process. Initially, a unit weighting scheme was used, but in the final stages of the refinement the weights were assigned using the method described by Carruthers & Watkin (1979), as incorporated in the *CRYSTALS* program package (Watkin, Carruthers & Betteridge, 1985). Programs used were *CRYSTALS*, *SHELXS86* (Sheldrick, 1986) and *SNOOPI* (Davies, 1983).

The authors are grateful to the Royal Society and TUBITAK (Scientific and Technical Research Council of Turkey) for financial support, and to Drs C. K. Prout and D. J. Watkin of the Chemical Crystallography Laboratory, University of Oxford, England, for provision of laboratory and computer facilities.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and bond distances and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71143 (18 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: AB1038]

References

Carruthers, J. R. & Watkin, D. J. (1979). *Acta Cryst.* A**35**, 698–699.
Chen, M. L. & Tulinsky, A. (1972). *J. Am. Chem. Soc.* **94**, 4144–4151.
Codding, P. W. & Tulinsky, A. (1972). *J. Am. Chem. Soc.* **94**, 4151–4157.
Davies, K. (1983). *SNOOPI. Program for Drawing Crystal and Molecular Diagrams*. Univ. of Oxford, England.
Davila, J. & Harriman, A. (1990). *J. Am. Chem. Soc.* **112**, 2686–2690.
Fleischer, E. B., Miller, C. K. & Webb, L. E. (1964). *J. Am. Chem. Soc.* **86**, 2342–2347.
Hoard, J. L. (1975). *Porphyrins and Metalloporphyrins*, edited by K. M. Smith, pp. 317–380. Amsterdam: Elsevier.
Kitaigorodskii, A. I. (1955). *Organic Chemical Crystallography*. New York: Consultants Bureau.
Lindsey, J. S., Schreiman, I. C., Hsu, H. C., Kearney, P. C. & Marguerettaz, A. M. (1987). *J. Org. Chem.* **52**, 827–836.
Lindsey, J. S. & Wagner, R. W. (1989). *J. Org. Chem.* **54**, 828–836.
Milgrom, L. R. (1984). *J. Chem. Soc. Perkin Trans.* 1, pp. 1483–1487.
Ostovic, C. & Bruice, T. C. (1989). *J. Am. Chem. Soc.* **111**, 6511–6517.
Robinson, L. R. & Hambright, P. (1991). *Inorg. Chim. Acta*, **185**, 17–24.
Scheidt, W. R., Mondal, J. U., Eigenbrot, C. W., Adler, A., Radonovich, L. J. & Hoard, J. L. (1986). *Inorg. Chem.* **25**, 795–799.
Shachter, A. M., Fleischer, E. B. & Haltiwanger, R. C. (1987). *Acta Cryst.* C**43**, 1876–1878.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Silvers, S. J. & Tulinsky, A. (1967). *J. Am. Chem. Soc.* **89**, 3331–3337.
Tabushi, I. & Kugimiya, S. (1986). *J. Am. Chem. Soc.* **108**, 6926–6931.
Ulman, A., Fisher, D. & Ibers, J. A. (1982). *J. Heterocycl. Chem.* **19**, 409–413.
Watkin, D. J., Carruthers, J. R. & Betteridge, D. W. (1985). *CRYSTALS. Program for Crystal Structure Solution*. Univ. of Oxford, England.

Acta Cryst. (1993). C**49**, 1670–1673

Structure of 5-[1-(Diaminomethylenehydrazono)ethyl]-4-methyl-2-methylthiopyrimidine

ALAIN COUSSON*

Laboratoire Léon Brillouin (CEA-CNRS), CE Saclay, 91191 Gif-sur-Yvette CEDEX, France

FRANÇOISE NECTOUX

Institut Curie, Section de Physique et Chimie, UA CNRS 448, 11 rue Pierre et Marie Curie, 75231 Paris CEDEX 05, France

BERNARD BACHET

Laboratoire de Minéralogie et Cristallographie, LA CNRS 09, Université Pierre et Marie Curie, 4 Place Jussieu, 75230 Paris CEDEX 05, France

BRUNO KOKEL AND MICHEL HUBERT-HABART

Institut Curie, Section de Physique et Chimie, Chercheurs INSERM, 11 rue Pierre et Marie Curie, 75231 Paris CEDEX 05, France

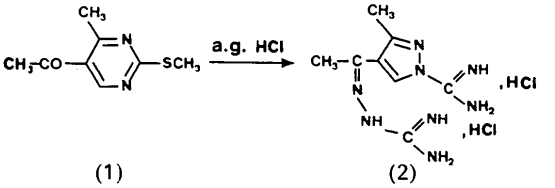
(*Received* 23 *November* 1992; *accepted* 5 *March* 1993)

Abstract

The detailed structure of the title compound (5-acetyl-4-methyl-2-methylthiopyrimidine diaminomethylenehydrazone) revealed distinct differences between it and its already published dichloride salt. It is obviously characterized by its diaminomethylenehydrazono chain and the more symmetrical pyrimidine ring. This observation helps in understanding the chemical behavior of the molecule and sheds more light on the possible mechanism of action of antitumor drugs such as mitoguazone.

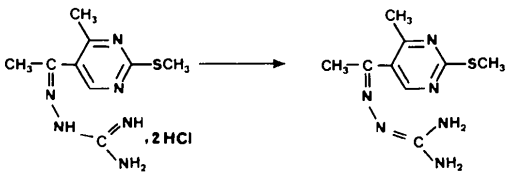
Comment

5-Acetyl-4-methyl-2-methylthiopyrimidine (1) is transformed by aminoguanidine hydrochloride (a.g. HCl) in acidic boiling methanol into 4-acetyl-1-amidino-3-methylpyrazole amidinohydrazone dihydrochloride (2) (Menichi, Naciri, Kokel & Hubert-Habart, 1984).



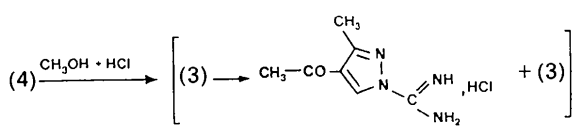
(1) (2)

In order to discover whether 5-acetyl-4-methyl-2-methylthiopyrimidine amidinohydrazone dihydrochloride (3) is the intermediate in such a transformation and also whether it has the capacity to undergo an intramolecular reaction leading to a pyrazole derivative, we isolated its free base (4).

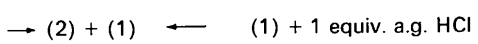


(3) (4)

We observed that derivative (4) remained unchanged after standing for several hours in boiling methanol, while it was transformed into the pyrazole (2) in about 50% yield when kept for a few hours in a boiling hydrochloric acid–methanol solution. Simultaneously, under the same experimental conditions, 50% of the starting pyrimidine (4) was transformed into pyrimidine (1). This pyrimidine (1) most likely originated from the trapping effect of the intermediate 4-acetyl-1-amidino-3-methylpyrazole hydrochloride (5) with regard to the amindinohydrazine (aminoguanidine), and shifts the equilibria in the direction of hydrolysis products of the starting pyrimidine (4), *i.e.* pyrimidine (1), and transforms pyrazole (5) into its amidinohydrazone (2). This interpretation befits the fact that when pyrimidine (1) is reacted with an equivalent quantity of aminoguanidine hydrochloride in boiling methanol solution, only pyrazole (2) is obtained in about 50% yield and not the expected pyrazole (5).



(5)



In order to better understand the difference in reactivity between pyrimidine (4) and its hydrochloride (3), the crystal structure of the former has been determined by X-ray diffraction and compared with that of the latter, which we have determined previously (Cousson, Nectoux, Bachet, Kokel & Hubert-Habart, 1993).

The structure is composed of stacks of parallel planes of molecules, crystalline cohesion being due to van der Waals contacts (Fig. 2). Pyrimidine (4) is nearly planar, though large deviations from the mean plane of the molecule are observed. Not taking into account the S atom and the methyl groups, the largest calculated deviations are 0.77 for C(5), −0.30 for C(9), −0.53 for H(22) and 0.25 Å for H(11) (Fig. 1). The spacing between atoms of the C(2)—N(4)—N(3)—C(1)—N(1) and —N(2) chain agrees with a diaminomethylenehydrazono structure and not with an amidinohydrazono one. Furthermore, an H atom that was expected to be bound to N(3) is in fact bound to the N atom N(1) or N(2) of the imino part of the amidino group. Indeed, in sharp contrast to what was observed with compound (3) (Cousson, Nectoux, Bachet, Kokel & Hubert-Habart, 1993), the C(1)—N(1) and C(1)—N(2) bond lengths are equal [1.349 (6) Å and 1.350 (6) Å] and longer than C(1)—N(3) [1.314 (6) Å]. The N(4)—C(2) [1.285 (6) Å] bond is almost a pure double bond and has a *trans* conformational (*E*) environment.

The C(7)—N(6) and C(7)—N(5) distances in the pyrimidine ring of (4) are comparable [1.322 (6) Å and 1.327 (6) Å] as are the lengths S(1)—C(7) [1.760 (5) Å] and S(1)—C(8) [1.763 (8) Å]. This is also a region that differenciates strongly between compounds (4) and (3).

The difference between the structures of pyrimidine (4) and of its dichloride salt (3), which is revealed by comparison of their crystal structures, does suggest an obvious reason for their contrasting chemical behaviors, especially for the necessity for pyrimidine (4) to be first transformed into its salt (3)

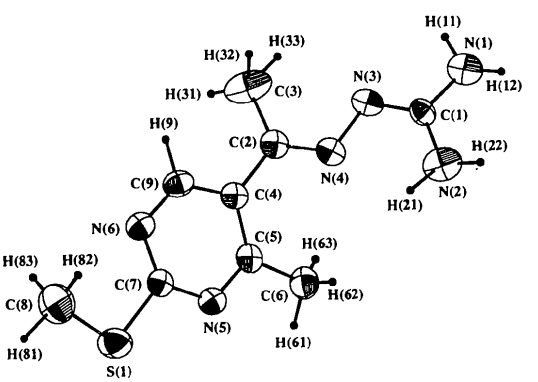


Fig. 1. *ORTEP* (Johnson, 1965) plot of the molecule.

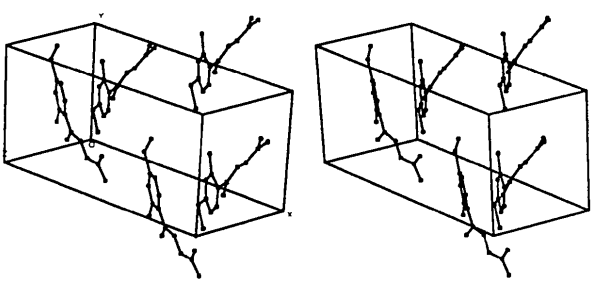


Fig. 2. *PLUTO* (Motherwell, 1976) stereoview of the title compound.

before undergoing an intramolecular ring contraction into pyrazole (2).

It also gives more insight into the possible mechanism of action of drugs bearing the amidinohydrazone group in their structure.

Experimental

Crystal data

$C_9H_{14}N_6S$
M_r = 238.313
Monoclinic
Cc
a = 17.231 (9) Å
b = 9.955 (6) Å
c = 7.611 (3) Å
β = 113.7 (5)°
V = 1196 (1) Å^3
Z = 4
D_x = 1.324 Mg m^{-3}

Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 23.0-26.4°
μ = 2.24 mm^{-1}
T = 293 K
Prism
0.45 × 0.25 × 0.11 mm
Pale yellow

Data collection

Enraf-Nonius CAD-4 diffractometer
ω-2θ scans
Absorption correction: empirical
T_{min} = 0.750, T_{max} = 1.539
1024 measured reflections
1024 independent reflections

908 observed reflections [$I \geq 3\sigma(I)$]
θ_{max} = 66°
$h = -20 \rightarrow 20$
$k = 0 \rightarrow 11$
$l = 0 \rightarrow 9$
2 standard reflections
frequency: 60 min
intensity variation: 0.007%

Refinement

Refinement on F
Final R = 0.0384
wR = 0.0364
S = 0.93
908 reflections
190 parameters
All H-atom parameters refined (one U_{eq} for all H atoms)
Unit weights applied
$(\Delta/\sigma)_{max}$ = 0.11

$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Extinction correction: Larson (1969)
Extinction coefficient: 7.2 (8)
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

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

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
S(1)	0.9724 (6)	0.2333 (1)	0.929 (1)	0.0541
C(1)	1.3003 (6)	0.9180 (5)	1.070 (1)	0.0324
C(2)	1.2396 (7)	0.6464 (5)	1.251 (1)	0.0337
C(3)	1.3098 (7)	0.6281 (8)	1.446 (2)	0.0559
C(4)	1.1697 (6)	0.5468 (5)	1.177 (1)	0.0269
C(5)	1.0851 (7)	0.5775 (5)	1.060 (1)	0.0268
C(6)	1.0499 (7)	0.7160 (6)	1.012 (2)	0.0450
C(7)	1.0530 (6)	0.3534 (5)	1.032 (1)	0.0312
C(8)	1.0292 (8)	0.0810 (7)	0.987 (2)	0.0689
C(9)	1.1861 (6)	0.4123 (5)	1.219 (1)	0.0387
N(1)	1.3603 (7)	1.0140 (5)	1.111 (1)	0.0407
N(2)	1.2370 (7)	0.9235 (5)	0.893 (2)	0.0444
N(3)	1.3042 (6)	0.8335 (4)	1.206 (1)	0.0325
N(4)	1.2371 (6)	0.7431 (4)	1.137 (1)	0.0317
N(5)	1.0274 (6)	0.4792 (4)	0.986 (1)	0.0324
N(6)	1.1298 (6)	0.3137 (4)	1.148 (1)	0.0365

Table 2. *Geometric parameters* (Å, °)

S(1)—C(7)	1.760 (5)	C(4)—C(5)	1.403 (6)
S(1)—C(8)	1.763 (8)	C(4)—C(9)	1.379 (7)
C(1)—N(1)	1.349 (6)	C(5)—C(6)	1.491 (7)
C(1)—N(2)	1.350 (6)	C(5)—N(5)	1.347 (6)
C(1)—N(3)	1.314 (6)	C(7)—N(5)	1.327 (6)
C(2)—C(3)	1.503 (7)	C(7)—N(6)	1.322 (6)
C(2)—C(4)	1.486 (7)	C(9)—N(6)	1.332 (6)
C(2)—N(4)	1.285 (6)	N(3)—N(4)	1.391 (5)
C(8)—S(1)—C(7)	102.3 (3)	N(5)—C(5)—C(4)	120.7 (4)
N(2)—C(1)—N(1)	116.1 (5)	N(5)—C(5)—C(6)	114.3 (4)
N(3)—C(1)—N(1)	118.5 (4)	N(5)—C(7)—S(1)	113.8 (3)
N(3)—C(1)—N(2)	125.2 (5)	N(6)—C(7)—S(1)	119.6 (4)
C(4)—C(2)—C(3)	120.2 (5)	N(6)—C(7)—N(5)	126.5 (4)
N(4)—C(2)—C(3)	123.6 (5)	N(6)—C(9)—C(4)	125.0 (4)
N(4)—C(2)—C(4)	116.1 (4)	N(4)—N(3)—C(1)	110.2 (4)
C(5)—C(4)—C(2)	125.0 (4)	N(3)—N(4)—C(2)	115.6 (4)
C(9)—C(4)—C(2)	120.0 (4)	C(7)—N(5)—C(5)	117.7 (4)
C(9)—C(4)—C(5)	115.0 (4)	C(9)—N(6)—C(7)	114.9 (4)
C(6)—C(5)—C(4)	124.9 (5)		

The preparation and description of compounds (1), (2), (3) and (5) have been reported already (Arya, David, Grewal, Marathe & Patil, 1977; Cousson, Nectoux, Bachet, Kokel & Hubert-Habart, 1992; Menichi, Naciri, Kokel & Hubert-Habart, 1984). Compound (3) was dissolved in iced water and a few drops of a cold solution of potassium hydroxide were added until a basic pH was reached. The precipitate which formed was filtered off, rinsed with cold water and dried under vacuum. Through two successive crystallizations in methanol, large crystals of the title compound (4) suitable for X-ray analysis were isolated. The structure was solved by direct methods and successive Fourier maps using *SHELXS*86 (Sheldrick, 1986) and refined using *CRYSTALS* (Watkin, Carruthers & Betteridge, 1985). H atoms were located on series differences. Analysis for $C_9H_{14}N_6S$ (= 238): calculated (observed) C 45.36 (45.52), H 5.92 (5.82), N 35.26 (35.40), S 13.45% (13.10%). MS (m/Z): 237 (M^+-1) (22), 223 (100), 195 (9), 181 (11), 43 (45). ^{1}H NMR (DMSO-d_6): 8.5 (*s*, 1H, aromatic H); 5.7 (*s*, 2H, NH_2); 5.5 (*s*, 2H, NH_2); 2.5 (*s*, 6H, $2CH_3$); 2.2 (*s*, 3H, CH_3). IR (cm^{-1}): 3305 (NH_2); 1534 (C=N).

This work was supported by a grant (Contrat coopératif, décision 90.24) from the Institut Curie.

Lists of structure factors, anisotropic thermal parameters, H-atom coordinates and bond distances and angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 71153 (9 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: DU1035]

References

Arya, V. P., David, J., Grewal, R. S., Marathe, S. B. & Patil, S. D. (1977). *Indian J. Chem.* **15B**, 1129–1132.

Cousson, A., Nectoux, F., Bachet, B., Kokel, B. & Hubert-Habart, M. (1993). *Acta Cryst.* C**49**. In the press.

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Larson, A. C. (1969). *Crystallographic Computing*, edited by F. R. Ahmed, pp. 291–294. Copenhagen: Munksgaard.
Menichi, G., Naciri, J., Kokel, B. & Hubert-Habart, M. (1984). *Heterocycles*, **22**, 2013–2017.
Motherwell, W. D. S. (1976). *PLUTO. Program for Plotting Molecular and Crystal Structures*. Univ. of Cambridge, England.
Sheldrick, G. M. (1986). *SHELXS86. Program for the Solution of Crystal Structures*. Univ. of Göttingen, Germany.
Watkin, D. J., Carruthers, J. R. & Betteridge, P. W. (1985). *CRYSTALS User Guide*. Chemical Crystallography Laboratory, Univ. of Oxford, England.

Acta Cryst. (1993). C**49**, 1673–1676

Structure of a 1:1 Complex Between L-Asp-L-Phe and L-His-Gly

CARL HENRIK GÖRBITZ

Department of Chemistry, University of Oslo, N-0315 Oslo 3, Norway

MARGARET C. ETTER†

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455, USA

(*Received* 13 *March* 1992; *accepted* 8 *March* 1993)

Abstract

Both molecules occur in slightly folded conformations, characterized by $\varphi_2 = -93.7°$ in L-His-Gly and an unusual $\varphi_2 = 60.2°$ in L-Asp-L-Phe. The peptide linkage of L-His-Gly displays a substantial deviation from planarity with $\omega_1 = -163.5°$. The crystal packing is arranged in thick hydrophilic layers separated by hydrophobic sheets composed of L-Phe aromatic side chains. There are numerous hydrogen bonds, including an extremely short contact [O···N = 2.532 (6) Å] between the ionized L-Asp and L-His side chains.

Comment

The problems of preparing peptide crystals suitable for diffraction purposes are familiar to most researchers working in the field. One solution to such difficulties is to utilize more sophisticated crystallization techniques (see, for example, Eggleston & Baures, 1992) than slow evaporation, the method most frequently used. Another alternative is to take advantage of the acidic and basic properties of peptides by crystallizing them as salts, usually as cations in *e.g.* hydrochlorides. When investigations are performed with regard to the biological activities exhibited by these molecules, the potentially most interesting ionization state is that observed in aqueous solution at physiological pH. In connection with this, the number of acidic residues in the peptide, n_A, and the number of basic residues, n_B, are of importance. When $n_A = n_B = 0$, or generally when $n_A = n_B$, peptide cations always possess protonated C-terminal carboxylate groups. Since associated pK_a values normally range from 1.7 to 2.6, this corresponds to unphysiologically low pH values. If, however, the peptide in question has $n_A > n_B$ or $n_B > n_A$ it can be crystallized as an anion or a cation in a salt while retaining its physiological protonation state. It is surprising that only a single example is known where this technique has been employed, namely in the structure of L-Pro-L-Lys acetate (Urpi, Coll, Subirana, Solans & Font-Alba, 1988). This means that for acidic and basic peptides there is a large unexplored potential for finding suitable counterions that could facilitate crystal growth. A special option, based on extensive studies of 1:1 amino acid–amino acid salts (Soman, Vijayan, Ramakrishnan & Row, 1990, and references therein), is to cocrystallize two different peptides with opposite charges, as in the L-His-L-Ser Gly-L-Glu 1:1 complex (Suresh & Vijayan, 1985). In the work presented here, we have used this latter approach to study the 1:1 cocrystalline complex between the dipeptides L-Asp-L-Phe and L-His-Gly. Neither of the two individual compounds has been subject to investigation by X-ray diffraction in the past. In addition to providing suitable crystals for X-ray analysis of molecular structure, cocrystallization also presents interesting opportunities to study intermolecular interactions between different molecules in the solid phase.

The asymmetric unit, which consists of one L-Asp-L-Phe anion, one L-His-Gly cation and a solvent water molecule, is depicted in Fig. 1. Molecular geometry is given in Table 2. There are no remarkable values, although the C3*A*—C4*A* bond length (1.564 Å) is clearly in the upper range of what is normally encountered for this kind of C—C single bond [average 1.520 Å (Allen *et al.*, 1987)].

The side chains of L-Asp-L-Phe have normal *gauche*$^-$ orientations, but the main chain exhibits a very unusual folded conformation that places both the side chains on the same side of the peptide plane, the result of an ordinary ψ_1 value (154.5°) combined with a unique positive φ_2 value (60.2°). Only once has a similar arrangement been observed in the structure of an L-L dipeptide, namely for L-Tyr-L-Lys (Urpi, Coll & Subirana, 1988) with $\psi_1 = 111.3$ and $\varphi_2 = 52.7°$. The L-His-Gly main-chain conformation is folded in a usual manner with $\varphi_2 = -93.7°$. The peptide bond unit of this molecule is remarkably

† Deceased June 1992.