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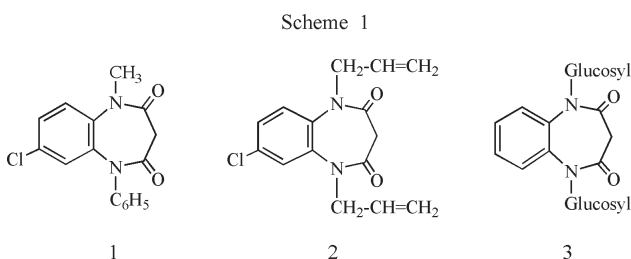
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Reaction of 1,5-benzodiazepin-2,4-dione with 3-*O*-substituted-5,6-anhydro-1,2-isopropylidene- α -D-glucopyranose gave the unexpected *N,N'*-di-glucopyranosyl benzimidazol-2-one by a novel rearrangement and ring closure reaction. A mechanism is proposed.

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Benzodiazepinic compounds such as Clobazam (**1**) (Scheme 1) are used as anxiolytics, anticonvulsants, myorelaxants and sedatives [1-6]. Similar biological activities have also been observed for 7-chloro-1,5-di-*N*-allyl-1,5-benzodiazepin-2,4-dione (**2**) (Scheme 1) [7-8].



In order to increase the water solubility of 1,4-benzodiazepine analogues, we have previously linked hydrophilic sugar residues to various hydrophobic 1,4-benzodiazepin-2,5-diones and 1,4-benzodiazepin-5,11-diones [9-10].

The aim of this study was to synthesize glucosyl-1,5-benzodiazepin-2,4-diones of the type **3** (Scheme 1), in which both *N*-1 and *N*-5 are attached to either a partially protected glucopyranosyl moiety, as in **6**, or a 6-deoxy-D-glucopyranos-6-yl group as in **7** (Scheme 2).

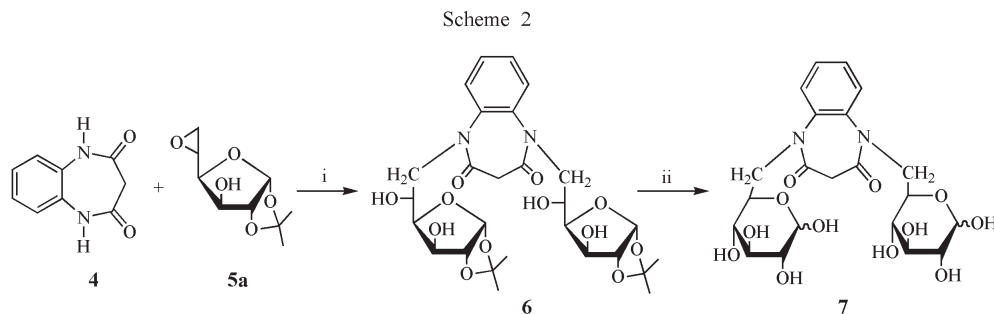
Results and Discussion.

The starting material, 1,5-benzodiazepin-2,4-dione (**4**) was prepared by condensing malonic acid with 1,2-diaminobenzene in hydrochloric acid [11-13].

Refluxing of 1,5-benzodiazepin-2,4-dione **4** with 5,6-anhydro-1,2-*O*-isopropylidene- α -D-glucopyranose (**5a**) [14] for 2 hours in the presence of K_2CO_3 in 4:1 toluene-DMSO gave the expected *N,N'*-bis-substituted derivative **6** (73% yield) (Scheme 2). It is of note that this derivative **6** was the only product detected in the reaction mixture when either a molar deficiency or an excess of **5a** was used.

Subsequent deprotection of **6** with 9:1 trifluoroacetic acid-water solution at room temperature [15], gave the corresponding *N,N'*-bis-(6-deoxy-D-glucopyranos-6-yl)-1,5-benzodiazepin-2,4-dione (**7**) in high yield (96% yield).

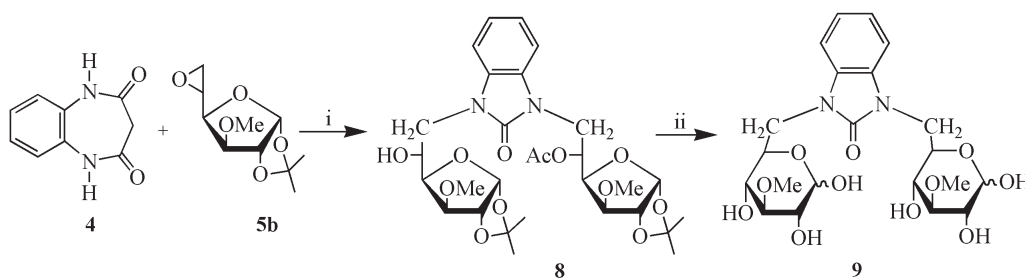
With the aim of modulating the hydrophilic-lipophilic balance, **5a** was subsequently replaced by the slightly more lipophilic homologue 3-*O*-methyl-5,6-anhydro-1,2-*O*-isopropylidene- α -D-glucopyranose (**5b**) in which the 3-OH group of **5a** is methylated. Under comparable reaction conditions, the reaction of **3** with **5b** for 2 hours gave exclusively the unexpected product **8** [1-*N*-(6-deoxy-5-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl- α -D-glucopyranos-6-yl)-3-*N*-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl- α -D-glucopyranos-6-yl]-1,3-benzimidazol-2-one in 51% yield (Scheme 3).



(i) K_2CO_3 , 4:1 toluene-DMSO, 100-110°C

(ii) 9:1 $CF_3COOH-H_2O$, R.T., 30 min

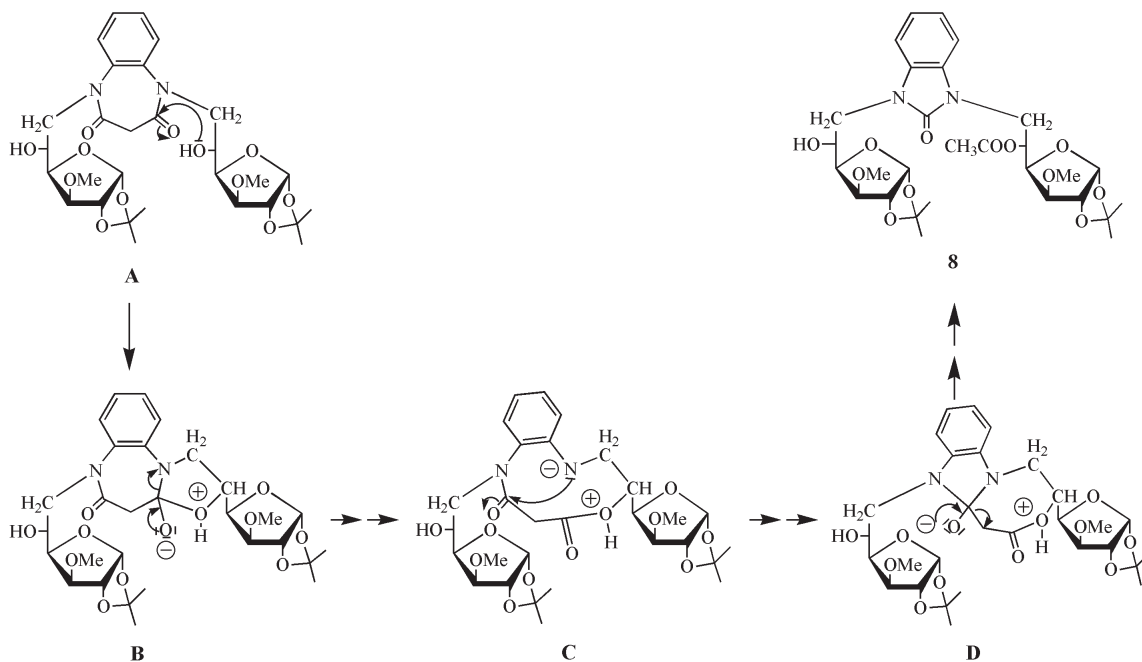
Scheme 3

(i) K_2CO_3 , 4:1 toluene-DMSO, 100-110°C(ii) 9:1 $\text{CF}_3\text{COOH-H}_2\text{O}$, R.T., 30 min

This reaction may have proceeded by N,N' -disubstitution of compound (4) with subsequent rearrangement and ring contraction from a 1,5-diazepin-2,4-dione to 1,3-imidazol-2-one. A plausible mechanism is presented in Scheme 4.

the cleavage of the $\text{N}_1\text{-C}_2$ bond give the intermediate C, which possesses a NH group easily deprotonated by basic catalyst (potassium carbonate) and attacking on the remaining carbonyl to give the tricyclic intermediate D. Lastly, cleavage of the $\text{C}_3\text{-C}_4$ bond of the putative

Scheme 4



It would seem reasonable that the first step in the reaction would involve formation of product A, which is analogous to compound 6. The next step in the proposed mechanism is the intramolecular attack of the OH group at C_5 of the sugar on the carbonyl of the diazepin-2,4-dione to give intermediate B. By comparison, the propensity for such an attack to take place in the analogous product 6 is perhaps diminished due to intramolecular hydrogen bonding between the OH groups at C_3 and C_5 , thus reducing the nucleophilicity of the OH group at C_5 . In the later steps,

oxazepine ring, would give the product 8. It is notable that this rearrangement is different from those already observed with 1,4- and 1,5-benzodiazepines [16-18], but had already been observed during the condensation of 1,5-benzodiazepin-2,4-diones 4 with other 3-O-alkyl- α -D-glucopyranose, such as 3-O-allyl or 3-O-octyl derivatives [14]. In contrast, no evidence of rearrangement reactions was observed in the reaction of the benzodiazepine 4 with monosaccharide 5a.

Subsequent deprotection of 8 performed in trifluoro-

roacetic acid-water solution gave benzimidazolone **9** in 81% overall yield (Scheme 3).

EXPERIMENTAL

General.

Melting points were determined on an automatic electrothermal apparatus, and are uncorrected. Optical rotations, for solutions in chloroform or methanol, were measured with a digital polarimeter JASCO model DIP-370, using a sodium lamp at 25 °C. NMR spectra were recorded with a Bruker WB-300 instrument for solutions in CDCl₃ or Me₂SO-d₆ (internal Me₄Si). Elemental analyses were performed by the IUT de Béthune, Département de Chimie (Béthune, France). Analytical TLC were performed on Merck aluminium backed silica gel (Silica Gel F254), spots were visualized in UV light. Column chromatography was performed on silica gel (60 mesh, Matrix) by elution with hexane-acetone mixture (in each case the ratio of silica gel to product mixture to be purified, was 30:1).

5,6-Anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose (**5a**).

The glucosidic precursor was synthesized according to a method described elsewhere [19]. The product was isolated as a white solid in 96% yield, mp 130-132 °C, [α]_D²⁵ -9.3° (c 1.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.88 (d, 1H, J_{1,2} = 3.6 Hz, H-1), 4.43 (d, 1H, J_{1,2} = 3.6 Hz, J_{2,3} = 0.0 Hz, H-2), 4.18 (d, 1H, J_{3,4} = 2.3 Hz, H-3), 3.82 (dd, 1H, J_{3,4} = 2.3 Hz, J_{4,5} = 5.3 Hz, H-4), 3.27 (m, 1H, H-5), 2.88 (dd, 1H, J_{5,6a} = 4.2 Hz, J_{6a,6b} = 4.8 Hz, H-6a), 2.76 (dd, 1H, J_{6a,6b} = 4.8 Hz, H-6b), 1.37, 1.22 (2s, 6H, CH₃_{iso}); ¹³C NMR (75 MHz, CDCl₃): δ 110.4 (C_{iso}), 104.0 (C-1), 84.1 (C-2), 79.2 (C-4), 74.0 (C-3), 48.5 (C-5), 45.3 (C-6), 25.7, 25.1 (CH₃_{iso}).

3-*O*-Methyl-5,6-anhydro-1,2-*O*-isopropylidene- α -D-glucofuranose (**5b**).

The glucosidic precursor was synthesized according to the literature [19]. The product was isolated as an oil in 95% yield, [α]_D²⁵ -65.0° (c 1.1, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 5.88 (d, 1H, J_{1,2} = 3.6 Hz, H-1), 4.43 (d, 1H, J_{1,2} = 3.6 Hz, J_{2,3} = 0.0 Hz, H-2), 4.18 (d, 1H, J_{3,4} = 2.5 Hz, H-3), 3.82 (dd, 1H, J_{3,4} = 2.5 Hz, J_{4,5} = 9.0 Hz, H-4), 3.41 (s, 3H, OCH₃), 3.04 (m, 1H, H-5), 2.88 (dd, 1H, J_{5,6a} = 5.2 Hz, J_{6a,6b} = 5.1 Hz, H-6a), 2.76 (dd, 1H, J_{5,6b} = 2.7 Hz, H-6b), 1.42, 1.32 (2s, 6H, CH₃_{iso}); ¹³C NMR (75 MHz, CDCl₃): δ 110.2 (C_{iso}), 104.1 (C-1), 84.1 (C-2), 81.5 (C-3), 79.6 (C-4), 58.2 (OCH₃), 48.1 (C-5), 45.4 (C-6), 26.5, 25.7 (CH₃_{iso}).

General Procedure for the Diglucosylation of 1,5-Benzodiazepin-2,4-dione (**4**).

The general procedure for the substitution step consisted first in the addition of α -D-glucofuranosyl derivative **5a** or **5b** (8.00 mmol) to a solution of the 1,5-benzodiazepin-2,4-dione **4** (0.74 g, 4.20 mmol) and K₂CO₃ (1.65 g, 10.40 mmol) in 4:1 toluene-DMSO. The solution was then heated to 110 °C for 2 hours and the reaction progress was measured by TLC (3:2 hexane-ether). After cooling, the mixture was filtered and the resulting filtrate was neutralized with a saturated aqueous solution of NH₄Cl and extracted with toluene. The organic phase was separated, washed with a saturated aqueous solution of

NaCl, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was chromatographed on silica gel using 7:3 hexane-acetone to give **6** and **8** in 73 and 51%, respectively.

1,5-*N,N'*-bis-(6-Deoxy-1,2-*O*-isopropylidene- α -D-glucopyranos-6-yl)-benzodiazepin-2,4-dione (**6**).

This compound was obtained as white crystals, mp 153-155 °C, [α]_D²⁷ -11.5° (c 0.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ _{glucose} 5.86 (d, 2H, J_{1,2} = 3.6 Hz, H-1), 4.44 (2xd, 2H, J_{1,2} = 3.6 Hz, J_{2,3} = 0.0 Hz, H-2), 4.30-4.20 (2xd, 2H, J_{3,4} = 2.2 Hz, H-3), 4.13 (m, 2H, H-5), 4.05 (2xdd, 2H, J_{3,4} = 2.2 Hz, J_{4,5} = 8.3 Hz, H-4), 3.90-3.61 (m, 4H, H-6), 1.30-1.15 (4xs, 12H, CH₃_{iso}), δ _{benzodiazepine} 7.18-7.00 (m, 4H, H_{arom}), 3.30-3.20 (m, 2H, H_{Bzd}); ¹³C NMR (75 MHz, CDCl₃): δ _{glucose} 111.6, 111.4 (C_{iso}), 105.0 (C-1), 84.9 (C-2), 81.5, 81.2 (C-4), 74.5, 74.2 (C-3), 67.2, 66.6 (C-5), 52.8, 50.1 (C-6), 26.4 (CH₃_{iso}), δ _{benzodiazepine} 167.2, 166.4 (C-2, C-4), 137.7, 133.9 (C-10, C-11), 127.3, 127.0 (C-7, C-8), 124.1, 123.8 (C-6, C-9), 44.5 (C-3).

Anal. Calcd. for C₂₇H₃₆N₂O₁₁ (mw 564): C, 57.44%; H, 6.42%; N, 4.96%. Found: C, 57.25%; H, 6.39%; N, 4.64%.

[1-*N*-(6-deoxy-5-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-methyl- α -D-glucofuranos-6-yl)-3-*N*-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl- α -D-glucofuranos-6-yl]-1,3-benzimidazol-2-one (**8**).

This compound was obtained as white crystals, mp 156-158 °C, [α]_D²⁷ -94.7° (c 0.6, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ _{glucose} 5.93 (d, 2H, J_{1,2} = 3.6 Hz, H-1), 5.25-4.20 (2xm, 2H, H-5), 4.51-4.50 (2xd, 2H, J_{1,2} = 3.6 Hz, J_{2,3} = 0.0 Hz, H-2), 4.42 (m, 2H, H-6b), 4.40-4.25 (2xdd, 2H, J_{5,6a} = 5.2 Hz, J_{6a,6b} = 12.0 Hz, H-6a), 4.16-3.91 (2xdd, 2H, J_{3,4} = 3.0 Hz, J_{4,5} = 8.6 Hz, H-4), 3.81-3.65 (2xd, 2H, J_{3,4} = 3.0 Hz, H-3), 3.45-3.24 (2xs, 6H, OCH₃), 1.95 (s, 3H, COCH₃), 1.45-1.15 (4xs, 12H, CH₃_{iso}), δ _{benzimidazolone} 7.25-7.00 (m, 4H, H_{arom}); ¹³C NMR (75 MHz, CDCl₃): δ _{glucose} 170.1 (COCH₃), 111.9 (C_{iso}), 105.6, 105.4 (C-1), 82.1, 81.7 (C-2), 82.8 (C-3), 80.4, 78.7 (C-4), 69.2, 68.9 (C-5), 58.5, 58.3 (OCH₃), 45.9, 42.0 (C-6), 26.9, 26.8, 26.7, 26.4 (CH₃_{iso}), 21.0 (COCH₃), δ _{benzimidazolone} 156.9 (CO), 130.1, 130.0 (C-5, C-6), 129.8, 129.6 (C-8, C-9), 108.8 (C-4, C-7); EIMS [M]⁺ m/z 608.

Anal. Calcd. for C₂₉H₄₀N₂O₁₂ (mw 608): C, 57.23%; H, 6.57%; N, 4.60%. Found: C, 57.05%; H, 6.55%; N, 4.62%.

General Procedure for the Deprotection of **6** and **8**.

The protected glucosidic derivative (50 mmol) was added to a stirred solution of 9:1 CF₃COOH-H₂O (200 mL) at 20 °C. After 30 min., the reaction medium was concentrated to dryness under reduced pressure. The crude product was purified by column chromatography using a hexane-acetone gradient to give **7** and **9** in 96 and 81% yield, respectively.

1,5-*N,N'*-bis-(6-deoxy-D-glucopyranos-6-yl)-benzodiazepin-2,4-dione (**7**).

This compound was obtained as white crystals, mp 94-96 °C, [α]_D²⁷ 37.7-42.9° (c 0.6, MeOH). ¹³C NMR (300 MHz, DMSO-d₆): δ _{glucose} 96.7 (C-1 β), 92.1, 91.9 (C-1 α), 76.1-67.7 (C-2, C-3, C-4, C-5), 52.3, 49.6 (C-6), δ _{benzodiazepine} 164.9, 164.6 (C-2, C-4), 136.9, 136.6 (C-10, C-11), 126.2 (C-8), 125.2 (C-7), 124.9, 124.4 (C-6, C-9), 44.0 (C-3).

Anal. Calcd. for C₂₁H₂₈N₂O₁₁ (mw 484): C, 52.06%; H, 5.82%; N, 5.78%. Found: C, 51.94%; H, 5.79%; N, 5.87%.

N,N'-bis-(6-deoxy-3-*O*-methyl-D-glucopyranos-6-yl)-benzimidazolone (**9**).

This compound was obtained as white crystals (α/β , 4:3), mp 124-126 °C, $[\alpha]_D^{27}$ 48.6-50.2° (c 0.6, MeOH); ^{13}C NMR (75 MHz, DMSO- d_6): δ_{glucose} 96.6 (C-1 β), 92.1 (C-1 α), 85.8 (C-3 β), 82.7 (C-3 α), 74.1-69.5 (C-2, C-4, C-5), 59.9 (OCH₃), 42.7 (C-6), $\delta_{\text{benzimidazolone}}$ 153.8 (C-2), 129.6 (C-8, C-9), 120.7 (C-5, C-6), 108.7, 108.4 (C-4, C-7).

Anal. Calcd. for C₂₀H₂₈N₂O₁₁ (mw 472): C, 50.8%; H, 5.97%; N, 5.93%. Found: C, 50.5%; H, 5.92%; N, 5.96%.

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