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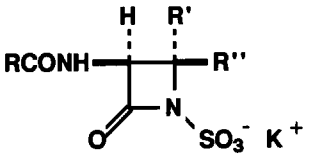
γ-LACTAM ANALOGUES OF MONOCYCLIC β-LACTAM ANTIBIOTICS

Maxwell J. Crossley,* Robyn L. Crumbie, Yik M. Fung, Jeffrey J. Potter
Department of Organic Chemistry, The University of Sydney, NSW 2006, Australia.

and Mary A. Pegler
Department of Infectious Diseases, The University of Sydney, NSW 2006, Australia.

Abstract: γ-Lactam analogues of monocyclic β-lactam antibiotics, the oxamazins, have been prepared from *N*-protected γ-nitro-α-amino acid esters. Unlike the oxamazins, these higher homologues are devoid of biological activity.

The recent discovery of the new class of bacterially produced monocyclic β-lactam antibiotics, the monobactams **1**,[1] has been accompanied by intense research into the synthesis and modification of this monocyclic system. As a consequence, a number of related compounds have also been prepared [tetrazolyl lactams **2a**,[2] monophosphams **2b**,[3] oxamazins **3a**,[4] monosulfactams **3b**[5]] and have been found to be



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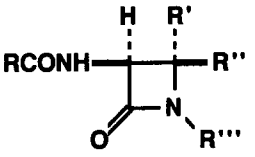

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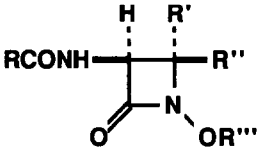
(a) R''' = tetrazol-5-yl
(b) R''' = PO(OAlkyl)O⁻ K⁺



3

(a) R''' = $CH_2CO_2^-$ K⁺
(b) R''' = SO_3^- K⁺

biologically active. The pronounced reactivity of the monobactam β-lactam system has been related to electron withdrawal from the lactam nitrogen by the sulfonate substituent.[6] However, structural features, and in particular the near planarity of the lactam nitrogen and the distance between the oxygen of the lactam group and the sulfur, are probably of greater importance.[7]

In order to investigate the effect that structural modification of the lactam nucleus has on the antibiotic properties of the monocyclic systems, the γ-lactam analogues, **12-17**, of the oxamazins were prepared. The rationale behind this work will be discussed in greater detail in a subsequent paper. However, it should be noted that, very recently, certain γ-lactam analogues of the bicyclic penems[8] and carbapenems[9] have been found to exhibit low levels of antibiotic activity, that several bicyclic pyrazolidinones exhibit broad spectrum antibiotic activity,[10] and that a naturally-occurring cycloserine derivative has been found to possess good antibiotic properties and to bind at the same site as penicillins.[11]

Conjugate addition of nitroalkanes to *N*-protected dehydroalaninates has provided a convenient route for the preparation of *N*-protected γ-nitro-α-amino acid esters, which are useful precursors to a number of synthetically desirable acyclic and cyclic compounds.[12] Two synthetic approaches to the desired *N*-alkoxy-γ-lactams, **12-17**, from such nitro compounds were investigated (Scheme 1).

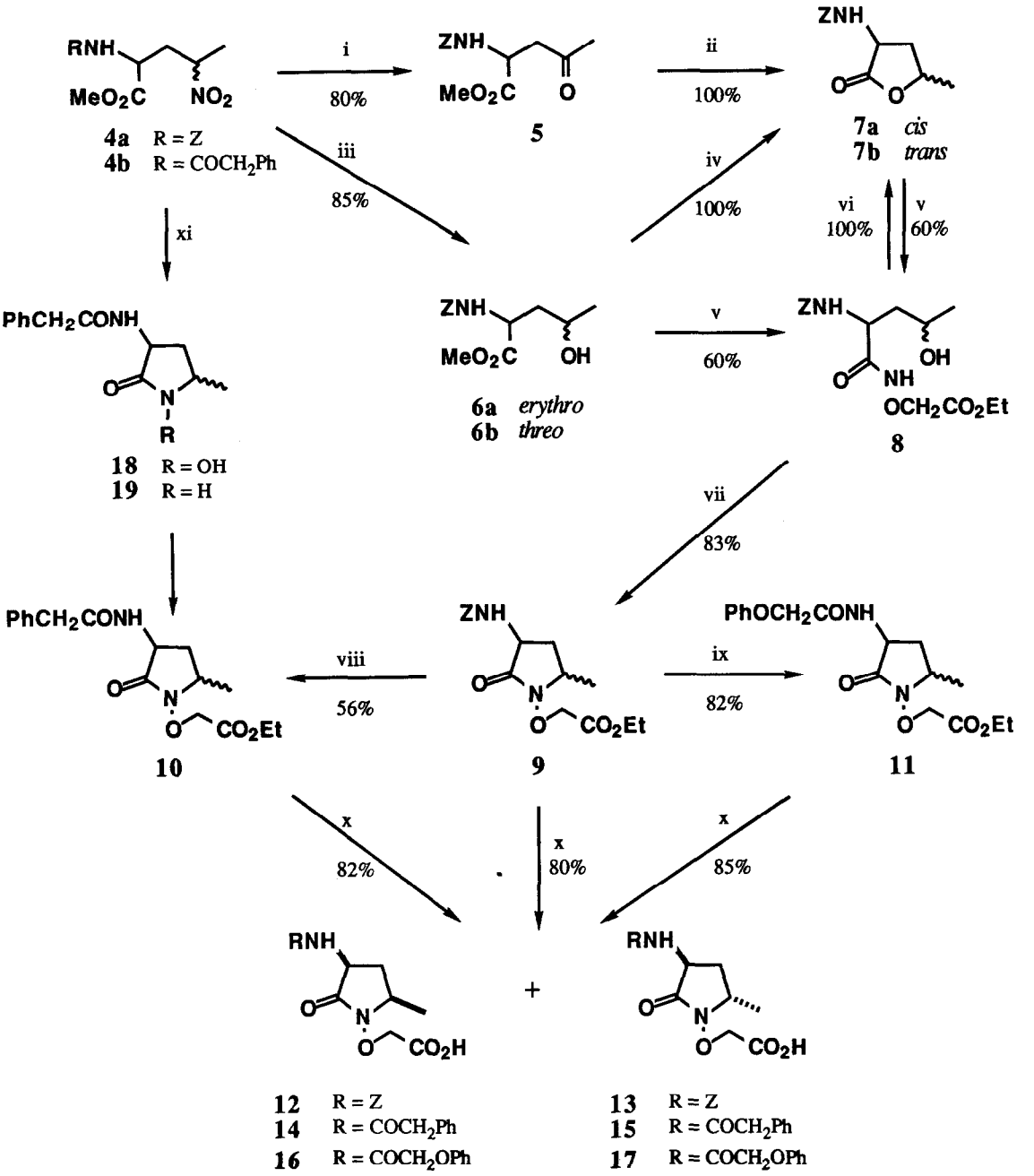
The first approach involved initial transformation of the *N*-protected γ-nitro-α-amino acid ester **4a** directly to the γ-hydroxylated products **6**, or to the corresponding γ-butyrolactones **7** via the γ-oxo intermediate **5**, depending on the experimental conditions employed. Direct hydroxaminolysis of the esters **6** or the lactones **7**, followed by *in situ* alkylation of the hydroxamate anion intermediates with ethyl bromoacetate, gave the *O*-alkyl hydroxamates **8** in moderate yield. Intramolecular cyclization of the hydroxamates **8**, on treatment with triphenylphosphine, carbon tetrachloride and triethylamine in acetonitrile, afforded the *N*-alkoxy-γ-lactams **9** in good yield. The 3-amino substituent on **9** was modified under hydrogenolysis conditions (Pd/C, H_2), in the presence of phenylacetic anhydride, to give the corresponding 3-phenylacetamido γ-lactams **10**, and in the presence of phenoxyacetic anhydride to give the corresponding 3-phenoxyacetamido-γ-lactams **11**. Deprotection of the carboxylic acid ester of the lactams **9** by hydrolysis (LiOH/THF/H_2O) then afforded the desired monocyclic γ-lactams **12** and **13**. Similar deprotection of **10** and **11** gave the γ-lactams **14** and **15**, and **16** and **17**, respectively. In each case, the two diastereomers were separated by HPLC.[13]

Separation of diastereomers was also possible at several other stages of these sequences but was most readily achieved at the stage of the esters **6**, which were easily separable by flash chromatography. The *erythro*- and the *threo*-diastereomers, **6a** and **6b**,[14] were taken separately through this route in similar yields to reactions on the diastereomeric mixture. In this way, the *erythro*-isomer **6a** was converted to the *cis*-isomer **14**, and the *threo*-isomer **6b** was converted into the *trans*-isomer **15**, without any epimerization being observed in any of the steps. The acids **12-17** were converted to the corresponding potassium salts by ion-exchange chromatography (Dowex 50W - K^+ form) for testing of antibacterial activity.

The second approach involved a more direct route to the γ-lactam system. Partial reduction by exchange hydrogenation (Pd/C, NH_4^+ HCO_2^-) of methyl 2-phenylacetamido-4-nitropentanoates **4b** gave the hydroxylamine intermediates which cyclized under the reaction conditions to the very labile cyclic hydroxamic acids **18** in 12% isolated yield. The major products in this reaction were the analogous lactams **19** which were isolated in 60% yield. The conversion of these lactams into monophospham and monocarbam[15] analogues will be described separately.[16] Attempts to improve the yield of cyclic hydroxamic acid by the use of controlled-potential electrochemical reduction, by the use of other chemical reductants, or to convert it directly to the ester **10** *in situ*, were not encouraging.

The biological activity of the monocyclic β-lactam antibiotics has, at least, been partially related to substituents on the ring periphery and on the amino functionality. The synthetic routes outlined above for the preparation of the γ-lactam analogues allow introduction of the amido-substituent (R) either in the earlier stages of the synthesis as the protecting group of the dehydroalaninate, or in the final stages after removal of the benzyloxycarbonyl protecting group. The substitution on the 5-position of the lactam ring (R' and R") is likewise easily adaptable by use of the relevant nitroalkane in the conjugate addition to dehydroalaninate in the initial preparation of the γ-nitro precursor. These modifications and their significance in the monocyclic γ-lactam systems will be elaborated in subsequent publications.

Compounds **12-18** (all as K^+ salts) were tested against a range of Gram positive and Gram negative bacteria and showed no significant antibacterial activity.[17]



Z = CO_2CH_2Ph

Scheme 1

Reagents and conditions: (i) a. Triton B/MeOH, b. O_3, -78°, c. Me_2S; (ii) $NaBH_4$/MeOH, -20°; (iii) a. Triton B/MeOH, b. O_3, -78°, c. $NaBH_4$, 4°, d. HCl/MeOH, -78°; (iv) standing on SiO_2; (v) a. $NH_2OH.HCl$/KOH (2 equiv)/EtOH, 4°, 0.75 h, b. $BrCH_2CO_2Et$/KI, 2.5 h; (vi) aq. Na_2CO_3 or warming to 50°; (vii) $PPh_3/CCl_4/Et_3N$/MeCN, 25°, 1.5 h; (viii) Pd-C/H_2/$(PhCH_2CO)_2O$/DME, 2 h; (ix) Pd-C/H_2/$(PhOCH_2CO)_2O$/DME, 2 h; (x) LiOH/THF/H_2O, 4°, 0.5 h; (xi) Pd-C/NH_4^+ HCO_2^-/MeOH.

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13. Each of these acids is racemic; for convenience of presentation, only one of the enantiomers is drawn in Scheme 1.

14. The assignment of the structures of the diastereomers **6a** and **6b** was based on analysis of the ^{1}H NMR data of the resultant *cis*- and *trans*-lactones **7a** and **7b**, respectively, obtained by silica-catalysed cyclization. The stereochemistry of 2-amido-4-substituted-γ-butyrolactones can be unequivocally assigned on the basis of the chemical shifts of the geminal protons, H-3 and H-3', on the lactone ring (Altman, J.; Gilboa, H.; Ben-Ishai, D. *Tetrahedron* 1977, **33**, 3173). Thus the *cis*-lactone **7a** [δ ($CDCl_3$) 1.79 and 2.87] has a stable conformation in which the 2- and 4-substituents are in *quasi*-equatorial positions, whereas the *trans*-lactone **7b** (δ 2.33 and 2.47) is conformationally mobile.

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17. With the exception of the unstable hydroxamic acid **18**, all new compounds have been adequately characterized by analytical or high-resolution mass spectral means, and all compounds show satisfactory spectral data.

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