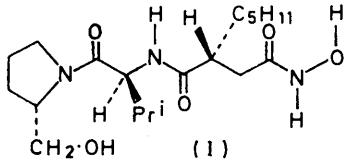
Studies Concerning the Antibiotic Actinonin. Part V.[1] Synthesis of Structural Analogues of Actinonin by the Anhydride–Ester Method

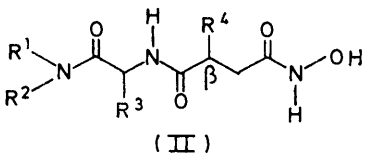
By **John P. Devlin, W. David Ollis,* and John E. Thorpe,** Department of Chemistry, The University, Sheffield S3 7HF

The anhydride–ester method for the synthesis of structural analogues (III) of the antibiotic actinonin (I) is described. This route involves reaction between the amino-amides (IV) and the anhydrides (V), giving the acids (VI; R^5 = H); their methyl esters (VI; R^5 = Me) with methanolic alkaline hydroxylamine give the structural analogues (III). The structural analogues (IX) and (X) have been synthesised by a similar route.

SYNTHESES of analogues of actinonin (I) by the isomaleimide method [2] and the anhydride–imide method [3] have been described. Both methods lead to structural analogues (II) in which the side chain R^4 is located in a β-relation to the hydroxamic acid residue. We now describe the anhydride–ester method, which may be used for the synthesis of analogues (III) in which the side chain R^4 is located in an α-relation to the hydroxamic acid residue. This method may also be conveniently used for the synthesis of the actinonin analogues (III; R^4 = H).



(I)



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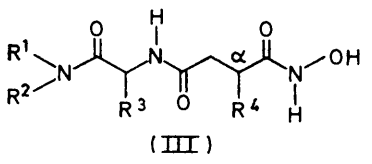

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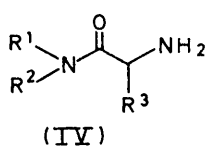
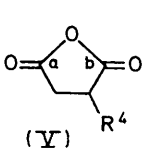


(IV)



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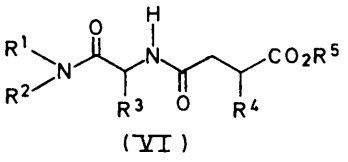

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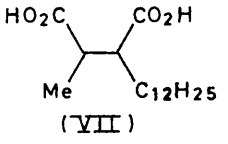


(VII)

On the basis of our earlier results [2,3] it was expected that the reaction of the anhydrides (V) with the amino-amides (IV) would involve the less hindered group (carbonyl a) of the anhydride (V). This distinction does not, of course, exist in simple anhydrides so that the anhydride–ester method is preferred for the synthesis of succinoyl analogues (III; R^4 = H).

The actinonin analogues (III) were synthesised by the following general method. The amino-amides (IV) and the anhydrides (V) in boiling dichloromethane yielded the dicarbamoyl-carboxylic acids (VI; R^5 = H), which gave the corresponding methyl esters (VI; R^5 = Me) (Table 1) with diazomethane. The methyl esters (VI; R^5 = Me) and methanolic alkaline hydroxylamine yielded the actinonin analogues (III) (Table 2).

In view of the inhibiting action [4] of dialkylsuccinic acid derivatives on the *in vitro* growth of acid-fast bacteria, we synthesised an analogue derived from roccellic acid (VII) isolated from *Lecanora rupicola*.[5] Roccellic anhydride (VIII) and L-valyl-L-prolinol yielded the mixture of acids (IX; R = OH) which was transformed *via* the methyl esters (IX; R = OMe) into the mixture of hydroxamic acids (IX; R = NH·OH). No attempt was made to separate these mixtures, whose formation was associated with a lack of selectivity in the reaction between roccellic anhydride (VIII) and L-valyl-L-prolinol.

Based upon the experience mentioned in Part III [3] that it was possible to retain some actinonin-like activity by replacement of the L-valyl-L-prolinol residue in

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

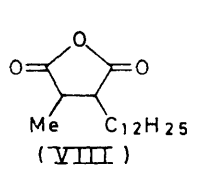
[2] Part II, N. H. Anderson, W. D. Ollis, J. E. Thorpe, and A. D. Ward, *J.C.S. Perkin I*, 1975, 825.

[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.

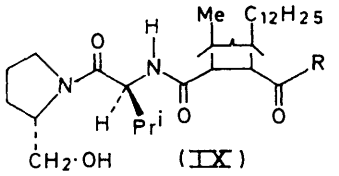
[4] V. C. Barry and P. A. McNally, *Nature*, 1945, **156**, 48.

[5] J. P. Devlin, C. P. Falshaw, W. D. Ollis, and R. E. Wheeler, *J. Chem. Soc.* (*C*), 1971, 1318.

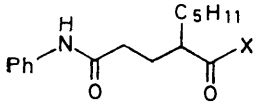
actinonin (I) by an anilino-group, the synthesis of a pentylglutaric acid analogue (X) was also examined. Michael addition of diethyl pentylmalonate (XIII) [6] to



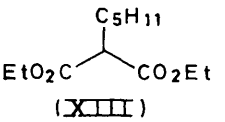
(VIII)



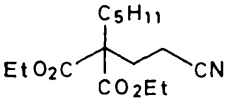
(IX)



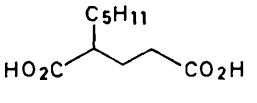
(X) X = NH·OH
(XI) X = OH
(XII) X = OMe



(XIII)



(XIV)



(XV)

acrylonitrile yielded the cyano-diester (XIV), which gave 2-pentylglutaric acid (XV). 2-Pentylglutaric anhydride and aniline yielded the phenylcarbamoyl-carboxylic acid (XI), which was transformed into the required hydroxamic acid (X) *via* the methyl ester (XII).

EXPERIMENTAL

General experimental directions are given in Part I.[7]

Roccellic Anhydride (VIII).—Natural roccellic acid [5] was heated under reflux with an excess of acetyl chloride for 3 h. Evaporation and distillation of the residue gave roccellic anhydride (85%), an oil, b.p. 230° at 0·5 mmHg, *m/e* 282 (M^+, $C_{17}H_{30}O_3$), $\nu_{max.}$ (film) 1850 and 1780 cm^{-1}.

Diethyl 2-(2-Cyanoethyl)-2-pentylmalonate (XIV).—Diethyl pentylmalonate [6] (35·5 g) was treated with a solution of sodium (1·5 g) in ethanol (30 ml) at 60° (30 min). Acrylonitrile (12 g) was then added and the mixture stirred at 60° for 8 h. Evaporation left a residue which was dissolved in ether (100 ml); the solution was shaken with saturated aqueous sodium hydrogen carbonate (2 × 50 ml), dried, and evaporated. Fractional distillation gave the *cyano-diester* (23·4 g, 54%), b.p. 138—144° at 1 mmHg (Found: C, 63·7; H, 8·8; N, 5·0. $C_{15}H_{25}NO_4$ requires C, 63·6; H, 8·9; N, 4·8%), $\nu_{max.}$ (film) 2280 and 1735 cm^{-1}.

2-Pentylglutaric Anhydride.—The foregoing cyano-diester (13 g) was heated under reflux with glacial acetic acid (200 ml) and hydrochloric acid (12N; 250 ml) for 48 h. After cooling the mixture was diluted with water (1 l) and extracted with ether. The extracts were dried and evaporated and the residue was purified by column chromatography on silica. Elution with chloroform gave 2-pentylglutaric acid (XV) as an oil (8·9 g), $\nu_{max.}$ (film) 1705 cm^{-1}. The acid was mixed with acetyl chloride (30 ml) and heated under reflux for 1 h. Fractional distillation gave *2-pentylglutaric anhydride* (6·9 g) as an oil, b.p. 110—112° at 0·15 mmHg (Found: C, 65·6; H, 8·8. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·8%), $\nu_{max.}$ (film) 1800 and 1760 cm^{-1}.

General Method for the Preparation of Esters (VI; R^5 = Me).—The amino-amide (IV) (0·1 mol) and the anhydride (V) (0·1 mol) were heated under reflux (1 h) in dichloromethane (50 ml). Evaporation gave the carbamoyl-acid (VI; R^5 = H) in almost quantitative yield. The product was dissolved in ether (methanol was added if necessary) and ethereal diazomethane was added. The excess of diazomethane was removed by addition of acetic acid. The solution was shaken with hydrochloric acid (2N; 2 × 10 ml), aqueous sodium hydroxide (2N; 2 × 10 ml), and water (20 ml) and dried. Evaporation yielded the *methyl esters* (VI; R^5 = Me) (see Table 1).

In a similar manner were prepared compounds (IX; R = OMe) [90% from (VIII) and L-valylprolinol [2]] as an oil, *m/e* 496 (M^+, $C_{28}H_{52}N_2O_5$), and (XII) (94% from aniline and 2-pentylglutaric anhydride) as an oil, *m/e* 291 (M^+, $C_{17}H_{25}NO_3$).

General Method for the Preparation of Hydroxamic Acids (III).—A solution of hydroxylamine hydrochloride (0·2 mol) in methanol (100 ml) was mixed with a solution of potassium hydroxide (0·3 mol) in methanol (50 ml) at 0° with stirring. The mixture was kept at 0° (15 min) and the precipitated potassium chloride removed. The filtrate was added to the methyl ester (0·1 mol) and kept at room

TABLE 1

Methyl esters [a] (VI; R^5 = Me)

Amino-acid residue	Base residue	R^1	R^2	R^3	R^4	Yield (%)	M.p. (°C)	Found C (%)	Found H (%)	Found N (%)	Found *M*	Formula	Required C (%)	Required H (%)	Required N (%)	Required *M*
Glycine	Pyrrolidine [b]	$[CH_2]_4$		H	H	70 [d]	110—112	54·7	7·5	11·3	242	$C_{11}H_{18}N_2O_4$	54·5	7·5	11·6	242
L-Alanine	Pyrrolidine [c]	$[CH_2]_4$		Me	H	75 [e]	64—66	56·2	7·8	10·8	256	$C_{12}H_{20}N_2O_4$	56·2	7·9	10·9	256
DL-Alanine	Pyrrolidine [c]	$[CH_2]_4$		Me	H	72 [e]	70—71			10·8	256	$C_{12}H_{20}N_2O_4$			10·9	256
L-Valine	Pyrrolidine [b]	$[CH_2]_4$		Pr^i	H	88	*f*	59·1	8·7	9·6	284	$C_{14}H_{24}N_2O_4$	59·2	8·5	9·9	284
L-Valine	L-Prolinol [c]	$CH(CH_2OH)\cdot[CH_2]_3$		Pr^i	C_5H_{11} [g]	89	*f*	62·7	9·5		370	$C_{20}H_{38}N_2O_5$	62·5	9·4		370

[a] For all esters, $\nu_{max.}$ ($CHCl_3$) 1730, 1670, and 1630 cm^{-1}. [b] The preparation of the amino-amide (IV) is described in Part III.[3] [c] The preparation of the amino-amide (IV) is described in Part II.[2] [d] From benzene–cyclohexane. The corresponding *acid* (VI; R^5 = H) had m.p. 170—172° (benzene–dichloromethane) (Found: C, 52·4; H, 7·3; N, 12·2. $C_{10}H_{16}N_2O_4$ requires C, 52·6; H, 7·1; N, 12·3%). [e] From ether–light petroleum (b.p. 40—60°). [f] Isolated as oils. [g] Pentylsuccinic anhydride is described in Part III.[3]

TABLE 2

Hydroxamic acids (III)

Amino-acid residue	Base residue	R^1	R^2	R^3	R^4	Yield (%)	M.p. (°C)
Glycine	Pyrrolidine	$[CH_2]_4$		H	H	23 [a]	130—133
L-Alanine	Pyrrolidine	$[CH_2]_4$		Me	H	52 [a]	Oil
DL-Alanine	Pyrrolidine	$[CH_2]_4$		Me	H	50 [a]	72—74
L-Valine	Pyrrolidine	$[CH_2]_4$		Pr^i	H	45 [a]	Oil
L-Valine	L-Prolinol	$CH(CH_2OH)\cdot[CH_2]_3$		Pr^i	C_5H_{11}	60 [b]	142—145

[a] Identical with samples prepared by alternative routes.[2,3] [b] From chloroform (Found: C, 58·9; H, 9·1; N, 11·0%, *M*+, 385. $C_{19}H_{35}N_3O_5$ requires C, 59·2; H, 9·2; N, 10·9%; *M*, 385).

[6] A. W. Dox and E. G. Jones, *J. Amer. Chem. Soc.*, 1928, **50**, 2034.

[7] 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.

temperature for 24 h. The solution was brought to pH 6·0 by addition of Dowex 50W-X8 resin, filtered, and evaporated. The residue was chromatographed (polyamide column); elution with benzene–propan-2-ol gave the *hydroxamic acids* (III) (see Table 2).

In a similar manner were prepared *compounds* (IX; R = NH·OH) (59%), m.p. 164—174° (from ether–light petroleum) (Found: C, 64·9; H, 10·1; N, 8·3%; M^+, 497. $C_{27}H_{51}N_3O_5$ requires C, 65·2; H, 10·3; N, 8·4%; M, 497) and (X) (58%), m.p. 130—132° (from chloroform–methanol) (Found: C, 65·55; H, 8·35; N, 9·35%; M^+, 292. $C_{16}H_{24}N_2O_3$ requires C, 65·75; H, 8·2; N, 9·6%; M, 292).

[4/1145 *Received*, 12*th June*, 1974]