Regiospecific and Stereoselective Synthesis of Analogues of the Antibiotic, Actinonin

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Summary Regiospecificity and stereoselectivity in the synthesis of actinonin structural analogues (**2**) and (**3**) are described; a stereospecific route to compounds (**2**) is described.

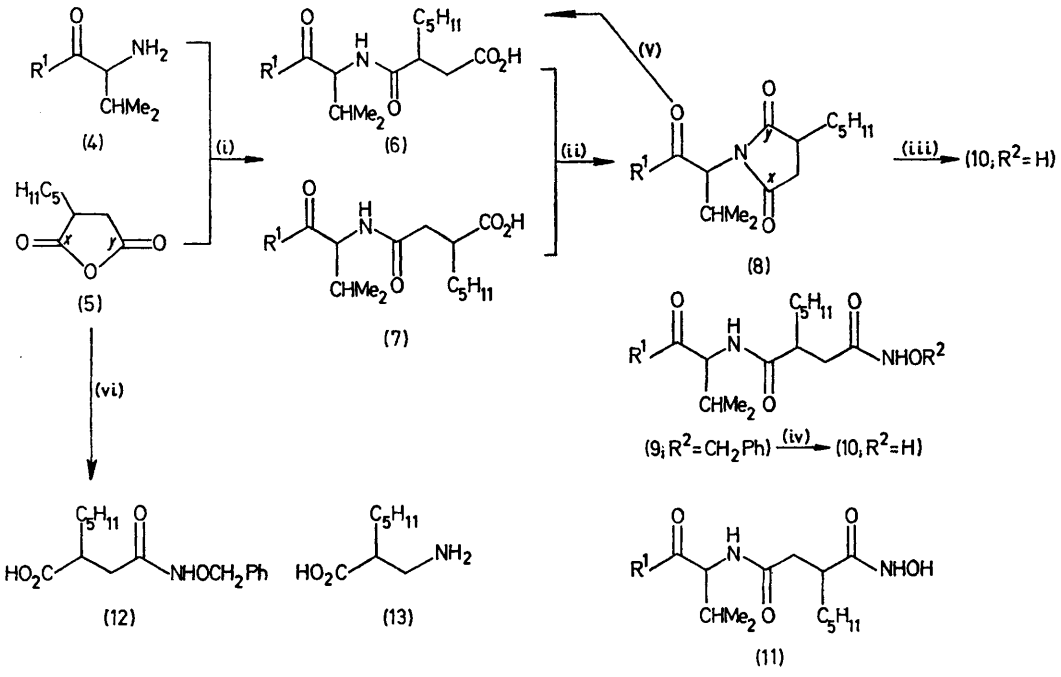
WE report stereoselective and regiospecific routes to analogues of the antibiotic, actinonin (**1**).[1] The general synthetic methods employed to prepare the structural analogues (**2**) and (**3**) in the morpholino- and pyrrolidino-series are summarised in the Scheme (routes i—vi).

DL-Valylmorpholine (**4a**) and pentylsuccinic anhydride (**5**) gave (i) a mixture of amido-acids (**6a**) and (**7a**) which was directly dehydrated (ii) giving *one* (±)-imide (**8a**), m.p. 79—81°. This (±)-imide (**8a**) gave (iii) *one* (±)-hydroxamic acid, m.p. 162—163°, which could have the constitution (**10a**) or (**11a**). The constitution (**10a**) was favoured because it was expected that reaction (iii) would involve a nucleophilic base-catalysed attack by the hydroxylamine upon the lesser hindered of the two carbonyl groups in the imide (**8a**; *x* less hindered than *y*). This opinion was shown to be well based because Lossen degradation of the (±)-hydroxamic acid, m.p. 162—163°, by treatment with methyl keten diethyl acetal[2] gave the corresponding isocyanate which by acid hydrolysis gave the β-amino acid (**13**).[1] This settled the regiospecificity of the transformation [(**8a**) $\xrightarrow{\text{(iii)}}$ (**10a**)], but it must be emphasised that the compounds (**8a**) and (**10a**) were both obtained as single racemates. This demonstrated that the sequence [(**4**) + (**5**) $\xrightarrow{\text{(i)}}$ (**6**) + (**7**) $\xrightarrow{\text{(ii)}}$ (**8**) $\xrightarrow{\text{(iii)}}$ (**10**)] was not only regiospecific but also remarkably stereospecific, but it did not establish whether the (±)-hydroxamic acid (**10**) had the relative configuration (**2**) or (**3**). However, the relative

configuration [(**2**) or (**3**)] of the (±)-hydroxamic acid (**10**) was established by repeating the synthesis starting with L-valylmorpholine (**14a**). This gave the single (−)-enantiomers (**8a**), m.p. 99—101°, and (**10a**), m.p. 134—135°, and mild acid hydrolysis of the latter gave L-valylmorpholine (**14a**) and (+)-D-pentylsuccinic acid (**15**).[3] This established the absolute configuration of the (−)-imide (**16a**) and the

$$(6) \xrightarrow{EtO_2CCl} \text{mixed anhydride} \xrightarrow{PhCH_2ONH_2\ (iv)} (9) \longrightarrow (10) \quad (1)$$

acid (**6b**), m.p. 135—136°, yielded a (±)-hydroxamic acid, m.p. 153—154°, of relative configuration (**2b**) previously established by the route (i) → (ii) → (iii). Similarly, the other (±)-carboxylic acid (**6b**), m.p. 153—154°, gave by the same sequence a (±)-hydroxamic acid (**10b**), m.p.

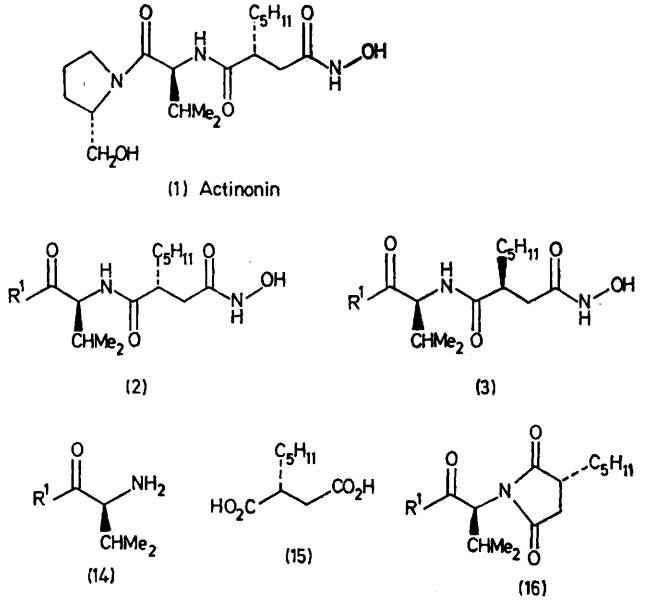


SCHEME. In formulae (**4**, **6**—**11**) (**a**; R¹=morpholino), (**b**; R¹ = pyrrolidin-1-yl).

Reagents and conditions: (i) boil in CH_2Cl_2; (ii) boil in acetyl chloride; (iii) methanolic alkaline hydroxylamine (room temperature); (iv) catalytic hydrogenation (methanol Pd–C); (v) aqueous ethanolic alkali (room temperature); (vi) *O*-benzylhydroxylamine in boiling CH_2Cl_2. Abbreviations (i—vi) are also used in the text.

(−)-hydroxamic acid (**2a**). It followed therefore that the (±)-imide (**8a**), m.p. 79—81°, and the (±)-hydroxamic acid (**10a**), m.p. 162—163°, obtained from racemic precursors (**4a**) and (**5**), had the relative configurations (**16a**) and (**2a**) respectively. Clearly the stereospecificity associated with this route had its origin in the stereospecific formation of one imide (**8**) ≡ (**16**) under equilibration conditions (ii) and the regiospecific ring cleavage (iii) of this imide giving *one* hydroxamic acid (**10**) ≡ (**2**). Thus, the synthetic route [Scheme: (i), (ii), and (iii)] leads stereospecifically to structural analogues of proven configuration (**2**) either as single racemates (relative configuration, **2**) from racemic aminoacylamides (**4**) or as single enantiomers (absolute configuration, **2**) from optically active L-aminoacylamides (absolute configuration, **14**). Identical regio- and stereo-specificities were also observed in the pyrrolidino-series (Scheme, b) for the reaction sequence (i, ii, and iii).

Alkaline hydrolysis (v) of the imides (**8**) resulted in equilibration of the (±)-imides (**8**) *at both chiral centres*. For example, either the racemic imide (**8b**) or the optically pure imide (**16b**) with alkali yielded an identical mixture of two diastereoisomeric racemates (**6b**), m.p. 135—136°, and 153—154°. The relative configurations of these racemic carboxylic acids (**6b**, m.p. 135—136°, and 153—154°) was firmly established by sequence (1). The (±)-carboxylic



In formulae (**2**), (**3**), (**14**), and (**16**), (**a**; R¹ = morpholino), (**b**; R¹ = pyrrolidin-1-yl).

159—160°, which must have the relative configuration (**3b**).

The route (i), (ii), and (iii) is regiospecific and stereospecific in that it leads only to structural analogues (**2**). The following alternative route is also regiospecific but has a useful complementary stereoselectivity in that it yields (**2**) as the minor product and (**3**) as the major product.

The regiospecific reaction (vi) between *O*-benzylhydroxylamine and the relatively less hindered carboxy-group (*y*) of the anhydride (**5**) yielded the amido-acid (**12**). This acid with ethyl chlorocarbonate gave a mixed anhydride, which was coupled with the amino-acylamide (**4**) giving, *via* the intermediate (**9**), the hydroxamic acid (**10**). Thus, DL-valylmorpholine (**4a**) and the acid (**12**) gave a mixture of diastereoisomeric racemates (**9a**) [m.p. 132—133° (minor product) and m.p. 167—168° (major product)] which were separated by fractional crystallisation. These *O*-benzyl compounds (**9a**) were separately converted (iv) into the corresponding (±)-hydroxamic acids (**10**); [(**9a**), m.p. 132—133° $\xrightarrow{\text{(iv)}}$ (**10a**), m.p. 162—163°] and [(**9a**), m.p. 167—168° $\xrightarrow{\text{(iv)}}$ (**10a**), m.p. 132—133°]. The constitution (**10a**) for both (±)-hydroxamic acids, m.p. 162—163°, and 132—133°, was firmly established by their Lossen degradation and acid hydrolysis yielding the β-amino-acid (**13**). Their relative configurations were established as follows. The (±)-hydroxamic acid (**10a**), m.p. 162—163°, had already been shown to have the relative configuration (**2a**); it follows that the (±)-hydroxamic acid (**10a**), m.p. 132—133°, has the other relative configuration (**3a**). Analogous results were obtained in the pyrrolidino-series for the route [(**4b**) + (**13**) → (**9b**) → (**10b**)] in which the major product had the configuration (**3b**) and the minor product (**2b**).

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[1] J. J. Gordon, B. K. Kelly, and G. A. Miller, *Nature*, 1962, **195**, 701; A. J. East, W. D. Ollis, and I. O. Sutherland in 'Chemistry of Microbial Products', Institute of Applied Microbiology Symposium No. 6, University of Tokyo, 1964, p. 204; N. H. Anderson, W. D. Ollis, J. E. Thorpe, and A. D. Ward, preceding communication.

[2] T. Mukaiyama, H. Nohira, and S. Asano, *Bull. Chem. Soc. Japan*, 1962, **35**, 71; H. Nohira, K. Inoue, H. Hattori, T. Okawa, and T. Makaiyama, *ibid.*, 1967, **40**, 664; S. M. McElvain and P. M. Walters, *J. Amer. Chem. Soc.*, 1940, **62**, 1482.

[3] A. Fredga, *Arkiv Kemi*, 1953, **6**, 277.