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Synthesis and Configurational Analysis of Aminocyclitols

Seiichiro OGAWA (小川 誠 一 郎)

This thesis is concerned with the new synthesis of aminocyclitols starting from readily accessible *myo*-inositol and the configurational studies using proton magnetic resonance (PMR) spectroscopy.

In general, amino derivative of inositol is called aminocyclitol. The discovery that aminocyclitols are component parts of the molecules of important antibiotics, such as streptomycin, neomycin, kanamycin etc., stimulated to study these substances intensively. In order to find the relationships between chemical structures and antibiotic activities, and new antibiotic substances, synthetic studies on aminocyclitols have been carried out by many workers. Especially, mono and diamino derivatives of inositols, inosamines and inosadiazines, compose the structural units of several antibiotics and attract much interest in synthetic and biological fields.

Though inosamines and inosadiazines have many stereoisomers, using the nucleophilic displacement reactions of the sulfonyl derivatives of inositols with azide ion, hydrazine etc., followed by hydrogenation, the author succeeded to prepare the aminocyclitols which had the specific configuration selectively in a comparatively good yield.

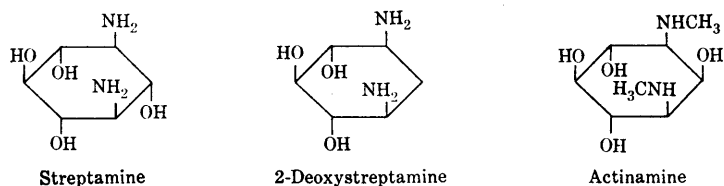
First, as a model compound, all three diastereomers of 2-amino-1,3-cyclohexanediol were synthesized from 2-nitro-1,3-cyclohexanediol obtained by base-catalyzed cyclization reaction of glutaraldehyde and nitromethane. On treatment with azide ion and reduction, the sulfonyl derivatives of 2-amino-1,3-cyclohexanediol gave two isomers of 2,3-diaminocyclohexanol.

Then *myo*-inositol was chosen as a starting material of the inosamine-synthesis. The unimolar sulfonylation of 1,4,5,6-tetra-O-acetyl-*myo*-inositol afforded 3-O-mesyl derivative preferentially. When excess reagent was used, 2,3-di-O-mesyl derivative was obtained in a good yield. Therefore it was found that, in cyclitols as well as in sugars, equatorial hydroxy group is more reactive for sulfonylating and acylating reagents than axial one. 3-O-Mesyl derivative was treated with sodium azide in 2-methoxyethanol and subsequent reduction of azido compound, followed by acetylation, gave hexaacetyl-*muco*-inosamine-1 selectively in 32% yield. On similar treatment of di-mesyl derivative, hexaacetyl-*muco*-inosadiazine-1, 5 (7.6%) was obtained as a sole product. In both cases, an anchimeric reaction mechanism could be proposed. On the other hand, dimethylformamide was used as a solvent instead of 2-methoxyethanol, hexaacetyl-*myo*-inosadiazine-1, 2 (6.4%) was obtained from the latter. In this case, azide ions might be considered to replace the sul-

fonyloxy groups in the direct S_N2 mechanism, owing to the increasing of the nucleoflicity of azide ion in dipolar aprotic solvent.

Following the procedure as described above, from sulfonyl derivatives of *epi*-inositol which was readily obtainable from *myo*-inositol, two new inosamines and one inosadiazine were synthesized: *epi*-inosamine-1 and -6, and *myo*-inosadiazine-4,6. From *muco*-inositol, two inosadiazines were prepared: *muco*-inosadiazine-3,6 and *myo*-inosamine-4,6 as a minor product. From 1,3-di-O-tosyl-*myo*-inositol, *muco*-inosadiazine-1,4 was obtained.

scyllo-Inosadiazine-1, 3 (streptomycin) was isolated from streptomycin. Another antibiotics, neomycin, paromomycin and kanamycin contained 2-deoxystreptomycin and actinospectacin had N, N'-dimethyl derivative of *myo*-inosadiazine-1, 3 (actinamine). The author could succeed to synthesize those naturally occurring aminocyclitols starting from inosadiazines or azido compounds obtained from sulfonyl derivatives of inositols in a comparatively good yield.



myo-Inosadiazine-4, 6 was converted into di-N-acetyl derivative, which was expected to be oxidized at C-2 selectively, since there was only one axial hydroxy group on C-2. Therefore, this compound was oxidized in the presence of platinum catalyst in a stream of oxygen. Then the ketone so obtained was reduced by sodium amalgam in an acidic solution. The reduction product was acetylated to afford hexaacetyl streptomine in 12.5% yield.

By the partially de-O-acetylation of tetraacetyl 4,6-diazido-4,6-dideoxy-*myo*-inositol which was prepared from 1, 6-di-O-mesyl-*epi*-inositol, 5-O-acetyl-4, 6-diazido-4,6-dideoxy-*myo*-inositol was obtained in 95% yield. Since there were two equatorial hydroxy groups and one axial one in this compound, a selective benzylation of equatorial hydroxy groups must be possible. When this compound was allowed to react with two moles of benzoyl chloride in pyridine at 0°C, 1, 3-di-O-benzoyl derivative was obtained in 84% yield. On mesylation, 5-O-acetyl-4, 6-diazido-1,3-di-O-benzoyl-2-O-mesyl-*myo*-inositol was obtained in 83% yield. From this compound, hexaacetyl-streptomine was prepared by treatment with acetate ion (37%), followed by hydrogenation and acetylation (80%), and hexaacetyl-*scyllo*-inosatriamine-1, 3, 5 was also obtained by azidation.

Furthermore, on selective benzylation and mesylation, 4, 6-diazido-4, 6-dideoxy-*myo*-inositol yielded 4, 6-diazido-1, 3-di-O-benzoyl-4, 6-dideoxy-2, 5-di-O-mesyl-*myo*-

inositol in 40% yield. The displacement of sulfonyloxy groups by acetate ions in 2-methoxyethanol occurred in the direct S_N2 mechanism to give tetraacetyl-1,3-diazido-1,3-dideoxy-*myo*-inositol in 17% yield. A catalytic hydrogenation of this compound, followed by acetylation, gave hexaacetyl-*myo*-inosadiazine-1,3 in 72% yield. Then hexaacetyl derivative was converted into dihydrochloride by acid hydrolysis and treated with ethyl chloroformate in an alkaline solution. Tetraacetyl-N,N'-di-ethoxycarbonyl-*myo*-inosadiazine-1,3 was isolated by acetylation of the crude product. Reduction of this compound with an excess amount of lithium aluminum hydride, followed by acetylation, afforded hexaacetyl actinamine in 45% yield.

When tetraacetyl 1,3-di-O-tosyl-*myo*-inositol was heated in a mixture of anhydrous hydrazine and 2-methoxyethanol under reflux for 22 hrs, an oily product was obtained. Reduction of the oily product in the presence of a catalyst, followed by acetylation, gave hexaacetyl-*myo*-inosadiazine-1,3 in a yield of 45%. Several attempts were made to isolate an intermediary compound in the hydrazinolysis and *axial, axial, axial, anti(equatorial)*-6,7-diazabicyclo[3.2.1]octane-2,3,4,8-tetrol was obtained. The structure was elucidated by PMR spectra using several deuterated derivatives. The reaction mechanism were considered as follows: the hydrazino group which had been introduced in the cyclohexane ring in a manner of trans-diaxial opening of the cyclic acetoxonium ion attacked another acetoxonium ion to give the bridge bicyclic compound. Therefore the formation of that kind of compound made it possible to obtain *cis*-1, 3-diamino derivative selectively and furthermore, it might be expected to apply this method to a preparation of other inaccessible *cis*-1, 3-inosadiazines.

myo-Inosadiazine-1, 3 dihydrochloride was heated in a mixture of acetyl bromide and acetic anhydride in a sealed tube at 130-135°C. The product was acetylated with acetic anhydride in pyridine to give pentaacetyl-2-bromo-2-deoxy-*scyllo*-inosadiazine-1,3 in 38% yield. The structure of this compound was deduced by a lack of a signal ascribed to axial acetoxy group in PMR spectrum. A catalytic hydrolysis of the bromide with Raney nickel and Amberlite IR-4B in aqueous ethanol afforded colorless prisms of pentaacetyl-2-deoxystreptamine in 45% yield.

The mechanism of the bromination reaction was proposed as "front-side participation" reaction in *cis* amine-ol arrangement.