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Synthesis and Biochemical Evaluation of Nucleosides of Naphthoquinone Heterocycles

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The synthesis, characterization, and biochemical evaluation of 1-β-D-ribofuranosylnaphtho[2,3-*d*]imidazole-4,9-dione (**3**), 2-β-D-ribofuranosylnaphtho[2,3-*d*]pyrazole-4,9-dione (**6**), and 2-β-D-ribofuranosylnaphtho[2,3-*d*]triazole-4,9-dione (**9**) are reported. These quinone nucleosides and the corresponding quinone heterocycles were tested as inhibitors of purine nucleotide biosynthesis in Ehrlich ascites cells. The nucleosides **3** and **9** and naphtho[2,3-*d*]imidazole-4,9-dione were effective inhibitors of hypoxanthine phosphoribosyltransferase.

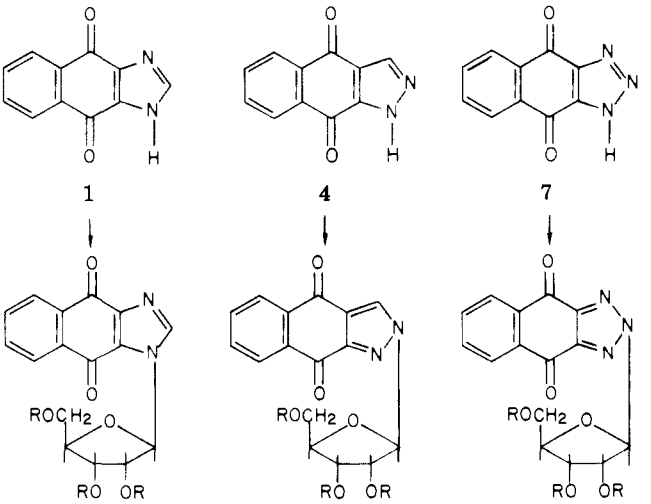
The involvement of quinones in numerous biochemical processes[1] has led to a study of a wide variety of synthetic derivatives. The facile reduction–oxidation of the quinone moiety appears to be the basis for the participation of a number of structurally diverse quinones in electron-transport and oxidative-phosphorylation processes.[1] The biological activity reported for quinones includes enzyme inhibition[2] and activity as antibacterial,[3] antifungal,[4] and anticancer agents.[5,6]

Heterocyclic quinones are one class of such compounds which have been investigated extensively.[7] Since synthetic nucleosides often exhibit enhanced biochemical activity compared to that of the aglycon,[8] it was of interest to investigate the synthesis and properties of nucleosides with the unique features of the quinone moiety.

Recently certain heterocyclic benzoquinone nucleosides were obtained by oxidation of the corresponding benzotriazoles.[9] The synthesis and biochemical activity of some benzoquinone *C*-nucleosides have also been described.[10] In the present work, the synthesis and characterization of ribonucleosides of imidazole, pyrazole, and triazole derivatives of 1,4-naphthoquinones are reported.

Ribosylation of these heterocyclic quinones by the Lewis acid-catalyzed procedure[11] proceeded readily (Scheme I). Thus, treatment of the *N*-trimethylsilyl derivative of naphtho[2,3-*d*]imidazole-4,9-dione[12] (**1**) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and stannic chloride afforded the blocked nucleoside **2**. Deacylation of **2** with sodium methoxide gave 1-β-D-ribofuranosylnaphtho[2,3-*d*]-imidazole-4,9-dione (**3**). Similarly, naphtho[2,3-*d*]-pyrazole-4,9-dione[13] (**4**) and naphtho[2,3-*d*]triazole-4,9-dione[14] (**7**) were converted to the corresponding ribonucleosides **6** and **9**, respectively.

Scheme I



The structures of these nucleosides were established on the basis of their carbon-13 and proton NMR data (Table I). Since the imidazole nucleoside **3** is formed from the symmetrical quinone **2** in which both nitrogens are equivalent, ribosylation must give 1-β-D-ribofuranosylnaphtho[2,3-*d*]imidazole-4,9-dione (**3**). The spectral data (Table I) are consistent with this structure. The position of the signal for the anomeric proton of **3** is at lower field

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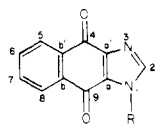
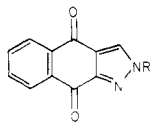
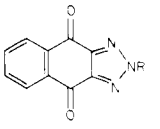
Table I. ^1H and ^{13}C Chemical Shifts of Methyl-Substituted Ribonucleosides of Imidazole, Pyrazole, and Triazole Derivatives of 1,4-Naphthoquinones

Compound	^1H shift, ppm			^{13}C shift, ppm							
	H-2	H-3	H-1′	C-4, C-9	C-2	C-3	C-a	C-a′	C-b, C-b′	C-5, C-8	C-6, C-7
 **3**[a]	8.82		6.46	178.2, 175.5	142.0		131.4	143.3	132.3, 132.1	133.8, 133.5	126.0, 125.8
 **6**[a]		9.00	5.95	178.3, 177.7		130.9	147.3	121.6	133.7, 133.7	133.9, 133.9	126.6, 126.4
1-Methylnaphtho-[2,3-*d*]pyrazole-4,9-dione[b]		8.10									
2-Methylnaphtho-[2,3-*d*]pyrazole-4,9-dione[b]		8.60									
 **9**[a]			6.16	176.6, 176.6			145.2	145.2	133.6, 133.6	134.6, 134.6	126.9, 126.9

[a] R = β-D-ribofuranosyl. [b] Reference 20.

(δ 6.46) than expected and this can be explained by the anisotropic effect of the quinone carbonyl group. A similar downfield shift of the anomeric proton has been observed for other nucleosides with a carbonyl group on the carbon β to the site of glycosylation.[15]

The pyrazole nucleoside **6** was assigned the 2-β-D-ribofuranosylnaphtho[2,3-*d*]pyrazole-4,9-dione structure, based on the proton NMR data (Table I). Comparison of the chemical shift for the H-3 resonance of **6** with the corresponding signals for the protons of the 1-methyl and 2-methyl derivatives shows a downfield shift of 0.40 ppm for the nucleoside **6** (H-3) compared to the 2-methyl derivative. This deshielding effect is approximately the same as that observed for other azole nucleosides compared to the corresponding *N*-methyl derivatives.[16] In addition, the anisotropic effect of the carbonyl group on the anomeric proton of a naphtho[2,3-*d*]pyrazole-4,9-dione nucleoside with the 1-β-D-ribofuranosyl structure would be expected to result in a downfield shift of the signal for the anomeric proton similar to that observed for the imidazole nucleoside **3**. The anomeric proton signal for **6** occurs at δ 5.95 while that for the imidazole is at significantly lower field (δ 6.46). These data are consistent with the 2-β-D-ribofuranosylnaphtho[2,3-*d*]pyrazole-4,9-dione structure for **6**.

The assignment of the ribosylation site of the naphtho[2,3-*d*]triazole-4,9-dione nucleoside was based on carbon-13 NMR data. Of the two possible structures (N-1 and N-2 isomers), the quinone portion of the nucleoside would exhibit C_2 symmetry only for the 2-β-D-ribofuranosylnaphtho[2,3-*d*]triazole-4,9-dione structure **9**. Table I shows the chemical shifts of the quinone carbons of **9**. The downfield resonance at 176.6 ppm is assigned to the keto carbons C-4 and C-9. The bridgehead carbons C-a, C-a′ and C-b, C-b′ can be differentiated from the remaining carbons in the proton-coupled spectra since no protons are bonded to the bridgehead carbons. The C-a and C-a′ carbons are assigned to the downfield resonance at 145.2 ppm as they are bonded to nitrogen atoms[17] while the C-b and C-b′ resonances can be assigned by elimination. The C-a and C-a′ carbons, as well as all the carbon pairs along the C_2 axis in **9**, i.e., C-a, C-a′; C-4, C-9; C-5, C-8; and C-6, C-7, have identical chemical shifts. Carbon shieldings in general are very sensitive to the electronic and steric effects of substituents, as is evidenced by the carbon-13 chemical shifts of nucleosides **3** and **6**, which are included in Table I. The absence of C_2 symmetry in these nucleosides results in carbon resonances that are well resolved. It is therefore apparent that the quinone carbons of the triazole nucleoside **9** which have identical chemical shifts are chemically equivalent and that their shieldings are not accidentally degenerate. These results establish that ribosylation must have occurred at the N-2 position, resulting in C_2 symmetry for the quinone portion of **9**. The anomeric proton signal in the proton NMR spectrum of **9** occurs at δ 6.16, close to that of the pyrazole nucleoside **6** which indicates no anisotropic effect on the anomeric proton as expected for this structure.

The configuration of each of the nucleosides **3**, **6**, and **9** was established as β by formation of the corresponding 2′,3′-*O*-isopropylidene derivatives. The NMR spectra show a difference in the chemical shift of the methyl groups >0.15 ppm which is consistent only with the β configuration.[18]

These compounds were tested as inhibitors of purine nucleotide biosynthesis in Ehrlich ascites tumor cells according to the assay described by Snyder et al.[19] Tumor cell suspensions are first incubated with 100 μM compound for 20 min, followed by addition of 100 μM [^{14}C]hypoxanthine and further incubation for 60 min. The uptake and subsequent conversion of the [^{14}C]hypoxanthine to purine nucleotides of both adenine and guanine are then determined by thin-layer chromatography of the disrupted cells. By comparing the radioactivity incorporated into individual nucleotides from both untreated and drug-treated cells, the apparent rates of a number of enzymes of purine metabolism can be determined, as well as the inhibition of these enzymes by the compound. The results

Table II. Inhibition of Hypoxanthine Phosphoribosyltransferase

Compd	% inhibn
1	82
3	68
4	5
6	0
7	1
9	72

of such an analysis demonstrated that some of the present compounds are potent inhibitors of the initial step in purine nucleotide biosynthesis, the conversion of hypoxanthine to inosinic acid by hypoxanthine phosphoribosyltransferase (Table II). Two of the nucleosides, **3** and **9**, were effective inhibitors in this assay. Of the three heterocyclic quinones tested, only naphtho[2,3-*d*]imidazole-4,9-dione (**1**) showed significant inhibition. Such inhibition could occur either by competition of the heterocycle with the substrate hypoxanthine or through a feedback inhibition of a 5′-nucleotide formed during preincubation of the compound with the cells.

The quinone heterocycles (**1**, **4**, **7**) and nucleosides (**3**, **6**, **9**) were inactive against type I herpes simplex virus, type 3 parainfluenza virus, and type 13 rhinovirus in a tissue culture assay.[21]

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Evaporations were accomplished with a rotary evaporator under reduced pressure with a bath temperature below 35 °C. ^{1}H NMR spectra were recorded at 60 MHz on a Hitachi Perkin-Elmer R-20A spectrometer in Me_2SO-d_6 using DSS as an internal standard. ^{13}C NMR spectra of 20% Me_2SO-d_6 solutions were obtained on a Bruker HX-90 NMR spectrometer operating at 22.62 MHz in the Fourier transform mode at a probe temperature of 35 °C. A Fabri-Tek 1074 signal averager with 4096 word memory was used for data accumulation and a Digital PDP-8/e computer for data processing. The ^{13}C chemical shifts were measured from Me_2SO-d_6 and converted to Me_4Si scale using the relationship $\delta_{Me_4Si} = \delta_{Me_2SO\text{-}d_6} + 39.5$ ppm. Specific rotations were determined with a Perkin-Elmer Model 141 polarimeter and ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and are within ±0.4% of the theoretical values.

The trimethylsilyl derivatives of the heterocyclic naphthoquinones were prepared by refluxing the compound with excess hexamethyldisilazane containing a catalytic amount of ammonium sulfate. The excess hexamethyldisilazane was removed under reduced pressure and the trimethylsilyl derivative was used without further purification.

1-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole-4,9-dione (2). A stirred solution of the trimethylsilyl derivative prepared from naphtho[2,3-*d*]imidazole-4,9-dione (1.5 g, 7.6 mmol) in 1,2-dichloroethane (100 mL) was treated with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (2.4 g, 7.6 mmol) and stannic chloride (2.84 g, 10.9 mmol). After 3 h the mixture was evaporated and the residue was treated with 175 mL of chloroform and 50 mL of saturated aqueous sodium bicarbonate and stirred for 30 min. The organic layer was separated, filtered, washed with saturated aqueous sodium bicarbonate and water, dried (Na_2SO_4), and evaporated. The product was crystallized from ethyl acetate to provide 1.82 g (54%) of colorless crystals, mp 133–135 °C. An analytical sample, recrystallized from ethyl acetate, had mp 135–136 °C: IR 1760, 1670, 1600 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 243 (36 000), 271 (16 000), 279 (16 900), 332 (4450); NMR (Me_2SO-d_6) δ 2.15 (s, 9, CH_3 of Ac), 4.45 (br s, 2, H-5′), 5.40–5.87 (m, 3, H-2′,3′,4′), 6.65 (d, 1, $J_{1'\text{-}2'}$ = 4 Hz, H-1′), 7.70–8.27 (m, 4, H-5,6,7,8), 8.65 (s, 1, H-2). Anal. ($C_{22}H_{20}N_2O_9$) C, H, N.

The general procedure used for the synthesis of **2** was followed for the preparation of **5** and **8** as described below.

2-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)naphtho[2,3-*d*]pyrazole-4,9-dione (5). The trimethylsilyl derivative prepared from naphtho[2,3-*d*]pyrazole-4,9-dione (1.74 g, 8.8 mmol) was treated in 1,2-dichloroethane (100 mL) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (2.80 g, 8.8 mmol) and stannic chloride (3.33 g, 12.8 mmol) as described for the preparation of **2**. The yield of **5** was 3.1 g (76%). Recrystallization from ethanol provided an analytical sample with mp 191–192 °C: IR 1760, 1675, 1600 cm^{-1}; UV (EtOH) λ_{max} (ϵ) 245 (51 700), 269 (sh) (15 200), 317 (4040); NMR (Me_2SO-d_6) δ 2.10 (s, 3, CH_3 of Ac), 2.15 (s, 6, CH_3 of Ac), 4.45 (m, 2, H-5′), 5.50–5.95 (m, 3, H-2′,3′,4′), 6.42 (d, $J_{1'\text{-}2'}$ = 3 Hz, H-1′), 7.80–8.30 (m, 3, 4, H-5,6,7,8), 8.95 (s, 1, H-3). Anal. ($C_{22}H_{20}N_2O_9$) C, H, N.

2-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)naphtho[2,3-*d*]triazole-4,9-dione (8). Naphtho[2,3-*d*]triazole-4,9-dione (2.0 g, 10.0 mmol) was silylated and the trimethylsilyl derivative was treated in 1,2-dichloroethane (100 mL) with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (3.18 g, 10.0 mmol) and stannic chloride (3.74 g, 14.4 mmol) as described above. The yield of **8** was 2.0 g (44%). An analytical sample recrystallized from ethyl acetate had mp 227–228 °C: UV (EtOH) λ_{max} (ϵ) 248 (sh) (40 800), 325 (4000); NMR (Me_2SO-d_6) δ 1.12 (s, 3, CH_3 of Ac), 1.22 (s, 6, CH_3 of Ac), 4.25–4.78 (m, 3, H-5′,4′); 5.62–6.10 (m, 2, H-2′,3′), 6.69 (d, $J_{1'\text{-}2'}$ = 3 Hz, H-1′), 7.87–8.40 (m, 4, H-5,6,7,8). Anal. ($C_{21}H_{19}N_3O_9$) C, H, N.

General Procedure for Deacylation with Sodium Methoxide in Methanol. The triacetyl nucleoside was added to methanol containing 3 equiv of sodium methoxide. The suspension was kept 12 h at room temperature and the resulting solution was neutralized with acetic acid and evaporated. The products were crystallized from water and an analytical sample was obtained by recrystallization from methanol.

1-β-D-Ribofuranosylnaphtho[2,3-*d*]imidazole-4,9-dione (3). Treatment of **2** (0.93 g, 2.05 mmol) with sodium methoxide as described above gave 0.60 g (89%) of **3** as yellow needles: mp 209–210 °C; $[\alpha]_D$ +130.0° (*c* 1, DMF); IR (KBr) 1670 cm^{-1}; UV (H_2O) λ_{max} (ϵ) 244 (37 200), 249 (37 700), 283 (17 100), 340 (4100); NMR (Me_2SO-d_6) δ 6.46 (s, 1, H-1′), 8.82 (s, 1, H-2). Anal. ($C_{16}H_{14}N_2O_6$) C, H, N.

2-β-D-Ribofuranosylnaphtho[2,3-*d*]pyrazole-4,9-dione (6). Deacylation of **5** (0.80 g, 1.75 mmol) gave 0.52 g (90%) of **6** as yellow needles: mp 248 °C dec; $[\alpha]_D$ −59.3° (*c* 1, DMF); IR (KBr) 1700, 1665, 1590 cm^{-1}; UV (H_2O) λ_{max} (ϵ) 250 (52 300), 268 (sh) (15 200), 327 (5090); NMR δ (Me_2SO-d_6) 5.95 (d, 1, $J_{1'\text{-}2'}$ = 4 Hz, H-1′), 9.00 (s, 1, H-3). Anal. ($C_{16}H_{14}N_2O_6$) C, H, N.

2-β-D-Ribofuranosylnaphtho[2,3-*d*]triazole-4,9-dione (9). Deacylation of **8** (0.50 g, 1.1 mmol) as above provided 0.34 g (94%) as greenish yellow plates: mp 205–207 °C dec; $[\alpha]_D$ −86.6° (*c* 1, DMF); IR (KBr) 1690, 1590 cm^{-1}; UV (H_2O) λ_{max} (ϵ) 252 (34 900), 335 (4700); NMR δ (Me_2SO-d_6) 6.16 (d, 1, $J_{1'\text{-}2'}$ = 4Hz, H-1′). Anal. ($C_{15}H_{13}N_3O_6$) C, H, N.

General Procedure for the Synthesis of 2′,3′-*O*-Isopropylidene Derivatives. To a suspension (0 °C) of 200 mg of nucleoside in 6 mL of acetone and 2 mL of 2,2-dimethoxypropane was added 3 drops of 70% perchloric acid. The mixture was stirred at 0 °C for 2 h and then was neutralized with 2 N potassium hydroxide. The neutralized mixture was evaporated to a small volume, 20 mL of water was added, and the product was extracted with chloroform (3 × 15 mL). The combined organic extract was washed with water (2 × 20 mL), and the solution was dried (Na_2SO_4) and evaporated to dryness. Crystallization of the products from methanol provided the isopropylidene derivatives described below.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)naphtho[2,3-*d*]imidazole-4,9-dione (10). This derivative was prepared from **3** in a yield of 32% as bright yellow-green needles: mp 214–215 °C; NMR (Me_2SO-d_6) δ 1.37 (s, 3, CH_3), 1.60 (s, 3, CH_3), 6.62 (d, 1, $J_{1'\text{-}2'}$ < 2 Hz, H-1′), 8.67 (s, 1, H-2). Anal. ($C_{19}H_{18}N_2O_6$) C, H, N.

2-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)naphtho[2,3-*d*]pyrazole-4,9-dione (11). Isopropylidenation of **6** provided a 42% yield of **11** as colorless crystals: mp 183–184 °C; NMR (Me_2SO-d_6) δ 1.39 (s, 3, CH_3), 1.57 (s, 3, CH_3), 6.28 (d, 1, $J_{1'\text{-}2'}$ < 2 Hz, H-1′), 8.90 (s, 1, H-3). Anal. ($C_{19}H_{18}N_2O_6$) C, H, N.

2-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)naphtho[2,3-*d*]triazole-4,9-dione (12). The triazole nucleoside **9** was converted to **12** in a yield of 40% as colorless crystals: mp 164–165 °C; NMR δ (Me_2SO-d_6) 1.42 (s, 3, CH_3), 1.58 (s, 3, CH_3), 6.55 (s,

1, H-1'). Anal. ($C_{18}H_{17}N_3O_6$) C, H, N.

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Antiarrhythmics. 2. Synthesis and Antiarrhythmic Activity of *N*-(Piperidylalkyl)trifluoroethoxybenzamides

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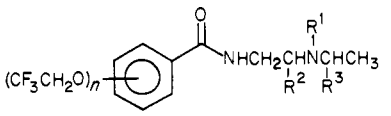
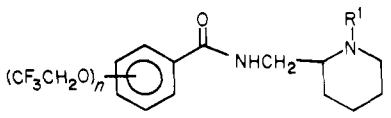
Benzamides characterized by one or more 2,2,2-trifluoroethoxy ring substituents and a heterocyclic amide side chain have been prepared and evaluated for oral antiarrhythmic activity in mice. The most potent compounds are derived from 2,5-bis(2,2,2-trifluoroethoxy)benzamide, and, within this group, both tertiary as well as secondary benzamides are active. Considerable variation in the heterocyclic ring is permissible, but antiarrhythmic activity is strongly influenced by the basicity of the amine nitrogen and the nature of the link between heterocycle and amide nitrogen. One of these compounds, *N*-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide acetate (flecainide acetate, USAN), was studied extensively in animals and selected for clinical trial as an antiarrhythmic.

In a previous paper[1] we described a series of *N*-(aminoalkyl)trifluoroethoxybenzamides which possessed potent antiarrhythmic properties. Within this series considerable variation of the amide side chain was possible without significant reduction in activity, but a structural feature common to a majority of the most potent compounds was an amide side chain with branching α to the basic nitrogen atom (I). We now wish to report a series of *N*-(piperidylalkyl)trifluoroethoxybenzamides, typified by the general structure II, which can be formally derived from I by linking R^2 and R^3.



I



II

Chemistry. The trifluoroethoxybenzamides studied in this investigation were prepared by the general routes outlined in Scheme I. Trifluoroethylation of hydroxy acids

Scheme I