ALTERNATIVE SYNTHESES OF AZEPINOMYCIN

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Abstract—Three alternative syntheses of the antibiotic azepinomycin (XI) have now become feasible through a route starting from the monocycles Va—c and proceeding through the intermediates VIa—c, VIIa—c, VIIIa—c, IXa—c, and XIla,b and 3-β-D-ribofuranosylazepinomycin (XIIc). The permutation IXa→Xa→XI was also found to be feasible. The starting materials Va—c were readily prepared from Ila—c through IIIa—c and IVa—c.

Azepinomycin (XI) is an antitumor antibiotic and guanine deaminase inhibitor isolated from the culture filtrate of Streptomyces sp. MP718-03. The recent communication by Ishiki et al. of the synthesis of this compound and its 3-β-D-ribofuranoside (XIIc) starting from 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxamide prompts us to record our own results obtained from three alternative synthetic approaches to XI. These approaches feature the use of 1-substituted N'-alkoxy-5-formamidomidazole-4-carboxamidines (type V), the ring-opened intermediate^5^ in the Dimroth rear-arrangement of 9-substituted 1-alkoxyadenines (type IV), as the starting materials by taking advantage of the "fission and reclosure" technology developed in our laboratory for modification of the adenine ring (I).

The first synthetic route started with the benzyl analogue Va (mp 132.5–133°C), which was prepared from adenine (1) through Ila, IIla, and IVa according to the previously reported procedure. In reaching the key intermediate IXa from Va, we took advantage of the methodology utilized by us for the syntheses of 3,9-disubstituted purines and 1-substituted 5-aminoimidazole-4-carboxamides and -4-carboxamides. Thus, alkylation of Va with 1,1-diehxy-2-iodoethane (HCONMe2, K2CO3/18-crown-6, 30°C, 21 h) gave Via in 93% yield. On treatment with boiling 1 N aqueous NaOH for 3 h, Via furnished the deformylated product VIIa (mp 74.5–75.5°C) in 94% yield. Conversion of VIIa into IXa (45% yield; mp 128–128.5°C) was effected by deethoxylation (Raney Ni/H2, H2O/HCl (1 equiv.), 1 atm, room temp., 6 h) and subsequent hydrolysis (boiling 1 N aq. NaOH, 4 h) of the resulting amidine VIIIa. The carboxamide IXa was then debenzylated (10% Pd-C/H2, MeOH, 1 atm, 50°C, 5 h) to yield X.
Scheme 1
and decacetilation and cyclization of X with 1 N aqueous HCl (room temp., 5 h) afforded the desired compound XI [mp 208-220°C (dec.); lit.² mp 230-235°C (dec.)] in 70% overall yield (from IXa). The UV (H₂O or 0.05 N aq. HCl), IR (KBr), and ¹H nmr (D₂O + DCl) spectra of the synthetic XI matched those of natural azepinomycin. In the permutation IXa→XIIa→XI, cyclization of IXa was carried out in 1 N aqueous HCl (room temp., 30 min), and the resulting bicyclic compound XIIa [mp 185-200°C (dec.)] was debenzyalted (10% Pd-C/H₂, MeOH, 1 atm, 50°C, 10 h) to provide XI in 46% yield. In a second version of the total synthesis, we employed the methoxymethyl analogues (series b) instead of the benzyl analogues (series a), as shown in Scheme 1. Treatment of adenine (I) with chloromethyl methyl ether in the presence of K₂CO₃ (AcNMe₂, room temp., 1.5 h) furnished the 9-(methoxymethyl) derivative IIb (39%; mp 202-203°C), which was oxidized with m-chloroperbenzoic acid (MeOH, room temp., 6 h) to give the N-oxide IIIb [77%; mp 264-265°C (dec.)]. Benzoylation of IIIb with benzyl bromide (AcNMe₂, room temp., 16 h) produced, after treatment of the primary product (IVb: X = Br in place of ClO₄⁻) with NaClO₄ in H₂O, the 1-benzyloxy derivative IVb (mp 171.5-172.5°C) in 97% yield. Ring opening of IVb in H₂O at pH 9.2 and 40°C for 5 h gave the monocycle Vb (90%; mp 114.5-115.5°C). The steps beyond Vb were parallel to those described above for series a: Vb→VIb (30°C, 27 h; 74% yield; mp 73.5-74°C)→VIIb·HCl (95%; mp 117.5-118°C)→VIIIb→IXb [57% (from VIIb·HCl); mp 158.5-159.5°C]→XIIb (room temp., 1 h; 97%; mp 165-167°C (dec.)]. Finally, removal of the methoxymethyl group in XIIb was effected in boiling 5% aqueous H₃PO₄ for 10 h, producing XI in 20% yield.

In a third version of the synthesis, we followed the steps included in series c in Scheme 1. The starting material Vc¹³ was prepared from adenosine (IIc) through IIIC¹⁴ and IVc⁷ according to our previous procedure, and the steps succeeding thereafter were parallel to those described above for series b: Vc→Vlc (room temp., 93 h)→VIIc [room temp., 2 h; 40% (from Vc)]→VIIIc→IXc [reflux, 30 min; 63% (from VIIc)]→XIIc (room temp., 30 min; 94%)→XI (95°C, 10 h;² 48%). The 3-riboside XIIc, isolated as a gum and presumed to be a diastereomeric mixture due to the newly formed asymmetric center at C(6), was identical (by comparison of the UV, IR, and ¹H nmr spectra and tlc mobility) with a sample synthesized by Ishihiki et al.²

The above results not only establish three new synthetic routes to azepinomycin (XI) but also demonstrate the synthetic utility of our "fission and reclosure" technology for modification of the adenine ring. Of the newly developed three versions of the synthesis, the one using the benzyl analogues (series a) seems to be superior to the other two with regard to simplicity in operation and the overall yield of XI. It also seems not more laborious than the recently reported one,² subject to the immediate availability of the starting monocycle Vc in sufficient quantity.

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REFERENCES


8. Our previous communication5 has not described the reaction conditions for the last step, but they were as follows: A solution of the free base of IVa in 20% (v/v) aqueous EtOH was stirred at 40°C for 42 h to give Va in 82% yield.


11. The assigned structures of all new compounds were supported by elemental analyses and/or satisfactory spectral data.

12. The elemental analysis pointed to the formula C₈₇₁₂N₄O₃·1/₃H₂O.


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