The Synthesis of 2-Amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidin-4-one (7-Deazaguanosine), a Nucleoside Q and Q* Analog (1)

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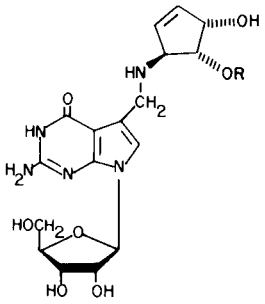
The synthesis of 2-amino-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidin-4-one (7-deazaguanosine), a nucleoside Q and Q* analog, has been accomplished by two independent routes.

J. Heterocyclic Chem., **13**, 1363 (1976).

Sir:

It has been reported (2) that the minor nucleoside Q is widely distributed in tRNA from various sources and in fact occupies the first position of the anticodon of *E. Coli* $tRNA^{Tyr}$, $tRNA^{His}$, $tRNA^{Asn}$ and $tRNA^{Asp}$. The structure of nucleoside Q was recently elucidated and reported (3) to be 2-amino-5-(4,5-*cis*-dihydroxy-1-cyclopenten-3-yl-*trans*-aminomethyl)-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidin-4-one (**1a**). Studies (4) on the

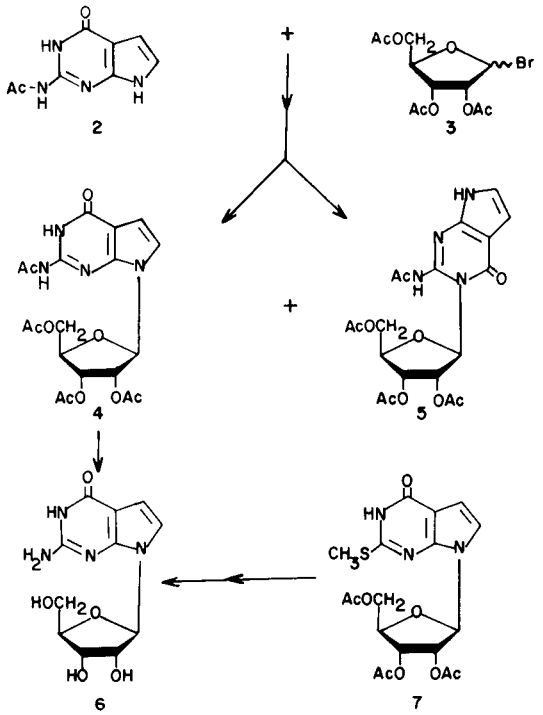


1a, R = H
b, R = glycosyl

biosynthesis of nucleoside Q has implicated guanine as a definite precursor. Studies on the closely related nucleoside Q* have established (5) that the R group is a mixture of *O*-glycosides (β-D-mannosyl, β-D-galactosyl/3:1) although the stereochemistry of the side chain is still not firm. This was of considerable interest to us since we have been involved in the synthesis of pyrrolo[2,3-*d*]pyrimidine nucleosides structurally related to the nucleoside antibiotics toyocamycin, sangivamycin and tubercidin for several years (6-7). These nucleosides can be viewed as 7-deazapurine nucleosides and complement some of our more recent research involving the synthesis of certain 3-deazapurine (8-9) and 1-deazapurine (10) nucleosides. We now wish to report on the synthesis of 7-deazaguanosine, *per se*, which can be viewed as the nucleoside Q and Q* *sans* the exocyclic substituent at C-5.

Our initial approach toward the synthesis of 7-deazaguanosine involved the use of a compound, 2-methylthio-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]-pyrimidin-4-one (**7**), which had been previously prepared in our laboratory (11). Treatment of **7** with 30% hydrogen peroxide in methanol furnished what we assumed to be the corresponding 2-methylsulfonyl derivative although this intermediate was not isolated and characterized. In fact, the hydrogen peroxide was simply destroyed with 5% excess palladium on charcoal, the catalyst was collected by filtration and the filtrate evaporated to dryness *in vacuo* to afford a syrup which was covered with liquid ammonia and heated at 85° in a sealed reaction vessel for 24 hours. The solvent was removed *in vacuo* and the residue was dissolved in the minimum amount of methanol. This solution was applied to a preparative plate (Mallinckrodt SilicAR 7GF) and developed with a mixture of ethyl acetate/1-propanol/-water (4:1:2/v:v) upper phase. The uv absorbing band with spectral properties similar to those reported (12) for 7-deazaguanine furnished a 10% yield of a tan material which we assumed was 7-deazaguanosine (**6**), uv (λ max in nm, $\epsilon \times 10^{-3}$) *p*H 1, 262 (11.1); *p*H 11, 262 (12.6). On the basis of our previous experience (13) with nucleophilic displacements in the pyrrolo[2,3-*d*]pyrimidine ring system, this low yield was not unexpected.

This prompted us to investigate an alternate route for the synthesis of **6** using 2-aminopyrrolo[2,3-*d*]pyrimidin-4-one as our starting material. Acetylation of 7-deazaguanine with pyridine and acetic anhydride furnished



a di-acetyl derivative (14) with one acetyl group residing on the exocyclic amino group and the other acetyl group attached to one of the ring nitrogens. The acetyl group attached to a ring nitrogen was selectively removed (15) under dilute basic conditions to furnish a 95% yield of 2-acetamidopyrrolo[2,3-*d*]pyrimidin-4-one (**2**). The silylation of **2** was accomplished by heating a suspension of **2** in hexamethyldisilazane with a small drop of sulfuric acid. The solvent was removed, the resultant residue was dissolved in anhydrous benzene and this was followed by the addition of mercuric oxide and mercuric bromide in anhydrous benzene. A benzene solution of tri-*O*-acetyl-D-ribofuranosyl bromide (**3**) was added and the reaction mixture was heated at reflux for 12 hours with the exclusion of moisture. The mercuric salts were removed by filtration, washed with chloroform and the combined filtrate and washings were extracted successivley with sodium bicarbonate, saturated potassium iodide solution and then water. Column chromatography using Baker silica gel and chloroform/methanol (24:1) furnished two major nucleosides (**4** and **5**) in 31% and 28% yields, respectively. The uv spectra of **4** and **5** were λ max (ethanol) 271 nm and λ max (ethanol) 275 nm, respectively. On this basis, we tenatively assigned these nucleosides as the 7-ribosyl and the 3-ribosyl derivatives. The nucleoside **4** was treated with methanolic sodium methoxide to remove the protecting groups. After neutralization of the reaction mixture with Dowex 50 W-X2, recrystallization of the solid from aqueous methanol furnished a 47% yield of 2-amino-7-(β-D-ribofuranosyl)-pyrrolo[2,3-*d*]pyrimidin-4-one (**6**, 7-deazaguanosine); m.p. 221-223°; uv (λ max in nm, $\epsilon \times 10^{-3}$) *p*H 1, 262 (11.2) 218 (20.3); ethanol, 280 sh (11.2), 260 (15.8); *p*H 11, 262 (12.7). This nucleoside was found to be identical (uv spectral comparisons and tlc comparisons in four different solvent systems) to the nucleoside which had been prepared from the 2-methylthio-derivative **7** *via* the methylsulfonyl intermediate. Since the nucleoside **7** was of established structure, this established the site of ribosylation as N-7 and β for all nucleosides reported in this communication (16,17).

REFERENCES AND NOTES

(1) This research was supported by research contract NO1-CM-43806 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

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(14) There was observed two distinct (3 proton) peaks in the δ 2.0 region of the pmr spectrum.

(15) The pmr spectrum of **2** revealed a low broad peak in the δ 11-12 region and a medium broad peak in the δ 7-8 region.

(16) The exception is nucleoside **5** which was definitely not the 7-ribosyl isomer as determined by a pmr spectrum. On this basis, we have tentatively assigned this nucleoside as the 3-ribosyl iosmer although additional work is required before a definite assignment can be made.

(17) Satisfactory analytical data (C,H,N), pmr and uv spectra were obtained for all new compounds.