Software (Molecular Structure Corporation, 1988) was used for data collection and cell refinement. *TEXSAN* (Molecular Structure Corporation, 1992) was used for data reduction. The structure was solved by Patterson methods (*PATTY* in *DIRDIF*; Beurskens *et al.*, 1992) and expanded using Fourier techniques (Beurskens *et al.* 1992). H atoms were located from a difference map and fixed at ideal positions with $U_{iso} = 1.2U_{eq}$(C). All calculations were performed using *TEXSAN*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: TA1039). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Banwell, M. G., Gable, R. G., Phyland, J. R. & Peters, S. C. (1995). *J. Chem. Soc. Chem. Commun.* In the press.

Beurskens, P. T., Admiraal, G., Beurskens, G., Bosman, W. P., Garcia-Granda, S., Gould, R. O., Smits, J. M. M. & Smykalla, C. (1992). *The DIRDIF Program System.* Technical Report. Crystallography Laboratory, University of Nijmegen, The Netherlands.

Molecular Structure Corporation (1992). *MSC/AFC Diffractometer Control Software.* Version 4.3.0. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Molecular Structure Corporation (1993). *TEXSAN. Single Crystal Structure Analysis Software.* Version 1.6c. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Nicolaou, K. C., Dai, W-M. & Guy, R. K. (1994). *Angew. Chem. Int. Ed. Engl.* **33**, 15–44.

North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

Zachariasen, W. H. (1968). *Acta Cryst.* A**24**, 212–216.

Acta Cryst. (1996). C**52**, 372–375

5-Amino-8-methyl-1,2-dihydrothieno-(and furo)[2,3-*h*][1,6]naphthyridines

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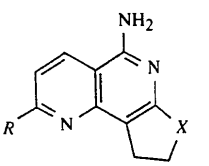
(*Received 11 August 1995; accepted 19 September 1995*)

Abstract

X-ray structure analyses of Smiles rearrangement and further cyclization products of 2-[3-cyanopropylthio-(and oxy)]pyridine-3-carbonitriles revealed the structures of 5-amino-8-methyl-1,2-dihydrothieno[2,3-*h*][1,6]-naphthyridine, $C_{11}H_{11}N_3S$, and 5-amino-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine, $C_{11}H_{11}N_3O$. The crystals of both compounds are isomorphous; monoclinic, space group $P2_1/n$. The molecules, related by a centre of symmetry, are linked through N—H···N hydrogen bonds. Common features of bond lengths and angles that characterize the thieno and furo[2,3-*h*][1,6]-naphthyridine skeletons are described.

Comment

We have found a novel method of synthesis of the thieno[2,3-*h*]naphthyridine skeleton from 2-(3-cyanopropylthio)pyridine-3-carbonitrile and its 5-methyl derivative (Sasaki, Rouf, Kashino & Hirota, 1994, 1995). Further application of the method to 2-(3-cyanopropyloxy)-6-methylpyridine-3-carbonitrile gave rise to the furo[2,3-*h*][1,6]naphthyridine skeleton (Rouf, 1995). This unique synthetic method, including Smiles rearrangement followed by cyclization, has proved useful for the syntheses of heterocyclic systems containing N, O and S atoms. 5-Amino-1,2-dihydrothieno[2,3-*h*][1,6]-naphthyridine, (I), 5-amino-8-methyl-1,2-dihydrothieno-[2,3-*h*][1,6]naphthyridine, (II) and 5-amino-8-methyl-1,2-dihydrofuro[2,3-*h*][1,6]naphthyridine, (III) showed relaxation activity against carbamylcholine chloride-induced tracheal muscular contraction (Rouf, 1995). In the present paper, the structures of (II) and (III) are reported and compared with that of (I) (Sasaki, Rouf, Kashino & Hirota, 1994).

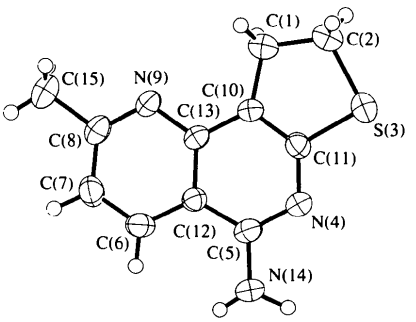


(I) R = H, X = S
(II) R = Me, X = S
(III) R = Me, X = O

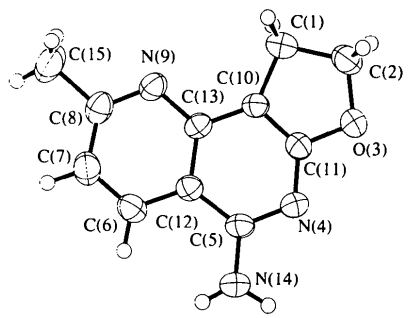
The overall ring systems of (I), (II) and (III) are planar with maximum deviation of 0.299 (4), 0.132 (4) and 0.094 (3) Å, respectively, at C(2). Among (I), (II) and (III), some differences are observed in the deviation of the amino and methyl substituents from the ring plane: the amino N(14) atom of (I) shows a significant deviation of 0.167 (4) Å from the ring plane, in contrast with those of (II) and (III) where the deviations are 0.003 (2) and 0.031 (2) Å, respectively. The methyl group in (III) is distorted by 0.106 (2) Å from the ring plane, which is larger than the deviation of 0.012 (3) Å in (II). However, shortening of the N(9)—C(8), C(6)—C(7), N(4)—C(5) and C(10)—C(11) bonds is commonly observed for the molecules of (I), (II) and (III). These molecules are also characterized by widening of the N(4)—C(11)—C(10) angle.

In the crystals of (I), (II) and (III), pairs of molecules, related by a centre of symmetry, are linked through

an N—H···N hydrogen bond to form a dimer. Each constituting molecule in the dimeric unit is linked to a neighbouring dimer through a hydrogen bond between the amino group and N(9) to form a three-dimensional hydrogen-bonded network.



(*a*)



(*b*)

Fig. 1. Displacement ellipsoid plots with atomic numbering for (*a*) (II) and (*b*) (III). Ellipsoids of 50% probability are drawn for non-H atoms; H atoms are represented as spheres equivalent to B = 1.0 Å^2.

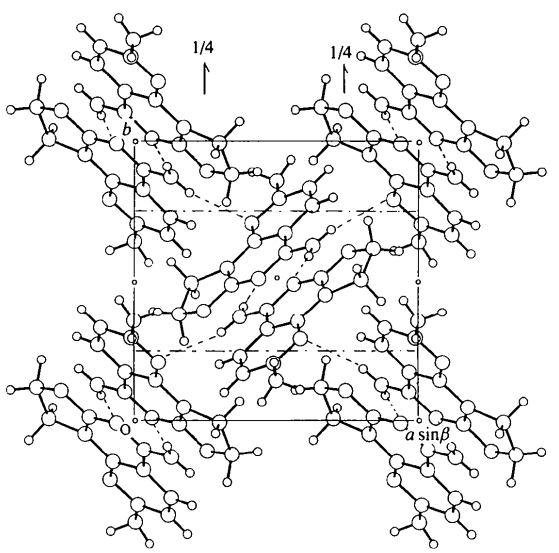


Fig. 2. The crystal packing of (III) viewed along the c axis. Hydrogen bonds are shown by broken lines. Convert a to c, and c to $-a$ to obtain the corresponding view for (II).

Experimental

Compound (II) was obtained by the synthesis method of Sasaki, Rouf, Kashino & Hirota (1994, 1995) and recrystallized from ethanol. Compound (III) was obtained by the synthesis method of Rouf (1995) and recrystallized from ethanol.

Compound (II)

Crystal data

$C_{11}H_{11}N_3S$
M_r = 217.29
Monoclinic
$P2_1/n$
a = 10.04 (1) Å
b = 9.572 (4) Å
c = 10.680 (5) Å
β = 98.16 (6)°
V = 1016 (1) Å^3
Z = 4
D_x = 1.420 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 10–11°
μ = 0.27 mm^{-1}
T = 296 K
Plate
0.45 × 0.25 × 0.15 mm
Yellow

Data collection

Rigaku AFC-5R diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2116 measured reflections
2003 independent reflections
1230 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.026
θ_{max} = 26°
h = 0 → 12
k = 0 → 11
l = −12 → 12
3 standard reflections monitored every 97 reflections
intensity decay: 1%

Refinement

Refinement on F
R = 0.038
wR = 0.031
S = 1.49
1230 reflections
181 parameters
H atoms refined
$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{max}$ = 0.11
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}
Extinction correction: $I_{corr} = I_o(1 + gI_c)$
Extinction coefficient: $g = 2.15 \times 10^{-6}$
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (II)*

$B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
S(3)	0.75225 (8)	0.14148 (9)	0.72812 (7)	4.59 (4)
N(4)	0.8248 (2)	0.0008 (2)	0.9436 (2)	3.4 (1)
N(9)	0.4503 (2)	−0.2002 (2)	0.9046 (2)	2.9 (1)
N(14)	0.9020 (3)	−0.1117 (3)	1.1276 (3)	4.8 (1)
C(1)	0.5144 (3)	0.0006 (4)	0.7091 (3)	3.9 (2)
C(2)	0.5805 (3)	0.1225 (4)	0.6497 (3)	4.3 (2)
C(5)	0.7996 (3)	−0.0896 (3)	1.0318 (2)	3.1 (1)
C(6)	0.6435 (3)	−0.2621 (3)	1.1127 (3)	3.3 (1)
C(7)	0.5205 (3)	−0.3263 (3)	1.0970 (3)	3.7 (1)
C(8)	0.4254 (3)	−0.2908 (3)	0.9917 (3)	3.3 (1)
C(10)	0.6010 (2)	−0.0373 (3)	0.8305 (2)	2.6 (1)
C(11)	0.7244 (3)	0.0237 (3)	0.8475 (2)	2.9 (1)
C(12)	0.6730 (2)	−0.1626 (3)	1.0253 (2)	2.6 (1)
C(13)	0.5724 (2)	−0.1345 (3)	0.9211 (2)	2.5 (1)
C(15)	0.2892 (4)	−0.3578 (5)	0.9739 (4)	5.0 (2)

Compound (III)

Crystal data

$C_{11}H_{11}N_3O$
$M_r = 201.23$
Monoclinic
$P2_1/n$
$a = 9.975$ (5) Å
$b = 9.695$ (5) Å
$c = 10.145$ (9) Å
$\beta = 97.92$ (6)°
$V = 972$ (2) Å^3
$Z = 4$
$D_x = 1.375$ Mg m^{-3}

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 25 reflections
$\theta = 10.5$–11°
$\mu = 0.09$ mm^{-1}
$T = 297$ K
Prismatic
0.52 × 0.40 × 0.25 mm
Brown

Data collection

Rigaku AFC-5*R* diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2014 measured reflections
1922 independent reflections
1345 observed reflections [$I > 3\sigma(I)$]

$R_{int} = 0.009$
$\theta_{max} = 26°$
$h = 0 \rightarrow 12$
$k = 0 \rightarrow 10$
$l = -12 \rightarrow 12$
3 standard reflections monitored every 97 reflections
intensity decay: 1%

Refinement

Refinement on F
$R = 0.038$
$wR = 0.036$
$S = 1.87$
1345 reflections
181 parameters
H atoms refined
$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{max} = 0.17$

$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.12$ e Å^{-3}
Extinction correction: $I_{corr} = I_o(1 + gI_c)$
Extinction coefficient: $g = 5.93 \times 10^{-6}$
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (III)*

$$B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
O(3)	1.2550 (1)	−0.1069 (1)	0.2556 (1)	4.38 (6)
N(4)	1.0621 (1)	0.0099 (2)	0.1690 (1)	3.57 (7)
N(9)	1.0862 (1)	0.2075 (2)	0.5412 (1)	3.45 (7)
N(14)	0.8715 (2)	0.1281 (2)	0.0854 (2)	4.57 (9)
C(1)	1.2990 (2)	−0.0067 (2)	0.4751 (2)	4.1 (1)
C(2)	1.3413 (2)	−0.1188 (2)	0.3833 (2)	4.2 (1)
C(5)	0.9676 (2)	0.1026 (2)	0.1898 (2)	3.21 (8)
C(6)	0.8729 (2)	0.2716 (2)	0.3402 (2)	3.74 (9)
C(7)	0.8829 (2)	0.3318 (2)	0.4627 (2)	4.2 (1)
C(8)	0.9902 (2)	0.2958 (2)	0.5617 (2)	3.77 (9)
C(10)	1.1732 (2)	0.0473 (2)	0.3941 (2)	2.95 (7)
C(11)	1.1579 (2)	−0.0120 (2)	0.2727 (2)	3.17 (8)
C(12)	0.9691 (2)	0.1728 (2)	0.3151 (2)	2.93 (7)
C(13)	1.0759 (2)	0.1445 (2)	0.4194 (2)	2.84 (7)
C(15)	0.9992 (3)	0.3570 (4)	0.6991 (3)	5.7 (1)

Table 3. *Bond lengths (Å) and angles (°) for (II) and (III)*

	(II) (X = S)	(III) (X = O)
X(3)—C(2)	1.816 (4)	1.458 (3)
S(3)—C(11)	1.754 (3)	1.364 (2)
N(4)—C(5)	1.330 (3)	1.340 (2)
N(4)—C(11)	1.351 (3)	1.338 (2)
N(9)—C(8)	1.321 (3)	1.323 (2)
N(9)—C(13)	1.367 (3)	1.369 (2)
N(14)—C(5)	1.360 (3)	1.350 (3)
C(1)—C(2)	1.525 (4)	1.528 (3)
C(1)—C(10)	1.500 (4)	1.497 (3)
C(5)—C(12)	1.443 (3)	1.440 (3)
C(6)—C(7)	1.369 (4)	1.364 (3)
C(6)—C(12)	1.394 (3)	1.404 (3)
C(7)—C(8)	1.410 (4)	1.407 (3)
C(8)—C(15)	1.499 (4)	1.506 (3)
C(10)—C(11)	1.358 (3)	1.348 (3)
C(10)—C(13)	1.402 (3)	1.401 (2)
C(12)—C(13)	1.419 (3)	1.421 (2)
C(2)—X(3)—C(11)	91.8 (1)	106.4 (1)
C(5)—N(4)—C(11)	116.6 (2)	115.1 (2)
C(8)—N(9)—C(13)	117.8 (2)	117.7 (2)
C(2)—C(1)—C(10)	108.1 (3)	101.3 (2)
X(3)—C(2)—C(1)	109.0 (2)	107.8 (2)
N(4)—C(5)—N(14)	115.7 (3)	116.0 (2)
N(4)—C(5)—C(12)	122.4 (2)	122.3 (2)
C(7)—C(6)—C(12)	120.0 (3)	119.4 (2)
C(6)—C(7)—C(8)	119.1 (3)	119.8 (2)
N(9)—C(8)—C(7)	123.1 (3)	123.0 (2)
N(9)—C(8)—C(15)	116.9 (3)	116.7 (2)
C(1)—C(10)—C(11)	114.7 (3)	109.4 (2)
C(1)—C(10)—C(13)	127.4 (2)	133.2 (2)
C(11)—C(10)—C(13)	117.7 (2)	117.4 (2)
X(3)—C(11)—N(4)	118.6 (2)	116.7 (2)
X(3)—C(11)—C(10)	114.5 (2)	114.3 (2)
N(4)—C(11)—C(10)	126.9 (2)	129.0 (2)
N(9)—C(13)—C(12)	122.7 (2)	122.8 (2)
C(10)—C(13)—C(12)	118.4 (2)	117.4 (2)
C(5)—C(12)—C(6)	124.6 (2)	124.0 (2)
C(5)—C(12)—C(13)	118.0 (2)	118.8 (2)
C(6)—C(12)—C(13)	117.3 (2)	117.2 (2)
C(7)—C(8)—C(15)	120.0 (3)	120.4 (2)

Table 4. *Geometry of hydrogen bonds (Å, °)*

D	A	$D\cdots A$	H$\cdots A$	D—H$\cdots A$
(II)				
N(14^{i})	N(4)	3.135 (4)	2.17 (3)	153 (2)
N(14^{ii})	N(9)	3.438 (4)	2.65 (3)	154 (1)
(III)				
N(14^{iii})	N(4)	3.060 (3)	2.17 (2)	174 (2)
N(14^{iv})	N(9)	3.238 (3)	2.43 (2)	167.8 (7)
(I)				
N(14^{v})	N(4)	3.051 (5)	2.08 (4)	179 (4)
N(14^{vi})	N(9)	3.043 (5)	2.21 (4)	163 (5)

Symmetry codes: (i) $2-x, -y, 2-z$; (ii) $x-\frac{1}{2}, -y-\frac{1}{2}, z-\frac{1}{2}$; (iii) $2-x, -y, -z$; (iv) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; (v) $-x, 1-y, 1-z$; (vi) $x, \frac{1}{2}-y, z-\frac{1}{2}$.

Structure refinement was carried out at the X-ray Laboratory of Okayama University

For both compounds, data collection: *RASA*II (Rigaku Corporation, 1990); cell refinement: *RASA*II; data reduction: *TEXSAN* (Molecular Structure Corporation, 1985); program(s) used to solve structures: *MITHRIL* (Gilmore, 1984); program(s) used to refine structures: *TEXSAN*; molecular graphics: *ORTEP*II (Johnson, 1976).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AS1216). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Gilmore, C. J. (1984). *J. Appl. Cryst.* **17**, 42–46.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Molecular Structure Corporation (1985). *TEXSAN. TEXRAY Structure Analysis Package*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Rigaku Corporation (1990). *RASAII. X-ray Data Collection Package*. Rigaku Corporation, Tokyo, Japan.
Rouf, A. S. (1995). Doctoral thesis, The Graduate School of Natural Science and Technology, Okayama University, Japan.
Sasaki, K., Rouf, A. S., Kashino, S. & Hirota, T. (1994). *J. Chem. Soc. Chem. Commun.* pp. 1767–1768.
Sasaki, K., Rouf, A. S., Kashino, S. & Hirota, T. (1995). *Heterocycles*, **41**, 1307–1318.

Acta Cryst. (1996). C**52**, 375–377

2-Bromoacetoxybenzoic Acid, a Brominated Aspirin Analog

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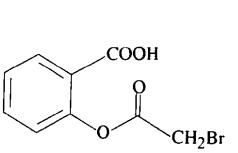
(*Received 9 January 1995; accepted 25 July 1995*)

Abstract

The crystal structure of 2-bromoacetoxybenzoic acid, $C_9H_7BrO_4$, shows it to be a close structural analog of aspirin. The carboxylic acid moiety is twisted by 7.7 (4)° out of the plane of the aromatic ring. The acetyl group, like that of aspirin, shows bond-angle distortions from ideal values while remaining essentially planar. The Br atom is rotationally disordered and has been modeled as occupying two sites related by a 13 (1)° rotation about the C8—C9 bond.

Comment

Aspirin exerts its anti-inflammatory and antipyretic effects through inactivation, *via* specific covalent modification, of the cyclooxygenase enzyme. In the course of our studies of this enzyme, we synthesized the title compound, (I), which covalently modifies and inactivates the cyclooxygenase in a manner analogous to aspirin. In addition, (I) carries the heavy Br atom, enabling us to employ it as a crystallographic probe of the enzyme's active site (Loll, Picot & Garavito, 1995).



(I)

Fig. 1 shows a perspective view of the title compound. Three distinct planar groups are seen in the molecule. The six members of the benzene ring show an r.m.s. deviation from the least-squares plane of 0.005 Å, while atoms O3, O4, C8 and C9 of the acetyl group show an r.m.s. deviation of 0.006 Å from their least-squares plane. The plane of the acetyl group makes an angle of 84.5 (1)° with that of the ring. As is the case for aspirin (Wheatley, 1964), the three atoms of the carboxylic acid moiety are not coplanar with the ring; in this case, however, the angle is more pronounced, being 7.7 (4)°. This large twist may be required to accommodate the packing of the bulky Br atom in the lattice, while maintaining the intermolecular hydrogen bonding between carboxylic acid groups across the center of symmetry.

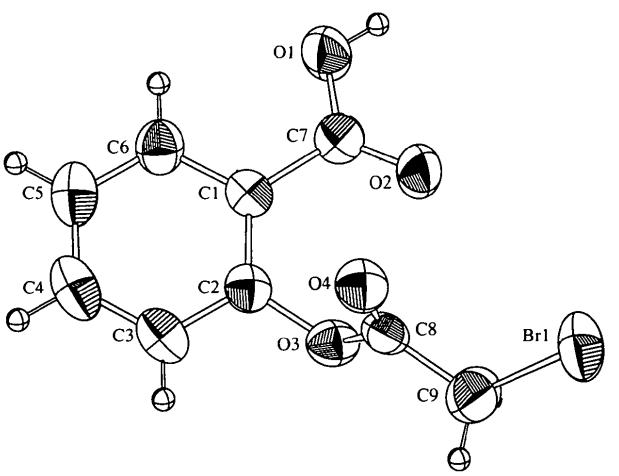


Fig. 1. View of the title compound showing the atomic labeling scheme (*ORTEP*II; Johnson, 1976). Displacement ellipsoids for non-H atoms are plotted at the 50% probability level and H atoms are drawn as spheres of arbitrary radii. Only one of the two rotameric positions of the Br atom is shown for clarity.

All bond lengths within the title molecule are normal. Slight distortions in the ring angles are observed around the C1 atom, suggesting that even with the large twist of the carboxylate group, repulsion between that group and the ring tends to pull C1 outward slightly from the ring center. Pronounced deviations from the ideal bond-angle value of 120° are found in the acetyl group, with the C9—C8—O3 angle being only 107.9 (3)°. Similar non-ideal angles are seen in the acetyl group of aspirin.

The C8—C9 bond has been modeled as existing in two rotameric states with O4—C8—C9—Br torsion angles of −31.2 (6) and −44.0 (9)°, and refined occupancies of 0.60 (2) and 0.40 (2), respectively (see Fig. 2). In each case, the Br atom is in van der Waals contact with the aromatic H3, H4 and H5 atoms from neighboring molecules. Details of the packing may be seen in Fig. 3.