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Studies on the Structure of Kanamycin, an Antibiotic, and Syntheses of the Related Substances

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This studies concern with the structure determination of kanamycin, an antibiotic, and the syntheses of derivatives and analouges of kanamycin.

The results of the investigations are summarized as follows.

1) The hydrolysis of exhaustively methylated N-acetyl kanamycin was undertaken in order to determine the site of glycosidic linkages occuring between the three constituents of kanamycin; namely, deoxystreptamine, 3-amino-3-deoxy-D-glucose and 6-amino-6-deoxy-D-glucose.

The hydrolyzates of tetra-N-acetyl-hepta-0-methyl-kanamycin were treated by a chromatography with a cellulose powder column to yield the crystalline hydrochroride (I) of mono-0-methyl-deoxystreptamine.

This hydrochloride (I) was a key substance for the structure proof of kanamycin and has been proved to be 5-0-methyl-deoxy-streptamine by the fact that this substance and its *N*-diacetyl derivative showed no optical rotation and by the data of the periodate oxidation of these compounds.

The above mentioned evidence, therefore, has led the author to conclude that the both amino sugars are directly joined deoxy-streptamine through its 4-and 6-hydroxyl groups by glucosidic linkages and the structure of kanamycin was established as 0-α-6-amino-6-deoxy-D-glucopyranosyl-(1→4 or 6)-0-[α-3-amino-3-deoxy-D-gluco-pyranosyl (1→6 or 4)]-1, 3-diamino-1, 2, 3-trideoxy-*myo*-inositol.

2) Subsequently, 3-acetamido-3-deoxy-2, 4, 6-tri-0-methyl-α-D-glucose (II) and 6-amino-6-deoxy-2, 3, 4-tri-0-methyl-α-D-glucose (III) have been isolated from the hydrolyzate of exhaustively methlated N-acetyl kanamycin.

Thus, the structure of amino sugar moieties of kanamycin were confirmed by the direct comparison of (II) and (III) with the authentic specimens, which have been prepared from D-glucose.

3) The structural modification of kanamycin was undertaken to find some derivatives with lower toxicity and with similar or higher activities.

Among the derivatives synthesized, some kinds of N-methanesulfonate of kanamycin, such as tetrasodium-kanamycin-tetra-N-methansulfonate and disodium-kanamycin-di-N-methanesulfonate, were found to have toxicity about twenty times lower than kanamycin monosulfate, retaining the antibacterial activities.

4) In addition, the analogous derivatives of neomycin (fradiomycin), the structure

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of which is closely related to kanamycin, were prepared and it was found that hexasodium-neomycin-hexa-N-methanesulfonate retains the antibacterial activities and has about eighty times lower toxicity than the original antibiotic.

5) Recently, it has been suggested that the presence of the amino-glucosyl deoxystreptamine moiety seems to be essential for the antibiotic activity as shown in kanamycin, neomycin and paromomycin.

Therefore, an attempt was made to synthesize some analouges of kanamycin and other glucosides related to kanamycin.

As major intermadiates for the syntheses of amino-sugar glucosides, 2, 4, 6-tri-0-acetyl-α-1-bromo-3-carbobenzoxyamino-1, 3-dideoxy-D-glucopyranose and 2, 3, 4-tri-0-acetyl-α-1-bromo-6-carbobenzoxyamino-1, 6-dideoxy-D-glucopyranose were synthesized.

6) On the other hand, N, N-dicarbobenzoxy-deoxystreptamine was synthesized.

This was, then, condensed with acetobromoglucose in nitromethane in the presence of mercuric cyanide as a catalyst.

Deacetylation of the product gave 4, 6-di-(D-glucopyranosyi)-deoxystreptamine.

Applying the above synthetic condition, N, N-dicarbobenzoxy-deoxystreptamine was caused to react with the above mentioned 2, 4, 6-tri-0-acetyl-α-1-bromo-3-carbobenzoxyamino-1, 3-dideoxy-D-glucopyranose to give 4, 6-di-(3-amino-3-deoxy-D-glucopyranosyl)-deoxystreptamine.

The structure determination of these glucosides revealed that in these compounds the sugar moieties are joined to deoxystreptamine through its 4- and 6-hydroxyl groups by glucosidic linkages in a similar mannar to kanamycin.