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NOVEL TYPES OF CYCLONUCLEOSIDES

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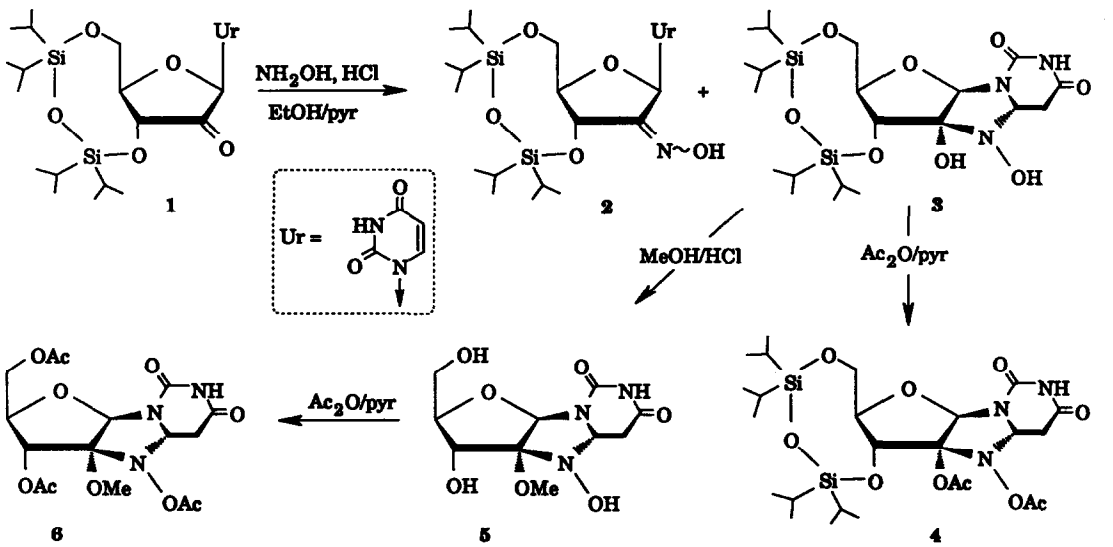
*Abstract : Reduction of 2'-deoxy-2'-hydroxyiminouridine derivatives led to a "**first generation**" hydroxylamine (2'-deoxy-2'-hydroxyaminouridine **8**, mostly* arabino *configuration) which on treatment with aldehydes afforded the corresponding nitrones **9** which were reduced to "**second generation**" hydroxylamines **12**. The modified nucleosides bearing a hydroxyamino group at the 2'-position, when of* arabino *configuration underwent conjugate addition onto the uracil ring leading to novel types of cyclonucleosides (**3**, **5**, **10**, **13**).*

Several examples of cyclonucleosides bearing a methylene bridge or one of its aza, oxa or thia analogs are known[1]. We describe here two novel types of cyclonucleosides characterized respectively by a *N*-hydroxyimino or an oxazaethylene bridge. Beside their general pharmacological interest as nucleoside analogs, the *N*-hydroxyimino derivatives, oxidizing spontaneously in the air[2] to give the corresponding nitroxide free radicals, afford the first examples of spin-labelled cyclonucleosides.

Oximation of the blocked "2'-ketouridine" **1**[3] in ethanol/pyridine gave a 7:3 resolvable mixture of *E* (m.p. 101.1-101.8 °C) and *Z* (m.p. 96.6-97.2 °C) isomers of **2**, together with 46% (average yield) of the cyclonucleoside **3** (Scheme 1).



Scheme 1

The fact that **3** had lost its aromaticity was established by its weak UV. absorbance on TLC and the lack in its ^{1}H-n.m.r. spectrum[4] of the two aromatic protons of the uracil replaced by an ABX system. Upon acylation, **3** gave the di-*O*-acetylated derivative **4**, thus confirming the existence of its two hydroxyl groups.

The cyclonucleoside **3** bears two anomeric centers (on C-1' and C-2') and when reacted with methanolic HCl, it underwent a glycosidation reaction to **5**[5] which was peracetylated to **6** whose configuration at the two new asymmetric centers (C-6 and C-2') was established by X-ray diffraction[6] (Figure 1). The e.s.r. spectra obtained by exposing to air solutions of **3** and **5** were very similar : one coupling with N (respectively 13.6 and 12.9 G) and one with H-C6 (respectively 16.4 and 16.0 G). The value of the a_H hyperfine coupling constant corresponding[9] to a 38° time-averaged dihedral angle between the p orbital on nitrogen and the H-C6 bond, was consistent with an H-C6 in axial position on the dihydrouracil ring.

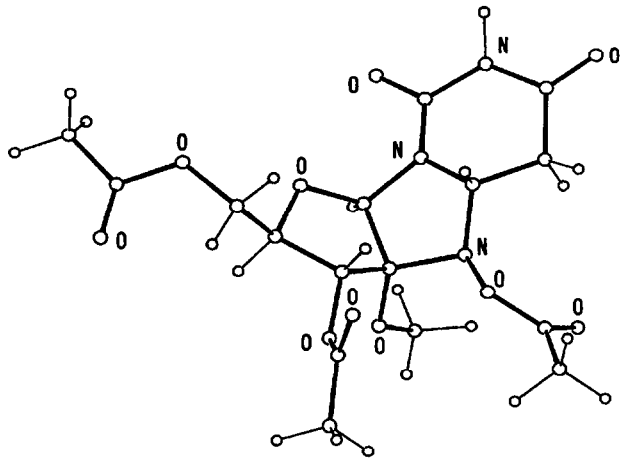
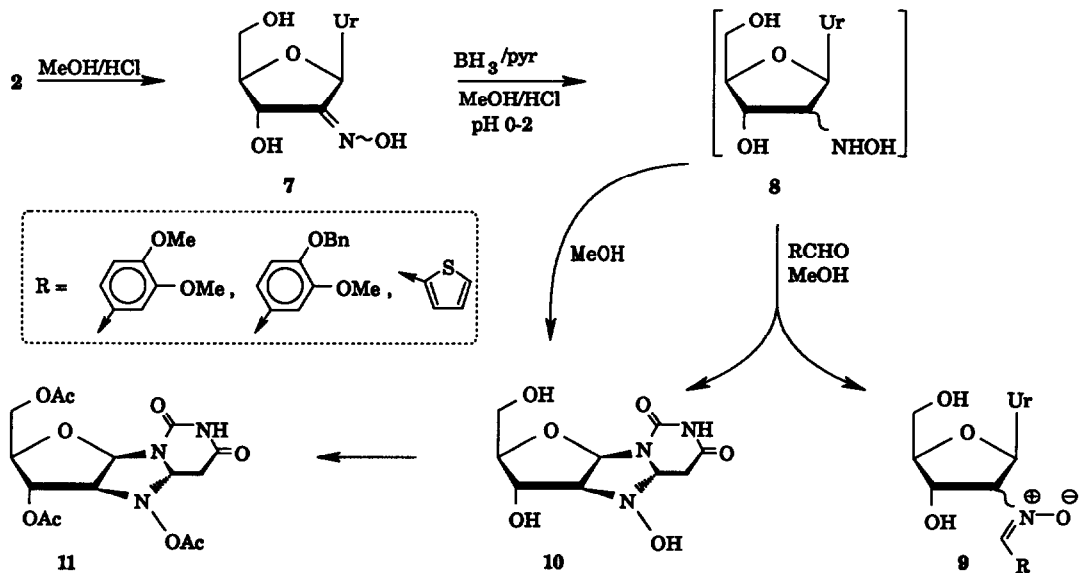


Figure 1. Crystal structure of **6**

Acidic methanolysis of **2** (Scheme 2) gave the oximes **7** which generally were not isolated but immediately treated with BH_3/pyridine complex[10] to give **8** which, after a rough purification removing the excess of reducing agent, was reacted with veratraldehyde to afford a mixture of the 2'-epimers of **9** (18.6% from **2**) and the cyclonucleoside **10** (75% from **2**). The same type of results were obtained with other aldehydes. The reduction reaction was always



Scheme 2

stereoselective leading to a *ca* 4:1 *arabino*-**8**/*ribo*-**8** ratio but, depending on the reaction conditions (time, pH, nature of the aldehyde) the ratios cyclonucleoside/nitrones and *arabino*-nitrone/*ribo*-nitrone varied in a way consistent with the *arabino* isomer of **8** being the only precursor of **10**. In the absence of aldehyde, **10** was also formed, albeit in poorer isolated yield (53% from **2**). The structure of **10** was established by formation of the tri-*O*-acetylated derivative **11** and its spectral data particularly e.s.r. (a_N 14.1 G, a_H 18.0, 19.3 G, plus extra small long-range couplings with a nitrogen

(0.6 G) and a proton (0.5 G)) and confirmed by X-ray diffraction[6] (Figure 2).

Upon reduction, *arabino*-nitrones **9** gave mostly the corresponding hydroxylamines **12** (e.s.r. hyperfine coupling with nitrogen, a methylene and a methine group) and as a minor (4-12%) product, another type of cyclonucleoside **13** giving no e.s.r. signals on oxidation and affording upon acetylation the di-*O*-acetyl derivative **14** (Scheme 3).

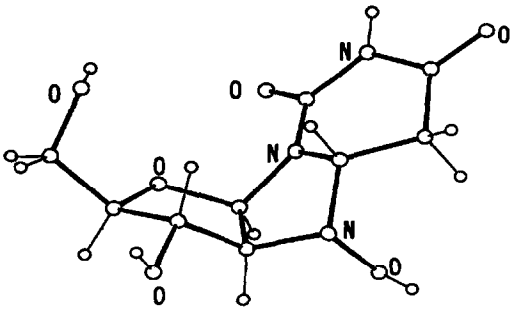
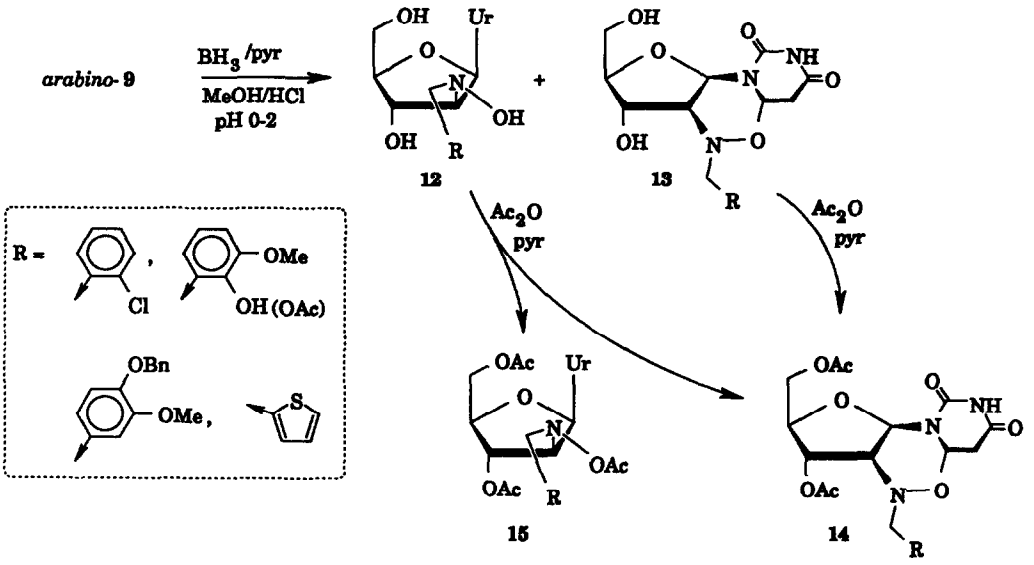


Figure 2. Crystal structure of **10**



Scheme 3

As the acetylation of **12** led mainly to **14**[11] (*ca* 60%) (only 10-25% of **15** being formed), this provided a good synthetic pathway to cyclonucleoside **14** (and consequently **13**).

The selectivity of the borane reduction allowed a one-pot reaction in which **2** was deprotected, treated with a large excess (35 eq.) of reducing agent then with 2-3 equivalent of aldehyde to give a mixture of **10**, **12** and **13**. In the most favourable case (R = 2-chlorophenyl) the yields of **10**, **12** and **13** were respectively 34, 5 and 40%.

The cyclonucleosides showed some antibacterial activity (*i.e.* $IC_{50} = 5\ \mu M$ for **10** against *Bacillus subtilis*). They are undergoing antiviral (particularly anti-HIV) testing.

In conclusion, the first (**8**) and second (**12**) generation hydroxylamines easily obtained from the readily available "ketonucleosides" both underwent conjugate addition on the uracil ring giving two novel types of cyclonucleosides. The spin-labelled nucleosides analogs prepared constitute new tools for the structural and biochemical study of nucleosides.

Acknowledgment

This work was supported by the Swiss National Fund for Scientific Research (grants No 2.492-0-8 and 20-26460-89).

REFERENCES AND NOTES

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2. For previous examples of deoxy-*N*-hydroxyamino nucleosides and nitroxides thereof, see : J. M. J. Tronchet, R. Benhamza, N. Dolatshahi, M. Geoffroy and H. Türler, *Nucleosides & Nucleotides*, **7**, 249 (1988).
3. F. Hansske and M. J. Robins, *Tetrahedron Lett.*, **24**, 1589 (1983); F. Hansske, D. Madej and M. J. Robins, *Tetrahedron*, **40**, 125 (1984).
4. All isolated new compounds had elemental analysis (or high resolution mass data for **7** and **13**, R = thien-2-yl) and spectra consistent with the assigned structures.
5. **5** : m.p. 99.6-101 °C, $[\alpha]_D^{26}$ -48.3° (*c* 1.2, MeOH); ^{1}H-n.m.r. (200 MHz, CD_3OD): δ 2.75 (*dd*, 1 H, $J_{5a,5b}$ 16.2, $J_{5a,6}$ 9.5 Hz, Ha-5), 2.95 (*dd*, 1 H, $J_{5b,6}$ 5.5 Hz, Hb-5), 3.46 (*s*, 3 H, OMe), 3.66 (*dd*, 1 H, $J_{5'a,5'b}$ 12, $J_{5'a,4'}$, 4 Hz, Ha-5'), 3.77 (*ddd*, 1 H, H-4'), 3.86 (*dd*, 1 H, $J_{5'b,4'}$ 1 Hz, Hb-5'), 4.42 (*d*, 1 H, $J_{3',4'}$ 8.7 Hz, H-3'), 4.65 (*dd*, 1 H, H-6), and 5.55 (*s*, 1 H, H-1'); ^{13}C-n.m.r (50 MHz, CD_3OD): δ 37.26 (C-5), 50.9 (MeO), 61.76 (C-5'), 68.79 (C-3'), 72.44 (C-6), 84.46 (C-4'), 87.28 (C-1'), 102.37 (C-2'), 151.73 (C-2), and 170.56 (C-4). MS: *m/z* 112 (100, Ur + H), 239 (0.3, $M^{+\cdot}$ - H_2O), 256 ($M^{+\cdot}$ - H), and 257 ($M^{+\cdot}$).
6. *Crystal data:* **6**, $C_{16}H_{21}N_3O_{10}$ / H_2O, m = 433.4, monoclinic, space group $P2_1$, a = 10.6418(12), b = 7.4341(7), c = 12.7910(14) Å, β = 96.04(1)°, Z = 2, Dc = 1.43 grcm^{-3}, μ = 0.11 mm^{-1}, F000 = 456. R = 0.068, ωR = 0.067 ($\omega = 1/\sigma^2(Fo)$) for 1099 observed reflections (|Fo| > 4σ(Fo)).
10, $C_9H_{13}N_3O_6$, m = 259.2; orthorhombic, space group $P2_12_12_1$, a = 6.7051(9), b = 10.2824(13), c = 15.593(2) Å, Z = 4, Dc = 1.60 grcm^{-3}, μ = 0.13 mm^{-1}, F000 = 544. R = 0.036, ωR = 0.028 ($\omega = 1/\sigma^2(Fo)$) for 812 observed reflections (|Fo| > 4σ(Fo)). Data were collected at room temperature on an automatic four-circle Nonius CAD-4 diffractometer with monochromated MoKα radiation. Both structures were solved by direct methods[7] and refined by full matrix least-squares analysis with XTAL-2.4[8] program. The coordinates of hydrogen atoms were calculated for the compound **10** and observed and refined for the compound **6**.
Crystallographic data have been deposited with the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.
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10. Y. Kikugawa and M. Kawaza, *Chem. Lett.*, 1279 (1977).
11. **14** (*R* = thien-2-yl) : m.p. 95.7-97.1 °C, $[\alpha]_D^{22}$ +42.3° (*c* 0.5, $CHCl_3$); ^{1}H-n.m.r. (200 MHz, $CDCl_3$): δ 2.05 and 2.13 (*2 s*, 2x3 H, 2 Ac), 2.71 (*dd*, 1 H, $J_{5a,6}$ 9.5 Hz, Ha-5), 3.00 (*bdd*, 1 H, $J_{5b,6}$ 6, $J_{5a,5b}$ 17 Hz, Hb-5), 3.31 (*bd*, 1 H, $J_{1',2'}$ 3.2 Hz, H-2'), 4.12 (*d*, 1 H, Ha-CH_2-N), 4.17 (*dd*, 1 H, H-4'), 4.27 (*dd*, 1 H, $J_{5'a,4'}$ 6.1 Hz, Ha-5'), 4.42 (*dd*, 1 H, $J_{5'b,4'}$ 6, $J_{5'b,5'a}$ 11 Hz, Hb-5'), 4.58 (*d*, 1 H, Hb-CH_2-N), 5.00 (*bs*, 1 H, H-3'), 5.48 (*dd*, 1 H, H-6), 6.05 (*d*, 1 H, H-1'), 7.00 (*m*, 2 H, H Ar), 7.26 (*s*, 1 H, H Ar), and 7.61 (*bs*, 1 H, NH). MS: *m/z* 97 (100), 81 (8), 298 (8), 267 (4), 327 (2), 310 (2), 299 (2), 439 (2, $M^{+\cdot}$), 422 (1), 238 (1), 440 (0.7), 421 (0.4), and 423 (0.4).

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