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Author	竜田, 邦明(Tatsuta, Kuniaki)
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Studies on the Syntheses and Stereochemistry of Aminosugars

Kuniaki TATSUTA (竜 田 邦 明)

The chemistry of aminosugars has extensively been developed in recent years. Many aminosugars have been found as the constituents of useful antibiotics, nucleotides of bacteria and lipo- and muco-polysaccharides.

In the configurational studies of aminosugars, the author keenly felt the need of a direct method serviceable for the elucidation of the absolute structures of a variety of aminosugar glycosides and attempted to study systematically the rotational shift of aminosugars in three kinds of cuprammonium solutions. The author found a copper complex method which provided a tool for the revelation of the spacial relationships between amino and hydroxyl groups on adjacent carbon atoms in a six-membered chair molecule, and obtained some significant generalizations. The generalizations were successfully applied to the determination of the absolute structure of kanamycin, a useful antibiotic.

On the other hand, the author synthesized some antibiotics, namely neamine, trehalosamine, etc. which contain aminosugars in their molecules, and some new aminosugar derivatives conducive to the conformational studies of aminoglycoside antibiotics.

Outlines and the results of the present studies are summarized as follows.

1) The optical rotatory behavior of glucopyranosides in a cuprammonium solution (Cupra B) was explained by Reeves by means of conformational considerations. However, as the findings of Reeves are concerned with the spacial relationships only between two hydroxyl groups on adjacent carbon atoms, they are not directly applicable to the elucidation of the spacial relationships between an amino and a hydroxyl groups on adjacent carbon atoms of aminosugars in which amino groups are not protected.

The present investigation was undertaken to find a practical method for the determination of the configurational relationships between adjacent amino and hydroxyl groups in a six-membered chair molecule.

Optical rotatory studies have been carried out with a series of aminoglycoside derivatives and aminocyclitols in a tetraamminecopper (II) sulfate solution (TACu), a solution of cuprous chloride in concentrated aqueous ammonia (CuAm), and the Cupra B solution.

The results obtained by experiments on a number of substances of known configurations have led to the following generalizations:

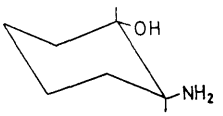
(i) In the case of a substance with a six-membered chair form, a pair of

adjacent amino (or methylamino) and hydroxyl groups in the molecule can form a copper complex when dissolved in TACu, and if the pair is located sterically so as to give near the $\pm 60°$ Newman-projected angle, the difference in the molecular rotations of the substance in TACu and in water, $\Delta[M]_{TACu}$, is approximately ± 1000, respectively. The sign of $\Delta[M]_{TACu}$ is in accord with the sign conventionally expected from the projected angle made by adjacent amino and hydroxyl groups in question.

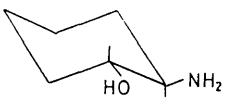
(ii) Both CuAm and Cupra B show significant $\Delta[M]_{CuAm}$ and $\Delta[M]_{Cupra\ B}$ values both in cases of compounds which have a pair of adjacent amino and hydroxyl groups and in cases of compounds which have a pair of adjacent hydroxyl groups. However, the magnitudes of the $\Delta[M]$ values in the former cases are about a half of those in the latter cases.

(iii) In compounds with pairs both of adjecent amino and hydroxyl groups and of adjacent hydroxyl groups, TACu shows $\Delta[M]$ values exclusively corresponding to the pair of the former groups, while CuAm and Cupra B show $\Delta[M]$ value exclusively corresponding to the pair of the latter groups.

The above-mentioned generalizations were then successfully applied to an elucidation of the absolute configurations of *d*- and *l-trans*-2-aminocyclohexanol which have been determined to be (1s : 2s)-2-aminocyclohexanol (I) and (1R : 2R)-2-aminocyclohexanol (II) respectively.



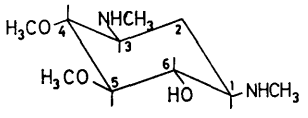
(I)



(II)

2) Moreover, the absolute structure of kanamycin was determined by the above-mentioned generalization as follows.

N, N′-dimethyl-di-O-methyldeoxystreptamine (III) has been prepared from kana-



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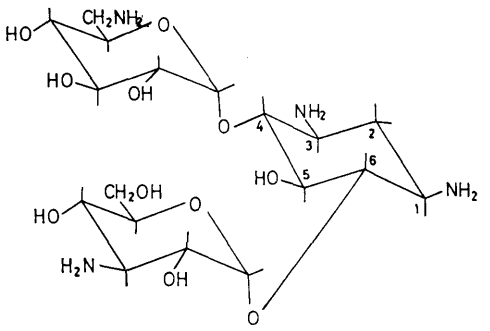


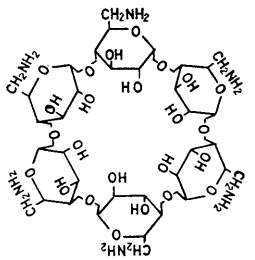
Kanamycin (IV)

mycin (IV) through the hydrolysis of the totally-methylated product of O-(3-acetamido-3-deoxy-α-D-glucopyranosyl)-N, N′-diacetyldeoxystreptamine. The three kinds of $\Delta[M]$ values for III measured in TACu, CuAm and Cupra B were all approximately+1100. These results, when subjected to the generalization described above, led to the conclusion that the projected angle between adjacent methylamino and hydroxyl groups is about +60° in the molecule of III, that is, that III is N, N′-dimethyl-4, 5-di-O-methyl-2-deoxystreptamine; thus, kanamycin is deduced to be 4-O-(6-amino-6-deoxy-α-D-glucopyranosyl)-6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine.

3) There are a number of antibiotics which contain aminosugars with the α-anomeric configuration in their molecules, for example, streptomycins, neomycins, kanamycins, gentamicin and kasugamycin, suggesting that the α-glycosidic linkage is essential for the exhibition of antibacterial activity.

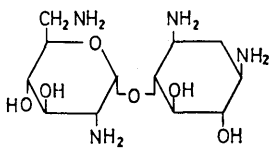
The author utilized some natural oligosaccharides with the α-anomeric configuration, namely, maltose, sucrose, trehalose, raffinose and Schardinger α-dextrin, in order to synthesize aminooligosaccharides for the investigation of the relationship between the structural and antibiotic characteristics of aminoglycosides.

The primary and anomeric hydroxyl groups of those oligosaccharides have preferentially been replaced by amino groups to give the corresponding amino derivatives in considerable yields. It has been found that the amino derivative (V) of Schardinger α-dextrin showed a significant antitumor activity.



(V)

4) Neamine (VI), an antibiotic aminoglycoside, has been synthesized likewise from paromamine. The absolute structure of the synthetic product and its identity with the natural neamine were confirmed by the above-mentioned copper complex method. Since the synthesis of paromamine has already been established (S. Umezawa et al.,

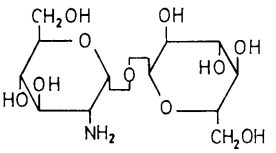


(VI)

1966), the synthesis is the first total synthesis of neamine.

Furthermore, a structural isomer of neamine, namely 6-O-(3, 6-diamino-3, 6-dideoxy-α-D-glucopyranosyl)-deoxystreptamine, was synthesized from 6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-deoxystreptamine which was obtained from kanamycin by partial hydrolysis.

5) An antibiotic trehalosamine (VII) has been synthesized by the condensation of 2, 3, 4, 6-tetra-O-benzyl-α-D-glucopyranose with 3, 4, 6-tri-O-acetyl-N-(4-methoxybenzylidene)-α-D-glucosaminyl bromide by a modified Koenigs-Knorr reaction. The synthetic trehalosamine completely inhibited the growth of *Mycobacterium tuberculosis* 607 at a dilution of 2 mcg/ml.



(VII)

6) As an approach to the total synthesis of kanamycin, 6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine (3 AD) which is a glycosidic component of kanamycin has been synthesized. Amino and hydroxyl groups of 2-deoxystreptamine were masked with carbobenzoxy and isopropylidene groups to give a racemic mono-O-isopropylidene-di-N, N′-carbobenzoxy-2-deoxystreptamine. The product was then condensed with 3-acetamido-2, 4, 6-tri-O-benzyl-3-deoxy-α-D-glucopyranosyl chloride by a modified Koenigs-Knorr reaction to give the desired glycoside. The absolute structure of the synthetic 3 AD was confirmed by the aboved-mentioned copper complex method. This product, 3 AD, is the key intermediate for the synthesis of kanamycin.