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CRYSTAL STRUCTURES OF TWO IMIDAZOLE DERIVATIVES

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2-n-Butyl-5-chloro-3H-imidazole-4-carbaldehyde (BCIC), $C_8H_{11}ClN_2O$. F.W. = 186.64, monoclinic, $P2_1/c$, $a = 7.2617(3)$ Å, $b = 13.2067(6)$ Å, $c = 9.8491(4)$ Å $\beta = 101.76(1)^\circ$, $V = 924.74(7)$ Å^3, $Z = 4$, $D_{cal} = 1.341$ Mgm^{-3}, $\mu = 0.367$ mm^{-1}, $F_{000} = 392$, λ (MoKα) = 0.71073 Å, final R1 and wR2 are 0.049 and 0.126, respectively. 2-n-Butyl-4-chloro-1 [(2′-cyanobiphenyl-4-yl)methyl]-5-hydroxymethyl imidazole (BCCI), $C_{22}H_{22}ClN_3O$, F.W. = 379.88, triclinic, $P\bar{1}$, $a = 8.198(2)$ Å, $b = 10.997(3)$ Å, $c = 11.524(2)$ Å, $\alpha = 90.83(2)^\circ$, $\beta = 94.31(2)^\circ$, $\gamma = 109.45(2)^\circ$, $V = 976.0(2)$ Å^3, $Z = 2$, $D_{cal} = 1.293$ Mgm^{-3}, $\mu = 1.856$ mm^{-1}, $F_{000} = 400$, λ (CuKα) = 1.5418 Å, final R1 and wR2 are 0.081 and 0.239, respectively. The imidazole ring in both the molecules is planar. The n-butyl group adopts a bent conformation in BCIC where it is in extended conformation in BCCI. The biphenyl ring system orients at an angle of 45.1(1)° in BCCI. The molecules are stabilized by N-H…N and O-H…N type hydrogen bonds in addition to van der Waals forces.

Keywords: crystal structure; conformation; hydrogen bonding; BCIC; BCCI

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INTRODUCTION

Imidazole is a heterocyclic five-membered ring containing nitrogen atoms. Various imidazole derivatives are found to possess biological activities. Interestingly, it is to be noted that biotin, a heterocyclic sulfur-containing B-complex vitamin, is fused of imidazole and thiophene rings and participates as a coenzyme in the carboxylation reaction [1].

Imidazole is a protonated five-membered ring, which promotes chemical reactions depending on the specific physical conditions at enzyme catalytic sites [2]. Imidazoles and benzimidazoles are the components of important structures used in pharmaceuticals, agrochemicals, dyestuffs, and high temperature polymer products. The crystal structure of cis-1-{[4-(1-Imidazolylmethyl) cyclohexyl] methyl} imidazole-succinic acid complex has been determined since it is an active nonsteroidal aromatase inhibitor [3, 4].

With a view to understand the conformation of the imidazole moiety and the influence of substituents at different positions of this five-membered ring, the crystal structure determination of two imidazole derivatives have been carried out. The chemical diagrams of BCIC and BCCI are shown in Figure 1.

X-RAY DATA COLLECTION, STRUCTURE SOLUTION, AND REFINEMENT

Data Collection

Intensity data were collected on a Siemens SMART CCD [5] area detector diffractometer using graphite monochromated MoKα radiation for BCIC.

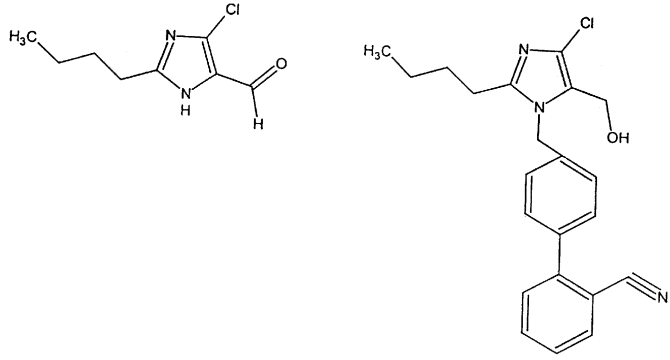

FIGURE 1 Chemical diagrams of BCIC and BCCI.

The entire data collection was covered over a hemisphere of reciprocal space by a combination of three sets of exposure, each having a different ϕ angle (0, 88, and 180°) for the crystal and each exposure time of 10 s covered 0.3° in ω. The crystal-to-detector distance was 4 cm and the detector swing angle was −35°. Coverage of unique set was complete by over 99%. Crystal decay, monitored by repeating thirty initial frames at the end of the data collection and analyzing the duplicate reflections, was found to be negligible.

For BCCI, the data were collected on a CAD4 diffractometer [6] using graphite monochromated CuKα radiation. Accurate unit cell parameters were derived from least-squares analysis using 25 reflections. In order to check the intensity deterioration due to the radiation damage or crystal degradation, three standard reflections were monitored for every 1 h or for every hundred reflections, whichever is the earliest. The intensity data were corrected for Lorentz, polarization, and absorption effects [7].

Structure Solution and Refinement

Both the structures were solved using direct methods in SHELXS97 [8] and refined in SHELXL97 [9]. Hydrogen atoms were placed at the calculated positions but not refined. The final cycles of full-matrix least-squares refinement were carried out applying anisotropic thermal parameters for all nonhydrogen atoms. The geometrical parameters were calculated using PARST [10], and the molecular graphics were drawn through ZORTEP [11].

RESULTS AND DISCUSSION

The crystal and refinement data are given in Table I. Figures 2 and 3 show the ZORTEP plot of the molecules of BCIC and BCCI with thermal ellipsoids at 30% probability level. The bond lengths and bond angles of the imidazole moiety in BCIC and BCCI are comparable with the standard values [12, 13]. The C-C1 distances (C4-C112=) 1.712(2) Å and 1.723(4) Å are within the range of values reported in the literature [14].

In BCIC molecule, the imidazole ring, carbaldehyde group, and C1 atom lie in the same plane except the n-butyl chain which adopts a bent conformation as can be seen from the conformational angles (N3-C2-C6-C7=) 63.5(2)°, (C2-C6-C7-C8=) 61.8(2)°, and (C6-C7-C8-C9=) 71.0(2)°. In BCCI molecule, the 2-n-butyl substitution at C2 lies almost in the plane of the imidazole moiety. This facilitates the atom C7 to form a C-H...N hydrogen bonding with the imidazole nitrogen N3 (C7...N3=)2.861(6)Å and (C7-H7B...N3=88.3(3)°). The n-butyl group of BCCI is in an

TABLE I Crystal Data for BCIC and BCCI

Parameter	BCIC	BCCI
Empirical formula	$C_8H_{11}Cl\ N_2O$	$C_{22}H_{22}Cl\ N_3O$
Formula weight	186.64	379.88
Temperature(K)	293(2)	293(2)
Wavelength	0.71073Å	1.5418Å
Crystal system	Monoclinic	Triclinic
Space group	P21/c	P $\bar{1}$
Unit cell dimensions	a = 7.2617(3)Å b = 13.2067(6)Å c = 9.8491(4)Å $\beta = 101.76(1)^\circ$	a = 8.198(2)Å b = 10.997(3)Å c = 11.524(2)Å $\alpha = 90.83(2)^\circ$ $\beta = 94.31(2)^\circ$ $\gamma = 109.45(2)^\circ$
Volume	924.74(7)Å^3	976.0(4)Å^3
Z	4	2
Calculated density	1.341 Mg/m^3	1.293 Mg/m^3
Absorption coefficient	0.367 mm^{-1}	1.856 mm^{-1}
F(000)	392	400
Crystal size	0.24 × 0.14 × 0.08 mm	0.35 × 0.20 × 0.10 mm
θ - range for data collection	2.62 to 28.29°	3.85 to 71.92°
Index ranges	$-9 \le h \le 9$ $-13 \le k \le 17$ $-11 \le l \le 13$	$-10 \le h \le 9$ $0 \le k \le 13$ $-14 \le l \le 14$
Reflections collected	6383	4023
Independent reflections	2268 [R(int) = 0.0597]	3821 [R(int) = 0.0891]
Observed reflections [$I > 2\sigma(I)$]	1664	2423
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	0.946	1.086
Final R-indices [$I > 2\sigma(I)$]	$R_1 = 0.049$, $wR_2 = 0.126$	$R_1 = 0.081$, $wR_2 = 0.239$
R-indices (all data)	$R_1 = 0.0634$, $wR_2 = 0.1333$	$R_1 = 0.1247$, $wR_2 = 0.2757$

extended conformation as evidenced by the conformational angles (N1-C2-C6-C7=)176.4(5)°. (C2-C6-C7-C8=)−177.1(5)°, and (C6-C7-C8-C9=) 178.5(5)°.

The imidazole ring is planar in both the molecules (maximum deviation 0.005(2)Å for N3 in BCIC and 0.008(5)Å for C5 in BCCI). This is also supported by the minimum q_2 values of 0.009(2) for BCIC and 0.005(4) for BCCI [10]. In BCCI, the sum of the bond angles around N1 is 360.0°, which confirms that the atom N1 is in sp^2 hybridized state. The bond length N1-C13 is comparable with the standard value [15].

In BCCI, the two phenyl rings (biphenyl ring system) are planar (maximum deviation ±0.014(5)Å), and the mutual orientation of these phenyl

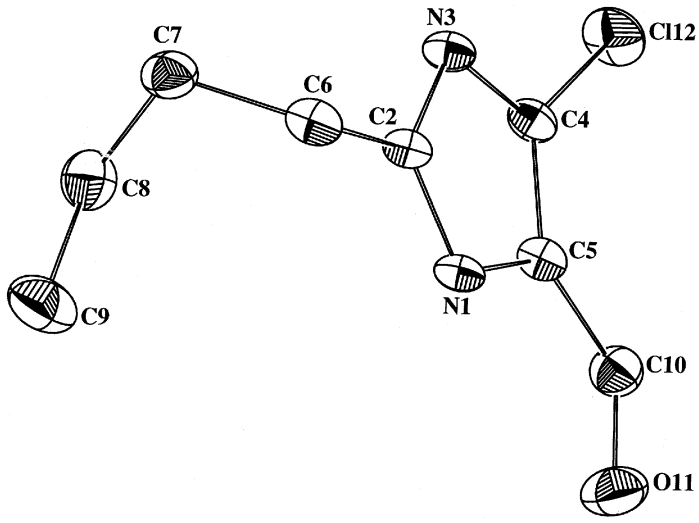

FIGURE 2 ZORTEP diagram of BCIC.

rings is 45.1(1)°, a common feature observed in many biphenyl derivatives [16]. In the biphenyl ring system, the endocyclic bond angles at C16 and C20 are contracted to 118.0(4)° and 118.3(4)°, respectively, due to steric hindrance between the rings. The cyano group (C≡N) attached to the phenyl ring is linear (C25-C26-N27=177.8(5)°). The two phenyl rings (biphenyl group) are oriented at angles of 85.3(2)° and 80.6(2)° with respect to the imidazole moiety.

In BCIC, the molecules are linked by a three-dimensional network of N-H . . . N type hydrogen bonds. But the O-H . . . N type hydrogen bonds stabilize the molecules in BCCI crystal. Weak intermolecular interactions of the type C-H . . . O and C-H . . . N are also observed in the crystals of both BCIC and BCCI.

Preparation of BCIC

A mixture of glycine (0.55 mol, 41.7 g), methanol (175.0 ml), and water (10 ml) was cooled to 0°C under stirring. Two drops of 30% NaOH was added into the mixture (pH 8.0–9.5). To this mixture, a solution of methyl pentanimidate (0.55 mol, 64.0 g) in toluene (106 ml) was added and stirred for 15 min. The mixture was stirred overnight. The pH of the mixture was then adjusted from 10.1 to 7.0 (conc. H_2SO_4) and charged with toluene (500 ml). The methanol was distilled completely and the mixture was cooled to 0°C. To the cooled mixture was added with $POCl_3$ (1.55 mol,

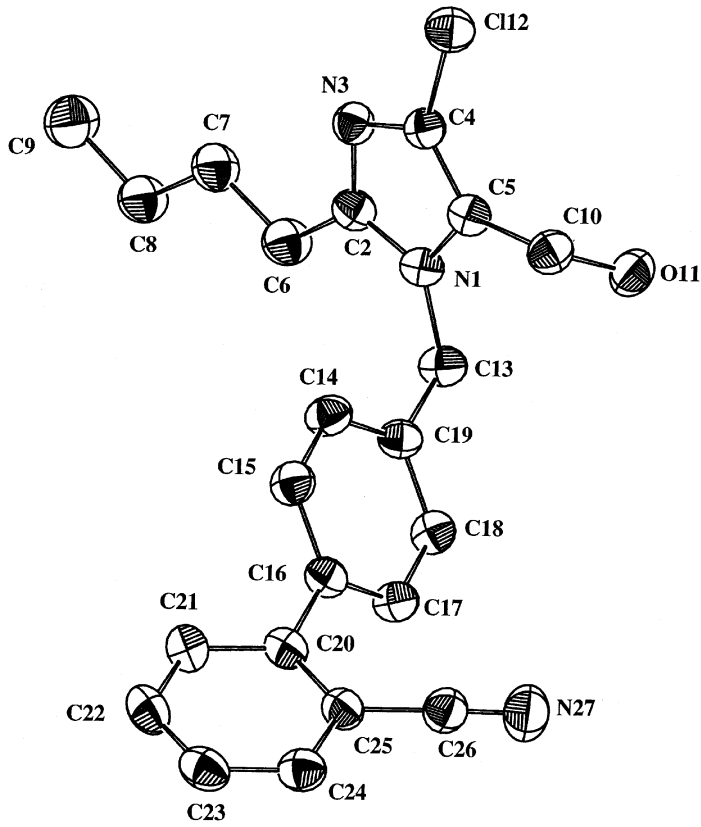

FIGURE 3 ZORTEP diagram of BCCI.

238.0 g) and DMF (1.55 mol, 113.6 g) at 80°C. The mixture was heated at 100°C for 2 h, cooled to room temperature and poured into ice water (370 ml) (temp. 30°C) with vigorous stirring for 2 h. The organic layer was separated after adjusting the pH of the mixture of 7.2. It was washed with water (2×50 ml), dried over anhydrous Na_2SO_4 concentrated, and cooled to −10°C for 2 h. The product separated was filtered off, washed with ice-cold toluene, and dried to get 57.5 g (55%) of pure product. It was recrystallized from CC14 to get white needles.

Preparation of BCCI

A solution of 2-n-butyl-4-chloro-5-formylimidazole (0.05 mol, 9.32 g) in methanol (40 ml) was cooled at 0°C. Sodiumborohydride (0.0125 mol, 0.4727 g) was added slowly with stirring. the reaction mixture was then

stirred at room temperature for 2–3 h. After completion of reaction (TLC), the mixture was concentrated to about 10 ml and poured into ice water (100 ml). The white product formed was filtered, washed, with water and dried under vacuum at 50°C to get 90% (8.4 g) of 2-n-butyl-4-chloro-5-hydroxymethyl imidazole. To a suspension of sodium methoxide (0.03 mol, 1.62 g) in DMF (25 ml) was added 2-n-butyl-4-chloro-5-hydroxymethylimidazole (0.03 mol, 5.655 g) in DMF (25 ml). The mixture was stirred at 25°C for 30 min. To this mixture was added in drops, a solution of 4-bromomethyl-2′-cyanobiphenyl (0.025 mol, 6.80 g) in DMF (25 ml). The mixture was stirred at room temperature for 24 h. The mixture was evaporated to a residue under vacuum and dissolved in ethyl acetate (70 ml), washed with brine solution (20 ml), water (50 ml), dried using Na_2SO_4, and evaporated to get a crude product which was purified by column chromatography using n-hexane-ethylacetate mixture (7:2) as the eluent to get the title product in 40% yield (3.11 g). It was recrystallized from CCl_4 to get white needles. Both BCCI and BCIC are white crystalline solids and serve as important key intermediates for preparing antihypertensive drug Losartan potassium [17]. Both compounds are soluble in chloroform, tetrahydrofuran, acetone, etc. It answers the tests for primary alcoholic and chloro groups.

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