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ADDITION OF 1-NITROALKANES TO METHYL 2,3-*O*-ISOPROPYLIDENE-β-D-*ribo*-PENTODIALDO-1,4-FURANOSIDE AND N^6-BENZOYL-2′,3′-*O*-ISOPROPYLIDENEADENOSINE-5′-ALDEHYDE*

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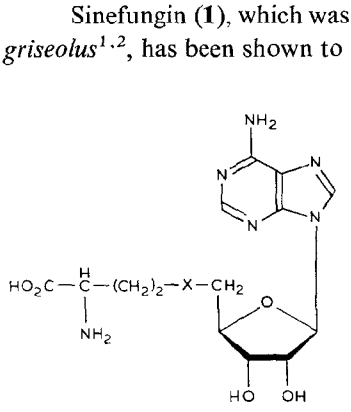
ABSTRACT

Various 1-nitroalkanes reacted with methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside to yield methyl 6-alkyl-6-deoxy-2,3-*O*-isopropylidene-6-nitro-β-D-ribofuranosides in 64–79% yield. Similarly, nitromethane and 1-nitropentane reacted with N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde, to yield the corresponding 9-[6-alkyl-6-deoxy-2,3-*O*-isopropylidene-6-nitro-α-L-talo(β-D-allo)furanosyl]-N^6-benzoyladenines in 74 and 44% yield, respectively. The potential utility of this nitroalkane addition for the synthesis of nucleosides having a C-5′–C-6′ bond is discussed.

INTRODUCTION

Sinefungin (**1**), which was isolated as an antifungal antibiotic from *Streptomyces griseolus*[1,2], has been shown to be a potent inhibitor of various *S*-adenosylmethionine



1 X = C(H)—NH_2

2 X = S^+—Me

*Taken, in part, from the Ph.D. dissertation of A.R.M., University of Kansas, Lawrence, KS, 1981.
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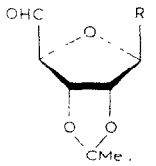
(AdoMet)-dependent methyltransferases[3,4]. Compound **1** is similar in structure to AdoMet (**2**), except for the $>C(H)NH_2$ that replaces the -S$^+$-Me. Apparently, the structural similarity is sufficient to permit tight binding of **1** to the AdoMet-binding site on various methyltransferases[3,4]. In fact, some methyltransferases bind this nucleoside more tightly[5] than **2**, suggesting that synthetic analogs of sinefungin might exhibit interesting, and significant, biological activity.

For the synthesis of **1**, or related nucleosides, a key step will be the formation of the unique C-5′–C-6′ bond. In earlier studies[6], we explored the addition of acetylenes to methyl 2,3-*O*-isopropylidene-*β*-D-*ribo*-pentodialdo-1,4-furanoside (**3**) as a possible route to formation of the C-5–C-6 bond. An alternative approach to the C-5′–C-6′ bond would be through the addition of 1-nitroalkanes to **3**, or to N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde (**4**). The addition of nitromethane to adenosine-5′-aldehyde[7] and 2′,3′-*O*-isopropylideneadenosine-5′-aldehyde[8,9] has been described. However, in the present study, we have developed a modified procedure for addition of a variety of 1-nitroalkanes to **3** and **4** to give the products in good yield.

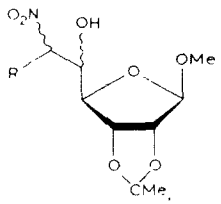


3 R = OMe

4 R = N^6-benzoyladenin-9-yl

RESULTS AND DISCUSSION

Preliminary studies on the reaction of the *β*-D-ribofuranoside **3** with various nitroalkanes indicated that the chain length of the nitroalkane, and the nature of the base, have little effect on the overall yield of the addition product. In contrast, the anhydrous nature of the solvent is critical. The resulting *α*-nitro alcohols **5–8** were



5 R = H

6 R = Me

7 R = Et

8 R = Bu

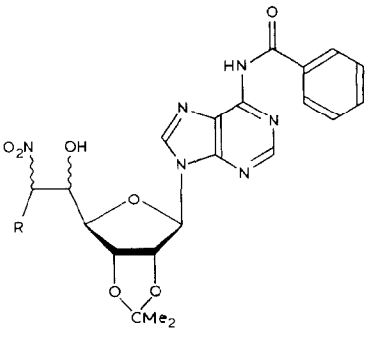
isolated as diastereoisomeric mixtures in yields of 64–79%. Separation of the diastereoisomers of **5**, resulting from the addition of nitromethane, was easily achieved by liquid chromatography.

The nitroalkane addition-products **5–8** exhibited characteristic absorptions in their infrared spectra at ~3400 (OH), 1500 (asymmetrical NO_2 stretch), and 1375 cm^{-1} (symmetrical NO_2 stretch, and isopropylidene). The e.i.–m.s. fragmentation-patterns of **5–8** failed to reveal molecular ions, although characteristic fragments at M − 15, M − 47, and *m/z* 173 were detected, indicative respectively of the isopropylidene and methoxyl groups and the α-nitro alcohol side-chain located at C-5.

The addition of nitromethane and 1-nitropentane to the nucleoside-5′-aldehyde **4** was also studied. Earlier workers[7–9] had reported low yields for similar additions of nitromethane to nucleoside-aldehydes; these poor yields probably resulted from the use of aqueous reaction-conditions, or organic solvents that were not totally anhydrous. Such reaction conditions would generate significant amounts of the aldehyde hydrate, a less reactive electrophile. The studies of Ranganathan and co-workers[10] on the addition of methyl Grignard reagent to nucleoside-5′-aldehydes support this hypothesis, in that greatly improved yields were obtained when the free aldehyde, rather than the aldehyde hydrate, was used.

N^6-Benzoyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde (**4**) was prepared by Pfitzner–Moffatt oxidation[10] of N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine[11]. The crude aldehyde reacted with 1,2-di-(4-aminophenyl)ethane to afford the 1,3-diphenylimidazolidine, which, on treatment with Dowex 50-W (H^+) resin in 1:1 oxolane–water, regenerated the aldehyde hydrate. The aldehyde hydrate was azeotropically dehydrated in benzene to[10] the free aldehyde **4**.

The addition of nitromethane to **4** afforded the diastereoisomeric mixture **9** in 74% yield. Based on the ^{1}H-n.m.r. spectra, the two diastereomers of **9** were present in the ratio of ~3:1. This is in good agreement with the findings of Hampton and co-workers[8,9] for the nonbenzoylated compounds (19.0:5.6), although it constitutes an almost three-fold increase in yield.



9 R = H

10 R = Bu

The addition of 1-nitropentane to **4** yielded a mixture of the diastereomers **10** in 44% yield. The lower yield obtained with 1-nitropentane, compared to that with nitromethane, may be due to the increased steric bulk of the nitropentane anion.

In the present study, we have refined the methodology for addition of various nitroalkanes to D-ribofuranoside **3** or nucleoside-5′-aldehyde **4**. This methodology may be useful for the preparation of sinefungin, or related C-5′ C-6′ nucleosides, or both.

EXPERIMENTAL

General. — Melting points were determined on a Thomas-Hoover, capillary, melting-point apparatus and are uncorrected. Elemental analyses were conducted with an F and M Model 185 C,H,N analyzer in the Department of Medicinal Chemistry, University of Kansas. Infrared spectra were recorded with a Beckman IR-33 dual-beam spectrophotometer. ^{1}H-N.m.r. spectra were recorded with a Varian T-60 (60 MHz, ambient-temperature probe) spectrometer operated in the continuous-wave mode. Chemical shifts are reported in δ from tetramethylsilane (as 0.000). Mass spectra were recorded with a Varian MAT-CH5, or Ribermag R-10-10, mass spectrometer interfaced to a digital computer.

Methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside[7] (**3**) and N^6-benzoyl-5′-deoxy-5′,5′-(1,3-diphenylimidazolidin-1,3-diyl)-2′,3′-*O*-isopropylideneadenosine[10] were prepared by literature procedures.

*Methyl 6-alkyl-6-deoxy-2,3-O-isopropylidene-6-nitro-β-*D-ribo-*furanosides. — General procedure.* To methyl 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside[6] (**3**) (1.5 g, 7.4 mmol) in absolute methanol (5 mL) was added the appropriate nitroalkane (59.2 mmol) under nitrogen. Sodium methoxide, generated by dissolving sodium (190 mg, 8.3 meq) in methanol (2.5 mL), was added dropwise to the mixture, which was stirred for 18 h at room temperature under nitrogen, and then cooled to 40°. Glacial acetic acid (0.5 mL) was now added, and the mixture allowed to warm slowly to room temperature. The resulting solution was partitioned between $CHCl_3$ (20 mL) and H_2O (20 mL), the aqueous layer extracted with $CHCl_3$ (4 × 10 mL), and the extracts were combined, washed with H_2O (5 × 5 mL), dried ($MgSO_4$), and evaporated.

*Methyl 6-deoxy-2,3-O-isopropylidene-6-nitro-γ-*L-*talofuranoside and methyl 6-deoxy-2,3-isopropylidene-6-nitro-β-*D-*allofuranoside* (**5**). — The nitromethane addition-products from **3** were purified by chromatography on a column of silica gel (45 g; pretreated with 1:9 H_2O–toluene). The products were eluted with a step gradient of 1:99 to 3:97 EtOH–toluene, affording a 79% yield of the diastereoisomeric mixture **5**. Liquid chromatography in a column (15 × 1000 mm) of silica gel at 40 lb.in^{-2} with $CHCl_3$ afforded separation of the two isomers as pure entities. The less-polar diastereoisomer (**5**-I) was obtained as a yellow oil, and the more-polar diastereoisomer (**5**-II) as a white, crystalline solid.

5-I: ν_{max}^{KBr} 3400 (OH), 2980, 2935 and 2840 (CH), 1550 (asymmetrical NO_2

stretch), and 1375 cm^{-1} (symmetrical NO_2 stretch and isopropylidene); n.m.r. ($CDCl_3$): δ 4.95 (s, 1 H, H-1), 4.80 (d, 1 H, H-2 or H-3), 4.53 (d, 1 H, H-2 or H-3), 4.47–3.60 (m, 5 H, H-4,5,6,6′, and OH), 3.47 (s, 3 H, OCH_3), 1.47 (s, 3 H, CCH_3), and 1.32 (s, 3 H, CCH_3); mass spectrum identical to that of **5-II**.

5-II: m.p. 116–117°; ν_{max}^{KBr} 3360 (OH), 2970, 2930, and 2840 (CH), 1540 (asymmetrical NO_2 stretch), and 1370 cm^{-1} (symmetrical NO_2 stretch and isopropylidene); n.m.r. ($CDCl_3$): δ 4.97 (s, 1 H, H-1), 4.85 (d, 1 H, H-2 or H-3), 4.70–4.00 (m, 5 H, H-3 or H-2, H-4,5,6,6′), 3.60 (br. s, 1 H, OH, exchanges with D_2O), 3.42 (s, 3 H, OCH_3), 1.47 (s, 3 H, CCH_3), and 1.33 (s, 3 H, CCH_3); *m/z* 248 (M − CH_3, 29.2%), 216 (248 − CH_3OH, 17.1%), 173 (M − $C_2H_4NO_3$, 27.4%), 141 (173 − CH_3OH, 6.3%), 115 (173 − C_3H_6O, 17.4%), 113 (173 − CH_3 − CH_2O, 30.9%), 85 (115 − CH_2O, 31.7%), and 59 (C_3H_6OH, 100.0%).

Anal. Calc. for $C_{10}H_{17}NO_7$: C, 45.63; H, 6.51; N, 5.32. Found: C, 45.72; H, 6.53; N, 5.22.

*Methyl 6,7-dideoxy-2,3-*O*-isopropylidene-6-nitro-β-*D*-*ribo*-heptofuranosides* (**6**). — Purification of the crude nitroethane adducts of **3** by column chromatography as described for **5** afforded a 67% yield of the diastereomeric mixture **6** as a light-yellow solid; m.p. 121–126°; ν_{max}^{KBr} 3400, 2980, 2935, 2835, 1545, and 1475 cm^{-1}; n.m.r. ($CDCl_3$): δ 5.07 (s, 1 H, H-1), 4.96 (d, 1 H, H-4), 4.80–4.40 (m, 2 H, H-2,3), 4.40–3.70 (m, 3 H, H-5,6, and OH), 3.50 (m, apparently 4 s, 3 H, OCH_3), and 1.90–1.20 (m, 9 H, CH_3-7 and CMe_2); *m/z* 262 (M − CH_3, 100.0%), 230 (262 − CH_3OH, 37.5%), 173 (M − $C_3H_6NO_3$, 88.4%), 141 (15.1%), 115 (37.2%), 113 (55.3%), 85 (47.8%), and 59 (85.6%).

Anal. Calc. for $C_{11}H_{19}NO_7$: C, 47.65; H, 6.91; N, 5.05. Found: C, 47.89; H, 7.07; N, 4.84.

*Methyl 6,7,8-trideoxy-2,3-*O*-isopropylidene-6-nitro-β-*D*-*ribo*-octofuranosides* (**7**). — The 1-nitropropane addition-products from **3** were purified by chromatography on a column of silica gel (50 g), eluting with 2:3 Skelly B–$CHCl_3$, to yield the diastereoisomeric mixture **7** as a pale-yellow oil in 71% average yield; ν_{max}^{KBr} 3400, 2980, 2940, 1545, and 1375 cm^{-1}; n.m.r. ($CDCl_3$): δ 4.97 (s, 1 H, H-1), 4.85 (d, 1 H, H-4), 4.55 (apparent d, 2 H, H-2,3), 4.27–3.73 (m, 3 H, H-5,6, and OH), 3.48 (s, 1.5 H, ½ OCH_3), 3.40 (s, 1.5 H, ½ OCH_3), 2.30–1.70 (m, 2 H, H-7,7′), 1.45 (s, 3 H, CCH_3), 1.30 (s, 3 H, CCH_3), and 1.00 (t, 3 H, CH_3-8); *m/z* 276 (M − CH_3, 40.5%), 244 (276 − CH_3OH, 15.5%), 173 (M − $C_4H_8NO_3$, 100.0%), 141 (7.6%), 115 (27.3%), 113 (58.5%), 85 (37.0%), and 59 (74.0%).

*Methyl 6,7,8,9,10-pentadeoxy-2,3-*O*-isopropylidene-6-nitro-β-*D*-*ribo*-decofuranosides* (**8**). — The crude 1-nitropentane reaction-mixture from **3** was purified by chromatography on a column of silica gel (50 g), eluting with 1:3 Skelly B–$CHCl_3$, to afford **8** as an oily mixture of the diastereoisomers in 64% yield; ν_{max}^{KBr} 3400, 2945, 2880, 1550, and 1380 cm^{-1}; n.m.r. ($CDCl_3$): δ 5.10–3.60 (m, 7 H, H-1–6, and OH), 3.43, 3.40, and 3.33 (3 s, 3 H, OCH_3), 2.30–1.80 (m, 2 H, 2 H-7), 1.70–1.20 (m, including 2 s at 1.40 and 1.23, 10 H, 2 H-8, 2 H-9, and CMe_2), 0.88 (s, 3 H, 3 H-10); *m/z* 304 (M − CH_3, 43.8%), 272 (304 − CH_3OH, 17.3%), 173 (M − $C_6H_{12}NO_3$,

100.0%), 141 (28.2%), 115 (29.4%), 113 (38.8%), 85 (36.4%), and 59 (70.6%).

9-(6-Alkyl-6-deoxy-2,3-O-isopropylidene-6-nitro-α-L-talofuranosyl)-N⁶-benzoyladenines and 9-(6-alkyl-6-deoxy-2,3-O-isopropylidene-6-nitro-β-D-allofuranosyl)-N⁶-benzoyladenines. — General procedure. N^6-Benzoyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde (**4**) was prepared by Pfitzner–Moffatt oxidation[10] of N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine[11]. Crude aldehyde **4** was purified by formation of the 1,3-diphenylimidazolidine, and regeneration of aldehyde **4** by using Dowex 50W-X8 resin[10].

The appropriate nitroalkane (8.00 mmol) in anhydrous, freshly distilled oxolane (THF; 5 mL) was chilled to 5 °, and triethylamine (405 mg, 4 mmol) in THF (5 mL) was added dropwise. After 15 min, aldehyde **4** (1 mmol) in anhydrous THF (15 mL) was added at such a rate that the temperature did not rise above 10 °. The mixture was stirred for 1 h at 0–10 °, warmed to room temperature, and stirred for an additional 18 h under nitrogen. The reaction was quenched by cooling to −40 °, adding glacial acetic acid (2 mL), and warming to room temperature. After partitioning between water (20 mL) and $CHCl_3$ (40 mL), the aqueous layer was extracted with $CHCl_3$ (4 × 10 mL); the extracts were combined, washed with water (5 × 5 mL), dried ($MgSO_4$), and evaporated *in vacuo*, to afford the crude products as yellow foams that could be purified by chromatography on a column of silica gel (25 g) in $CHCl_3$, eluting with a gradient of 0–2% of methanol in $CHCl_3$.

N⁶-Benzoyl-9-(6-deoxy-2,3-O-isopropylidene-6-nitro-α-L-talofuranosyl)adenine and N⁶-benzoyl-9-(6-deoxy-2,3-O-isopropylidene-6-nitro-β-D-allofuranosyl)adenine (**9**). — Yield: 349 mg (74%); m.p. 122–125 °; ν_{max}^{KBr} 3400–3200 (OH), 2980 and 2940 (CH), 1690 (C=O, amide) 1605 and 1578 (purine), 1548 (asymmetrical NO_2 stretch), and 1375 cm^{-1} (symmetrical NO_2 stretch); n.m.r. ($CDCl_3$): δ 9.55 (br. s, 1 H, NH), 8.65 (s, 1 H, H-2 or H-8), 8.15 (s, 1 H, H-8 or H-2), 8.00 (m, 2 H, Ar), 7.60 (m, 3 H, Ar), 6.06 (d, 1 H, H-1′), 5.19 (m, 3 H, H-2′,3′,4′), 4.58 (m, 3 H, H-5′ and 2 H-6′), 4.33 (br. s, 1 H, OH, exchanges with D_2O), 1.60 and 1.53 (2 s, 3 H, CCH_3: the two singlets are in the ratio of ~3:1), and 1.37 and 1.28 (2 s, 3 H, CCH_3: ratio of the two singlets ~3:1); c.i.-m.s. (methane): *m/z* 471 (M + H, 9.5%), 453 (471 − H_2O, 1.9%), 438 (453 − CH_3, 12.6%), 410 (471 − CH_3NO_2, 100%), 380 (410 − CHOH, 4.5%), 352 (410 − C_3H_6O, 18.4%), 268 (PhCOAdCH=O⁺H, 10.7%), 240 (PhCOAd + H, 83.7%), and 136 (Ad + H, 3.6%).

N⁶-Benzoyl-9-(6,7,8,9,10-pentadeoxy-2,3-O-isopropylidene-6-nitro-β-D-ribo-decofuranosyl)adenines (**10**). — Yield: 230 mg (44%); m.p. 95–97 °; ν_{max}^{KBr} 3400–3200 (OH), 2960, 2935, and 2870 (CH), 1700 (C=O, amide), 1610 and 1570 (purine), 1550 (asymmetrical NO_2 stretch), and 1375 cm^{-1} (symmetrical NO_2 stretch); n.m.r. ($CDCl_3$): δ 9.50 (br. s, 1 H, NH), 8.65 (d, 1 H, H-2 or H-8, decoupling studies suggested possibility of two singlets), 8.20–7.80 (m, 3 H, H-8 or H-2 and 2 Ar-H), 7.67–7.30 (m, 3 H, Ar), 6.00 (br. s, 1 H, H-1′), 5.17 (br. s, 2 H, H-2′,3′), 4.90–4.10 (m, 3 H, H-4′,5′, and OH), 3.73 (complex t, 1 H, H-6′), 2.30–1.07 (m, 12 H, CMe_2,

2 H-7′, 2 H-8′, and 2 H-9′, includes two apparent singlets at 1.62 and 1.37), and 0.90 (complex t, 3 H, CH_3-10′); c.i.-m.s. (methane): *m/z* 527 (M + H, 3.1%), 410 (527 − $C_6H_{12}NO_3$, 8.3%), 240 (PhCOAd + H, 2.9%), and 165 (AdCH=O$^+$H, 11.5%).

ACKNOWLEDGMENTS

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