Crystal structure of 4-hydroxy-2-methyl-5*H*-naphtho[1′,2′:5,6]pyrano [4,3-b]pyridin-5-one: a new heterohelicene

Viktor Kettmann* and Jan Světlík

Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University, Bratislava SK-83 232, Slovakia

X-ray analysis of the title compound reveals that the molecule relieves steric strain in the fjord region by small adjustments of some bonding parameters rather than any remarkable helical twist. The results show that a (C–)H···N contact shorter than the van der Waals radii of the H and N atoms is an energetically favourable interaction.

Keywords: crystal structure, helicene, fused naphthalenes, pyrans, pyridines, hydrogen bonds

Although the molecular spiral staircase motif is well known, molecules with helical conformation are still the focus of considerable attention in both chemical and biological communities.[1] Over the last few years, [6]- and [7]helicenes have been of particular interest due to their unique optical, electronic and material properties.[2,3] In contrast, less attention has been devoted to lower homologues. Of the latter compounds, mainly those which show tumorigenicity and contain the so-called fjord region (contained in ortho-fused tricyclic or tetracyclic aromatic systems) have been investigated to some extent with respect to metabolism (diol epoxidation), mode of action, molecular structure and carcinogenicity. Relatively clear interrelationships can be found among the metabolic activation, nonplanarity (helicity), site of DNA binding and carcinogenic potency of both the parent compounds and their metabolites. For instance, while benzo[c]phenanthrene 1 is only a weak carcinogen[4] and shows substantial helicity[5] due to its highly congested fjord region, its diol epoxide metabolite is one of the most tumorigenic agents synthesised to date; it selectively alkylates the N(6)-amino group of deoxyadenosine residues in the major groove[6,7] and the carcinogen-modified DNA is known to be unavailable for recognition by the repair enzymes in the cell.[8] On the other hand, the planar polycyclic aromatic hydrocarbons with sterically unhindered fjord region (such as benzo[a]pyrene, chrysene, and benzo[a]anthracene) are known to be potent carcinogens[9,10] due to DNA intercalative binding, but their metabolites show reduced carcinogenicity as they preferentially alkylate the N(2) nitrogen of deoxyguanosine residues in the minor groove to form DNA adducts which are readily susceptible to the repair machinery.[5,8,11]

Similar studies are not available for corresponding homologues containing one or two hetero (nitrogen) atom(s) in the fjord region. It has been reported only that a series of benzoquinolines possess significant carcinogenic potency in newborn mice and rats.[12] Also, the X-ray structure of the tetracyclic diaza-analogue quino[7,8-*h*]quinoline (**3**) has been determined and surprisingly it was found to be exactly planar in the limits of experimental error.[13] To extend our knowledge on this type of compound, we recently reported a simple synthesis of the title compound (**4**), containing an ortho-fused tetracyclic system.[14] To the best of our knowledge, crystallographic data on molecules of this type and the closely related monoaza-analogue, naphtho[2,1-*h*]quinoline (**2**), are not available in the literature. We now report on the single-crystal X-ray structure of **4**.

An ORTEP-II[15] view of the molecule of **4,** along with the atom-numbering scheme, is shown in Fig. 2. As can be seen in Fig. 1, the present compound is directly comparable with its tricyclic analogue **5**, described previously.[16] The comparison has shown that the bond lengths and angles in the A and B rings of the two structures are identical within experimental error, *i.e.* the hetero (A) ring exists in a 4-hydroxy tautomeric form and is stabilised by an intramolecular hydrogen bond acting between the O(4)–H hydroxyl and O(5) carbonyl atom [H···O = 1.75(3), O···O = 2.617(2) Å]. In contrast, significant differences occur in the dimensions of the C ring and these are discussed below.

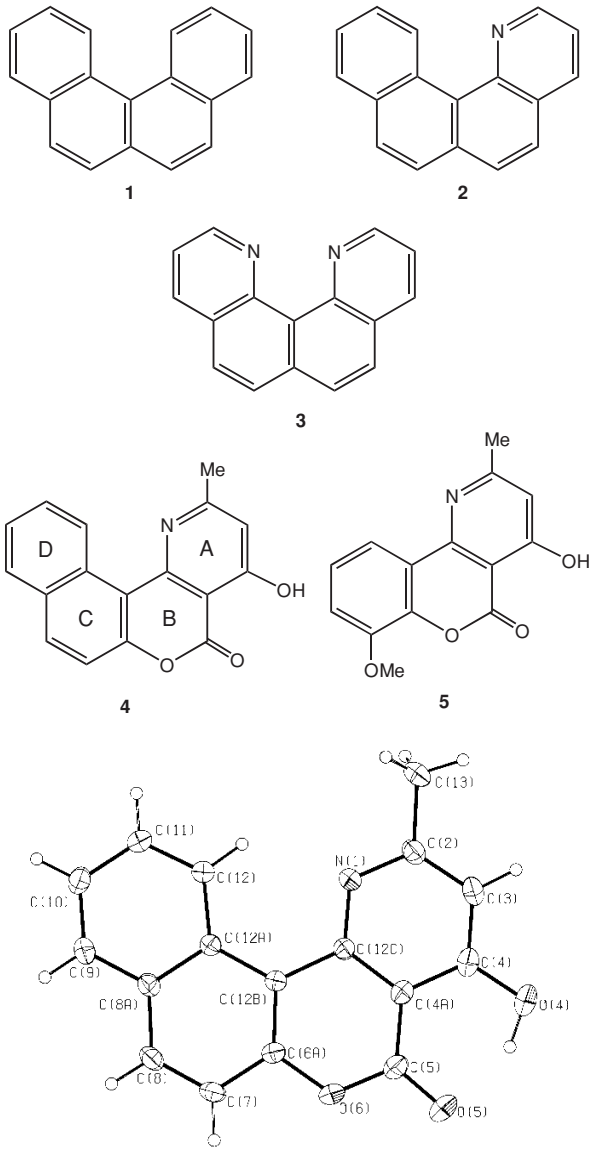

Fig. 1 A perspective view of the molecule of **4** showing the atom labelling.
Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small circles of arbitrary radii.

* Correspondent. E-mail: kettmann@fpharm.uniba.sk

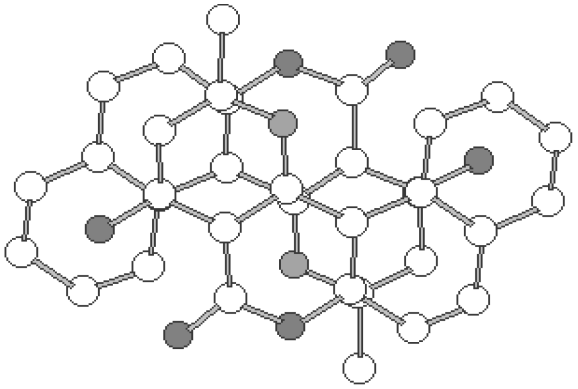

Fig. 2 An overlapping diagram of two neighbouring molecules in the stack as viewed along the stacking axis

As noted above, the main purpose of this work was to assess the possible helicity in the present molecule **4**. This parameter is quantitatively measured by a dihedral angle between the outermost (A/D) rings; calculation of the least-squares planes has shown that these rings are planar to within experimental error [r.m.s. deviations 0.002(1) and 0.004(1) Å for rings A and D, respectively] and make an angle of 4.9(1)° to each other. Thus, although the title compound **4** is, according to the chemical structure, halfway intermediate between the limiting structures **1** and **3**, its helicity is much closer to the planar compound **3**[13] rather than the propeller-like nonplanar geometry of **1** (helicity 26.7°).[5] The small distortion from planarity of molecule **4** originates from twisting around the C(12A)–C(12B) bond with an exocyclic C(12)–C(12A)–C(12B)–C(12C) torsion angle of 4.0(2)°.

It is of particular interest to examine the way in which the molecule **4** relieves the steric strain introduced into the fjord region by the additional (D) aromatic ring, *viz.* by short C(12)H···N1 contact. This contact is 2.22(3) Å long in the relaxed molecule observed in the crystal structure which is more than 0.5 Å shorter than the sum of the van der Waals radii of the H and N atoms[17] and supports the view that (C–)H···N contacts shorter than the sum of the van der Waals radii can be regarded as weak hydrogen-bonding interactions.[18] Furthermore, inspection of the bond lengths and angles in the fjord region of **4** and comparing them with the corresponding parameters in **5** have revealed that the overcrowding molecule relieves the (C–)H···N contact by (i) increasing the exocyclic bond angles at the C(12A) and C(12B) atoms by 4–6° relative to the value of 120° while the valence angle at the C(12C) atom remains at the trigonal value and (ii) lengthening of the C(12A)–C(12B) bond distance from 1.405(3) Å observed in **5** to 1.450(2) Å in **4**; however, such a large decrease in the bond order of one bond in the C ring is balanced by concomitant shortening of the remaining bonds of the ring so that the aromaticity in **4** remains unchanged relative to the unhindered molecule **5**. This also imply that the mode of distortion of the molecules **1** and **4**, in order to relieve the steric hindrance in the fjord region, are quite different and again points to the existence of an attractive (C–)H···N interaction.

The crystal packing is dominated by stacks of parallel molecules related by centres of symmetry at (0,0,½) and (½,0,½). The mean interplanar spacing is 3.415(2) Å, and the shortest contact, C(2)···C(6A), is 3.360(2) Å. The molecules within the stacks are oriented in an antiparallel fashion and the stacking geometry is shown in Fig. 2. Such an overlapping pattern of the adjacent molecules along the stack is in line with the model of π–π interactions presented by Hunter and Saunders.[21] The stacks are packed by electrostatic and van der Waals interactions.

Experimental

The title compound **4** was prepared by cyclocondensation of 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic lactone), 2-hydroxy-1-naphthaldehyde and ammonium acetate, as described previously.[14] Single crystals (m.p. 240–242 °C) suitable for an X-ray analysis were prepared by recrystallisation from dimethylformamide .

Crystal data: $C_{17}H_{11}NO_3$, M = 277.27, triclinic, a = 7.436(2), b = 9.674(3), c = 10.237(4) Å, α = 108.34(4), β = 97.21(3), γ = 111.92(4) °, V = 623.3(4) Å^{-3}, space group P-1, Z = 2, D_c = 1.477 g cm^{-3}, μ(Mo–Kα) = 0.103 cm^{-1}, 5° < 2θ < 60°.

Structure analysis: Diffraction intensities were measured at ambient temperature (*ca* 25 °C) on a Siemens P4 diffractometer using graphite-monochromated Mo-Kα radiation and corrected for Lorentz and polarisation effects. The 3525 independent reflections, of which 2448 had $I > 2\sigma(I)$, were used for structure solution and refinement. The structure was solved by direct methods[19] and refined by least squares[20] using isotropic and anisotropic displacement parameters for the hydrogen and non-hydrogen atoms respectively. The weighted R-index wR_2 (based on F^2 and all 3525 reflections) converged to 0.157 while the final value of the conventional R-factor R_1 (based on F and including only the 2448 'observed' reflections) was 0.050. Details of the crystal sructure are obtainable from a cif file by application to the corresponding author.

This work was supported by the Grant Agency of the Slovak Republic (Project Nos. 1/1167/04 and 1/1196/04).

Received 28 July 2004; accepted 16 December 2004
Paper 04/2686

References

1 C. Schmuck, *Angew. Chem. Int. Ed. Engl.*, 2003, **42**, 2448.
2 K. Paruch, L. Vyklicky, D.Z. Wang, T.J. Katz, C. Incarvito, L. Zakharov and A.L. Rheingold, *J. Org. Chem.*, 2003, **68**, 8539.
3 J.E. Field, T.J. Hill and D. Venkataraman, *J. Org. Chem.*, 2003, **68**, 6071.
4 H.J. Einolf, S. Amin, H. Yagi, D.M. Jerina and W.M. Baird, *Carcinogenesis*, 1996, **17**, 2237.
5 M.K. Lakshman, P.L. Kole, S. Chaturvedi, J.H. Saugier, H.J.C. Yeh, J.P. Glusker, H.L. Carrell, A.K. Katz, C.E. Afshar, W.M. Dashwood, G. Kanniston and W.M. Baird, *J. Am. Chem. Soc.* 2000, **122**, 12629.
6 A. Dipple, in *DNA Adducts: Identification and Biological Significance,* eds. K. Hemminki, A. Dipple, D.E.G. Shuker, F.F. Kadlubar, D. Sagerbäck and H. Bartsch, International Agency for Research on Cancer, Lyon, 1994, pp. 107 - 129.
7 A. Dipple, M.A. Pigott, S.K. Agarwal, H. Yagi, J.M. Sayer and D.M. Jerina, *Nature*, 1987, **327**, 535.
8 C.H. Lin, X.W. Huang, A. Kolbanovskii, B.E. Hingerty, S. Amin, S. Broyde, N.E. Geacintov and D.J. Patel, *J. Mol. Biol.*, 2001, **306**, 1059.
9 *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure-Activity Relationships*, eds. S.G. Yang nad B.D. Silverman, CRS Press, Boca Raton, FL, 1988, Vols. I and II.
10 S.S. Hecht, *Environ. Mol. Mutagen.*, 2002, **39**, 119.
11 I.L. Karle, H. Yagi, J.M. Sayer and D.M. Jerina, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 1433.
12 E.J. LaVoie, S. Dolan, P. Little, C.X. Wang, S. Sugie and A. Rivenson, *Food Chem. Toxicol.*, 1988, **26**, 625.
13 C. Krieger, I. Newsom, M.A. Zirnstein and H.A. Staab, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 84.
14 J. Světlík, N. Pronayova and V. Hanuš, *J. Heterocycl. Chem.*, 2000, **37**, 395.
15 C.K. Johnson, ORTEPII, Program for Drawing Thermal Ellipsoids of Crystal Structures, Oak Ridge National Laboratory, Tennessee, USA, 1976.
16 V. Kettmann, J. Světlík and C. Kratky, *Acta Crystallogr.*, 2001, **C57**, 590.
17 A. Bondi, *J. Phys.Chem.* 1964, **68**, 441.
18 R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, 1982, **104**, 5063.
19 G.M. Sheldrick, *Acta Crystallogr.*, 1990, **A46,** 467.
20 G.M. Sheldrick, SHELXL97, Program for Crystal Structure Refinement, University of Göttingen, 1997.
21 C.A. Hunter and J.K.M. Saunders, *J. Am. Chem. Soc.*, 1990, **112**, 5525.