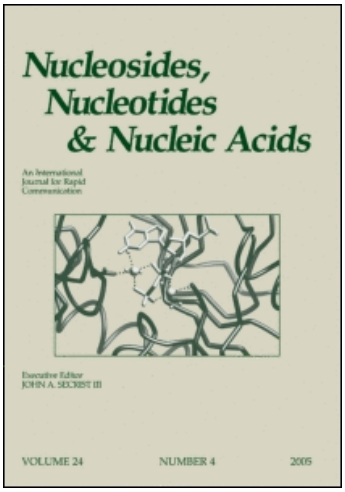

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An Unusual Reaction Observed in Sulfonylation and Acylation of 2',3'-O-Isopropylidenenebularine

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AN UNUSUAL REACTION OBSERVED IN SULFONYLATION AND ACYLATION OF 2',3'-O-ISOPROPYLIDENENEBULARINE

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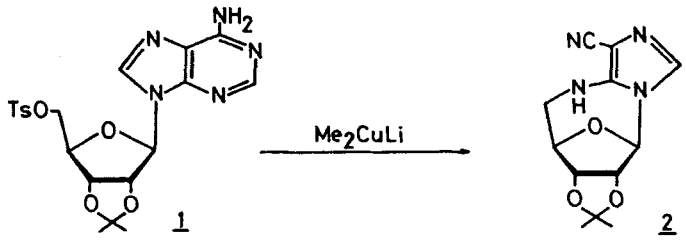
Abstract: Treatment of 2',3'-O-isopropylidenenebularine with p-toluenesulfonyl chloride in pyridine afforded 7,8-dihydro-2',3'-O-isopropylidene-N^7-(p-toluenesulfonyl)-8(R),5'-O-cyclonebularine as the major product, the structure of which was determined by X-ray crystallography. The reactions with other sulfonyl and acyl (aroyl) chlorides were also examined.

During our continuing efforts to employ organometallics in the synthetic chemistry of nucleosides,[1] we were interested in the use of organocopper reagents for C-C bond forming reactions at the 5'-position. A series of reactions using uracil nucleosides suggested that the 5'-p-toluenesulfonates would be suitable substrates for our purpose.[2]

However, when 2',3'-O-isopropylidene-5'-O-(p-toluenesulfonyl)adenosine (1) was reacted with a Gilman reagent, Me_2CuLi, in THF-ether for 4 h at 0 °C, the sole product iso-

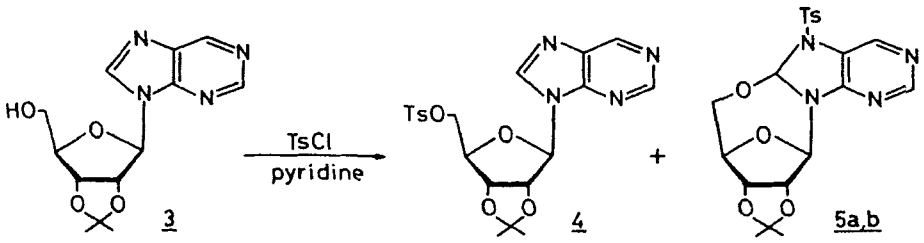


Scheme 1

lated was found to be a 5,5'-N-cycloimidazole nucleoside (2) as shown in Scheme 1 (Ts= p-toluenesulfonyl).[3] The formation of 2 apparently resulted from two consecutive proton-abstractions from the 6-amino group in 1. This result led us to prepare the 5'-O-(p-toluenesulfonyl) derivative of the simplest purine nucleoside, nebularine.

2',3'-O-Isopropylidenenebularine (3) was sulfonylated in pyridine at 0 °C for 18 h by the use of 1.2 equiv of p-toluenesulfonyl chloride (TsCl), whereupon three products were detected by TLC ($CHCl_3$:EtOH = 15:1). The desired product (4) was isolated in 19% yield after silica gel column chromatography. Both the two other products, which ran faster than 4, showed an identical mass spectral pattern with the intensity of [M^+: m/z 446] being higher than that of [M^+– Me: m/z 431]. This observation was suggestive of a mono-sulfonylated cyclo-structure for these products. Although there is seemingly no other position available in 3 for the sulfonylation, one possible process that can thwart the desired 5'-O-sulfonylation is formation of 7,8-dihydro-8,5'-O-cyclo derivative —— a process that can be initiated with sulfonylation at the N^7-position.[4] This turned out to be the case.

Of the two products (5a,b), the less polar one (5a: yield 39%) was crystallized from MeOH and its X-ray crystallographic analysis was then carried out. The result is depicted in Fig. 1 by an ORTEP drawing. Though the quality of crystal[5] was not high enough to determine the location of hydrogens, Fig. 1 clearly shows its 8(R)-configuration, indi-



Scheme 2

cating that re-face attack of the 5'-hydroxyl had occurred at the C-8 position of the corresponding N^7-sulfonylpurinium intermediate.[6]

Since the other product (5b: yield 14%), which could not be obtained in a crystalline form, gave an almost identical UV spectrum with that of 5a, we assumed it to be the epimeric 8(S)-counterpart. Examination of a molecular model suggested that the configurational difference would be reflected in their NOE spectra. To ascertain this point, the two-dimensional NOE (NOESY) spectra of 5a and 5b were measured in $CDCl_3$.

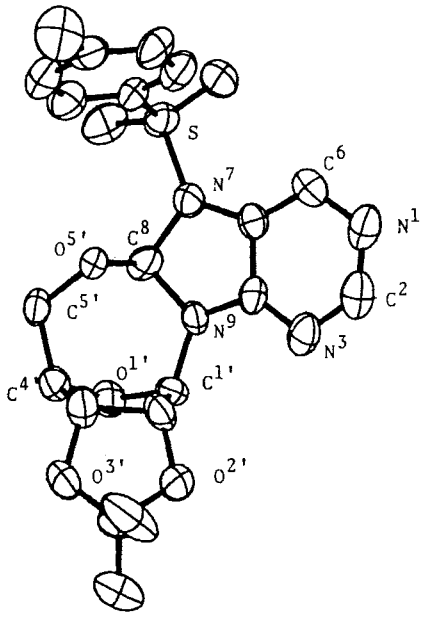
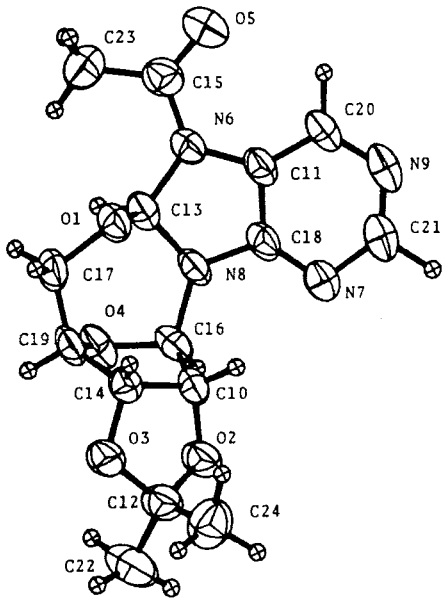


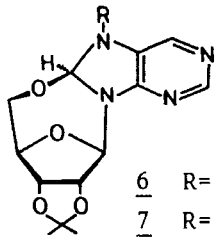
Fig. 1 ORTEP drawing of 7,8-dihydro-2',3'-O-isopropylidene-N^7-(p-toluenesulfonyl)-8(R),5'-O-cyclonebularine (5a).

In the case of the former, an NOE correlation was observed between H-8 (singlet: 6.51 ppm) and CH_2-5' (mutiplet: 3.97 ppm), while in the case of the latter, its H-8 (singlet: 6.72 ppm) correlated with H-2' (doublet: 4.86 ppm), but not with CH_2-5' (doublet: 3.37 ppm, double-doublet: 3.77 ppm).

In contrast to the above results, when a similar sulfonylation of 3 was carried out by the use of methanesulfonyl chloride, the 5'-O-methanesulfonyl derivative was isolated in 71% yield without concomitant formation of the cyclized product.

To see whether a similar type of reagents would bring about the cyclization process, we next subjected benzoyl and p-toluoyl chlorides to the reaction with 3 in pyridine. TLC analysis of both reaction mixtures showed the formation of the corresponding 5'-O-aroyl derivatives, but again N^7-aroyl-7,8-dihydro-2',3'-O-isopropylidene-8(R),5'-O-cyclonebularines were the major products (6: 70%, 7: 65%).[7,8]





6 R= benzoyl
7 R= p-toluoyl
8 R= acetyl

Fig. 2 ORTEP drawing of N^7-acetyl-7,8-dihydro-2',3'-O-isopropylidene-8(R),5'-O-cyclonebularine (8).

Most dramatically and quite unexpectedly, the use of acetyl chloride furnished only the cyclized product (8) in 78% yield, which was crystallized from EtOH and analyzed by X-ray crystallography. In Fig. 2 is visualized the 8(R)-stereochemistry of 8[9] by ORTEP drawing with all hydrogens being depicted in the observed positions. The atomic coordinates are given in Table 1.

In conclusion, the present article has shown that the formation of 7,8-dihydro-8,5'-O-cyclonebularines was the dominant reaction path when 2',3'-O-isopropylidenenebularine was treated with p-toluenesulfonyl or acyl (aroyl) chlorides in pyridine. Although a similar reaction path has been reported in the case of 2',3'-O-isopropylideneadenosine, concurrent formation of both the 8(R)- and 8(S)-stereoisomers seems to be unprecedented. Finally, we would like to add a comment that the observed cyclization process can be eliminated by changing reaction conditions. For example, we have

Table 1 Atomic coordinates of non-hydrogen atoms used for crystallographic analysis of compound 8.

Atom	x/a	y/b	z/c	Beq.
O1	0.5309(2)	0.4162(1)	0.5341(3)	4.04(7)
O2	0.5803(3)	0.6712(1)	0.4694(4)	4.81(8)
O3	0.7448(2)	0.6208(1)	0.6110(5)	5.21(10)
O4	0.6455(2)	0.5264(1)	0.3262(3)	4.60(9)
O5	0.2138(3)	0.2878(1)	0.4187(5)	6.06(11)
N6	0.3392(3)	0.3873(1)	0.4000(5)	4.13(10)
N7	0.2284(3)	0.5695(2)	0.3899(6)	5.29(12)
N8	0.4254(3)	0.4992(2)	0.3623(4)	3.99(9)
N9	0.0350(3)	0.4971(2)	0.4388(6)	5.99(14)
C10	0.5353(4)	0.6002(2)	0.5066(5)	3.57(10)
C11	0.2382(4)	0.4386(2)	0.4104(5)	3.90(12)
C12	0.6873(4)	0.6881(2)	0.5744(6)	4.55(13)
C13	0.4652(4)	0.4246(2)	0.3879(5)	3.80(11)
C14	0.6500(4)	0.5642(2)	0.5936(5)	3.71(11)
C15	0.3233(4)	0.3131(2)	0.3997(6)	4.57(13)
C16	0.5223(4)	0.5581(2)	0.3520(5)	4.07(12)
C17	0.6709(4)	0.4298(2)	0.5211(7)	4.75(13)
C18	0.2931(3)	0.5074(2)	0.3880(5)	3.88(11)
C19	0.7015(4)	0.5068(2)	0.4799(6)	4.23(12)
C20	0.1059(4)	0.4345(2)	0.4366(6)	4.70(13)
C21	0.0964(5)	0.5585(3)	0.4169(8)	5.98(17)
C22	0.7841(6)	0.7335(4)	0.4821(10)	7.04(22)
C23	0.4428(6)	0.2684(3)	0.3763(9)	5.94(17)
C24	0.6360(7)	0.7243(3)	0.7224(8)	6.54(18)

been successful in a high-yield preparation of 4 from 3 by the use of TsCl in a CH_3CN-DMAP-Et_3N system.[10]

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. PMR spectra were measured with TMS as an internal standard, with a JEOL JNM-GX 400 NMR spectrometer. The abbreviations used are as follows: s, singlet; d, doublet; dd, double-doublet; m, multiplet; br, broad. Mass spectra were taken on a JEOL JMS-D 300 spectrometer. UV spectra were recorded on a Shimadzu UV-240 spectrophotometer. Column chromatography was carried out on silica gel (Wakogel® C-200). TLC was performed on pre-coated silica gel plates F_{254}, Merck.

X-ray crystallography—— The crystallographic data were collected on a Rigaku AFC-5 diffractometer using graphite monochromated $CuK\alpha_1$ radiation by θ-2θ scan method. The scan speed was 16° min^{-1}. The data were corrected for Lorenz and polarization factors, but no absorption correction was applied. The crystal structures were determined by the direct method and refined by the full-matrix least-squares.

5-Amino-N^5,5'-anhydro-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole-4-carbonitrile (2)—— A THF (6 ml) solution of 1 (305 mg, 0.66 mmol) was added to an ether (6 ml) solution of Me_2CuLi, prepared from CuI (3 eq.) and MeLi (6 eq.), at 0 °C under positive pressure of dry argon. The resulting yellow solution was stirred for 4 h at the same temperature. After being quenched with AcOH, the reaction mixture was evaporated to dryness and the whole residue was chromatographed on a silica gel column. Elution with 2% EtOH in $CHCl_3$ gave 2 (84 mg, 49%), which was crystallized from EtOH to give an analytical sample (mp 279-280 °C). Anal. Calcd. for $C_{12}H_{14}N_4O_3$: C, 54.96; H, 5.38; N, 21.36. Found: C, 54.74; H, 5.27; N, 21.14. UV absorption in MeOH: max 249 nm (ε 12600), min 212 nm (ε 2800). IR (KBr): 2200 cm^{-1} (CN). PMR ($CDCl_3$) δ: 1.34 and 1.54 (6H, each as s, isop.-Me), 3.29 (1H, dd, J= 1.5 and 13.2 Hz, H-5'), 3.40 (1H, m, H-5'), 4.63 (1H, d, J= 5.5 Hz, H-3'), 4.68 (1H, m, H-4'), 4.77 (1H, br, NH), 4.91 (1H, d, H-2'), 5.77 (1H, s, H-1'), 7.21 (1H, s, H-2). MS m/z: 262 (M^+), 247 (M^+ − Me).

General procedure for sulfonylation or acylation of 3 —— A mixture of 3 (1.0 mmol) and the chloride (1.2 mmol) in pyridine (6 ml) was stirred at 0 °C for 3-20 h. After ice was added, the reaction mixture was partitioned between H_2O and $CHCl_3$. The organic layer was separated, dried, and evaporated to dryness. The residue was chromatographed to give the respective product.

2',3'-O-Isopropylidene-5'-O-(p-toluenesulfonyl)nebularine (4)—— This compound was obtained in 19% yield as a syrup. UV absorption in MeOH: max 225 and 260 nm, min 242 nm. PMR ($CDCl_3$) δ: 1.39 and 1.62 (6H, each as s, isop.-Me), 2.40 (3H, s, MeC_6H_4), 4.24 (2H, m, CH_2-5'), 4.46-4.59 (1H,

m, H-4'), 5.07 (1H, dd, J= 2.9 and 5.9 Hz, H-3'), 5.38 (1H, dd, J= 5.9 and 2.0 Hz, H-2'), 6.16 (1H, d, H-1'), 7.18 and 7.62 (4H, each as d, J= 8.3 Hz, Ph), 8.15, 8.90, and 9.15 (3H, each as s, purine ring protons). MS m/z: 446 (M^+), 431 (M^+– Me).

7,8-Dihydro-2',3'-O-isopropylidene-N^7-(p-toluenesulfonyl)-8(R),5'-O-cyclonebularine (5a)—— This compound was obtained in 39% yield. Crystallization from MeOH gave an analytical sample (mp 176-177 °C). Anal. Calcd. for $C_{20}H_{22}N_4O_6S$: C, 53.80; H, 4.93; N, 12.55. Found: C, 54.05; H, 4.97; N, 12.60. UV absorption in MeOH: max 230 nm (ε 14000), 257 nm (ε 10700), and 286 nm (ε 7900), min 219 nm (ε 11000), 244 nm (ε 9500), and 279 nm (ε 7800). PMR ($CDCl_3$) δ: 1.29 and 1.52 (6H, each as s, isop.-Me), 2.43 (3H, s, MeC_6H_4), 3.93-4.01 (2H, m, CH_2-5'), 4.63-4.67 (3H, m, H-2', H-3', and H-4'), 5.74 (1H, s, H-1'), 6.51 (1H, s, H-8), 7.31 and 7.77 (4H, each as d, J= 8.1 Hz, Ph), 8.18 and 8.40 (2H, each as s, H-6 and H-2). MS m/z: 446 (M^+), 431 (M^+– Me).

7,8-Dihydro-2',3'-O-isopropylidene-N^7-(p-toluenesulfonyl)-8(S),5'-O-cyclonebularine (5b)—— This compound was obtained in 14% yield as a powder. Attempted crystallizations gave a gel. UV absorption in MeOH: max 228 nm, 256 nm, and 287 nm, min 218 nm, 241 nm, and 277 nm. PMR ($CDCl_3$) δ: 1.34 and 1.49 (6H, each as s, isop.-Me), 2.43 (3H, s, MeC_6H_4), 3.37 (1H, d, J= 13.7 Hz, H-5'), 3.77 (1H, dd, J= 13.7 and 5.4 Hz, H-5'), 4.30 (1H, d, H-4'), 4.86 (1H, d, J= 5.4 Hz, H-2'), 4.99 (1H, d, H-3'), 5.99 (1H, s, H-1'), 6.72 (1H, s, H-8), 7.31 and 7.76 (4H, each as d, J= 7.7 Hz, Ph), 8.49 (2H, br, H-2 and H-6). MS m/z: 446 (M^+), 431 (M^+– Me).

N^7-Benzoyl-7,8-dihydro-2',3'-O-isopropylidene-8(R),5'-O-cyclonebularine (6)—— This compound was obtained in 70% yield. Crystallization from EtOH gave an analytical sample (mp 211-212 °C). Anal. Calcd. for $C_{20}H_{20}N_4O_5$: C, 60.60; H, 5.09; N, 14.13. Found: C, 60.73; H, 5.02; N, 14.18. UV absorption in MeOH: max 265 nm (ε 13000) and 291 nm (ε 10600), min 243 nm (ε 9600) and 285 nm (ε 10500). PMR ($CDCl_3$) δ: 1.33 and 1.53 (6H, each as s, isop.-Me), 3.33 (1H, br, H-5'), 3.74 (1H, d, J= 12.8 Hz, H-5'), 4.53 (1H, s, H-4'), 4.66 (1H,

d, J= 5.9 Hz, H-3'), 4.77 (1H, d, H-2'), 5.83 (1H, s, H-1'), 6.36 (1H, br, H-8), 7.48-7.60 (5H, m, Ph), 8.51 (2H, s, H-2 and H-6). MS m/z: 396 (M^+), 381 (M^+– Me).

7,8-Dihydro-2',3'-O-isopropylidene-N^7-toluoyl-8(R),5'-O-cyclonebularine (7)—— This compound was obtained in 65% yield. Crystallization from MeOH gave an analytical sample (mp 200-201 °C). Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.57; H, 5.38; N, 13.63. UV absorption in MeOH: max 266 nm (ε 12100) and 292 nm (ε 10400), shoulder 230 nm (ε 11600), min 247 nm (ε 9300) and 283 nm (ε 10000). PMR ($CDCl_3$) δ: 1.33 and 1.53 (6H, each as s, isop.-Me), 2.44 (3H, s, MeC_6H_4), 3.44 (1H, br, H-5'), 3.77 (1H, d, J= 13.2 Hz, H-5'), 4.54 (1H, s, H-4'), 4.66 (1H, d, J= 5.9 Hz, H-2'), 4.77 (1H, d, H-3'), 5.82 (1H, s, H-1'), 6.38 (1H, br, H-8), 7.29 and 7.50 (4H, each as d, J= 7.7 Hz, Ph), 8.49 (2H, s, H-2 and H-6). MS m/z: 410 (M^+), 395 (M^+– Me).

N^7-Acetyl-7,8-dihydro-2',3'-O-isopropylidene-8(R),5'-O-cyclonebularine (8)—— This compound was obtained in 78% yield. Crystallization from EtOH gave an analytical sample (mp 234-235 °C). Anal. Calcd. for $C_{15}H_{18}N_4O_5$: C, 53.89; H, 5.43; N, 16.76. Found: C, 54.19; H, 5.36; N, 16.81. UV absorption in MeOH: max 261 nm (ε 11500) and 286 nm (ε 8600), min 230 nm (ε 2000) and 277 nm (ε 8300). PMR ($CDCl_3$) δ: 1.34 and 1.55 (6H, each as s, isop.-Me), 2.26 (3H, s, Ac), 3.89 and 4.03 (2H, each as d, J= 12.8 Hz, CH_2-5'), 4.66 (1H, s, H-4'), 4.72 and 4.75 (2H, each as d, J= 5.9 Hz, H-2' and H-3'), 5.86 (1H, s, H-1'), 6.54 (1H, s, H-8), 8.46 and 8.69 (2H, each as s, H-2 and H-6). MS m/z: 334 (M^+), 319 (M^+– Me).

ACKNOWLEDGEMENT

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5) Crystal data of 5a are as follows: space group P1, Z= 2 (two independent molecules are included in an asymmetric unit), a= 11.069(1), b= 13.087(1), c= 8.741(5)Å, α= 99.30 (2), β= 102.16(2), γ= 109.80(1)°, V= 1126.5(1)Å^3, Dc=1.31 gcm^{-3}. A total of 3843 reflections were measured within the 2θ angle of 130°. The final R value was 0.139 including anisotropic thermal parameters for non-hydrogen atoms.

6) A similar reaction path has recently been postulated for the halogenation of 2',3'-O-isopropylidene derivatives of purine nucleosides with N-bromosuccinimide: Y. Maki, M. Sako, T. Saito, and K. Hirota, Heterocycles, 27, 347 (1988).

7) The 8(R)-stereochemistry of 6 and 7 was confirmed on the basis of their NOESY spectra.

8) A small amount of a product which could be assumed to be the corresponding 8(S)-epimer was also detected by TLC in both the reactions.

9) Crystal data of 8 are as follows: space group $P2_12_12_1$ (orthorhombic), Z= 4, a= 10.193(1), b= 18.388(1), c= 8.399(4)Å, V= 1574.5(9)Å^3, Dc= 1.411gcm^{-3}. A total of 1424 reflections were measured within the 2θ angle of 120°. The final R value was 0.052 including anisotropic

thermal factors for non-hydrogen atoms and isotropic thermal factors for hydrogen atoms.

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