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New Types of Spin-labelled Sugar and Nucleoside Analogs: Pyrrolidine, Morpholine and Piperidine *N*-Oxyls

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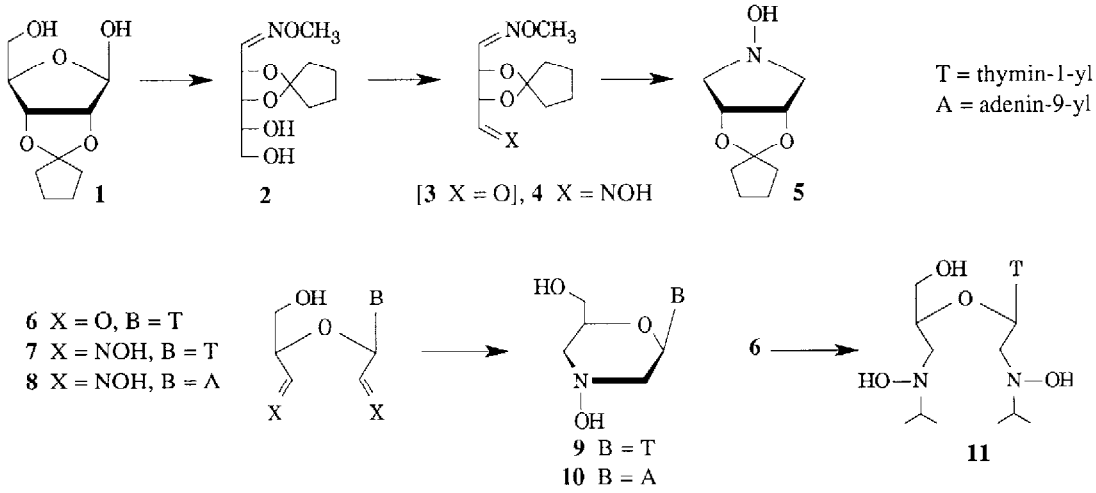
Abstract : *Analogs of blocked furanose (**20**) or pyranose sugars (i e **15**) and of nucleosides (i e **23**)in which the ring oxygen has been replaced with a -N(OH)- bridge have been prepared in generally good yields by a general reductive cyclization procedure preserving the configuration of the preexistant asymetric centers and proceeding stereoselectively (in more favorable cases stereospecifically) when creating a new asymetric center The title compounds oxidized to nitroxide free radicals affording usable ESR spectra*

Spin-labelled sugar analogs differing from the natural compounds only in the replacement of a -O- group with a -N(O')- magnetic probe give ESR spectra providing useful structural information [1] These free radicals are formed by spontaneous oxidation in the air of solutions of the corresponding deoxy *N*-hydroxyaminosugars[2] (sugar hydroxylamines). We have described[3] a number of such sugar analogs in which a hydroxy group has been replaced with a *N*-hydroxyamino group. We report hereunder the extension of these syntheses to blocked anhydroalditol, sugar and nucleoside analogs in which the ring oxygen has been replaced with a *N*-hydroxyimino bridge.

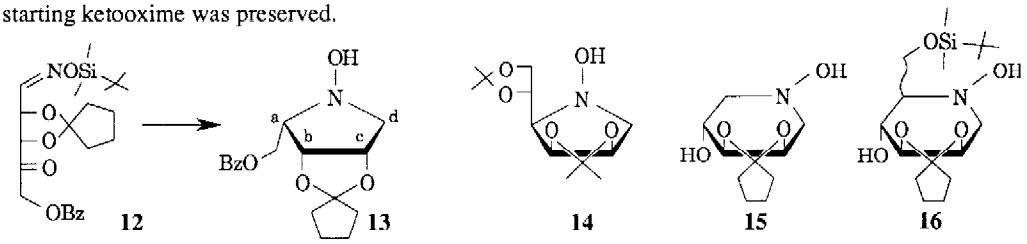
Sodium cyanoborohydride reduction[4] of the dioxime **4**[5] (obtained in 62% yield from **1**[6] *via* **2** and **3**) gave in 70% yield the *meso N*-hydroxypyrrolidine derivative **5** Applied to acyclonucleoside dioximes **7** (obtained from **6**)[7] and **8**,[8] novel types of nucleosides analogs **9**[9] and **10** were obtained in respective yields of 84 and 78% Treatment of **6** with *N*-prop-2-ylhydroxylamine and reduction of the intermediate dinitrone led to the acyclonucleoside analog **11** (52%) (Scheme 1),



Scheme 1

Another synthetic route to *N*-hydroxypyrrolidine and *N*-hydroxypiperidine analogs of sugars consisted in the cyanoborhydride reduction of sugar γ- or δ-ketooximes respectively.[10] Compound **12**, easily obtained using standard procedures from the known 5-*O*-benzoyl-2,3-*O*-cyclopentylidene-α-D-ribofuranose,[6] was stereospecifically converted in 50% yield to **13** by treatment with sodium cyanoborohydride at pH 2. The one-pot reaction consisted in de-*O*-silylation, reduction of the oxime into a hydroxylamine, cyclization to a nitrone finally reduced to **13** from the *exo* face of the molecule.

Compounds **14-16** have ben prepared from D-mannose following the same general lines (Scheme 2). They represent the three possible stereochemical situations. In the case of **15**, the reduction of the intermediate cyclic nitrone does not create any new asymmetric center and a unique isomer is formed as for **14** where the reduction is stereospecific, the cyclic ketal hindering one of the faces of the nitrone. On the contrary, the reaction leading to **16** was only stereoselective (D-*manno*/L-*gulo ratio* of 3:2). In any case, the stereochemistry of the chiral centers of the starting ketooxime was preserved.

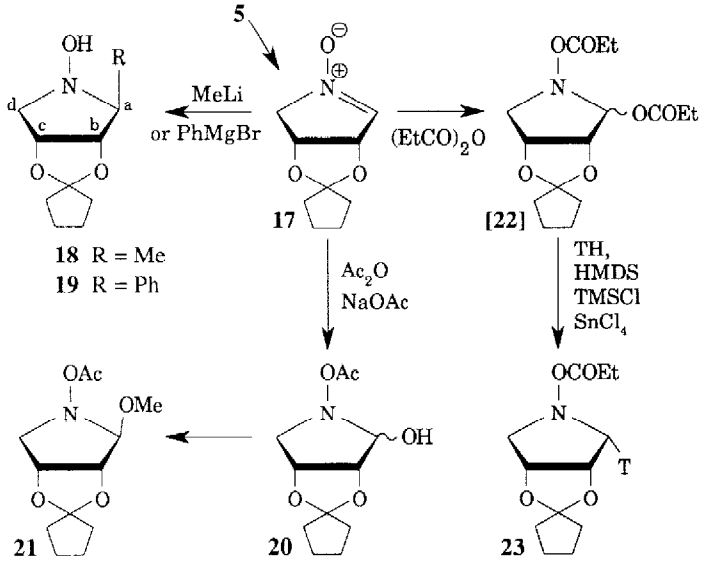


Scheme 2

The major interest of these *N*-hydroxypyrrolidines and -piperidines resides in the fact that they can be oxidized (HgO) to a cyclic nitrone which constitutes a useful synthetic intermediate. The oxidation is not regiospecific but in the case of **5**, owing to its *meso* configuration, the oxidation led to racemic **17** (90% yield).[11]

A variety of carbon nucleophiles reacted with **17** leading to *C*-glycoside analogs, f. ex. the methyl β-*C*-glycoside **18** and its phenyl congener **19** were obtained respectively in 70% and 72% yields. Upon acetylation, **17** led in 80% yield to a 2.5:1 mixture of the α and β anomers of the blocked sugar analog **20**. The methyl β-glycoside **21** was obtained by adding methanol to the reaction mixture of the preparation of **20**. The nucleosidation of **17** was effected *via* the dipropionyl derivative **22** (β:α *ratio* 9:1) which was not isolated but directly reacted with thymine to give **23**[12] obtained in 44% yield from **17** (Scheme 3). At first sight, **20** appears to behave like a normal sugar, undergoing in particular *O*- and *N*-glycosidations. In fact, significative differences exist, these pyrrolidine analogs being more easily glycosylated than their parent sugars and their anomeric hydroxyl group less easily acylated.

The configurations of the described pyrrolidine derivatives have been assessed by PMR (Table 1). The consistantly high value of $J_{b,c}$ indicated that these compounds existed essentially in envelope forms (N_{endo} or N_{exo} with $J_{c,dendo} = 0$ for the N_{endo} conformer). Except for β-**20-22** where $J_{a,b}$ values inferior to 3 Hz established the *trans* relationship of Ha and Hb, the configurational assign-



Scheme 3

ments were in all other cases based on the $J_{c,d\ endo}$ value null for the α anomers owing to the fact the N_{endo} envelope was prefered in this case. The difference in chemical shifts of the Hd_{endo} and Hd_{exo}, small for β compounds, larger for α anomers was also usable.

Table 1

Selected PMR Data of Some N-hydroxypyrrolidine derivatives (J in Hz).

Cmpd	δ^{exo}_{Hd}	δ^{endo}_{Hd}	$J_{a,b}$	$J_{b,c}$	$J_{c,dexo}$	$J_{c,d\ endo}$	Ha configuration
18	3.20	3.41	4	7	3	5	*endo*
19	3.18	3.79	6	7	5	6	*endo*
β-20	3.45	3.50	1	7	2.5	4	*endo*
21	3.49[a]	3.49[a]	1	7	3.5[a]	3.5[a]	*endo*
β-22	3.49	3.32	0 5	7	1 2	5.2	*endo*
13	2.80	3 55	4.8	7	4 3	0	*exo*
14	3.47	2 71	4 7	6.5	5	0	*exo*
α-20	2.75	3.67	5	7	5	0	*exo*
α-22	3.16	3 62	4.5	?	5	0	*exo*
23	2.98	3 88	5	7	5	0	*exo*

[a] H_{dendo} and H_{dexo} are isochronous in these conditions

All *N*-hydroxy compounds oxidized in the air generally spontaneously[13] to give the corresponding nitroxide free radicals Time-averaged ESR spectra (Fig. 1) were observed at temperatures superior to 20° A detailed conformational study of these radicals using low temperature ESR measurements, molecular mechanics and molecular dynamics computations will be reported later. The nucleoside analogs are undergoing cytotoxic and antiviral testing

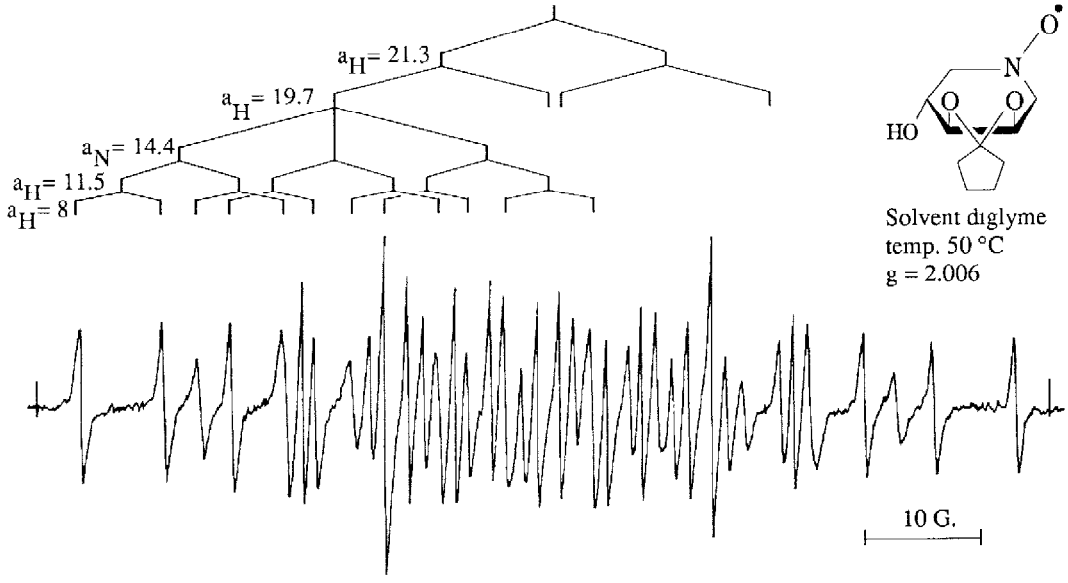


Fig 1 ESR spectra of the nitroxide free radical generated from **15**

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9. M.p. 219.9-220.7 °C, after a transition at 113.2-126.1 °C. The hyperfine coupling constants of the corresponding nitroxide free radicals were the following : a_N 16.7, a_H 14.7, 14.7, 3.5, 3.5, 0.6, and 0.6 G.
10. For related reaction in carbohydrate chemistry see: Tronchet, J. M. J. ; Baehler, B.; Zumwald J.-B. *Helv. Chim. Acta* **1977**, *60*, 1932-1934 and Rertz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777-6780 and references therein.
11. For the sake of simplicity, only the D enantiomer is represented throughout.
12. M.p. 172.8-173-2 °C.
13. In some cases, the stationary concentration of radical species was increased by UV. irradiation.

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