Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

4-Hydroxy-7-methoxy-2-methyl-5*H*-1-benzopyrano[4,3-*b*]pyridin-5-one

Viktor Kettmann,[a]* Jan Světlík[a] and Christoph Kratky[b]

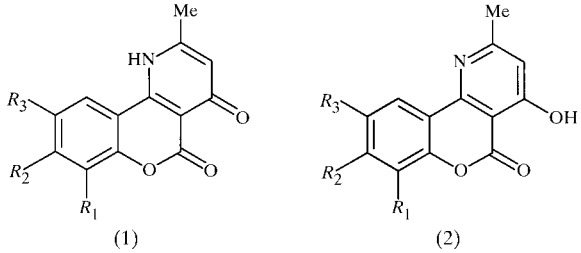
[a]Faculty of Pharmacy, Comenius University, Odbojarov 10, Bratislava 83232, Slovak Republic, and [b]Institut für Physikalische Chemie, Karl-Franzens-Universität Graz, Heinrichstrasse 28, Graz, A-8010, Austria
Correspondence e-mail: kettmann@fpharm.uniba.sk

Received 29 September 2000
Accepted 2 February 2001

The title compound, $C_{14}H_{11}NO_4$, consists of a methoxy-substituted coumarin skeleton fused to a 2-methyl-4-pyridone ring. The ring system of the molecule is approximately planar and the methoxy group is roughly coplanar with the ring plane. The 4-pyridone ring exists in a 4-hydroxy tautomeric form and is stabilized by an intramolecular hydrogen bond between the O—H and C=O groups. Comparison of the results with those found for other structures containing the 4-pyridone substructure reveals a substantial effect of the nature of the substituents bonded to the pyridine ring on the keto–enol tautomerism.

Comment

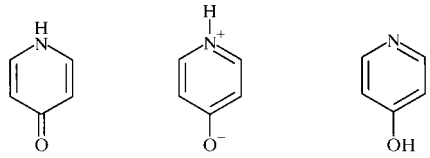
Compounds incorporating the 2*H*-pyran-2-one moiety, and especially the coumarin substructure, have attracted much attention because of their widespread occurrence in natural products (Dickinson, 1993) and their broad spectrum of biological activities (Patil *et al.*, 1993), the ability to inhibit HIV protease being one of the most important. Following



(1) (2)

(1*a*), (2*a*): $R_1 = R_2 = R_3 = H$
(1*b*), (2*b*): $R_1 = R_3 = H$; $R_2 = NEt_2$
(1*c*), (2*c*): $R_1 = R_3 = Cl$; $R_2 = H$
(1*d*), (2*d*): $R_1 = R_2 = H$; $R_3 = Br$
(1*e*), (2*e*): $R_1 = OMe$; $R_2 = R_3 = H$
(1*f*), (2*f*): $R_1 = R_2 = H$; $R_3 = NO_2$

reports (Thaisrivongs *et al.*, 1996) that 3-substituted 4-hydroxypyranones and 4-hydroxycoumarins display potent and selective HIV protease inhibitory activity, we prepared a series of 1,5-dihydro-2-methyl-4*H*-1-benzopyrano[4,3-*b*]pyridine-4,5-diones, (1) (Světlík *et al.*, 2000), as potential non-peptidic antiviral agents. As the pyridone ring in (1) is, in principle, able to exist in tautomeric forms (I) and (II), detailed structural information on these heterocycles is indispensable for an analysis of the structure–activity relationships.



(I*a*) (I*b*) (II)

To establish the structure of compounds (1), standard spectroscopic methods were first employed. In the ^{1}H NMR spectra, a relatively low-field resonance of the *peri*-proton H10 (δ_H 8.13–8.80 p.p.m.) was observed; the downfield shift, as compared with the value reported for the analogously positioned atom H5 (δ_H 7.46 p.p.m.) in unsubstituted coumarin (Brueger, 1979), is rather unusual and may be due to an anisotropy of the nearby pyridone ring (Světlík *et al.*, 2000). We were also surprised that only the unsubstituted benzopyranopyridine, (1*a*), and the 8-diethylamino analogue, (1*b*), showed two absorption bands for lactone (*ca* 1720 cm^{-1}) and pyridone (*ca* 1660 cm^{-1}) carbonyls in the IR spectra, whereas the remaining derivatives, (1*c*)–(1*f*), revealed only single peaks in the range 1683–1697 cm. To resolve this ambiguity of the spectral data and, at the same time, to determine the precise molecular structures of the compounds, we selected the title compound (1*e*), since it was the only derivative which gave good crystals suitable for single-crystal X-ray analysis.

An *ORTEP*II (Johnson, 1976) view of the molecule of (1*e*) and the atom-numbering scheme are shown in Fig. 1. The 14-atom ring system of the molecule is essentially planar [r.m.s. deviation 0.013 (2) Å], and atoms O4 and O5 are displaced by −0.035 (3) and 0.028 (3) Å, respectively, on opposite sides of the plane [out-of-plane displacements of atoms O7 and C11 are 0.031 (2) and 0.072 (4) Å, respectively]. The C atom of the methoxy group also lies approximately in the ring plane [torsion angle C8—C7—O7—C12 = 11.1 (4)°].

Bond lengths and angles (Table 1) within the 7-methoxycoumarin moiety are normal and agree with those found previously for a vast number of coumarin derivatives, as revealed by a search of the Cambridge Structural Database (CSD; Allen *et al.*, 1983). The coumarin skeleton appears to be rather insensitive to substitutional effects, except for the C4a=C10b double bond, which varies in the broad range 1.30–1.41 Å depending on the groups attached at C4a and/or C10b. This distance in (1*e*) is at the upper limit of the range [1.398 (3) Å], obviously due to the fusion of the N-heterocyclic ring.

As for the 4-pyridone ring, which is of prime interest here, the ring clearly occurs in tautomeric form (II), as evidenced by (i) the position of the acidic H atom, which was found in the $\Delta\rho$ map bonded to O4, not to the N atom, (ii) the pattern of bond orders within the pyridone ring, which are all close to 1.5, as estimated from the bond-length–bond-order curves

proposed by Burke-Laing & Laing (1976), and (iii) the C4—O4 bond distance [1.348 (3) Å], which falls in the range normally observed for a hydroxy group bonded to an aromatic carbon (Ulický *et al.*, 1987). Thus, the actual structure of the title compound is (2*e*), not (1*e*). The OH group is oriented so as to form an intramolecular hydrogen bond with the adjacent carbonyl O5 atom; the details of this O4—H···O5 hydrogen bond are: O—H 0.99, H···O 1.75 and O···O 2.634 (3) Å, and O—H···O 147°.

In order to examine the keto–enol tautomerism in the 4-pyridone system in a more general way, we searched the CSD for compounds containing this molecular fragment (in either keto or enol form) and found the following six structures: 3,5-dichloro-2,6-dimethyl-4-pyridinol [clopidol; hereinafter (3)], 2-amino-5-cyano-6-methyl-4(1*H*)-pyridone, (4), 3-hydroxy-2-methyl-4-pyridinone, (5), 2-(2-butenyl)-3,7-dihydro-3-[methoxy(hydroxy)methyl]-3-methyl-5-phenylfuro-[2,3-*b*]pyridin-4(2*H*)-one, (6), 2,3,5,6-tetrachloro-4-hydroxypyridine, (7), and ethyl 5-formyl-4-hydroxy-6-phenylpyridine-2-carboxylate, (8). The central pyridone ring in compounds (3)–(6) exists in the keto form, whereas molecules (7) and (8) have the pyridinol structure.

Comparison of the molecular dimensions in compounds (2*e*) and (3)–(8) has revealed that, while the corresponding bond lengths and angles in the 4-pyridinol fragment vary in narrow ranges, the opposite is true for molecules (3)–(6) incorporating the pyridone structure. The structural variability of the latter compounds originates from various degrees of π-electron delocalization of the lone pair on the N atom through the π system of the ring up to the carbonyl function, implying that both neutral, (I*a*), and zwitterionic, (I*b*), canonical forms contribute to the (π) electronic structure of the molecules. The extent of polarization of the π-electron cloud, and hence the relative contribution of (I*a*):(I*b*), can be estimated from the pattern of bond lengths and angles, and in particular from the endocyclic bond angle at the N atom, α, and the length of the formal C═O double bond, *d*. These two parameters gradually change from 123.0 (6)° and 1.253 (7) Å, respectively, in (3), through 122.8 (3)° and 1.255 (4) Å in (4), and 121.8 (2)° and 1.280 (2) Å in (5), to 114.0 (4)° and 1.329 (4) Å in (6), as the contribution of (I*b*) increases. It is interesting to note that for (6), in which the percentage of (I*b*) approaches 100%, the values of α and *d* are similar to those found in the 4-hydroxy tautomers, even though the H atom remains bonded to the N atom. Although the keto–enol tautomerism and the proportion of (I*a*):(I*b*) can be easily monitored by a geometry consideration, the factors (*i.e.* effects of the nature and position of the substituents) that govern these equilibria are somewhat unclear. For the present molecule, the hydroxy tautomer, (2*e*), is favoured over the keto isomer, (1*e*), on thermodynamic grounds, as shown by both molecular mechanics (MM^+ force field; ΔE_s = 18.2 kcal mol^{-1}; 1 cal = 4.1868 J) and *AM*1 quantum chemical ($\Delta\Delta H_f$ = 12.4 kcal mol^{-1}) calculations using the *HyperChem* (Hypercube, 1994) suite of programs.

As mentioned above, another purpose of this structure determination was to provide a clue for resolving the inconsistency of the spectral data from compounds (1) [or (2)]. Although the calculated ^{13}C NMR chemical shift values (*ACD CNMR Predictor*; Advanced Chemistry Development, 1996) for the critical C4 atoms, *i.e.* C═O and C—OH, are clearly different for the two tautomers (*ca* 186 *versus* 164 p.p.m.), the literature data of some simple pyridines appear not to be useful for resolving the problem. Thus, δ_C(C═O) for *N*-methyl-4-pyridone is 176.60, δ_C(C—OH) for 4-hydroxypyridine 175.70, and δ_C(C—OMe) for 4-methoxypyridine 164.90 p.p.m. (Voegeli & Philipsborn, 1973). All our products consistently showed the corresponding C4 signal at about 165–168 p.p.m. (Světlík *et al.*, 2000), demonstrating that it is somewhat difficult to distinguish between the two isomers on the basis of the ^{13}C NMR data, even though the observed values fit better those calculated for the hydroxy structure, (2). Nevertheless, in the light of the 4-hydroxypyridine structure determined here, the low-field shift of atom H10 mentioned above can be rationalized in terms of a deshielding anisotropic effect induced by the lone pair lying in-plane on the adjacent N*sp*^{2} atom. On the other hand, the observed single absorption band near 1690 cm^{-1} can be assigned to a stretching vibration of the coumarin carbonyl, the frequency of which is lowered due to intramolecular hydrogen bonding with the neighbouring hydroxy function.

As the only hydrogen-bond donor of the molecule is involved in intramolecular hydrogen bonding, the crystal packing is governed by van der Waals forces.

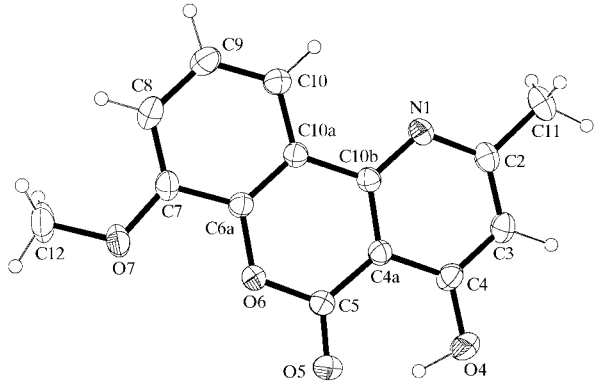


Figure 1
A view of the molecule of (2*e*) showing the atom-labelling scheme. Displacement ellipsoids are shown at the 35% probability level and H atoms are drawn as small spheres of arbitrary radii.

Experimental

The synthesis of the title product, (2*e*), was described previously by Světlík *et al.* (2000). In short, ammonium acetate (0.70 g, 9.0 mmol) was added to a solution of 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.60 g, 4.75 mmol) and 2-hydroxy-3-methoxybenzaldehyde (0.72 g, 4.75 mmol) in acetic acid (15 ml), and the mixture was refluxed for 15 h. After cooling, the crystallized product was collected by concentration of the mixture and finally crystallized from acetonitrile to afford colourless crystals of (2*e*) (0.42 g, 32% yield, m.p. 480–481 K).

Crystal data

$C_{14}H_{11}NO_4$
M_r = 257.24
Monoclinic, $P2_1/c$
a = 7.333 (3) Å
b = 9.389 (4) Å
c = 17.161 (7) Å
β = 95.05 (4)°
V = 1176.9 (8) Å^3
Z = 4
D_x = 1.452 Mg m^{-3}
D_m = 1.45 (1) Mg m^{-3}
D_m measured by flotation in bromoform/*c*-hexane
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 7–21°
μ = 0.108 mm^{-1}
T = 293 (2) K
Plate, colourless
0.35 × 0.30 × 0.10 mm

Data collection

Siemens *P*4 diffractometer
$\omega/2\theta$ scans
3692 measured reflections
2698 independent reflections
1543 reflections with $I > 2\sigma(I)$
R_{int} = 0.045
θ_{max} = 27.51°
$h = -9 \rightarrow 1$
$k = -1 \rightarrow 12$
$l = -22 \rightarrow 22$
3 standard reflections
every 97 reflections
intensity decay: 2%

Refinement

Refinement on F^2
$R(F)$ = 0.054
$wR(F^2)$ = 0.150
S = 1.022
2698 reflections
172 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1035P)^2 + 0.1985P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C10b	1.349 (3)	C4a—C5	1.445 (3)
N1—C2	1.354 (3)	C5—O5	1.220 (3)
C2—C3	1.382 (4)	C5—O6	1.365 (3)
C3—C4	1.380 (3)	O6—C6a	1.387 (3)
C4—O4	1.348 (3)	C6a—C10a	1.388 (3)
C4—C4a	1.415 (3)	C10a—C10b	1.463 (3)
C4a—C10b	1.398 (3)		
C10b—N1—C2	116.7 (2)	C10b—C4a—C4	118.2 (2)
N1—C2—C3	123.5 (2)	O6—C5—C4a	118.6 (2)
C4—C3—C2	119.9 (2)	C5—O6—C6a	120.87 (17)
C3—C4—C4a	117.9 (2)	N1—C10b—C4a	123.70 (19)
C8—C7—O7—C12	11.1 (4)		

H atoms were located from a difference Fourier map and were fixed at these positions, with U_{iso} set to 1.2 (1.5 for the methyl H atoms) times U_{eq} of the parent atom. The H—C—H angles at the methyl groups are in the range 96–126° and the C—H distances in the molecule are in the range 0.92–1.14 Å.

Data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

This work was supported by the Grant Agency of the Slovak Republic (project No. 1/5014/98).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: AV1068). Services for accessing these data are described at the back of the journal.

References

Advanced Chemistry Development (1996). *ACD CNMR Predictor*. Version 1.1. ACD, Toronto, Ontario, Canada M5H 3V9.
Allen, F. H., Kennard, O. & Taylor, R. (1983). *Acc. Chem. Res.* **16**, 146–153.
Brueger, W. (1979). *Handbook of NMR Spectral Parameters*, Vol. 1, pp. 180–185. London: Heyden.
Burke-Laing, M. & Laing, M. (1976). *Acta Cryst.* B**32**, 3216–3224.
Dickinson, J. M. (1993). *Nat. Prod. Rep.* **10**, 71–80.
Hypercube (1994). *HyperChem*. Version 4.0. Hypercube Inc., 419 Philip Street, Waterloo, Ontario, Canada N2L 3X2.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Patil, A. D., Freyer, A. J., Eggleston, D. S., Haltiwanger, R. C., Bean, M. F., Taylor, P. B., Caranfa, M. J., Breen, A. L., Bartus, H. R., Johnson, R. K., Hertzberg, R. P. & Westley, J. W. (1993). *J. Med. Chem.* **36**, 4131–4140.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1997). *SHELXL*97. University of Göttingen, Germany.
Siemens (1991). *XSCANS*. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Světlík, J., Prónayová, N. & Hanuš, V. (2000). *J. Heterocycl. Chem.* **37**, 395–399.
Thaisrivongs, S., Janakiraman, M. N., Chong, K.-T., Tomich, P. K., Dolak, L. A., Turner, S. R., Strohbach, J. W., Lynn, J. C., Horng, M.-M., Hinshaw, R. R. & Watenpaugh, K. D. (1996). *J. Med. Chem.* **39**, 2400–2410.
Ulický, L., Kettmann, V., Soldánová, J. & Betina, V. (1987). *Acta Cryst.* C**43**, 335–339.
Voegeli, U. & von Philipsborn, W. (1973). *Org. Magn. Res.* **5**, 551–559.