Arch. Pharm. Res. 12(4), 300-305 (1989)

Synthesis of Acyclonucleosides (4)
—Synthesis of 3′-substituted secouridines—

Young Hoon Cho, Jae-Wook Yang, Byung Kwon Chun, Moon Hwan Kim
Moon Woo Chun and Won-Keun Chung
College of Pharmacy, Seoul National University, Seoul 151-742, Korea
(Received November 30, 1989)

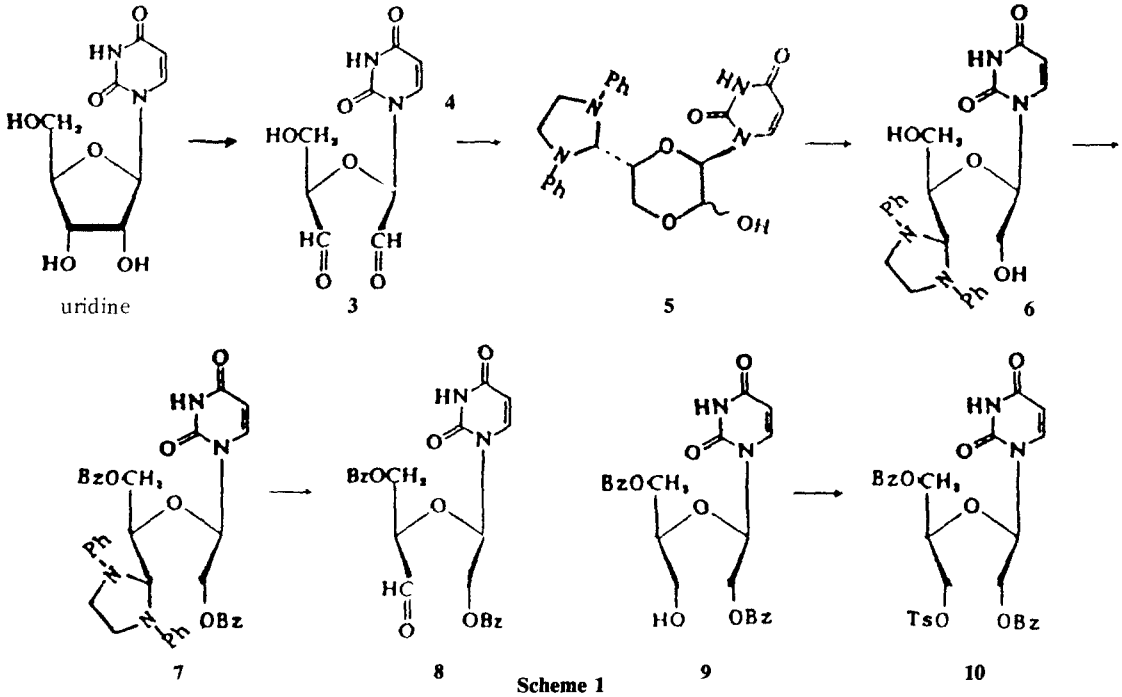
Abstract □ The synthetic study of 3′-azido and 3′-fluoro secouridines toward development of new antiviral agents is described. These acyclic nucleosides were synthesized from uridine by the method of ring opening reaction of sugar moiety.

Keywords □ Acyclonucleoside, fluorosecouridine, azidosecouridine.

In our laboratory, the synthesis of the new type acyclic nucleoside has been under active investigation aiming to find more efficient antiviral agents. In the previous paper of these series, the synthesis of several derivatives of 2′-substituted-2′,3′-secouridine[1], 2′,3′-disubstituted-2′,3′-secouridine[2] and 2′-substituted-2′,3′-secoribavirin[3] was described. The present paper describes the synthesis of 3′-azido-2′-3′-secouridine(**1**) and 3′-fluoro-2′, 3′-secouridine (**2**).

The synthesis of the first target molecule **1** was initiated by oxidation of uridine with sodium metaperiodate[4] (Scheme 1). Thereafter, the 3′-aldehyde group of the resulting dialdehyde **3** was protected selectively with 1,2-dianilinoethane (**4**). For this strategy, we referred to the report by Nemec[5].

According to this report, the reaction of **13** with equimolar amount of 1,2-dianilinoethane (**4**) is highly regioselective, leading to monoimidazolidine **15**(80%) and bisimidazolidine **17**(10%). Under



Scheme 1

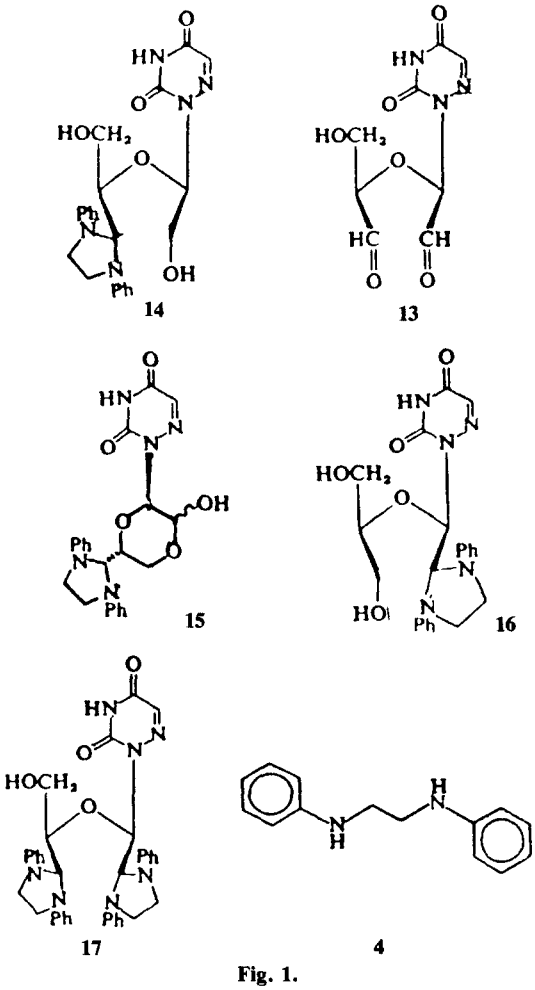


Fig. 1.

more vigorous condition, two equivalent of **4** per one mole of **13** produced **17** in 90% yields, while the monoimidazolidine **16** was not found in either experiment (Fig. 1).

Similar observations were reported[6] when dialdehyde of pyrimidine and purine nucleosides were reduced under slightly acidic condition with sodium borohydride; thus, the aldehyde group distal to the nucleoside base reacted selectively. These facts were also held true in our experiments.

We guess that this regioselectivity is due to the combinantion of the following steric effects. The 2′-aldehyde group proximal to nucleoside base is more hindered than 3′-aldehyde group and reacts with the 5′-hydroxyl group to form thermally more stabled hemiacetal in equilibrium state. Thus, the 2′-aldehyde group of **3** becomes less reactive toward 1,2-dianilinoethane than 3′-aldehyde group

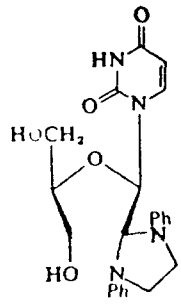


Fig. 2.

(Scheme 3).

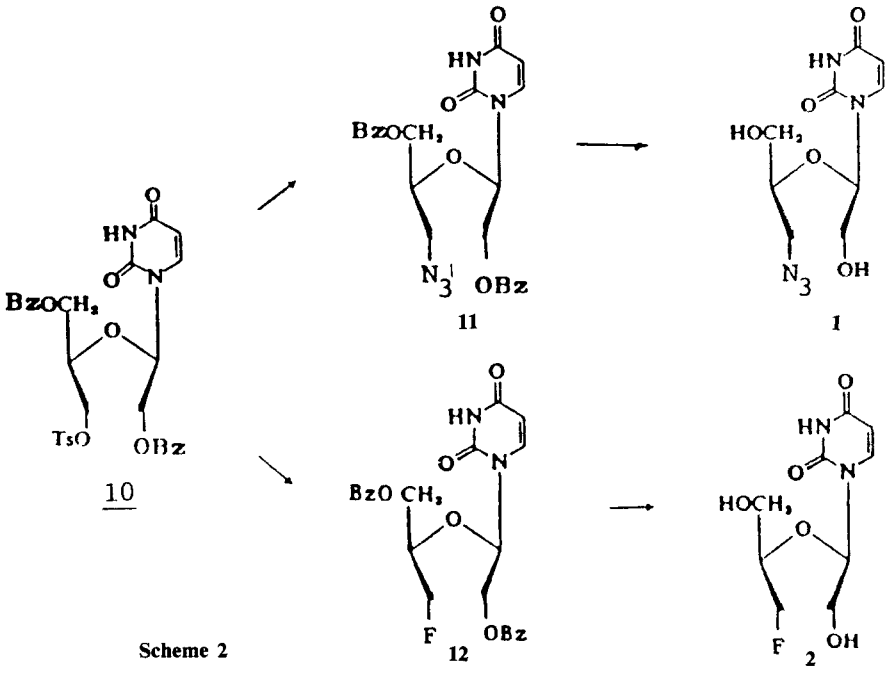
The IR spectrum of this imidazolidine **5** displayed no distinct bands attributable to C-H stretching of the aldehyde proton at 2740 and 2855 cm^{-1}. The carbonyl region of 1720-1740 cm^{-1} was equivocal, because the carbonyl groups of the heterocyclic base exhibited an absorption band in that area. On the other hand, the spectrum did not show a strong and broad band around 1120 cm^{-1}, which is the characteristic of C-O-C group in the polymerized aldehyde[7]. Significantly, no signal was found for a free aldehyde proton in the NMR sprectrum at 9-10 ppm.

These spectral data suggest that imidazolidine **5**, is the major form rather than aldehyde form or polymerized form. Actually **5** was observed as two compounds on thin layer chromatography and converted to only one compound **6** by reduction with sodium borohydride in 96%. This also confirms the facts described above.

Benzoylation of the diol **6** with benzoyl chloride gave dibenzoate **7** in 66% yield. Comparison of the NMR spectrum of the diol **6** and its benzoate revealed a downfield shift($\delta = 0.47$) for the anomeric proton in **6** and **7**. This indicates the proximity of the benzoate group and the anomeric proton and suggests the structure **5** rather than its regioisomer **18** (Fig. 2). The unequivocal proof of the structure, however, remains to be established.

We tried to hydrolyze the imidazolidinyl group to aldehyde group with dilute tosic acid in THF but did not obtain a satisfactory result. Fortunately, the problem was solved by using Amberlite cation resin (IR-120). The released 1,2-dianilinoethane was adsorbed to the resin and easily removed by filtering the reaction mixture.

The aldehyde **8** was carefully reduced with aqueous sodium borohydride to the monoalcohol **9** at 0 °C for 20 minutes. On the other hand, at room temperature many other products having lower R_f



Scheme 2

value than desired product **9** occured, which suggested that chemoselectivity of sodium borohydride decreases at higher temperature. The remaining alcohol group of **9** was successfully converted to the tosylate **10** by tosylation in 85% yield. In addition, the azidation of the tosylate **10** with sodium azide gave the sidium azide **11.** The azido group was found in the IR spectrum of **11** at 2110 cm^{-1}. The benzoate groups of **11** were easily removed with sodium methoxide to give final product **1** (Scheme 2).

Our preparation of the other target molecule **2** is synthesized by fluorination of tosylate **10** with potassium fluoride in anhyd. DMF and deprotection of benzoate with sodium methoxide in anhyd. MeOH (Scheme 2).

EXPERIMENTAL

Proton NMR spectra were measured at 80 MHz on a Bruker instrument and chemical shifts were reported in δ units relative to internal tetramethylsilane.

Infrared spectra were measured on perkin-Elmer 735B and Analect FX-6160 FT-IR and frequences are given in reciprocal centimeters.

The extent of reaction was checked on thin layer chromatogrphy. Analytical thin layer chromatography was performed on precoated silica gel (0.25 mm, 60G254, Merk) and was used silica gel(Kiesel gel, 70-230 mesh, Merk) for column chromatography and all chromatographic solvents were distilled before used.

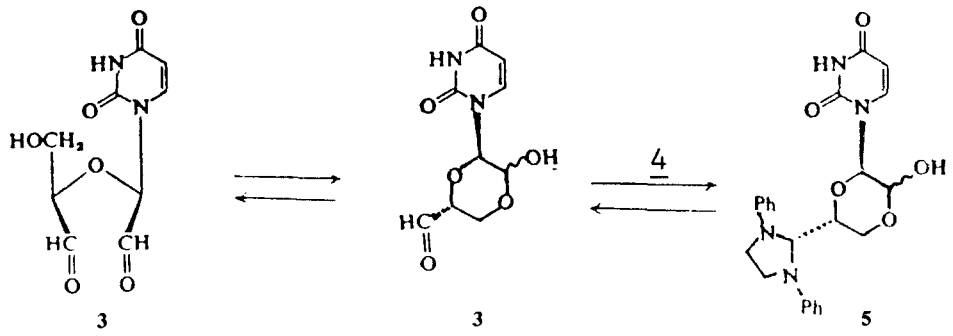
5(R)-Formyl-2(R,S)-hydroxy-3(R)-(uracyl-1-yl)-1,4-dioxane(3)

To the solution of uridine(1.2g, 4.92mmol) in 40m*l* of water was added 1.4g of sodium metaperiodate(6.54mmol) at room temperature. After kept for 4hrs at room temperature the reaction mixture was poured into 70 m*l* of ethyl alcohol and stirred for 20 minutes. The mixture containing the precipitate was filtered and the filtrate was evaporated to dryness under reduced pressure. The dialdehyde **3** was obtained as a colorless foam.

Yield: 1.1g (92%), IR (KBr): 1730, 1700, 1600(C=O), ^{1}H-NMR(D_2O): 3.5-4.4(m, 3H, H-4′,5′), 5.0-5.9(m, 3H, H-1′,2′,3′), 5.9(d, 1H, J=8Hz H-5), 7.85(d, 1H, J=8Hz H-6).

5(S)-(1,3-Diphenylimidazolidine-2-yl)-2(R,S)-hydroxy-3(R)-(uracil-1-yl)-1,4-dioxane(5)

To the suspension of the dialdehyde **3**(403mg, 1.67mmol) in 10m*l* of anhydrous THF was added the solution of 1,2-dianilinoethane **4**(350mg, 1.65mmol) in 7m*l* of anhydrous THF under nitrogen atmosphere. The mixtue was kept for 2 days at room temperature, and then evaporated to dryness



3 3 5

Scheme 3

under diminished pressure. The residue was suspended in 20m*l* of absolute ethyl alcohol and kept for 1 day at room temperature. After evaporation under diminished pressure, the residue was suspended in 20m*l* of chloroform and washed with water(5m*l*×4) in order to remove the unreacted dialdehyde **3**. The chloroform solution was evaporated to dryness under diminished pressure. After purification with column chromatography ($CHCl_3$: MeOH = 20:1), the imidazolidine **5** was obtained as a colorless solid.

Yield: 491 mg (67%), IR (KBr): 1700, 1600 (C=O), ^{1}H-NMR(DMSO-d_6): 3.21-4.02(m, 7H, H-5′, -N-CH_2CH_2-N-, OH), 4.40(m, 1H, H-4′), 4.99(, J=2Hz, 1H, H-2′), 5.56(d, J=1Hz, 1H, H-3′), 5.63(d, J=2Hz, 1H, H-1′), 5.88(d, J=8Hz, 1H, H-5), 6.4-6.93(m, 6H, Aromatic H), 7.0-7.4(m, 5H, Aromatic H and H-6), 11.25(br s, 1H, -NH-).

3′-Deoxy-3′-(1, 3-diphenylimidazolidin -2-yl)-2′,3′-secouridine(6)

The imidazolidine **5**(408mg, 0.94mmol) was dissolved in 15m*l* of methyl alcohol, and sodium borohydride (40mg, 1.06mmol) was added with stirring and kept at room temperature for 1hr. The mixture was neutralized with 80% acetic acid, and then evaporated to dryness under diminished pressure. The diol **6** was obtained as a brown solid after purification with column chromatography ($CHCl_3$:MeOH = 15:1).

Yield: -395mg (96%), ^{1}H-NMR(DMSO-d_6): 2.94-3.81(m, 9H, H-2′, 3′, 4′ and -N-CH_2-CH_2-N-), 4.83(t, 1H, 5′-H), 5.04(t, 1H, 2′-OH), 5.54(d, 1H, H-5), 5.59(d, 1H, H-3′), 5.78(t, 1H, H-1′), 6.69-7.29(m, 10H, Aromatic H), 7.53(d, 1H, H-6), 11.14(s, 1H, -NH-).

2′,5′-O-Dibenzoyl-3′-deoxy-3′-(1,3-diphenylimidazolidin-2-yl)-2′,3′-secouridine(7)

To the dried mixture of the diol **6**(120mg, 0.27mmol) and 20mg of DMAP was added 5m*l* of anhydrous pyridne and 0.5m*l* of benzoyl chloride. After kept at room temperature for 24hrs, 1m*l* of water was added to the reaction mixture, which was stirred for 30 minutes. After complete removal of pyridine by coevaporation with toluene(5m*l*×5), the residue was quenched with cold water and extracted with chloroform. The organic layer was concentrated and the residue was chromatographed to give colorless solid dibenzoate **7**(eluent; EtOAc :Hexane = 1:3).

Yield: 115mg (66%), ^{1}H-NMR ($CDCl_3$): 3.80 (m, 4H, -N-CH_2CH_2-N-), 4.28-4.49(m, 4H, H-2′,5′), 5.19(d, 1H, H-5), 5.45(d, 1H, H-3′), 6.25(t, 1H, H-1′), 6.81-7.48(m, 21H, Aromatic H), 8.90(s, 1H, -NH-).

2′,5′-Dibenzoyl-2′,3′-secouridine (9)

To the solution of the dibenzoate **7**(117mg, 0.18mmol) in 20m*l* of the solvent(THF: H_2O = 1:1) was added 10g of Amberlite cation resin(IR-120) with stirring. The mixture was kept at room temperature for 5hrs and filtered. The resin was washed with a small portion of chloroform several times. The filtrate and washings were combined and evaporated to dryness. The crude product **8** which was not purified was dissolved in the solvent (CH_3OH:H_2O = 5:3) and cooled to 0°C. To the solution was added sodium borohydride (14mg, 2eq) portionwise with stirring and washed with water. The monoalcohol **9** was obtained as a colorless solid by column chromatogrphy(eluent; -EtOAc:Hexane = 1:2).

Yield: 67mg(82%), IR(nujol): -1710, 1660 (C=O), ^{1}H-NMR($CDCl_3$):3.72(d, 2H, H-5′), 3.80(m, 1H, H-4′), 4.02(t, 1H, 3′-OH), 4.36(d, 2H, H-3′), 4.50(d, 2H, H-2′), 5.49(d, 1H, H-5), 6.28(t, 1H, H-1′), 7.28-7.96(m, 11H, Aromatic H and H-6), 10.02(s, 1H, -NH-)

2',5'-O-Dibenzoyl-3'-O-tosyl-2',3'-secouridine(10)

The solution of tosyl chloride(140mg, 5eq) in 2m*l* of anhydrous methylene chloride was added to the solution of **9**(67mg, 0.147mmol) and DMAP (5mg) in 1m*l* anhydrous pyridine at 0°C under nitrogen atmosphere. The mixture was stirred at room temperature for 48hrs. After complete removal of pyridine by azeotropic evaporation with toluene (5m*l*×7), the residue was dissolved in chloroform and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and then evaporated to dryness. The tosylate **10** was obtained as a yellow solid by purification with colum chromatography (eluent; $CHCl_3$:MeOH = 60:1).

Yield: 73mg (82%) IR (nujol): 1760, 1710, 1618 (C = O), ^{1}H-NMR($CDCl_3$): 2.39(s, 3H, CH), 4.08-4.45(m, 7H, H-2',3', and 5'), 5.49(d, 1H, H-5), 6.22(t, 1H, H-1'), 7.26-7.99(m, 15H, Aromatic H and H-6), 8.90(s, 1H, -NH-)

3'-Azido-3'-deoxy-2',5'-dibenzoyl-2'3'-socouridine(11)

To the solution of the tosylate **10** (51mg, 0.084mmol) in 3m*l* of anhydrous acetonitrile was added sodium azide(30mg, 0.48mmol). The mixture was kept at 60°C for 12hrs. From the mixtue was removed dimethylformamide by evaporation nuder diminished pressure at 40°C. The residue was dissolved in chloroform and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified on silica gel column (eluent: -EtOAc: Hexane = 1:3) to give the azide **11** as a colorless solid.

Yield: 39mg (97%), IR (nujol): 1610, 1650, 1700, 1720 (C = O), 2100(-N_3), ^{1}H-NMR($CDCl_3$): 3.62(t, 2H, H-3'), 4.12(m, 1H, H-4'), 4.36-4.56(m, 4H, H-2',5'), 5.52(d, 1H, H-5), 6.33(t, 1H, H-1'), 7.30-8.03(m, 11H, Aromatic H and H-6), 8.74(s, 1H, -NH-)

3'-Azido-3'-deoxy-2'-secouridine(1)

The azide **11** (38mg, 0.079mmol) was dissolved in 10m*l* of anhydrous methanol. To this solution 0.5m*l* of 0.2M-NaOMe was added dropwise. The solution was stirred at room temperature. After 4 hours, the reaction mixture was neutralized with Amberlite IR-120 (H^+) resin, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified on silica gel column (eluent; -$CHCl_3$:MeOH = 8:1) to afford desired product as a colorless solid.

Yield: 19mg (92%), IR (nujol): 2110 (-N_3), ^{1}H-NMR(DMSO-d_6): 3.29-3.67(m, 7H, H-2',3',4' and 5'), 4.72(t, 1H, 5'-OH), 5.06(t, 1H, 2'-OH), 5.60(d 1H, H-5), 5.82(t, 1H, H-1'), 7.60(d, 1H, H-6), 11.19(s, 1H, -NH-)

2',5'-O-Dibenzoyl-3'-deoxy-3'-fluoro-2',3'-secouridine(12)

To the solution of the tosylate **10**(455mg, 0.75mmol) in DMSO(10m*l*) was added potassium fluoride(218mg, 3.75mmol) and the mixture was stirred at 140°C. After 2 hours, the solvent was removed in vacuo to dryness. The residue was quenched with water(2m*l*), and extracted with ethyl acetate(5m*l*×3). The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (EtOAc:Hexane = 1:2) to give 252mg of protected fluoride **12** as colorless solid form.

Yield: 252mg(73%), m.p=116-118°C, ^{1}H-NMR ($CDCl_3$): 4.06-4.79(m, 7H, H-2',3',4' and 5'), 4.59(d, J = 8Hz, 1H, H-5), 6.48(t, J = 5.6Hz, 1H, H-1'), 7.23-8.08(m, 11H, Aromatic H and H-6), 9.56(s, 1H, -NH-).

3'-Deoxy-3'-fluoro-2'3'-secouridine(2)

To the solution of the protected fluoride **12**(110mg, 0.24mmol) in 10m*l* of anhydrous methanol, was added dropwise 1.32m*l* of 0.2M-NaOMe/MeOH solution. The solution was stirred at room temperature for 4 hours and th reaction mixture was neutralized with Amberlite IR-120 (H^+) resin. After the resin was filtered out, the filtrate was concentrated under reduced pressure and the residue was purified on silica gel ($CHCl_3$:MeOH = 8:1) to afford **2** as colorless oil form.

Yield: 54mg(95%), ^{1}H-NMR(DMSO-d_6): 2.67-3.62(m, 7H, H-2',3',4' and 5'), 4.57(5, J = 4.8Hz, 1H, 5'-OH), 5.04(t, J = 6Hz, 1H, 2'-OH), 5.58(d, J = 7.8Hz, 1H, H-5), 5.79(t, J = 5.6Hz, 1H, H-1'), 7.62(d, J = 8Hz, 1H, H-6), 11.14(br, 1H, -NH-).

ACKNOWLEDGEMENT

We are very grateful to the Korea Science and Engineering Foundtion for financial support (1987-1990).

LITERATURE CITED

1. Kim, H.O., Chun, M.W., and Chung, W.K.: Synthesis of Acyclonucleosides(1)-Synthesis of 2'-substituted secouridines-. *Seoul University*

Journal of Pharmaceutical Sciences, **12,** 62 (1987).
2. Yang, J.W., Hong, K.A., Han, H.K., Chun, M.W., and Chung, W.K.: Synthesis of Acyclonucleosides(2)-Synthesis of 2′,3′-disubstituted secouridines-. *Yakhak Hoeji,* **33**(5), 296 (1989).
3. Moon, H.R., Yang, J.W., Kim, M.H., Chun, M.W., and Chung, W.K.: Synthesis of Acyclonucleosides(3)-Synthesis of Ribavirin derivatives-. *Seoul University Journal of Pharmaceutical Sciences,* in press (1989).
4. Lerner, L.M.: Preperation of trialcohols and some of their derivatives from nucleosides. *Carbohydr. Res.,* **13,** 465 (1970).
5. Nemec, J. and Rhoades, J.M.: Regiochemical aspects in reactions of 6-azauridine dialdehyde. *Nucleosides & Nucleotides,* **2,** 99 (1983).
6. Khym, J.X. Cohn, W.E.: Characterizations and some chemical reactions of periodate-oxidized nucleosides. *J. Am. Chem. Soc.,* **82,** 6380 (1960).
7. Hansske, F. and Coamer, F.: Untersuchungen zur strukture perjodatoxydierter Ribonucleoside und Ribonucleotide. *Carbohydr. Res.* **54,** 75 (1977).