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Nucleosides. LIX. Synthetic Studies on Nucleoside Antibiotics. 1. Synthesis of 1-(4-Amino-4-deoxy-β-D-glucopyranosyl)cytosines and Their Identity with Products derived from Gougerotin[1]

Gougerotin, an aminoacyl nucleoside antibiotic isolated by Kanzaki and co-workers,[2a] has been the subject of extensive chemical investigation.[2b] Chemical studies designed toward the total synthesis of this antibiotic and analogs thereof have been undertaken in our laboratories because of the importance of such antibiotics as tools for biochemical and chemotherapeutic investigation.[3] The structure of gougerotin was recently established[4,5] by physicochemical and degradative studies as 1-(cytosinyl)-4-sarcosyl-D-serylamino-1,4-dideoxy-β-D-glucopyranuronamide. We report herein the first synthesis of the 4′-acetamido-4′-deoxyhexopyranosyl nucleoside (VII) and its derivatives and their identity with gougerotin–derived products.

The easily–accessible starting material, methyl 2,3,6-tri-O-benzoyl-4-O-methanesulfonyl-α-D-galactoside (I)[6] was obtained in 22% overall yield from D-galactose in 3 steps. Treatment of I with HBr-acetic acid for 14 hr at room temperature afforded the syrupy α-halogenose II [NMR: 15 aromatic H at δ 8.05 and δ 7.45; anomeric H (doublet) at δ 6.88, $J_{1,2}$=4.0 Hz (indicative of the α-configuration); H2 and H3 (multiplet) at δ 5.4—6.1; H4, H6 and H6′ (multiplet 3H) at δ 4.4—5.1; and mesyl signal at δ 3.06]. Condensation of II with N^4-acetylcytosine by the general nitromethane-$Hg(CN)_2$ procedure[7] gave the blocked β-nucleoside III[8] in quantitative yield, mp 259—263° (decomp.), $[\alpha]_D^{25}$ +38° (DMF): [UV λ_{max}^{EtOH}: 300, 282, 232 mμ (ε 6000, 6600, 45000), λ_{min}^{EtOH}: 288, 278, 227 (5500, 6300, 24800). IR λ_{max}^{KBr}: 3.0 (NH), 5.8 (C=O benzoyl) 5.89 (N-acetyl), 6.02, 6.14 (pyrimidine), 7.90 (C–O–C benzoyl) 8.5 (sulfonate) 9.1 (C–O–C sugar) 14.0 μ (phenyl). NMR (DMSO-d_6), 17 aromatic H, H1′ (doublet) δ=6.63, $J_{1',2'}$=9.0 Hz (β-configuration), mesyl H δ=3.42 and N-acetyl H δ=2.08]. Reaction of III with sodium azide in hexamethylphosphoric triamide[9] at 80° for 4 hr displaced the mesyloxy group with inversion to afford the crystalline 4-azido derivative (IV) in 76% yield, mp 240—242°, $[\alpha]_D^{27}$ +48° (DMF): [UV λ_{max}^{EtOH}: 300, 282, 232 mμ (ε 6100, 6800, 38800), λ_{min}^{EtOH}: 288, 278, 227 (5600, 6100, 22800); IR λ_{max}^{KBr}: 3.0μ(NH), 4.70 (N_3), 5.8 (C=O benzoyl), 5.98 (N-acetyl), 6.02, 6.14 (pyrimidine), 7.92 (C–O–C benzoyl), 9.2 (C–O–C sugar), 14.1 (phenyl)].

Deacylation of IV with sodium methoxide in methanol afforded the crystalline nucleoside V in quantitative yield: mp 232—234° (decomp.), $[\alpha]_D^{25}$ +58° (H_2O): [UV λ_{max}^{pH14}: 268 mμ (ε 9800), λ_{min}^{pH14}: 253 (8600), $\lambda_{max}^{pH6.8}$: 267, 235, 198 (8600, 8100, 21000), λ_{max}^{pH1}: 276 (12700), λ_{min}^{pH1}: 240 (2500); IR λ_{max}^{KBr}: 2.86μ (OH), 3.06 (NH), 4.69 (N_3), 6.02, 6.20 (pyrimidine), 9.25, 9.43 (C–O–C

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2) *a*) T. Kanzaki, E. Higashide, H. Yamamoto, M. Shibata, K. Nakazawa, H. Iwasaki, T. Takewaka and A. Miyake, *J. Antibiot.* (Japan), **15A**, 93 (1962); *b*) H. Iwasaki, *Yakugaku Zasshi*, **82**, 1358 (1962), 11 papers.

3) J.J. Fox, K.A. Watanabe and A. Block, *Progrr. Nucleic Acid Res. Mol. Biol.*, **5**, 251 (1966), and leading references therein.

4) J.J. Fox, Y. Kuwada, K.A. Watanabe, T. Ueda and E.B. Whipple, *Antimicrobial Agents and Chemotherapy*, 1964, 518.

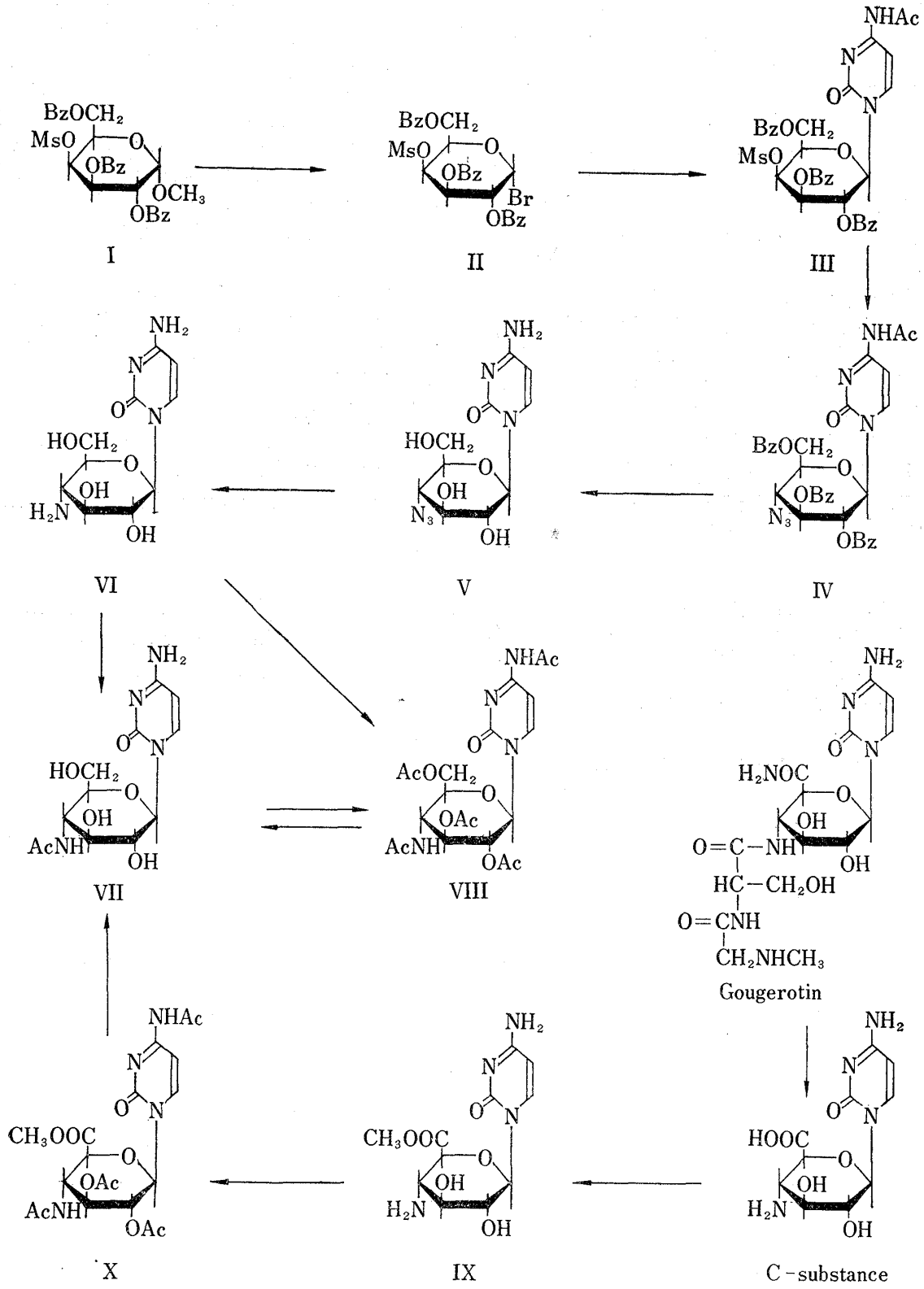
5) J.J. Fox, Y. Kuwada and K.A. Watanabe, *Tetrahedron Letters*, **1968**, 6029.

6) E.J. Reist, R.P. Spencer, D.F. Kalkins, B.R. Baker and L. Goodman, *J. Org. Chem.*, **30**, 2312 (1965).

7) N. Yamaoka, K. Aso, and K. matsuda, *J. Org. Chem.*, **30**, 149 (1965); K.A. Watanabe and J.J. Fox, *J. Heterocyclic Chem.*, **1969**, in press.

8) Satisfactory elemental analyses were obtained for all new crystalline compounds reported herein.

9) Poor yeilds were obtained when DMF was used as the solvent. We are very grateful to Dr. E.J. Reist of Standford Research Institute, California, who called our attention to hexamethylphosphorotriamide.



sugar)]. Nucleoside V was hydrogenated over 5% Pd on charcoal to 1-(4-amino-4-deoxy-β-D-glucopyranosyl)cytosine (VI), 209—211° (eff), $[\alpha]_D^{25}$ +14° (H_2O): [UV λ_{max}^{pH13}: 368 mμ (ε 8500), λ_{min}^{pH13}: 253 (7600), $\lambda_{max}^{pH6.8}$: 267, 235, 198 (8200, 8000, 21400), $\lambda_{min}^{pH6.8}$: 252, 223 (7400, 7600), λ_{max}^{pH2}: 275 (11800), λ_{max}^{pH2}: 239 (2300); IR λ_{max}^{KBr}: 2.85μ (OH), 3.0 (NH), 6.0, 6.2 (pyrimidine), 9.3 (C–O–C

sugar)]. N-Acetylation[10] of VI afforded the acetamido derivative VII, mp 317—319° (decomp.), $[\alpha]_D^{25}$ +32° (H_2O): [UV λ_{max}^{pH13}: 268 mμ (ε 8400), λ_{min}^{pH13}: 253 (7500), $\lambda_{max}^{pH6.8}$: 267, 235, 198 (8200, 8000, 22200), $\lambda_{min}^{pH6.8}$: 252, 222 (7500, 7600), λ_{max}^{pH2}: 276 (12000), λ_{min}^{pH2}: 240 (2400); IR λ_{max}^{KBr}: 2.78μ (OH), 3.07 (NH), 6.02 (C=O N-acetyl), 6.02, 6.22 (pyrimidine), 9.1, 9.55 (C–O–C sugar)]. Poly-acetylation of VI gave the tetraacetate VIII, mp 293—294° (decomp.), $[\alpha]_D^{25}$ +27° (DMF): [UV λ_{max}^{EtOH}: 300, 249, 210 mμ (ε 6000, 15200, 16900), λ_{min}^{EtOH}: 276, 226 (4100, 4800); IR λ_{max}^{KBr}: 2.85μ (OH), 2.98 (NH), 5.68 (C=O ester), 5.96, 6.1 (pyrimidine), 8.18 (C–O–C ester), 9.28, 9.48 (C–O–C sugar); NMR (DMSO-d_6), H5 (doublet) δ=7.24, $J_{5,6}$=7.6, H6 (doublet) δ=8.31, H1′ (unresolved doublet with half width 12 Hz) δ=6.00, acetyl signals at δ=1.80, 1.86, 1.96, 2.01, 2.12]. Treatment of VIII with sodium methoxide in methanol also gave VII.

Grougerotin was converted to nucleoside IX by the procedure of Iwasaki.[2b] Acetylation of IX with acetic anhydride in pyridine gave the tetraacetate X, mp 283—284° (decomp.), $[\alpha]_D^{25}$ +35° (DMF) [UV λ_{max}^{EtOH}: 297, 240, 196 mμ (ε 6600, 16600, 18000), λ_{min}^{EtOH}: 272, 215 (4300, 3800)] (The NMR spectrum was described previously[4,11]). Treatment of X with sodium borohydride afforded 1-(4-acetamido-4-deoxy-β-D-glucopyranosyl)cytosine (VII) identical with the synthetic material. Acetylation of the gougerotin-derived VII gave VIII which was also identical with the synthetic material obtained by acetylation of VI.

These data afford confirmatory evidence of the structure of gougerotin and constitute a partial synthesis of this antibiotic.

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10) N^4-Acetylcytosine derivatives are very susceptible to hydrogenation. H.A. Friedman, K.A. Watanabe and J.J. Fox, *J. Org. Chem.*, 32, 3775 (1967).

11) This compound had previously[4] been assigned the *galacto* configuration. In a recent report[5] it was shown to be of the *gluco* configuration by degradative studies.