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## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information: http://www.informaworld.com/smpp/title~content=t713597286

# Bicyclonucleosides and Ring-Chain Interconversion

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 $\label{eq:continuous} \textbf{To cite this Article} \ \ \textbf{Tronchet}, \ J. \ M. \ J. \ , \ Zs\'ely, \ M. \ , \ Brenas, \ L. \ , \ Lassout, \ O. \ , \ Grand, \ E. \ , \ Seuret, \ P. \ , \ Grigorov, \ M. \ , \ Rivaraminten, \ E. \ and \ Geoffroy, \ M. (1999) \ 'Bicyclonucleosides and Ring-Chain Interconversion', \ Nucleosides, \ Nucleotides and \ Nucleic Acids, \ 18:4,1077-1078$ 

To link to this Article: DOI: 10.1080/15257779908041651 URL: http://dx.doi.org/10.1080/15257779908041651

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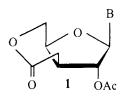
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#### BICYCLONUCLEOSIDES AND RING-CHAIN INTERCONVERSION

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Abstract: Four types of bicyclonucleosides differing in the easiness of their ring-chain interconversion have been prepared. some exhibited anti-HIV activity and the ratio of their cyclic and open-chain forms could have some bearing on their biological actitity.



Four different types of bicyclonucleosides have been prepared, the branched-chain nucleoside lactones 1, the pyrrolidinonucleosides 2, the perhydro-1,3-oxazinonucleosides 3, and

the spironucleosides 4 bearing either an 1,3-oxazolidine (4, n = 1) or a perhydro-1,3-oxazine ring (4, n = 2). The lactones 1 open extremely easily in basic medium and the position of the ring-chain equilibrium, depending almost exclusively on the pH, cannot be

controlled in biological media. At the opposite end of the ring-chain interconversion spectrum are compounds 2, prepared using a reverse Cope elimination, the mechanism of which has been studied by quantum mechanical methods, which do not undergo ring opening in normal conditions. In an intermediate situation, one finds compounds 3 and 4 only slightly differing in energy from their

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respective open-chain counterparts 3' and 4'. This theoretically opens to these compounds the possibility to act, in biological media, either as their open form or as bicycles, i.e. the ring form could be considered as a masked form of the open-chain electrophilic nitrone or vice-versa.

Concerning compounds 3 = 3', they exist exclusively in the cyclic form except when R and R' are larger than a methyl group or when one group is a large electron donating group like a p-methoxyphenyl, the second being a hydrogen atom. In this series, all the compounds found active against HIV-1 and HIV-2 (IC<sub>50</sub> in the 0.3-3 μM range) exist in their cyclic form. As they need to be phosphorylated to become active,<sup>2</sup> the question is risen of whether they are phosphorylated on the N-OH group or on the habitual HO-5' group after a non-spontaneous ring opening catalyzed by some biochemical agent, i.e. thymidylate kinase. It seems nevertheless more probable that the phosphorylation would take place on the N-OH group of the bicyclic form. When incorporated into the new DNA chain, the nitrogen atom of the phosphorylated bicyclonucleoside could be mistakenly attacked by HO-3' of the incoming next nucleotide in place of the phosphorous atom of the first phosphate unit of a natural dNTP. To test this hypothesis, we determined the electrophilicity of this nitrogen atom. Whereas the classical Fukui approach did not reveal any electrophilicity at this site, the novel DFTbased method we have developped<sup>3</sup> indicates, at this position, a reactivity toward hard nucleophiles and no reactivity toward soft nucleophiles.

Only methylene nitrones 4' underwent cyclization, any substitution on the nitrone sp<sup>2</sup> carbon atom preventing the ring closure. Generally both open-chain and ring forms are present [in benzene  $\Delta H = 4.4$  kcal/mol,  $\Delta S = 13.6$  e.u for  $4^{-1}$  (n = 2)].

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