Crystal structure of 2-carbonylethoxy-5-carbonylmethoxy-4-(2-chlorophenyl)-6-methyl-4,7-dihydrothiene-[2,3-*b*]pyridine, $C_{19}H_{18}NO_4SCl$

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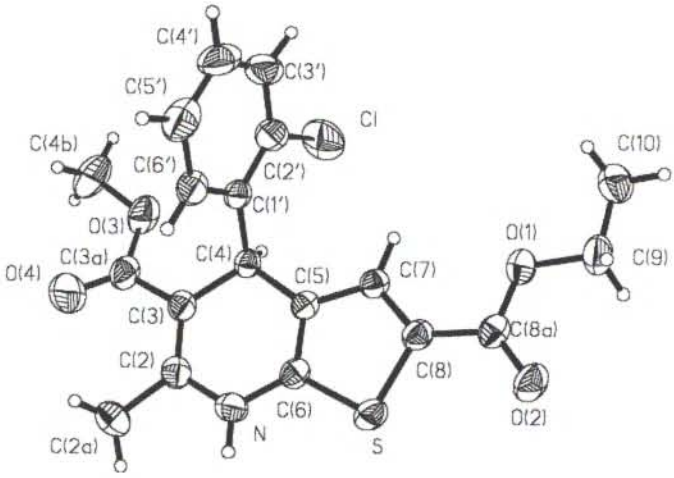

Abstract

$C_{19}H_{18}ClNO_4S$, monoclinic, $P12_1/c1$ (No. 14), a = 15.510(3) Å, b = 9.213(2) Å, c = 12.888(3) Å, β = 96.52(3)°, V = 1829.7 Å^3, Z = 4, $R_{gt}(F)$ = 0.048, $wR_{ref}(F^2)$ = 0.107, T = 293 K.

Source of material

A mixture of the appropiate pyridine (methyl-4-aryl-6-chloro-5-formyl-2-methyl-1,4-dihydropyridine-3-carboxylates) 1,8 mmoles) in ethanolic sodium ethoxide [prepared from sodium (0.04 g) in dry ethanol (20 ml)] was refluxed for 10 hours. The reaction solution was evaporated to dryness under reduced pressure. The residue was triturated with water (20 ml) and the solid was collected by filtration. Further purification was accomplished by recrystallization from methanol [1].The crystals were obtained by slow evaporation from ethanol.

Discussion

4-Aryl-1,4-dihydropyridines (aryl-1,4-DHPs) such as nifedipine [10] are calcium channel antagonists that are used clinically for the treatment of angina and hypertension. The structure-activity features argue for a distinct rotameric preference about the C4—C1' bond in the receptor bound state. As a result, considerable speculation and experimentation has been aimed at deriving the rotameric preference and barrier to this rotation [2]. The two low energy rotameric conformations place the ring planes orthogonal to one another. The rotamers are designated *syn* (with C2' substituent closet to the C4H) and *anti* (with the 2'-substituent facing away from the C4H).

In the crystal structure from the X-ray data of 4-[2-chlorophenyl]-2-carbonylethoxy-5-carbonylmethoxy-6-methyl-4,7-dihydrothiene-[2,3-*b*]pyridine, the phenyl ring is 76.4° off of the perpendicular bisector of the dihydropyridine ring, the same angle in 3-acetyl-4-phenyl-2,7,7-thremethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoleine is 88.2° [4]. The substituents in position 2 and 3 of the dihydropyridine ring adopt equal rotameric disposition about their respective thiophene-ester carbonyl carbon bonds in both positions 5 and 6. The ester in this position assumes the synperiplanar conformation (ester carbonyl with respect to dihydropyridine double bond) and the substituents in 2 and 3 positions adopts the synperiplanar conformation. The dihydropyridine ring in this structure is planar, the maximum deviation of the plane is only 0.006 Å (C2), in analogues compounds this ring is a flattened "boat" [5]. The influence of rotameric preference on DHP ring pucker can be gauged from the DHP ring conformations of the 2'-Cl. The Cl atom is "synperiplanar" the C_4-plane, this esffect is presumed to be due to the electronic repulsion between the Cl and N atom. The sum of the absolute values of the six interior torsion angles (∠(NC(2)C(3)C(4) = –0.96°; ∠C(2)C(3)C(4)C(5) = 0.30°; ∠C(3)C(4)C(5)C(6) = –0.07°; ∠C(4)C(5)C(6)N = 0.52°; ∠C(2)NC(6)C(5) = –1.18°; ∠C(6)NC(2)C(3) = 1.38°) of the compound is only 4.41°. This parameter has been shown to correlate with pharmacologic potency as calcium channel antagonist. For reference, the analogous sum in nifedipine is 72.1° [6]. These data can be used for the prediction of IC50's for inhibition of tonic response in guinea pig ileal longitudinal muscle. When the plane of the phenyl ring is perpendicular to the plane of the base of the "boat", activity increases [7]. In the title compound, the values od some geometrical characteristics apoint to the very very low biological activity. In this structure, the N hydrogen atom is involved in an intermolecular hydrogen bond [d(N—H···O2) = 2.848(3) Å].

Table 1. Data collection and handling.

Crystal:	colourless, size 0.08 × 0.24 × 0.72 mm
Wavelength:	Mo K_α radiation (0.71069 Å)
μ:	3.475 cm^{-1}
Diffractometer, scan mode:	Enraf-Nonius CAD-4, ω/2θ
$2\theta_{max}$:	59.94°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	6111, 5317
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 4\ \sigma(I_{obs})$, 2833
$N(param)_{refined}$:	307
Programs:	SHELXS-90 [8], SHELXL-97 [9], SHELXTL [10], PARST [11, 12], PARSTCIF [13]

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Table 2. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{iso}
H	4e	0.318(2)	0.325(4)	0.212(3)	0.06(1)
H(3')	4e	0.201(3)	0.953(5)	–0.216(3)	0.10(1)
H(4')	4e	0.109(2)	1.044(4)	–0.092(3)	0.07(1)
H(5')	4e	0.083(2)	0.899(4)	0.058(3)	0.08(1)
H(6')	4e	0.152(2)	0.681(3)	0.075(2)	0.038(8)
H(4)	4e	0.269(2)	0.496(3)	–0.106(2)	0.040(7)
H(7)	4e	0.414(2)	0.704(3)	–0.045(2)	0.045(8)
H(9)	4e	0.691(2)	0.836(4)	0.042(3)	0.07(1)
H(9A)	4e	0.637(2)	0.960(3)	0.097(2)	0.050(9)

Table 2. Continued.

Atom	Site	x	y	z	U_{iso}
H(10)	4e	0.681(3)	1.049(4)	–0.060(3)	0.07(1)
H(10A)	4e	0.632(2)	0.926(4)	–0.126(3)	0.06(1)
H(10B)	4e	0.582(3)	1.041(5)	–0.071(3)	0.09(1)
H(2A)	4e	0.159(4)	0.166(6)	0.114(5)	0.14(2)
H(2B)	4e	0.202(3)	0.203(5)	0.217(4)	0.11(2)
H(2C)	4e	0.121(4)	0.269(6)	0.161(4)	0.12(2)
H(4A)	4e	0.027(3)	0.499(5)	–0.266(4)	0.10(2)
H(4B)	4e	–0.018(3)	0.487(5)	–0.162(3)	0.11(2)
H(4C)	4e	0.009(3)	0.346(5)	–0.221(3)	0.10(2)

Table 3. Atomic coordinates and displacement parameters (in $Å^2$).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	4e	0.45906(4)	0.50866(8)	0.18794(5)	0.0376(3)	0.0457(4)	0.0352(3)	–0.0006(3)	–0.0074(2)	0.0018(3)
Cl	4e	0.29001(7)	0.7066(1)	–0.23310(6)	0.0865(6)	0.0941(7)	0.0424(4)	–0.0057(6)	0.0152(4)	0.0160(4)
N	4e	0.3023(2)	0.3750(3)	0.1576(2)	0.042(1)	0.039(1)	0.038(1)	–0.004(1)	–0.0013(9)	0.008(1)
O(1)	4e	0.5635(1)	0.8074(2)	0.0265(2)	0.036(1)	0.047(1)	0.051(1)	–0.0119(9)	–0.0069(8)	0.0027(9)
O(2)	4e	0.6149(1)	0.7010(2)	0.1776(2)	0.041(1)	0.054(1)	0.045(1)	–0.0063(9)	–0.0104(8)	–0.0057(9)
O(3)	4e	0.1070(1)	0.4535(3)	–0.1421(2)	0.037(1)	0.071(2)	0.044(1)	–0.007(1)	–0.0093(8)	–0.008(1)
O(4)	4e	0.0561(2)	0.3200(3)	–0.0203(3)	0.052(1)	0.104(2)	0.133(3)	–0.040(2)	–0.025(2)	0.056(2)
C(1')	4e	0.2129(2)	0.6789(3)	–0.0541(2)	0.028(1)	0.032(1)	0.037(1)	–0.005(1)	–0.0059(9)	0.001(1)
C(2')	4e	0.2251(2)	0.7655(3)	–0.1398(2)	0.042(1)	0.050(2)	0.039(1)	–0.008(1)	–0.009(1)	0.006(1)
C(3')	4e	0.1868(2)	0.9010(4)	–0.1540(3)	0.055(2)	0.050(2)	0.069(2)	–0.012(2)	–0.022(2)	0.022(2)
C(4')	4e	0.1353(2)	0.9519(4)	–0.0831(4)	0.053(2)	0.033(2)	0.104(3)	0.002(2)	–0.023(2)	0.010(2)
C(5')	4e	0.1217(2)	0.8693(4)	0.0023(3)	0.043(2)	0.044(2)	0.089(3)	0.002(2)	–0.002(2)	–0.013(2)
C(6')	4e	0.1605(2)	0.7340(3)	0.0163(2)	0.037(1)	0.034(1)	0.053(2)	–0.001(1)	0.004(1)	–0.004(1)
C(2)	4e	0.2231(2)	0.3498(3)	0.1018(2)	0.037(1)	0.027(1)	0.046(1)	–0.000(1)	0.008(1)	–0.002(1)
C(2A)	4e	0.1714(3)	0.2385(4)	0.1530(3)	0.055(2)	0.042(2)	0.066(2)	–0.009(2)	0.009(2)	0.013(2)
C(3)	4e	0.1985(2)	0.4205(3)	0.0111(2)	0.033(1)	0.028(1)	0.044(1)	–0.003(1)	0.003(1)	–0.003(1)
C(3A)	4e	0.1140(2)	0.3905(3)	–0.0478(3)	0.036(1)	0.036(2)	0.064(2)	–0.005(1)	–0.004(1)	–0.002(1)
C(4)	4e	0.2563(2)	0.5305(3)	–0.0369(2)	0.029(1)	0.033(1)	0.032(1)	–0.002(1)	–0.0010(9)	–0.001(1)
C(4B)	4e	0.0231(2)	0.4474(6)	–0.2017(4)	0.041(2)	0.094(3)	0.067(2)	0.003(2)	–0.016(2)	–0.013(2)
C(6)	4e	0.3594(2)	0.4706(3)	0.1214(2)	0.032(1)	0.033(1)	0.033(1)	0.001(1)	–0.0007(9)	–0.004(1)
C(5)	4e	0.3418(2)	0.5474(3)	0.0310(2)	0.030(1)	0.027(1)	0.033(1)	0.001(1)	–0.0003(9)	–0.003(1)
C(7)	4e	0.4109(2)	0.6396(3)	0.0147(2)	0.033(1)	0.030(1)	0.033(1)	–0.001(1)	–0.0008(9)	–0.002(1)
C(8)	4e	0.4786(2)	0.6326(3)	0.0928(2)	0.034(1)	0.035(1)	0.036(1)	–0.001(1)	–0.003(1)	–0.001(1)
C(8A)	4e	0.5588(2)	0.7141(3)	0.1045(2)	0.034(1)	0.037(1)	0.038(1)	0.001(1)	–0.001(1)	–0.008(1)
C(9)	4e	0.6390(2)	0.9006(4)	0.0333(3)	0.037(2)	0.052(2)	0.057(2)	–0.010(1)	0.000(1)	–0.003(2)
C(10)	4e	0.6347(3)	0.9858(4)	–0.0655(3)	0.055(2)	0.046(2)	0.060(2)	–0.008(2)	0.006(2)	–0.003(2)

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References

1. Suarez, M.; Ochoa, E.; Pita, B.; Espinosa, R.; Gonzalez, L.; Martin, N.; Quintero, M.; Seoane, C.; Soto, J. L.: Synthesis and structural characterization of substitued thieno[2,3-b]pyridines from *o*-chloroformyl-1,4-dihydropyridines.J. Heterocyclic Chem. **34** (1997) 931-935.
2. Natale, N. R.; Triggle, D. J.; Palmer, R. B.; Lefler, B. J.; Edwards, W. D.: 4-Isoxazoyl-1,4-dihydropyridines - biological, theorectical, and structural studies. J. Med. Chem. **33** (1990) 2255-2259.
3. Berntsson, P.; Carter, R. E.: Determination of the conformation of felodipine by H^1-NMR spin-lattice relaxation-time measurements. Acta Pharm. Suec. **18** (1981) 221-224.
4. Janis, R. A.; Triggle, D. J.: New developments in Ca^{2+} channel antagonits. J. Med. Chem. **26** (1983) 765-769.
5. Alajarin, R.; Vaquero, J.; Alvarez-Builla, J.; Pastor, M.; Sunkel, C.; Fau de Casa-Juana, M.; Priego, J.; Statkow, P. R.; Sanz-Aparicio, J.; Fonseca, I.: Synthesis, structure, and pharmacological evaluation of the stereoisomers of furnidipine. J. Med. Chem. **38** (1995) 2830-2841.
6. Miyamae, A.; Koda, S.; Morimoto, Y.: Structural studies of a new dihydropyridine calcium-channel antagonist, nilvadipine. Chem. Pharm. Bull. **34** (1986) 3071-3075.
7. Duque, J.; Pomés, R.; Suárez, M.; Ochoa, E.; Verdecia, Y.; Punte, G.; Echevarría, G.: Crystal structure of 3-carboxymethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline. Bol. Soc. Chil. Quim. (2000), in press.
8. Sheldrick, G. M.: Direct Methods for Larger Structures. Acta Crystallogr. A**46** (1990) 467-473.
9. Sheldrick, G. M.: The SHELXL-97 Manual. University of Göttingen, Germany 1997.
10. Sheldrick, G. M.: SHELXTL-Plus. Release 4.1. Siemens Analytical X-ray Instrument Inc., Madison, Wisconsin, USA 1991.
11. Nardelli, M.: System of computer routines for calculating molecular structure parameters from the results of the crystal structure analysis. Comput. Chem. **7** (1983) 95-98.
12. Nardelli, M.: PARST95- an update to PARST: A system of Fortran routines for calculating molecular structure parameters from the results of the crystal structure analysis. J. Appl. Cryst. **28** (1995) 659.