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Crystal Structure of an Adduct: 2,3,5-Substituted Derivative of Pyridine

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The structure of 2-[(2-chloro-5-methyl-3-pyridinyl)(hydroxy)methyl]-2-cyclohexene-1-one, $C_{13}H_{14}NO_2Cl$, was determined: F.W. = 251.7, triclinic, P-1, a = 8.0511(6), b=8.0820(6), c=10.9894(8) Å; α=103.02(1)°, β=97.24(1)°, γ=114.04(1)°; V= 616.9(8) Å^3, Z=2, λ=0.71073Å, μ(MoKα) 0.299 mm^{-1}, F_{000}=264, and T= 273(2) K. Final R and wR are 0.0479 and 0.1339 respectively. The pyridine ring is planar, and the cyclohexene ring adopts a sofa conformation. The dihedral angle between the pyridine and cyclohexene rings is 89.9(1). In the crystal lattice, the molecules are packed via O–H…O and C–H…O intermolecular interactions. In addition, the structure is further stabilized by C–H…Π interactions.

Keywords: Baylis–Hillman adduct; crystal structure; hydrogen bonding

INTRODUCTION

Baylis–Hillman (BH) adducts [1] are well known in organic synthesis because of their biological relevance [2,3]. The BH processes also have become increasingly important because the resulting adducts are packed with functional groups and stereochemistry that can be subjected to numerous transformations [4]. However, there are numerous problems commonly associated with this process, most notably the slow reaction. For example, BH reaction of 2-cyclopentene-1-one or

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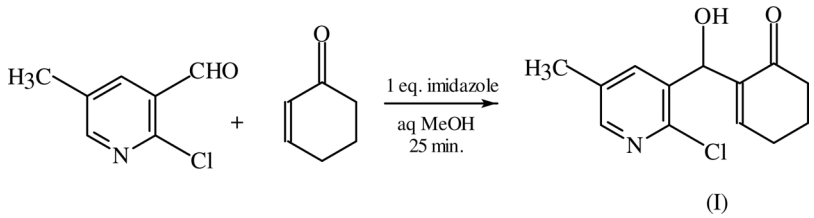

FIGURE 1 Scheme.

2-cyclohexene-1-one is sluggish or does not occur under traditional conditions [5,6]. A literature survey reveals that the BH reaction between pyridine carboxaldehyde/furfuraldehyde and cyclic-enones produces unstable adducts [7]. Further, the BH reactions involving cyclic enones and heterocyclic compounds are less explored. In our efforts to study the chemical transformations of substituted 2-chloropyridine-3-carboxaldehydes [8], we have observed that these molecules undergo extremely fast BH reactions under normal conditions. The chloro-substituent in the title molecule may be involved in enhancing the reactivity and stability of the BH adduct. These adducts were evaluated for having *in vitro* antimalarial activity [8], and evaluating the biological function of the molecule is under progress. In continuation of our studies on these important BH adducts [9,10], we report here the crystal structure of the title molecule (Fig. 1 (I)).

EXPERIMENTAL

Necessary activated alkene and tertiary amine catalyst were obtained commercially. The substrate aldehyde was prepared in our laboratory according to our earlier published work [11]. The melting point was determined on a Mel-Temp apparatus and is uncorrected. IR were recorded with a Perkin-Elmer model 1600 series FTIR spectrometer. ^{1}HNMR and ^{13}CNMR spectra were recorded on Gemini 200 MHz and 300 MHz instruments. EIMS was detected on a VG Micromass 7070H (70 eV).

Synthesis and Characterization

The clear solution of 2-chloro-5-methylnicotinaldehyde (1 mmol) and imidazole (1 equiv) in 5 mL of MeOH was slowly charged with 5 mL of deionized water. To a stirred homogeneous reaction mixture, 2-cyclohexene-1-one (1.2 mmol) was added at room temperature, and the reaction progress was monitored by thin-layer chromatography

(TLC) for 25 min. (approx). Upon completion of the reaction, the reaction mixture was quenched by 0.5 N HCl (5 mL for 200 mg of the aldehyde) and extracted with $CHCl_3$ (3×20 mL). Combined organic layers were washed with a brine solution (2×10 mL). The organic layer was concentrated, and column chromatography of the crude product on silica gel, using 30% ethyl acetate in hexane as eluent, gave pure Baylis–Hillman adduct (yield, 90%). Later, the product was recrystallized by dissolving it in hot chloroform solution.

Mp, 105–107°C; ^{1}HNMR (200 MHz, $CDCl_3$): δ 8.11 (d, $J = 2.3$ Hz, 1H), 7.78 (d, $J = 2.3$ Hz, 1H), 6.47 (t, $J = 4.1$ Hz, 1H), 5.72 (s, 1H), 2.5 (m, 2H), 2.38 (s, 3H), 2.38 (m, 2H), 2.03 (m, 2H); ^{13}CNMR: (50 MHz, $CDCl_3$): δ 200.3, 148.5, 148.2, 138.7, 137.9, 134.7, 132.5, 68.4, 38.3, 25.7, 22.3, 17.7; MS EI (m/z): 251(M+), 216, 198, 116, 84, 65, 48; IR (KBr): 3425, 2957, 1673 cm^{-1}. Anal. calcd. for $C_{13}H_{14}ClNO_2$: C, 62.01; H, 5.64; N, 5.56%. Found: C, 62.24; H, 5.74; N, 5.68%.

Crystal Structure Determination and Refinement

Diffraction data were measured at room temperature with a Bruker Smart CCD area detector [12]. Preliminary lattice parameters and orientation matrix were obtained from three sets of frames. Intensity data were collected using graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å).

Integration and scaling of intensity data were accomplished using SAINT [13], and absorption corrections were performed using SADABS [14]. The structure was solved by direct methods and refined by a full matrix least-squares procedure based on F^2 [15]. Nonhydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were included in the models in their calculated positions in the riding model approximation. The details of the data collection and refinement are gathered in Table 1. The geometrical calculations and molecular graphics were computed using programs PARST [16], ORTEP-3 [17], and PLATON [18].

RESULTS AND DISCUSSION

The numbering scheme employed is shown in Fig. 2, drawn at 30% probability level with PLATON. The selected intramolecular bonding parameters involving the nonhydrogen atoms of the molecules are presented in Table 2. The title compound possesses a stereogenic center, C(6), with a relative configuration (S) (Fig. 2), though it belongs to a centro-symmetric space group and thus represents a racemate. The pyridine ring is planar with the atoms Cl and C13 (deviation from

TABLE 1 Crystal and Experimental Data

Parameter	Value
CCDC No.	290510
Empirical formula	$C_{13}H_{14}NO_2Cl$
Formula weight	251.7
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a=8.0511(6) Å, α=103.02(1) b=8.0820(6) Å, β=97.24(1) c=10.9894(8) Å, γ=114.04(1)
V	616.9(8) Å^3
Z	2
D_{cal}	1.355 Mg/m^3
μ	0.299 mm^{-1}
Radiation (MoKα)	0.71073 Å
F(000)	264
Θ range for data collection	1.96–27.98
Reflections collected	7060
Independent reflections	2818
No. of reflections [I>2σ(I)]	2513
No. of parameters	156
Final R indices R/wR	0.0479/0.1339
Goodness of fit on F^2	1.074
Refinement method	full-matrix least-squares on F^2
Measurement	Bruker SMART CCD
Program system	SAINT
Structure determination/refinement	SHELXS97/SHELXL97
Molecular graphics	ORTEP-3 and PLATON

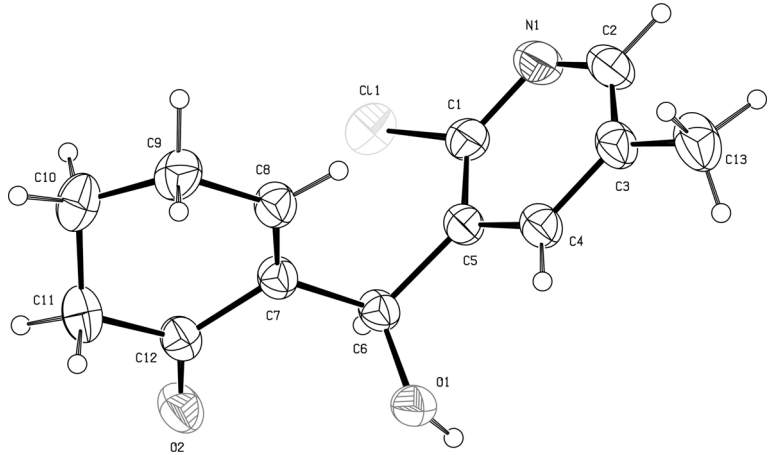

FIGURE 2 A view of (I), with atomic numbering scheme. Displacement ellipsoids are drawn at 30% probability level.

TABLE 2 Selected Geometric Parameters [Å,°]

Parameter	Value
C1–N1	1.313 (2)
C2–N1	1.332 (4)
C6–O1	1.418 (2)
C12–O2	1.223 (2)
C7–C6–O1	106.4 (1)
C5–C6–O1	111.5 (1)
C7–C8–C9–C10	−21.5 (3)
C7–C12–C11–C10	26.7 (3)

the least-squares plane are 0.063(1) and 0.072(3) Å) lying almost in the same plane. Least-squares plane calculations show that the cyclohexene ring is puckered in such a manner that the atoms C7–C9, C11, and C12 are coplanar (maximum deviation of 0.012(1) Å from the mean plane) and the sixth atom C10 is displaced 0.593(3) Å above the least-squares plane. The same is reflected in the values of torsion angles C7–C8–C9–C10 and C7–C12–C11–C10 (Table 2). Thus, the conformation of the cyclohexene ring can be described as a sofa ($\Delta Cs[C10] = 6.83$) [19]. The cyclohexene ring is oriented at right angles (dihedral angle of 89.9(1)°) to the pyridine ring. The hydroxyl oxygen is tilted toward the cyclohexene ring. This can be seen clearly in terms of bond angles as O1–C6–C5 is distinctly larger than that of O1–C6–C7 (Table 2). We have earlier reported similar structures [9,10,20] where the difference in the tilt angle of the hydroxyl group with respect to the pyridine ring ranges from 2–3°, whereas in the present structure it is 5.1°. Further, the centroid distance of the hydroxy oxygen with respect to the pyridine ring in the reported structures is in the range of 3.593–3.604 Å, and in the present structure it is 3.683 Å. In other words, the tilt angle increases with increasing the centroid distance. From a simple geometric analysis of all possible conformers, an important factor for the tilting of the hydroxyl group may be from the steric interactions between the cyclohexene and pyridine rings.

An intramolecular C−H...O interaction (weak) between atoms C4 and O1 is also observed that closes the five-membered pseudo-ring O1–C6–C5–C4–H4 according to the S(5) pattern [21]. Similar interactions were observed in the literature [22].

In the crystal structure, inversion-related molecules are linked by O−H...O and C−H...O hydrogen bonding interactions (Table 3) to form dimers that run along the a axis. Interestingly, each molecule

TABLE 3 Hydrogen Bonding Geometry [Å, °]

D–H...A	D–H	H...A	D...A	D–H...A
O1–H1... O2^{i}	0.82	2.00	2.818(2)	177
C10–H10A... O2^{ii}	0.97	2.52	3.402(3)	151
C4–H4... O1	0.93	2.81	2.483(1)	101
C13–H13B... Cg1^{iii}	0.96	3.19	3.605	108

Note: Symmetry code: (i) −x+1, −y+2, −z+1; (ii) −x, −y+1, −z+1; (iii) 1−x, 2−y, −z. Cg1 is the centroid of the pyridine ring.

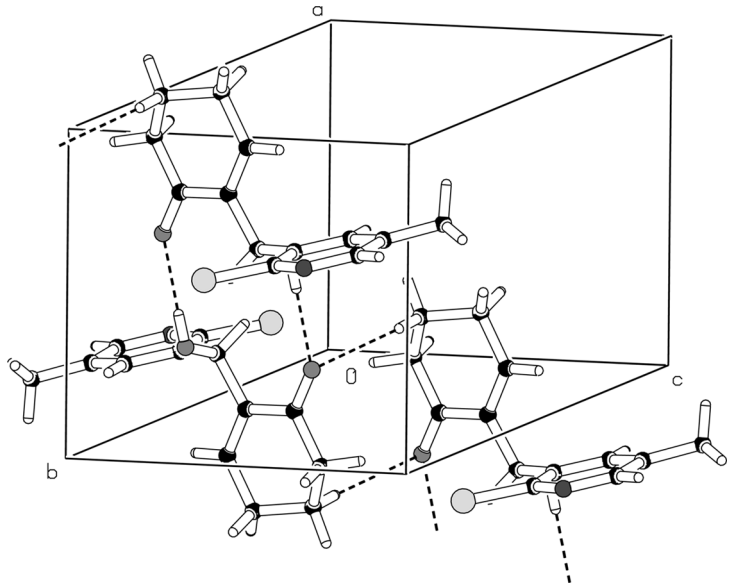

FIGURE 3 Partial packing diagram of (I) showing the dimerization through $R_2^2(6)$ and $R_2^2(5)$ type of hydrogen bonding.

is participating in two types of dimerization (Fig. 3) ($R_2^2(6)$ through O–H...O and $R_2^2(5)$ through C–H...O interactions) [21]. The crystal packing is further stabilized by C–H...Π and van der Wals interactions.

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