

Polyazanaphthylene Nucleosides II.  
Synthesis of  $\beta$ -D-Ribofuranosyl Derivatives of 4-Quinazolone (1,2)

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The preparation of  $N^1$ -(2,3-*O*-isopropylidene- $\beta$ -D-ribofuranosyl)-4-quinazolone (**6**) and  $N^3$ - $\beta$ -D-ribofuranosyl-4-quinazolone (**3b**) are reported. The  $N^3$  derivative was prepared by the direct condensation of 4-trimethylsilyloxyquinazoline (**2**) and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide. The  $N^1$  derivative was prepared from the previously reported  $N^1$ - $\beta$ -D-ribofuranosyl-2,4-quinazolinone *via* the cyclonucleoside **4**.

In continuing our study of the nucleosides of quinazolines we have now prepared  $N^3$ - $\beta$ -D-ribofuranosyl-4-quinazolone (**3b**) and the 2,3-*O*-isopropylidene of  $N^1$ - $\beta$ -D-ribofuranosyl-4-quinazolone (**6**). The  $N^3$  derivative was prepared by the direct condensation of 4-trimethylsilyloxyquinazoline and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in dry acetonitrile followed by methanol-ammonia removal of the benzoate groups. The anomeric configuration was presumed to be beta by analogy to the high specificity for beta configuration obtained using the silyl condensation method for nucleoside synthesis (2). The point of alkylation was established as  $N^3$  by comparison of the ultraviolet spectra of the known  $N^3$ -methyl-4-quinazolone (**3**),  $N^1$ -methyl-4-quinazolone (**3**) and 4-methoxyquinazoline (**3,4**), with that of the product of direct alkylation. The difference in the extinction coefficient of the two envelopes (each containing two peaks) centered at 305  $m\mu$  and 268  $m\mu$  was very striking. The extinction coefficient for the  $N^3$ -methyl-4-quinazolone (and also for the alkylation product **3b**) at 305  $m\mu$  was considerably greater than for the envelope at 268  $m\mu$  while the opposite was true for  $N^1$ -methyl-4-quinazolone and for the  $N^1$ - $\beta$ -D-ribofuranosyl-4-quinazolone derivative (**6**). The possibility of *O*-glycoside formation is excluded by a comparison of the ultraviolet spectrum of 4-methoxyquinazoline reported by Armarego (4) and the spectrum of **3b** both run at pH 0.3. The reported 4-methoxyquinazoline has peaks at 305  $m\mu$  and 235  $m\mu$  while **3b** has maxima at 276  $m\mu$  and 234  $m\mu$ .

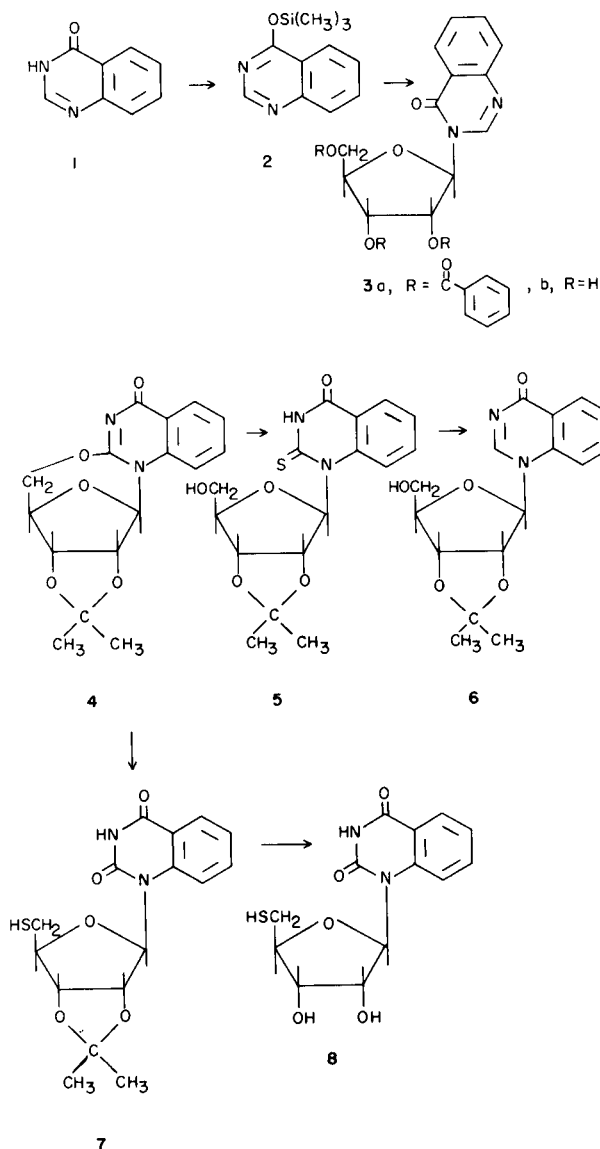
Synthesis of the  $N^1$  derivative (**6**) was accomplished in a five step procedure from  $N^1$ - $\beta$ -D-ribofuranosyl-2,4-quinazolinone. The first three steps, isopropylideneation,

methanesulfonylation and the formation of the  $O^{2,5'}$ -cyclonucleoside have been outlined in a previous paper (2). In our earlier report (2), cyclonucleoside formation was accomplished in dimethylformamide containing potassium *tert*-butoxide at 100° for 1.5 hours. Subsequent experiments have shown that these results are not always uniform and can lead to complete degradation of the product. Termination of the reaction 3-6 minutes after gel formation gave yields up to 80% of **4**. The cyclonucleoside (**4**) was then treated with hydrogen sulfide gas in dry dimethylformamide and triethylamine for three hours at room temperature to give a mixture of  $N^1$ -(2,3-*O*-isopropylidene- $\beta$ -D-ribofuranosyl)-2-thio-4-quinazolone (**5**) and  $N^1$ -(2,3-*O*-isopropylidene-5-thio- $\beta$ -D-5-deoxyribofuranosyl)-2,4-quinazolinone (**7**). The two products were readily separated by column chromatography on a silica gel column to give pure **5** and **7** in a ratio of ca. 1:2. The opening of a  $O^{2,5'}$ -cyclonucleoside with hydrogen sulfide to give mixtures of 2-thiones and 5'-thiols has been reported previously (5,6).

$N^1$ -(2,3-*O*-Isopropylidene- $\beta$ -D-ribofuranosyl)-2-thio-4-quinazolone (**5**) was dethiated in boiling ethanol with Raney Nickel to give the isopropylidene derivative (**6**). The sugar-*N* bond in **6** was so labile that the isopropylidene group could not be selectively removed without concomitant hydrolysis of the glycoside linkage.

Interest in the ribosyl derivatives of 4-quinazolone as potential physiologically active compounds was stimulated by the various *N*-alkylated 4-quinazolones which have been found in nature such as febrifugine (7,8) ( $N^3$ - $\beta$ -keto- $\gamma$ -(3-hydroxy-2-piperidyl)propyl-4-quinazolone) and glycorine (9) ( $N^1$ -methyl-4-quinazolone). In addition

*in vitro* antiviral activity of  $N^1$ - $\beta$ -D-ribofuranosyl-2,4-quinazolinedione (10) gave added interest to the synthesis of these derivatives.



## EXPERIMENTAL

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were run on a Beckman DK-2 spectrophotometer. All evaporations were done *in vacuo*.

### 4-Trimethylsilyloxyquinazoline (2).

A mixture of 5 g. of 4-quinazolinedione (11) and 250 ml. of toluene was refluxed for 3 hours using a Dean-Stark trap. After the reaction had been cooled to ca. 50°, 4.7 ml. of trimethylchlorosilane was added and the solution was again brought to reflux. Triethylamine (6.2 ml.) in toluene (25 ml.) was added and the reflux was continued for 3 hours. The reaction was cooled and

stirred overnight. The salts were removed by filtration and the filtrate was evaporated. The residual oil was distilled at 0.07 mm of Hg and 90° to give 6.1 g. (81%) of a clear colorless oil.  $N^3$ - $\beta$ -D-(2,3,5-Tri-*O*-benzoylribofuranosyl)-4-quinazoline (3a).

2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl bromide prepared from 21.5 g. (42.6 mmoles) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose and 9.4 g. (42.6 mmoles) of 4-trimethylsilyloxyquinazoline (2) were dissolved in 250 ml. of dry acetonitrile and left at room temperature for 44 hours. The solution was then evaporated and the resulting oil was dissolved in 120 ml. of hot ethanol to which 30 ml. of water was then added. The mixture was cooled and filtered to give 22.5 g. (90%) of material which melted at 143-151°. An analytical sample was prepared by crystallization of the product from methanol to yield crystals, m.p. 152-154°; uv  $\lambda$  max (methanol) 312 ( $\epsilon$ , 2,700), 301 ( $\epsilon$ , 3,400), 272 ( $\epsilon$ , 9,800), 263 ( $\epsilon$ , 10,400), 229  $m\mu$  ( $\epsilon$ , 71,000).

*Anal.* Calcd. for  $C_{34}H_{26}N_2O_8$  (mol. wt. 590.57): C, 69.14; H, 4.44; N, 4.74. Found: C, 69.12; H, 4.35; N, 4.57.

### $N^3$ - $\beta$ -D-Ribofuranosyl-4-quinazoline (3b).

A mixture of 2 g. of 3a in 125 ml. of methanol, previously saturated with ammonia at 0°, was heated in a sealed bomb at 100° for 10.5 hours. The solution was filtered, evaporated, and the residue was triturated with dichloromethane and filtered. The resulting brown solid which weighed 0.80 g. (85%) was crystallized from a 1:1 dioxane-benzene mixture. An analytical sample was prepared by crystallization from ethyl acetate to give product 3b, m.p. 164-165°; uv,  $\lambda$  max (pH 1) 292 infl. ( $\epsilon$ , 5,300), 274 ( $\epsilon$ , 7,000), 232  $m\mu$  ( $\epsilon$ , 28,000);  $\lambda$  max (pH 11) 312 ( $\epsilon$ , 2,700), 301 ( $\epsilon$ , 3,400), 272 ( $\epsilon$ , 5,800), 263 ( $\epsilon$ , 6,700), 226  $m\mu$  ( $\epsilon$ , 29,000);  $\lambda$  max (methanol) 312 ( $\epsilon$ , 3,000), 301 ( $\epsilon$ , 3,700), 273 ( $\epsilon$ , 7,000), 264 ( $\epsilon$ , 7,700), 225  $m\mu$  ( $\epsilon$ , 30,600).

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_5$  (mol. wt. 278.26): C, 56.11; H, 5.07; N, 10.07. Found: C, 55.65; H, 5.09; N, 9.85.

### Preparation of $O^2,5'$ -anhydro- $N^1$ -(2,3-*O*-isopropylidene- $\beta$ -D-ribofuranosyl)-4-quinazoline (4).

In reference 2 (method B) a reflux period of 1.5 hours was indicated. Subsequent experiments have shown that a time nearer 10 minutes is preferable. The *tert*-butyl alcohol is unnecessary. Completion of the reaction is best determined by the formation of a thick gel-like mixture.

### $N^1$ -(2,3-*O*-Isopropylidene- $\beta$ -D-(ribofuranosyl)-2-thio-4-quinazoline (5) and $N^1$ -(2,3-*O*-isopropylidene-5-thio- $\beta$ -D-5-deoxyribofuranosyl)-2,4-quinazolinedione (7).

A solution of 5.2 g. of  $O^2,5'$ -anhydro- $N^1$ -(2,3-*O*-isopropylidene- $\beta$ -D-ribofuranosyl)-4-quinazoline (4) in 210 ml. of dry dimethylformamide and 7.2 ml. of triethylamine was treated with hydrogen sulfide gas. The solution changed from colorless to blue to green during the reaction. After a total time of 3 hours the green solution was evaporated and the residue coevaporated twice with methanol-*n*-butanol. The resulting foam was dissolved in chloroform and applied to a dry packed column of silica gel (12) (454 g. 4.6 cm x 72 cm). The 5'-thio compound 7 was eluted with the same solvent. The first 2.8 l. of chloroform contained nothing and 7 was eluted in the next 1.8 l. After 7 had been eluted the solvent was changed to chloroform-ethyl acetate (2:1) and the 2-thio compound (5) was eluted with the new solvent front. The foam resulting from concentration of the fractions containing 5 was crystallized from benzene-cyclohexane and provided 1.72 g. (30%) of 5. An analytical sample was prepared by crystallization from the same solvent pair and had a m.p. of 136-137°;

uv  $\lambda$  max (pH 1) 282  $m\mu$  ( $\epsilon$ , 12,100);  $\lambda$  max (pH 11) 310 ( $\epsilon$ , 5,500), 277 ( $\epsilon$ , 11,100), 223  $m\mu$  infl. ( $\epsilon$ , 25,300);  $\lambda$  max (methanol) 288  $m\mu$  ( $\epsilon$ , 11,500).

*Anal.* Calcd. for  $C_{16}H_{18}N_2O_5S$  (mol. wt. 350.39): C, 54.84; H, 5.18; N, 8.00. Found: C, 55.01; H, 5.34; N, 7.70.

The fractions containing compound **7** were concentrated and the residue was crystallized from benzene-cyclohexane to give 3.15 g. (55%) of the 5'-thiol derivative. An analytical sample was crystallized from the same solvents and had an indefinite m.p. but was completely melted by 65°. The analytical sample was dried in a vacuum at 100° for 24 hours; uv  $\lambda$  max (pH 1) 306 ( $\epsilon$ , 3,400);  $\lambda$  max (pH 11), 306 ( $\epsilon$ , 3,800);  $\lambda$  max (methanol) 306  $m\mu$  ( $\epsilon$ , 3,400).

*Anal.* Calcd. for  $C_{16}H_{18}N_2O_5S$  (mol. wt. 350.39): C, 54.84; H, 5.18; N, 8.00. Found: C, 54.71; H, 5.18; N, 7.85.

$N^1$ -(5-Thio- $\beta$ -D-5-deoxyribofuranosyl)-2,4-quinazolinedione (**8**).

Eight hundred mg. of  $N^1$ -(2,3-O-isopropylidene-5-thio- $\beta$ -D-5-deoxyribofuranosyl)-2,4-quinazolinedione (**7**) was stirred in 16 ml. of 50% formic acid at room temperature for 21 hours. During this period the product precipitated from the formic acid solution. The solid was filtered off and washed with water, and dried giving 0.52 g. (73%), m.p. 237°. Crystallization of the solid from water-methanol provided an analytical sample which had a melting point of 246-247°; uv  $\lambda$  max (pH 1) 305 ( $\epsilon$ , 3,800),  $\lambda$  max (pH 11) 306 ( $\epsilon$ , 4,200),  $\lambda$  max (methanol) 305  $m\mu$  ( $\epsilon$ , 3,800).

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_5$  (mol. wt. 310.32): C, 50.31; H, 4.55; N, 9.03. Found: C, 50.40; H, 4.33; N, 8.84.

$N^1$ -(2,3-O-Isopropylidene- $\beta$ -D-ribofuranosyl)-4-quinazolone (**6**).

A mixture of 1.5 g. of  $N^1$ -(2,3-O-isopropylidene- $\beta$ -D-ribofuranosyl)-2-thio-4-quinazolone (**5**) and 15 g. of Raney nickel in 300 ml. of ethanol was stirred at reflux for 2 hours at which time an additional 3.5 g. of Raney nickel was added and the reflux was continued for 1 hour. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated to dryness. The residue was crystallized from methanol-benzene to give 0.49 g. (36%) of product which had a m.p. of 235-237°. An analytical sample was crystallized from the same solvent pair, m.p. 237.5-239°; uv  $\lambda$  max (pH 1) 302 ( $\epsilon$ , 5,100), 292 ( $\epsilon$ , 5,500), 235  $m\mu$  ( $\epsilon$ ,

24,000);  $\lambda$  max (pH 11) 313 ( $\epsilon$ , 6,700), 302 ( $\epsilon$ , 8,000), 232 ( $\epsilon$ , 14,400);  $\lambda$  max (methanol) 313 ( $\epsilon$ , 7,700), 302 ( $\epsilon$ , 8,900), 273 ( $\epsilon$ , 4,500), 264 ( $\epsilon$ , 4,300), 229  $m\mu$  ( $\epsilon$ , 16,700).

*Anal.* Calcd. for  $C_{16}H_{18}N_1O_5$  (mol. wt. 318.32): C, 60.37; H, 5.70; N, 8.80. Found: C, 60.26; H, 5.67; N, 8.66.

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