SYNTHESIS OF N,N'-DIGLUCOSYLATED BENZIMIDAZOL-2-ONE VIA AN UNEXPECTED REARRANGEMENT OF BENZODIAZEPINE DERIVATIVE

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Abstract

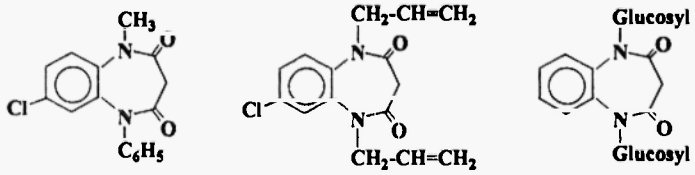
Reaction of 1,5-benzodiazepin-2,4-dione with 3-O-substituted-5,6-anhydro-1,2-isopropylidene-α-D-glucofuranose gave the unexpected N,N'-di-glucofuranosyl benzimidazol-2-one by a novel rearrangement and ring closure reaction. A mechanism is proposed.

Keywords

1,5-benzodiazepin-2,4-dione / N-glucosylation / rearrangement / benzimidazol-2-one / mechanism

Introduction

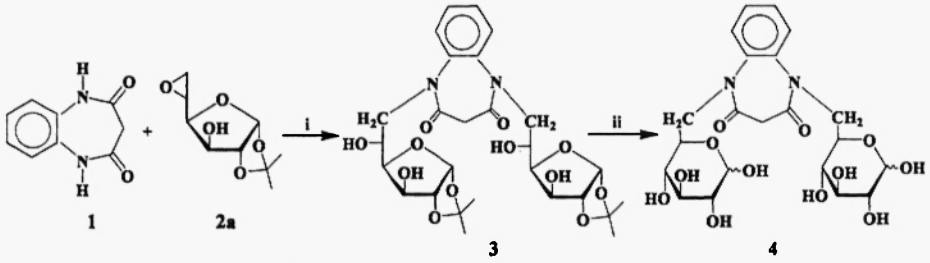
Benzodiazepinic compounds such as Clobazam **I** (scheme 1) are used as anxiolitics, anticonvulsivants, myorelaxants and sedatives.(1-6) Similar biological activities have also been observed for 7-chloro-1,5-di-*N*-allyl-1,5-benzodiazepin-2,4-dione **II** (scheme 1).(7-8)



I II III

Scheme 1: Exemples of biologically active benzodiazepinic derivatives.

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 **III** (scheme 1), in which both *N*-1 and *N*-5 are attached to either a partially protected glucofuranosyl moiety, as in **3**, or a 6-deoxy-D-glucopyranos-6-yl group as in 4 (scheme 2).

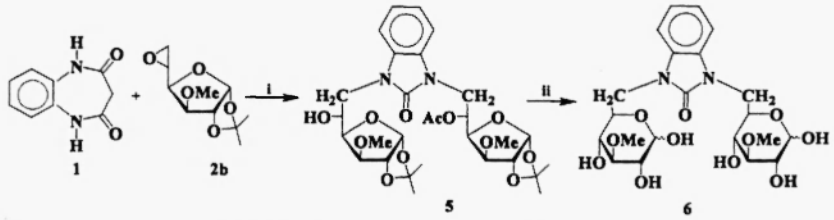


(i) K_2CO_3, 4:1 toluene-DMSO, 100-110°C, 2 h
(ii) 9:1 CF_3COOH-H_2O, R.T., 30 min.

Scheme 2: Reaction pathway followed for the synthesis of 1,5-N,N'-bis-(6-deoxy-D-glucopyranos-6-yl)-benzodiazepin-2,4-dione **4**.

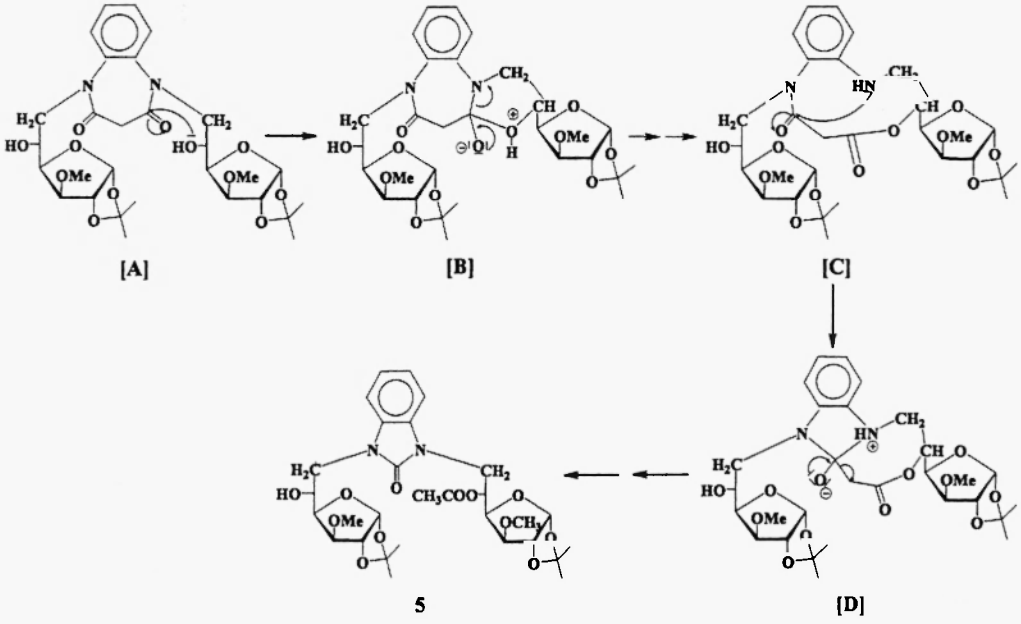
Results and Discussion

The starting material, 1,5-benzodiazepin-2,4-dione (**1**) was prepared by condensing malonic acid with 1,2-diaminobenzene in HCl. (11-13)
Refluxing of 1,5-benzodiazepin-2,4-dione **1** with **2a** (14) for 2 hours in the presence of K_2CO_3 in 4:1 toluene-DMSO gave the expected *N,N'*-bis-substituted derivative **3** (73% yield). It is of note that this derivative **3** was the only product detected in the reaction mixture when either a molar deficiency or an excess of **2a** was used.
Subsequent deprotection of **3** with 9:1 CF_3COOH-H_2O at room temperature,(15) gave the corresponding *N,N'*-bis-(6-deoxy-D-glucopyranos-6-yl)-1,5-benzodiazepin-2,4-dione (**4**) in high yield (96%).
With the aim of modulating the hydrophilic-lipophilic balance, **2a** was subsequently replaced by the slightly more lipophilic homologue **2b** in which the 3-OH group is methylated. Under comparable reaction conditions, substitution of the methylated glucosyl units also occurred on each nitrogen atoms, after 2 hours, but gave exclusively the unexpected product **5** (51% yield), which was [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 (**5**) (scheme 3).



Scheme 3: Reaction pathway for the synthesis of unexpexted N,N'-bis-(6-deoxy-3-O-methyl-D-glucopyranos-6-yl)-benzimidazolone 6.

Thus in addition to *N,N'*-bis-substitution, a rearrangement also occurred resulting in ring contraction from a 1,5-diazepin-2,4-dione to 1,3-imidazol-2-one system along with simultaneous acetylation on C_5-OH of one of the glucose units. A plausible mechanism is presented in scheme 4.



Scheme 4: Mechanism leading to the rearranged product **5**.

It would seem reasonable that the first step in the reaction would involve formation of product **A**, which is analogous to compound **3**. 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 product **B**. By comparison, the propensity for such an attack to take place in the analogous product **3** 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, the cleavage of the N_1-C_2 bond give the intermediate **C**, which possesses a NH group easily deprotonated by basic catalyst (K_2CO_3) and attacking on the remaining carbonyl to give the tricyclic intermediate **D**. Lastly, cleavage of the C_6-C_7 bond of the putative oxazepine ring, would give

the product **5**. 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 **1** with other 3-*O*-alkyl-α-D-glucofuranose, such as 3-*O*-allyl or 3-*O*-octyl derivatives.(14) In contrast, no evidence of rearrangement reactions was observed in the reaction of benzodiazepine **1** with monosaccharide **2a**.
Subsequent deprotection of **5** was achieved in CF_3COOH-H_2O to give benzimidazolone **6** in 81% overall yield.

Experimental Section

General.

Melting points were determined on an automatic electrothermal apparatus, and are uncorrected. Optical rotations, for solutions in $CHCl_3$ or MeOH, 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 $CDCl_3$ or Me_2SO-d_6 (internal Me_4Si). 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). Column chromatography was performed on silica gel (60 mesh, Matrex) 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 (**2a**).
Glucosidic precursor was synthesized according to a method described elsewhere.(14) The product was isolated as a white solid with 96% yield, mp 130-132°C, $[\alpha]_D^{25}$ -9.3° (c 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 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, $J_{4,5}$ = 5.3 Hz, H-4), 3.27 (m, 1H, $J_{5,6a}$= 4.2 Hz, $J_{5,6b}$= 2.7 Hz, H-5), 2.88 (dd, 1H, $J_{6a,6b}$ = 4.8 Hz, H-6a), 2.76 (dd, 1H, H-6b), 1.37, 1.22 (2s, 6H, CH_{3iso}); ^{13}C NMR (75 MHz, $CDCl_3$): 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 (CH_{3iso}).

3-O-methyl-5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose (**2b**).
The glucosidic precursor was synthesized according to the literature.(19) The product was isolated as an oil with 95% yield, $[\alpha]_D^{25}$ -65.0° (c 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): 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, $J_{4,5}$ = 9.0 Hz, H-4), 3.41 (s, 3H, OCH_3), 3.04 (m, 1H, $J_{5,6a}$= 5.2 Hz, H-5), 2.88 (dd, 1H, $J_{6a,6b}$ = 5.1 Hz, H-6a), 2.76 (dd, 1H, H-6b), 1.42, 1.32 (2s, 6H, CH_{3iso}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.2 (C_{iso}), 104.1 (C-1), 84.1 (C-2), 81.5 (C-3), 79.6 (C-4), 48.1 (C-5), 45.4 (C-6), 58.2 (OCH_3), 26.5, 25.7 (CH_{3iso}).

General procedure for the diglucosylation of 1,5-benzodiazepin-2,4-dione (**1**).
The general procedure for substitution step consisted first in the addition of α-D-glucofuranosyl derivative **2a** or **2b** (8.00 mmol) to a solution of the 1,5-benzodiazepin-2,4-dione **1** (0.74g, 4.20 mmol) and K_2CO_3 (1.65g, 10.40 mmol) in 4:1 toluene-DMSO. The solution was then heated to 110°C for 2 hours and the reaction progress was controlled by TLC (3:2 hexane-ether). After cooling, the mixture was filtered and the resulting filtrate was neutralized with a saturated aqueous solution of NH_4Cl and extracted with toluene. The organic phase was separated, washed with a saturated aqueous solution

of NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was chromatographed on silica gel using 7:3 hexane-acetone to give **3** and **5** 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 (**3**).
This compound was obtained as white crystals, mp 153-155°C, $[\alpha]_D^{27}$ -11.5° (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta_{glucose}$ 5.86 (d , 2H, $J_{1,2}$ = 3.6 Hz, H-1), 4.44 (2d, 2H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 0.0 Hz, H-2), 4.30, 4.20 (2d, 2H, $J_{3,4}$ = 2.2 Hz, H-3), 4.13 (m, 2H, H-5), 4.05 (2dd, 2H, $J_{4,5}$ = 8.3 Hz, H-4), 3.90–3.61 (m, 4H, $J_{6a,6b}$ = 12.4 Hz, H-6), 1.30–1.15 (4s, 12H, CH_{3iso}), $\delta_{benzodiazepine}$ 7.18–7.00 (m, 4H, H_{arom}), 3.30–3.20 (m, 1H, H_{Bzd}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta_{glucose}$ 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 (CH_{3iso}), $\delta_{benzodiazepine}$ 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 $C_{27}H_{36}N_2O_{11}$ (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 (**5**).
This compound was obtained as white crystals, mp 156–158°C, $[\alpha]_D^{27}$ –94.7° (c 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta_{glucose}$ 5.93 (d, 2H, $J_{1,2}$ = 3.6 Hz, H-1), 5.25, 4.20 (2m, 2H, $J_{5,6a}$= 3.1 Hz, $J_{5,6b}$= 5.6 Hz, H-5), 4.51, 4.50 (2d, 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 (2dd, 2H, $J_{6a,6b}$= 12.0 Hz, H-6a), 4.16, 3.91 (2dd, 2H, $J_{4,5}$ = 8.6 Hz, H-4), 3.81, 3.65 (2d, 2H, $J_{3,4}$ = 3.0 Hz, H-3), 3.45, 3.24 (2s, 6H, OCH_3), 1.95 (s, 3H, $COCH_3$), 1.45–1.15 (4s, 12H, CH_{3iso}), $\delta_{benzimidazolone}$ 7.25–7.00 (m, 4H, H_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$); $\delta_{glucose}$ 170.1 ($COCH_3$), 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 (OCH_3), 45.9, 42.0 (C-6), 26.9, 26.8, 26.7, 26.4 (CH_{3iso}), 21.0 ($COCH_3$), $\delta_{benzimidazolone}$ 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 $C_{29}H_{40}N_2O_{12}$ (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 **3** and **5**.
The protected glucosidic derivative (50 mmol) was added to a stirred solution of 9:1 CF_3COOH-H_2O (200 mL) at 20°C. After 30 min., the reaction media was concentrated to dryness under reduced pressure. The crude product was purified by column chromatography using a hexane-acetone gradient to give 4 and 6 in 96 and 81% yield, respectively.

1,5-N,N'-bis-(6-deoxy-D-glucopyranos-6-yl)-benzodiazepin-2,4-dione (4).
This compound was obtained as white crystals, mp 94-96°C, $[\alpha]_D^{27}$ 37.7-42.9° (c 0.6, MeOH). ^{13}C NMR (300 MHz, DMSO-d^6):. $\delta_{glucose}$ 96.7 (C-1β), 92.1, 91.9 (C-1α), 76.1-67.7 (C-2, C-3, C-4, C-5), 52.3, 49.6 (C-6), $\delta_{benzodiazepine}$ 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 $C_{21}H_{28}N_2O_{11}$ (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 (6).

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): $\delta_{glucose}$ 96.6 (C-1β), 92.1 (C-1α), 85.8 (C-3β), 82.7 (C-3α), 74.1-69.5 (C-2, C-4, C-5), 59.9 (OCH_3), 42.7 (C-6),), $\delta_{benzimidazolone}$ 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 $C_{20}H_{28}N_2O_{11}$ (472): C, 50.8; H, 5.97; N, 5.93. Found: C, 50.5; H, 5.92; N, 5.96.

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