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SYNTHESES OF RACEMIC DIAMINO-DIDEOXY-LYXOPYRANOSE DERIVATIVES USING ACYLNITROSO DIENOPHILES (1).

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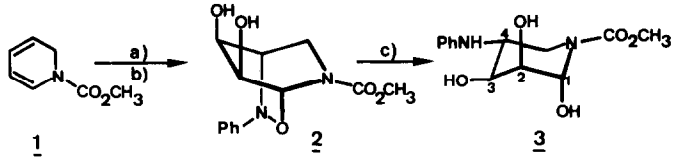
Summary. Acylnitroso derivatives, which are obtained by in situ oxidation of the corresponding hydroxamic acids with tetraalkylammonium iodate, react instantaneously in the presence of dihydropyridine 1 leading to the Diels-Alder adducts 4 and 5. These latter ones were transformed stereospecifically into the racemic diaminodideoxylyxose derivatives 8 and 9.

In a preceding communication we described a regio- and stereospecific model synthesis of the racemic diaminodideoxylyxopyranose 3 (2). This amino-sugar was easily obtained in three steps : i) regiospecific Diels-Alder cyclo-addition of dihydropyridine 1 with nitrosobenzene led to the "direct" adduct; ii) stereospecific cis-hydroxylation with potassium permanganate gave 2; iii) hydrogenolysis of the N-O bond of 2 yielded 3. High-field ^{1}H-NMR permitted the unambiguous determination, both of the relative configuration and of the predominant conformation, as depicted in formula 3 for the α-D enantiomer (Scheme 1) (2).

The introduction of an anilino-group -instead of a free primary amine- is a major drawback of this first synthetic approach, since the phenyl moiety is difficult to remove -if at all- in a latter step. It shoud be noted however that in a few instances some para-substituted anilino derivatives could be cleaved, leading to the corresponding free amino groups (3).

Scheme 1



In order to circumvent this difficulty we turned our attention to the highly reactive acylnitrosoderivatives which were obtained by in situ oxidation

of the corresponding hydroxamic acids with tetraalkylammonium periodate (4). With these experimental conditions and in the presence of dihydropyridine 1 Diels-Alder cycloaddition occurs instantaneously, leading in high yield to one, or to both, of the two possible regioisomers 4 and 5 (4) (Scheme 2). By repeating a three-step reaction sequence, which is similar to the one depicted in Scheme 1, one obtaines aminosugar derivatives which bear acylamino-groups; either in position 1 (axial orientation), or in position 4 (equatorial orientation), depending on the regiospecificity or the regioselectivity of the cycloaddition step. Quite obviously, acylamino-groups can be cleaved more easily to the corresponding free amino-derivatives, than would be the case for the anilino-group.

It turned out that the five acylnitroso derivatives, which we let react with dihydropyridine 1, can be divided into two classes (Table 1) :

- the benzoylnitroso PhCON=O and the phenylacetylnitroso $PhCH_2CON=O$ dienophiles led in a regiospecific way, and in close to quantitative yields, to the "inverse" cycloadducts 5a and 5b respectively;
- the methoxycarbonylnitroso $CH_3OCON=O$, the benzyloxycarbonylnitroso $PhCH_2OCON=O$, and the dimethylcarbamoylnitroso $Me_2NCON=O$ dienophiles led in a non-regiospecific way to the "direct" adducts 4c-4e, as well as to the "inverse" adducts 5c-5e; once again in high overall yields.

Table 1 : relative yields of isolated cycloadducts 4 and 5 obtained when letting Z-N=O dienophilesreact with dihydropyridine 1.

Z	"direct" adducts 4	"inverse" adducts 5
a) PhCO	0 %	100 %
b) $PhCH_2CO$	0 %	100 %
c) CH_3OCO	50 %	50 %
d) $PhCH_2OCO$	50 %	50 %
e) Me_2NCO	75 %	25 %

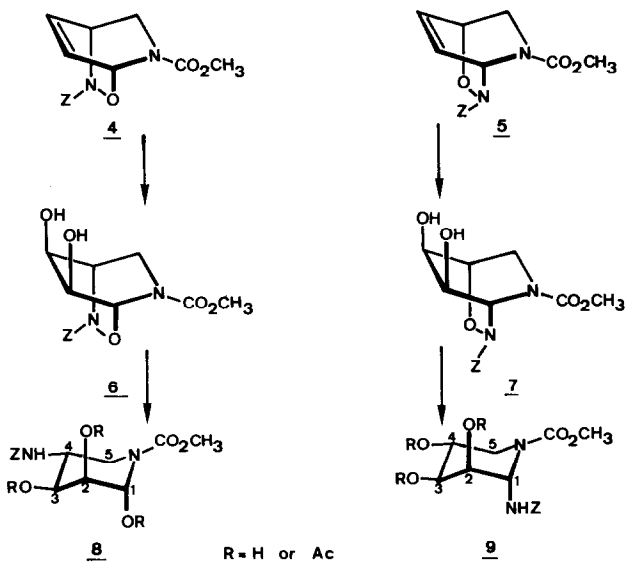
In a typical experiment tetra-n-propylammonium periodate (0.4 equiv.) was added to a methylene chloride solution of methoxyhydroxamic acid MeOCONHOH (1.1 equiv.) and dihydropyridine 1 (1.0 equiv.); this reaction mixture was stirred and kept at 0°C, whereby 1 is consumed rapidly without being notably oxidized. The two cycloadducts 4c and 5c formed quantitatively in equal amounts and were separated by flash-chromatography (5), which was performed at -10°C in order to prevent the less stable cycloadduct 4c from being decomposed on silica. Cis-hydroxylation of the mixtures of compounds 4 and 5 was performed with catalytic amounts of OsO_4 in the presence of an excess of N-methylmorpholine-oxide in a water/acetone solution (6). These oxidation reactions proceeded in a ste-

reospecific fashion -i.e. through anti-approach of OsO_4 with respect to the N-O bridge-, albeit in moderate yields only (50 to 60 %), and led to the cis-glycols 6a and 6b in the "inverse" series, and to the cis-glycol pairs 6c/7c, 6d/7d and 6e/7e in the "direct-inverse" series. All glycols were characterized via their diacetate derivatives (7); only a few of them could be characterized as such. Hydrogenolysis of the N-O bond of these diacetates over Pd/C, followed by exhaustive acetylation, led in excellent yields to the expected racemic peracetyl diamino-dideoxy-lyxopyranose compounds 8 and 9 respectively (Scheme 2).

There are two notable exceptions though : treatment of glycol 6d, mp 110-111°C, with H_2/Pd/C led to the hydrogenolysis of both the N-O and of the benzyl-oxygen bonds, and gave in high yield the free aminotrihydroxypiperidine derivative 8 (R = Z = H) which was characterized as its tetraacetate 8 (R = Z = Ac) mp 177.5-178° C. The bis-acetylated derivative of the regioisomer 7d, when treated with the same experimental hydrogenation conditions, underwent also the double hydrogenolysis, leading after exhaustive acetylation to the tetraacetyl derivative 9 (R = Z = Ac), mp 179-180° C (Scheme 2).

Determination of the structure, the relative configuration and the major conformation of all diamino-dideoxy-lyxopyranose derivatives 8 and 9 could be achieved unambiguously, using high-field pmr measurements. In Table 2 we reproduce pmr data of the ring hydrogen atoms of the triacetylated amino-sugars 8c and 9c (R = Ac). These spectra were taken at 50° C, a temperature which is slightly higher than the coalescence temperature of the urethane rotamer pairs.

Scheme 2



We notice in particular that both stereoisomers have essentially the same chair conformation, the hydrogen atoms H-3, H-4 and H-5a being axial, while H-2 is equatorial. Since the C-4 substituent is equatorial in all amino-sugars, it follows -if only for chemical reasons- that the C-1 substituent must be axial. For all amino-sugars we notice the α-anomer effect (i.e. an axial orientation) for the D-enantiomers, a configuration which has been observed for all amino-sugars bearing a nitrogen atom in the ring (8).

Table 2 : ^{1}H NMR spectra of the ring hydrogen atoms of the triacetate diamino-dideoxy-lyxose derivatives 8c and 9c (R = Ac)*.

	H-1	H-2	H-3	H-4	H-5e	H-5a	
8c	6.70 m $J_{1,2}$=2.8	5.28 m $J_{2,3}$=3.2	5.16 dd $J_{3,4}$=11.0	4.13 ddd $J_{4,NH}$=7	4.39 dd $J_{4,5e}$=5.5	2.90 dd $J_{4,5a}$=11.4	$J_{5a,5e}$=13.0
9c	5.90 dd $J_{1,2}$=2.9	5.36 t $J_{1,NH}$=7	5.28 dd $J_{2,3}$=2.9	5.14 dt $J_{3,4}$=9.3	4.35 dd $J_{4,5e}$=5.0	3.06 dd $J_{4,5a}$=10.0	$J_{5a,5e}$=13.5

* Chemical shifts measured at 50°C in $CDCl_3$, expressed in δ (ppm); coupling constants in Hz; internal reference : $SiMe_4$.

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