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Syntheses of Nucleosides

Yoshiro TAKEDA (武 田 義 郎)

In a course of our studies on the relations between nucleoside-structures and antitumor and antimicrobial activities, some nucleosides of new types have been synthesized and tested for biological activities. In this investigation, 6-adenyl-6-deoxy-α-D-methylglucoside (I), 6-(2,6-diaminopurinyl)-6-deoxy-α-D-methylglucoside (II), 6-cytosinyl-6-deoxy-α-D-methylglucoside (III), 5-adenyl-5-deoxy-$\alpha(\beta)$-D-methylriboside (IV), 5-uracilyl-5-deoxy-$\alpha(\beta)$-D-methylriboside (V), and 9-furfuryladenine (VI) have been synthesized.

6-Deoxy-6-iodo-2,3,4-tri-O-acetyl-α-D-methylglucoside (VII), which was synthesized from α-D-methylglucoside, was condensed with 6-benzamidopurine (VIII), or 2,6-diaminopurine in DMP in the presence of NaH, and followed by deacylation to afford I or II. Similarly III was synthesized from VII and N-acetylcytosine.

5-Deoxy-5-iodo-2,3-O-isopropylidene-D-methylriboside (IX) was prepared from D-ribose, and caused to react with VIII in DMF in the presence of LiH and followed by deacylation and deisopropylidenation to afford IV. Similarly, V was synthesized from IX and uracil.

Furfuryl alcohol was iodinated with triphenoxyphosphonium-methyliodide in dry ether, and caused to react with VIII in DMF in the presence of NaH. Deacylation gave VI, which showed a significant inhibition of the growth of E. Coli and X. Oryzae.

The Total Synthesis of Kanamycin C

Takayuki TSUMURA (津 村 孝 有 紀)

The author synthesized kanamycin C, a member of kanamycin congeners. Tri-N-carbobenzoxyparomamine was treated with 2,2-dimethoxypropane and *p*-toluenesulfonic acid in N,N-dimethylformamide (DMF). Benzylation of the diisopropylidene derivative with benzyl bromde in the presence of barium salt in DMF gave the mono-O-benzyl-derivative, which, by deacetonation and successive partial acetonation gave 4-O-(3-O-benzyl-2-carbobenzoxyamido-2-deoxy-4,6-O-isopropylidene-α-D-glucopyranosyl)-bis-N,N′-carbobenzoxy-2-deoxystreptamine.

The condensation of this compound with 3-acetamide-2,4,6-tri-O-benzyl-3-deoxy-α-D-glucopyranosyl chloride in a mixture of benzene-dioxane in a presence of

mercuric cyanide and Drierite gave the condensation product. After removal of the all protecting groups by deacetonation, hydrogenation and successive de-N-acetylation, the resulting free base was dinitrophenylated and O-acetylated. The resulting product, which showed about four spots with Rf-value of 0.56, 0.46, 0.35 and 0.25 on a thin-layer chromatogram (TLC) with a solvent system (A): toluene-MEK (2 : 1), was chromatographed on a silica-gel column with the same solvent. The substance having an Rf-value of 0.35 was isolated to afford yellow crystals: 15% over-all yield from condensation process. The melting point, optical rotation, IR spectrum and Rf-value on TLC with a solvent system A of the yellow crystals were identical with hepta-O-acetyl-tetra-N-(2,4-dinitrophenyl) derivative of natural kanamycin C. Hydrolysis of this yellow crystals with methanolic ammonia followed by treatment with Dowex 1×2 (OH) gave a free base. The Rf-value on descending paper chromatogram with a solvent system: *n*-butanol-pyridine-water-acetic acid (6 : 4 : 3 : 1) and antibiotic spectra and minimal inhibitory concentrations of the synthetic product against test organisms were in agreement with those of the natural kanamycin C.

As the synthesis of paromamine has already been cstablished in our laboratory, the above-mentioned synthesis is the first total synthesis of kanamycin.

Syntheses of a Dilactone Compound

Michiaki TORII (鳥 井 迪 明)

The antibiotic antimycin A has a structure of nine-membered dilactone in the molecule. The author synthesized dilactone compounds from hydroxyamino acid and γ-hydroxy acid in order to investigate the relationship between the structure antifungal activity.

N-Benzyloxycarbonyl-O-*t*-butyl-L-serine (I) was prepared from L-serine by carbobenzyloxylation and *t*-butylation. Levulinic acid *t*-butyl ester, which was obtained from levulinic acid by esterification with isobutylene, was hydrogenated in the presence of Raney nickel to give γ-hydroxyvaleric acid *t*-butyl ester (II). Reaction of the protected serine (I) with the hydroxy ester (II) in ether using N,N′-dicyclohexylcarbodiimide in the presence of pyridine as a catalyst gave γ-(N-benzyloxycarbonyl-O-*t*-butyl-L-seryloxy) valeric acid *t*-butyl cster (III). Alternatively, the linear ester (III) was obtained by using isobutylchoroformate or isovalerylchloride. *t*-Butyl groups of the linear ester (III) were removed by the action of trifluoroacetic acid to afford γ-(N-benzyloxycarbonyl-L-seryloxy) valeric acid (IV). The linear hydroxy-acid (IV) was converted into the corresponding acid chloride with