Regioselective *N*-Acetylation of 4-(2-Hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine Using Protection by an Intramolecular Hydrogen Bond

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Since the amino and the hydroxyl groups of 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine can both act as nucleophiles, the introduction of both an *N*-acetyl and an *O*-acetyl group is expected when the compound is allowed to react with an excess of an electrophile such as acetic anhydride. An intramolecular hydrogen bond between OH and N-5 of the benzodiazepine has been used to obtain differentiation between the two possible sites of acetylation. Thus, this feature offers a preparatively utilizable protecting effect for the OH group and allows for a regioselective *N*-acetylation at ambient temperature. Both mono- and diacetylated compounds were prepared and characterized by crystal structure analysis.

Key words: 1,5-Benzodiazepine, Intramolecular Hydrogen Bond, Protecting Group Effect, Regioselectivity, *N*-Acetylation

Introduction

The selective functionalization of a particular group, among others of similar reactivity, in a polyfunctionalized compound represents a major problem if any orthogonal protection-deprotection strategy is available. Differentiation between the reactivities of different groups, using other strategies than those provided by protecting groups, has been studied mainly in carbohydrate chemistry. There, regioselectivity or differentiation between the different OH groups has been achieved through the formation of hydrogen bonds. In this context, it has been demonstrated that hydrogen bonding networks play a decisive role in the acetylation of unprotected carbohydrates [1] controlling the relative reactivity of the four secondary hydroxyl groups. Attempts to control the reactivities of carbohydrate OH groups by intramolecular hydrogen bonds formed by means of an H bond acceptor protecting group were also successfull [2, 3]. Selective acylation of quinic and shikimic acid derivatives has been performed using a lipase as catalyst providing also the formation of hydrogen bonds [4]. In contrast, outside of carbohydrate chemistry, examples of regioselectivity due to H bond formation seem to be scarce. Selective *N*- and *O*-acylation directed by hydrogen bonds has been performed in secondary ammonium salts using a 24-membered crown ether [5]. Here the key step consists in modifying the ionization state of the amino group to provide an H bond formation (*i. e.* protection) with the crown ether. The same type of chemoselectivity between *N*- and *O*-acylation has been achieved by using enzymatic acylation in ionic liquids [6]. We want to report here the selective *N*-acylation of a 4-(2-hydroxyphenyl)-1,5-benzodiazepine moiety mediated through a hydrogen bond.

Results and Discussion

Since the amino and the hydroxyl groups of 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine can both act as nucleophiles, the introduction of both an *N*-acetyl and an *O*-acetyl group is expected when the compound is allowed to react with an excess of an electrophile such as acetic anhydride (Scheme 1). This is the situation when the reaction is performed by refluxing for five minutes in excess acetic anhydride. In contrast, when the reaction is performed in excess acetic anhydride at r. t., only the formation of the *N*-acetylated product **1** (Fig. 1)

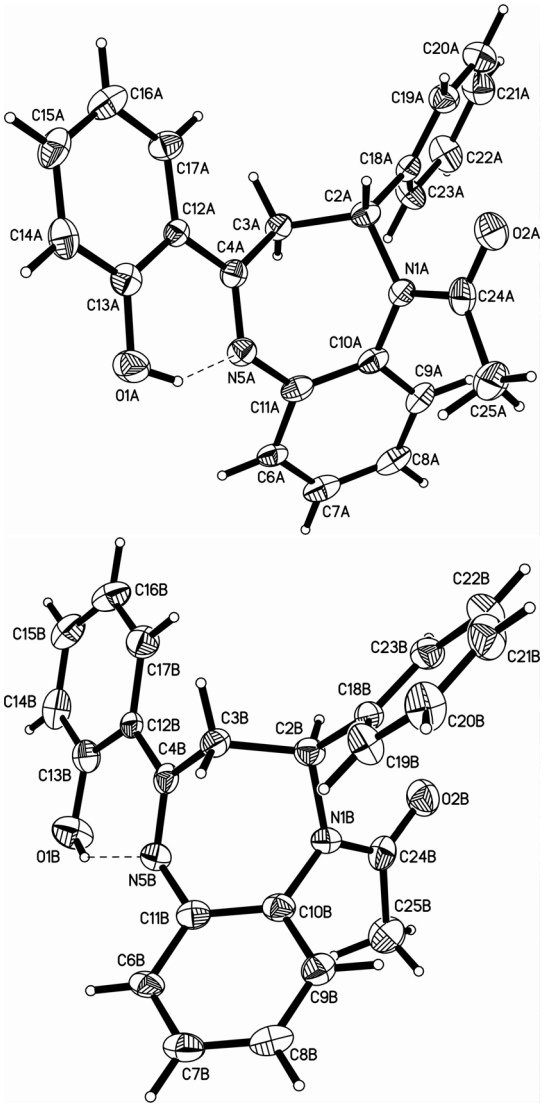
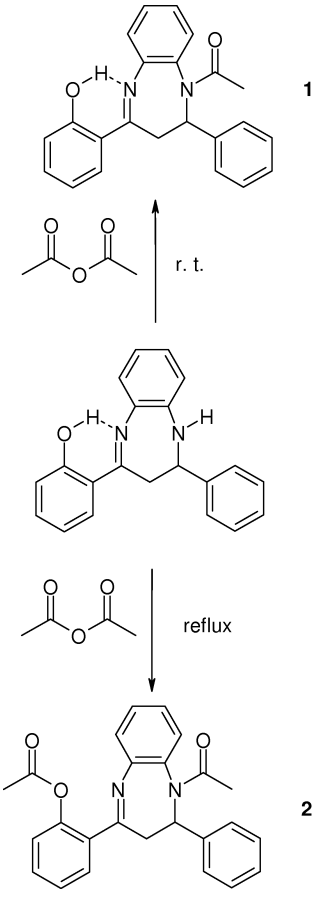


Fig. 1. Structures of the two crystallographically independent molecules of **1** in the crystal and atom numbering scheme adopted. Displacement ellipsoids are at the 50 % probability level, and H atoms are shown as spheres of arbitrary radii.

is observed. As was previously described for the precursor benzodiazepine [7], the H atom of the 2-hydroxyphenyl substituent is involved in an intramolecular O–H···N hydrogen bond providing a way to selectively control the course of the reaction. This control provided by the hydrogen bond works under the reaction conditions at r. t. (*i. e.* giving the *N*-acetylated benzodiazepine **1**). In contrast, when the reaction is performed at higher temperatures (reflux), both positions are acetylated (*i. e.* giving the di-acetylated ben-



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

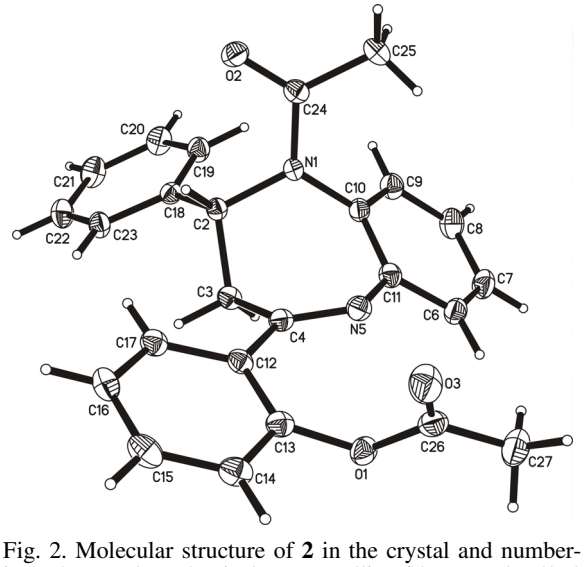


Fig. 2. Molecular structure of **2** in the crystal and numbering scheme adopted. Displacement ellipsoids are at the 50 % probability level, and H atoms are shown as spheres of arbitrary radii.

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

	1	**2**
Formula	$C_{23}H_{20}N_2O_2$	$C_{25}H_{22}N_2O_3$
M_r	356.41	398.45
Crystal size, mm^3	$0.20 \times 0.15 \times 0.10$	$0.40 \times 0.45 \times 0.30$
Crystal system	monoclinic	orthorhombic
Space group	*Cc*	$Pna2_1$
a, Å	31.453(2)	7.51970(10)
b, Å	7.6781(3)	15.2081(2)
c, Å	15.6253(8)	17.0724(3)
α, deg	90	90
β, deg	104.162(5)	90
γ, deg	90	90
V, Å^3	3658.8(3)	1952.41(5)
Z	8	4
D_{calcd}, g cm^{-3}	1.294	1.356
μ(MoK_α), cm^{-1}	0.083	0.090
F(000), e	1504	840
hkl range	$-44 \le h \le +43$	$-10 \le h \le +9$
	$-10 \le k \le +10$	$-21 \le k \le +21$
	$-22 \le l \le +22$	$-24 \le l \le +24$
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	0.714	0.714
Refl. measured/unique	15250/5565	10916/3072
R_{int}	0.0646	0.0222
Param. refined	489	273
$R1(F)/wR2(F^2)$[a] (all refls.)	0.1048/0.0992	0.0384/0.0837
$S\,(F^2)$[b]	0.878	1.031
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	0.271/−0.225	0.280/−0.195

[a] $R1 = \||F_o| - |F_c|\|/\Sigma|F_o|$, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = 1/\sigma^2(F_o^2)$; [b] S = GoF = $[\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

zodiazepine **2**, Fig. 2). The hydrogen bond of the OH group in 2′-hydroxyacetophenone and in 2′-hydroxychalcone (the chalcone and the benzodiazepine precursor, respectively) have been reported to be retained under basic reaction conditions [8], now their derivatives are shown to behave similarly when reacting with excess acetic anhydride at r. t. Hydrogen bonding is strong enough in the 1,5-benzodiazepine moiety to survive the reaction conditions at r. t. Thus, this feature offers a preparatively utilizable protecting group effect for the OH group.

Experimental Section

The precursor 4-(2-hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine was prepared as previously described by us [7, 9]. Melting points were determined using a Stuart Scientific SMP3 melting point apparatus. IR spectra were recorded on a FTIR-Labstation IR Prestige 21 from Shimadzu in KBr. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker NMR spectrometer.

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

4-(2-Hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (1.4 g) was vigorously stirred at ambient temperature for 0.5 h in excess acetic anhydride (100 mL). Then the mixture was concentrated in a rotatory evaporator, redissolved in ethyl acetate (150 mL), and allowed to crystallize: light-yellow crystals (0.71 g 47 %), m. p. 239.7 – 241.2 °C. – IR (KBr): ν = 3451 (OH), 1558 (NH) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (3H, s, CH_3), 3.05 (1H, t, *J* = 14 Hz, CH), 3.39 (1H, dd, *J* = 13.6 Hz, *J* = 4.4 Hz, CH), 6.36 (1H, dd, *J* = 14 Hz, *J* = 4.4 Hz, CH), 6.93 (1H, t, *J* = 7.6 Hz, H_{arom}), 7.06 (1H, d, *J* = 8.0 Hz, H_{arom}),

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

1		**2**	
N1A-C24A	1.364(4)	N1-C24	1.368(2)
N1A-C10A	1.422(4)	N1-C10	1.4300(19)
N1A-C2A	1.477(4)	N1-C2	1.4731(19)
C24A-O2A	1.222(4)	C24-O2	1.2236(19)
N1B-C24B	1.370(4)		
N1B-C10B	1.427(4)		
N1B-C2B	1.479(4)		
C24B-O2B	1.215(4)		
C24A-N1A-C10A	122.8(3)	C24-N1-C10	122.67(12)
C24A-N1A-C2A	117.2(3)	C24-N1-C2	117.72(12)
C10A-N1A-C2A	119.8(2)	C10-N1-C2	119.53(12)
O2A-C24A-N1A	120.0(3)	O2-C24-N1	120.81(14)
O2A-C24A-C25A	121.8(3)	O2-C24-C25	120.98(15)
C24B-N1B-C10B	123.2(3)		
C24B-N1B-C2B	117.3(3)		
C10B-N1B-C2B	119.4(3)		
O2B-C24B-N1B	120.5(3)		
O2B-C24B-C25B	121.7(3)		
C10A-N1A-C24A-O2A	174.9(3)	C10-N1-C24-O2	171.87(15)
N1A-C2A-C18A-C23A	67.0(4)	N5-C4-C12-C13	−30.3(2)
C10A-N1A-C24A-C25A	−7.2(5)	C10-N1-C24-C25	−10.1(2)
C2A-N1A-C24A-O2A	−9.2(5)	N1-C2-C18-C23	−178.59(13)
C2A-N1A-C24A-C25A	168.7(3)	C10-N1-C2-C3	30.23(19)
C10A-N1A-C2A-C3A	31.1(4)	C12-C13-O1-C26	106.16(17)
N1A-C2A-C3A-C4A	53.5(3)	N1-C2-C3-C4	52.69(16)
C2A-C3A-C4A-N5A	−78.9(3)	C14-C13-O1-C26	−80.78(19)
C3A-C4A-N5A-C11A	3.3(4)	C2-C3-C4-N5	−74.76(19)
N5A-C4A-C12A-C13A	−2.6(4)	C13-O1-C26-O3	7.8(2)
C10B-N1B-C24B-O2B	−174.0(3)	C3-C4-N5-C11	−0.9(2)
C10B-N1B-C24B-C25B	8.3(4)	C13-O1-C26-C27	−172.64(15)
C10B-N1B-C2B-C3B	−31.6(3)		
N1B-C2B-C3B-C4B	−52.8(3)		
C2B-C3B-C4B-N5B	79.1(4)		
C3B-C4B-N5B-C11B	−3.1(4)		
N5B-C4B-C12B-C13B	4.0(4)		
N1B-C2B-C18B-C23B	112.5(3)		

Table 3. Hydrogen bonding geometry (Å, deg) for **1**[a].

D–H···A	D–H	H···A	D···A	D–H···A
O1A–H1A···N5A	0.82	1.86	2.526(3)	138
O1B–H1B···N5B	0.82	1.82	2.526(3)	143
C21A–H21A···O2A[i]	0.93	2.51	3.253(4)	137
C21B–H21B···O2B[ii]	0.93	2.50	3.223(4)	135

[a] Symmetry code: [i] $x, -y+1, z+1/2$; [ii] $x, -y, z+1/2$.

7.11 (1H, d, J = 7.6 Hz, H_{arom}), 7.26 – 7.44 (8H, m, H_{arom}), 7.50 (1H, t, J = 7.6 Hz), 7.67 (1H, d, J = 8.0 Hz), 14.3 (1H, s, OH). – ^{13}C NMR (400 MHz, $CDCl_3$): δ = 23.3, 34.1, 66.9, 118.3, 118.8, 119.1, 126.0, 126.8, 126.9, 128.4, 128.9, 128.94, 129.6, 130.9, 131.7, 134.3, 140.1, 144.3, 162.8, 170.5, 174.8.

*1-Acetyl-4-(2-acetoxyphenyl)-2-phenyl-2,3-dihydro-1H-1,5-benzodiazepine (**2**)*

4-(2-Hydroxyphenyl)-2-phenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (1.0 g) was refluxed for 0.5 h in excess acetic anhydride (100 mL). Then the mixture was allowed to cool to ambient temperature, and concentrated in a rotatory evaporator. The mixture obtained was subjected to column chromatography (silica gel 60, ethyl acetate: hexane = 1 : 10 v/v). The fraction that resulted to be a solid was collected and crystallized from methanol: light-yellow crystals (0.627 g; 50 %), m. p. 166.5 – 168.1 °C. – IR (KBr): ν = 1740 (CO), 1670 (N-CO), 1344 (O-CO) cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (3H, s, $COCH_3$), 2.35 (3H, s, $COCH_3$), 3.00 – 3.06 (2H, m, CH_2), 6.53 (1H, dd, J = 12 Hz, J = 6.6 Hz, CH), 7.06 (1H, dd, J = 7.6 Hz, J = 1.2 Hz, H_{arom}), 7.1 – 7.3 (9H, m, H_{arom}), 7.45 – 7.50 (2H, m, H_{arom}), 7.74 (1H, dd, J = 8 Hz, J = 1.6 Hz H_{arom}). – ^{13}C NMR (400 MHz, $CDCl_3$): δ = 21.5, 23.1, 38.1, 66.8, 123.7, 125.8, 126.3, 126.4, 126.9, 128.2, 128.9, 129.4, 130.0, 130.7, 130.8, 131.4, 132.6, 140.1, 147.3, 148.5, 169.3, 170.5, 170.7.

X-Ray crystal structure determination

For both compounds data collection, cell refinement and data reduction were done with CrysAlis CCD (V.1.171. 32.15). The structures were solved by Direct Methods with SHELXS-97 [10], completed by difference Fourier syntheses and refined with SHELXL-97 [10]. The positions of hydrogen atoms were calculated after each cycle of refinement with SHELXL-97 using a riding model for each structure, with C–H distances in the range 0.93 to 0.98 Å. U_{iso}(H) values were set equal to 1.5 U_{eq} of the parent carbon atom for methyl groups and 1.2 U_{eq} for the others and for O–H. Compound **1** crystallizes in the non-centrosymmetric space group *Cc* with Z = 8 molecules in the unit cell. Checks of the metrical symmetry of the lattice and the coordinate set with the program MISSYM as incorporated in PLATON did not indicate any higher symmetry [11]. Details of the crystal structure determination and refinement are given in Table 1. In Tables 2 and 3 selected bond lengths and angles for **1** and **2** and the hydrogen bond parameters for **1** are summarized, respectively.

CCDC 716546 and 716547 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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