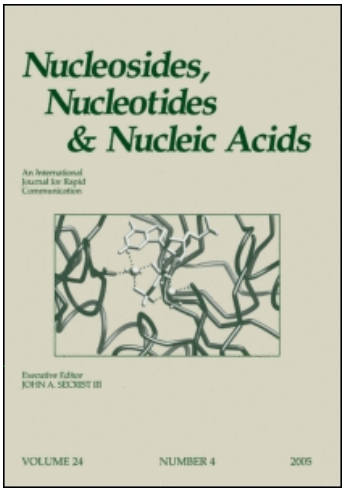

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J. M. J. Tronchet[a]; M. Zsély[a]; L. Brenas[a]; O. Lassout[a]; E. Grand[a]; P. Seuret[a]; M. Grigorov[a]; E. Rivara-minten[a]; M. Geoffroy[b]
[a] Departments of Pharmaceutical Chemistry, University of Geneva, Geneva 4, Switzerland [b] Departments of Physical Chemistry, University of Geneva, Geneva 4, Switzerland

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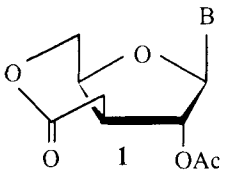
BICYCLONUCLEOSIDES AND RING-CHAIN INTERCONVERSION

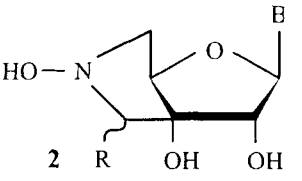
J. M. J. Tronchet,[a*] M. Zsély,[a] L. Brenas,[a] O. Lassout,[a] E. Grand,[a] P. Seuret,[a]
M. Grigorov,[a] E. Rivara-Minten,[a] and M. Geoffroy[b]

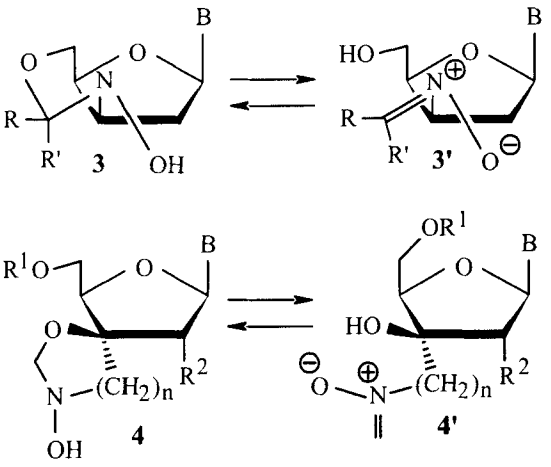
University of Geneva, Departments of Pharmaceutical Chemistry[a] and Physical Chemistry,[b] Sciences II, CH-1211 Geneva 4, Switzerland

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,[1] 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





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** $\rightleftharpoons$ **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_{50} in the 0.3-3 μM range) exist in their cyclic form. As they need to be phosphorylated to become active,[2] 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 DFT-based method we have developped[3] 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^2 carbon atom preventing the ring closure. Generally both open-chain and ring forms are present [in benzene ΔH = 4.4 kcal/mol, ΔS = 13.6 e.u for **4'** $\rightleftharpoons$ **4** (n =2)].

REFERENCES

1. Komaromi, I; Tronchet, J. M. J. *J. Phys. Chem. A*, **1997**, *101*, 3554.
2. Profs. E. De Clercq and J. Balzarini, personal communication.
3. Grigorov, M.; Weber, J; Vulliermet, N.; Chermette, M., Tronchet, J. M. J. *J. Chem. Phys.*, **1998**, *108*, 8790.