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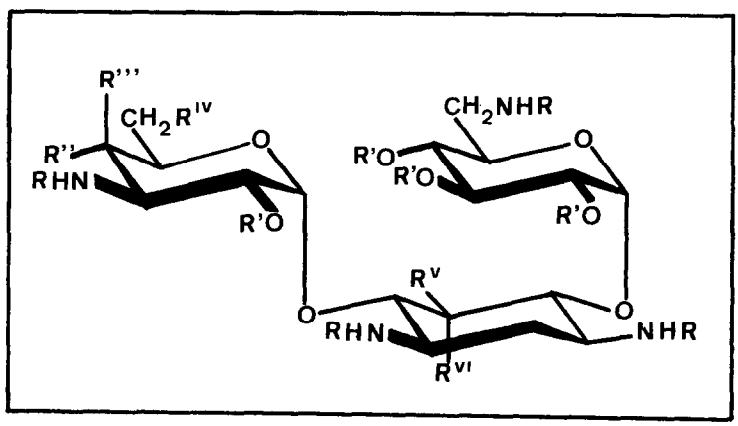
SYNTHESIS OF FLUORINATED KANAMYCIN A DERIVATIVES

R. Albert, K. Dax+, and A.E. Stütz
Institute of Organic Chemistry, Technical University Graz, A-8010 Graz, Austria

Abstract: Replacement of OH-5 and/or OH-6" by fluoride in kanamycin A; no substitution of OH-4" but inversion of configuration when using DAST.

Regio- and stereospecific fluorination of polyfunctional molecules has recently become attractive by introduction of new fluorinating reagents.[1] For our program on chemical modification of aminoglycoside antibiotics this advancement became of special interest, since substitution of hydroxyl group in position 4" by fluoride in kanamycin A [2] only slightly reduced the antibacterial activity whereas the basicity of the amino group at C-3" was lowered considerably.[3]

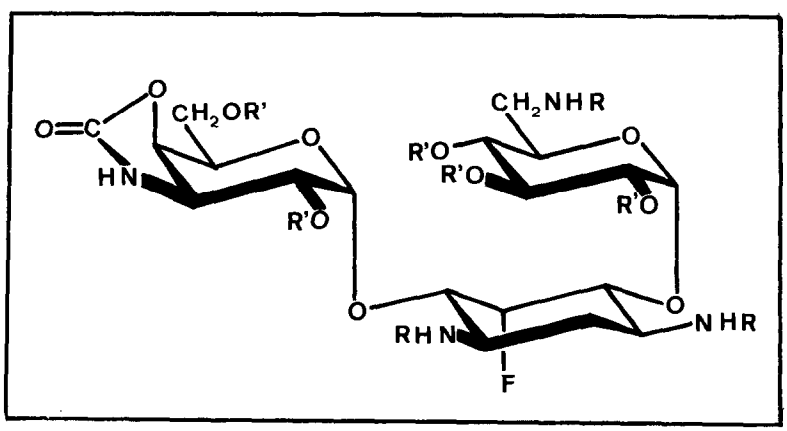


1: R = BOC; R' = Ac; R" = OAc; $R^{III} = R^{VI}$ = H; $R^{IV} = R^{V}$ = OH
2: R = BOC; R' = Ac; R" = OAc; $R^{III} = R^{VI}$ = H; R^{IV} = F; R^{V} = OH
3: R = BOC; R' = Ac; R" = OAc; $R^{III} = R^{V}$ = H; $R^{IV} = R^{VI}$ = F
4: R = BOC; R' = Ac; R" = R^{V} = OH; $R^{III} = R^{VI}$ = H; R^{IV} = OAc
5: R = BOC; R' = Ac; R" = R^{V} = H; R^{III} = OH; R^{IV} = OAc; R^{VI} = F

7: R = R' = $R^{III} = R^{VI}$ = H; R" = R^{V} = OH; R^{IV} = F
8: R = R' = $R^{III} = R^{V}$ = H; R" = OH; $R^{IV} = R^{VI}$ = F
9: R = R' = R" = R^{V} = H; $R^{III} = R^{IV}$ = OH; R^{VI} = F

Starting from 2',3',4',2",4"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-kanamycin A [4] (1) the corresponding 6"-triflate was prepared; its reaction with dry tetrabutylammonium fluoride in acetonitrile at ambient temperature gave 2',3',4',2",4"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-6"-deoxy-6"-fluoro-kanamycin A (2) [m.p. 155-158°, $[\alpha]_D^{20}$ +82° (c=1, $CHCl_3$), R_f^5 0.70] in 76% yield. Treatment of 1 with diethylaminosulfur trifluoride (DAST)[6] in dichloromethane at -70° in 79% yield gave 2',3',4',2",4"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-5,6"-dideoxy-5,6"-difluoro-5-epi-kanamycin A (3) [m.p. 170° (dec.), $[\alpha]_D^{20}$ +91° (c=1.2, $CHCl_3$), R_f^5 0.65] involving position 5 as expected according to the synthesis of 5-deoxy-5-fluoro-5-epi-kanamycin A.[7]

Reaction of 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl kanamycin A [4] (4) under the same conditions did not lead to 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-5,4"-dideoxy-5,4"-difluoro-5,4"-di-epi-kanamycin A, but resulted in the formation of 2',3',4',2",6"-penta-O-acetyl-tetra-N-tert.-butyloxycarbonyl-5-deoxy-5-fluoro-5,4"-di-epi-kanamycin A (5) [m.p. 158-160°, $[\alpha]_D^{20}$ +73° (c=1.9, $CHCl_3$), R_f^5 0.46] together with 2',3',4',2",6"-penta-O-acetyl-1,3,6'-tri-N-tert.-butyloxycarbonyl-3"-N,4"-O-carbonyl-5-deoxy-5-fluoro-5,4"-di-epi-kanamycin A (6) [m.p. 165-171°, $[\alpha]_D^{20}$ +85° (c=1.4, $CHCl_3$), R_f^5 0.19]. In this reaction the intermediate (R_f^5 0.70; type 4"-O-SF_2NEt_2[6]) obviously is rather subject to intramolecular attack of the tert.-butyloxycarbonyl group at 3"-N (forming 6) than to substitution by external fluoride. Considering a time-dependency of the product ratio (68/24 after 3 h and 42/51 after 24 h, resp.), compound 5 is unambigueously generated from the same intermediate during aqueous work-up.



6: R = BOC; R' = Ac

10: R = R' = H

Zemplén de-O-acetylation of 2, 3, 5, and 6, resp., followed by treatment with trifluoroacetic acid gave the deprotected kanamycin A derivatives, which were purified by chromatography on Amberlite CG 50 [NH_4^+]:

6"-deoxy-6"-fluoro-kanamycin A (7), $[\alpha]_D^{20}$ +122° (c=1.3, H_2O), R_f[8] 0.70; ^{13}C-NMR[9]: C-3" 56.0 [56.0]; C-4" 70.0 (7.4 Hz) [65.9 (7.4 Hz)]; C-5" [72.6 (17.7 Hz)]; C-6" 84.0 (170.9 Hz) [83.3 (169.2 Hz)].

5,6"-dideoxy-5,6"-difluoro-5-epi-kanamycin A (8), $[\alpha]_D^{20}$ +123° (c=0.9, H_2O), R_f[8] 0.56; ^{13}C-NMR[9]: C-1 49.0 (2.9 Hz) [48.9 (4.4 Hz)]; C-2 37.3 [29.2]; C-3 48.1 (2.9 Hz) [48.3 (4.4 Hz)]; C-4 80.0 (17.65 Hz) [74.5 (17.65 Hz)]; C-5 90.3 (192.7 Hz) [88.2 (185.3 Hz)]; C-6 85.7 (17.65 Hz) [79.9 (17.65 Hz)]; C-3" 55.8 [56.5]; C-4" 70.4 (7.35 Hz) [66.4 (7.35 Hz)]; C-6" 84.5 (164.7 Hz) [83.6 (167.7 Hz)].

5-deoxy-5-fluoro-5,4"-di-epi-kanamycin A (9), $[\alpha]_D^{20}$ +125° (c=2, H_2O), R_f[8] 0.51; ^{13}C-NMR[9]: C-1 48.6 (4.41 Hz); C-2 36.6; C-3 47.8 (2.94 Hz); C-4 78.8 (17.65 Hz); C-5 90.1 (178.0 Hz); C-6 85.1 (17.65 Hz); C-3" 52.3; C-4" 70.8; C-6" 62.8. This compound can also be obtained by hydrazinolysis of compound 6.

3"-N,4"-O-carbonyl-5-deoxy-5-fluoro-5,4"-di-epi-kanamycin A (10), $[\alpha]_D^{20}$ +89° (c=1.2, H_2O), R_f[8] 0.54; ^{13}C-NMR[9]: C-1 48.4 (4.37 Hz); C-2 36.8; C-3 47.8 (2.94 Hz); C-4 78.9 (17.65 Hz); C-5 90.0 (178.0 Hz); C-6 85.3 (17.65 Hz); C-3" 54.7; C-4" 69.4; C-6" 61.6; C=O 162.4.

Except 10, these compounds show antibacterial activity comparable to that of kanamycin A.[10] Preparation of derivatives fluorinated at other positions, i.a. those involved in predominant enzymatic deactivation mechanisms, will be published in a different context.

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Notes and references:

1 A.A.E. Penglis, Advan. Carbohydr. Chem. Biochem., 38, 195 (1981) and references cited therein.

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

3 H. Loibner and G. Schulz, Sandoz Forschungsinstitut, Vienna, on the basis of the protonation induced shift for the signals of carbons in ß-position to amino groups [S. Omoto, S. Inouye, M. Kojima, and T. Niida, J. Antibiot., 26, 717 (1973)], determined the pK_b-values for the 3"-amino group in kanamycin A and 4"-deoxy-4"-fluoro-4"-epi-kanamycin A, resp., as follows: A solution of kanamycin A sulfate and 4"-deoxy-4"-fluoro-4"-epi-kanamycin A sulfate, resp., in D_2O was titrated with NaOD and, within the range of pH 6 to pH 10 in inter-

vals of 0.3 pH units, ^{13}C-NMR spectra were recorded; from the pH-dependency of the C-2" chemical shift, i.e. point of inflection of the titration curve [R.J. Cookson, Chem. Rev., 74, 5 (1974)], the pK_b-values were calculated to be 8.3 for the 3"-amino group in kanamycin A and 7.4 for that in the 4"-epi-fluoride, resp.

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

5 Merck 5554, toluene/ethyl acetate 1:2 (v/v).

6 W.J. Middleton, J. Org. Chem., 40, 574 (1975).

7 P.J.L. Daniels and D.F. Rane, S. Afr. Pat., 78 06,385 (1978); Chem. Abstr., 90, 104 301 (1979).

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

9 Bruker WH 90; D_2O, dioxane as internal standard; C-F couplings in parantheses; shifts and couplings after acidification (pD $\lesssim$2) with DCl in square brackets; kanamycin A: C-3" 55.5 [56.3]; C-4" 70.6 [67.0]; 4"-epi-kanamycin A [4]: C-3" 52.4 [53.2]; C-4" 70.2 [66.7].

10 We thank J. Hildebrandt, Sandoz Forschungsinstitut, Vienna, for the evaluation of the in vitro data.

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