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SYNTHESIS OF Q BASE (QUEUINE)

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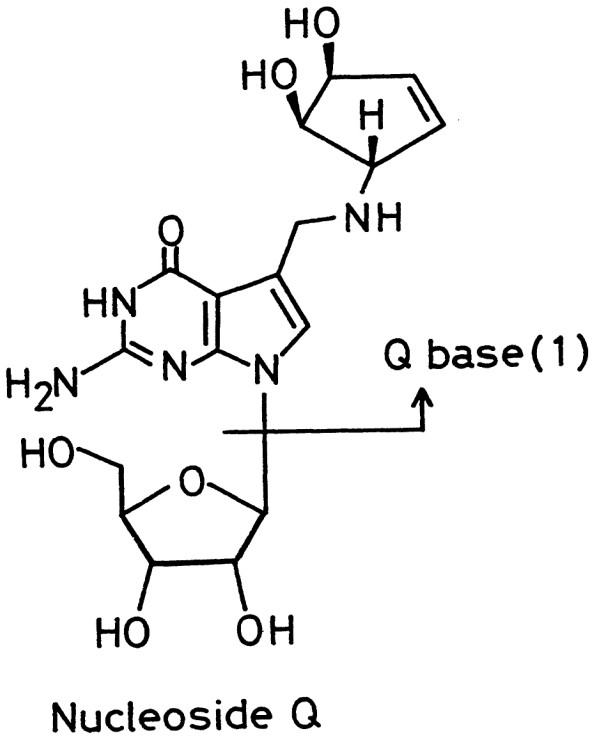
Q base (queuine), 2-amino-5-[(3S,4R,5S)-4,5-dihydroxycyclopent-1-en-3-yl-aminomethyl]pyrrolo[2,3-d]pyrimidin-4(3H)-one, was synthesized *via* the Schiff base intermediate.

Nucleoside Q (queuosine) is a unique hyper-modified nucleoside found in the first position of the anticodon of $tRNA^{Tyr}$, $tRNA^{His}$, $tRNA^{Asp}$, and $tRNA^{Asn}$.[1,2] Nishimura *et al.*[3] reported that in *Escherichia coli* it is biosynthesized at the first position of the anticodon by exchange of guanine with $preQ_1$ base or $preQ_0$ base and then by modification of these precursors to Q base. The enzyme that catalyzes this reaction is *E. coli* tRNA transglycosylase.[4] The similar enzyme isolated from rat liver, however, catalyzes exchange of guanine with Q base directly.[5] Thus, the biosynthetic route of nucleoside Q in mammals differs from that of bacteria. Interestingly, although tRNA from normal mammalian cells contains Q base at the first position of the anticodon, tRNA isolated from various tumors has defficiency of Q base; they contain guanine instead of Q base.[6] Recently, Katze attempted to determine if the administration of Q base could relieve the deficiency of nucleoside Q in tumor tRNA *in vivo*. He observed[7] that the administration of Q base to Ehrlich ascites tumor-bearing mice reverses the deficiency of nucleoside Q in the tRNA and, coincidentally, causes an inhibition of tumor growth. Farkas reported[8] that mammals cannot synthesize Q base, but accept it from diet or intestinal bacteria. It is widely distributed in nature.[9] Incidentally, Q base (1) could not be obtained from nucleoside Q by acid hydrolysis since the glycosylic linkage of the deazaguanosine type nucleosides strongly resists acid



Nucleoside Q

hydrolysis. We already reported [3] in a very brief form a total synthesis of Q base (1). Now, we wish to describe a new route for its more efficient synthesis.

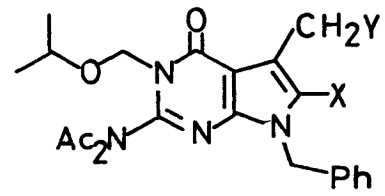
The monobromide 2 (2.54 g), N-bromosuccinimide (1.05 g) and potassium carbonate (2.71 g) were refluxed in carbon tetrachloride (440 ml) in the presence of a catalytic amount of benzoyl peroxide for 5 h. The insoluble material was filtered and the filtrate was evaporated in vacuo. The residual dibromide 3 was dissolved in a mixture of dioxane and water (10:1) and treated with silver carbonate (12 g) at room temperature for 16 h with stirring. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in methanol (130 ml) and treated with conc. ammonia (100 ml) at room temp. for 16 h. The mixture was concentrated in vacuo to one-half volume, when crystalline solid of the bromo-alcohol 4 was precipitated almost quantitatively [m/z 422 and 420 (M^+); $\delta(CDCl_3)$ 1.24 (6H, d), 3.90 (1H, heptet), 4.70 (2H, br.s), 5.24 (2H, s), 5.40 (2H, br.s, exchangeable with D_2O), 5.60 (2H, s), 7.24 (5H, br.s)].

The bromo-alcohol 4 (1.87 g) and potassium acetate (0.66 g) were dissolved in methanol (180 ml) and the mixture was hydrogenated in the presence of palladium catalyst. After filtration of the catalyst, the filtrate was concentrated to give the debrominated alcohol 5 as a pale yellow solid (1.4 g) [m/z 342 (M^+); $\delta(CDCl_3)$ 1.20 (6H, d), 3.84 (1H, heptet), 4.64 (2H, s), 5.04 (2H, s), 5.48 (2H,br.s), 5.52 (2H,s), 6.34 (1H,s), 7.20(5H,m)]. The alcohol 5 (1.0 g) in benzene (100 ml) was treated with active MnO_2 (1 g) at room temp. for 22 h. After filtration, the residue was extracted several times with methanol-dichloromethane (1:1). The extracts were combined with the filtrate and evaporated to dryness to yield crude crystalline mass (800 mg). Purification by silica gel tlc gave the pure aldehyde 6 (685 mg) as a pale yellow crystalline solid [m/z 340 (M^+); $\delta(CDCl_3)$ 1.20 (6H, d), 3.88 (1H, heptet), 5.12 (2H, s), 5.52 (2H, br.s), 5.56 (2H, s), 7.10-7.40 (6H, m), 10.20 (1H, s)].

To a solution of the aldehyde 6 (685 mg) in benzene (70 ml) was added one mole equivalent of the (+)-cyclopentenylamine 7 [10] in benzene (10 ml) and the mixture was allowed to stand at room temp. for 17 h. Evaporation of the solvent in vacuo gave in quantitative yield a yellow crystalline solid of the Schiff base 8, m.p. 167-168 °C [$\delta(CDCl_3)$ 1.28 (6H, d), 1.36 (3H, s), 1.48 (3H, s), 3.88 (1H, heptet), 4.56 (1H, br.s), 4.64 (1H, d), 5.12 (2H, s), 5.32 (1H, br.d), 5.52 (2H, br.s), 5.56 (2H, s), 5.78 (1H, d), 6.00 (1H, br.d), 7.00-7.40 (6H, m), 8.88 (1H, s)]. A solution of the Schiff base 8 (980 mg) in ethanol-dichloromethane was treated with $NaBH_4$ at 0°C for 1.5 h. Water was added to destroy the reagent and the mixture was evaporated to dryness in vacuo. The residue was purified by silica gel tlc to give the amine 9 (826 mg) [m/z 521 (as its monoacetate); $\delta(CDCl_3)$ 1.20 (6H, d), 1.32 (3H, s), 1.36 (3H, s), 3.68-4.00 (4H, m), 4.52 (1H, d), 5.00 (2H, s), 5.20 (1H, d), 5.28 (2H, br.s), 5.48 (2H, s), 5.80 (2H, br.s), 6.36 (1H, s), 7.00-7.30 (5H, m)].

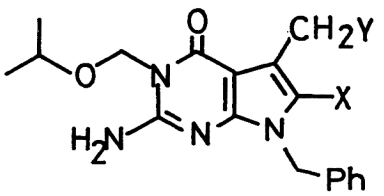
The amine 9 (26.5 mg) was dissolved in a mixture of trifluoroacetic acid and water (5:1; 0.5 ml) and the solution was allowed to stand at room temp. for

30 min. Evaporation of the solvent gave in quantitative yield the crude diol 10 as its trifluoroacetic acid salt. The diol 10 was dissolved in dimethoxyethane (0.1 ml) and treated with sodium hydride (52% in oil; 9.0 mg) under Ar atmosphere at room temp. for 30 min, and then the mixture was cooled to -78°C. To this mixture was introduced anhydrous ammonia gas until the total volume reached to 1 ml. Lithium metal (2.4 mg) was added to it at the same temp., when the deep



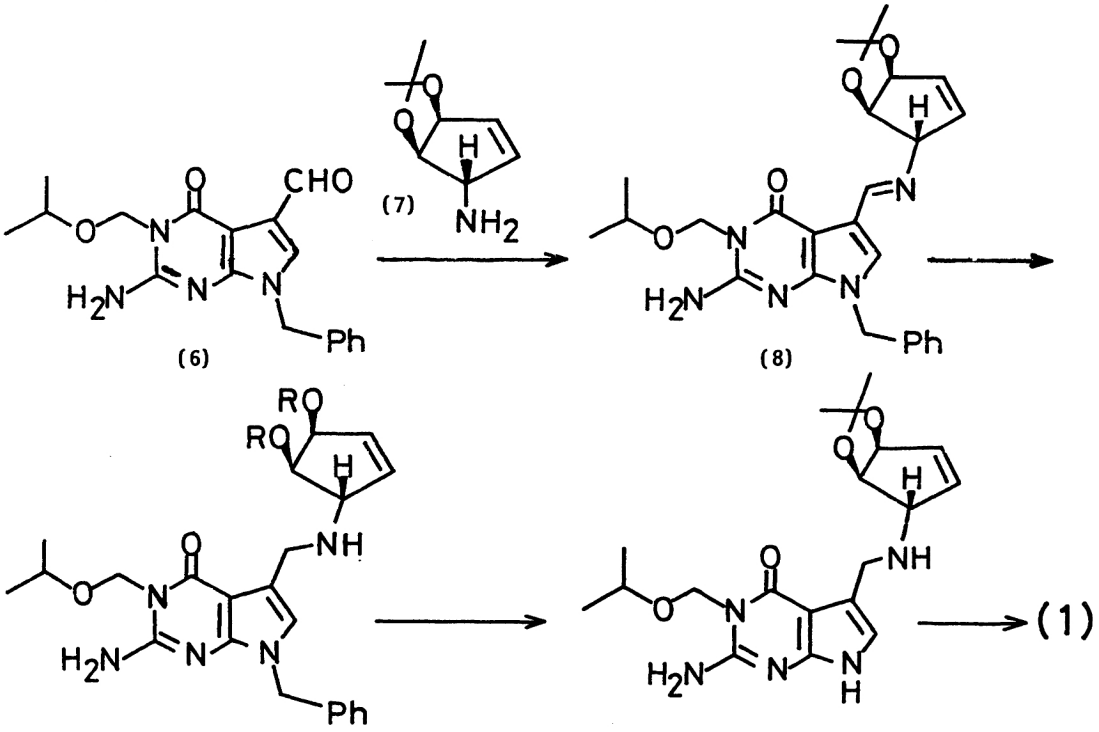
(2) X = Br, Y = H

(3) X = Y = Br



(4) X = Br, Y = OH

(5) X = H, Y = OH



(6)

(7)

(8)

(9) R,R = isopropylidene

(10) R = H

(11)

blue color developed. After 10 min (the blue color still remained) ammonium chloride (50 mg) was added to it and the mixture was evaporated in vacuo to dryness. The residue was treated with a mixture of acetone (5 ml), 2,2-dimethoxypropane (2.5 ml) and camphorsulfonic acid (20 mg) at room temp. for 24 h. After filtration, the filtrate was evaporated to dryness and the residue was purified by silica gel tlc to give the debenzylated acetonide 11 (13.6 mg) [m/z 431 (as its monoacetate); $\delta(CD_3OD)$ 1.16 (6H, d), 1.32 (6H, br.s), 3.60-4.00 (3H,

m), 4.52 (1H, br.d), 5.16 (1H, br.d), 5.48 (2H, s), 5.80 (2H, m), 6.56 (1H, s)]. The acetonide 11 (6 mg) was hydrolyzed with 1M HCl (3 ml) and methanol (0.5 ml) at 80°C for 5 h. Evaporation of the solvent gave in quantitative yield the Q base (1) as its hydrochloride, colorless prisms, m.p. 230-235°C (dec.) [Found: C, 40.43; H. 5.10; N. 19.40; Cl, 19.50%. $C_{12}H_{15}N_5O_3 \cdot 2HCl \cdot 1/2H_2O$ requires: C, 40.12; H, 5.05; N, 19.50; Cl, 19.74%; $[\alpha]_D^{26}$ +113°(c 0.3, H_2O); $\delta(D_2O)$ 4.28-4.60 (2H, m), 4.50 (2H, br.s), 6.13 (1H, dd), 6.35 (1H, m), 7.12 (1H, s)].

In the previous report [2] the dibromide 3 was condensed with the (+)-amine 7. In that case, however, a large excess of the (+)-amine 7 had to be used, because otherwise the hardly separable bis-deazaguanine derivative was contaminated.

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References

1) H. Kasai, Z. Ohashi, F. Harada, S. Nishimura, N. J. Oppenheimer, P. F. Crain, J. G. Liehr, D. L. von Minden, and J. A. McCloskey, Biochem., 14, 4198 (1975) and references therein.
2) T. Ohgi, T. Kondo and T. Goto, J. Am. Chem. Soc., 101, 3629 (1979).
3) N. Okada, S. Noguchi, H. Kasai, N. Shindo-Okada, T. Ohgi, T. Goto, and S. Nishimura, J. Biol. Chem., 254, 3067 (1979); T. Ohgi, T. Kondo, and T. Goto, Chem. Lett., 1979, 1283; T. Kondo, S. Nakatsuka, and T. Goto, Chem. Lett., 1980, 559.
4) N. Okada and S. Nishimura, J. Biol. Chem., 254, 3061 (1979).
5) N. Shindo-Okada, N. Okada, T. Ohgi, T. Goto, and S. Nishimura, Biochem., 19, 395 (1980).
6) N. Okada, N. Shindo-Okada, S. Sato, Y. H. Itoh, K. Oda, and S. Nishimura, Proc. Natl. Acad. Sci. USA, 75, 4247 (1978).
7) J. R. Katze and W. T. Beck, Biochem. Biophys. Res. Comm., 96, 313 (1980).
8) W. R. Farkas, J. Biol. Chem., 255, 6832 (1980); J. P. Reyniers, J. R. Pleasants, B. S. Wostmann, J. R. Katze, and W. R. Farkas, J. Biol. Chem., 256, 11591 (1981).
9) J. R. Katze, B. Basile, and J. A. McCloskey, Science, 216, 55 (1982).
10) T. Ohgi, T. Kondo, and T. Goto, Chem. Lett., 1979, 1283.

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