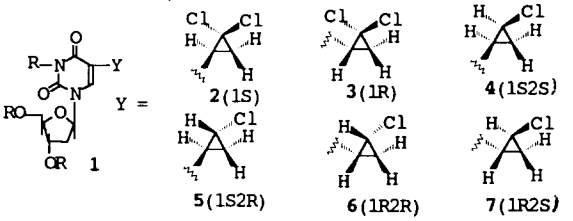
4

Design, Synthesis And Configuration Of 5-[2,2-Dichloro(or 2-chloro)cyclopropyl]-2'-deoxyuridines. E. E. Knaus, M. Tandon, M. L. Temptest and L. I. Wiebe. Faculty of Pharmacy, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

(E)-5-(2-Chlorovinyl)-2'-deoxyuridine (ClVDU) is a potent antiviral agent against herpes simplex virus type 1 (HSV-1) that is selectively phosphorylated by HSV-1 encoded thymidine kinase and metabolically trapped in infected cells. The 5-(chlorocyclopropyl) moiety can be considered as a potential bioisostere of the 5-(2-chlorovinyl) substituent present in ClVDU since the C-C bonds are more like those of ethylene than ethane. Reaction of **1** (R=Bz, Y=vinyl) with $PhHgCBrCl_2$ yielded a mixture of **2** and **3** (R=Bz) which were separated and individually hydrolyzed to yield **2** and **3** (R=H). Monodechlorination of **2** and **3** (R=H), gave the separable diastereomers **4** and **5**, and **6** and **7**, respectively. The configuration of **4** was establisined by X-ray, whereas the configuration of **2-3**, **5-7** were determined using H and C NMR spectrometry. Correlations between H and C NMR chemical shifts for the cyclopropyl atoms at the C-1 (**2-3**), and C-1 and C-2 (**4-7**), positions will be presented.



5

Novel Non-Nucleoside Inhibition Of Reverse Transcriptase (RT) For Human Immunodeficiency Virus-1 (HIV-1)

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The spread of HIV-1 infection requires the enzyme, RT, to synthesize pro-viral DNA. A screening program was initiated at Boehringer Ingelheim Pharmaceuticals Inc. to identify inhibitors of HIV-1 RT, using purified recombinant enzyme produced in E. coli. We have found a novel class of tricyclic dipyrido diazepinones, intermediates in the synthesis of muscarinic antagonists related to the pirenzepine structure, which are selective inhibitors of HIV-1 RT. This class of molecules does not inhibit mammalian DNA polymerase or other reverse transcriptases including HIV-2 RT. The structure activity relationships of the tricyclic series will be addressed. The enzymology and mechanism of action, as well as anti-viral activity in cell culture will be presented. Finally, the discussion will lead to the description of compound BI-RG-587, our development candidate for the treatment of HIV-1 infection in AIDS patients.