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Synthesis and structure of 2-pyransoylperimidines

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ABSTRACT

The first examples of 2-pyranosylperimidines are reported. The β-D-glucopyranosyl nitrile oxide **5**, generated by base-induced dehydrochlorination of the hydroximoyl chloride **4**, reacted with 1,8-diaminonaphthalene to afford the 2-(β-D-glucopyranosyl)perimidine **8**. The D-*xylo*-, D-*galacto*-, D-*manno*- and D-*glycero* analogues **12**, **15**, **16** and **19** were prepared similarly. The glycals **9** and **13** were formed as by-products resulting from elimination of acetic acid from the corresponding pyranosylperimidines. The structure of D-glucose-derived perimidine **8** was established by X-ray crystallography.

1. Introduction

There is increasing interest in developing methods for the synthesis of pyranosyl-substituted heterocycles[1–14] in view of their potential biological activity. Recent examples include pyranosyl oxadiazoles,[1–3] tetrazoles,[1,2,5,6] benzothiazoles[1,2,5,7] and benzimidazoles,[2,5,7,8] which have been shown to act as glycosidase and/or glycogen phosphorylase inhibitors. Most routes to benzimidazoles involve acid-catalysed cyclocondensation of 1,2-diaminobenzene (DAB) with carboxylic acids or their derivatives, or reaction with aldehydes followed by oxidation of the resulting benzimidazolines.[9,10] Some time ago, however, it was established[11–13] that 2-aryl benzimidazoles could also be prepared from nitrile oxides and DAB, and we have recently reported[14] that this approach can be used for the synthesis of 2-pyranosylbenzimidazoles from pyranosyl nitrile oxides (Scheme 1). We now describe the results of an investigation into the corresponding reaction of pyranosyl nitrile oxides with 1,8-diaminonaphthalene (DAN) as a potential route to pyranosylperimidines.[15]

Perimidines (**1**)[†] are *peri*-naphtho-fused derivatives of pyrimidine and are of particular interest as they are a rare example of an azine in which the lone pair of electrons of a pyrrole-like nitrogen participates in the π-system of the molecule. Perimidine has 14 π-electrons, is isoelectronic with the phenalenyl anion, and there is some transfer of electron density from the heterocycle to the naphthalene ring.[16] They therefore have the characteristics of both π-deficient and π-excessive systems.[17,18] Perimidines and their derivatives have found a variety of applications ranging from dyestuffs[16,19] to fluorescent molecular sensors.[20] Their biological activity has also been examined, for example as antiulcer, antimicrobial and antifungal agents.[16] The DNA-binding properties and antitumour activity of various perimidines have been studied,[21] as have the thermochromic properties and EPR spectra of perimidine (diazaphenalenyl) radicals.[20,22,23] The pK_a value of perimidine (6.02) lies between those of imidazole (7.10) and benzimidazole (5.49) and its potential as a nucleophilic catalyst, for example for ester hydrolysis, has attracted attention.[24] Perimidines are also useful starting materials for the synthesis of more complex polycyclic heterocycles.[16,25–27] *N*,*N*′-Diisopropylperimidine provides the core of a novel N-heterocyclic carbene ligand.[28]

The spacial arrangement of the two amino groups in 1,8-diaminonaphthalene (DAN) is similar to that in 1,2-diaminobenzene and most synthetic approaches to perimidines are therefore, by analogy with benzimidazole synthesis, based on reaction of DAN with a one-carbon unit, usually a carbonyl-containing compound. For example, carboxylic acids, acyl halides and anhydrides afford the mono-amide derivatives **2**,[16,29–31] which can be converted into **1** by acid-catalysed cyclisation. Aldehydes react with DAN to form dihydroperimidines **3** that can readily be dehydrogenated to yield **1**.[16,29,32–36] Perimidines have also been prepared from 1-amido-8-azidonaphthalenes,[37] by reaction of DAN with 1,3,5-triazine,[38] and from α-amido-α-aminonitones.[39] These methods allow for the preparation of perimidines bearing a range of substituents at the 2-position including alkyl, aryl, heterocycles, halogens and amines, but until the present work there have been no reported examples of pyranosyl-substituted perimidines.

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† Alternative names include: 1*H*-benzo[*de*]quinazoline; 1*H*-naphtho[1,8-*de*]pyrimidine; 1*H*-1,3-diazaphenalene.

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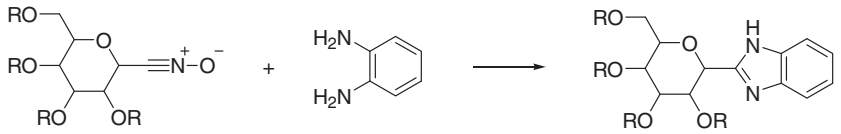
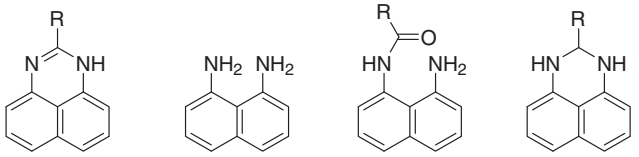


Scheme 1.



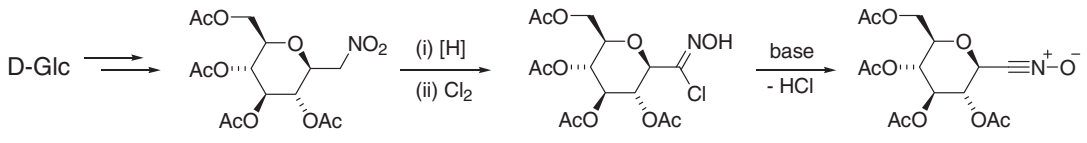
1 **DAN** **2** **3**

2. Results and discussion

The key step in the synthetic route to the pyranosylperimidines (**1**, R = pyranosyl) involves reaction of DAN with a pyranosyl nitrile oxide. As nitrile oxides are generally short-lived and are prone to dimerisation to furoxans (1,2,5-oxadiazole N-oxides) they are usually generated in situ in the presence of the co-reactant, either by base-induced dehydrohalogenation of hydroximoyl halides or by dehydration of nitromethyl compounds.[40] We have previously reported that pyranosyl hydroximoyl chlorides can be prepared from the parent aldose via the pyranosylnitromethane derivative as illustrated in Scheme 2 for the D-glucopyranosyl hydroximoyl chloride **4**,[41] and these precursors were therefore used in the present work. The pyranosyl nitrile oxide **5** is then generated by treatment of **4** with base.

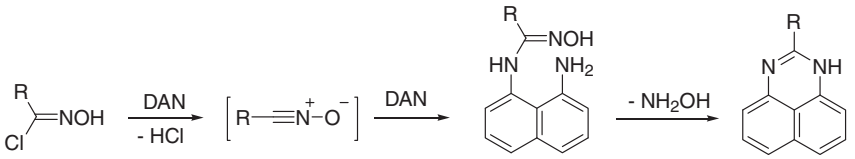
Before attempting to synthesise pyranosyl perimidines the method was first tested for the known 2-phenylperimidine (**1**, R = Ph)[29,30,42,43] and 2-(9-anthryl)perimidine (**1**, R = 9-anthryl)[42] by reaction of DAN with, respectively, benzonitrile oxide (generated from benzohydroximoyl chloride[44]) and anthracene-9-carbonitrile oxide;[45] the latter nitrile oxide can be isolated and does not require in situ generation. A solution of benzohydroximoyl chloride and DAN (1:2 molar ratio) in ethanol was heated at reflux for 5 h. Work-up of the reaction mixture included washing with aq $CuSO_4$, which we find to be an effective means of removing unreacted DAN. 2-Phenylperimidine was isolated (68%) as an orange solid and identified by comparison of its physical and spectroscopic properties with those reported in the literature.[42,43] Reaction of the anthracene nitrile oxide with DAN afforded the corresponding perimidine (**1**, R = 9-anthryl)[42] in low yield (30%), but the product could not be isolated in a pure state. The proposed reaction mechanism is outlined in Scheme 3. Initial dehydrochlorination of the hydroximoyl chloride by DAN acting as a base generates the nitrile oxide **6**, which is then subject to nucleophilic addition by one of the amino groups of a second molecule of DAN to form the mono-amidoxime **7**. Subsequent cyclisation with elimination of hydroxylamine yields the perimidine **1**. An alternative pathway to amidoxime **7** involving nucleophilic addition of the amine to the C=N of the hydroximoyl chloride, followed by elimination of HCl, cannot be excluded. However, for the corresponding reaction of hydroximoyl chlorides with aniline itself affording *Z*-amidoximes, the pathway via the nitrile oxide is favoured.[41b]

Having demonstrated that simple aryl perimidines could be prepared by combination of a nitrile oxide and DAN, the potential of this method for the synthesis carbohydrate-substituted analogues was investigated, using D-glucose-derived nitrile oxide **5** as an example. Heating a solution of hydroximoyl chloride **4** and DAN (1:2.5 molar ratio) in ethanol at reflux for 5 h, followed by work-up as described above for benzohydroximoyl chloride, afforded a mixture of two products that were separated by chromatography. The more polar compound was identified from its spectroscopic properties as the D-glucopyranosyl-perimidine **8** (16%) (Table 1, entry 2). Its ^1H and ^{13}C NMR spectra in DMSO-d_6 had characteristic peaks for the perimidine moiety (Table 2)[42] in addition to those expected for the tetra-*O*-acetylglucopyranosyl substituent, vide infra. The mass spectrum showed the required molecular ion peak at *m/z* 499 $[M+1]^+$. The less polar product (34%) was assigned the corresponding glucal-perimidine structure **9**. In contrast to **8**, only three acetate groups were detected in the



4 **5**

Scheme 2.



6 **7** **1**

Scheme 3.

Table 1
Formation of 2-substituted perimidines

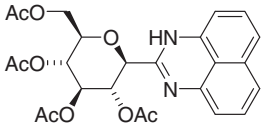
Entry	RCCl=NOH	Conditions[a]	Pyranosyl-perimidine	Glycal-perimidine[b]	Product ratio[c]
1	PhCCl=NOH	A	**1** R = Ph (68%)	—	—
2	D-Glc (**4**)	A	**8** (16%)	**9** (34%)	1:2.12
3	D-Glc (**4**)	B	**8** (65%)	**9** (Trace)	—
4	D-Xyl (**11**)	A	**12** (16%)	**13** (43%)	1:3.17
5	D-Xyl (**11**)	B	**12** (60%)	**13** (Trace)	—
6	D-Gal (**14**)	B	**15** (69%)	—	—
7	D-Man (**17**)	B	**16** (55%)	**9** (Trace)	—
8	D-Man (**17**)	A	**16** (4%)	**9** (34%)	1:8.50
9	**18**	A	**19** (61%)	—	—

[a] (A) 5 h, reflux; (B) 15 h, room temperature.
[b] 2-(2-Deoxy-1-enopyranosyl)perimidines.
[c] Ratio of pyranosyl-perimidine to glycal-perimidine (**8**:**9**, **12**:**13**, **16**:**9**).

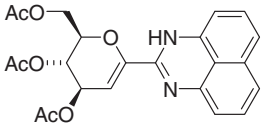
NMR spectra and there was no signal in the anomeric proton region; in addition to the perimidine signals, there were also distinctive peaks for the glucal carbons C-1′ and C-2′ at 148.1 and 99.1 ppm, respectively. Its mass spectrum showed the molecular ion peak at *m/z* 439 $[M+1]^+$. In an attempt to mimimise the formation of the glucal, the experiment was repeated under less forcing conditions; after 15 h at room temperature the reaction was complete (TLC) and the major product (65%) was the target pyranosyl-perimidine **8** (Table 1, entry 3), with only traces (<1%) of the glucal **9** being detected. This by-product is believed to result from base-catalysed elimination of acetic acid at C-1′/C-2′ of the glucopyranosyl ring forming the glucal in which the alkene unit is conjugated to the perimidine. There was no evidence for formation of the 3,4-diglucopyranosyl furoxan **10** that might have resulted from dimerisation of the intermediate nitrile oxide.[41b]

pyranosyl-perimidine **12**, with only traces of the glycal-perimidine **13** being detected. In contrast, in ethanol at reflux a mixture of **12** and **13** was obtained. The corresponding reaction at room temperature of DAN with the D-galactose-derived hydroximoyl chloride **14** also afforded the expected pyranosyl-perimidine **15** (69%) (Table 1, entry 6).

It has been reported that alkyl groups attached to the highly electrophilic 2-position of perimidene have acidic α-hydrogens.[16d] The elimination of acetic acid to form the glycal might therefore occur via an E1cB mechanism in view of the potential for delocalisation of a negative charge at the anomeric position into the adjacent perimidine ring system. Deprotonation could occur with either DAN or the newly-formed perimidine acting as the base; the pK_a of DAN is ca. 5, whereas those for 2-substituted perimidines are reported to be ca. 6.[16a] It has also been reported that



8



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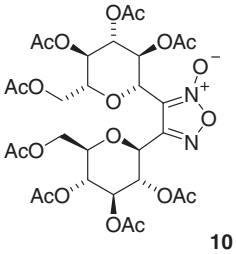

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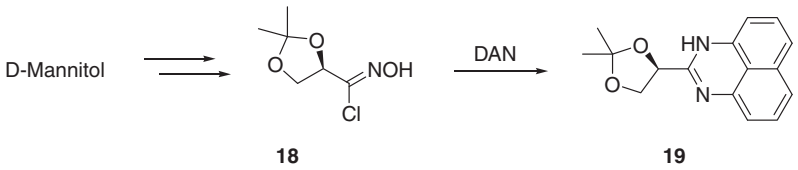
A similar pattern of reactivity was found for the reaction of DAN with the D-xylopyranosyl hydroximoyl chloride **11** (Table 1, entries 4 and 5). At room temperature the major product (60%) was the analogous 2-acetyl-protected glucopyransoyl-benzimidazole undergoes similar base-induced elimination of HOAc to form the corresponding glucal.[5] In order to provide more evidence for the

Table 2
Selected ^{13}C NMR chemical shifts[a] for 2-substituted perimidines

Compd	C-2	C-3a	C-4	C-5	C-6	C-6a	C-7	C-8	C-9	C-9a	C-9b
1a[b]	152.7	145.1	114.0	128.9	119.3	135.1	117.8	128.0	102.8	138.6	121.7
1b[b]	153.4	145.4	113.9	129.0	119.6	135.3	118.0	128.0	102.3	138.7	121.9
8	153.8	145.7	115.3	130.3	121.3	136.6	119.3	129.5	104.0	139.3	123.5
9	148.6	145.8	115.3	130.4	121.1	136.6	119.5	129.5	104.6	139.1	123.7
12	154.0	145.8	115.0	130.3	121.1	136.6	119.2	129.5	104.1	139.4	123.6
13	150.1	145.9	115.2	130.4	121.0	136.6	119.5	129.5	104.7	139.2	123.8
15	153.6	145.7	115.0	130.3	121.1	136.6	119.3	129.4	104.4	139.3	123.6
16	153.8	145.6	114.8	130.3	120.8	136.6	119.7	129.4	104.5	139.0	123.4
19	155.5	144.3	113.4	128.5	119.0	134.9	117.6	127.7	104.5	137.5	121.8

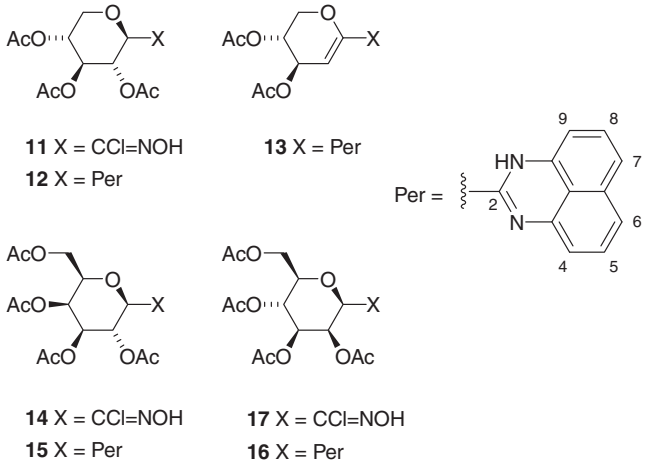
[a] ppm in DMSO-d_6.
[b] **1a**, 2-phenylperimidine; **1b**, 2-(9-anthryl)perimidine; data for **1a** and **1b** taken from Ref. 42.



Scheme 4.

reaction pathway, an attempt was made to prepare mannopyranosyl-perimidine **16**. In this case the 2-acetoxy group would be antiperiplanar to the anomeric hydrogen atom and well placed to undergo E2 as well as E1cB elimination, and thus be more likely to form the glycal. Conducting the reaction of DAN with the D-mannose-derived hydroximoyl chloride **17** in ethanol at room temperature afforded pyranosyl perimidine **16** (55%) together with traces of the glycal **9**. When the reaction was carried out in refluxing ethanol, however, glycal **9** was indeed the dominant product (**9** 34%, **16** 4%; **9**:**16** = 8.5:1). The increased proportion of the glycal perimidine **9** can thus be attributed to the availability of the more favoured E2 pathway.

Also investigated was the condensation reaction of DAN with dioxolanyl hydroximoyl chloride **18**, which is formally derived from D-glyceraldehyde. The hydroximoyl chloride **18** was prepared by chlorination of 2,3-*O*-isopropylidene-D-glyceraldehyde oxime, which is readily accessible from D-mannitol by oxidative cleavage of its 1,2;5,6-diisopropylidene derivative and oximation of the resulting aldehyde, as reported by Thomas and co-workers.[46] Heating DAN with hydroximoyl chloride **18** in ethanol at reflux for 5 h afforded the D-glyceryl-perimidine **19** in 61% yield (Scheme 4).



Strong supporting evidence for the proposed structures is provided by their ^{1}H and ^{13}C NMR spectra. Not only do they show the characteristic features of the peracetylated carbohydrate substituents, but there is also good correlation between the observed signals for the perimidine ring system and those reported in the literature.[42,43,47] Spectra recorded in $CDCl_3$ had broad signals in the aromatic region attributable to amidine-type degenerate tautomerism previously reported for perimidines[42,43,47–49] and similar to that observed for benzimidazoles.[50] Repeating the NMR experiments in DMSO-d_6, however, suppressed the interconversion sufficiently to provide well-resolved aromatic signals; the same effect was observed by Yavari et al. on cooling below −60 °C.[49] In Table 2 the perimidine ring ^{13}C chemical shifts in DMSO-d_6 for the new glycosyl-perimidines are compared with those[42] for the 2-phenyl and 2-(9-anthryl) analogues. The nature of the substituent at the

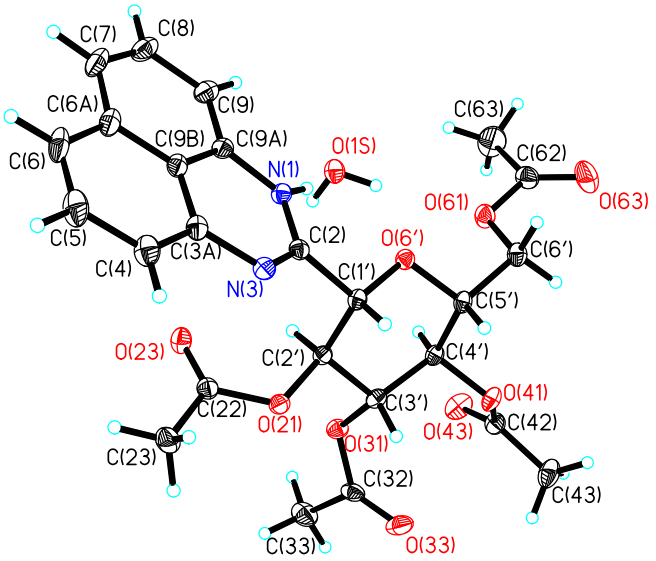


Figure 1. Crystal structure of glucopyranosyl-perimidine **8**.

2-position does not significantly affect the chemical shifts for the naphthalene portion of the perimidine; only the signal for C-2 itself is substituent dependent. A notable feature of the ^{13}C NMR spectra of 2-substituted perimidines is the difference in chemical shift between C-4 and C-9 ($\Delta\delta = \delta_{C\text{-}4} - \delta_{C\text{-}9}$). For example, C-4 and C-9 of D-glucose-derived perimidine **8** resonate at 115.3 and 104.0 ppm, respectively. For all the glycosyl-perimidines $\Delta\delta$ = 10–11 ppm, similar to the values reported by Llamas-Saiz et al. for the 2-phenyl and 2-(9-anthryl) analogues.[42] Similarly, in the ^{1}H NMR spectra H-4 absorbs at higher frequency than H-9 ($\Delta\delta = \delta_{H\text{-}4} - \delta_{H\text{-}9}$ = ca. 0.2 ppm).

The structure of D-glucose-derived perimidine **8** was confirmed by X-ray crystallography (Fig. 1). Selected bond lengths and bond angles for the perimidine ring system are given in Table 3, and are found to be very similar to those reported[42] for the anthryl analogue **1** (R = 9-anthryl). The naphthalene unit has similar bond lengths and angles to those of naphthalene itself.[51,52]

The Cremer and Pople[53] puckering parameters for the glucopyranose ring [Q = 0.5756(19) Å, θ = 13.54(19)°, φ = 357.0(9)°] are comparable with those of the ideal cyclohexane chair [Q = 0.630 Å, θ = 0°, φ = 0°] indicating that, as expected, it adopts a predominantly $^{4}C_1$ conformation. The proton–proton ^{1}H NMR couplings for the glucose ring [$J_{1'\text{-}2'}$ 9.7, $J_{2'\text{-}3'}$ 8.9, $J_{3'\text{-}4'}$ 9.5, $J_{4'\text{-}5'}$ 8.6 Hz] are also typical of β-D-glucopyranosides and are consistent with the observed H–C–C–H torsion angles from the X-ray data [$H_{1'}C_{1'}C_{2'}H_{2'}$ +172.5°, $H_{2'}C_{2'}C_{3'}H_{3'}$ −160.3°, $H_{3'}C_{3'}C_{4'}H_{4'}$ +159.1°; $H_{4'}C_{4'}C_{5'}H_{5'}$ −174.6°]. The atoms of the perimidine ring system are near planar [maximum deviation 0.0850(17) Å], as are the atoms N(1), C(2), C(2′), N(3) linking the pyrimidine part of the perimidine to the two pyranosyl substituent. The dihedral angle in the crystal between the best plane of the perimidine ring system and that made by the atoms C(1′), C(3′) and C(5′) of the pyran ring is 68.79(5)°. The water molecule in the crystal is located adjacent

Table 3
Selected experimental bond lengths and bond angles for pyranosyl-perimidine **8** and anthryl-perimidine (**1** R = 9-anthryl)[a]

Length (Å)	**8**	**1** (R = 9-anthryl)	Bond angle (°)	**8**	**1** (R = 9-anthryl)
N(1)–C(2)	1.351(3)	1.352(2)	C(2)–N(1)–C(9a)	121.21(17)	121.9(2)
N(1)–C(9a)	1.396(3)	1.398(2)	N(1)–C(2)–N(3)	125.57(18)	124.4(2)
C(2)–C(1′)	1.506(3)	1.493(2)	N(1)–C(2)–C(1′)	116.64(16)	115.8(1)
C(2)–N(3)	1.300(2)	1.301(2)	N(3)–C(2)–C(1′)	117.46(18)	119.7(1)
N(3)–C(3a)	1.410(3)	1.408(2)	C(2)–N(3)–C(3a)	116.94(18)	117.5(1)
C(3a)–C(4)	1.377(3)	1.378(3)	N(3)–C(3a)–C(4)	120.3(2)	120.1(2)
C(3a)–C(9b)	1.425(3)	1.416(2)	N(3)–C(3a)–C(9b)	120.26(18)	120.8(1)
C(4)–C(5)	1.409(4)	1.404(3)	N(1)–C(9a)–C(9)	122.8(2)	123.0(2)
C(5)–C(6)	1.359(4)	1.358(4)	N(1)–C(9a)–C(9b)	116.08(18)	116.0(2)
C(6)–C(6a)	1.420(4)	1.416(3)	C(3a)–C(9b)–C(9a)	119.6(2)	119.4(2)
C(6a)–C(7)	1.423(4)	1.412(3)			
C(6a)–C(9b)	1.426(3)	1.420(2)			
C(7)–C(8)	1.367(4)	1.355(3)			
C(8)–C(9)	1.412(3)	1.408(3)			
C(9)–C(9a)	1.378(3)	1.374(3)			
C(9a)–C(9b)	1.414(3)	1.412(2)			

[a] Data from Ref. 42.

to both N(1)–H of the perimidine and the pyranose ring oxygen, O(6′). There are hydrogen bonds between the permidine and the water molecule [N(1)H(1)···O(S1)] and between the water molecule and the ring oxygen O(6′), [O(1S)H(2S)···O O(6′). Both of these interactions serve to H-bond molecules along the [1 0 0] direction. There are no other H-bonding interactions.

In conclusion, a short synthetic route to novel glycosyl-perimidines has been developed based on combination of 1,8-diaminonaphthalenes and readily accessible glycosyl hydroximoyl chlorides. The key steps in the process are believed to involve initial base-induced dehydrochlorination of the hydroximoyl chloride to generate the glycosyl nitrile oxide, followed by nucleophilic addition of the diaminonaphthalene with loss of hydroxylamine. In view of the known biological activity of analogous 2-pyranosyl-benzimidazoles and of perimidines in general, we consider that this new class of heterocyclic C-glycosides are worthy of further investigation.

3. Experimental

3.1. General methods and materials

Melting points were measured on a Gallenkamp capillary tube apparatus and are uncorrected. Optical rotations were measured at 21 °C on an Optical Activity Polaar 20 polarimeter using 2 ml of filtered solution. The ^{1}H and ^{13}C NMR spectra were recorded with Varian WP200SY, Brucker AX250 and Brucker avance 360 spectrometers. Chemical shifts (δ_X) are reported in parts per million (ppm) using tetramethylsilane as internal standard. Positive-ion FAB and high resolution mass spectra were obtained on a Kratos MS50TC instrument using either glycerol or thioglycerol matrices. Merck aluminium-backed plates coated with Kieselgel $GF_{254\ silica}$ (0.2 mm) were used for analytical TLC; detection was by UV or with a staining solution [$P_2O_5 \times 24MoO_3 \times xH_2O$ (10 g), $(NH_4)_2Ce(NO_3)_6$ (5 g), H_2O (450 ml), and H_2SO_4 (50 ml)] and heat. Dry flash chromatography was carried out using Kieselgel GF_{254} and eluted under water pump vacuum.

3.2. Hydroximoyl chlorides

The D-gluco-, D-*xylo*-, D-*galacto*-, and D-*manno*-hydroximoyl chlorides **4**, **11**, **14** and **17** were prepared, as previously reported,[14,41b] by passing dry chlorine gas through a solution of the corresponding pyranosylformaldoxime[14,41d] in dry CH_2Cl_2 at −78 °C until the colour changed from blue to green. On warming to room temperature the colour faded and the products were isolated as solids by removing the solvent in vacuo and trituration with ice-cold Et_2O. 4*R*-4-Chloro-oximino-2,2-dimethyl-1,3-dioxolan (**18**)[46] was prepared similarly from 2,3-*O*-isopropylidene-D-glyceraldehyde oxime, which is readily accessible from 1,2;5,6-diisopropylidene-D-mannitol by oxidative cleavage followed by oximation of the resulting aldehyde, as reported in the literature.[46] Benzohydroximoyl chloride was prepared by chlorination of *syn*-benzaldoxime.[44]

3.3. Synthesis of the 2-substituted perimidines

3.3.1. General procedure

The hydroximoyl chloride (1 equiv) and 1,8-diaminonaphthalene (2.5 equiv) were dissolved in EtOH (10 mL) and the mixture stirred under an atmosphere of nitrogen, either at reflux for 5 h or at room temperature for 16 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), and then washed first with saturated aq K_2CO_3 (50 mL) and then with 4% aq $CuSO_4$ (50 mL) until a dark precipitate formed. The combined layers were filtered through a pad of Celite. The organic layer was separated, dried ($MgSO_4$), and the solvent removed in vacuo. The products were isolated by dry-flash chromatography (silica, hexane/Et_2O, gradient elution).

3.3.2. 2-Phenylperimidine (1, R = Ph)

Orange crystalline solid (68%): mp 187–188 °C [lit.[43b] mp 187–188 °C]; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.85–7.90 (m, 2H, ArH), 7.47–7.55 (m, 2H, ArH), 7.14–7.26 (m, 4H, ArH), 6.65 (br s, 2H, H-4, H-9); EIMS: *m/z* 244 (M^+); HREIMS: Found: M^+ 244.1004, $C_{17}H_{12}N_2$ requires M^+ 244.1001.

3.3.3. 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)perimidime (8)

Yellow solid (65%): mp 105–106 °C; $[\alpha]_D^{20}$ −233 (*c* 0.15, $CHCl_3$); R_f 0.18 (Et_2O); ^{1}H NMR (CD_3SOCD_3, 360 MHz): δ 10.44 (br s, 1H, NH), 7.21–6.94 (m, 4H, H-5, H-6, H-7, H-8), 6.55 (m, 1H, H-4), 6.38 (m, 1H, H-9), 5.45 (dd, 1H, $J_{3',4'}$ 9.5, $J_{3',2'}$ 8.9 Hz, H-3′), 5.35 (dd, 1H, $J_{4',3'}$ 9.5, $J_{4',5'}$ 8.6 Hz, H-4′), 5.05 (dd, 1H, $J_{2',1'}$ 9.7, $J_{2',3'}$ 8.9 Hz, H-2′), 4.33 (d, 1H, $J_{1',2'}$ 9.7 Hz, H-1′), 4.19–4.08 (m, 3H, H-5′, H-6′a, H-6′b), 1.91, 1.99, 2.05 (4 × s, 12H, 4 × $COCH_3$); ^{13}C NMR (CD_3SOCD_3, 93 MHz): δ 171.7, 171.1, 171.0, 170.6 (4 × *C*OCH_3), 153.8 (C-2), 145.7 (C-3a), 139.3 (C-9a), 136.6 (C-6a), 130.3 (C-5), 129.5 (C-8), 123.5 (C-9b), 121.3 (C-6), 119.3 (C-7), 115.3 (C-4), 104.0 (C-9), 78.2, 75.8, 74.1, 70.9, 69.5 (C-1′, C-2′, C-3′, C-4′, C-5′), 63.1 (C-6′), 22.2, 22.0, 21.9, 21.8 (4 × $COCH_3$); FAB-

MS: *m/z* 499 $[M+1]^+$; HRFABMS: Found: *m/z* 499.1717, $C_{25}H_{26}N_2O_9$ requires $[M+1]^+$ 499.1717. Crystals suitable for X-ray diffraction studies (vide infra) were obtained by recrystallisation of a purified sample from EtOAc/40–60 petroleum ether.

3.3.4. 2-(3,4,6-Tri-*O*-acetyl-2-deoxy-1,2-didehydro-D-*arabino*-hexopyranosyl)perimidine (9)

Yellow solid (34%): mp 154–155 °C; $[\alpha]_D^{20}$ 175 (*c* 0.2, $CHCl_3$); R_f 0.34 (Et_2O); ^1H NMR (CD_3SOCD_3, 360 MHz): δ 10.28 (br s, 1H, NH), 7.18–7.00 (m, 4H, H-5, H-6, H-7, H-8), 6.58 (m, 1H, H-4), 6.56 (m, 1H, H-9), 5.92 (d, 1H, $J_{2',3'}$ 3.8 Hz, H-2′), 5.44 (m, 1H, H-4′), 5.22 (m, 1H, H-3′), 4.69 (m, 1H, H-5′), 4.59 (dd, 1H, $J_{6'b,6'a}$ 12.3, $J_{6'b,5'}$ 5.5 Hz, H-6′b), 4.24 (m, 1H, H-6′a), 2.07, 2.06 (3 × s, 9H, 3 × $COCH_3$); ^{13}C NMR (CD_3SOCD_3, 93 MHz): δ 171.6, 171.3, 170.7 (3 × $COCH_3$), 148.6 (C-2), 148.1 (C-1′), 145.8 (C-3a), 139.1 (C-9a), 136.6 (C-6a), 130.4 (C-5), 129.5 (C-8), 123.7 (C-9b), 121.1 (C-6), 119.5 (C-7), 115.3 (C-4), 104.6 (C-9), 99.1 (C-2′), 76.1, 69.7, 69.7 (C-3′, C-4′, C-5′), 61.6 (C-6′), 22.2, 22.1, 21.9, 21.8 (3 × $COCH_3$); FABMS: *m/z* 439 $[M+1]^+$; HRFABMS: Found: *m/z* 439.1507, $C_{25}H_{26}N_2O_7$ requires $[M+1]^+$ 439.1505.

3.3.5. 2-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)perimidine (12)

Orange solid (60%): mp 169–170 °C; $[\alpha]_D^{20}$ −40 (*c* 0.2, $CHCl_3$); R_f 0.27 (Et_2O); ^1H NMR (CD_3SOCD_3, 360 MHz): δ 10.48 (br s, 1H, NH), 7.17–6.99 (m, 4H, H-5, H-6, H-7, H-8), 6.54 (m, 1H, H-4), 6.42 (m, 1H, H-9), 5.41 (dd, 1H, $J_{3',2'}$ 9.6, $J_{3',4'}$ 9.5 Hz, H-3′), 5.24 (dd, 1H, $J_{2',1'}$ 9.7, $J_{2',3'}$ 9.6 Hz, H-2′), 5.02 (m, 1H, H-4′), 4.24 (d, 1H, $J_{1',2'}$ 9.7 Hz, H-1′), 4.10 (dd, 1H, $J_{5'e,5'a}$ 11.0, $J_{5'e,4'}$ 5.5 Hz H-5′e), 3.67 (dd, 1H, $J_{5'e,5'a}$ 11.0, $J_{5'e,4'}$ 10.9 Hz H-5′a), 2.05, 2.03, 1.93 (3 × s, 9H, 3 × $COCH_3$); ^{13}C NMR (CD_3SOCD_3, 93 MHz): δ 171.2, 171.1, 170.7 (3 × $COCH_3$), 154.0 (C-2), 145.8 (C-3a), 139.4 (C-9a), 136.6 (C-6a), 130.3 (C-5), 129.5 (C-8), 123.6 (C-9b), 121.1 (C-6), 119.2 (C-7), 115.0 (C-4), 104.1 (C-9), 78.8, 73.6, 71.2, 69.8 (C-1′, C-2′, C-3′, C-4′), 66.8 (C-5′), 22.0, 21.9, 21.8 (3 × $COCH_3$); FABMS: *m/z* 427 $[M+1]^+$; HRFABMS: Found: *m/z* 427.1510, $C_{22}H_{22}N_2O_7$ requires $[M+1]^+$ 427.1505.

3.3.6. 2-(3,4-Di-*O*-acetyl-2-deoxy-1,2-didehydro-D-*threo*-pentopyranosyl)perimidine (13)

Orange solid (43%): mp 148–149 °C; $[\alpha]_D^{20}$ −113 (*c* 0.15, $CHCl_3$); R_f 0.35 (Et_2O); ^1H NMR (CD_3SOCD_3, 360 MHz): δ 10.49 (br s, 1H, NH), 7.51–7.47 (m, 4H, H-5, H-6, H-7, H-8), 6.60 (m, 1H, H-4), 6.58 (m, 1H, H-9), 6.02 (d, 1H, $J_{2',3'}$ 5.1 Hz, H-2′), 5.12 (m, 1H, H-4′), 5.04 (m, 1H, H-3′), 4.48 (m, 1H, $J_{5'b,5'a}$ 12.3 Hz, H-5′b), 4.14 (m, 1H, $J_{5'a,5'b}$ 12.3 Hz, H-5′a), 2.12, 2.10 (3 × s, 9H, 3 × $COCH_3$); ^{13}C NMR (CD_3SOCD_3, 93 MHz): δ 171.0, 170.9 (2 × $COCH_3$), 150.1 (C-2), 149.2 (C-1′), 145.9 (C-3a), 139.2 (C-9a), 136.6 (C-6a), 130.4 (C-5), 129.5 (C-8), 123.8 (C-9b), 121.0 (C-6), 119.5 (C-7), 115.2 (C-4), 104.7 (C-9), 99.9 (C-2′), 67.6, 66.2, 65.5 (C-3′, C-4′, C-5′), 61.6 (C-6′), 22.3, 22.2 (2 × $COCH_3$); FABMS: *m/z* 467 $[M+1]^+$; HRFABMS: Found: *m/z* 367.1298, $C_{20}H_{18}N_2O_5$ requires $[M+1]^+$ 367.1294.

3.3.7. 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl) perimidine (15)

Yellow glass (69%): $[\alpha]_D^{20}$ −120 (*c* 0.20, $CHCl_3$); ^1H NMR (CD_3SOCD_3, 360 MHz): δ 10.42 (br s, 1H, NH), 7.13–7.04 (m, 4H, H-5, H-6, H-7, H-8), 6.5 (m, 2H, H-4, H-9), 5.42–5.22 (m, 3H, H-2′, H-3′, H-5′), 4.39 (m, 1H, H-4′), 4.26 (d, 1H, $J_{1',2'}$ 8.6 Hz, H-1′), 4.18 (dd, 1H, $J_{6'b,6'a}$ 11.5, $J_{6'b,5'}$ 5.8 Hz, H-6′b), 4.13 (dd, 1H, $J_{6'a,6'b}$ 11.5, $J_{6'a,5'}$ 7.1 Hz, H-6′a), 2.21, 2.04, 1.98, 1.95 (4 × s, 12H, 4 × $COCH_3$); ^{13}C NMR (CD_3SOCD_3, 93 MHz): δ 171.6, 171.5, 171.1, 170.2 (4 × $COCH_3$), 153.6 (C-2), 145.7 (C-3a), 139.3 (C-9a), 136.6 (C-6a), 130.3 (C-5), 129.4 (C-8), 123.6 (C-9b), 121.1 (C-6), 119.3 (C-7), 115.0 (C-4), 104.4 (C-9), 78.0, 75.3, 72.3, 69.0, 68.4 (C-1′, C-2′, C-3′, C-4′, C-5′), 63.2 (C-6′), 22.2, 22.0, 21.9, 21.8 (4 × $COCH_3$); FABMS: *m/z* 499 $[M+1]^+$; HRFABMS: Found: *m/z* 499.1721, $C_{25}H_{26}N_2O_6$ requires $[M+1]^+$ 499.1717.

3.3.8. 2-(2,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranosyl)perimidine (16)

Yellow solid (55%): mp 120–121 °C; $[\alpha]_D^{20}$ −193 (*c* 0.75, $CHCl_3$); R_f 0.20 (Et_2O); ^1H NMR (CD_3SOCD_3, 360 MHz): δ 10.06 (br s, 1H, NH), 7.19–7.03 (m, 4H, H-5, H-6, H-7, H-8), 6.60 (m, 1H, H-4), 6.50 (m, 1H, H-9), 5.67 (dd, 1H, $J_{2',3'}$ 3.4, $J_{2',1'}$ 1.1 Hz, H-2′), 5.36 (dd, 1H, $J_{3',4'}$ 10.1, $J_{3',2'}$ 3.4 Hz, H-3′), 5.17 (dd, 1H, $J_{4',3'}$ 10.1, $J_{4',4'}$ 10.0 Hz, H-4′), 4.83 (d, 1H, $J_{1',2'}$ 1.1 Hz, H-1′), 4.34 (dd, 1H, $J_{6'b,6'a}$ 12.2, $J_{6'b,5'}$ 5.7 Hz, H-6′b), 4.14 (dd, 1H, $J_{6'a,6'b}$ 12.2, $J_{6'a,5'}$ 2.5 Hz, H-6′a), 4.09 (m, 1H, H-1′), 2.08, 2.04, 2.00 (4 × s, 12H, 4 × $COCH_3$); ^{13}C NMR (CD_3SOCD_3, 93 MHz): δ 171.7, 171.2 (4 × $COCH_3$), 153.8 (C-2), 145.6 (C-3a), 139.0 (C-9a), 136.6 (C-6a), 130.3 (C-5), 129.4 (C-8), 123.4 (C-9b), 120.8 (C-6), 119.7 (C-7), 114.8 (C-4), 104.5 (C-9), 78.0, 75.3, 72.3, 69.0, 68.4 (C-1′, C-2′, C-3′, C-4′, C-5′), 63.1 (C-6′), 22.2, 22.0, 21.9, 21.8 (4 × $COCH_3$); FABMS: *m/z* 499 $[M+1]^+$; HRFABMS: Found: *m/z* 499.1713, $C_{25}H_{26}N_2O_9$ requires $[M+1]^+$ 499.1717.

3.3.9. 2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]perimidine (19)

Yellow solid (55%): mp 101–102 °C; $[\alpha]_D^{20}$ 60 (*c* 0.2, $CHCl_3$); R_f 0.60 (Et_2O); ^1H NMR (CD_3SOCD_3, 360 MHz): δ 10.13 (br s, 1H, NH), 7.04–6.68 (m, 4H, H-5, H-6, H-7, H-8), 6.37 (m, 2H, H-4, H-9), 4.67 (dd, 1H, $J_{4',5'a}$ 6.4, $J_{4',5'b}$ 6.4 Hz, H-4′), 4.02 (m, 2H, H-5′a, H-5′b), 1.26, 1.21 (2 × s, 6H, 2 × CH_3); ^{13}C NMR (CD_3SOCD_3, 93 MHz): δ 155.5 (C-2), 144.3 (C-3a), 137.5 (C-9a), 134.9 (C-6a), 128.5 (C-5), 127.7 (C-8), 121.8 (C-9b), 119.0 (C-6), 117.6 (C-7), 113.4 (C-4), 109.8 (C-2′), 104.5 (C-9), 73.9 (C-4′), 66.6 (C-5′), 25.66, 25.2 (2 × CH_3); FABMS: *m/z* 268 $[M+1]^+$; HRFABMS: Found: *m/z* 268.1121, $C_{25}H_{26}N_2O_9$ requires $[M+1]^+$ 268.1212.

3.3.10. 2-(9-Anthryl)perimidine (1, R = 9-anthryl)

A solution of anthracene-9-carbonitrile oxide[53] (192 mg, 0.88 mmol) and 1,8-diaminonaphthalene (166 mg, 1.05 mmol) in ethanol (10 mL) was heated under reflux for 17 h. The solvent was removed in vacuo and dichloromethane (20 mL) added. The resulting solution was washed three times with aq $CuSO_4$ (20 mL, 4%) and filtered through Celite. The organic layer was washed with aq $NaHCO_3$ (30 mL), dried ($MgSO_4$), the solvent removed in vacuo, and the residue crystallised from ethyl acetate/hexane. Chromatography (silica/0–5% diethyl Et_2O in hexane, gradient elution) afforded an orange solid (90 mg, 30%); mp 194–196 °C; FABMS: *m/z* 345 $[M+1]^+$; HRFABMS: Found: *m/z* 1389, $C_{25}H_{16}N_2$ requires $[M+1]^+$ 345.1392.

3.4. Crystal structure of glucopyranosyl-perimidine 8

Diffraction data were collected with graphite-monochromated Cu Kα radiation (λ = 0.71073 Å) on a Brucker SMART Apex diffractometer equipped with an Oxford Cryosystems low-temperature device operating at 150 K. The structure was solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXS-97).[54] All non-H atoms were refined with anisotropic displacement parameters; H-atoms were placed in idealised positions. Crystal data: $C_{25}H_{26}N_2O_9{\cdot}H_2O$, *M* 498.48, yellow block, crystal dimensions 0.50 × 0.36 × 0.20 mm^3, orthorhombic, space group $P2_12_12_1$, *a* = 9.9570(9), *b* = 13.8850(12), *c* = 18.0620(18) Å, α = 90°, β = 90°, γ = 90°, *V* = 2497.1(4) $Å^3$, space group $P2_12_12_1$, D_c = 1.326 mg m^{-3}, *Z* = 4, 16966 reflections collected, 7043 independent reflections [*R*(int) = 0.0323], giving R_1 = 0.0546 [6329 data] [$F > 4\sigma F$)] and wR_2 = 0.1302 for all data. Complete crystallographic data for the structural analysis have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number 775479. Copies of this information can be obtained free of charge from the

Director, the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033, email: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk).

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