Discovery of the antibiotics such as gougerotin and blasticidin S has drawn a growing attention to the synthesis of the nucleosides containing 4-amino-4-deoxy sugar moiety. Recently Fox et al. 1) have succeeded in synthesizing a cytosine nucleoside, 1-(4-amino-4-deoxy-\(\beta\)-D-glucopyranosyl)cytosine, in the course of a total synthesis of C-substance, a degradation product of gougerotin. In this report a synthesis of 1-(4-amino-4-deoxy-\(\beta\)-D-glucopyranosyl)uracil (I) is described.

Fox et al. 1) used as a starting material for the synthesis of the cytosine nucleoside methyl 2,3,6-tri-O-benzoyl-4-O-mesityl-\(\alpha\)-D-galactoside, 4-position of which was already differentiated from 2, 3, and 6 positions by introduction of a mesyl group, which was finally converted to an amino group. Our route consists in the synthesis of an uracil nucleoside from aceto bromogalactose followed by differentiation of the 4-position of the sugar moiety of the nucleoside by selective benzoylation.

Condensation of aceto bromogalactose with 2,4(dimethylsiloxy)pyrimidine 2) afforded a mixture of nucleosides. Since this condensation was accompanied with partial deacetylation, the product was acetylated with acetic anhydride and pyridine to give a mixture of \(\alpha\)- and \(\beta\)-anomers of 1-(2,3,4,6-tetra-O-acetyl-\(\alpha\)-D-galactopyranosyl)uracil in a ratio of ca. 1:4 (calculated from its NMR integration curve). Crystallization from isopropanol gave the \(\beta\)-anomer (II) in nicely crystalline form. The \(\alpha\)-anomer (III) was obtained only in an amorphous solid from the mother liquor after repeated tlc separations. The UV absorption spectra of II (257 nm) and III (258 nm) indicate an N1-glycosyl linkage of uracil. The spacing of anomeric doublet in NMR spectrum of II (\(\delta\) 5.90; \(J=9.4\) Hz) and the positive Cotton effect 3) show the glycosyl linkage to be in \(\beta\)-configuration of pyranose type, while \(\alpha\)-configuration can be assigned to the glycosyl linkage of III from the coupling constant of the anomeric doublet (\(\delta\) 6.25; \(J=2.5\) Hz) and the negative Cotton effect, although the possibility of furanose type structure of the latter cannot be eliminated rigorously from the examination of the NMR spectrum. Deacetylation of the \(\beta\)-anomer II with sodium methoxide afforded crystalline 1-\(\beta\)-D-galactopyranosyluracil (IV) in 75% yield. This compound was first synthesized by Hilbert 4) from aceto bromogalactose and 2,4-diethoxy pyrimidine followed by hydrolysis with methanolic hydrogen chloride in a low yield.

The next step is the selective benzoylation of IV to the 2,3,6-tribenzoate V having free hydroxyl group at the 4-position. Since the difference in reactivity between axial and equatorial hydroxyl group in methyl \(\alpha\)-D-
galactoside had been used by Reist et al. for the selective benzylation of the glycoside to methyl 2,3,6-tri-O-benzoyl-α-D-galactoside and since the anomeric proton coupling constant in the NMR spectrum of IV (8.1 Hz) showed that the sugar part of the nucleoside IV is to be a pyranose ring of chair conformation indicating that the Cα-hydroxyl group has an axial orientation, a direct benzylation of the nucleoside IV was carried out; the more restricted condition than that used for the preparation of the methyl tribenzylgalactoside was actually necessary. Thus, treatment with 3.0 eq. of benzoyl chloride in pyridine at -12°C afforded the desired tribenzoate (V) in 68% yield, but a mixture of the tri- and tetra-benzoates was obtained by treatment with 3.5 eq. of benzoyl chloride at 0°C and a mixture of di- and tri-benzoates with 3.0 eq. of benzoyl chloride at -15° to -18°C.

Mesylation of the tribenzoate V gave in an 81% yield crystalline 4-O-mesylate VI, which on treatment with sodium azide in hexamethylphosphoreric triamide afforded an amorphous material (VII), which was isolated by means of tlc. The structure of VII was assigned as 1-(4-azido-4-deoxy-2,3,6-tri-O-benzoyl-β-D-glucopyranosyl)uracil by analysis of its NMR spectrum using proton spin decoupling technic; the coupling constants, \( J_1^\alpha,2^\alpha = 9.5 \text{ Hz}, J_2^\alpha,3^\alpha = 9.5 \text{ Hz}, \) and \( J_3^\alpha,4^\alpha = ca. 9 \text{ Hz} \), indicate trans arrangements of the substituents at 1', 2', 3' and 4' positions (glucopyranose type), and that the chemical shift of 4'-H was higher than that of 2'-H and 3'-H by 1.5 ppm indicates the azido group at 4'-position.

Hydrolysis of the azido-tribenzoate VII with sodium methoxide gave 4-azido-4-deoxy nucleoside VIII which was then hydrogenated over 10% palladium on charcoal to give the 4-amino-4-deoxy nucleoside I, NMR spectrum of which (anomeric proton at \( \delta 5.63, J=8.8 \) Hz) indicates a β-pyranosyl type structure.

\[ \text{FIG. 1.} \]

EXPERIMENTAL

Mps were determined on a micro hot stage and uncorrected. The following spectrometers were used for spectral measurements: (IR) JASCO IR-G; (NMR) JEOL JNM-4H-100 (100 MHz); (UV) Hitachi EPS-3T; (ORD) Yanagimoto SPR-185. Unless otherwise indicated chemical shifts (\( \delta \)) were expressed in ppm from internal TMS and coupling constants (\( J \)) in Hz. Silica gel G was used for tlc.

1-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)uracil (II). Acetobromogalactose (20 g) was intimately mixed with 2,4-bis(trimethylsiloxy)pyrimidine (20 ml) in a flask which was then evacuated and closed by a stop-cock. The mixture was fused at 80°C and then heated at 140°C for 45 min. After being cooled, the reaction mixture was treated with methanol (20 ml) and acetic anhydride (30 ml) and the mixture was allowed to stand at room temp. for 20 hr. It was then poured into a cold saturated aqueous sodium bicarbonate solution (300 ml) and the aqueous mixture was extracted with dichloromethane. The organic layer was dried over calcium chloride and evaporated to dryness. The residue was added to a mixture of pyridine (40 ml) and acetic anhydride (30 ml) and the mixture was allowed to stand at room temp. for 20 hr. It was then poured into a cold saturated aqueous sodium bicarbonate solution (300 ml) and the aqueous mixture was extracted with dichloromethane. The organic layer was dried over calcium chloride and evaporated to dryness to give a syrup (23 g). Crystallization from isopropanol yielded needles, mp 106°-108°C (7.3 g, 34%). Anal. Found: C, 49.99; H, 5.88; N, 5.26. Calcd. for C₁₈H₂₀O₁₁N₂(CH₃)₂CHOH: C, 50.01; H,
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6.01; N, 5.55%. \( \lambda_{\text{max}} \text{MeOH} \times 257 \text{ nm} \times (\varepsilon 8900); [\alpha]_D +30^\circ \text{ (MeOH, } c=0.58) \); \( \delta_{\text{CDCl}_3} 5.51 \text{ (1H, } d^*, J=1.5, 4'-\text{H}), 5.84 \text{ (1H, br. d, } J=8.1, 5-\text{H}), 5.90 \text{ (1H, } d^*, J=9.4**, 1'\text{-H}), 7.39 \text{ (1H, d, } J=8.1, 6-\text{H}), 9.50 \text{ (1H, br. s, OH).}

The 3-anomer (III) was isolated as amorphous powder from the mother liquor by means of tlc on silica gel. Characterization was made only by analysis of IR, UV, and NMR spectra as well as optical dispersion measurements. \( \lambda_{\text{max}} \text{MeOH} \times 258 \text{ nm} \times (\varepsilon 7600); [\alpha]_D +17^\circ \text{ (MeOH, } c=0.36), \delta_{\text{trough}} 277-8870^\circ \); \( \delta_{\text{CDCl}_3} 2.07, 2.08, 2.16, 2.18 \text{ (s, } 4\times \text{CH}_3\text{CO}), 5.70 \text{ (1H, d, } J=8.1, 5-\text{H}), 6.25 \text{ (1H, d, } J=2.5, 1'\text{-H}), 7.44 \text{ (1H, d, } J=8.1, 6-\text{H}), 9.50 \text{ (1H, d, } d^*, J=7.5, 1'-\text{H).}

1-β-D-Galactopyranosyluracil (IV). A suspension of the tetraacetate of the 3-anomer (II) (7.31 g) in methanolic IN sodium methoxide (73 ml) was refluxed for 1.5 hr. After being cooled at room temp., it was neutralized to pH 7 by addition of Dowex 50 (H+ type) resin. The resin was removed by filtration and the filtrate was evaporated to a small volume and treated with ethanol to give the nucleoside IV as crystalline mass (3.40 g, 76%). Recrystallization from water-ethanol gave needles, mp 234°C (lit.4) mp 250°C-251°C). Anal. Found: C, 43.41; H, 5.13; N, 9.88. Calcd. for C10H1407N2: C, 43.80; H, 5.15. N, 10.22%. \( \lambda_{\text{max}} \text{MeOH} \times 260 \text{ nm} \times (\varepsilon 9700); \delta_{\text{DMSO-d}_6} 5.33 \text{ (1H, d, } J=8.3, 1'\text{-H}), 5.70 \text{ (1H, dd, } J=8.1, 1.5-\text{H}), 7.64 \text{ (1H, d, } J=8.1, 6-\text{H}), 11.24 \text{ (1H, d, } J=1.5, \text{ OH).}

1-(2,3,6-Tri-O-benzoyl-β-D-galactopyranosyl)uracil (V). To a solution of the nucleoside IV (2.39 g) in anhydrous pyridine (45 ml) was added benzoyl chloride (3.68 g) dropwise with vigorous stirring at -12°C to -15°C in a period of 45 min. After being allowed to stand below 0°C for 10 hr, the reaction mixture was set aside at 10°C for 20 hr. The precipitate resulted was filtered and treated with hot chloroform to give the tribenzoate V as needles (3.25 g, 68%). Recrystallization from chloroform afforded an analytical sample, mp 217°C-219°C. Anal. Found: C, 63.06; H, 4.38; N, 4.75. Calcd. for C31H26010N2: C, 63.48; H, 4.47; N, 4.22. \( \lambda_{\text{max}} \text{MeOH} \times 232 \text{ nm} \times (\varepsilon 39200), 260 \text{ sh nm} \times (\varepsilon 9500); \delta_{\text{DMSO-d}_6} 6.26 \text{ (1H, d, } d^*, J=2.5, 1'-\text{H).}

1-(2,3,6-Tri-O-benzoyl-4-O-methanesulfonyl-β-D-galactopyranosyl)uracil (VI). To a solution of the tribenzoate V (1.00 g) in anhydrous pyridine (10 ml) was added methanesulfonyl chloride (0.75 ml) with stirring at 0°C, and the mixture was allowed to stand at room temp. for 5 hr. It was then poured dropwise into a cold saturated sodium bicarbonate solution (300 ml) with stirring. The precipitate resulted was filtered, dried in air and dissolved in dichloromethane. The solution was treated with Norit A and evaporated to dryness to give crystalline residue. Recrystallization from ethanol gave needles, mp 207-208°C (0.91 g, 81%). Anal. Found: C, 57.95; H, 4.22; N, 400. Calcd. for C32H28012N2S: C, 57.82; H, 4.24; N, 4.21%. \( \lambda_{\text{max}} \text{MeOH} \times 232 \text{ nm} \times (\varepsilon 38800), 260 \text{ nm} \times (\varepsilon 11300); \delta_{\text{CDCl}_3} 5.52 \text{ (1H, t, } J=9.5, 2'\text{-H), 5.76 (1H, br. d, } J=8.0, 5'-\text{H), 5.91 (1H, dd, } J=9.5 \text{ and ca. 9, 3'\text{-H), 6.19 (1H, d, } J=9.5, 1'\text{-H); } J_{\text{v,5}} , J_{\text{v,6}}, \text{ and } J_{\text{v,4}} \text{ were confirmed by proton decoupling technic.}

1-(4-Azido-4-deoxy-β-D-glucopyranosyl)uracil (VIII). A suspension of the mesylate VI (1.69 g) and powdered sodium azide (0.93 g) in hexamethylphosphor triamide (6 ml) was heated at 80°C with stirring for 5 hr. The reaction mixture was cooled, and poured into water (300 ml). The aqueous solution was extracted three times with chloroform (200 ml each) and the chloroform layer was washed twice with water, dried over calcium chloride, and evaporated to dryness to give the crude azide as a syrup (1.71 g). From the syrup was isolated amorphous 1-(4-azido-4-deoxy-2,3,6-tribenzoyl-β-D-glucopyranosyl)uracil (VII) (1.31 g, 84%) by means of tlc on silica gel G using benzene-ethyl acetate (2 : 1) as the solvent. vKBr 2100 cm⁻¹ (N3); \( \lambda_{\text{max}} \text{MeOH} \times 232 \text{ nm} \times (\varepsilon 38800), 260 \text{ sh nm} \times (\varepsilon 11300); \delta_{\text{CDCl}_3} 3.8-4.3 (2H, m, 4',5'-\text{H}), 4.5-4.9 (2H, 6', 6'-\text{H}), 5.52 (1H, t, } J=9.5, 2'\text{-H), 5.76 (1H, br. d, } J=8.0, 5'-\text{H), 5.91 (1H, dd, } J=9.5 \text{ and ca. 9, 3'\text{-H), 6.19 (1H, d, } J=9.5, 1'\text{-H); } J_{\text{v,5}} , J_{\text{v,6}}, \text{ and } J_{\text{v,4}} \text{ were confirmed by proton decoupling technic.}

* With small virtual couplings.
** J was obtained from the NMR spectrum taken in CDCl₃.
nitrile gave analytical sample of the azide VIII, mp 226°C (dec.). Anal. Found: C, 40.17; H, 4.30; N, 22.89. Calcd. for C₁₇H₁₃O₆N₅: C, 40.14; H, 4.38; N, 23.41%. νKBr 2100 cm⁻¹ (N₃); λmaxH₂O 260 nm (ε 8100); δ(D₂O; acetone was used as an internal standard and taken as 2.21 ppm) 5.58 (1H, d*, J=8.8, 1'-H), 5.94 (1H, d, J=8.1, 5-H), 7.78 (1H, d, J=8.1, 6-H).

1-(4-Amino-4-deoxy-β-D-glucopyranosyl)uracil (I). To a solution of the azide VIII (0.120 g) in ethanol-water (1:1) (4.5 ml) was added 10% palladium on charcoal (40 mg) and the mixture was hydrogenated at room temp. under H₂ (1 atm) for 3 hr. The catalyst was removed by filtration and the filtrate was evaporated to a small volume, from which the crude amine I was separated as crystals (0.100 g, 86%). Recrystallization from aqueous ethanol gave analytical sample (dried over P₂O₅ at 90°C in vacuo), mp 245-247°C (dec.). Anal. Found: C, 41.55; H, 5.37; N, 14.42. Calcd. for C₁₀H₁₅O₆N₃·H₂O: C, 41.23; H, 5.88; N, 14.43%. λmaxH₂O 260 nm (ε 11700); δ(D₂O; acetone was used as an internal standard and taken as 2.21 ppm) 5.63 (1H, d, J=8.8, 1'-H), 5.96 (1H, br. d, J=8.1, 5-H), 7.87 (1H, d, J=8.1, 6-H).