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SYNTHESIS AND STEREOCHEMISTRY OF CHIRAL AZETIDIN-2-ONES AND AZETIDINE-2-THIONES. 3.* STEREODIRECTED CONSTRUCTION OF THE β-LACTAM FRAGMENT OF THE THIENAMYCIN MOLECULE

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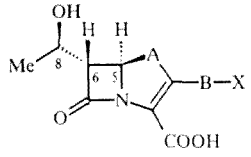
It has been shown possible to introduce an α-hydroxyethyl group trans-stereospecifically into position 3' of 4-methyl-1-(α-methyl-benzyl)azetidin-2-one. The stereochemistry of the asymmetric centers $C_{(3')}$, $C_{(3)}$, and $C_{(4)}$ of the diastereoisomers of the 3-α-hydroxyethyl derivative obtained in larger amount and of the corresponding three adjacent chiral centers $C_{(8)}$, $C_{(6)}$, and $C_{(5)}$ in thienamycin are the same.

Almost twenty years have passed since the discovery of thienamycin (I), which unlike penicillins and cephalosporins has an α-hydroxyethyl group in position 3 of the β-lactam in place of the customary amide group and an unusual trans configuration of the substituents in the β-lactam ring. It also is a β-lactamase inhibitor and displays the broadest spectrum of antimicrobial activity. No competitor to thienamycin with its exceptional biological action has yet appeared in the literature among the β-lactam antibiotic of the penem and carbapenem series.



(8*R*, 6*S*, 5*R*)-Ia, b

I a A = CH_2, B = S carbapenems, X = $(CH_2)_2$–NH_2 thienamycin,
b A = S, B = CH_2, penems

One of the most widespread strategies in thienamycin synthesis is the stereocontrolled preparation of 3,4-trans-3-(α-hydroxyethyl)azetidin-2-one, with the same stereochemistry of the three adjacent chiral centers $C_{(3')}$, $C_{(3)}$, and $C_{(4)}$ as in thienamycin, and the subsequent construction of a carbapenem ring system from it. For this purpose it is necessary that the substituent at atom $C_{(4)}$ may be readily transformed into an acyloxy group and the substituent at the nitrogen atom removed under mild conditions. Several methods exist for the synthesis of 3,4-trans-(3S, 3'R)-diastereoisomers of various 3-(α-hydroxyethyl)azetidin-2-ones based on the use of starting materials of optically pure natural products. These include 6-aminopenicillanic acid [2, 3], L-threonine [4], L-aspartic acid [5], aminosugars [6] and the commercially available (Fluka) (R)-(+)- or (S)-(−)-β-hydroxybutyric acid ethyl esters [7].

However the α-hydroxyethylation of 1,4-disubstituted azetidin-2-ones by a trans stereospecific method is still the most important reaction in the synthesis of thienamycin and of carbapenem antibiotics related to it. The diastereoselectivity of this reaction is determined by the nature of both substituents of the β-lactam ring [8, 9].

*For part 2 see [1].

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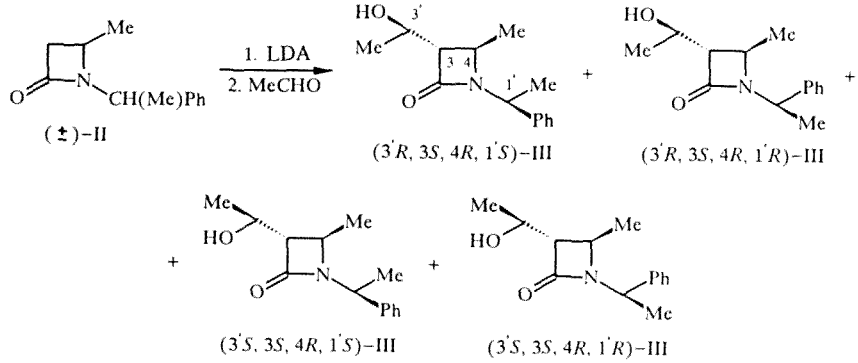
The reaction of lithium derivatives of 4-substituted azetidin-2-ones with acetaldehyde proceeds with high 3,4-trans-stereoselectivity, reaching 76-100% [10-17]. In conjunction with the formation of a new chiral center at $C_{(3')}$ during the α-hydroxyethylation of azetidin-2-ones the ratio of diastereometers varies from 1:1 [10] to 4:1 [13].

It was noted above that the choice of protecting group plays a significant role when developing routes for the synthesis of thienamycin and its analogs from 4-substituted azetidin-2-ones. For example, in the case of the trialkylsilyl group the trans-stereoselectivity is not maximal (85%), and the ratio of diastereomers relative to the three chiral centers is 46:37 [14]. Dialkyl-aminomethyl is another good protecting group leading to trans-stereospecificity but with a 1:1 ratio of diastereomers [10]. The best ratio of diastereomers of 4:1 was detected on hydroxyethylation of 1,4-diarylazetidin-2-ones [13].

Previously we obtained the (1'S, 4S) and (1'S,4R) diastereomers of 4-methyl-1-(α-methylbenzyl)azetidin-2-one (II) [18] by the cyclization of the (3'S,3S) and (3'S,3R) diastereomers respectively of β-aminobutyric acid [17]. Their absolute configuration was proved and their chiroptical properties studied in [1]. It was shown that the joint action of the two inducing centers $C_{(1')}$ and $C_{(4)}$ provided complete trans-stereospecificity in the methylation of both (1'S,4S) and (1'S,4R) diastereomers of the azetidinone (II). We also showed that the substituent at the nitrogen atom is readily removed by sodium in liquid ammonia without affecting the asymmetric centers at $C_{(3)}$ and $C_{(4)}$ [18, 19]. It therefore seemed expedient to study the stereochemistry of the α-hydroxyethylation of 4-methyl-1-(α-methylbenzyl)-azetidin-2-one (II) and the possibility of constructing the β-lactam substructure of thienamycin (I).

We isolated 3,4-trans-3-(α-hydroxyethyl)-4-methyl-1(α-methylbenzyl)azetidin-2-one (III) by chromatography in 48% yield from the reaction of excess acetaldehyde and the lithium derivative of the azetidin-2-one (±)-(II). The composition and structure of (III) were confirmed by elemental analysis and data of mass spectrometry. The compound obtained was a mixture of four diastereomeric racemates in the ratio 3:3:1:1* according to PMR data (Bruker WM 400):



The size of the vicinal constant $^3J_{34}$ for all four isomers at 2.2 Hz indicates the trans orientation of the substituents. Therefore on reacting the lithium derivative of azetidin-2-one (II) with acetaldehyde the stereospecific formation of the α-hydroxyethyl derivative of (III) with 3,4-trans geometry only is observed, with a predominance of two of the four possible 3,4-trans diastereomeric racemates. A significant enrichment of the mixture of diastereomeric racemates was successfully achieved with the aid of repeated column chromatography to a ratio of 16:16:1:1. In the PMR spectrum there were signals (doublets of quadruplets) for the 4-H protons of the two diastereomeric racemates formed in larger amount (3.55 and 3.63), and quadruplets corresponding to the 3'-H proton of the same diastereomers (4.14 and 4.07 ppm), which appeared at lower field than the signals of the same protons of the two minor diastereomeric racemates (at 3.29 and 3.38 ppm, and 4.02 and 3.94 ppm respectively).

Since the signals of the 5-H and 8-H protons of (8R)-thienamycin (4-H and 3'-H respectively for azetidin-2-one) are also found at lower field than for the (8S) diastereomers [13, 20] then the spatial structure of the two predominantly formed diastereomeric racemates of azetidinone (III) obtained by us corresponds, according to PMR spectral data, to the (8R, 6S, 5R) stereochemistry of the β-lactam fragment of natural thienamycin (I) and corresponds to a (3'R, 3S, 4R, 1'S) and (3'R, 3S, 4R, 1'R) configuration of the β-lactam ring.

The route proposed to azetidinone (III), which is the β-lactam base of thienamycin and related carbapenem and penem antibiotics, using substances commercially available α-methylbenzylamine as a chiral source and trans-crotonic acid) [9], is

*Each of the diastereomeric racemates is represented by one of its enantiomeric forms for simplicity.

therefore preferable to existing routes in view of its simplicity, the availability of starting materials, and the diversity of the synthetic possibilities.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in films, and UV spectra were taken with a Varian Cary 15 instrument. The PMR spectra were taken in deuterochloroform on a Bruker WM 400 spectrometer at room temperature with TMS as internal standard.

3,4-trans-3-(α-Hydroxyethyl)-4-methyl-1-(α-methylbenzyl)azetidin-2-one (III). The (+)-azetidinone (II) (2.72 mmole) in THF (5 ml) was added dropwise with stirring in an argon atmosphere at −78°C to lithium diisopropylamide (2.72 mmole) obtained from diisopropylamine (2.72 mmole) in THF (4 ml) and a 2N hexane solution of butyllithium (1.3 ml: 2.72 mmole). After 30 min, acetaldehyde (1 ml: 6 mmole) was added dropwise, and the mixture stirred at −78°C for 45 min. The reaction mixture was neutralized with glacial acetic acid to pH 5-6 and evaporated in vacuum. The residue was washed with water and extracted with ethyl acetate. The solution was dried over magnesium sulfate. After removal of the solvent the residue was chromatographed on a column (Kieselgel 100, product No. 10184 Merck, hexane−ethyl acetate, 1:1). The initial azetidinone (II) (0.168 g: 25%) was obtained together with a mixture of four diastereomeric racemates of azetidinone (III), in a ratio of 3:3:1:1. IR spectrum 1735, (C=O), 3430 cm^{-1} (O−H); UV spectrum (hexane), λ_{max} (ε): 255 (150). The PMR spectrum of the two diastereomeric racemates obtained in larger amount: 1.07 and 1.20 (3H, d, 4-CH_3); 1.25 (3H, d, 1′-CH_3), 1.60 and 1.69 (3H, d, 3′-CH_3); 2.66 (1H, m, 3-H); 2.81 (1H, br s, OH); 3.55 and 3.63 (1H, d, q, 4-H); 4.07 and 4.14 (1H, q, 3′-H); 4.65 and 4.92 (1H, q, 1′-H); 7.25-7.36 ppm (5H, m, C_6H_5). The PMR spectrum of the two minor diastereomeric racemates: 1.07 and 1.19 (3H, d, 4-CH_3); 1.20 (3H, d, 1′-CH_3); 1.61 and 1.69 (3H, d, 3′-CH_3); 2.66 (1H, m, 3-H); 2.81 (1H, br s, O−H); 3.29 and 3.38 (1H, d g, 4-H); 3.94 and 4.02 (1H, q, 3′-H); 4.64 and 4.93 (1H, q, 1′-H); 7.25-7.36 ppm (5H, m, C_6H_5).

After repeated chromatographic resolution of the mixture obtained (100 mg) on a column of the same support and elution with chloroform a mixture (33.8 mg) of the diastereomeric racemates of (III) was separated with a ratio of 16:16:1:1 according to PMR spectra.

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