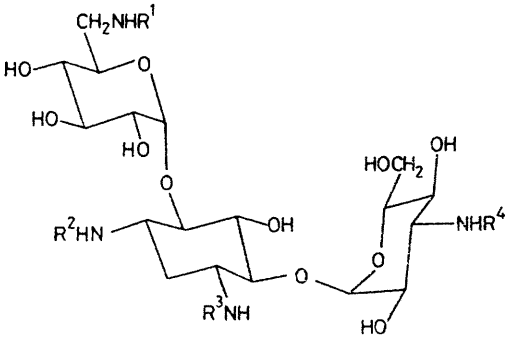
Selective *N*-Acylation of Kanamycin A

By MARTIN J. CRON, JOHN G. KEIL, JENG-SHYONG LIN, MARIO V. RUGGERI, and DEREK WALKER
(*Bristol-Myers Industrial Division, P.O. Box* 657, *Syracuse, New York* 13201)

Summary The *N*-acylation of partially trimethylsilylated kanamycin A in acetone has been found to proceed selectively at the 1-N position rather than the usual 6′-N position.

SELECTIVE chemical modification of aminoglycosides has been hampered by difficulties in separating the activities of the functional groups; thus, direct acylation of kanamycin A yields a mixture of *N*-acylated products, the major component of which is (Ia).[1] We here report a novel procedure for the selective *N*-acylation of kanamycin A to give primarily (Ic).



(Ia) R^1 = $COCH(OH)[CH_2]_2NH_2$, R^2 = R^3 = R^4 = H
(Ib) R^1 = R^3 = R^4 = H, R^2 = $COCH(OH)[CH_2]_2NH_2$
(Ic) R^1 = R^2 = R^4 = H, R^3 = $COCH(OH)[CH_2]_2NH_2$
(Id) R^1 = R^2 = R^3 = H, R^4 = $COCH(OH)[CH_2]_2NH_2$

When kanamycin A free base (10 g, 0·0206 mol) containing 1% kanamycin A sulphate was refluxed in acetonitrile (100 ml) with hexamethyldisilazane (HMDS; 7 mol. equiv.) for 5 h, two clear liquid phases were produced. Removal of the acetonitrile and excess of HMDS *in vacuo* gave polytrimethylsilylated kanamycin A as a clear liquid, which was acylated in two ways.

Firstly, a solution of the polytrimethylsilylated kanamycin A in acetone (10% w/v) was treated with 1 mol. equiv. of *N*-[(2*S*)-4-benzyloxycarbonylamino-2-hydroxybutanoyloxy]succinimide (BHBA active ester) at 5 °C for 1 h and the mixture was hydrolysed with water at pH 2·5, hydrogenolysed, and chromatographed. The principal product was (Ia) (*ca.* 50%); smaller amounts of (Ib) (*ca.* 5%), (Ic) (*ca.* 5%), and polyacylated kanamycin A (*ca.* 20%) were also obtained, but (Id) was not detected. About 20% of kanamycin A was recovered.†

Secondly, the polytrimethylsilylated kanamycin A in acetone was first stirred, *in vacuo* or under nitrogen, with 10 mol. equiv. of water at 5 °C for 30 min, and the resulting solution was acylated and worked up as in the first experiment. In this case the major product isolated was (Ic) (50%). Small amounts of (Ia) (6%), (Ib) (12%), polyacylated kanamycin A (8%), and unchanged kanamycin A (22%) were obtained. Again (Id) was not detected.

These results indicate that the acylating agent is guided to attack the 1-N position only when the polytrimethylsilylated kanamycin A molecule is partially hydrolysed. As far as we are aware this is the first instance of acylation selectivity occurring as a consequence of appropriately placed trimethylsilyl groups. No 3″-*N*-acylation occurs,

† A control experiment in which kanamycin A base was acylated with BHBA active ester in 50% aq. tetrahydrofuran gave a similar result, except that (Id) was also produced; yields were (Ia) 45—55%, (Ib) 5—10%, (Ic) *ca.* 5%, (Id) *ca.* 5%, polyacylated kanamycin A 15—20%, and unchanged kanamycin A 10—15%.

presumably because of the bulky flanking $SiMe_3$ groups. The relative inaccessibility of the 6′-N position to electrophilic attack is more difficult to explain, though models indicate that when the 4′-hydroxy group is trimethylsilylated, the 6′-NH_2 group can be shielded by appropriate folding of the sugar rings.

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[1] T Naito, S. Nakagawa, Y. Abe, S. Toda, K. Fujisawa, T. Miyaki, H. Koshiyama, H. Ohkuma, and H. Kawaguchi, *J. Antibiotics* 1973, **26**, 297.