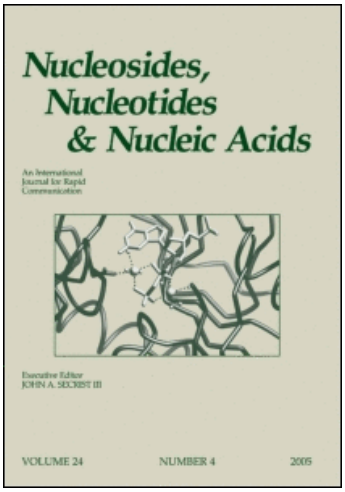


Nucleosides, Nucleotides and Nucleic Acids

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

Steric and Electronic Properties of the 3'-spiro Moiety of TSAO-T and Analogues

M. J. Pérez-Pérez[a]; R. Alvarez[a]; M. L. Jimeno[a]; A. San-Félix[a]; A. Lozano[b]; M. J. Camarasa[a]
[a] Instituto de Química Médica (CSIC), Madrid, Spain [b] Instituto de Ciencia y Tecnología de Polímeros (CSIC), Madrid, Spain

To cite this Article Pérez-Pérez, M. J. , Alvarez, R. , Jimeno, M. L. , San-Félix, A. , Lozano, A. and Camarasa, M. J.(1999) 'Steric and Electronic Properties of the 3'-spiro Moiety of TSAO-T and Analogues', Nucleosides, Nucleotides and Nucleic Acids, 18: 4, 1107 — 1108
To link to this Article: DOI: 10.1080/15257779908041661
URL: http://dx.doi.org/10.1080/15257779908041661

NUCLEOSIDES & NUCLEOTIDES, 18(4&5), 1107–1108 (1999)

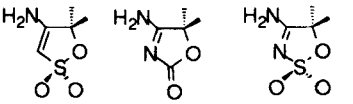
STERIC AND ELECTRONIC PROPERTIES OF THE 3'-SPIRO MOIETY OF TSAO-T AND ANALOGUES

M. J. Pérez-Pérez,[1] R. Alvarez,[1] M. L. Jimeno,[1] A. San-Félix,[1] A. Lozano[2] and M. J. Camarasa[1]*

[1]Instituto de Química Médica, [2]Instituto de Ciencia y Tecnología de Polímeros; (CSIC), Madrid, Spain

ABSTRACT: The synthesis and study of geometrical and stereoelectronic properties of the spiro moiety of tof novel TSAO analogues modified at the 3'-spiro moiety is described.

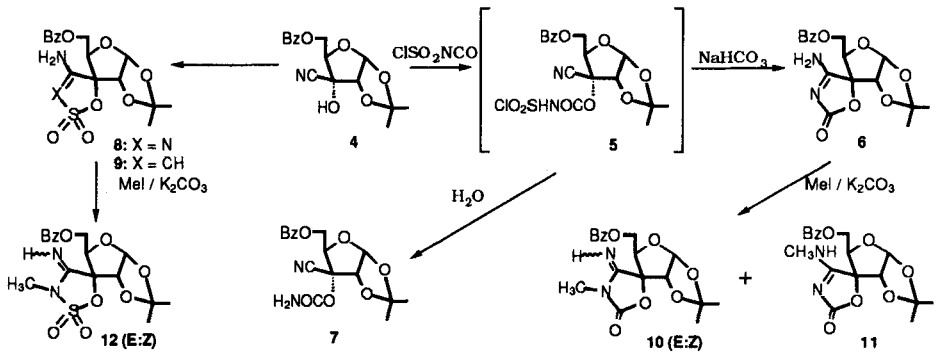
We have recently reported[1,2] the synthesis and the *"in vitro"* anti-HIV-1 activity of novel TSAO analogues modified at the 3'-spiro moiety in which the spiro aminooxathiole-dioxide (**1**) of the prototype TSAO-T[3] was replaced by closely related spiro moieties [4-amino-2-oxazolone (**2**) or a 4-amino-1,2,3-oxathiazole-2,2-dioxide (**3**)] However, although these novel analogues fulfilled the structural requirements of the TSAO family for activity, their anti-HIV-1 activity was 100 fold lower.[1]



1 **2** **3**

We now considered of interest to learn about the geometrical and stereoelectronic properties of the spiro moiety of these nucleosides that may help to explain the experimental results. Thus, we carried out an *ab-initio* theoretical study, with medium-high basis set, comparing the spiro rings **2** and **3** with the spiro ring of TSAO-T[3] (**1**), and their corresponding imine isomers. The imine-enamine equilibrium was also studied experimentally in solution by NMR techniques on sugar derivatives, as simplified models of the TSAO nucleosides.

The 3-spiro sugar derivatives were prepared by functionalization and ring closure of the cyanohydrin **4**. Thus, reaction of cyanohydrin **4**[4] with chlorosulfonyl isocyanate followed by treatment with saturated aqueous $NaHCO_3$ afforded compound **6** (Scheme 1). When the reaction was quenched with water, the carbamoyl derivative **7** was obtained instead. Sulfamoylation of **4**[4] with sulfamoyl chloride and DMAP afforded directly the cyclised compound **8**. Treatment of **6** with CH_3I / K_2CO_3 gave a (1:1) mixture of isomeric 4-imino-3-*N*-methyl-spiro oxazolidinone derivatives **10E** and **10Z**, together with the 4-*N*-methyl-spiro-oxazolone derivative **11**. A similar alkylation of compound **8** afforded, exclusively, an isomeric mixture of the E and Z imino derivatives **12**. Finally, when **9** (sugar model of TSAO-T) was subjected to similar reaction conditions, no alkylation took place, the starting compound being recovered unchanged.



Scheme 1

The predominant tautomer (in acetone-d_6) of the spiro moieties at 3-position of compounds **6** and **8** was the enamine as demonstrated by ^1H-^{15}N (HMQC) correlation spectroscopy experiments. The site of methylation and the stereochemistry (E,Z) of compounds **10-12** were determined by ^1H, ^{13}C and ^{15}N NMR spectroscopy .

An *ab-initio* theoretical study was carried out on the structures **1**, **2** and **3** and their imine isomers to establish a differential order of nucleophilicity and reactivity of these amines and their corresponding imine isomers. All the studied molecules present an almost planar ring, this can be associated (in the amines) to the conjugation of the double bond and the ketone or sulfone group. The main geometrical parameters that account for the reactivity of these molecules as nucleopliles are the distance C_{ring}-N_{NH2} (d_1) and the separation from planarity of the amino group, represented by the sum of angles around amine nitrogen (Σ). All three amines have a Σ value of 360°, typical for sp^2 amines, and therefore their nucleoplilicity should be very low. In that concerning d_1 values, structure **1** showed a higher value (1.350Å) than **2** and **3** (1.332Å), indicating a lower conjugation and hence a higher reactivity. The geometrical parameters were very similar for all imine forms.

The E_{HOMO} and the $HOMO_{coefficients}$ were calculated for all amine and imine isomers of **1**, **2** and **3**. These studies indicated that, if the electrophilic substitution reaction is orbital controlled, it would take place preferentially on the endo nitrogen for the amines and on the exo nitrogen for the imines. Combining the values obtained of E_{HOMO} and the $HOMO_{coefficients}$ for each isomer, it is possible to explain the reactivity and selectivity of the methylation reaction of these spiro rings, that were in agreement with the experimental results observed in the methylation of **6**, **7** and **9**.

The Spanish CICYT, the NATO and the BIOMED (EU) is Acknowledged for financial support.

REFERENCES

1 Alvarez, R., Jimeno, M.L., Pérez-Pérez, M.J., De Clercq, E., Balzarini, J.; Camarasa, M.J. *Antivir. Chem. Chemother.* **1997**, *8*, 507-517.

2 Alvarez, R., Jimeno, M.L.; Gago, F.; Balzarini, J.; Pérez-Pérez, M.J., Camarasa, M.J. *Antivir. Chem. Chemother.* **1998**, *9*, 333-340.

3 (a) Balzarini, J.; Camarasa, M.J.; Karlsson, A. *Drugs of the Future* **1993**, *18* , 1043-1055. (b) Camarasa, M.J.; Pérez-Pérez, M.J.; Velázquez, S.; San-Félix, A.; Alvarez, R.; Ingate, S.; Jimeno, M.L.; Karlsson, A.; De Clercq, E.; Balzarini, J. *Nucleosides & Nucleotides* **1995**, *14*, 585-594.

4 Pérez-Pérez, M.J.; San-Félix, A.; Balzarini, J.; De Clercq, E.; Camarasa, M.J. *J. Med. Chem.* **1992**, *35*, 2988-2995.