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ALTERNATIVE SYNTHESES OF AZEPINOMYCIN

Tozo Fujii,* Tohru Saito, and Tetsunori Fujisawa

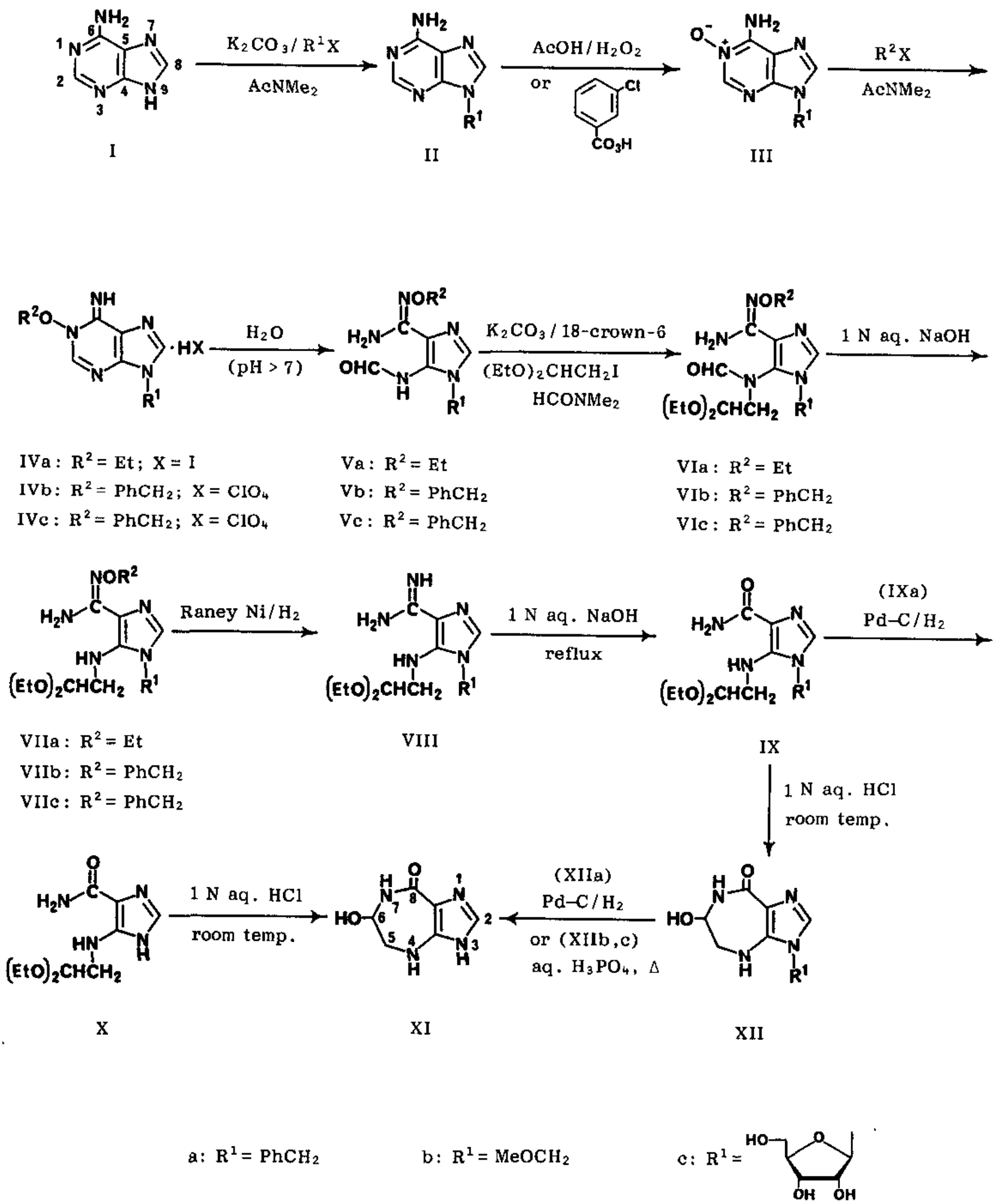
Faculty of Pharmaceutical Sciences, Kanazawa University,

Takara-machi, Kanazawa 920, Japan

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 XIIa,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 IIa–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. MF718-03.[1] The recent communication by Isshiki et al.[2] 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-formamidoimidazole-4-carboxamidines (type V), the ring-opened intermediates[3,4] in the Dimroth rearrangement of 9-substituted 1-alkoxyadenines (type IV), as the starting materials by taking advantage of the "fission and reclosure" technology[4] developed in our laboratory for modification of the adenine ring (I).

The first synthetic route started with the benzyl analogue Va[5](mp 132.5–133°C), which was prepared from adenine (I) through IIa,[6] IIIa,[7] and IVa[7] according to the previously reported procedure. In reaching the key intermediate IXa from Va, we took advantage of the methodology[4,5,9] utilized by us for the syntheses of 3,9-disubstituted purines and 1-substituted 5-aminoimidazole-4-carboxamidines and -4-carboxamides. Thus, alkylation of Va with 1,1-diethoxy-2-iodoethane[10] ($HCONMe_2$, K_2CO_3/18-crown-6, 30°C, 21 h) gave VIa[11] 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/H_2, H_2O/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/H_2, MeOH, 1 atm, 50°C, 5 h) to yield X,


I
II
III
K_2CO_3 / R^1X
$AcNMe_2$
$AcOH/H_2O_2$
or
R^2X
$AcNMe_2$
H_2O
(pH > 7)
K_2CO_3 / 18-crown-6
$(EtO)_2CHCH_2I$
$HCONMe_2$
1 N aq. NaOH
IVa : R^2 = Et; X = I
IVb : R^2 = $PhCH_2$; X = ClO_4
IVc : R^2 = $PhCH_2$; X = ClO_4
Va : R^2 = Et
Vb : R^2 = $PhCH_2$
Vc : R^2 = $PhCH_2$
VIa : R^2 = Et
VIb : R^2 = $PhCH_2$
VIc : R^2 = $PhCH_2$
Raney Ni/H_2
1 N aq. NaOH
reflux
(IXa)
Pd–C/H_2
VIIa : R^2 = Et
VIIb : R^2 = $PhCH_2$
VIIc : R^2 = $PhCH_2$
VIII
IX
1 N aq. HCl
room temp.
1 N aq. HCl
room temp.
(XIIa)
Pd–C/H_2
or (XIIb,c)
aq. H_3PO_4, Δ
X
XI
XII
a: R^1 = $PhCH_2$
b: R^1 = $MeOCH_2$
c: R^1 =

Scheme 1

and deacetalization 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 (H_2O or 0.05 N aq. HCl), ir (KBr), and ^1H nmr (D_2O + 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 [92%; mp 185–200°C (dec.)] was debenzylated (10% Pd–C/H_2, 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 K_2CO_3 ($AcNMe_2$, 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.)]. Benzylation of IIIb with benzyl bromide ($AcNMe_2$, room temp., 16 h) produced, after treatment of the primary product (IVb: X = Br in place of ClO_4) with $NaClO_4$ in H_2O, the 1-benzyloxy derivative IVb (mp 171.5–172.5°C) in 97% yield. Ring opening of IVb in H_2O 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.)[12]]. Finally, removal of the methoxymethyl group in XIIb was effected in boiling 5% aqueous H_3PO_4 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 Vc[13] was prepared from adenosine (IIc) through IIIc[14] and IVc[7] according to our previous procedure, and the steps succeeding thereafter were parallel to those described above for series b: Vc→VIc (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 Isshiki 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[4] 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 Va in sufficient quantity.

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