# Dimers of solid 4-arylhexahydro-1*H*,3*H*-pyrido[1,2-*c*] pyrimidine-1,3-diones. <sup>13</sup>C CP/MAS NMR, x-ray diffraction and semi-empirical MO studies

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ABSTRACT: <sup>13</sup>C cross-polarization magic angle spinning NMR data are reported for eight derivatives of 4-aryl-hexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones **1**–**8** and the x-ray diffraction data for **4** with R = 4′-Me. The crystal structure of **4** shows the formation of centrosymmetric dimers via intermolecular hydrogen bonds with an N2···O11 distance of 2.797(3) Å. Deshielding of carbonyl carbons in the solids **1**–**8** as compared with solution shows that such dimers probably also exist in other compounds. According to the PM3 calculations, three types of dimers with two C1═O···HN, two C3═O···HN bonds and 'mixed,' i.e. with one C1═O···HN and one C3═O···HN bond, are possible. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: 4-aryl-hexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones; dimers; cross-polarization magic angle spinning NMR; x-ray diffraction; semi-empirical MO methods

## INTRODUCTION

In the course of our studies on potential drug molecules, the 4-arylhexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones **1**–**8** (Fig. 1) were synthesized as starting compounds for the synthesis of buspirone (an anxiolytic agent) analogues. A topographical, three-point pharmacophore model has recently been proposed[1–3] in which the carbonyl group of a ligand is involved in the interaction with a serotonine receptor. The presence of an acylurea moiety in **1**–**8** suggests that these fragments may constitute active sites. As a consequence, when connected with the appropriate piperazinylbutyl spacer, the compounds (analogues of **9**, Fig. 1) should exert an effect on the central nervous system. Therefore, data concerning the structure, conformational flexibility and properties of carbonyl groups (especially their hydrogen bonding ability) of compounds **1**–**8** are of interest. The derivatives of 4-arylhexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine-1,3-dione with an *ortho*-, *meta*- and *para*-substituted aromatic ring at C4 were examined using the combined approach of solid-state NMR spectroscopy, x-ray diffraction measurements and theoretical semi-empirical MO methods.

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## EXPERIMENTAL

The 4-arylhexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine-1,3-dione derivatives were prepared by catalytic hydro-



**1** R= H
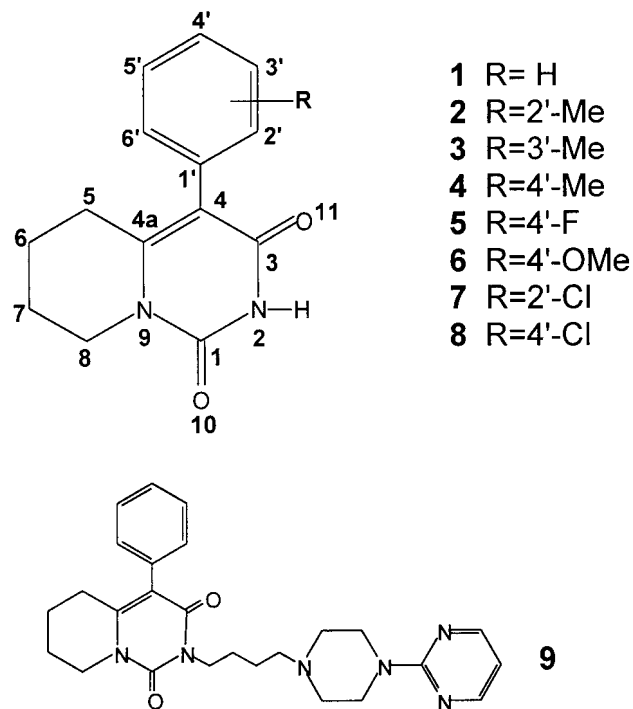**2** R=2′-Me
**3** R=3′-Me
**4** R=4′-Me
**5** R=4′-F
**6** R=4′-OMe
**7** R=2′-Cl
**8** R=4′-Cl

**9**

**Figure 1.** Structures of compounds **1**–**9**

**Table 1.** Crystal data and structure refinement for **4**

| Parameter | Value |
|---|---|
| Molecular formula | $C_{15}H_{16}N_2O_2$ |
| Molecular weight | 256.30 |
| Crystal system | Monoclinic |
| Space group | $P2_1/c$ |
| Z | 4 |
| $a$ (Å) | 12.045(2) |
| $b$ (Å) | 8.343(2) |
| $c$ (Å) | 12.943(3) |
| $\beta$ (°) | 93.93(3) |
| Volume (Å$^3$) | 1297.6(5) |
| Density (calc.) (g cm$^{-3}$) | 1.312 |
| $F(000)$ (e) | 544 |
| Wavelength (Å) | 1.54178 |
| $\mu$ (mm$^{-1}$) | 0.713 |
| Crystal size (mm) | $0.6 \times 0.5 \times 0.15$ |
| Index ranges | $-14 \leq h \leq 14$, |
| | $0 \leq k \leq 9$ |
| | $0 \leq l \leq 14$ |
| Reflections collected | 2266 |
| Reflection independent | 2155 ($R_{int} = 0.013$) |
| No. of parameters | 187 |
| Final $R(F)$ [$F^2 > 2\sigma(F^2)$] | 0.0488 |
| $wR(F^2)$ (all data) | 0.1572 |
| S | 1.022 |
| Max. shift (e.s.d) | <0.001 |
| Max./min. $\Delta\rho$ (e Å$^{-3}$) | 0.305/$-0.192$ |

genation of 4-aryl-1*H*,2*H*-pyrido[1,2-*c*]pyrimidine-1,3-diones.[4] The $^{13}$C NMR spectra were recorded at 125.76 MHz on a Bruker AM-500 spectrometer for CDCl$_3$ solutions. Cross-polarization magic angle spinning (CP/MAS) solid-state $^{13}$C NMR spectra were recorded at 75.5 MHz on a Bruker MSL-300 instrument. Powder samples were spun at 10.0–10.5 kHz in a 4 mm ZrO$_2$ rotor; a contact time of 4–5 ms, a repetition time of 6 s and spectral width of 20 kHz were used for the accumulation of 700–1200 scans. A dipolar dephasing pulse sequence, with a 50 µs delay time inserted before the acquisition, was used to observe selectively the non-protonated carbons. Chemical shifts were calibrated indirectly through the glycine CO signal recorded at 176.0 ppm relative to TMS.

Single crystals of **4** suitable for x-ray analysis were grown from ethanol by slow evaporation. The data were collected on a KM4 KUMA diffractometer,[5] with graphite monochromated Cu Kα radiation. The θ–2θ scan technique and a variable scan speed range from 1.2 to 18.0 ° min$^{-1}$ depending on the reflection intensity were applied. Intensity data were corrected for the Lorenz and polarization effects.[5] The structure was solved using the direct method with the SHELXS86 program[6] and refined by the full-matrix least-squares method with SHELXL93[7] on $F^2$. The function $\sum w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma(F_o)^2 + (0.0882P)^2 + 0.49P]$, where $P = (F_o{}^2 + 2F_c{}^2)/3$. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed

in the calculated positions and refined as a 'riding model,' i.e. they were restrained to move together with their carrier atoms in order to maintain the starting geometry. The isotropic thermal parameters of the hydrogen atoms were set at 1.2 (1.5 for the methyl group) times $U_{eq}$ of the bonded atom. Only for the hydrogen atom involved in the hydrogen bonding were the positional and thermal parameters refined. The empirical extinction correction was also applied according to the equation[7] $F_c' = kF_c[1 + (0.001\chi F_c{}^2 \lambda^3/\sin 2\theta)]^{-1/4}$ and the extinction coefficient $\chi$ was equal to 0.0037 (8).

Crystal data and structure refinement for **4** are given in Table 1.

All positional, geometric and thermal parameters are deposited at the Cambridge Crystallographic Data Centre (CCDC Identification Number 135010). Semi-empirical calculations were performed with the PM3 method implemented in the HyperChem 5.01 package.[8]
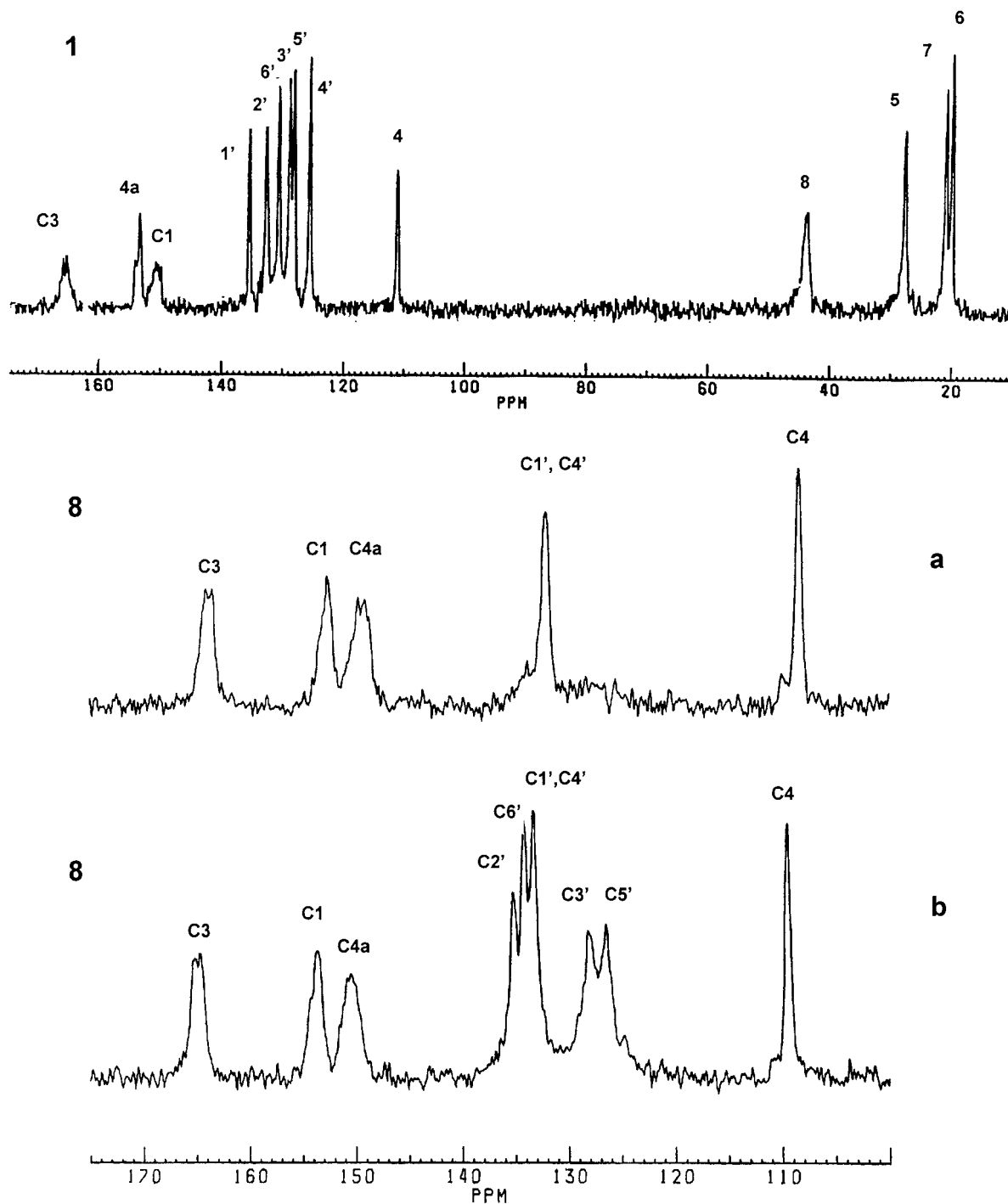
## RESULTS AND DISCUSSION

### $^{13}$C NMR

The results of $^{13}$C NMR measurements on solid compounds **1**–**8** are reported in Table 2 and illustrated in Fig. 2. The majority of the $^{13}$C resonances in the spectra of solids could be assigned directly by comparison with the solution data. The dipolar dephasing pulse sequence was used to eliminate the signals of protonated carbons. By comparing the $^{13}$C CP/MAS NMR spectrum measured with the standard pulse sequence [Fig. 2, **8**(b)] and the quaternary carbons spectrum obtained from the dipolar dephased experiment [Fig. 2, **8**(a)], it was possible to assign the resonances of C1′ and C4′. The signals of the carbons bound to nitrogen (C8, C4a, C1=O, C3=O) are broader and/or split into asymmetric doublets owing to the residual $^{13}$C–$^{14}$N coupling. The number of resonances does not exceed the number of carbons in the spectra of **1**–**5**. However, in the spectrum of **6** most of the resonances appear as doublets, indicating that there are two molecules in the asymmetric crystal unit. The interpretation of the solid-state structure of **6** is not straightforward in the absence of x-ray diffraction (XRD) data and attempts to grow suitable single crystals are in progress.

Considering the structure of solid **1**–**8** three problems are worth discussing: (i) the conformation of the saturated ring, (ii) the orientation of the aryl substituent and (iii) the intermolecular hydrogen bonding pattern involving NH and C=O groups.

For structural analysis the differences between the liquid and the solid state are interesting ($\Delta\delta = \delta_{solution} - \delta_{solid}$). The widely varying values of $\Delta\delta$ ($-2.8$ to $+3.3$ ppm) for carbons C5–C8 indicate that the conformation of the saturated fragment of the ring is not the same in solid and in solution. However, neither

**Table 2.** $^{13}$C NMR chemical shifts for compounds **1–8** in the solid state and solution (in parentheses) at room temperature

| Compound No. | C1 | C3 | C4 | C4a | C5 | C6 | C7 | C8 | C1' | C2' | C3' | C4' | C5' | C6' | R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 153.0 | 164.9 | 110.9 | 150.5 | 27.7 | 19.9 | 20.9 | 43.6 | 135.2 | 132.4 | 128.7 | 125.3 | 128.0 | 130.4 | — |
| (R = H) | (152.09) | (162.10) | (113.03) | (150.95) | (26.80) | (18.49) | (21.45) | (41.86) | (132.51) | (128.56) | (130.68) | (127.90) | (130.68) | (128.56) | — |
| **2** | 156.0 | 164.8 | 111.9 | 149.6 | 24.9 | 17.7 | 21.7 | 39.3 | 133.1 | 140.8 | 132.3 | 128.6 | 123.6 | 128.6 | 20.1 |
| (R = 2'-Me) | (151.92) | (161.73) | (112.36) | (151.32) | (26.57) | (18.48) | (21.52) | (42.60) | (132.09) | (137.73) | (130.71) | (128.35) | (126.14) | (130.30) | (19.63) |
| **3** | 152.9 | 165.0 | 112.3 | 150.4 | 28.1 | 17.1 | 21.1 | 44.6 | 135.3 | 130.8 | 140.0 | 130.0 | 133.8 | 127.1 | 21.1 |
| (R = 3'-Me) | (151.90) | (162.29) | (113.11) | (151.10) | (26.74) | (18.45) | (21.40) | (41.81) | (132.40) | (128.59) | (138.06) | (128.36) | (131.24) | (127.60) | (21.40) |
| **4** | 152.8 | 164.5 | 109.9 | 150.5 | 27.5 | 19.2 | 21.2 | 43.7 | 131.7 | 129.0 | 131.7 | 135.3 | 131.7 | 128.0 | 21.2 |
| (R = 4'-Me) | (151.90) | (162.26) | (112.92) | (150.99) | (26.77) | (18.49) | (21.45) | (41.84) | (129.44) | (129.28) | (130.37) | (137.63) | (130.37) | (129.28) | (21.26) |
| **5** | 154.0 | 164.9 | 109.9 | 150.6 | 27.6 | 19.0 | 21.1 | 43.9 | 133.8 | 134.5 | 113.9 | 161.8 | 115.0 | 131.1 | — |
| (R = 4'-F) | (152.34) | (161.88) | (111.98) | (150.68) | (26.85) | (18.48) | (21.43) | (41.95) | (128.40) | (132.43) | (115.68) | (162.38) | (115.68) | (132.43) | — |
| **6** | 155.5 | 166.5 | 111.6 | 150.5 | 26.9 | 17.8 | 20.8 | 41.3 | 125.9 | 133.0 | 115.7 | 159.7 | 110.5 | 132.3 | 57.3 |
|  |  | 165.8 |  |  | 24.9 |  |  | 38.9 | 125.5 | 132.3 | 114.8 |  | 109.5 | 131.4 | 56.8 |
| (R = 4'-OMe) | (152.06) | (162.18) | (112.61) | (150.82) | (26.83) | (18.55) | (21.49) | (41.91) | (124.55) | (131.80) | (114.13) | (159.27) | (114.3) | (131.80) | (55.30) |
| **7** | 152.7 | 163.5 | 109.2 | 150.5 | 27.4 | 19.0 | 21.5 | 43.7 | 134.2 | 130.5 | 127.1 | 127.1 | 127.1 | 132.8 | — |
| (R = 2'-Cl) | (152.89) | (161.43) | (110.62) | (151.17) | (26.50) | (18.31) | (21.50) | (42.19) | (135.08) | (131.62) | (129.71) | (129.75) | (127.15) | (132.58) | — |
| **8** | 153.5 | 164.5 | 109.5 | 150.3 | 28.0 | 19.3 | 21.5 | 43.9 | 133.2 | 135.1 | 128.1 | 133.2 | 126.4 | 134.1 | — |
| (R = 4'-Cl) | (152.37) | (161.79) | (111.84) | (150.70) | (26.83) | (18.44) | (21.40) | (41.94) | (130.90) | (132.09) | (128.86) | (134.00) | (128.86) | (132.09) | — |

**Figure 2.** $^{13}C$ CP/MAS NMR spectra of solid **1** and **8** [**8**(a) dipolar diphase experiment: **8**(b) standard experiment]

the size of the effect nor the directions of the shielding changes show any regularity. The highest values of $\Delta\delta$ are observed for C8, although considerable changes and/or structural disorder were expected for C6 and C7, which have the most conformational freedom. The aryl substituent at C4 cannot be coplanar with the pyrido-[1,2-c]pyrimidine-1,3-dione system for steric reasons (as established by XRD, the twist angle of aromatic ring is 113.6°; Table 3). The twisting of the two π-systems

reduced the conjugation and the electronic effects of the substituents are transmitted less efficiently. In solution there is only one resonance for each pair of aromatic carbons, *ortho* and *meta*, because of rapid rotation around the C4—C1′ bond. In the solid-state spectra, separate signals for C2′ and C6′ appear, as in those of **1** and **8** (Fig. 2). The locked orientation of aryl substituent results in the deshielding of C1′ (1.0–5.4 ppm) and an increase in the shielding of C4 and C4a (0.1–3.0 ppm) in all compounds.

**Table 3.** Selected bond lengths, bond angles, torsion angles and hydrogen bonding parameters for **4**

| Bond lengths (Å) | | Torsion angles (°) | |
|---|---|---|---|
| N2—C1 | 1.364(3) | C4a—C4—C1′—C6′ | 113.6(3) |
| N2—C3 | 1.377(3) | O11—C3—C4—C4a | −176.2(3) |
| C3—C4 | 1.433(3) | O11—C3—C4—C1′ | 2.7(4) |
| C4—C4a | 1.363(3) | N2—C3—C4—C4a | 4.1(3) |
| C4a—N9 | 1.387(3) | C5—C4a—N9—C1 | 177.3(2) |
| C4a—C5 | 1.504(3) | C4—C4a—N9—C8 | 171.5(3) |
| C1 = O10 | 1.221(3) | C5—C4a—N9—C8 | −9.2(4) |
| C3 = O11 | 1.238(3) | O10—C1—N9—C8 | 9.1(4) |
| N9—C1 | 1.379(3) | C4a—C4—C1′—C2′ | −67.9(3) |
| N9—C8 | 1.483(3) | | |
| C8—C7B | 1.45(1) | Hydrogen bonds (Å) | |
| C8—C7A | 1.492(5) | | |
| C7A—C6 | 1.456(7) | N2 · · ·O11[a] | 2.797(3) |
| C6—C5 | 1.477(4) | H· · ·O11[a] | 1.91(3) |
| | | N2—H | 0.89(3) |
| | | N2—H· · ·O11[a] | 172(3) |

| Valence angles (°) | | Short contacts (Å) | |
|---|---|---|---|
| C1—N2—C3 | 126.1(2) | C8· · ·O10[b] | 3.182(3) |
| C1—N2—H | 116(2) | C7A· · ·O10[b] | 3.291(5) |
| C3—N2—H | 118(2) | C7B· · ·O10[b] | 3.47(1) |
| N2—C3—C4 | 115.8(2) | | |
| C4a—C4—C3 | 119.4(2) | | |
| C4a—C4—C1′ | 123.2(2) | | |
| C3—C4—C1′ | 117.4(2) | | |
| C4—C4a—N9 | 120.9(2) | | |
| C4—C4a—C5 | 122.0(2) | | |
| C1—N9—C4a | 121.7(2) | | |
| C1—N9—C8 | 114.6(2) | | |
| C7B—C8—N9 | 112.3(5) | | |
| C7A—C8—N9 | 114.7(3) | | |
| C6—C7A—C8 | 114.0(5) | | |
| C6—C7B—C8 | 118.3(9) | | |
| C7A—C6—C5 | 111.9(4) | | |
| C2′—C1′—C4 | 121.6(2) | | |

[a] Symmetry codes 1−*x*, −*y*, 2−*z*.
[b] Symmetry codes 1−*x*, 0.5+*y*, 1.5−*z*

The deshielding of carbonyl carbons was usually observed upon formation of NH· · ·O=C hydrogen bonds. In solid peptides containing glycine a linear relationship between C=O chemical shifts and hydrogen bond lengths (known from XRD) was established.[9] The downfield shift of the C3=O and/or C1=O resonances of **1**–**8** shows that in the solid state the molecules are linked by NH· · ·O=C hydrogen bonds. The resulting $\Delta\delta$ is 2.3 –3.0 ppm for C3=O and <1 ppm for C1=O in **1, 3** –**5, 7** and **8**, whereas in **2** and **6** both signals of carbonyl groups are shifted downfield by 3–4 ppm. It is possible that in these compounds dimers with two kinds of intermolecular hydrogen bonds involving C3=O· · ·H and C1=O· · ·H can be formed. The problem was studied further by theoretical methods.

## Crystal structure analysis

The NMR spectra were recorded prior to the XRD analysis and verification of our hypothesis concerning the mode of hydrogen bonding and the twisting of the aromatic ring was necessary. A single crystal of sufficient quality was obtained for **4**, although the XRD measurements on the derivatives **2** and **6** would also be interesting. Selected bond lengths, bond angles and torsion angles for **4** (R = 4′-Me) are given in Table 3. The relatively short C4—C4a bond [insignificantly longer than a typical C(sp$^2$)—C(sp$^2$) bond length[10]] is in agreement with the bond notation given in Fig. 1. The C7 atom was found to be disordered. The occupancies of the alternative positions were refined at 0.70(2) and 0.30(2). Similar disorder was found for the respective methylene carbons in **1**,[11] **7**[4] and **9**.[12] The conformation of the piperidine ring with the C7A atom is slightly distorted from the typical sofa form ($\Delta c_s = 6.7°$), but this with the C7B atom adopts a distorted boat conformation ($\Delta c_s = 19.5°$).[13]

The C5 carbon is located approximately 2° out of the plane formed by the C3—C4—C4a atoms (the C3—
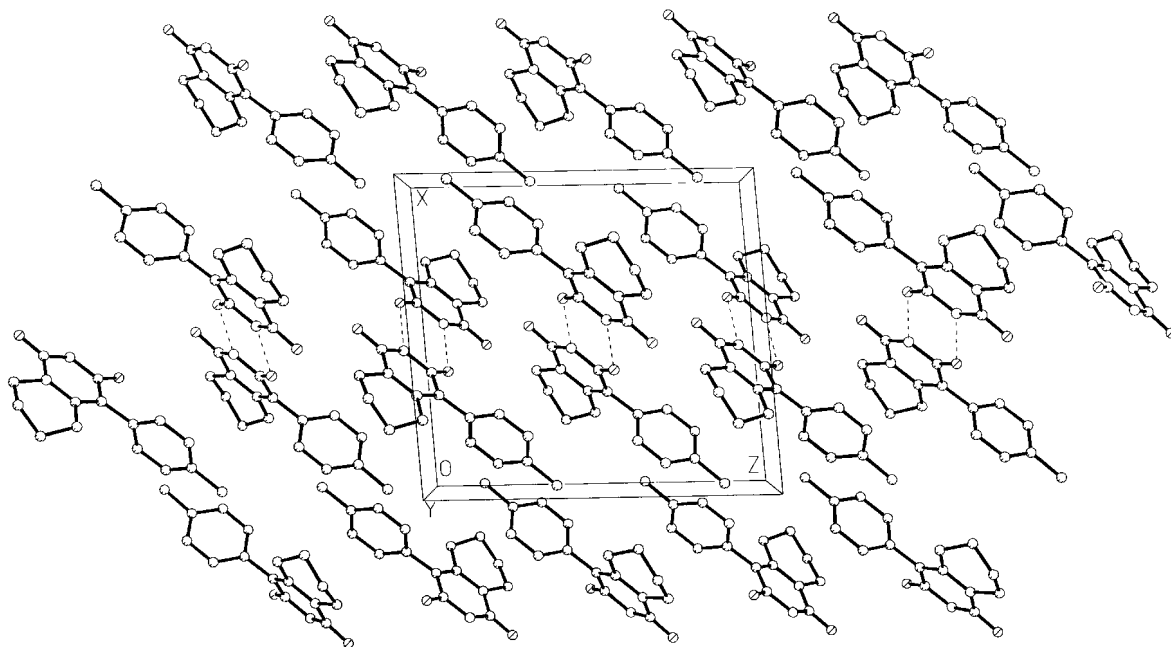
**Figure 3.** Perspective drawing of the packing arrangement of **4** along the *b*-axis with dashed lines indicating the hydrogen bonding scheme[15]

C4—C4a—C5 dihedral angle is 178.6°) and the deviation of C8 is ca 10° larger (the N2—C1—N9—C8 angle is −170.1°). The packing arrangement is shown in Fig. 3. The most interesting feature is the formation of centrosymmetric dimers by means of the intermolecular hydrogen bond C3=O···HN2 with N2···O11 distance of 2.797(3) Å in **4** (Fig. 4), and neither static non dynamic proton disorder was observed; the proton is located near the nitrogen atom. The second carbonyl group, C1=O, is involved in short intermolecular contacts with the protons HC7 and HC8 (the distances are given in Table 3).

## Semi-empirical PM3 MO calculations

Semi-empirical PM3 calculations were performed on molecules **1–8** and on the dimers discussed above. Heat of association and hydrogen bonding are reproduced by the PM3 level of theory with chemically useful accuracy for molecules with bonds involving C, H, N and O atoms.[14] Having assumed that the directions of the net charge changes had been reproduced properly within the set of molecules, the net charges were used as an aid to the signal assignment in the NMR spectra. It was also of interest to obtain more structural information on those molecules for which we have no XRD data.

In all of the calculated structures the aromatic ring is almost perpendicular to the plane of the pyrido[1,2-*c*]pyrimidine-1,3-dione fragment, which is in accordance with the x-ray data for **4**. The atomic charge at C2′ is less negative than that at C6′ and based on this the resonances at a higher frequency were assigned to C2′. The

assignment of C6 and C7 was not immediately apparent. However, the proton spectra were scrutinized,[4] leading to non-equivalent positions of the corresponding carbon signals at 17.1–19.3 and 20.7–21.7 ppm, respectively. The saturated ring adopts a slightly distorted chair conformation, but the calculated differences in energy (for particular conformers with different locations of C6
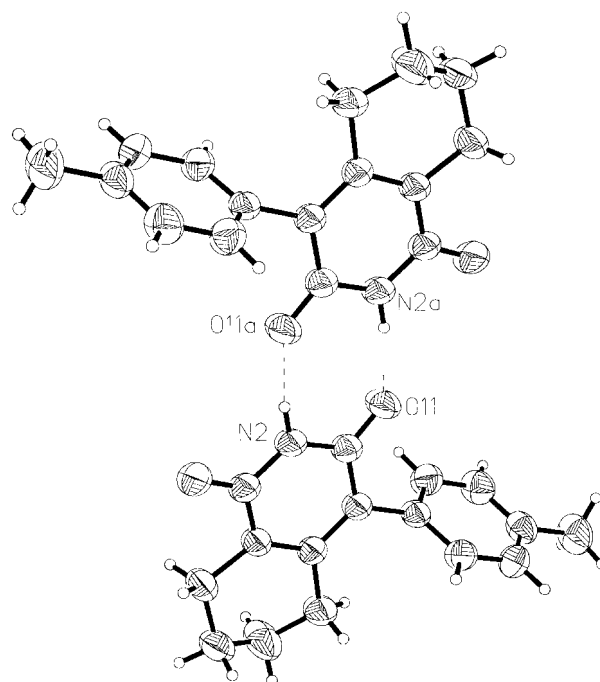


**Figure 4.** Hydrogen-bonded dimers of **4**. Displacement ellipsoids are plotted at the 50% probability level[15]

dimer 1-1



dimer 3-3



dimer 1-3
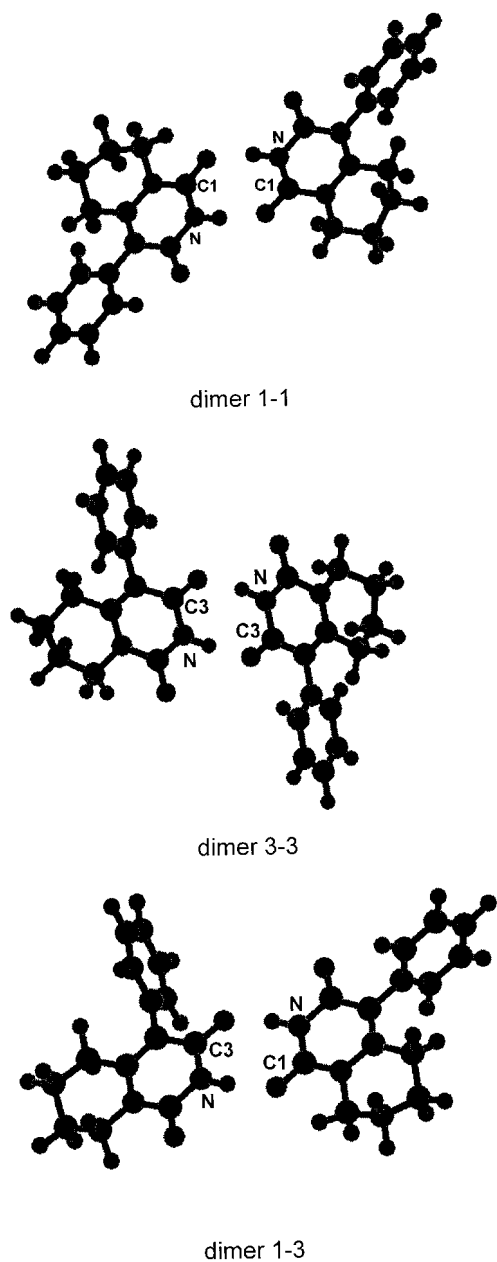
**Figure 5.** Dimeric structures with (i) two C1=O···HN bonds, (ii) two C3=O···HN bonds and (iii) 'mixed' dimer with C1=O···HN and C3=O···HN bonds as calculated by the PM3 semi-empirical method

and C7) are too small to draw reliable conclusions concerning their stability. The atomic charge at the carbonyl C1 atom is less positive (by 0.090) than that of the C3 atom, and resonances in the range 152.7–155.5 ppm are assigned to the C1 atom in the range and 163.5–165.5 ppm to the C3 atom. It is worth mentioning that according to the PM3 level of theory, the values of these charges are independent in terms of the position and nature of the R substituent, but the formation of dimers increases the positive charge at the respective atoms, i.e. those engaged in the hydrogen bonding. Taking into

**Table 4.** Differences of energy between respective dimer and two monomers

| | $\Delta E = E_{dim} - 2E_{mon}$ (kJ mol$^{-1}$) | | |
|---|---|---|---|
| Compound No. | Two C1=O | Two C3=O | C1=O, C3=O |
| **1** | −17.1 | −14.8 | −15.9 |
| **2** | −15.6 | −13.3 | −15.8 |
| **4** | −16.6 | −14.7 | −15.5 |
| **6** | −16.3 | −14.3 | −15.4 |

account the higher values of the chemical shifts of the C3 atom and the more positive net charge obtained by calculations, this carbonyl group should preferably be involved in hydrogen bonding. However, looking at the structures in Fig. 1, it is clear that three structures of dimer are possible: (i) with two NH···O=C1 bonds, (ii) with two NH···O=C3 bonds and (iii) a 'mixed' dimer with NH···O=C1 and NH···O=C3 bonds.

On the basis of the PM3 calculations we evaluated the ability of the title compounds to form these dimers. The three possible combinations of monomers (shown for **1** in Fig. 5) of compounds **1, 2, 4** and **6** were calculated to identify low-energy conformations. The starting geometries of the dimers were generated by placing two optimized monomers in the same file. The position of each monomer was chosen in such a way that the starting distances between the oxygen and the hydrogen atoms (C=O···HN) in adjacent molecules varied from 1.0 to 1.5 and 2.0 Å. Then the optimization of these files was performed. This procedure produced at the minimum of the heat of formation the dimers with two NH···O=C bonds at a distance of 1.81 Å and forming two N—H···O angles of ca 171°, which is in good agreement with x-ray data for **4**. The energy of dimers is smaller by −16 kJ mol$^{-1}$ compared with the two molecules of the monomer (Table 4). Apparently, the dimers represent a favourable structure in the solid state by means of which the molecules relieve part of their energy. All three types of dimers are theoretically possible since the $\Delta E$ values are close. However, in the 'mixed' structure the benzene rings do not form parallel planes, which seems to be less probable in the crystal. The roughly 90° orientation of the benzene plane in relation to the pyrido[1,2-*c*]pyrimidine system reduces the steric repulsion between the carbonyl C3=O and the *ortho* substituent R (or H) and for this reason the structures with two NH···O=C3 bonds also seemed probable for the compounds with *ortho* substitution.

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