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Preparation and Stereoselectivity of 1,3-Dipolar Cycloaddition of *D*-Glucose-Derived Nitrones to N-Arylmaleimides

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Summary. Nitrones **2** derived from *D*-glucose oxime and benzaldehydes without employing any protection of hydroxyl group were isolated in pure state. The 1,3-dipolar cycloaddition of **2** to N-arylmaleimides gave predominantly the *anti* isoxazolidines **3** and was rationalized by *Z*/*E* isomerization of N-glycosylnitrones **2**. The structure and steric configuration of the products have been assigned on the basis of ^{1}H- and ^{13}C-NMR spectroscopy. AM1 calculations of the nitrones and MM2 calculations of the adducts were performed.

Keywords. 1,3-Dipolar cycloaddition of chiral nitrones; *D*-Glucose-derived nitrones; Stereoselectivity of 1,3-dipolar cycloaddition; AM1 Calculations.

Darstellung und Stereoselektivität der 1,3-dipolaren Cycloaddition von *D*-Glucose-abgeleiteten Nitronen an N-Arylmaleimiden

Zusammenfassung. Die Nitrone **2** wurden aus *D*-Glucoseoxim und Benzaldehyden ohne Schutz von Hydroxylgruppen in reinem Zustand erhalten. Die 1,3-dipolare Cycloaddition von **2** an N-Arylmaleimiden ergab bevorzugt die *anti*-Isoxazolidine **3**; dies wurde über eine *Z*/*E*-Isomerisierung der N-Glycosylnitrone **2** rationalisiert. Struktur und Stereochemie wurden auf Basis von ^{1}H- und ^{13}C-NMR-Spektroskopie ermittelt. Außerdem wurden AM1-Berechnungen an den Nitronen und MM2-Rechnungen an den Addukten ausgeführt.

Introduction

The 1,3-dipolar cycloaddition reaction has a nearly singular capability of establishing large numbers of stereochemical centers in one synthetic step [1]. In this line an impressive effort has been devoted to the synthetic application of the cycloaddition of nitrones to alkenes to give isoxazolidines [2–4]. A large part of the research of stereo-controlled versions of 1,3-dipolar cycloaddition in the last few years dealt with the influence exerted by a stereo center located in either one of the two cycloaddends [5]. Recently we have shown that nitrile oxides [6] and nitrones [7] react with chiral sugar-derived alkenes to produce mainly *anti*-adducts with $\geqslant 95\%$

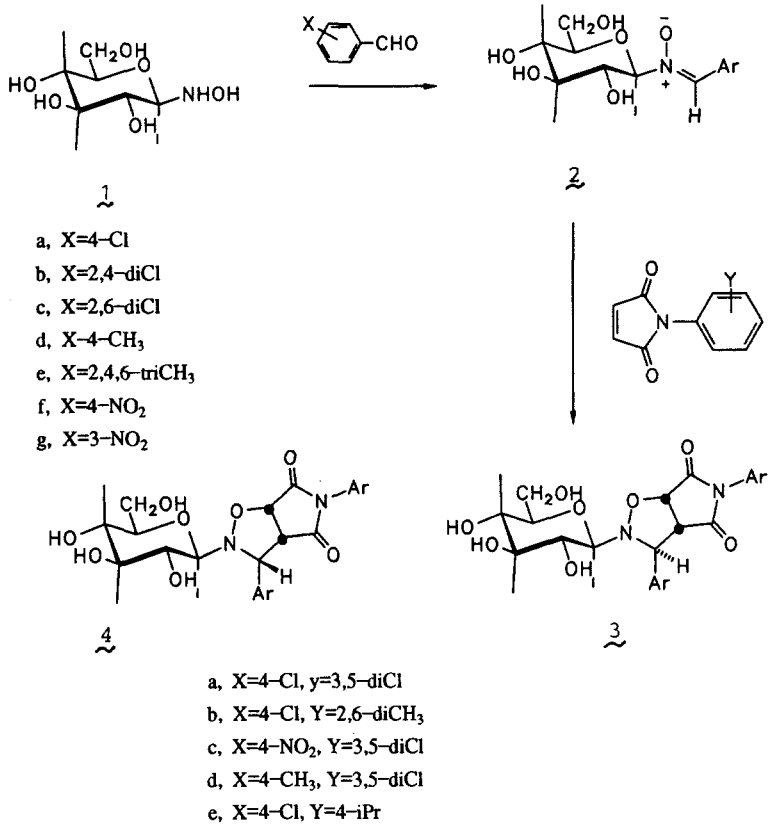
π-facial stereoselectivity and that the stereoselectivity of the C-sugar substituted nitrones to N-arylmaleimides is stereoelectronically preferred through the hydrogen bond or sterically preferred avoiding the repulsions between reactants [8, 9].

With the aim of a further study of the stereochemical results in such cycloadditions we now report on the preparation of *N*-sugar derived nitrones. We also discuss how AM1 and MM2 calculations can be used and refined to predict this stereochemical outcome.

Results and Discussion

Nitrones **2a–g** derived from *D*-glucose oxime (**1**) and *X*-substituted benzaldehydes (where *X* is 4-Cl, 2,4-diCl, 2,6-diCl, 2,4,6-triCH_3, 4-NO_2, 3-NO_2) without employing any protection of hydroxyl group has been prepared, isolated in a pure state and treated with N-arylmaleimides (Scheme 1). The nitrone used, together with details of the products isolated, are given in the Experimental Part and Tables 1–2. The preparation of nitrones was accomplished from the corresponding benzaldehydes, which were converted to the *Z*-nitrones **2** by treatment with *D*-glucose oxime **1** in dry ethanol at room temperature.

Recently, the successful *in situ* preparation of nitrone **2h** (X = H) derived from *D*-glucose oxime and benzaldehyde without protecting hydroxyl groups has been described [10]. It has been the first example



Scheme 1

Table 1. C-(*X*-Phenyl)-N-(*D*-glucoso)-nitrones **2**

Compound	M.p. (°C) Yield (%)	Formula M.w.	Calculated/Found %C	%H	%N	$[\alpha]_D$ (°)	(*c*)
a	215–216 75	$C_{13}H_{16}ClNO_6$ 317.7	49.14 49.01	5.07 5.14	4.40 4.14	−11.70	1.7
b	110–112 60	$C_{13}H_{15}Cl_2NO_6$ 352.2	44.32 44.46	4.29 4.12	3.97 3.78	−7.46	1.3
c	197–199 65	$C_{13}H_{15}Cl_2NO_6$ 352.2	44.32 44.61	4.29 4.33	3.97 3.70	+43.24	1.5
e	210–213 80	$C_{16}H_{23}NO_6$ 325.3	59.07 58.80	7.12 7.29	4.30 4.15	−32.5	1.6
f	190–192 74	$C_{13}H_{16}N_2O_8$ 328.2	47.57 47.22	4.91 4.65	8.53 8.74	−5.88	1.3
g	130–131 77	$C_{13}H_{16}N_2O_8$ 328.2	47.57 47.27	4.91 4.94	8.53 8.35	−1.68	1.1

Table 2. 2-(*D*-Glucoso)-3,5-diaryl-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazoles **3** and **4**

Compound	M.p. (°C) Yield (%)	Formula M.w.	Calculated/Found %C	%H	%N	$[\alpha]_D$ (°)	(*c*)
3a	162–164 33	$C_{23}H_{21}Cl_3N_2O_8$ 559.7	49.35 49.00	3.78 4.10	5.00 4.77	−64.75	1.2
4b	118–120 30	$C_{25}H_{27}ClN_2O_8$ 518.9	57.86 57.52	5.24 5.43	5.39 5.38	−65.90	1.3
3c	168–170 51	$C_{23}H_{21}Cl_2N_3O_{10}$ 570.4	48.42 48.13	3.71 4.01	7.36 7.07	−48.20	1.4
3d	198–200 40	$C_{24}H_{24}Cl_2N_2O_8$ 539.4	53.43 53.75	4.48 4.87	5.19 4.90	−49.30	1.4
3e	160–161 25	$C_{26}H_{29}ClN_2O_8$ 533.0	58.58 58.33	5.48 5.88	5.25 5.62	−69.71	1.4

of this type of dipole, but the nitrone **2h** was not isolated and was reacted *in situ* with dipolarophiles such as acrylonitrile, styrene and N-phenylmaleimide. The stereochemistry of the so prepared isoxazolidines has not been established [10].

In our case the nitrones **2** possessing an electron-withdrawing substituent on the benzene ring are stable crystalline compounds, they are, however, not stable towards water. In wet ethanol hydrolysis proceeds with the formation of the starting benzaldehydes and *D*-glucose oxime. The nitrones having an electrondonating group such as methyl or methoxy can be prepared only *in situ*. On the other hand the *o,o*-disubstituted nitrones are unusually stable. All nitrones **2a–g** are diastereomerically pure.

The ^{1}H-NMR spectrum of nitrones **2** in deuterated dimethyl sulphoxide can be measured, also the assignment of C–OH signals, in terms of a β-cyclic structure in the normal C_1^4 conformation was

possible. Spectral assignments and parameters (Experimental Part) were made by deuterium exchange, double quantum filtered ^{1}H-^{1}H correlation spectroscopy (DQF ^{1}H-^{1}H COSY) and ^{1}H-^{13}C COSY. Some ambiguity remained in assignment of proton signals of the sugar moiety because of an overlap in proton spectra at δ 3.10–3.75. For example, the signal at δ 8.09 for 4-chloroderivate **2a** was assigned to H-1 nitrone proton. The ^{1}H-NMR spectrum of **2a** exhibits significant doublets at δ 5.48 (J = 5.4 Hz), 5.19 (J = 5.1 Hz), 5.10 (J = 5.1 Hz), and a triplet at δ 4.73, which were assigned to OH groups. The proposed structure of **2a** is further supported by the presence of doublets at δ 99.62 (C-1′), 79.98, 76.88, 70.01 and 69.55 (C-2′, C-3′, C-4′, C-5′), as well as a triplet at δ 60.93. The presence of the β-pyranose form of nitrone **2a** is indicated by a doublet at δ 4.87 with the coupling constant $J_{1'-2'}$ = 8.4 Hz for the H-1′ proton. This is also supported by the fact that the starting *D*-glucose oxime **1** exists in the cyclic β-pyranose form in the solid state and isomerizes to a mixture of β-pyranose (23%), α-pyranose (7%), *anti*-(*Z*-) (13.5%) and *syn*-(*E*-) (56.5%) forms in aqueous solution [11]. The exclusive formation of the β-cyclic form is consistent with steric considerations. We suppose that the nitrones **2** have the *Z*-configuration, since there is strong evidence that nitrones derived from aromatic aldehydes possess a configuration in which the C-aryl and N-alkyl group are in a *trans* relationship [12]. This consideration is in accord with Vasella's results that the N-glycosylaldehydonitrones possess a *Z*-configuration [13–15].

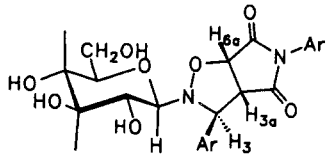
It is a well known practice to derivatize polyhydroxyl compounds, prior to measuring their MS spectra to more volatile derivatives. We, however, measured the mass spectra of native polyhydroxyl compounds **2**, without resorting to derivatization.

The EI mass spectra of compounds **2a–e** showed molecular ion peaks of very low intensity (less than 1%). These compounds were characterized by a loss of 16 atomic units (atomic oxygen), which is typical of spectra of nitrones. The typical degradation process in this type of compounds was the loss of the sugar component from the molecular ion, accompanied by a hydrogen shift to give fragment ions of the corresponding substituted benzaldoximes. The fragmentation of the corresponding benzaldoxime ion proceeds by a split off of fragments such as $^{\bullet}$OH, H_2O, HCN, as well as $CH_3^{\bullet}$, $CO^{\bullet}$, $Cl^{\bullet}$, depending on the substituents present.

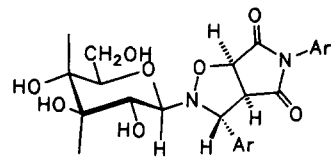
1,3-Dipolar cycloaddition of N-glycosylnitrones **2a–g** and N-arylmaleimides in ethanol at 78 °C affords the isoxazolidines **3** and **4** as a mixture of diastereoisomers, from which only the preponderant *anti* isomers **3** can be isolated in pure state (Table 2). The ratios of *anti* **3** to *syn* **4** diastereoisomers **3a**:**4a** (77:23), **3c**:**4c** (70:30), **3d**:**4d** (95:5) and **3e**:**4e** (75:25) were determined by integration of the H-3a signals in the ^{1}H-NMR spectra.

In contrast to the examples mentioned, the 1,3-dipolar cycloaddition to N-(2,6-dimethylphenyl) maleimide of the N-glycosylnitrone **2a** gave predominantly the *syn*-isoxazolidine **4b** with a diastereomeric excess of more than 90%. The crude residue (after cycloadditions) was chromatographed, and the corresponding major products could be obtained in >95% purity. In the case of *o,o*-disubstituted C-(2,4,6-trimethylphenyl)- **2e** and C-2,6-dichlorophenyl-N-glycosylnitrones **2c** with N-arylmaleimides, the cycloaddition reaction did not take place, only the unreacted starting compounds were isolated.

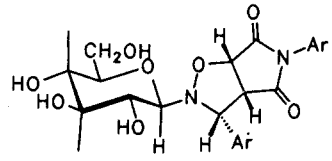
Three new chiral centers C-6a, C-3a, and C-3 were generated in the cycloaddition, since the condensed adducts possess a *cis*-relationship of H-3a and H-6a bridgehead protons; therefore, four diastereomeric products, *syn-anti* **3**, *anti-anti* **3**, *anti-syn* **4** and *syn-syn* **4** could be formed. The first prefix *anti* or *syn* shows the relationship between H-1′ and H-3 atoms and the second the relationship between H-3 and H-3a atoms (Scheme 2).



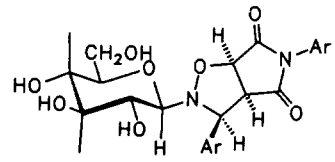
syn – anti 3



anti – anti 3



anti – syn 4



syn – syn 4

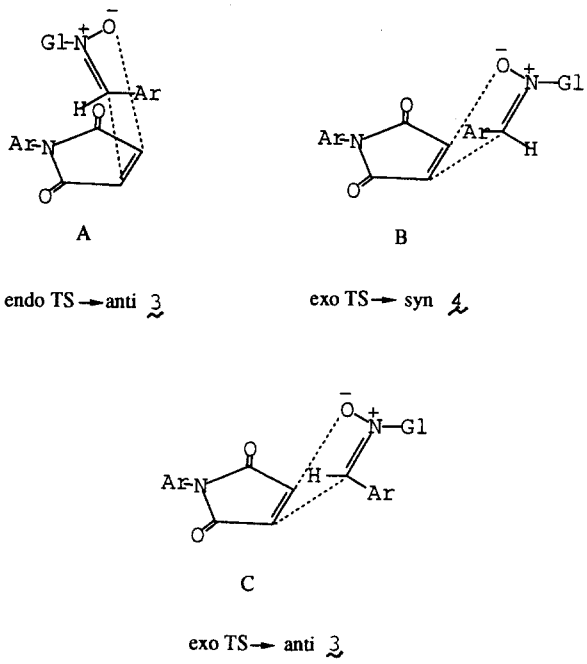
Scheme 2

The distinction between the arrangements of H-3, H-3a and H-6a atoms is based on spectroscopic data, in particular using the J_{3-3a} and J_{3a-6a} coupling constants (Experimental Part). That the bridgehead protons H-3a and H-6a have always *cis*-arrangement is indicated by coupling constants $J_{3a-6a} \sim 9.0$ Hz. Proton NMR analysis of major isoxazolidines **3** revealed that each diastereomer has H-3, H-3a *anti* relationship. In **3a**, for example, the signals for the H-6a and H-3a appear as doublets at δ 5.15 and 3.90, respectively, with a coupling constant of $J_{3a-6a} = 8.4$ Hz from coupling solely to the H-6a. In the H-3, H-3a *anti* adducts, the proton H-3 and H-3a fail to display coupling since $\Phi 90°$. This feature of the NMR spectrum is uniquely diagnostic for the H-3, H-3a *anti* relationship. Proton H-1′ at δ 5.22 is coupled solely to H-2′ with the coupling constant $J_{1'-2'} = 8.4$ Hz indicative of a β-cyclic form of the sugar moiety.

On the other hand, the isolated major adduct **4b** from the cycloaddition of N-(2,6-dimethylphenyl)-maleimide, as well as the minor products **4** from the cycloaddition of other N-arylmaleimides showed the presence of doublet for H-6a proton and doublet of doublets for H-3a proton. For example, in **4b** the doublet appears at δ 4.52 with coupling constants J_{3a-6a} and $J_{3-3a'}$ both equal 8.4 Hz, which is in the range expected of a H-3, H-3a *syn* relationship.

The *anti*-isoxazolidines **3** arise from cycloaddition of *Z*-nitrone through an *endo* transition state, or the *E*-nitrone in an *exo*-mode. Conversely the *syn*-isoxazolidines **4** could be formed by the *Z*-nitrone reacting in the *exo*-fashion or the *E*-nitrone in an *endo*-mode (Scheme 3).

Both *anti*-**3** and *syn*-**4** adducts obtained in this cycloadditions using N-arylmaleimide as the dipolarophile must arise from the *exo* transition state; the *E*-isomer of the nitrone **2** yields the *anti* adduct **3**, while the *Z*-isomer yields the *syn* adduct **4**. *Endo* transition states would be restricted by suffering from unfavourable steric interactions between the N-arylmaleimide moiety in the incoming dipolarophile and the N-glycosyl moiety of the nitrone. *Z*/*E* Nitrone isomerization was assumed also by Vasella to account for the diastereoselectivity of 1,3-dipolar cycloaddition of N-sugar derived nitrones with ethylene [14, 16]. The formation of **3** via a transition state in comparison with the formation **4** through transition state B, C is favourable for steric reasons. The van der Waals nonbonding interaction between two aryl



Scheme 3

groups in transition state B should be larger as compared to transition state C involving the *E*-form of nitrone **2**.

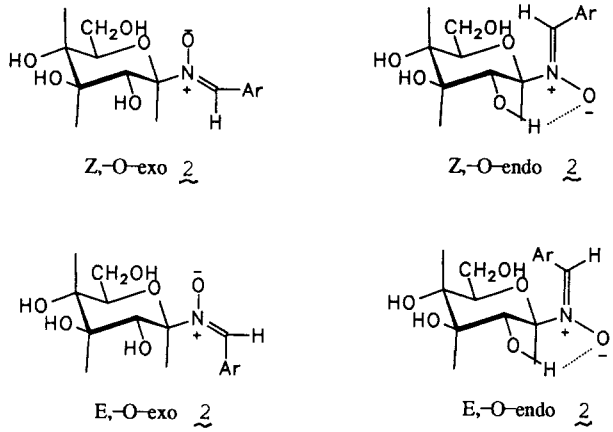
From the spectroscopic data available it was not possible to establish the *syn*- or *anti*-relationship between H-1′ and H-3 atoms. In a series of papers Vasella [13, 14] found that the 1,3-dipolar cycloaddition of N-glycosylnitrones to methyl methacrylate leads to N-glycosylisoxazolidines with a high degree of diastereoselectivity (diastereomeric excess of over 90%). The observed diastereoselectivity has been rationalized on the basis of a stereoelectronic effect in combination with steric effects. AM1 calculations showed that the steric effects, which determine both the relative population of the relevant conformers and the direction of attack of the 1,3-dipolarophile, appear to be more important than the difference of the stereoelectronic effects in the *antiperiplanar* vs. *synperiplanar* orbital arrangement [15].

According to these results, the O-*endo* conformer of nitrone **2** should be preferred in the ground state, since the steric interaction between the *E*-nitrone C-substituents and the glycosyl moiety destabilize the O-*exo* conformation, and should lead to the major products **3**. Moreover, in both *Z*,O-*endo* and *E*,O-*endo* conformations, there is an intramolecular hydrogen bond between the C-2′ hydroxyl group and oxygen of the nitrone (Scheme 4).

In order to rationalize the above cycloadditions we have carried out some quantum mechanical calculations. The geometry of nitrone **2** was totally optimized by the semiempirical AM1 method [17]. The calculated relative energies of the conformers of nitrone **2** in kJ/mol are expressed as energy differences, the energy of the most stable conformer being the reference:

$$Z,\text{O-}exo = 5.4; \quad Z,\text{O-}endo = 0.0; \quad E,\text{O-}exo = 8.9; \quad E,\text{O-}endo = 20.4.$$

The energies of frontier orbitals, MO coefficients, and atomic charges on carbon and oxygen for the above mentioned conformers are given in Table 3. AM1 calculations showed the *Z*,O-*endo* nitrone **2** to be more stable by 20.4 kJ/mol than



Scheme 4

the corresponding *E*,O-*endo* conformer, a fact that can be accounted for mainly on steric considerations, mainly by the presence of van der Waals steric repulsions between C-aryl substituents and the sugar rest. In the case of *Z*-nitrones **2** both forms *Z*,O-*endo* and *Z*,O-*exo* are almost equally stable, with a small preference of the *Z*,O-*endo* conformer (ca. 5 kJ/mol), which can be rationalized by the presence of the intramolecular hydrogen bond between the C-2′ hydroxyl group and oxygen of the nitrone (Fig. 1). Its length was calculated to be 2.16 Å. The relative stability of products with *syn-anti* **3**, *anti-anti* **3**, *syn-anti* **4** and *syn-syn* **4** configuration for the dipolarophiles N-phenylmaleimide **5** and N-(2,6-dimethylphenyl)maleimide **6** have been assessed by molecular mechanics (MM2) calculations (Fig. 2) [18].

5: *syn-anti*-**3** = 0.0; *anti-anti*-**3** = 1.0; *anti-syn*-**4** = 2.1; *syn-syn*-**4** = 11.7.
6: *syn-anti*-**3** = 0.0; *anti-anti*-**3** = 0.6; *anti-syn*-**4** = 1.7; *syn-syn*-**4** = 20.6.

The quantum mechanical calculations are complicated, since the products are very flexible and can have many local minima through rotation about the bond between hexose – condensed isoxazolidine, but they are separated by very high energy rotational barriers (ca. 60–90 kJ/mol).

Dipolar cycloaddition of chiral nitrones had been shown to occur preferentially via a Felkin-Anh [19–21] transition state in which the developing carbon-carbon bond avoided steric interaction with the bulky group. Both conformations D (the ring oxygen atom is perpendicular to the plane of the nitrogen-carbon double bond) and E (the C-2′ carbon atom is perpendicular) can be stabilized by the presence of

Table 3. Energies of frontier orbitals, MO coefficients, and atomic charges on carbon and oxygen for **2**, calculated by means of AM1

Dipole	E (eV)		HOMO		LUMO		Charges	
	HOMO	LUMO	C	O	C	O	C	O
Z,O-*exo*	−8.42	−0.29	0.48	−0.53	0.40	0.35	−0.20	−0.43
Z,O-*endo*	−8.72	−0.50	0.45	−0.52	0.42	0.32	−0.16	−0.48
E,O-*exo*	−8.79	−0.23	0.56	−0.59	0.33	0.28	−0.21	−0.44
E,O-*endo*	−8.75	−0.39	0.54	−0.59	0.33	0.29	−0.20	−0.44

exo TS anti attack → syn – anti 3

exo TS syn attack → anti – anti 3

Scheme 5

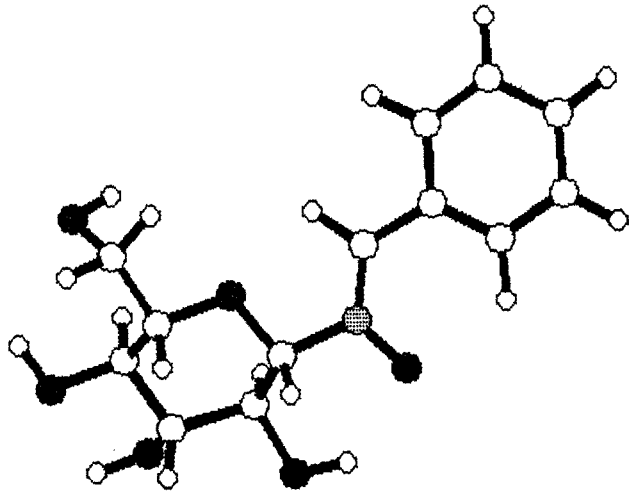


Fig. 1. Optimized geometry of the *Z,O-endo* nitrone **2**

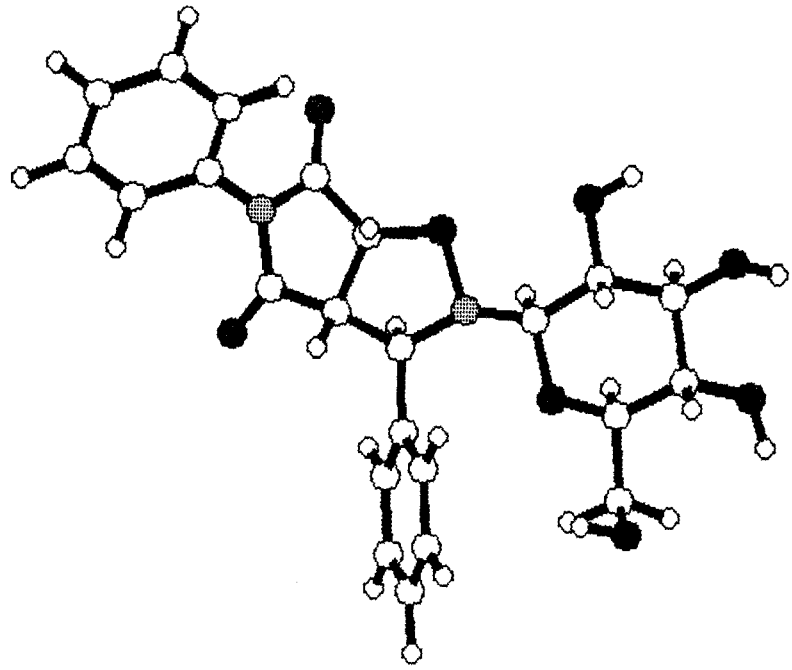


Fig. 2. Optimized geometry for the cycloadduct *syn-anti* **3** (MM2)

intramolecular hydrogen bonds and produce the *syn-anti* product **3** by an *anti* attack (Scheme 5) and *anti-anti* product **3** by a *syn* attack. From the hypothesis that the *Z*-configuration of the nitrone **2** reacts via its O-*endo* conformer and that an *anti*-attack in *exo* transition state is prefered the formation of *syn-anti* **3** adducts may be expected.

Experimental Part

Melting points were determined on a Kofler hot plate apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian VXR 300 and TESLA BS 487 C (80 MHz), respectively, and ^{13}C-NMR spectra on Varian VXR 300 spectrometers (*TMS* as internal standard, $CDCl_3$, δ-values in ppm, J in Hz). *D*-Glucose oxime (**1**) was prepared from the powdered anhydrous *D*-glucose and hydroxylamine hydrochloride in dry methanol by treatment with sodium methoxide according to [11].

D-Glucose Derived Nitrones **2a–g** (Table 1)

D-Glucose oxime (3.90 g, 20 mmol) dissolved in absolute ethanol (40 ml) was cooled to 10 °C with stirring. To this stirred solution was added the corresponding substituted benzaldehyde (20 mmol) dissolved in ethanol (5 ml) dropwise during 10–15 min. After stirring for 2 h at room temperature the nitrones **2** were collected from the reaction mixtures as crystalline materials.

C-(4-Chlorophenyl)-N-(D-glucoso)-nitrone (**2a**)

^{1}H-NMR: 3.10–3.70 (m, 6H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 4.74 (dd, 1H, OH), 4.89 (d, 1H, H-1′, $J_{1',2'} = 8.4$ Hz), 5.13 (d, 1H, OH), 5.19 (d, 1H, OH), 5.48 (d, 1H, OH), 7.52 (d, 2H, aromat. H), 8.09 (s, 1H, H-1), 8.33 (d, 2H, aromat. H). ^{13}C-NMR: 60.93 (t, CH_2), 69.55, 70.01, 76.88, 79.98 (d, C-2′, C-3′, C-4′, C-5′), 99.62 (d, C-1′), 128.59, 129.44, 130.06, 134.24 (aromat. C), 134.18 (d, C-1).

C-(2,4-Dichlorophenyl)-N-(D-glucoso)-nitrone (**2b**)

^{1}H-NMR: 3.09–3.84 (m, 6H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 4.71 (d, 1H, OH), 4.91 (d, 1H, H-1′, $J_{1',2'} = 8.0$ Hz), 5.13 (d, 2H, 2 × OH), 5.34 (d, 1H, OH), 6.57–9.24 (m, 3H, aromat. H), 7.91 (s, 1H, H-1). ^{13}C-NMR: 60.92 (t, CH_2), 69.64, 69.91, 76.92, 79.59 (d, C-2′, C-3′, C-4′, C-5′), 99.37 (d, C-1′), 129.08, 129.11, 129.19, 129.26, 158.55, 162.17 (aromat. C).

C-(2,6-Dichlorophenyl)-N-(D-glucoso)-nitrone (**2c**)

^{1}H-NMR: 3.12–3.75 (m, 6H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 5.06 (d, 1H, H-1′, $J_{1'-2'} = 8.4$ Hz), 7.48–7.54 (m, 3H, aromat. H), 8.11 (s, 1H, H-1). ^{13}C-NMR: 60.74 (t, CH_2), 69.34, 70.77, 76.93, 79.77 (d, C-2′, C-3′, C-4′, C-5′), 98.01 (d, C-1′), 128.17, 128.41, 130.26, 130.28, 131.49 (aromat. C), 134.68 (d, C-1).

C-(2,4,6-Trimethylphenyl)-N-(D-glucose)-nitrone (**2d**)

^{1}H-NMR: 2.18 (s, 6H, 2 × CH_3), 2.23 (s, 3H, CH_3), 3.14–3.76 (m, 6H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 4.72 (d, 1H, OH), 4.96 (d, 1H, H-1′, $J_{1'-2'} = 8.7$ Hz), 5.13 (d, 2H, 2 × OH), 5.47 (bs, 1H, OH), 6.85 (s, 2H, aromat. H), 8.03 (s, 1H, H-1). ^{13}C-NMR: 19.70 (q, CH_3), 20.78 (q, CH_3), 60.91 (t, CH_2), 69.54, 70.34, 77.06, 79.78 (d, C-2′, C-3′, C-4′, C-5′), 98.32 (d, C-1′), 126.22, 127.74, 137.41, 138.12 (aromat. C), 135.50 (d, C-1).

C-(4-Nitrophenyl)-N-(D-glucose)-nitrone (**2e**)

^{1}H-NMR: 3.10–3.75 (m, 6H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 4.72 (dd, 1H, OH), 4.88 (d, 1H, H-1′, $J_{1'-2'} = 8.7$ Hz), 5.11 (d, 1H, OH), 5.19 (d, 1H, OH), 5.47 (d, 1H, OH), 7.53 (d, 2H, aromat. H), 8.09 (s, 1H, H-1), 8.33 (d, 2H, aromat. H). ^{13}C-NMR: 60.94 (t, CH_2), 69.57, 69.99, 76.89, 80.02 (d, C-2′, C-3′, C-4′, C-5′), 99.64 (d, C-1′), 128.60, 129.47, 130.04, 134.21 (aromat. C), 134.17 (d, C-1).

C-(3-Nitrophenyl)-N-(D-glucoso)-nitrone (**2g**)

^{1}H-NMR: 3.14–3.74 (m, 6H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 4.94 (d, 1H, H-1′, $J_{1'-2'} = 8.7$ Hz), 7.75–9.46 (m, 4H, aromat. H), 8.32 (s, 1H, H-1). ^{13}C-NMR: 60.96 (t, CH_2), 69.56, 70.19, 76.78, 80.09 (d, C-2′, C-3′, C-4′, C-5′), 99.92 (d, C-1′), 121.95, 124.67, 130.11, 131.86, 133.55, 147.72 (aromat. C), 134.66 (d, C-1).

2-(D-Glucoso)-3,5-diaryl-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazoles **3** *and* **4** (*Table 2*)

N-Glycosylnitrone **2a–g** (2.0 mmol) and corresponding N-arylmaleimide (2.0 mmol) in dry ethanol (50 ml) were heated under reflux for 48 h. Concentration under reduced pressure and column chromatography over silica gel using chloroform-methanol (9:1) gave corresponding cycloadducts after purification by crystallization.

2-(D-Glucoso)-3-(4-chlorophenyl)-5-(3,5-dichlorophenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazole (**3a**)

^{1}H-NMR: 3.10–3.80 (m, 7H, H-3, H-2′, H-3′, H-4′, H-5′, H_2-6′), 3.88 (d, 1H, H-3a, $J_{3a-6a} = 9.0$ Hz), 4.57 (dd, 1H, OH), 4.91 (d, 1H, OH), 4.96 (d, 1H, OH), 5.00 (d, 1H, OH), 5.14 (d, 1H, H-6a), 5.22 (d, 1H, H-1′, $J_{1'-2'} = 8.1$ Hz), 6.81–7.69 (m, 7H, aromat. H). ^{13}C-NMR: 56.00 (d, C-3a), 62.00 (t, CH_2), 66.00 (d, C-3), 70.25, 70.50, 78.00, 79.00 (d, C-2′, C-3′, C-4′, C-5′), 80.50 (d, C-6a), 92.50 (d, C-1′), 125.28, 128.06, 129.80, 134.03, 135.50 (aromat. C), 171.80 (s, C=O), 172.20 (s, C=O).

2-(D-Glucoso)-3-(4-chlorophenyl)-5-(2,6-dimethylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazole (**4b**)

^{1}H-NMR: 2.08 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.97–3.80 (m, 6H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 4.52 (dd, 1H, H-3a, $J_{3-3a} = 8.1$ Hz, $J_{3a-6a} = 9.0$ Hz), 4.76 (d, 1H, H-3), 4.91 (d, 1H, H-1′, $J_{1'-2'} = 6.6$ Hz), 5.45 (d, 1H, H-6a), 7.17–7.78 (m, 7H, aromat. H). ^{13}C-NMR: 17.39 (q, CH_3), 17.40 (q, CH_3), 55.42 (d, C-3a), 61.51 (t, CH_2), 68.84 (d, C-3), 69.85, 69.95, 77.51, 78.62 (d, C-2′, C-3′, C-4′, C-5′), 82.30 (d, C-6a), 90.19 (d, C-1′), 128.29, 128.76, 129.58, 131.82, 133.79, 135.67, 136.03 (aromat. C), 171.59 (s, C=O), 173.91 (s, C=O).

2-(D-Glucoso)-3-(4-nitrophenyl)-5-(3,5-dichlorophenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazone (**3c**)

^{1}H-NMR: 3.00–3.80 (m, 6H, H-2′, H-3′,. H-4′, H-5′, H_2-6′), 3.91 (d, 1H, H-3a, $J_{3a-6a} = 9.3$ Hz), 4.41–4.46 (m, 2H, OH, H-3), 4.59 (dd, 1H, OH), 4.98 (d, 2H, OH), 5.25 (d, 1H, H-1′, $J_{1'-2'} = 7.8$ Hz), 5.32 (d, 1H, H-6a), 6.80–8.24 (m, 7H, aromat. H). ^{13}C-NMR: 56.27 (d, C-3a), 61.83 (t, CH_2), 65.91 (d, C-3), 70.20, 70.53, 77.68, 79.19 (d, C-2′, C-3′, C-4′, C-5′), 80.47 (d, C-6a), 92.75 (d, C-1′), 123.29, 123.49, 125.41, 125.49, 128.64, 129.68, 133.65, 134.42, 144.63, 147.26 (aromat. C), 171.99 (s, C=O), 172.88 (s, C=O).

2-(D-Glucoso)-3-(4-methylphenyl)-5-(3,5-dichlorophenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazole (**3d**)

^{1}H-NMR: 2.16 (s, 3H, CH_3), 3.01–3.74 (m, 7H, H-3, H-2′, H-3′, H-4′, H-5′, H_2-6′), 3.89 (d, 1H, H-3a, $J_{3a-6a} = 8.4$ Hz), 4.28–5.04 (m, 4H, 4 × OH), 5.06 (d, 1H, H-6a), 5.18 (d, 1H, H-1′, $J_{1'-2'} = 8.1$ Hz), 6.89–7.28 (m, 7H, aromat. H).

2-(D-Glucoso)-3-(4-chlorophenyl)-5-(4-isopropylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazole (**3e**)

^{1}H-NMR: 1.15 (d, 3H, CH_3), 1.18 (d, 3H, CH_3), 2.84–3.41 (m, 7H, C–H, H-2′, H-3′, H-4′, H-5′, H_2-6′), 3.52 (s, 1H, H-3), 3.90 (d, 1H, H-3a, $J_{3a-6a} = 9.3$ Hz), 4.33–4.97 (m, 4H, 4 × OH), 5.23 (d, 1H, H-6a), 5.25 (d, 1H, H-1′, $J_{1'-2'} = 8.1$ Hz), 6.70–7.63 (m, 8H, aromat. H). ^{13}C-NMR: 23.79 (q, CH_3), 23.96 (q, CH_3), 33.23 (d, CH), 55.93 (d, C-3a), 61.60 (t, CH_2), 65.69 (d, C-3), 70.03, 70.38, 77.62, 78.15 (d, C-2′, C-3′, C-4′, C-5′), 80.52 (d, C-6a), 92.79 (d, C-1′), 126.41, 126.50, 126.79, 129.10, 129.29, 129.81, 131.49, 132.33, 136.07, 148.93 (aromat. C), 172.48 (s, C=O), 173.15 (s, C=O).

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