CONFORMATION OF THE STRUCTURE OF MYO-INOSAMINE COMPONENTS OF MINOSAMINOMYCIN SYNTHESIS OF DERIVATIVES OF D-MYO-INOSAMINE-1

Sir:

The chemotherapeutic success of the aminocyclitol antibiotics has stimulated a wealth of research into the chemistry and modification of their aminosugar components. In contrast only few instances are known where the "cyclitol nucleus" of the antibiotics has been modified.[1~4]

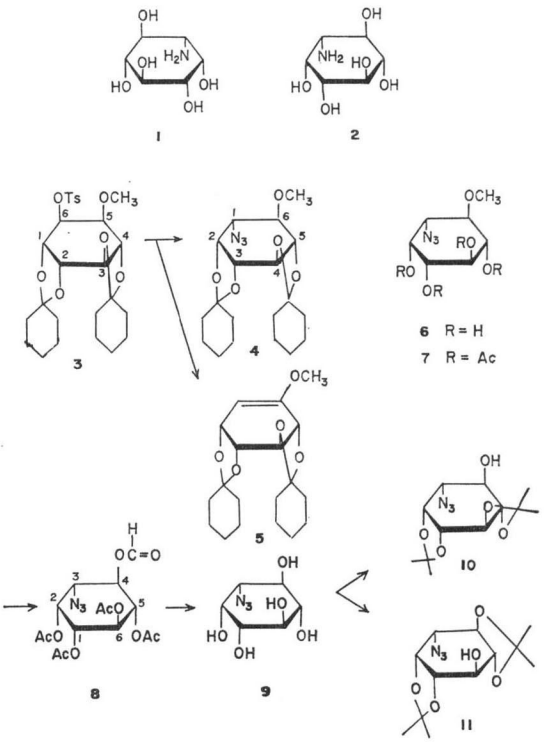
Recently a new, as yet uncharacterized antibiotic minosaminomycin[5], containing 1D-1-amino-1-deoxy-myo-inositol (**1**) has been discovered as a product of *Streptomyces* No. MA 514-A1. This is to our knowledge the first discovery of a 1-amino-1-deoxy-myo-inositol derivative in nature.[6]

The chemical synthesis of neither enantiomer of the optically active 1-amino-1-deoxy-myo-inositol has previously been fully reported, although the rotation and Rf the 1L-enantiomer (**2**) have been quoted[7,8]. The latter myo-inosamine **2** and its epimer 1L-1-amino-1 deoxy-*chiro*-inositol were prepared[8] in 1959 by reduction of the phenylhydrazone of 2L-2, 3, 5/4, 6-pentahydroxycyclohexanone.

In view of the possible biological and synthetic importance of the optically active 1-amino-1-deoxy-myo-inositol, we now report a facile synthesis of 1L-enantiomer **2**, which corroborates the structure and absolute stereochemistry previously assigned to the acid hydrolysis product of minosaminomycin.

The starting material for the synthesis of myoinosamine **2** was 1L-1, 2 : 3, 4-di-*O*-cyclohexylidene-5-*O*-methyl-6-*O*-toluene-*p*-sulphonyl-*chiro*-inositol (**3**), recently reported[9] from our laboratory.

Treatment of the tosylate **3** with sodium azide in dimethylformamide at 130°C for 16 hours, gave a mixture of two products (78%) from which 1L-1-azido-1-deoxy-2, 3 : 4, 5-di-*O*-cyclohexylidene-6-*O*-methyl-myo-inositol (**4**), m.p. 99~101°C, $[\alpha]_D$+40° (*c* 1.00, $CHCl_3$) and a minor unsaturated product (**5**), m.p. 151~153°C, $[\alpha]_D$−26° (*c* 1.34, $CHCl_3$), were isolated in the ratio 4:1 by chromatography on silica gel. Proof of the structure of the azide **4** and the olefine **5** was provided by n.m.r. analysis. Acid hydrolysis of **4** using 60% aqueous acetic acid gave the crystalline 1L-1-azido-1-deoxy-6-*O*-methyl-myo-inositol (**6**) in 81% yield, m.p. 178~179°C, $[\alpha]_D$−29° (*c* 1.04, MeOH). Acetylation of **6** with acetic anhydride in pyridine furnished 1D-1, 2, 5, 6-tetra-*O*-acetyl-3-azido-3-deoxy-4-*O*-methyl-myo-inositol (**7**), m.p. 174~175°C, $[\alpha]_D$−39° (c 1.6, $CHCl_3$).



The crucial step in the preparation of myoinosamine-1 derivatives was the demethylation of **7** using the reagent chromium trioxide in acetic acid. When **7** was treated with chromium trioxide in glacial acetic acid at room temperature for 5 hours, crystalline 1D-1, 2, 5, 6-tetra-*O*-acetyl-3-azido-3-deoxy-4-*O*-formyl myoinositol (**8**) was isolated exclusively in 80% yield, m.p. 188~190°C, $[\alpha]_D$−13.5° (*c* 0.82, $CHCl_3$). Catalytic de-esterification of **8**, using sodium methoxide in methanol gave 1L-1-azido-1-deoxy-myo-inositol (**9**) in 76% yield, m.p. 170~172°C, $[\alpha]_D$−6° (*c* 1.28, MeOH). Hydrogenation of **9** in the presence of ADAM's catalyst in methanol afforded 1L-1-amino-1-deoxy-myo-inositol **2**, readily characterized as its hydrochloride, m.p. 205~207°,

$[\alpha]_D+9.20°$ (*c* 2.2, H_2O) (Lit. 8: m.p. 201~203°C, $[\alpha]_D+9.5°$ (*c* 6.2, H_2O).

For synthetic purpose **9** was readily transformed into the diketals **10** and **11** which each have a single free hydroxyl group for subsequent glycosylation reactions. Treatment of **9** with 2, 2-dimethoxypropane-dimethyl-formamide in the presence of toluene-*p*-sulphonic acid gave two ketals; the mixture was separated by preparative thin-layer chromatography in silica gel to yield 34% of the major product (**10**), m.p. 144~145°C, $[\alpha]_D+24.5°$ (*c* 1.42, $CHCl_3$), and 21% of the minor component (**11**), m.p. 132~133°, $[\alpha]_D-8°$ (9.8, $CHCl_3$).

Proof of structure of the diketals **10** and **11** was provided by chemical correlation. The diketal **10** was converted by methylation followed by acid hydrolysis to the 1L-1-azido-1-deoxy-6-*O*-methyl myoinositol (**6**). Consequently the minor diketal **11** must have structure as shown.

It has been reported that a mutant of *Streptomyces fradiae* (A.T.C.C. 21401) is capable of synthesizing neomycin only in the presence of added 2-deoxy-streptamine. In the presence of streptamine and 1, 3-diamino-1, 3-dideoxy-myo-inositol (epistreptamine), new antibiotics, the hybrimycins, were formed[8]. We therefore tested 1L-1-amino-1-deoxy-myo-inositol (**2**), as a supplement to the growth medium for the mutant to see whether it was transformed into active antibiotic. No active antibiotic was detected.

Lack of formation of antibiotic activity indicates that either any antibiotic-like molecule formed was inactive, or that the amino-cyclitol was not incorporated. The latter seems more porbable.

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