SYNTHESIS OF 9-(*t*-2,*c*-3-DIHYDROXYMETHYL-*r*-1-CYCLOPROPYL)-9H-ADENINE (A LOWER METHYLENE HOMOLOG OF CARBOCYCLIC OXETANOCIN) AND RELATED COMPOUNDS[1)]

Nobuya KATAGIRI,* Hiroshi SATO, and Chikara KANEKO *
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

To clarify the relationship of side chain conformation and flexibility to biological activity, a series of carbocyclic analogs of oxetanocin having a one-methylene unit shorter in the cyclobutane ring, 9-(*t*-2,*c*-3-dihydroxymethyl-*r*-1-cyclopropyl)-9H-adenine (**11**) and the related compounds (**15**, **18**, and **19**) were synthesized.

KEYWORDS carbocyclic oxetanocin; cyclopropane; adenine; thymine; high pressure; antiviral activity; BLV

Though most of all nucleoside antibiotics contain a β-D-ribofuranosyl linked to a heterocyclic ring (**A**), the recent finding of oxetanocin (**B**; Z=O),[2)] acyclovir (**C**; Z=O)[3)] and their carba analogs (Z=CH_2)[4,5)] still exhibiting interesting biological activity (antitumor and/or antiviral) has aroused much interest in modifying these nucleosides somewhat drastically to make new medicinal agents. Though synthesis of the corresponding C-nucleosides is one way to accomplish this aim,[6)] it is worthwhile to synthesize lower methylene homologs of the sugar moiety of oxetanocin and its carbocyclic analogs and to examine their biological activity.

Here, we report the synthesis of nucleic acid bases (adenine, thymine etc.) having a cyclopropane vicinally occupied by hydroxymethyl groups and their preliminary biological tests.

The structure-activity relationship between 2'-deoxynucleosides (**A**) and oxetanocin (**B**) probably indicates, at least partly, that all heteroatoms (three oxygen atoms of the sugar moiety and a nitrogen atom linked to sugar of the base) occupy similar positions in space. Extention of this reasoning as well as the well-known puckered conformation in cyclobutane derivatives[7)] then suggests that the corresponding cyclopropane derivative (**D**) would also mimic the biological activity of the corresponding carbocyclic oxetanocin (**B**:Z=CH_2).

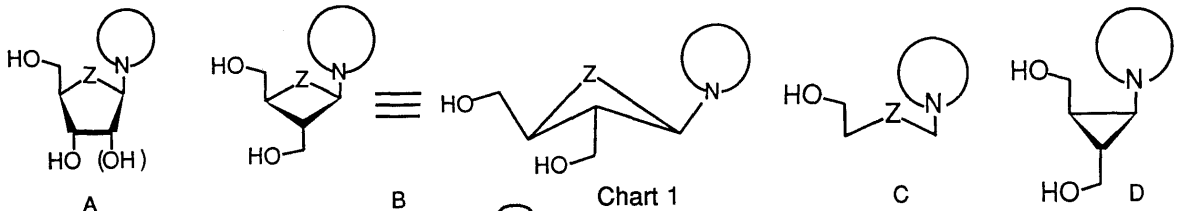

Chart 1

Throughout this paper, N- refers 9-adenyl group.

First, 9-(*t*-2,*c*-3-dihydroxymethyl-*r*-1-cyclopropyl)-9H-adenine (**11**) was synthesized. The cyclopropanation of *trans*-1,4-dibenzyloxy-2-butene (**1**) with ethoxycarbonylcarbene (generated *in situ* from ethyl diazoacetate) afforded the cyclopropane (**2**)[8)] as a sole isolable product, with retention of the stereochemistry of **1**. The acid (**3**) derived from **2** was converted to the azide (**4**). Curtius rearrangement of **4** to the methyl carbamate (**6**) *via* the isocyanate (**5**)[9)] followed by hydrolysis afforded the cyclopropylamine (**7**).

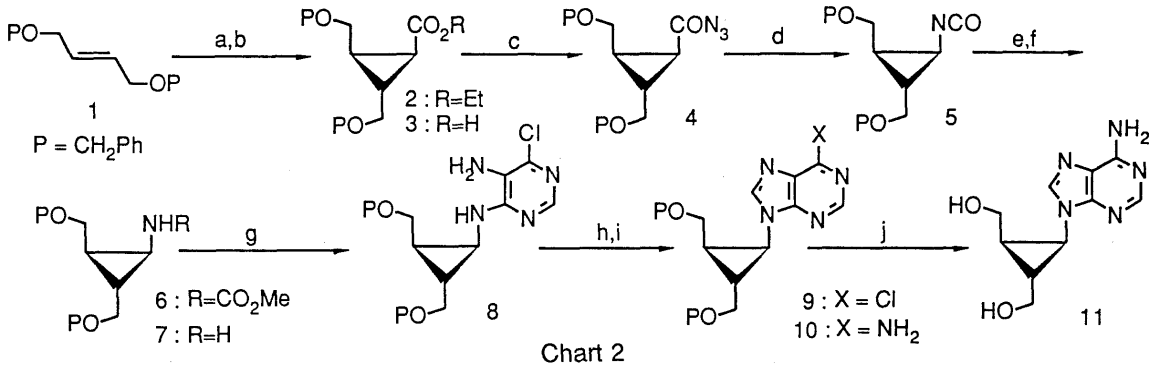

Chart 2

Reagents and conditions: a, N_2CHCO_2Et, Cu, 110 °C (34% based on the diazoester); b, 1N NaOH/EtOH, reflux (quant.); c, $ClCO_2Et$, Et_3N/aq. acetone, 0 °C, then NaN_3/H_2O, 0 °C- room temperature (64%); d, toluene, 90 °C; e, MeOH/reflux (74% from 4); f, 2.5N KOH/MeOH, reflux (95% from 6); g, 5-amino-4,6-dichloropyrimidine, Et_3N/EtOH, 10 kbar, 60 °C (82%); h, $CH(OEt)_3$, concentrated HCl (trace), 10 kbar, 60 °C (93%); i, NH_3/MeOH, 90 °C (sealed tube) (86%); j, BCl_3, CH_2Cl_2, -78 °C (89%).

The usual construction of adenine by manipulation of the amine function of **7** via **8**, **9**, and **10** followed by deblocking of the benzyl groups afforded the final target molecule (**11**).[10]

The isocyanate (**5**) derived from the azide (**4**) was treated with ammonia to give the urea (**12**). Conversion of the urea unit of **12** via **13** to thymine by the previously reported method[11] via **13** gave, after deblocking of the benzyl group, 1-(*t*-2,*c*-3-dihydroxymethyl-*r*-1-cyclopropyl)thymine (**15**).[12] The following comments seem to be indicated by the above conversions: 1) the use of high-pressure in step g was essential in order to obtain **8** in a satisfactory yield[13] and 2) in step m, a minor amount (15%) of the isomeric thymine derivative (**16**)[14] was obtained as a by-product.

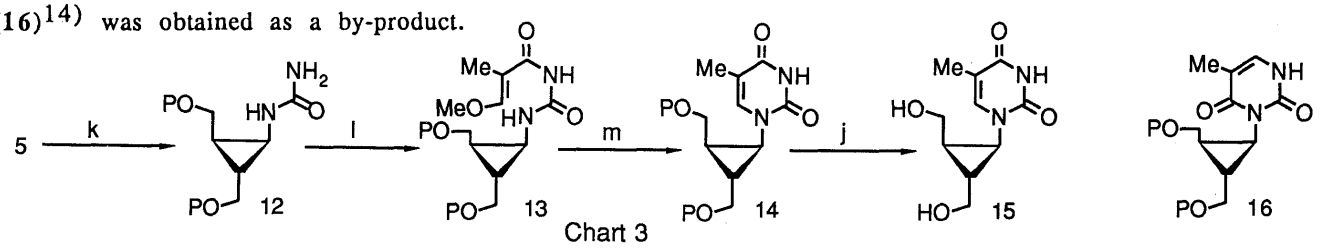

Chart 3

Reagents and conditions: P and j are the same as those in Chart 2. k, toluene saturated by NH_3, room temperature (89%); l, *[E]*-MeOCH=CMeCOCl/CH_2Cl_2-pyridine, 12 h, 0 °C - room temperature (80%); m, 25% aq. NH_4OH-MeOH, 85 °C (sealed tube) (65%).

The corresponding analogs having two hydroxymethyl groups in the *cis*-relationship, 9-(*t*-2,*t*-3-dihydroxymethyl-*r*-1-cyclopropyl)-9H-adenine (**18**)[15] and 1-(*t*-2,*t*-3-dihydroxymethyl-*r*-1-cyclopropyl) thymine (**19**)[16], have also been synthesized from *cis*-1,4-dibenzyloxy-2-butene (**17**). The former compound

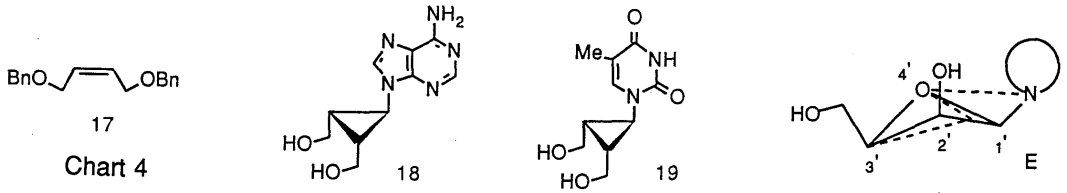

Chart 4

(**18**) has three heteroatoms in nearly the same space as epinor-oxetanocin (**E**) which exhibited significant antiviral activity[17] (Note that, taking a plane of $C_{3'}$, $C_{4'}$ and the midpoint of $C_{1'}$-$C_{2'}$ in **E**, two oxygen atoms occupy the opposite side of the adenine ring).

All compounds (**11**, **15**, **18**, and **19**) thus obtained showed no significant antiviral activity against HSV (herpes simplex virus types 1 and 2). However, in antiviral tests using Bat2Cl1 cells consistently infected by BLV (Bovine Leukemia Virus), compounds **18** and **19** at 5-50 μg/ml inhibited 20-50% and 45-75%, respectively.

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7) T. Chiba, Y. Takada, C. Kaneko, F. Kiuchi, and T. Tsuda, *Chem. Pharm. Bull.*, in press and references cited therein.
8) Though only spectral data for final target compounds (**11**, **15**, **18**, and **19**) are given in this paper, all structures for new compounds were supported by acceptable spectral data.
9) Due to instability, the isocyanate (**5**) was used for further reactions as it was formed from 4 without any purification. The formation of the isocyanate was, however, verified by IR spectrum showing a strong absorption band at 2300 cm^{-1} .
10) **11**: mp 194-196 °C; UV (MeOH) λ_{max} nm (ε): 206 (15803), 259 (11658); ^{1}H-NMR (CD_3OD) δ: 1.73, 1.96 (each 1H, quint., J=7.1 Hz, C_2'-, C_3'-H), 3.29 (1H, dd, *J*=12.0, 7.1 Hz, one proton of CH_2OH *cis* to the adenyl group), 3.58 (1H, dd, *J*=8.0, 4.0 Hz, C_1'-H), 3.62, 3.73, 3.82 (each 1H, dd, *J*=12.0, 7.1 Hz, CH_2OH), 8.38, 8.40 (C_2-, C_8-H).
11) N. Katagiri, M. Muto, and C. Kaneko, *Tetrahedron Lett.*, **30**, 1645 (1989). See also M. Sato, N. Yoneda, and C. Kaneko, *Chem. Pharm. Bull.*, **34**, 621 (1986).
12) **15**: mp 159-161 °C; UV (MeOH) λ_{max} nm(ε): 207.5 (9968), 268 (8132); ^{1}H-NMR (CD_3OD) δ: 1.45-1.60 (2H, m, C_2'-, C_3'-H), 1.87 (3H, s, Me), 3.24 (1H, dd, *J*=8.0, 3.0 Hz, C_1'-H), 3.40, 3.50, 3.59, 3.78 (each 1H, m, 2 x CH_2OH), 7.48 (1H, s, C_6-H).
13) If this reaction was carried out under an ordinary atmosphere under a variety of conditions, the yield of desired product (**8**) became much less and many unidentified products were formed.
14) Though the NMR spectrum of **16** was similar to that of **14**, the olefinic proton signal of the former appeared as a doublet (*J*=4 Hz) due to coupling with NH.
15) **18**: mp 214-216 °C: UV (MeOH) λ_{max} nm (ε) : 205.5(19022), 259 (13723); ^{1}H-NMR (DMSO-d_6) δ: 1.92 (2H, m, C_2'-, C_3'-H), 3.48 (1H, t, *J*=5.0 Hz, C_1'-H), 3.57-3.80 (4H, AB part of ABX pattern centered at 3.60 and 3.78, J_{AB}=12.0, J_{AX}=8.0, J_{BX}=7.5 Hz, 2 x CH_2OH), 8.42, 8.48 (each 1H, s, C_2-,C_8-H).
16) **19**: mp 182-184 °C: UV (MeOH) λ_{max} nm (ε): 207 (8133), 269 (9049); ^{1}H-NMR (CD_3OD) δ: 1.70 (2H, m, C_2'-, C_3'-H), 1.86 (3H, s, Me), 2.88 (1H, t, *J*=4.0 Hz, C_1'-H), 3.63-3.84 (4H, AB part of ABX pattern centered at 3.67 and 3.82, J_{AB}=12.0, J_{AX}=J_{BX}=7.0 Hz), 7.40 (1H, s, C_6-H).
17) Private communication from Dr. T. Takita, Nippon Kayaku Co. Ltd. See also: S. Nishiyama, T. Ohgiya, S. Yamamura, K. Kato, M. Nagai, and T. Takita, *Tetrahedron Lett.*, **31**, 705 (1990).
18) The antiviral activities were evaluated by the Division of Viral Disease Research, Tokushima Res. Ist., Otsuka Pharmaceuticals Ltd., which is acknowledged.

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