Synthesis of *N*-Acylated 1,5-Benzodiazepines: Differentiation between Two Possible Acylation Sites *via* Hydrogen Bonding

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Temperature-dependent regioselectivity between amino and hydroxyl groups mediated by hydrogen bonding was observed in the reaction of acetic anhydride with 2-(2,3-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**1**), obtaining 1-acetyl-2-(2,3-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**1a**), when these were reacted at room temperature, and 4-(2-acetoxyphenyl)-1-acetyl-2-(2,3-dimethoxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**1b**), when they were refluxed (148 – 150 °C). Acylation of the less hindered analog 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**2**) *via* crotonyl chloride (a bulky acylating agent compared with acetic anhydride) afforded by refluxing only 1-crotonyl-4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**2a**). All compounds were characterized spectroscopically, and the molecular structures of compounds **1a** and **2a** were determined by X-ray diffraction analysis.

Key words: 1,5-Benzodiazepine, Intramolecular Hydrogen Bond, N-Acylation, Regioselectivity

Introduction

Differentiation between functional groups in a polyfunctionalized compound is the key step in a synthetic route if any orthogonal protection-deprotection strategy is available. Differentiation between groups of different reactivities, using other strategies than those provided by the protecting groups, in particular, those mediated by hydrogen bonds, has been a subject of limited attention in the literature. Most of the examples covering protection by hydrogen bonds are in the area of sugar chemistry [1 – 4], but in other areas of chemistry examples are scarce [5, 6].

In the chemistry of benzodiazepines, for example, if both an amino and a hydroxyl group are present in the benzodiazepine core, but the hydroxyl group is not taking part in an intramolecular hydrogen bond, acetylation at both centers (*i. e.* the amino and the hydroxyl) has been observed when refluxing with acetic anhydride [7].

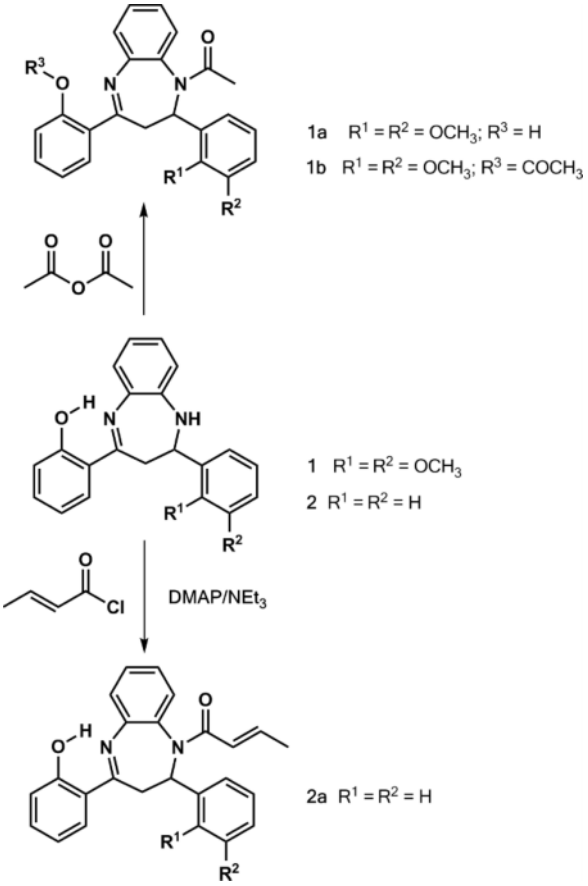
In contrast, differentiation in the acetylation reaction between amino and hydroxyl groups has been achieved in 2,3-dihydro-1*H*-1,5-benzodiazepines using acetic anhydride [8]. In this case, when a 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine, a molecule presenting two possible acetylation sites (*e. g.* the amino and the hydroxyl groups) was reacted with excess acetic anhydride, differentiation between the two possible acylation sites was observed. This differentiation was temperature dependent, and mediated through an intramolecular hydrogen bond between the imine and the hydroxyl group of the 1*H*-1,5-benzodiazepine core.

In this work we report on (i) the synthesis of 1-acetyl-2-(2,3-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**1a**), its *N*,*O*-diacetylated analog **1b** and 1-crotonyl-4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**2a**). The presence of the 2,3-dimethoxyphenyl substituent in the case of **1a** and **1b** was

intended to augment the steric hindrance at the amino side of the benzodiazepine, and thus, help to evaluate its effect on the regioselectivity differentiation between the two possible acylation sites mediated by both the temperature and the hydroxyl hydrogen bond, using acetic anhydride as acylating agent. The use of crotonyl chloride as acylating agent for the preparation of **2a** was intended to evaluate again the same differentiation effect, but this time focused on the size of the acylating agent. In this work, we report also (ii) the complete spectroscopic characterization of each compound and (iii) the crystal and molecular structures of compounds **1a** and **2a** as determined by X-ray diffraction analysis.

Results and Discussion

The benzodiazepine **1a** was obtained as the only product when an excess of acetic anhydride was reacted with 2,3-dihydro-1*H*-1,5-benzodiazepine **1** at room temperature for 24 hours (Scheme 1). In contrast, compound **1b** was obtained as the only product when benzodiazepine **1** was refluxed (148 – 150 °C) with excess acetic anhydride. Acylation of the less hindered 2,3-dihydro-1*H*-1,5-benzodiazepine **2** with crotonyl chloride (a bulky acylating agent compared with acetic anhydride), afforded on refluxing only 1-crotonyl-4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**2a**). All compounds were characterized spectroscopically (see Experimental Section for details), and the molecular structures of compounds **1a** and **2a** were determined by X-ray diffraction analysis (*vide infra*).



Scheme 1. Acylation pathways of 2-(2,3-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**1**) and 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**2**).

The solid-state IR spectrum of **1a** exhibits a medium intensity band at 3434 cm^{-1}, which can be attributed to a phenolic OH group connected with an sp^2 nitrogen atom through a hydrogen bond. A strong band at 1660 cm^{-1} can be attributed to a *N*,*N*-disubstituted amide, and a strong absorption band at 1590 cm^{-1} to the CN and/or CC vibrations; the characteristic band observed at 756 cm^{-1} is attributed to the aromatic δ(C–H) mode in *ortho* position. The more remarkable feature of the ^{1}H NMR spectrum of **1a** recorded at room temperature in deuterated chloroform is the presence of three sets of signals corresponding to the two diastereotopic protons (*i. e.* double doublet signals at $\delta = 3.48$ and 6.51 ppm) and the adjacent isolated sp^3 CH proton (*i. e.* a triplet signal at 2.73 ppm). The singlet signals at $\delta = 1.86$, 3.89, 4.06, and 14.2 ppm can be assigned to the acetyl, two methoxy and the phenolic OH proton, respectively.

The solid-state IR spectrum of **2a** exhibits a medium intensity band at 3434 cm^{-1} which can be attributed to an OH group associated with an sp^2 nitrogen atom through a hydrogen bond. A medium-intensity band at 3032 cm^{-1} can be assigned to C(sp^2)–H vibrations, and a strong band at 1666 cm^{-1} to an *N*,*N*-disubstituted amide. The characteristic band at 758 cm^{-1} is observed again, which is attributed to the aromatic δ(C–H) mode in the *ortho* substitution. The ^{1}H NMR data (with double doublet signals at $\delta = 3.43$ and 6.33 ppm corresponding to the two diastereotopic protons, and the neighboring isolated sp^3 CH proton with a triplet signal at 3.10 ppm) are very similar to those of **1a** (see above). One of the olefinic protons

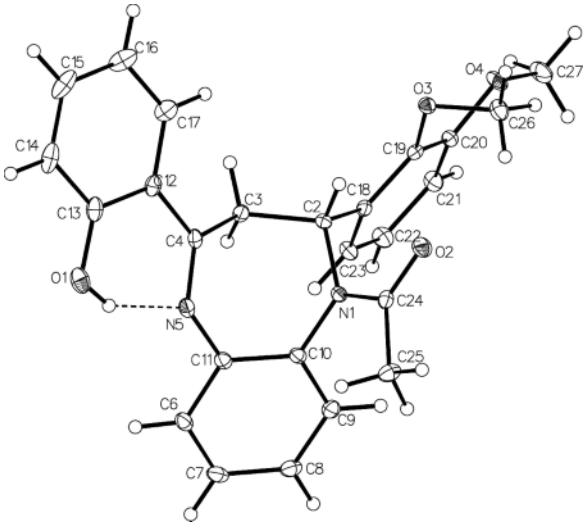


Fig. 1. ORTEP diagram of **1a** (displacement ellipsoids at the 30 % probability level).

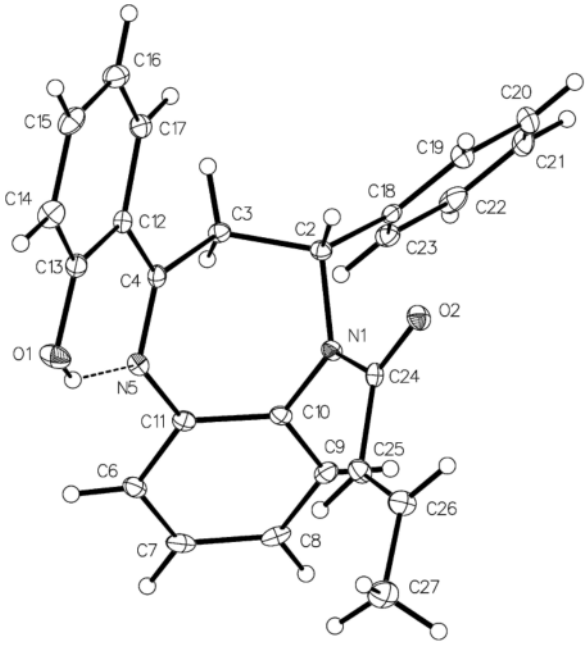


Fig. 2. ORTEP diagram of **2a** (displacement ellipsoids at the 30 % probability level).

can be seen as a doublet at $\delta = 5.54$ ppm, the other one being covered by the more complex aromatic multiplets. The singlet signal at $\delta = 14.3$ ppm can be assigned to the phenolic OH proton. Finally, the double doublet signal at $\delta = 1.70$ ppm can be attributed to the methyl group.

Compounds **1a** and **2a** crystallize in the monoclinic space groups $P2_1/c$ and $C2/c$, respectively. The molecular plots of compounds **1a** and **2a** along with the atom labeling schemes are presented in Figs. 1 and 2, respectively. Selected bond lengths and angles are presented in Table 1. Tables 2 and 3 list the O–H···N and C–H···O hydrogen bond parameters for **1a** and **2a**.

The molecular structures of the two benzodiazepine compounds exhibit seven-membered rings in a boat-like conformation. Two folding angles can be stated along the imaginary N1–N5 and C2–C4 axes, 49.56(8) and 48.83(13)° for **1a** and 50.55(10) and 53.20(16)° for **2a**. In both compounds the hybridization of C4 and N5 atoms is sp^2, the bond length N5–C4 is 1.300(2) Å for **1a** and 1.302(2) for **2a** indicating the presence of a C=N double bond.

The molecular structure of compound **2a** contains one crotonyl substituent, the bond lengths C24–O2 and C25–26 are 1.224(2) and 1.314(2), respectively, corresponding to C=O and C=C double bonds, while the bond lengths N1–C24, C24–C25 and C26–C27 correspond to C–N and C–C single bonds. Additionally, the framework N1/C24/O2/C25/C26/C27 is nearly planar (rms deviation: 0.049 Å) corroborating the conjugated sp^2 character along the crotonyl group.

The compounds **1a** and **2a** are stabilized by a strong intramolecular O–H···N hydrogen bond between the hydroxyl group and the N1 atom forming a six-membered ring conferring rigidity to the system characterized by the planarity of the N5/C4/C12/C13/O1 skeleton (rms deviation **1a**: 0.039 Å; **2b**: 0.014 Å). This feature is also observed in other related 1,5 benzodiazepines [8]. Also, the intramolecular weak C–H···O interactions C2–H2···O3, C2–H2···O2, C26–H26A···O4 in **1a** and C2–H2···O2 in **2a** stabilize the molecular structures.

On the other hand, considering weak intermolecular C–H···O interactions, the molecular packing of compound **1a** in the crystal shows an intricate three-dimensional network generated by: (i) a C14–H14···O2^3 interaction along the *b* axis, (ii) a C25–H25A···O3^2 interaction along the *a* axis, and (iii) the C6–H6···O1^1 and C27–H27C···O4^4 interactions along the [–1 1 0] direction. In the same manner, the crystal structure of **2a** exhibits infinite chains along the *c* axis *via* the C22–H22···O2^2 interaction. Finally, a C26–H26···O2^1 intermolecular interaction forms a dimeric unit in the crystal structure of **2a**.

Table 1. Selected bond lengths (Å) and angles (deg) for **1a** and **2a** with estimated standard deviations in parentheses.

	1a	**2a**
Distances		
N1–C2	1.483(2)	1.482(2)
C2–C3	1.538(2)	1.538(2)
C3–C4	1.511(2)	1.509(2)
C4–C5	1.300(2)	1.302(2)
N1–C10	1.435(2)	1.436(2)
N5–C11	1.414(2)	1.419(2)
C24–O2	1.225(2)	1.224(2)
N1–C24	1.370(2)	1.378(2)
C24–C25	1.509(2)	1.482(2)
C25–C26		1.314(2)
C26–C27		1.491(3)
Angles		
C10–N1–C2	118.22(9)	118.28(13)
C24–N1–C2	119.39(10)	117.77(13)
C24–N1–C10	122.03(10)	122.58(13)
N5–C4–C3	120.96(11)	121.00(15)
N5–C4–C12	118.34(11)	118.10(15)
C12–C4–C3	120.41(10)	120.67(14)
C4–N5–C11	120.02(10)	118.70(14)
N1–C2–C3	109.07(9)	108.16(13)
N1–C2–C18	112.90(9)	113.41(13)
C18–C2–C3	110.12(10)	114.15(13)

Table 2. Hydrogen bond parameters for **1a**[a].

D	H	A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	D–H···A (deg)
O1	H1	N5	0.82	1.83	2.558(1)	147.2
C2	H2	O3	0.98	2.38	2.865(1)	109.9
C2	H2	O2	0.98	2.36	2.754(2)	103.3
C26	H26A	O4	0.96	2.35	2.940(2)	119.5
C6	H6	O1[1]	0.93	2.57	3.384(2)	146.6
C25	H25A	O3[2]	0.96	2.36	3.265(2)	156.9
C14	H14	O2[3]	0.93	2.53	3.349(2)	147.2
C27	H27C	O4[4]	0.96	2.53	3.282(2)	135.0

[a] Symmetry operations: [1] $-1-x, 2-y, -z$; [2] $-1+x, +y, +z$; [3] $-x, 1/2+y, 1/2-z$; [4] $1-x, 1-y, -z$.

Conclusion

To sum up, as a result of our studies, we have found differentiation in the acylation reaction between amino and hydroxyl groups in a 2,3-dihydro-1*H*-1,5-benzodiazepine core using both acetic anhydride and crotonyl chloride. In the first case, when 2,3-dihydro-1*H*-1,5-benzodiazepine **1**, a molecule presenting two possible acylation sites (*i. e.* the amino and the hydroxyl group), was reacted with excess acetic anhydride, differentiation between the two possible acylation sites was observed. This differentiation was temperature dependent, and mediated trough an intramolecular hydrogen bond between the imine portion and the aromatic hydroxyl group of the 1*H*-1,5-benzodiazepine core. As a result, *N*-acetylated **1a** or its *N*,*O*-diacetylated analog **1b**, were obtained depending on the reaction temperature. The presence of the 2,3-dimethoxyphenyl substituent in the case of **1** was intended to augment the steric hindrance at the amino side of the benzodiazepine, and thus help to evaluate its effect on the regioselectivity or differentiation between the two possible acylation sites mediated by both the temperature and the hydroxyl hydrogen bond, using acetic anhydride as acylating agent. Also the use of crotonyl chloride as acylating agent for **2** was intended to evaluate the same differentiation effect, but this time focused on the size of the acylating agent. The results have shown that the size of the acylating agent in **2** or the steric hindrance imposed by the methoxyl groups in **1** did not affect the acylation reaction at the amine moiety of the benzodiazepine core. This is in accordance with the fact that amino groups are more reactive than hydroxyl groups toward electrophilic reagents [9]. In both cases excess acylating agent was not enough at room temperature to produce acylation at the OH group, suggesting a protective effect of the hydrogen bond, as previously reported by us [8].

Table 3. Hydrogen bond parameters for **2a**[a].

D	H	A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	D–H···A (deg)
O1	H1	N5	0.82	1.82	2.547(2)	146.7
C2	H2	O2	0.98	2.30	2.717(2)	104.6
C26	H26	O2[1]	0.93	2.53	3.411(2)	157.5
C22	H22	O2[2]	0.93	2.58	3.357(2)	141.1

[a] Symmetry operations: [1] $1/2-x, 3/2-y, -z$; [2] $+x, 1-y, 1/2+z$.

Experimental Section

Solvents were used as purchased. Reagents were purchased from commercial suppliers and used without further purification. 2-(2,3-Dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1*H*-1,5-benzodiazepine (**1**) and 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (**2**), were synthesized according to a published procedure [10, 11]. Melting points were determined using a Stuart Scientific SMP3 melting point apparatus. IR spectra were obtained from KBr disks on a Perkin Elmer Spectrum BX FTIR spectrometer in the range of $4000-400\,cm^{-1}$. ^1H and ^{13}C NMR spectra were acquired at 297 K on a Bruker Avance 400 spectrometer. All chemical shifts are reported in ppm

(δ) relative to tetramethylsilane. Coupling constants (J) are reported in Hertz (Hz) and integrations are reported as numbers of protons. The following abbreviations are used to describe peak patterns: br, broad; s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra were recorded in the EI mode on a MAT 95XP Thermo Finnigan instrument, using perfluorokerosene as a reference.

*1-Acetyl-2-(2,3-dimethoxyphenyl)-4-(2-hydroxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepine (**1a**)*

Compound **1** (200 mg, 0.534 mmol) was dissolved in excess acetic anhydride (40 mL, 0.39 mol). The reaction mixture was stirred at room temperature for 24 h. Then, water (20 mL) was added, and the mixture was extracted twice with ethyl acetate. The organic fractions were concentrated in a rotatory evaporator and then submitted to column chromatography (silica gel 60, ethyl acetate-hexane = 1 : 10, v/v). The combined fractions containing the 1,5-benzodiazepine **1a** were dried ($MgSO_4$), filtered and concentrated to afford a yellow solid. The solid was recrystallized from methanol to give pale-yellow crystals (102.2 mg, 51 %); m. p. 180.5 – 181.5 °C. – IR (KBr): ν = 3434 (OH), 3004 (=C–H), 1660 (CO), 1002 (=C–H) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.86 (s, 3H, $COCH_3$), 2.73 (t, 1H, CH, J = 13.7 Hz), 3.48 (dd, 1H, CH_2a, J = 3.3 Hz, J = 13.6 Hz), 3.89 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 6.51 (dd, 1H, CH_2b, J = 3.3 Hz, J = 13.8 Hz), 6.86 (t, 1H, H_{arom}, J = 4.7 Hz), 6.95 (t, 1H, H_{arom}, J = 7.5 Hz), 7.04 (m, 3H, H_{arom}), 7.42 (m, 5H, H_{arom}), 7.95 (d, 1H, H_{arom}, J = 7.9 Hz), 14.2 (s, 1H, OH). – ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 23.4, 34.7, 55.8, 60.8, 63.3, 111.5, 116.8, 118.2, 118.4, 118.9, 124.5, 126.4, 126.6, 129.0, 129.2, 130.6, 132.6, 134.0, 136.4, 143.9, 144.9, 152.8, 162.6, 170.7, 175.0. – EI-MS: m/z (%) = 416.1 (64) $[M]^+$, 401.1 (38), 385.1 (100), 373.1 (78), 282.1 (33), 210.1 (57). – $C_{25}H_{24}N_2O_4$ (416.5): calcd. C 72.10, H 5.81, N 6.73; found C 72.10, H 6.03, N 7.15.

*4-(2-Acetoxyphenyl)-1-acetyl-2-(2,3-dimethoxyphenyl)-2,3-dihydro-1H-1,5-benzodiazepine (**1b**)*

Compound **1** (200 mg, 0.534 mmol) was dissolved in excess acetic anhydride (40 mL, 0.39 mol). The reaction mixture was stirred under reflux (148 – 140 °C) for 8 h. Then, water (20 mL) was added, and the mixture was extracted twice with ethyl acetate. The organic fractions were concentrated in a rotatory evaporator and then submitted to column chromatography (silica gel 60, ethyl acetate-hexane = 1 : 2, v/v). The combined fractions containing the diacetylated 1,5-benzodiazepine **1b** were dried ($MgSO_4$), filtered and concentrated to afford a yellow solid. The solid was recrystallized from ethanol to give yellow crystals (70 mg, 35 %); m. p. 229 – 231 °C. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.07 (s,3H, $COCH_3$), 2.18 (s, 2H, CH_2), 2.84 (s, 3H, $COCH_3$), 3.81 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.36 (dd, 1H, CH, J = 1.0 Hz, J = 7.7 Hz), 6.63 (t, 1H, H_{arom}, J = 8.0 Hz), 6.70 (dd, 1H, H_{arom}, J = 1.2 Hz, J = 8.1 Hz), 6.80 (m, 1H, H_{arom}), 6.85 (dd, 1H, H_{arom}, J = 1.6 Hz, J = 7.7 Hz), 7.13 (m, 1H, H_{arom}), 7.27 (d, 1H, H_{arom}, J = 8.1 Hz), 7.32 (d, 1H, H_{arom}, J = 4.6 Hz), 7.36 (d, 1H, H_{arom}, J = 7.2 Hz), 7.39 (dd, 1H, H_{arom}, J = 1.2 Hz, J = 7.9 Hz), 7.52 (m, 1H, H_{arom}), 8.56 (dd, 1H, H_{arom}, J = 1.5 Hz, J = 8.0 Hz). – ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 18.2, 23.0, 31.3, 54.4, 56.2, 61.1, 112.9, 114.8, 117.4, 121.4, 123.7, 124.5, 125.2, 126.2, 128.2, 128.4, 130.0, 131.6, 132.0, 132.6, 144.4, 147.2, 151.1, 152.6, 153.8, 158.3, 169.5.

*1-Crotonyl-4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine (**2a**)*

To a solution of 2,3-dihydro-1*H*-1,5-benzodiazepine **2** (1.0 g; 3.2 mmol), 4-dimethylaminopyridine (0.6 g, 4.91 mmol) and triethylamine (1 mL, 1.36 g, 13 mmol) were dissolved in dry methylene chloride (80 mL). Then, under nitrogen, crotonyl chloride (0.66 g, 6.4 mmol) was added. The reaction mixture was kept under nitrogen and stirred under reflux for 24 h. Then, water (20 mL) was added, and the mixture was extracted with ethyl acetate. The organic fractions were concentrated in a rotatory evaporator and then submitted to column chromatography (silica gel 60, ethyl acetate-hexane = 1 : 10, v/v). The combined fractions containing the crotonylated 1,5-benzodiazepine **2a** were dried ($MgSO_4$), filtered and concentrated, to afford a yellow

Table 4. Crystal structure data for **1a** and **2a**.

	1a	**2a**
Formula	$C_{25}H_{24}N_2O_4$	$C_{25}H_{22}N_2O_2$
M_r	416.46	382.45
Crystal size, mm^3	$0.20 \times 0.18 \times 0.12$	$0.38 \times 0.21 \times 0.19$
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$C2/c$
a, Å	7.80978(12)	30.0009(11)
b, Å	19.4246(3)	7.5964(2)
c, Å	14.1513(2)	17.0719(6)
β, deg	103.7673(15)	93.392(3)
V, $Å^3$	2085.10(5)	3883.8(2)
Z	4	8
$D_{calcd.}$, g cm^{-3}	1.33	1.31
$\mu(Mo K_\alpha)$, cm^{-1}	0.1	0.1
$F(000)$, e	880	1616
hkl range	$\pm10, \pm26, \pm19$	$\pm40, \pm10, \pm22$
$((\sin\theta)/\lambda)_{max}$, $Å^{-1}$	0.687	0.683
Refl. measured / unique / R_{int}	58749 / 5396 / 0.0513	30149 / 4806 / 0.0686
Param. refined	284	264
$R(F)$ / $wR(F^2)$ (all refls.)	0.0575 / 0.1052	0.0876 / 0.1151
GoF (F^2)	1.034	1.088
$\Delta\rho_{fin}$ (max / min), e $Å^{-3}$	0.300 / −0.211	0.265 / −0.261

solid. The solid was recrystallized from ethyl acetate to give yellow crystals (254 mg, 21 %); m. p. 216.7 – 217.2 °C. – IR (KBr): ν = 3434 (OH), 3032 (=C–H), 1666 (CO), 1630 (CO), 1002 (=C–H) cm^{-1}. – ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.70 (3H, dd, CH_3, J = 1.6 Hz, J = 6.9 Hz), 3.10 (1H, t, CH, J = 13.9 Hz), 3.43 (1H, dd, CH, J = 4.4 Hz, J = 13.6 Hz), 5.54 (1H, dd, CH, J = 1.6 Hz, J = 15.0 Hz), 6.33 (1H, dd, J = 4.3 Hz, J = 14.0 Hz), 6.86 (1H, m), 6.95 (1H, dd, CH, J = 1.1 Hz, J = 8.2 Hz), 7.07 (1H, dd, H_{arom}, J = 1.0 Hz, J = 8.3 Hz), 7.12 (1H, dd, H_{arom}, J = 1.1 Hz, J = 7.8 Hz), 7.37 (8H, m, H_{arom}), 7.53 (1H, ddd, H_{arom}, $J_1 = J_2$ = 7.7 Hz, J_3 = 1.3 Hz), 7.69 (1H, dd, H_{arom}, J = 1.3 Hz, J = 8.1 Hz), 14.3 (1H, s, OH). – ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 18.1, 34.4, 67.43, 118.5, 118.6, 118.8, 119.0, 119.3, 119.7, 122.8, 123.2, 126.2, 127.1, 128.6, 129.1, 129.6, 131.3, 131.5, 132.1, 134.5, 140.7, 144.5 (C=), 163.0 (C–OH), 166.3 (C=O), 174.8 (C=N). – EI-MS: m/z (%) = 382.1 (52) $[M]^+$, 341.1 (17), 313.1 (100), 237.1 (17), 222.1 (30). – $C_{25}H_{22}N_2O_2$ (382.4): calcd. C 78.51, H 5.80, N 7.32; found C 77.96, H 6.11, N 7.62.

X-Ray crystal structure determination of compounds ***1a*** *and* ***2a***

Suitable single crystals of compounds **1a**, and **2a** were obtained as described in the previous section. In each case, a well-shaped crystal was mounted with epoxy cement on the tip of a glass fiber. A summary of the experimental and crystallographic data for each compound are given in Table 4. Intensity data were collected at 120 K on an Oxford Diffraction Gemini CCD diffractometer and processed using the Oxford Diffraction CrysAlis^{PRO} software using graphite-monochromatized MoK_α radiation (λ = 0.71073 Å). Using Olex2 [12], the structures were solved with the Shelxs [13] structure solution program using Direct Methods. They were refined with the Shelxl [14] refinement package using full-matrix least-squares techniques based on F^2. All non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms were finally included in their calculated positions.

CCDC 816714 (**1a**) and 816715 (**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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