Tetrahedron Letters No. 46, pp 4051 - 4054, 1977. Pergamon Press. Printed in Great Britain.

TOTAL SYNTHESIS OF NUCLEOSIDE Q

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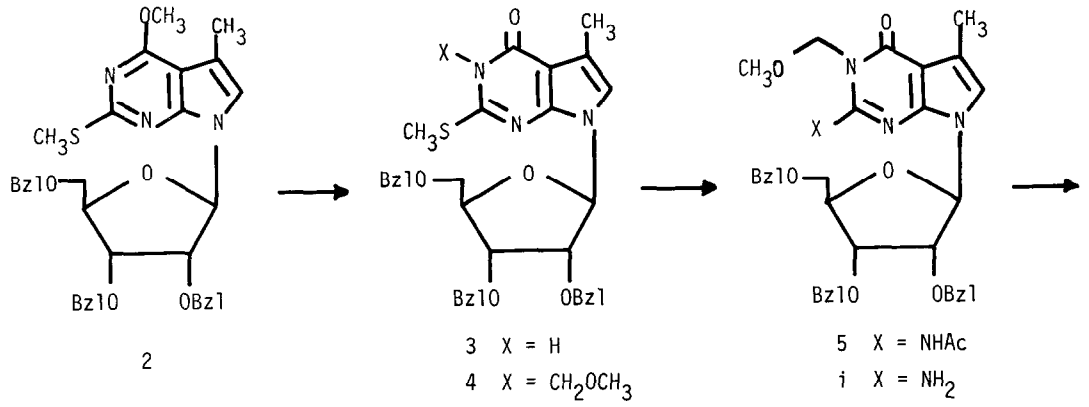
(Received in Japan 5 September 1977; received in UK for publication 26 September 1977)

Nucleoside Q was found in the first position of the anticodon of E. coli $tRNA^{Tyr}$, $tRNA^{His}$, $tRNA^{Asn}$, and $tRNA^{Asp}$, and its structure proposed to be 1 from mainly spectral analysis;[1,2] anomeric and absolute configurations being undetermined. The nucleoside bond could not be hydrolyzed with acids as expected from its 7-deazapurine structure. Recently nucleoside Q^*, a mixture of 4"-O-mannosyl and 4"-O-galactosyl derivatives of Q, was found in tRNA's of various animals.[3] A synthetic approach to these nucleosides was reported by Townsend et al.[4] We wish to report a total synthesis of nucleoside Q using (±)-3β-aminocyclopent-1-ene-4α,5α-diol acetonide 10,[2] the nucleoside Q synthesized must contain its side-chain enantiomer, but neither its 270 MHz nmr spectrum nor high-pressure liquid chromatography (HPLC) of the acetonide 12 showed any indication of heterogeneity; only slight difference on the magnitudes of the cd spectra was observed between the diacetonide 14 of the natural and the synthetic nucleoside Q. Synthesis of optically pure nucleoside Q is now under way.

Condensation of the anion of 4-methoxy-5-methyl-2-methylthiopyrrolo[2,3-d]pyrimidine with 2,3,5-tri-O-benzyl-D-ribofuranosyl bromide gave in 25% yield the β-nucleoside 2, m.p. 105°,[5] whose anomeric configuration was rigorously established by deriving it to a quaternary 1,5'-cyclonucleoside.[5] Refluxing 2 in dioxan with 0.5N hydrochloric acid containing a trace of 4,4'-thiobis(6-t-butyl-3-methylphenol)[6] for 24 hours furnished deazainosine 3 [mp 140°,[7] uv λ_{max}^{MeOH} 278 nm (ε 12200), 298 (13600)] in 87% yield. Methoxymethylation of 3 with sodium hydride and chloromethyl methyl ether in 1,2-dimethoxyethane afforded the N-methoxymethyl derivative 4[8] [mp 97°,[7] uv λ_{max}^{MeOH} 278sh nm (ε 8380), 308 (11300)] in 84% yield. Sodium hydride (53% in mineral oil, 62 mg) and acetamide (600 mg) were mixed and heated at 120° under nitrogen atmosphere. The deazainosine 4 (100 mg) was added and the mixture was heated for further 40 min to give deazaguanosine 5 [mp 115°,[7] uv λ_{max}^{MeOH} 275 nm (ε 6050), 304 (8550)] in 99% yield.[9] Debenzylation of 5 was carried out in methanol with 10% palladium on charcoal

and hydrogen; the product was then treated with 2,2-dimethoxypropane and camphorsulfonic acid in acetone to furnish the acetonide 6 [mp 180-182°,[7] 62% yield], which on acetylation with acetic anhydride and pyridine gave the N,N,O-triacetyl derivative 7 [mp 56-57°,[7] nmr ($CDCl_3$) δ 2.36 (6H,s,NAc_2), 6.71 (1H,br.s,6-H)] in quantitative yield. A benzene solution of 7 was treated with N-bromosuccinimide (1.3 eq.) and a catalytic amount of benzoyl peroxide at room temp. to give monobromide 8 [mp 63-65°,[7b] nmr ($CDCl_3$) δ 2.36 (9H,s,C-Me,NAc_2), no signal around 6.71; exact mass $C_{23}H_{29}O_9N_4{}^{79}Br$: 584.1118, found: 584.1096] in nearly quantitative yield. A mixture of the monobromide 8, N-bromosuccinimide (2 eq.), potassium carbonate, and a catalytic amount of benzoyl peroxide in carbon tetrachloride was refluxed for 2 hrs [tlc gave a spot of dibromide 9; nmr ($CDCl_3$) δ 4.80 (2H,s,CH_2Br)]. To this reaction mixture was added the racemic cyclopentenylamine 10 (5 eq.) and diisopropylethylamine (14 eq.) in benzene and the mixture was stirred at room temp. for 2 hrs. Tlc separations gave the protected 6-bromo-nucleoside Q 11 as a syrup[7b,11] [nmr ($CDCl_3$) δ 2.28 (3H,s,NHAc), 3.92 (2H,C-CH_2N)] in 80% yield. To a suspension of zinc-copper couple[10] in dioxan was added the bromide 11 and the mixture was refluxed for 3 hrs. After filtration, the solution was evaporated to dryness and the residual syrup was stirred at room temp. with a mixture of conc. ammonia and methanol (1:2) for 12 hrs. Tlc of the product gave the 3-methoxymethyl-nucleoside Q diacetonide 12 [powder, mp 87-93°,[7b] field desorption mass spec. (fd) m/e 534 (M+1), uv λ_{max}^{MeOH} 265 nm (ε 7310), 293 (5400), $[\alpha]_D^{32}$ -38.1° (c 0.097, $CHCl_3$), nmr ($CDCl_3$) δ 6.61 (1H,br.s,H-6)] in 50% yield. The diacetate 13[9] [exact mass $C_{29}H_{39}O_{10}N_5$: 617.2696, found: 617.2726] obtained from 12 gave a single peak on HPLC[12] even after 6 times recycling, whereas two peaks were clearly observable in the case of its α-anomer.[13]

All protecting groups of 12 were removed by heating in a sealed tube with 2N hydrochloric acid at 80° for 6 hrs. The mixture was dried up in vacuo to give as a sole product nucleoside Q (1) hydrochloride [single spot on tlc; fd m/e 410 (M+1); nmr (270 MHz, D_2O, pD 2.3) δ 3.81 and 3.84 (H-5'), 4.19 (H-4'), 4.30 (H-3"), 4.35 (H-3'), 4.40 (H-4"), 4.43 and 4.49 (CH_2N), 4.61 (H-2'), 4.70 (H-5"), 5.98 (H-1'), 6.12 (H-1"), 6.29 (H-2"), 7.18 (H-6), $J_{1",2"}$= 6.5 Hz, $J_{2",3"}$= 2.5, $J_{3",4"}$= 5.2, $J_{4",5"}$= 5.2, $J_{1",3"}$= ca 0.5, $J_{1",5"}$= 1.5, $J_{2",5"}$= 1.7, $J_{1',2'}$= 6.3, $J_{2',3'}$= 5.4, $J_{3',4'}$= 3.6, $J_{4',5'}$= 3.4 and 4.0, $J_{5',gem}$= 13; (270 MHz, D_2O, pD above 11) δ 3.78 (H-3"), 4.01 (H-4"), 4.65 (H-5"), 5.97 (H-2"), 6.01 (H-1"), 6.85 (H-6)]. All of the chemical shift values and the coupling constants agreed within ±0.01 ppm and ±0.1 Hz, respectively, with the values reported for natural nucleoside Q (220 MHz).[1] Any signals which might indi-



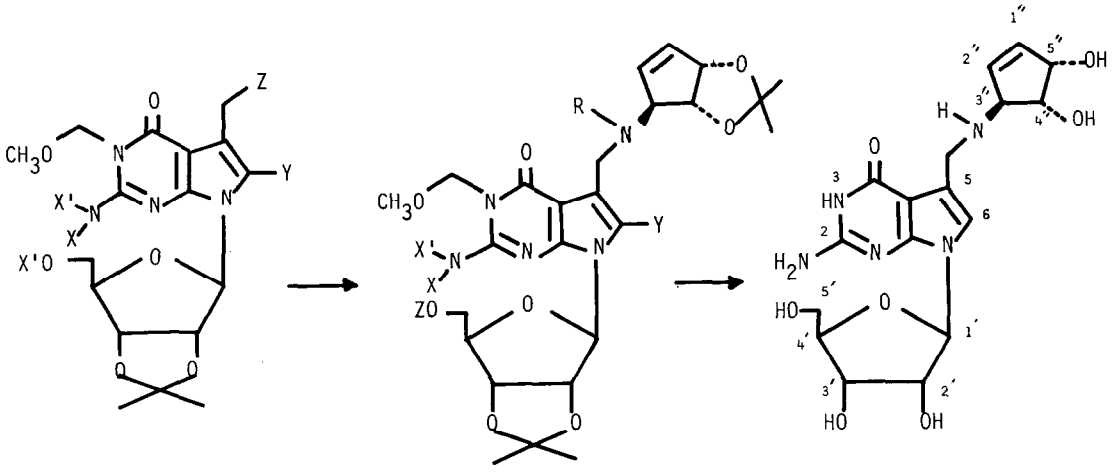
2

3 X = H

4 X = CH_2OCH_3

5 X = NHAc

i X = NH_2



6 X'=Y=Z=H, X=Ac

7 Y=Z=H, X=X'=Ac

8 Y=Br, Z=H, X=X'=Ac

9 Y=Z=Br, X=X'=Ac

11 Y=Br, R=X=H, X'=Ac

12 R=X=X'=Y=Z=H

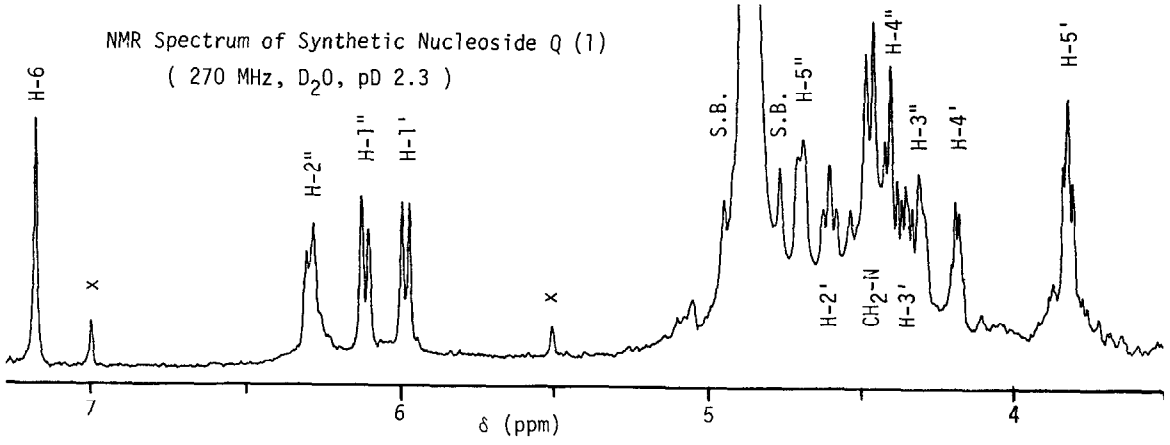
13 R=Ac, X=X'=Y=H, Z=Ac

ii Y=Br, R=X=X'=Z=Ac

1 (natural) absolute config. unknown

1 (synthetic) cyclopentene part is DL mixture

14 2',3':4",5"-Diacetonide of 1



cate the presence of the diastereomer were not detected; α-anomer of Q[13] gave a nmr spectrum clearly different from that of natural Q. Uv spectra of synthetic Q in water at various pH's (neutral, 0.1N HCl, 1N HCl, and 0.1N NaOH) were completely superimposable to those of natural Q.[1] Nucleoside Q diacetonide (14) prepared according to Kasai et al.[1] was shown to be identical with the acetonide of natural Q by fd mass spectra and HPLC.[14]

We are grateful to Prof. T. Miyazawa and Dr. F. Inagaki, Department of Biological Sciences, University of Tokyo, for measurement of 270 MHz nmr spectra (Brucker), and Dr. S. Nishimura, National Cancer Center Research Institute, for providing us samples of nucleoside Q and its acetonide for comparison.

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2. T. Ohgi, T. Goto, H. Kasai and S. Nishimura, Tetrahedron Lett., 367 (1976).
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6. Without this antioxidant the reaction proceeded sluggishly.
7 (a) Satisfactory analytical data (C, H, and N) were obtained; (b) full characterization was done by ir (except 11), uv, nmr, and mass spectrometry.
8. 4-O-Methoxymethylated compound of 3, mp 88°,[7] was obtained in 9% yield, which could be converted to the starting material by treatment with acetic acid.
9. Interestingly, acetylation of the monoacetate 5 with acetic anhydride and pyridine gave N,N-diacetyl derivative of i, whereas no N-acetylation occurred with the amine i in the same condition. Similarly, acetylation of 11 and 12 afforded ii and 13, respectively.
10. R. J. Rawson and I. T. Harrison, J. Org. Chem., 35, 2057 (1970).
11. Acetylation of 11 with acetic anhydride and pyridine gave ii having the acetamidocyclopentene moiety, which could be debrominated, but acid hydrolysis of the product was accompanied by severe decomposition.
12. MicroPak Si-5, isooctane:dichloromethane containing 2.5% isopropanol (1:3), flow rate 0.7 ml/min, retention time: β-anomer 9.0 min, α-anomer 20 min.
13. Prepared from the α-anomer of 2[5] in the similar manner to the preparation of the corresponding β-anomer.
14. MicroPak Si-5, 12% methanol in dichloromethane, flow rate 1.0 ml/min, retention time 3.5 min.