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CHEMICAL MODIFICATIONS OF KANAMYCIN A
SYNTHESIS OF 4"-DEOXY AND 4"-EPI-HALOGENODEOXY KANAMYCIN A*

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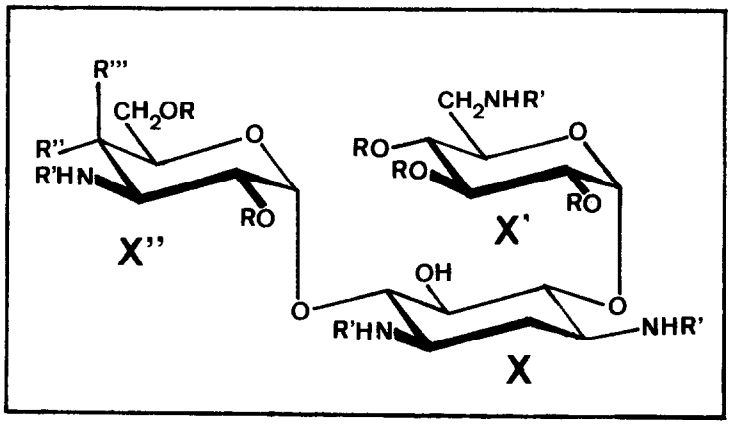
Abstract: Stereospecific direct replacement with inversion of configuration of 4"-OH by halogen in kanamycin A. Hydrogenolysis.

Chemical modifications[1] in kanamycin A (1) have hitherto primarily focussed on the 6-aminodeoxy-D-glucose (X') part, found to be the predominant site of enzymatic deactivation. Except for the transformations at 6", alterations in the kanosamine (X") part are rather rare.[2,3]



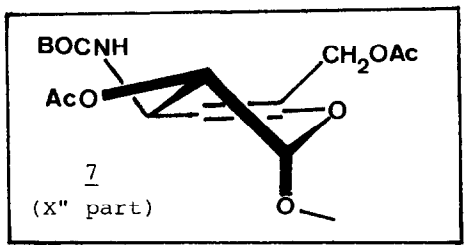
1: R=R'=R'''=H; R"=OH
2: R=Ac; R'=BOC; R"=OH; R'''=H
3: R=Ac; R'=BOC; R"=H; R'''=Cl
4: R=Ac; R'=BOC; R"=H; R'''=Br
5: R=Ac; R'=BOC; R"=H; R'''=I
6: R=Ac; R'=BOC; R"=R'''=H
8: R=R'=R"=H; R'''=Cl
9: R=R'=R"=H; R'''=Br
10: R=R'=R"=H; R'''=I
11: R=R'=R"=R'''=H

We recently described[4], inter alia, a very effective preparation of 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-kanamycin A (2) by O-4"⟶-6" acetyl migration. Reaction of 2 with

a) triphenylphosphane / carbon tetrachloride[5] yielded 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-4"-epi-chloro-4"-deoxy-kanamycin A (3) [m.p. 150-155°(dec.), $[\alpha]_D^{20}$ +93° (c=1, $CHCl_3$), R_f^6 0.70] in 86%.
b) triphenylphosphane dibromide[7] formed 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-4"-epi-bromo-4"-deoxy-kanamycin A (4) [m.p. 140-145° (dec.), $[\alpha]_D^{20}$ +88° (c=1.4, $CHCl_3$), R_f^6 0.70] in 82% yield.
c) triphenyl phosphite / methyl iodide[8] afforded 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-4"-deoxy-4"-epi-iodo-kanamycin A (5) [m.p. 145-147°(dec.), $[\alpha]_D^{20}$ +90° (c=2.4, $CHCl_3$), R_f^6 0.70] in 85% yield.

The synthesis of the corresponding fluoro derivative, obtained by a completely independent approach, will be published in a different context.

Hydrogenolysis of 5 in absol. ethanol employing Raney nickel (FLUKA 83440) in the presence of equimolar amounts of triethyl amine gave 95% of 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-4"-deoxy-kanamycin A (6) [m.p. 145-150°(dec.), $[\alpha]_D^{20}$ +75°(c=1, $CHCl_3$), R_f^6 0.55]. Attempts to use 3, 4 or 5 as substrates for displacement reactions with a variety of nucleophiles in order to obtain 4"-modified kanamycins, invariably resulted in elimination with quantitative formation of 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-4"-deoxy-4"-eno-kanamycin A (7) [m.p. 130-135°, $[\alpha]_D^{20}$ +100°(c=3, $CHCl_3$), R_f^6 0.56, ^{13}C-NMR: C-4" 99.3, C-5"152.4].



7
(X" part)

Compounds 3, 4, 5, and 6 were subjected to Zemplén de-O-acetylation followed by treatment with trifluoroacetic acid to give the deprotected kanamycin A derivatives, which were purified by gradient elution with ammonia from Amberlite CG 50 [NH_4^+]:

4"-epi-chloro-4"-deoxy-kanamycin A (8), $[\alpha]_D^{20}$ +149° (c=3, H_2O), R_f^9 0.70; ^{13}C-NMR[10]: C-3" 53.8 (54.4), C-4" 64.0 (60.8).

4"-epi-bromo-4"-deoxy-kanamycin A (9), $[\alpha]_D^{20}$ +137° (c=1, H_2O), R_f^9 0.70; ^{13}C-NMR[10]: C-3" 53.6 (54.2), C-4" 62.7 (54.2).

4"-epi-iodo-4"-deoxy-kanamycin A (10), $[\alpha]_D^{20}$ +107° (c=1, H_2O), R_f^9 0.70; ^{13}C-NMR[10]: C-3" 53.6 (54.2), C-4" 47.0 (34.9).

4"-deoxy-kanamycin A (11), $[\alpha]_D^{20}$ +133° (c=1, H_2O), R_f^9 0.58; ^{13}C-NMR[10]: C-3" 50.4 (51.4), C-4" 39.9 (32.4).

Compared to kanamycin A, all compounds described exhibit a reduced antibiotic activity.

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Notes and references:

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1 J. Reden and W. Dürckheimer, Top. Curr. Chem., 83, 138 (1979) and references cited therein.

2 S. Inouye, Chem. Pharm. Bull., 15, 1888 (1967).

3 T. Miyasaka, D. Ikeda, S. Kondo, and H. Umezawa, J. Antibiot., 33, 527 (1980).

4 R. Albert, K. Dax, A. E. Stütz, and H. Weidmann, J. Carbohydr. Chem., in press.

5 R. Appel and H.-D. Wihler, Chem. Ber., 109, 3446 (1976).

6 Merck 5554, toluene/ethyl acetate 1:2 (v/v); starting material 2: R_f 0.52.

7 L. Horner, H. Oediger, and H. Hoffmann, Liebig's Ann. Chem., 626, 26 (1959).

8 N. K. Kochetkov and A. I. Usov, Tetrahedron, 973 (1963).

9 Merck 5554, $CHCl_3/CH_3OH/NH_4OH$(25%) 1:2:2 (v/v/v); kanamycin A (1): R_f 0.51.

10 Bruker WH 90; D_2O; shifts after acidification (pD <2) with DCl in parantheses; kanamycin A (1): C-3" 57.2 (58.0), C-4" 72.3 (68.7).

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