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Original Scientific Article

Synthesis, Crystal and Molecular Structure of Novel Adamantyl Derivatives of *N*-Aryl Substituted 3-Hydroxy-2-methylpyridine-4-ones

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Abstract. Two novel potentially bioactive compounds, esters 2-methyl-1-phenylpyridine-4-one-3-yl adamantan-1-ylethanoate (**1**) and 1-(*p*-methoxyphenyl)-2-methylpyridine-4-one-3-yl adamantan-1-ylethanoate (**2**), were synthesized by esterification of adamantan-1-ylacetic acid with appropriate *N*-aryl substituted 3-hydroxypyridine-4-one derivatives. Both compounds are fully characterized using standard spectroscopic methods. Crystal and molecular structures of **1** and **2** were determined by the single crystal X-ray diffraction method. The crystal packing of both **1** and **2** shows separation of the hydrophobic and hydrophilic regions. The crystal structure of **1** is characterized by the two-dimensional hydrogen bonding layers parallel to (001). The crystal packing of **2** is characterized by hydrogen-bonded chains extended in the direction [010].(doi: 10.5562/cca2339)

Keywords: adamantan-1-ylacetic acid, 3-hydroxypyridine-4-ones, single crystal X-ray diffraction, Steglich esterification

INTRODUCTION

3-Hydroxypyridine-4-ones (3,4-HPOs) are a family of heterocyclic compounds with nitrogen atom in the ring and hydroxyl and keto groups at positions 3 and 4, respectively (Figure 1). The presence of the latter two functionalities allows them to exhibit their excellent chelating properties especially towards M(II) / M(III) metal ions.[1–5] In therapeutic applications 3,4-HPOs are primarily used as potential sequesters of metal ions in various diseases that can cause metal overload[6,7] as well as in such conditions that are elicited by metal poisoning.[8] Furthermore, it has been shown that these ligands present their highest affinity for metal ions under physiological conditions in which they are quite stable, nontoxic and even resistant to enzyme-catalyzed cleavage.

Variation of substituents at positions 1, 2, 5 and even at position 3 can strongly influence their biological activity. For example, several 3,4-HPOs glycosylated at position 3 have shown great promise for developing multifunctional treatment for Alzheimer's disease.[8–11] Incorporation of an adequate substituent at a position responsible for pyridine-4-ones chelating ability, in order to increase their solubility and improve pharmacokinetics, can temporarily mask the metal binding site and make these compounds useful and effective prodrugs.[9–12]

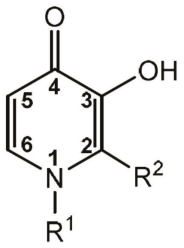

Figure 1. General structure of 3,4-HPO derivatives.

Adamantyl based compounds are used clinically primarily for the treatment of neurological conditions, as antiviral and antitumor agents and potential drugs against type 2 diabetes.[13,14] In almost all cases compounds that bear the bulky adamantyl group tend to be more lipophilic than their des-adamantyl analogues. Furthermore, this group can modulate therapeutic activity of many experimental drugs and prodrugs by varying their mechanism of action.[13] These are certainly good enough reasons for its incorporation in any potential or already biologically active compound.

Given the fact that the structure and function are closely related one can only benefit from the obtained X-ray structure data of potential drugs or prodrugs. The

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detailed structure of such compounds can provide extremely useful information that can be subsequently used in elucidation of their mechanism of action. According to the Cambridge Structural Database, CSDB,[15] a search using the ConQuest Version 1.15, gave only 22 structures containing the adamantan-1-ylacetyl unit yet no structures which contain both adamantan-1-ylacetyl and 3,4-HPO units.

We have prepared two adamantyl modified 3,4-HPOs which are currently used in our ongoing biological study on similar 3,4-HPO derivatives. Preliminary tests have shown that these compounds possess a biological potential.[16] Pyridinone esters of adamantan-1-ylacetic acid were prepared in Steglich esterification conditions.[17] Crystal and molecular structures of both products were determined by the single crystal X-ray diffraction method.

EXPERIMENTAL

Synthesis of Adamantan-1-ylacetic Acid Pyridinone Esters

Materials and Methods

The chemical reagents used in syntheses were obtained from Fluka or Aldrich Corp. All solvents were purified using standard procedures. Column chromatography (solvents and proportions are given in the text) of products were performed on Merck silica gel 60 (size 70–230 mesh ASTM) and thin layer chromatography monitoring (TLC) on Fluka silica gel (60 F 254) plates (0.25 mm). Visualization was effected by the use of UV light at 254 nm. Melting points were determined in open capillaries using Büchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded using Perkin Elmer FT-IR Spectrometer Spectrum Two. ^{1}H and ^{13}C NMR spectra were recorded with Bruker Avance spectrometer at room temperature at 300.130 MHz and 75.468 MHz, respectively. Chemical shifts are given in ppm downfield from TMS as internal standard. Electrospray ionization mass spectrometry (ESI-MS) was performed using Agilent 6410 MS instrument. CHN elemental analyses were carried out by the Analytical Service Laboratory of the Ruđer Bošković Institute.

General Procedure

An appropriate pyridinone derivative (0.5 mmol) was added to a solution of adamantan-1-ylacetic acid (95 mg, 0.5 mmol) in dry CH_2Cl_2 (3 mL), *N*,*N*-dimethylaminopyridine (DMAP; 6 mg, 0.05 mmol). The mixture was cooled down to 0 °C and 1-ethyl-3-(3-dimethyaminopropyl)carbodiimide hydrochloride (EDC·HCl; 105 mg, 0.55 mmol) was added next. The solution was stirred for 30 min at 0 °C and subsequently 24 h at room temperature. The reaction was monitored by TLC (ethyl acetate / methanol 5:2). Dichloromethane was added and the organic layer was washed twice with 0.5 M HCl, then with saturated aqueous $NaHCO_3$ solution and finally dried over $MgSO_4$. After filtration, the organic extract was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate / methanol 5:2) giving the corresponding ester, **1** or **2**.

*2-Methyl-1-phenylpyridine-4-one-3-yl adamantan-1-ylethanoate (**1**):* White crystals (125 mg, 67 %); R_f = 0.49 (ethyl acetate / methanol 5:2); m.p. 184.5–185.8 ºC (decomp). IR (KBr) ν_{max} / cm^{-1}: 3044, 3005 (C−H$_{arom.}$), 2901 (C−H$_s$), 2847 (C−H$_{as}$), 1748 (C=O, ester), 1645 (C=O, ketone), 1497 (C=C$_{arom.}$), 1286 (C−N), 1160 (C−O, ester). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.65 (br s, 6H, 3 Hγ-Ad), 1.72 (m, 6H, 3 Hα-Ad), 1.91 (s, 3H, CH_3), 1.94 (s, 3H, 3 Hβ-Ad), 2.30 (s, 2H, CH_2), 6.24 (d, 1H, J = 7.6 Hz, H-5), 7.48–7.51 (m, 2H, H-Ar), 7.54–7.60 (m, 3H, H-Ar), 7.69 (d, 1H, J = 7.5 Hz, H-6). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.20 (CH_3), 27.92 (Cβ-Ad), 32.38 (C-Ad), 36.13 (Cγ-Ad), 41.40 (Cα-Ad), 47.51 (CH_2), 115.39 (C-5), 127.04 (2 CH-Ar), 129.31 (CH-Ar), 129.75 (2 CH-Ar), 139.13 (C-3), 140.15 (C-2), 140.71 (C-6), 141.03 (C−N), 167.79 (C=O, ester), 169,56 (C=O). ESI-MS: *m*/*z* [M+H]$^+$ 378.3. *Anal.* Calcd. mass fraction of elements, *w* / %, for $C_{24}H_{27}NO_3$ (M_r = 377.48) are: C 76.36, H 7.21, N 3.71, found: C 76.26, H 7.27, N 3.75.

*1-(*p*-Metoxyphenyl)-2-methylpyridine-4-one-3-yl adamantan-1-ylethanoate (**2**):* White crystals (61 mg, 59 %); R_f = 0.6 (ethyl acetate / methanol 5:2); m.p. 196.6–197.7 ºC. IR (KBr) ν_{max} / cm^{-1}: 3066, 3049 (C−H$_{arom.}$), 2907 (C−H$_s$), 2845 (C−H$_{as}$), 1752 (C=O, ester), 1638 (C=O, ketone), 1511 (C=C$_{arom.}$), 1287 (C−N), 1243 (C−O−C, ether), 1154 (C−O, ester). ^{1}H NMR (DMSO-d_6) δ (ppm): 1.65 (s, 6H, 3 Hγ-Ad), 1.72 (s, 6H, 3 Hα-Ad), 1.90 (s, 3H, CH_3), 1.95 (s, 3H, 3 Hβ-Ad), 2.29 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.21 (d, 1H, J = 7.6 Hz, H-5), 7.09 (d, 2H, J = 8.9 Hz, H-Ar), 7.4 (d, 2H, J = 8.8 Hz, H-Ar), 7.63 (d, 1H, J = 7.6 Hz, H-6). ^{13}C NMR (DMSO-d_6) δ (ppm): 14.10 (CH_3), 27.90 (Cβ-Ad), 32.32 (C-Ad), 36.11 (Cγ-Ad), 41.38 (Cα-Ad), 47.48 (CH_2), 55.43 (OCH_3), 114.65 (2 CH-Ar), 115.24 (C-5), 128.19 (2 CH-Ar), 133.89 (C−N), 139.02 (C-3), 140.53 (C-2), 140.97 (C-6), 159.38 (C-Ar), 167.74 (C=O, ester), 169.49 (C=O). ESI-MS: *m*/*z* [M+H]$^+$ 408.2. *Anal.* Calcd. mass fraction of elements, *w* / %, for $C_{25}H_{29}NO_4$ (M_r = 407.50) are: C 73.68, H.7.17, N 3.44, found: C 73.80, H 7.01, N 3.47.

X-ray Crystallography

The single-crystal X-ray diffraction data of **1** and **2** were collected by ω-scans on an Oxford Diffraction Xcalibur 3 CCD diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Data reduction was performed using the CrysAlis software package.[18] Solution, refinement and analysis of the structures were done using the programs integrated in the WinGX system.[19]

Table 1. Crystallographic data and structure refinement details for compounds **1** and **2**

	1	**2**
chemical formula	$C_{24}H_{27}NO_3$	$C_{25}H_{29}NO_4$
*M*r	377.47	407.49
crystal colour, habit	colourless, plate	colourless, plate
crystal dimensions/ mm	0.58×0.48×0.08	0.47×0.33×0.15
crystal system	triclinic	monoclinic
space group	*P*-1	*C* 2/*c*
unit cell parameters		
a/ Å	6.9482(4)	25.669(2)
b/ Å	9.1811(5)	9.9870(3)
c/ Å	15.6785(8)	22.2003(18)
α, β, γ / °	96.302(4), 100.405(4), 957.59(9)	90, 132.283(14), 90
V/ Å^3	957.59(9)	4210.5(11)
Z	2	8
D_{calc}/ g cm^{-3}	1.309	1.286
temperature/ K	150(2)	295(2)
wavelength/ Å	0.71073	0.71073
μ / mm^{-1}	0.086	0.086
F(000)	404	1744
number of unique data	3758	3702
number of data [$F_o \geq 4\sigma(F_o)$]	2999	2842
number of parameters	361	375
R_1[a], [$F_o \geq 4\sigma(F_o)$]	0.038	0.050
wR_2[b]	0.104	0.127
Goodness of fit on F^2, S[c]	1.05	1.04
$\Delta\rho_{max}$,$\Delta\rho_{min}$ (e Å^{-3})	−0.17, 0.23	−0.20, 0.29

[a] $R = \sum \| |F_o| - |F_c| \| / \sum |F_o|$; [b] $wR = \left[\sum \left(F_o^2 - F_c^2 \right)^2 / \sum w \left(F_o^2 \right)^2 \right]^{1/2}$; [c] $S = \sum \left[w \left(F_o^2 - F_c^2 \right)^2 / \left(N_{obs} - N_{param} \right) \right]^{1/2}$

The structures were solved using SHELXS by direct methods. The refinement procedure was performed by the full-matrix least-squares method based on F^2 against all reflections using SHELXL.[20] The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located in the difference Fourier maps and refined isotropically. Exceptions were hydrogen atoms on atom C18 (methyl group) in **2** which were placed in calculated positions and refined using the riding model. Geometrical calculations were done using PLATON. [21] The structure drawings were prepared using the MERCURY program.[22] Crystallographic and structure refinement data for **1** and **2** are summarized in Table 1, whereas the selected bond distances and angles are listed in Table 2.

RESULTS AND DISCUSSION

Synthesis

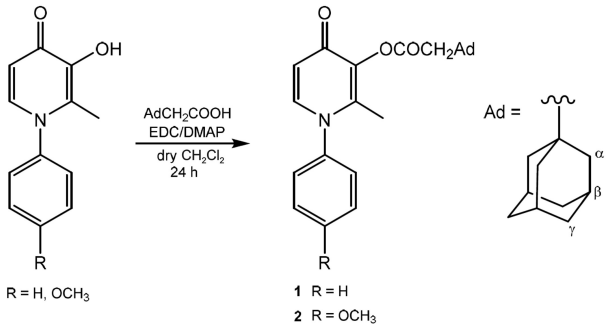
Two different *N*-aryl substituted 3,4-HPOs, namely 3-hydroxy-2-methyl-1-phenylpyridine-4-one and 3-hydroxy-1-(*p*-methoxyphenyl)-2-methylpyridine-4-one, were used as an alcohol component in the esterification of adamantan-1-ylacetic acid (Scheme 1). Both pyridinone derivatives were synthesized following the procedure reported by Jakopčić *et al.*[2] The incorporation of adamantyl moiety into 3,4-HPO structures was carried out in mild Steglich esterification conditions in the presence of coupling carbodiimide reagent and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP).[17]

As 1-ethyl-3-(3-dimethyaminopropyl)carbodiimide hydrochloride (EDC·HCl) was used as the coupling reagent, a byproduct, water soluble urea, can be easily removed by extraction and does not contaminate the product. After column chromatography purification, pyridinone esters of adamantan-1-ylacetic acid, 2-methyl-1-phenylpyridine-4-one-3-yl adamantan-1-yl-ethanoate (**1**) and 1-(*p*-methoxyphenyl)-2-methylpyridine-4-one-3-yl adamantan-1-ylethanoate (**2**) were isolated in good yields, 67 % and 59 %, respectively. Both compounds were characterized using

Table 2. Selected bond lengths (Å) and angles (°) for compounds **1** and **2**

	1	**2**
O1−C1	1.2015(17)	1.194(3)
O2−C1	1.3621(17)	1.364(4)
O1−C13	1.4061(16)	1.403(3)
O3−C14	1.2516(15)	1.244(2)
N1−C19	1.4484(16)	1.451(2)
C1−C2	1.5009(19)	1.497(5)
C2−C3	1.5442(18)	1.541(3)
C3−C4	1.540(2)	1.525(3)
C3−C10	1.5384(19)	1.530(6)
C3−C11	1.538(2)	1.522(5)
C1−O2−C13	115.92(10)	116.30(17)
C16−N1−C17	119.28(11)	119.68(17)
C16−N1−C19	118.98(11)	119.4(2)
C17−N1−C19	121.63(11)	120.8(2)
O1−C1−O2	123.09(12)	122.3(3)
O1−C1−C2	125.63(13)	126.0(3)
O2−C1−C2	111.28(12)	111.7(2)
C1−C2−C3	113.89(11)	114.7(3)
C4−C3−C10	108.64(11)	109.6(3)
C4−C3−C11	108.40(11)	107.3(3)
C21−C22−C23	119.78(14)	120.25(19)

standard spectroscopic methods, electrospray ionization mass spectrometry and X-ray structural analysis.



Scheme 1. Synthesis of adamantyl derivatives of 3,4-HPOs.

X-ray Crystallography

The molecular geometry, as determined by X-ray analysis, and the atom labelling scheme of **1** and **2** are shown in Figure 2. Differences in the molecular structure of the **1** and **2** are revealed by their overlay (Figure 3), the greatest being at the methoxy group in **2**, and by dihedral angles between the pyridinone and phenyl rings. Analysis of the bond lengths revealed only small or insignificant differences in the molecular structure of **1** and **2** (Table 2).

The adamantane unit in **1** and **2** consists of four cyclohexanes fused with each other, all approaching the ideal chair conformations. The values of the bond lengths and angles in the adamantane unit are similar to those found in other related compounds.[23–25] The six-membered pyridinone and phenyl rings in both **1** and **2**

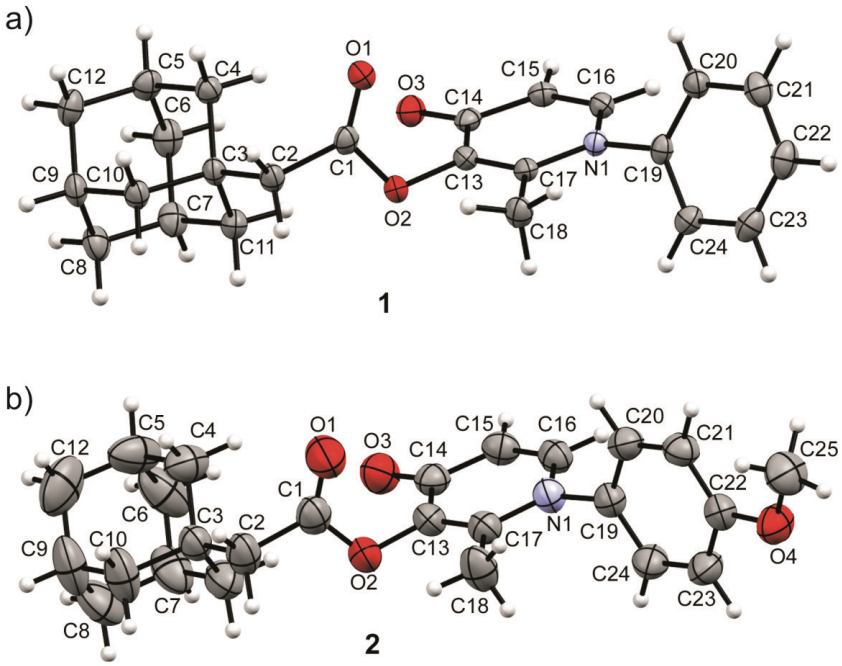


Figure 2. a) The ORTEP drawing of **1**. **b)** The ORTEP drawing of **2**. Ellipsoids are shown at the 50% probability and hydrogen atoms are shown as spheres of arbitrary radii.

Table 3. Geometry of intermolecular hydrogen bonds (Å, °) for compounds **1** and **2**

	D–H···A	D–H / Å	H···A / Å	D···A / Å	D–H···A / °
1	C15–H15···O1^{i}	0.983(15)	2.580(15)	3.1877(17)	120.1(11)
	C16–H16···O1^{i}	0.970(14)	2.659(14)	3.1971(17)	114.4(12)
	C20–H20···O3^{i}	0.967(15)	2.315(15)	3.2689(17)	168.8(12)
	C24–H24···O3^{ii}	0.958(15)	2.383(15)	3.2087(17)	144.2(12)
	C18–H18C···O2	0.964(18)	2.423(17)	2.7931(18)	102.4(12)
2	C15–H15···O1^{iii}	0.95(2)	2.71(3)	3.291(4)	120.2(11)
	C20–H20···O3^{iii}	0.96(2)	2.47(2)	3.348(3)	152(3)
	C21–H21···O3^{iv}	0.96(2)	2.66(2)	3.600(4)	168(2)

^{i} $2-x, 1-y, 1-z$; ^{ii} $1-x, 1-y, 1-z$; ^{iii} $2-x, 1-y, -z$; ^{iv} $x, -1+y, z$.

are planar with the dihedral angles between the two planes 78.39(13) ° and 60.95(7) °, respectively.

In the previously reported structure of 1-(*p*-methoxyphenyl)-3-hydroxy-2-methyl-4-pyridinone(Hpap) the pyridinone ring is slightly nonplanar and the phenyl ring is planar. The dihedral angle between the two planes is 73.7 °, which is quite different than in **2**.[26] The pattern of the bond lengths within the pyridinone and phenyl rings in **2** is similar to that observed in the Hpap molecule. Exception is a longer O2–C13 bond (1.403(3) Å in **2** and 1.357(2) Å in Hpap).

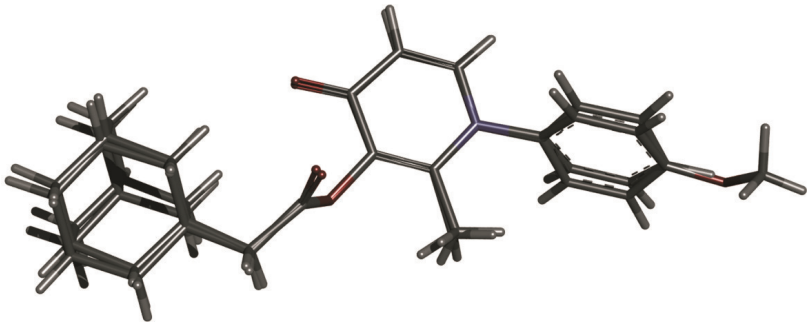


Figure 3. Superposition of the molecules of **1** and **2**.

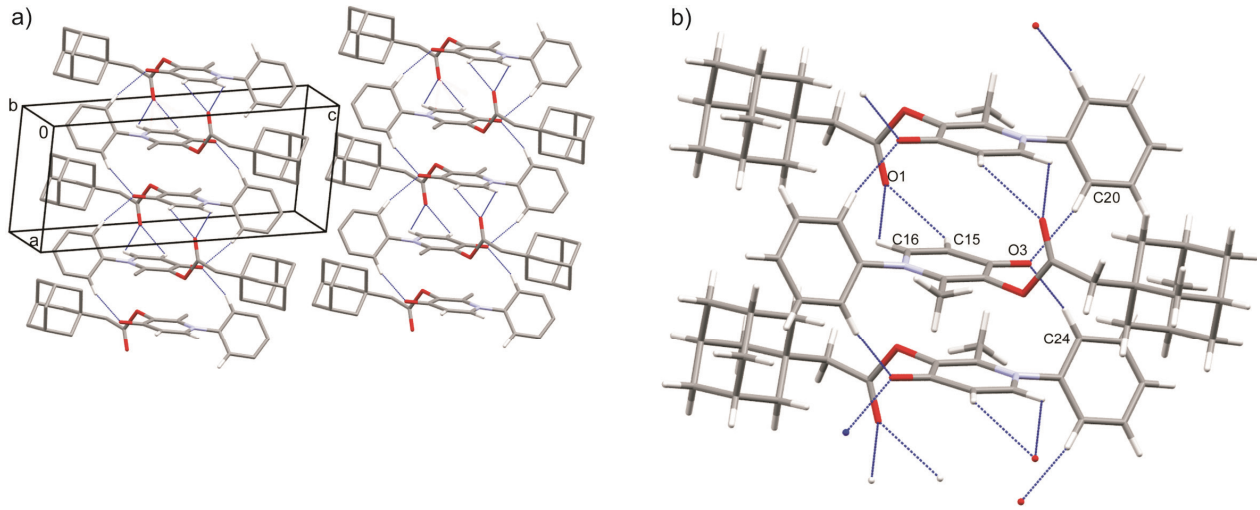


Figure 4. The crystal packing of **1**: **a)** Partial structural motif of the two-dimensional hydrogen bonding network, layers parallel to (001) (hydrogen atoms that are not participating in intermolecular hydrogen bonds including the intramolecular C18–H18C···O2 hydrogen bond are omitted for clarity). Hydrogen-bonds are shown by blue dotted lines. **b)** Weak C–H···O hydrogen bonds (C15−H15···O1[2−x,1−y,1−z] 3.1877(17) Å, C16–H16···O1[2−*x*,1−*y*,1−*z*] 3.1971(17) Å, C20−H20···O3[2−*x*,1−*y*,1−*z*] 3.2689(17) Å and C24−H24···O3 [1−*x*,1−*y*,1−*z*] 3.2087(17) Å). Hydrogen-bonds are shown by blue dotted lines.

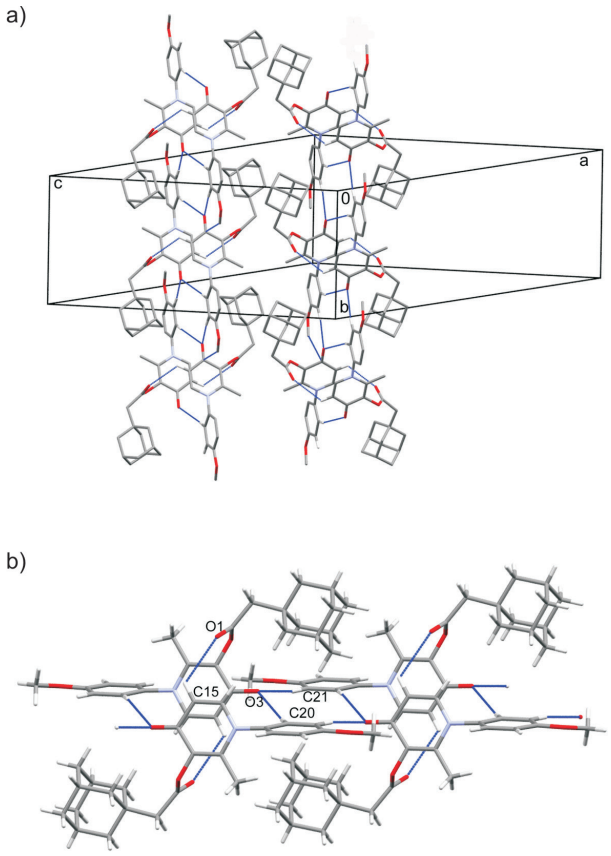


Figure 5. Packing in the unit cell of **2**: **a)** Partial structural motif of the hydrogen bonded chains extended in the direction [010] (hydrogen atoms not participating in hydrogen bonds are omitted for clarity). Hydrogen-bonds are shown by blue dotted lines. **b)** Weak C–H···O hydrogen bonds (C15–H15···O1[2−*x*,3−*y*,−*z*] 3.291(4) Å, C20–H20···O3[2−*x*,1−*y*,−*z*] 3.348(3) Å and C21−H21···O3 [*x*,−1+*y*,*z*] 3.600(4) Å). Hydrogen-bonds are shown by blue dotted lines.

There are no classical hydrogen bonds in the crystal structures of **1** and **2**, however weak intermolecular C–H···O hydrogen bonds are present (Table 3). The X-ray structure of **1** also reveals an intramolecular hydrogen bond C18–H18C···O2 (Table 3). The crystal packing of both **1** and **2** shows separation of the hydrophobic and hydrophilic regions. In **1** the hydrogen bonds connect the molecules into layers parallel to (001) (Figure 4a). Hydrogen bonds in **1** involve double acceptors, the ester carbonyl oxygen atom (O1) and the keto group oxygen atom from the pyridinone moiety (O3). C and H atoms from the phenyl (C20 and C24) and from the pyridinone ring (C15 and C16) serve as hydrogen bond donors (Figure 4b). The crystal packing of **2** is characterized by hydrogen-bonded chains extended in the direction [010] (Figure 5a). Hydrogen bonds in **2** involve a double acceptor function of the keto group oxygen atom O3 and donors from the aromatic C20–H20 and C21–H21 atoms. Additionaly, the ester carbonyl oxygen atom (O1) serves as the hydrogen bond acceptor and C15–H15 from the pyridinone unit as the hydrogen bond donor (Figure 5b).

CONCLUSION

Two pyridinone esters of adamantan-1-ylacetic acid were prepared in satisfactory yields. The procedure involved mild Steglich esterification in which two *N*-aryl substituted 3,4-HPO derivatives were used as the alcohol part. The final pyridinones **1** and **2** bearing the adamantyl moiety were fully characterized by standard spectroscopic methods and also by the X-ray structural analysis. The crystal packing of both **1** and **2** shows separation of the hydrophobic and hydrophilic regions. There are no classical hydrogen bonds in the crystal structures of **1** and **2**, however weak intermolecular C–H···O hydrogen bonds are present. The crystal packing of **1** is characterized by the hydrogen bonds connecting molecules into layers parallel to (001) while the crystal packing of **2** is characterized by hydrogen-bonded chains extended in the direction [010].

Supplementary Materials. – CCDC 950307 and 950308 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data request/cif, or by e-mailing to data request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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