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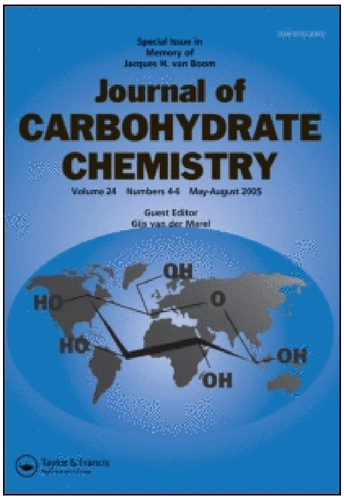

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DERIVATIVES OF 3-DEOXY-3-(*N*-HYDROXYAMINO)-D-RIBOSE

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ABSTRACT

A series of 3-(*N*-arylmethyl-*N*-hydroxyamino)-1,2-*O*-cyclopentylidene-3-deoxy-5-*O*-toluoyl-α-D-riboses has been prepared. The blocking groups used were chosen to allow an easy nucleosidation of these compounds to spin labelled analogs of natural nucleosides. The conformational behavior of the *N*-arylmethyl-*N*-hydroxyamino group has been studied using $^3J_{CH}$ NMR coupling data and molecular mechanics computations. Upon spontaneous oxidation, these hydroxylamines led to the corresponding aminoxyl free radicals which were submitted to EPR spectroscopy and quantum mechanical computations at a semiempirical level (PM3).

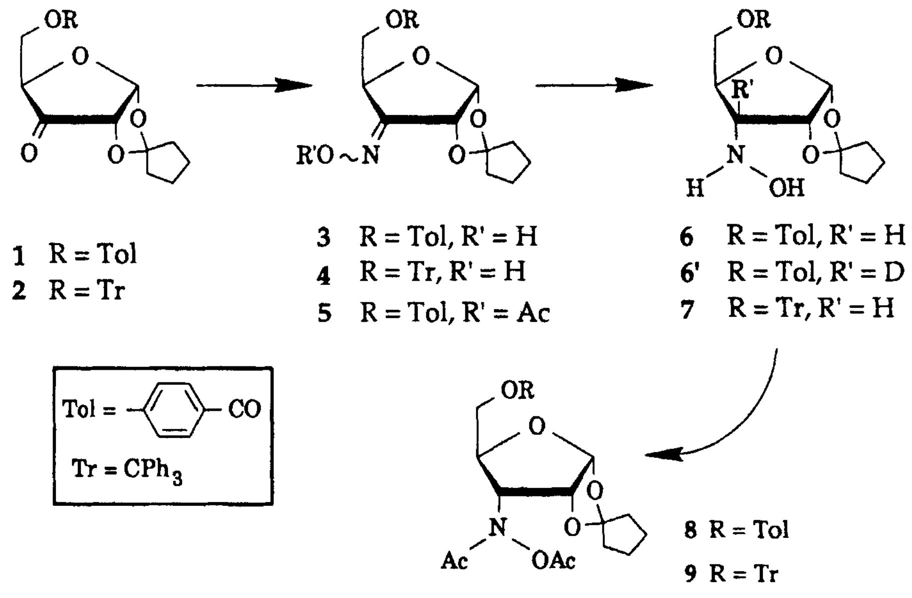
INTRODUCTION

Spin-labelled close analogs of natural nucleosides should constitute useful tools for the study of the biological events triggered by these bioactive species. We have given a preliminary account[1] of the synthesis of 3'-(*N*-arylmethyl-*N*-hydroxyamino)-3'-deoxy-5-halogenouridines which oxidize spontaneously to the corresponding aminoxyl free radicals. EPR spectra of these compounds afford useful configurational and conformational information.[2,3,4] As the reduction of 3'-deoxy-3'-(*N*-hydroxyimino)uridine leads mainly or exclusively to the *xylo* epimer,[5] we resorted to the stereospecific synthesis of 3-deoxy-3-(*N*-hydroxyamino)-D-ribose derivatives which were then submitted to nucleosidation. We describe here the synthesis and conformational properties of such modified ribose moieties adequately blocked to allow their easy transformation into starting material for nucleosidation reactions.

RESULTS AND DISCUSSION

Ketosugar derivatives **1** and **2** in which an easily hydrolyzable group blocks the two first positions[6] treated with hydroxylamine, led to the corresponding oximes **3** and **4** in 62 and 96% yields, respectively (SCHEME 1). These oximes were obtained as *ca.* 1:1 unresolvable *E*/*Z* mixtures, the configurational assignments being obtained from the H-2 and H-4 chemical shifts (TABLE 1), the OH group of the oxyimino group deshielding the *cis* proton.[7] Conversely, the C-2 carbon atom was more shielded in Z than in *E* compounds (TABLE 2). Acetylation of **3** yielded **5**. Sodium cyanoborohydride reduction at pH 3 of **3** and **4** gave in moderate yields the "first generation" hydroxylamines **6** and **7**, respectively. The **3-d$_1$** analog of **6**, **6'**, was prepared in substituting sodium cyanoborodeuteride to the corresponding hydride. The *ribo* epimer was the only isolated product of the reduction reaction. This stereospecificity has already been described in other series.[8] The *ribo* configuration of **6** and **7** was established from the large $J_{3,4}$ and the medium $J_{2,3}$ coupling constants (TABLE 3). These and other coupling constants of the protons of the furanose ring indicate a $^3T_2$ conformation. Upon acetylation (acetic anhydride pyridine) **6** and **7** led in good yields to the *O*-*N*-diacetylated derivatives **8** and **9**, respectively.

Treated with a variety of aromatic aldehydes, **6** led in fair to high yields to the expected nitrones **10a-h** obtained as one (classically the Z)[9] of the two possible diastereoisomers. Reduction (sodium borohydride) of **10a-f** yielded the corresponding "second generation" hydroxylamines **11a-f** (SCHEME 2). NMR data of compounds **10** and **11** are collected in TABLES 4-6. Two regiospecifically deuteriated analogs of **11c** (**11'c** and **11"c**) were obtained by sodium borohydride reduction of the unisolated nitrone formed by treating **6'** with *p*-methoxybenzaldehyde (**11'c**) or by sodium borohydride reduction of **10c** (**11"c**).



SCHEME 1

TABLE 1. Proton Chemical Shifts (200 MHz, $CDCl_3$) of the Furanose Moiety of Compounds 1-9.

Compd	H-1	H-2	H-3	H-4	Ha-5, Hb-5
1	6.12	4.42		4.63	4.45, 4.68
2	6.33	4.57		4.37	3.30, 3.52
(*Z*)-3	6.00	5.32		5.11	4.41, 4.67
(*E*)-3	6.04	5.11		5.39	4.59, 4.76
(*Z*)-4	6.19	5.38		4.91	3.20, 3.47
(*E*)-4	6.29	5.24		5.15	3.29, 3.55
(*E*)-5	6.10	5.24		5.29	4.59, 4.71
6	5.81	4.70	3.49	4.06	4.40, 4.70
7	5.88	4.65	3.47	3.87	3.24, 3.38
8[a]	5.79	4.65	5.01	4.57	4.31, 4.68
9[a]	5.82	4.63	5.05	4.29	3.12, 3.29

a. NMR spectra were measured at 60 °C.

TABLE 2. ^{13}C Chemical Shifts (50 MHz, $CDCl_3$) of the Furanose Moiety of Compounds 1-9.

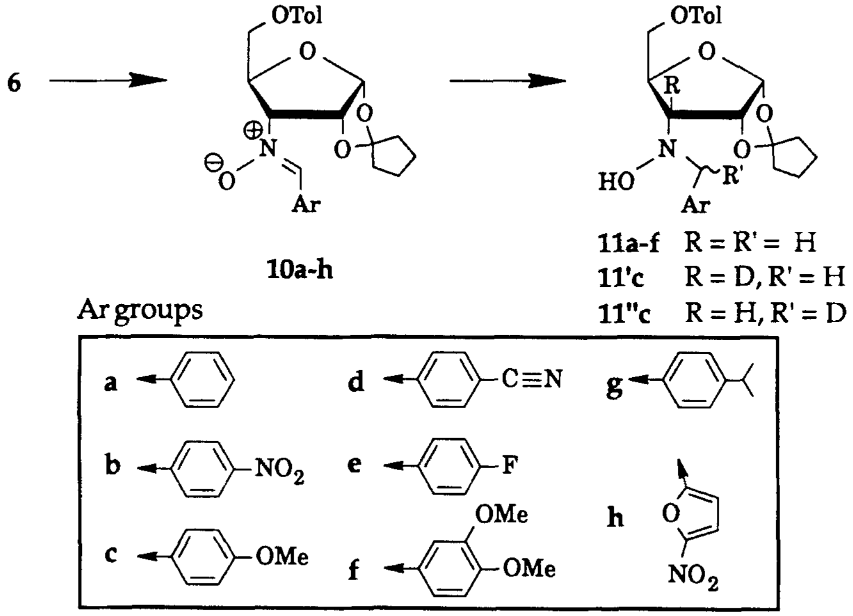
Compd	C-1	C-2	C-3	C-4	C-5
1	102.70	77.30	208.90	76.00	63.50
2	103.20	80.00	211.42	76.70	64.60
(*Z*)-3	104.31	73.36	156.90	75.49	65.50
(*E*)-3	104.48	77.94	158.08	75.72	64.01
(*Z*)-4	104.72	74.29	158.78	77.07	66.09
(*E*)-4	104.72	86.87	159.88	78.36	63.60
(*E*)-5	104.37	78.03	165.24	76.07	63.96
6	104.29	77.89	64.13	65.37	76.16
7	104.50	78.40	65.76	77.14	64.09
$8^{a,b}$	103.46	78.38	57.17	73.12	62.87
9^{b}	103.58	75.91	57.48	74.38	62.45

a. From a ^{13}C-^{1}H heterocorrelation experiment. b. NMR spectra were measured at 60 °C.

TABLE 3. Coupling Constants (in Hz) of the Furanose Moiety of Compounds 1-9.

Compd	$J_{1,2}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$
1	4.5		1		3	4.5	13.5
2	5		1		2.5	2.8	10
(*Z*)-3	4.7		1		5.5	2.5	12
(*E*)-3	4.7		1		2	3	12
(*Z*)-4	4.5		2		4	3	10
(*E*)-4	4.5		2		3	3.5	10
(*E*)-5	4.5		1.5		3	3	11
6	4	4.5	0	9.5	5	2	12
7	3.8	5	0	10	4.5	3	10.5
$8^{a,b}$	3.5	4	0	10	5	2.7	12
9^{b}	3.5	4.3	0	9.8	4	3	10.5

a. From a ^{13}C-^{1}H heterocorrelation experiment. b. NMR spectra were measured at 60 °C.



10a-h

Ar groups

11a-f R = R' = H
11'c R = D, R' = H
11"c R = H, R' = D

SCHEME 2

TABLE 4. Chemical Shifts ($CDCl_3$) of Representative Protons of Compounds 10 and 11.

Compd	H-1	H-2	H-3	H-4	Ha-5, Hb-5	CH=N or CH_2N
10a[a]	5.91	5.00	4.41	5.02	4.53, 3.79	7.54
10b[b]	5.98	5.00	4.45	5.02	4.57, 4.80	7.69
10c[b]	5.91	5.00	4.38	4.97	4.51, 4.84	7.47
10d[b]	5.94	5.02	4.42	4.98	4.52, 4.77	7.60
10e[a]	5.92	5.00	4.38	4.98	4.52, 4.80	7.53
10f[b]	5.94	5.03	4.40	4.98	4.54, 4.85	7.50
10g[b]	5.93	5.00	4.42	4.97	4.53, 4.81	7.53
10h[b]	4.97	4.96	4.47	4.96	4.59, 4 75	7.90
11a[a]	5.80	4.66	3.13	4.67	4.33, 4.78	3.94, 4.24
11b[a]	5.91	4.80	3.28	4.75	4.46, 4.80	4.05, 4.36
11c[a]	5.84	4.78	3.20	4.74	4.38, 4.80	3.93, 4.29
11d[a]	5.88	4.78	3.25	4.76	4.42, 4.79	3.99, 4.41
11e[a]	5.85	4.71	3.21	4.76	4.40, 4.81	3.92, 4.28
11f[a]	5.82	4.78	3.21	4.79	4.40, 4.79	3.92, 4.28

a. 400MHz. b. 200MHz

TABLE 5. Some Representative ^{13}C Chemical Shifts of Compounds 10 and 11.

Compd	C_1	C_2	C_3	C_4	C_5	CH=N or CH_2N
10a[a]	103.80	79.08	75.59	74.66	63.70	138.68
10b[b]	103.90	79.10	76.40	74.60	63.50	129.70
10c[b]	103.70	79.00	75.07	74.62	63.71	134.50
10d[b]	103.90	79.10	76.20	74.60	63.90	134.20
10e[a]	103.90	79.10	75.90	74.80	63.80	134.50
10f[b]	103.50	78.70	74.90	74.20	63.50	137.00
10g[b]	103.80	79.08	75.50	74.68	63.73	135.56
10h[b]	103.97	78.84	74.88	74.88	63.15	125.09
11a[a]	104.22	79.94	67.67	64.88	64.88	62.72
11b[b]	104.27	79.83	68.26	77.55	64.82	61.67
11c[b]	104.08	79.84	67.49	77.17	64.86	61.87
11d[a]	104.40	80.10	68.20	77.40	64.80	62.20
11e[a]	104.40	80.10	67.70	77.40	64.80	62.10
11f[a]	104.40	80.10	67.00	77.10	64.60	62.70

a. 100 MHz. b. 50 MHz

TABLE 6. Interproton Coupling Constants (in Hz) of the Furanose Ring of Compounds 10 and 11.

Compd	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5b}$	$J_{5a,5b}$
10a[a]	3.5	5	10	5	3	12
10b[b]	4	5	10	5	3.5	12.5
10c[b]	4	5	10	5	3	12
10d[b]	4	5	10.5	5.5	3.5	12
10e[b]	3.6	5	10	5	3.4	12.5
10f[b]	3.8	5	10	5	3	12.5
10g[b]	4	5	10	5	3	12.5
10h[b]	4	5	10	4.5	3.5	13
11a[a]	4	5	9	5	2	12
11b[a]	4	5.5	9.5	5	2	12.5
11c[a]	3.5	5	9	5	2	12
11d[a]	4.2	5	9.5	5	2	12
11e[a]	4	5	9	5	2	12
11f[a]	4	5	9	4.5	2	12.5

a. 400 MHz b. 200 MHz

To study the conformational features of the C3-N bond, we measured the heteronuclear coupling constant between H3 and the benzylic carbon of **11f** using the INEPT procedure.[10] The time-averaged value of 2.6 Hz was obtained. The classical relationship $[^3J_{CH} = 4.26 - 1.00\cos\theta + 3.56\cos(2\theta)]$,[11] theoretically established for propane, was shown to be generally applicable even for H-C-N-C dihedral angles.[12] This experimental coupling should correspond to pure conformers of θ (H_3-C_3N-CH_2 dihedral angle) values of either ± 54° or ± 117°, thus, respectively, close to a synclinal or an anticlinal conformer. For these types of conformational equilibria implying low energy barriers, NMR experiments give no indication as to whether the measured values correspond to a pure conformer or to a conformational mixture. We thus resorted to molecular mechanics to sort out the more likely conformers. For this, we used MM2(87)[13] as implemented in the MacroModel[14] version 3.1 software, the continuum solvation model ($CHCl_3$) provided with the software being activated. Our parameters established for the N(sp^3)-O(sp^3) bond from *ab initio* computations[15] were used. As MM2 does not invert pyramidal nitrogen atoms, both invertomers of **11f** were submitted to a Monte Carlo analysis, randomly varying the most significant dihedral angles (FIG. 1).

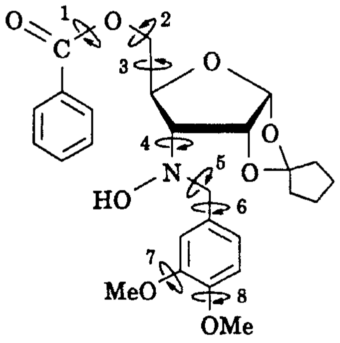


FIG. 1 Hydroxylamine **11f** and dihedral angles (1-8) randomly varied in the Monte Carlo experiments.

For the *(R) N*-invertomer, 3000 conformers were generated and minimized, the most stable (-108.6 kJ mol^{-1}), corresponding to a θ value of -66.7°. The MM2 minimization procedure used by default in the Monte Carlo search does not upgrade the "approximate solvent accessible surface area",[16] used in particular to compute the effective Born radius (α). This means that the computed energies strongly depend on the starting structure. In other terms, the energy ranking of the found conformers is not reliable and the procedure represents mainly a quick useful way of generating a large number of acceptable structures. We thus searched the 200 most stable structures for conformers significantly different from the most stable one and found some having a θ value of *ca.* +40°. One of these was chosen for a new Monte Carlo search which yielded as the most stable conformer (-112.6 kJ mol^{-1}) a structure

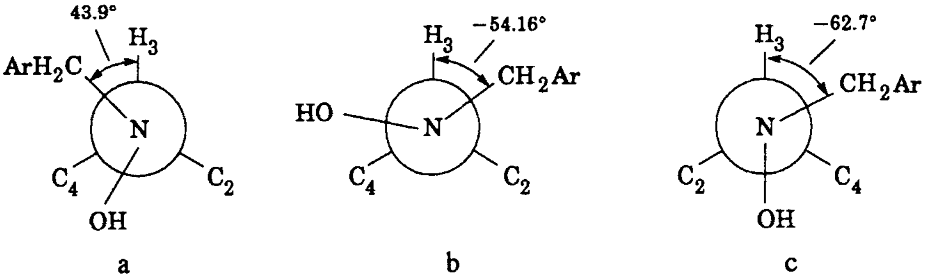


FIG. 2 The three most stable conformers of **11f** as found by molecular mechanics. Partial view along the N-C_3 bond : a and b, *(R)*-invertomer, c *(S)* invertomer.

corresponding to a θ value of 43.9° (FIG. 2a). The 300 most stable structures from the first Monte Carlo experiment and the 500 lowest energy ones from the second experiment were minimized. A large number of local energy minima with θ *ca.* -60° and energies close to -112 kJ mol^{-1} were found. The global minimum remained the same (FIG. 2a, -112.6 kJ mol^{-1}, θ = +43.9°) but another favorable conformer close in energy (FIG. 2b, -112.4 kJ mol^{-1}, θ = -54.2°) was found.

For the *(S)* invertomer, 1000 structures were generated using the same Monte Carlo procedures and the 355 most stable minimized. The most stable conformer found (FIG. 2c) had an energy of -111.8 kJ mol^{-1} and a θ value of -62.7°.

These results show that both invertomers should coexist at room temperature, the *(R)* one being only slightly favored. The predicted $^3J_{CH}$ coupling constants for rotamers a, b, and c of FIG. 2 are, respectively, 3.7, 2.6 and 1.7 Hz, all close to the experimental value. The molecular mechanics computation cannot reliably assess the relative populations of these synclinal or almost synclinal rotamers but can exclude the likelihood of the experimental value to be explained either by the existence of an anticlinal or a mixture of synclinal and antiperiplanar rotamers.

Hydroxylamines **11** spontaneously oxidized in the air to give the corresponding aminoxyl radicals, EPR data of which are collected in TABLE 7. The regiospecific deuteriation experiments allowed the assignments of the larger a_H value to the coupling with H-3. The benzylic protons showed two medium couplings, sum of which being in the range 16.9-17.8 G. For aminoxyl radicals

TABLE 7. EPR Data (in diglyme, a values in G) of the Aminoxyl Free Radicals Spontaneously Formed from "Second Generation" Hydroxylamines.

Starting Hydroxyl-amines	t (°C)	g	a_N	a_{CH2N}		a_{H3}	extra a_H
11a	20	2.0060	14.50	7	10	13.4	0.45
	50		14.15	7.2	9.70	13	0.45
11b	50	2.0062	14.50	7.5	9.70	13	0.50
	75		14.50	7.5	9.70	12.5	0.50
11c	40	2.0058	14.70	7	10.50	12.8	0.45
	65		14.70	7.4	10.40	12.5	0.30
11'c	20	2.0060	14.65	6.75	10.40	1.95[a]	
	60		14.65	7.2	10.35	1.90[a]	0.40
11"c	30	2.0064	14.60	7.3	1.55[a]	12.9	
	62		14.60	7.3	1.55[a]	12.9	
11d	20	2.0062	14.40	7.4	9.50	13.5	0.55
	60		14.50	7.6	9.60	12.8	0.40
11e	20	2.0061	14.50	7.4	10	13.20	0.60
	60		14.60	7.5	9.80	12.6	0.40
11f	20	2.0060	14.75	7	10.35	12.6	0.50
	60		14.60	7.2	10.20	12.2	0.40

a. Coupling with deuterium.

supposedly planar (for the influence of out-of-plane deformation, see ref 16), the a_H^β value is given by equation 1)

$$a_H^\beta = \rho_N(B_0 + B_2.\cos^2\theta) \qquad 1)$$

where ρ_N is the spin density in the p_z orbital of the nitrogen atom, θ the dihedral angle between the C-H bond and the axis of the p_z orbital on nitrogen and B_0 and B_2 two constants. As B_0 is considered to be negligible, equation 1) reduces to equation 2)

$$a_H^\beta = \rho_N B_2 . \cos^2\theta \qquad 2)$$

For a methyl group, the $\cos^2\theta$ value averaged for the three hydrogen atoms is constant (0.5) regardless of the value of θ, this allowing the experimental determination of $\rho_N . B_2$. From the study of a series of *N*-methylaminoxyl radicals, Rassat[18] proposed a value of 26 G for $\rho_N . B_2$, we had to slightly modify to the more conservative value of (25 ± 1) G.[3] We recently measured for the aminoxyl radical corresponding to 3'-C-cyano-3'-deoxy-3'(*N*-hydroxy-*N*-methylamino)thymidine a still lower value of 23.3 G.[19] Methylene groups directly fixed onto an aminoxyl group very often, but not invariably,[3] establish a conformational equilibrium involving only conformers in which a C-H group lies in the aminoxyl plane. For each of these conformers one coupling is null, the other taking the value $\rho_N B_2 \cos^2(30)$. In these conditions, the sum of the two a_H^β couplings is independent of the position of the equilibrium and its value ($\rho_N B_2 \cos^2(30)$) constant over any attainable range of temperatures. Using the lowest value ever measured of $\rho_N B_2$ (23.3 G), the sum of the two a_H values should amount to 17.5 G, close to the experimental one. From this, the hypothesis of such a conformational equilibrium cannot be formally excluded. No good EPR spectra could be obtained, in these cases, at temperatures below 20° but the trends observed in the limited range of temperatures used did not either allow to exclude the former hypothesis.

To confirm or disprove this hypothesis, we submitted a model compound, the aminoxyl corresponding to **11c** in which the large 5-O-toluoyl group was replaced with a 5-O-methyl group, to quantum mechanics at a semiempirical level, using MOPAC 6.0[20] (UHF PM3 PRECISE PULAY). Two general constraints were imposed; the N-O bond length was fixed to 1.28 Å and the aminoxyl group kept planar by fixing the appropriate dihedral angle. The dihedral angle φ (C_{ipsoPh}-$C_{benzylic}$-N-C_3) was then varied from 0 to 360°. Two different experiments were conducted starting from the same initial structure obtained from a CHARMM[21] minimization including parameters developed for the N-O bond.[22] The results are represented in FIG. 3, the curve ***a*** corresponding to an increase of φ by 30° increments and the curve ***b*** to 10° increments. The large difference between the two curves corresponds to an

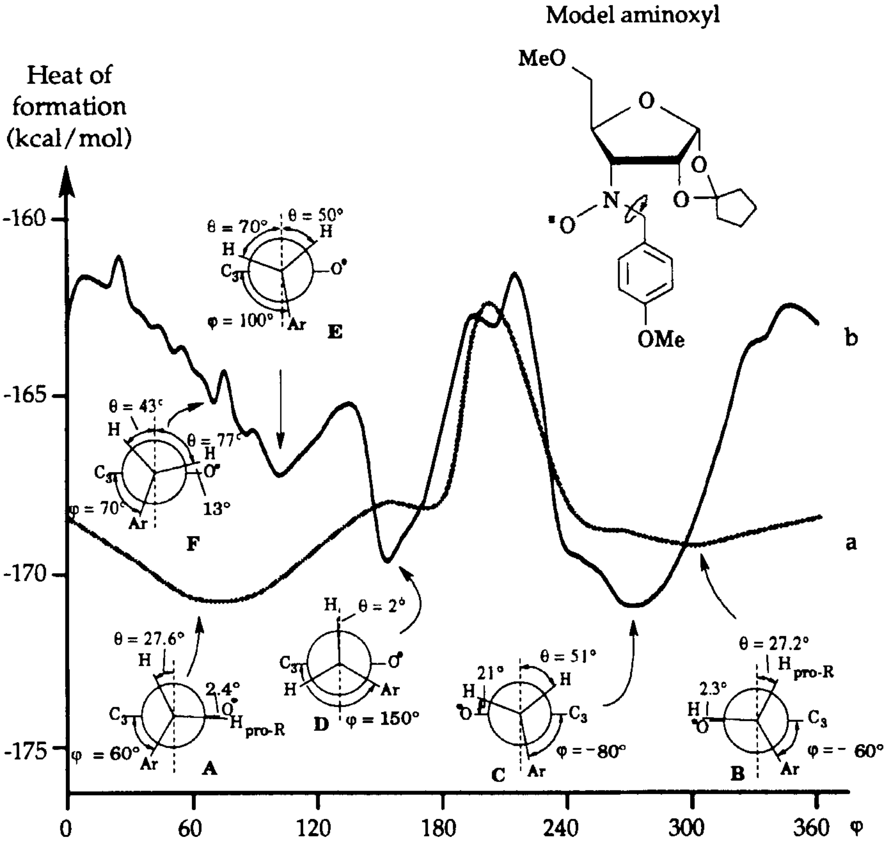


FIG. 3. PM3 heats of formation of a model aminoxyl *versus* the φ dihedral angle and structure of conformers **A-F** with the phenyl group on the β (curve a) or the α (curve b) faces.

artifact which could be called "artificial atropisomerism". The dihedral constraint imposed on the molecule renders it impossible for the benzyl group to move from one side of the furanose ring to the other for all values of φ but those close to 180°. In the curve *a*, the benzyl group was trapped on the β face where it stayed for all φ values, whereas the *b* curve corresponds to a benzyl group lying on the α face. The most stable conformer of curve *a* is eclipsed (A, -170.67 kcal mol^{-1}). Its closest analog bearing the benzyl group on the α face and corresponding to a local minimum (F) being less favorable by more than 5 kcal mol^{-1}. The second conformer in which a C-H bond eclipses the N-O bond (B, -169.25 kcal mol^{-1}) is much less favorable than A and corresponds to a local minimum. The global minimum of curve *b* corresponds to an almost staggered conformer (C, -170.849 kcal mol^{-1}). Conformers B and C were submitted to a new PM3 optimization after removal of the φ dihedral constraint. In neither case, the benzyl group moved from a face of the furanose ring to the other. The novel structure of B (B') was almost identical with the starting one (φ 300°, heat of formation -169.23 kcal mol^{-1}), whereas the reoptimized C (C') showed negligible changes in heat of formation (-170-854 kcal mol^{-1}) and φ value (279.6°) but, owing to some modification in bond angles, small changes in θ values (68.7 and 46.3°) were noted.

In the hypothesis of an equilibrium between conformers A and C', their representative populations can be estimated independently from each a_H value. Assigning to $H_{pro\text{-}R}$ the smaller coupling (7 G) measured for **11a** at 20° and using the most probable value for $\rho_N B_2$ (25 G), we found 59% of C' and 41% of A. The same results were obtained using the other experimental a_H value (10 G) for $H_{pro\text{-}S}$. This second hypothesis which also explains the variation of the hyperfine couplings with the temperature, seems more probable than the former one invoking two eclipsed conformers.

EXPERIMENTAL

General Procedures.[23] Optical rotations were measured in chloroform solutions (*c* 1.0 ± 0.2). For 400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR, a Bruker AMX 400 spectrometer was used.

Preparation of oximes 3 and 4. To a solution of hydroxylamine hydrochloride (0.97 g, 14 mmol) in anhydrous pyridine (60 mL), 12.7 mmol of one ketosugar derivative **1** or **2** was added. The mixture was stirred 12 h at room temperature under nitrogen, then cold (0 °C) water (150 mL) added and the mixture stirred for 30 min. The reaction mixture was extracted with CH_2Cl_2 (3x100 mL) and the organic phase dried ($CaCl_2$), and concentrated. After elimination of the last traces of pyridine by codistillation with toluene (3x50 mL), the compound was recrystallized (ether/hexane).

(*E*)-3-(*N*-Acetoxyimino)-1,2-*O*-cyclopentylidene-3-deoxy-5-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (5). Oxime **3** (500 mg, 1.28 mmol) was acetylated using Ac_2O and pyridine following classical procedures. Column chromatography (hexane/AcOEt 2:1) followed by recrystallization (AcOEt/hexane) yielded **5**.

TABLE 8. Yields and Some Physico-chemical Properties of Compounds 3-9.

Compd	Yield	Mp (°C)	$[\alpha]_D^{22}$	R_F[a]	Elementary Analysis		C	H	N
3	62	117.0-117.6	+181°	0.4	$C_{18}H_{21}NO_6$	Calcd	62.24	6.09	4.03
					(347.37)	Found	62.28	6.06	3.98
4	96	57.2-58.2	+130°	0.6	$C_{29}H_{29}NO_5$	Calcd	73.87	6.20	2.97
					(471.56)	Found	73.60	6.28	3.09
5	72	148.1-152.8	+226°	0.65	$C_{20}H_{23}NO_7$	Calcd	61.69	5.95	3.60
					(389.41)	Found	61.49	5.93	3.57
6	54	102.9-104.6	+55.5°	0.3	$C_{18}H_{23}NO_6$	Calcd	61.88	6.64	4.01
					(349.39)	Found	62.00	6.75	4.04
7	42	67.1-71.2	+53.5°	0.45	$C_{29}H_{31}NO_5$	Calcd	73.55	6.60	2.96
					(473.57)	Found	73.29	6.86	2.79
8	85	79.5-86.5	+69°	0.4	$C_{22}H_{27}NO_8$	Calcd	60.96	6.28	3.23
					(433.46)	Found	61.21	6.50	3.18
9	85	168.1-173.4	+69°	0.4	$C_{33}H_{35}NO_7$	Calcd	71.08	6.33	2.51
					(557.65)	Found	70.84	6.57	2.35

a. Hexane/AcOEt 2:1

Reduction of oximes 3 and 4. To a solution of one of the oximes **3** and **4** (7.8 mmol) in MeOH (50 mL) $NaBH_3CN$ (5.39 g, 85.8 mmol) was added and the pH kept at 3 (pH meter) by addition of 3M HCl. After 5 h the solvents were removed under vacuum and the dry residue extracted with citrate-HCl buffer pH 3, Titrisol® Merck (200 mL). The aqueous solution was extracted with CH_2Cl_2 (5x100 mL) and the organic phase neutralized (saturated aqueous $NaHCO_3$, 100 mL), washed (H_2O, 2x100 mL), dried ($CaCl_2$) and concentrated, then submitted to column chromatography (hexane/AcOEt 2:1) to give the expected hydroxylamine (**6** or **7**) which was recrystallized (ether/hexane). [3-$^2H_1$]-**6** was prepared following the same procedure but substituting $NaBD_3CN$ to $NaBH_3CN$.

TABLE 9. Some Spectroscopic Properties of Compounds 3-9.

Compd	UV [$\lambda(\varepsilon)$]	IR [$\bar{\nu}$/cm^{-1}]	MS [*m*/*z* (%)]
3	205 (24000), 240 (18000)	3380 (OH), 1700 (CO), 1670 (C=N)	347 (1, $M^{\cdot +}$), 318 (2), 263 (0.6), 182 (10), 127 (13), 119 (100), 91 (25), 85 (20), 65 (9), 55 (27)
4	205 (43000)	3400 (OH), 1705 (C=N)	454 (0.2, $M^{\cdot +}$ - $OH^{\cdot}$), 394 (0.4) 259 (0.8), 243 (100), 228 (12), 183 (21), 165 (87), 115 (10), 105 (67), 85 (51)
5	204 (9800), 239 (6700)	1750 (CO Ac), 1710 (CO, toluoyl), 1660 (C=N)	389 (12, $M^{\cdot +}$), 360 (15), 305 (8) 224 (7), 188 (7), 166 (8), 152 (7) 136 (20), 119 (100), 91 (34)
6	202 (23500), 239 (13700)	3490 (OH), 3280 (NH), 1715 (CO)	347 (0.1, $M^{\cdot +}$ - H_2), 318 (0.2), 265 (2), 206 (22), 119 (100), 91 (23), 85 (12), 65 (7), 55 (21)
6'			348 (0.3, $M^{\cdot +}$ - H_2), 318 (1), 266 (5), 207 (13), 136 (5), 126 (37) 119 (100), 97 (10), 91 (24)
7	208 (29600)	3420 (OH), 3260 (NH)	455 (0.01, $M^{\cdot +}$ - H_2O), 396 (0.01) 243 (100), 165 (55), 105 (17), 97 (4), 85 (19), 77 (14), 67 (9), 55 (62)
8	204 (21000), 283 (14000)	1818 (O=CON), 1715 (CO, toluoyl), 1672 (O=CN)	433 (1, $M^{\cdot +}$), 404 (4), 391 (4), 349 (4), 307 (7), 290 (3), 206 (8), 119 (100), 91 (18), 55 (10)
9	207 (33000), 230 (8400)	1790 (O=CON), 1680 (O=CN)	557 (0.1, $M^{\cdot +}$), 515 (0.2), 314 (1) 243 (100), 230 (39), 200 (7), 165 (48), 103 (24), 97 (7), 77 (13)

TABLE 10. Yields and Some Physico-chemical Properties of Compounds 10 and 11.

Compd	Yield	Mp (°C)	$[\alpha]_D^{22}$	R_F	Elementary Analysis				
							C	H	N
10a	75	137.5-140.2	+162.5°	0.2[a]	$C_{25}H_{27}NO_6$	Calcd	68.64	6.22	3.20
					(437.50)	Found	68.51	6.19	3.22
10b	92	161.2-163.7	+164.5°	0.25[a]	$C_{25}H_{26}N_2O_8$	Calcd	62.23	5.43	5.81
					(482.49)	Found	62.01	5.62	5.72
10c	80	133.3-134.3	+153°	0.17[b]	$C_{26}H_{29}NO_7$	Calcd	66.80	6.25	3.00
					(467.52)	Found	66.56	6.16	3.07
10d	69	43.3-45.7	+150.5°	0.2[a]	$C_{26}H_{26}N_2O_6$	Calcd	67.52	5.67	6.06
					(462.51)	Found	67.41	5.88	5.83
10e	63	134.7-135.1	+155.6°	0.13[c]	$C_{26}H_{26}FNO_6$	Calcd[d]	65.92	5.75	3.08
					(455.49)	Found[d]	65.87	5.68	3.25
10f	90	54.7-58.5	+122.8°	0.3[e]	$C_{27}H_{31}NO_8$	Calcd	65.18	6.28	2.82
					(497.55)	Found	65.33	6.29	3.02
10g	85	127.3-134.9	+83°	0.3[c]	$C_{28}H_{33}NO_6$	Calcd	70.13	6.94	2.92
					(479.58)	Found	69.99	7.00	2.89
10h	40	165.9-167.5	+259.3°	0.2[c]	$C_{23}H_{24}N_2O_9$	Calcd	58.47	5.12	5.93
					(472.46)	Found	58.43	5.17	5.91
11a	80	120.5-122.7	+81.6°	0.4[c]	$C_{25}H_{29}NO_6$	Calcd	68.32	6.65	3.19
					(439.51)	Found	68.12	6.68	3.29
11b	68	45.0-46.4	+75.6°	0.45[a]	$C_{25}H_{28}N_2O_8$	Calcd	61.98	5.83	5.78
					(484.51)	Found	61.70	6.10	5.74
11c	60	51.4-52.1	+88.5°	0.4[c]	$C_{26}H_{31}NO_7$	Calcd	66.51	6.65	2.98
					(469.54)	Found	66.41	6.48	2.98
11d	86	48.4-50.2	+80.2°	0.4[a]	$C_{26}H_{28}N_2O_6$	Calcd	67.23	6.08	6.03
					(464.52)	Found	66.97	5.97	5.96
11e	83	118.7-119.8	+75°	0.4[c]	$C_{25}H_{28}FNO_6$	Calcd[f]	65.63	6.17	3.06
					(457.50)	Found[f]	65.70	6.19	3.09

a. Hexane/AcOEt 2:1. b. Hexane/AcOEt 1:1. c. Hexane/AcOEt 3:1.

d. F: calcd 4.17, found: 3.82. e. Hexane/AcOEt 1:3. f. F: calcd 4.15, found 3.76.

TABLE 11. Some Spectroscopic Properties of Nitrones 10.

Compd	UV [λ(ε)]	IR [$\bar{\nu}$/cm^{-1}]	MS [*m/z* (%)]
10a	204 (25000), 234 (18500), 298 (17500)	1715 (C=O), 1570 (C=N)	437 (1, $M^{\cdot+}$), 421 (3), 408 (3), 392 (4), 354 (8), 338 (4), 287 (8), 160 (14), 119 (100), 91 (30)
10b	202 (45500), 240 (28000), 346 (17000)	1728 (C=O), 1570 (C=N)	482 (0.01, $M^{\cdot+}$), 437 (0.6), 399 (3), 287 (6), 191 (4), 119 (100), 91 (65), 84 (23), 65 (17), 55 (58)
10c	204 (31000), 237 (24000), 312 (27000)	1715 (C=O), 1563 (C=N)	467 (0.1, $M^{\cdot+}$), 384 (0.5), 151 (24), 135 (11), 119 (100), 108 (6), 91 (34), 81 (17), 65 (11), 55 (35)
10d	204 (22000), 237 (22500), 318 (15200)	2228 (C≡N), 1717 (C=O), 1564 (C=N)	462 (0.1, $M^{\cdot+}$), 445 (0.1), 433 (0.5), 379 (2), 287 (5), 119 (100), 91 (50), 81 (29), 65 (23), 55 (56)
10e	206 (22000), 235 (20000), 297 (18000)	1722 (C=O), 1597 (C=N)	455 (0.05, $M^{\cdot+}$), 372 (0.2), 287 (0.2), 189 (17), 164 (10), 136 (28), 119 (100), 107 (10), 91 (48), 75 (8), 65 (16), 55 (53)
10f	203 (33000), 237 (23000), 322 (16000)	1715 (C=O), 1590 (C=N)	497 (0.3, $M^{\cdot+}$), 414 (0.9), 181 (53), 151 (6), 138 (3), 119 (100), 91 (21), 81 (17), 65 (5), 55 (26)
10g	203 (37000), 236 (24000), 302 (25000)	1730 (C=O), 1570 (C=N)	463 (0.2, $M^{\cdot+} - O^{\cdot}$), 396 (1), 287 (1), 256 (0.3), 163 (2), 133 (3), 119 (100), 91 (13), 81 (8), 55 (15)
10h	202 (25000), 240 (27000), 295 (5000), 378 (10500)	1730 (C=O), 1580 (C=N)	472 (0.1, $M^{\cdot+}$), 455 (0.6), 427 (0.7), 389 (3), 371 (1), 287 (4), 236 (2), 208 (2), 119 (100), 91 (34)

TABLE 12. Some Spectroscopic Properties of "Second Generation" Hydroxylamines 11.

Compd	UV [λ(ε)]	IR [$\bar{\nu}$/cm^{-1}]	MS [*m/z* (%)]
11a	204 (27000), 238 (15500)	3402 (OH), 1715 (C=O)	437 (2, $M^{\cdot+}$ - H_2), 421 (7), 408 (4), 392 (7), 354 (6), 338 (7), 214 (11), 160 (21), 119 (100), 91 (77)
11b	202 (44500), 240 (18000), 270 (11000)	3420 (OH), 1705 (C=O)	482 (0.6, $M^{\cdot+}$ - H_2), 437 (18), 400 (44), 341 (86), 206 (38), 136 (79), 126 (91), 119 (75), 97 (100)
11c	204 (27000), 229 (22000)	3420 (OH), 1705 (C=O)	451 (25, $M^{\cdot+}$ - H_2O), 422 (23), 385 (38, $M^{\cdot+}$ - C_5H_8O), 329 (45), 274 (48), 218 (23), 190 (92), 160 (46), 121 (100), 91 (18)
11'c			470 (0.1, $M^{\cdot+}$), 452 (3, $M^{\cdot+}$ - H_2O), 386 (2, $M^{\cdot+}$ - C_5H_8O), 329 (45), 191 (10), 161 (69), 136 (20), 126 (41), 121 (100), 119 (49), 91 (18)
11"c			386 (0.5, $M^{\cdot+}$ - C_5H_8O), 275 (0.4), 233 (0.4), 203 (0.4), 161 (1), 137 (13), 122 (100), 119 (26), 97 (13), 91 (15)
11d	202 (68000), 235 (52000)	3400 (OH), 2230 (C≡N), 1715 (C=O)	465 (0.2, $M^{\cdot+}$ + 1), 321 (2), 155 (7), 126 (18), 119 (100), 97 (17), 91 (32), 85 (8), 65 (12)
11e	206 (22500), 238 (17500)	3426 (OH), 1719 (C=O)	455 (0.3, $M^{\cdot+}$ - H_2), 439 (1), 410 (2), 373 (3), 356 (2), 314 (10), 206 (9), 178 (12), 119 (81), 109 (100), 91 (32), 55 (25)
11f	202 (73000), 234 (24000)	3440 (OH), 1710 (C=O)	497 ($M^{\cdot+}$ - H_2), 481 (43), 452 (14), 415 (26), 398 (28), 261 (55), 248 (10), 151 (100), 136 (19), 119 (56), 91 (30), 55 (23)

Acetylation of 6 and 7 to 8 and 9, respectively. Same procedure as that applied to oxime **3**. Yields and some properties of compounds **3-9** are collected in TABLES 8 and 9.

Preparation of nitrones 10a-h. To a solution of **6** (3 g, 8.59 mmol) in toluene (25 mL) a substituted benzaldehyde (9.44 mmol) was added and the mixture treated under reflux for 2 h. The reaction mixture was then concentrated to dryness, and submitted to column chromatography (hexane/AcOEt 2:1). Yields and some properties of these nitrones are collected in TABLES 10 and 11.

Preparation of hydroxylamines 11a-f. To a solution of one of the nitrones **10a-f** (2.07 mmol) in EtOH (50 mL), $NaBH_4$ (0.23 g, 6.21 mmol) was added in small fractions and the reaction mixture stirred at room temperature for 90 min, then concentrated and extracted with CH_2Cl_2 (25 mL). The organic phase was washed with water (2x20 mL), dried ($CaCl_2$), concentrated, and then submitted to column chromatography (hexane/AcOEt 2:1). Yields and some properties of compounds **11** are collected in TABLES 10 and 12.

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