. 115—117° at 0·4 mmHg (Found: C, 59·1; H, 9·0. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%).

Di-t-butyl pentylmalonate.—A mixture of di-t-butyl malonate [9] (92 g) and a solution of potassium (17 g) in t-butyl alcohol (500 ml) was heated under reflux for 1 h. 1-Bromopentane (62 g) was added and the solution heated under reflux for 24 h and concentrated (to 200 ml). Addition of water (200 ml), extraction with ether (3 × 200 ml), and evaporation of the dried extract followed by fractional distillation in the presence of magnesium oxide (200 mg) gave *di-t-butyl pentylmalonate* as an oil (100 g, 82%), b.p. 130—140° at 30 mmHg (Found: C, 67·4; H, 10·5. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·4%), $\nu_{max.}$ (film) 1740 and 1730 cm^{-1}; τ ($CDCl_3$) 6·94 (1H, t, *J* 7 Hz, C*H*·C_5H_{11}) and 8·54 (18H, s, 2 × Bu^t).

2-Methyl 1,1-Di-t-butyl Heptane-1,1,2-tricarboxylate.—A mixture of di-t-butyl malonate [9] (38 g), potassium (6·7 g), and anhydrous benzene (800 ml) was heated under reflux for 24 h. Methyl 2-bromoheptanoate [10] (21 g) was added and the mixture was heated under reflux for 24 h; more (12·7 g) methyl 2-bromoheptanoate was then added and heating was continued for 48 h. The solution was washed with water (2 × 20 ml), dried, and evaporated. Fractional distillation in the presence of magnesium oxide (50 mg) gave the *triester* as an oil (32 g, 51%), b.p. 114—116° at 0·2 mmHg, which crystallised; m.p. 30—31° (Found: C, 63·5; H, 9·4. $C_{19}H_{34}O_6$ requires C, 63·7; H, 9·5%), $\nu_{max.}$ (film) 1730 cm^{-1}, τ (CCl_4) 6·36 (3H, s, CO_2Me), 6·56 [1H, d, *J* 10·2 Hz, C*H*(CO_2Bu^t)$_2$], and 8·53 (18H, s, 2 × Bu^t).

1-Methyl 2,2-Di-t-butyl Heptane-1,2,2-tricarboxylate.—This compound was prepared from di-t-butyl pentylmalonate and methyl bromoacetate by the foregoing method but with the addition of magnesium oxide (1 g). It was obtained (48%) as an *oil*, b.p. 104—110° at 0·1 mmHg (Found: C, 63·5; H, 9·6. $C_{19}H_{34}O_6$ requires C, 63·7; H, 9·5%), $\nu_{max.}$ (film) 1730 cm^{-1}, τ ($CDCl_3$) 6·36 (3H, s, OMe), 7·13 (2H, s, CH_2·CO_2Me), and 8·53 (18H, s, 2 × Bu^t).

[5] B. H. Chase and D. H. Hey, *J. Chem. Soc.*, 1952, 553; J. Cason and R. D. Smith, *J. Org. Chem.*, 1953, **18**, 1201.

[6] 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.

[7] A. W. Dox and E. G. Jones, *J. Amer. Chem. Soc.*, 1928, **50**, 2033.

[8] C. Paal and Th. Hoffman, *Ber.*, 1890, **23**, 1495.

[9] A. L. McCloskey, G. S. Fonken, R. W. Kluiber, and W. S. Johnson, *Org. Synth.*, Coll. Vol. IV, 1963, p. 261.

[10] H. Reinheckel, *Chem. Ber.*, 1960, **93**, 2222.

3-*Methoxycarbonyloctanoic Acid* (XI).—A solution of 2-methyl 1,1-di-t-butyl heptane-1,1,2-tricarboxylate (31 g) in formic acid (98%; 100 ml) was kept at room temperature overnight. Evaporation gave an oil from which the crude dicarboxylic acid was obtained by extraction with saturated aqueous sodium hydrogen carbonate. This acid (16 g) in xylene (300 ml) was heated under reflux for 2 h and evaporated. The residue was extracted with saturated aqueous sodium hydrogen carbonate (200 ml) and the extract was washed with chloroform (3 × 100 ml). The aqueous solution was acidified and extracted with chloroform (3 × 100 ml). Evaporation of the chloroform extract and fractional distillation gave 3-*methoxycarbonyloctanoic acid* (9 g, 51%) as an oil, b.p. 60° at 5 × 10^{-5} mmHg (Found: C, 59·4; H, 9·0%; M^+, 202. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%; *M*, 202), $\nu_{max.}$ (film) 1734 and 1710 cm^{-1}.

2-(*Methoxycarbonylmethyl*)*heptanoic Acid* (X).—This compound was prepared from 1-methyl 2,2-di-t-butyl heptane-1,1,2-tricarboxylate by the foregoing method and was obtained (42%) as an *oil*, b.p. 60° at 5 × 10^{-5} mmHg (Found: C, 59·6; H, 8·8%; M^+, 202. $C_{10}H_{18}O_4$ requires C, 59·4; H, 9·0%; *M*, 202), $\nu_{max.}$ (film) 1737 and 1708 cm^{-1}.

General Method for the Preparation of Carbamoyl-esters (*Table* 1).—To a cooled (−5°) solution of the amino-amide (I) (0·1 mol) and the monoester (V) (0·1 mol) in dichloromethane (100 ml) was added *NN'*-dicyclohexylcarbodiimide (0·102 mol) and the mixture was kept at −5° for 2 h and at room temperature for 12 h. The precipitated *NN'*-dicyclohexylurea was removed and the filtrate was washed with dilute hydrochloric acid (2N; 2 × 100 ml), saturated aqueous sodium hydrogen carbonate (2 × 100 ml), and water (2 × 50 ml), and dried. Evaporation gave the carbamoyl-esters (Table 1).

In a similar manner, aniline and ethyl hydrogen pentylmalonate gave the *carbamoyl-ester* (VIIIa) (58%), m.p. 64—66° (from ether–light petroleum) (Found: N, 5·1%; M^+, 277. $C_{16}H_{23}NO_3$ requires N, 5·1%; *M*, 277), $\nu_{max.}$ (film) 3310, 1738, 1660, and 1602 cm^{-1}. Aniline and ethyl hydrogen adipate [11] gave the *carbamoyl-ester* (VIIIb) (63%), m.p. 36—39° (from ether–light petroleum) (Found: C, 67·2; H, 7·7; N, 5·4. $C_{14}H_{19}NO_3$ requires C, 67·5; H, 7·8; N, 5·6%), $\nu_{max.}$ (film) 3350, 1730, 1665, and 1603 cm^{-1}.

General Method for the Preparation of Hydroxamic Acids (*Table* 2).—The method for the preparation of the hydroxamic acids (VIIb; R = Me or Pr^i) from the corresponding carbamoyl-esters (VIIa; R = Me or Pr^i) (Table 1) and methanolic alkaline hydroxylamine has been previously reported.[1] The hydroxamic acids described in Table 2 were obtained in a similar manner.

Reaction of L-*Valylpyrrolidine with* 2-(*Methoxycarbonylmethyl*)*heptanoic Acid* (X); *Formation of the Isomeric Carbamoyl-esters* (XII) *and/or* (XIII) *and their Conversion into the Corresponding Hydroxamic Acids* (XIV) *and/or* (XV).—L-Valylpyrrolidine [3] (0·85 g) and the acid (X) (1·01 g) were treated with *NN'*-dicyclohexylcarbodi-imide (1·10 g) according to the foregoing general method for the preparation of carbamoyl-esters. The mixture of carbamoyl-esters was separated by thick-layer chromatography (silica; benzene–ethyl formate–formic acid, 6 : 5 : 1), elution of the zones gave (a) a *carbamoyl-ester* as a gum (Found: C, 64·5; H, 9·7; N' 7·7%; M^+, 354. $C_{19}H_{34}N_2O_4$ requires C, 64·4; H, 9·7; N' 7·9%; *M*, 354), $\nu_{max.}$ (film) 1735, 1665, and 1630 cm^{-1}, which, by the method described, gave the corresponding hydroxamic acid as an amorphous solid, *m/e* 355 (M^+, $C_{18}H_{33}N_3O_4$), and (b) an isomeric *carbamoyl-ester* as a gum (Found: C, 64·5; H, 9·7; N, 7·8%; M^+, 354), $\nu_{max.}$ (film) 1735, 1665, and 1630 cm^{-1}, which gave the corresponding hydroxamic acid as a gum, *m/e* 355 (M^+, $C_{18}H_{33}N_3O_4$).

TABLE 1

Carbamoyl-esters from amino-amides (I) and monoalkyl esters (V)

	Amino-acid residue	Base residue	Yield (%)	M.p. (°C)
(VIIa; R = Pr^i)	L-Valine	Pyrrolidine [a]	71	Oil [c]
(VIIa; R = Me)	L-Alanine	Pyrrolidine [b]	58	64—66 [c,d]
(VIIa; R = Me)	DL-Alanine	Pyrrolidine [b]	65	70—71 [e,d]
(VIa)	DL-Valine	Morpholine [a]	51	71—72 [e,f]
(VIb)	DL-Valine	Morpholine [a]	58	73—74 [e,g]
	L-Valine	L-Prolinol [b]	47	Oil [h]

[a] The preparation of the amino-amide is described in Part III.[3] [b] The preparation of the amino-amide is described in Part II.[2] [c] Identical with samples prepared by an alternative route.[1] [d] From ether–light petroleum. [e] From light petroleum. [f] Found: C, 61·4; H, 9·2; N, 7·5. $C_{19}H_{34}N_2O_5$ requires C, 61·6; H, 9·3; N, 7·6%. [g] Found: C, 61·1; H, 9·2; N, 7·4. $C_{19}H_{34}N_2O_5$ requires C, 61·6; H, 9·3; N, 7·6%. [h] Purified by column chromatography (polyamide; ethanol); $\nu_{max.}$ (film) 1720, 1670, and 1630 cm^{-1}, and directly converted into the hydroxamic acid (Table 2).

TABLE 2

Hydroxamic acids

	Yield (%)	M.p. (°C)	Found C (%)	Found H (%)	Found N (%)	Found *M*	Formula	Required C (%)	Required H (%)	Required N (%)	Required *M*
(VIc)	29	144—145 [a]	57·0	8·6	11·3		$C_{17}H_{31}N_3O_5$	57·1	8·7	11·8	
(VId)	10	128—134 [a]	56·2	8·9	11·3		$C_{17}H_{31}N_3O_5,0·5H_2O$	55·7	8·8	11·5	
(XVII)	19	147—148 [b]									
(IXb)	64	180—183 [c]	61·1	7·0	11·7	236	$C_{12}H_{16}N_2O_3$	61·0	6·8	11·9	236
(IXa)	58	155—159 [d]	64·0	7·9	10·9	264	$C_{14}H_{20}N_2O_3$	63·6	7·6	10·6	264

[a] From ethyl acetate. [b] From chloroform–carbon tetrachloride; identical with natural actinonin.[6] [c] From methanol; $\nu_{max.}$ (Nujol) 1660, 1638, 1610, and 1560 cm^{-1}. [d] From acetone–chloroform.

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[11] G. B. Brown, M. D. Armstrong, A. W. Moyer, W. P. Anslow, B. R. Baker, M. V. Querry, S. Bernstein, and S. R. Safir. *J. Org. Chem.*, 1947, **12**, 160.