Synthesis of cis-perhydropyrrolo [3, 4-c]pyridine-3,4-dione and Its X-ray Structure

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***Abstract*—cis-perhydropyrrolo[3,4-c]pyridine-3,4-dione, a kind of nontoxic and nootropic agent, was synthesized in laboratory with a milder method than literature methods. The colorless crystal was derived from ethanol solution by solvent evaporation and the crystal structure was determined by using X-ray diffraction method. The Crystal system is monoclinic and the formula is $C_7H_{10}N_2O_2$ which is different from that in the consulted reports in reference.**

Keywords-cis-perhydropyrrolo[3,4-c]pyridine-3,4-dione; synthesis; crystal; X-ray diffraction

I. INTRODUCTION

Along with the growth of age, people's memory will be a recession and their cognitive capacities are changing to bad, especially the memory ability. The incidence of cognitive disorders in the population is likely to grow [1], therefore, it is significant to research and develop an effective nootropic drug for the people who need necessary medical care. Cosimo Altomare et al. [2] synthesized some mono- and bi-cyclic lactam derivatives by reductive cyclization reactions under the condition of high pressure. The cognition activating properties of *cis*-perhydropyrrolo [3,4-c]pyridine-3,4-dione was evaluated in enhancing retention for passive avoidance learning in rats. It was also found to be more potent than piracetam in the amnesia-reversal testing [2].

In this paper, we disclose the reductive cyclization synthesis of cis-perhydropyrrolo [3,4-c]pyridine-3,4-dione in good yield under mild conditions. The crystal was obtained from ethanol solution, by evaporation slowly, and the crystal formula is $C_7H_{10}N_2O_2$.

II. EXPERIMENTAL

All chemicals are of reagent grade. The infrared spectras (IR) were recorded with KBr discs on a Bio-Rad FTS-165 spectrometer at a range of 4000-500 cm^{-1}. The ^1H NMR and ^{13}C were obtained with a Bruker DPX-400 NMR. *Cis*-perhydropyrrolo [3,4-c]pyridine-3,4-dione was synthesized by five steps which are illustrated in Fig.1.

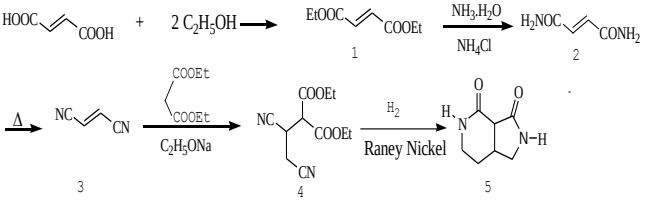

Figure 1. Synthesis scheme of cis-perhydropyrrolo[3,4-c]pyridine-3,4-dione

A. Diethyl Fumarate [3, 4]

Fumaric acid (116g, 1.0mol), absolute ethyl alcohol (250ml, 4.3mol), p-toluenesulfonic acid (8.0g) and cyclohexane (200ml) were stirred at 130℃ for 8 hours in 1000 ml of three-necked flask which was equipped with thermometer, reflux condenser and water separator. The alcohol solution and cyclohexane were removed by rotary evaporation and the residue was distilled to give 154.8 g diethyl fumarate, the yield was 90%. IR (cm^{-1}/film): 2985, 1729, 1645, 1300 and 776. ^1H NMR (400MHz, $CDCl_3$): 1.319ppm (6H, t, $-CH_3$), 4.233-4.286ppm (4H, m, $-CH_2-$), 6.851ppm (2H, s, -CH=).

B. Fumaramide [5]

Diethyl fumarate (136.8, 0.8mol), 220 ml of concentrated ammonium hydroxide (25%), and 16.0g of ammonium chloride were placed in a 500ml round bottom flask. The mixture was stirred at room temperature for 4 h and the color of the mixture turned to white as the mixture reacted. White solid was got after filtering, washing with distilled water and ethanol in turn. The white solid was dried in a drying oven below 70℃ to produce 68.5g fumaramide, the yield was 75%. IR (cm^{-1}/film): 3334, 3162, 1690, 1625. ^1H NMR (400MHz, *d*-DMSO): 6.763ppm (2H, s, -C=H), 7.329ppm (2H, s, -NH, -NH), 7.790ppm (2H, -NH, -NH).

C. Fumaronitrile [5, 6]

The dry fumaramide (43.60g, 0.38mol) and phosphorus pentoxide (116.92g, 0.83mol) were placed in a 500ml round bottom flask. The mixture was mixed well by stirring and the flask was connected to an air condenser. The reaction progressed at 160 ℃ for 30 minutes under the condition of reduced pressure, the mixture became black gradually and

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got white needle-like crystal in air condenser. The product was recrystallized by dissolving it in absolute ethyl alcohol and got fumaronitrile (20.7g), the yield was 70%.^{1}H NMR (400MHz, $CDCl_3$): 6.293ppm (2H, s, =CH). ^{13}C NMR (100MHz, $CDCl_3$), 114.08ppm (2C, -CH=), 119.27ppm (2C, -CN).

D. 1, 2-Dicyano-3, 3-propanedicarboxylic Acid Bis (ethy1 ester) [2]

EtONa (13.6g, 0.2mol) was dissolved in absolute ethyl alcohol (50mL) under the condition of ice bath for 30 minutes with magnetic stirring. Ethyl malonate (32g. 0.2 mol) in absolute ethyl alcohol (10ml) was added dropwise with cooling and stirring. Fumaronitrile (10.15g, 0.13mol) was then added slowly after the mixture was heated to ambient temperature. When the reaction ended with TLC test, the reaction mixture was neutralized to pH =7 with acetic acid and the solvent was removed by rotary evaporation. The residue was partitioned in water and CCl_4 in separatory funnel and the organic layer was separated by Column chromatography after solvent removal to give 11.7g of (4). The yield was 60%. IR (cm^{-1}/film):2986, 2940, 2253, 1735, 1179, 1021. ^{1}H NMR (400MHz, $CDCl_3$): 1.299-1.345ppm (6H, m, $-CH_3$), 2.966ppm (2H, d, $-CH_2CN$), 3.591-3.643ppm (1H, m, -CHCN), 3.797ppm (1H, d, -CHCO), 4.255-4.354ppm (4H, m, $-CH_2O$).

E. Cis-perhydropyrrolo [3,4-c]pyridine-3,4-dione [2]

1, 2-Dicyano-3, 3-propanedicarboxylic Acid Bis(ethy1 ester) (1.19g, 0.05mol) in 150 ml absolute ethyl alcohol and activated Ra-Ni (0.9g) were added to an autoclave. The mixture was stirred under hydrogen at 60℃ and 45 atm pressure for 24h. The catalyst was removed by filtration and the solution was evaporated by rotary evaporation to produce oily sample .The residue which was dissolved in 150 ml toluene was added to an autoclave and reacted for 8h at 120℃. The solution was evaporated by rotary evaporation to produce white powder after adding dichloromethane. The powder was obtained by filtration. The yield was 65%. IR (cm^{-1}/film): 3196, 3083, 2954, 2880, 1696. ^{1}H NMR (400MHz, $CDCl_3$): 1.457-1.546ppm (1H, m, H (5ax)), 1.722-1.792ppm (1H, m, H(5eq)), 2.675-2.753ppm (1H, m, H (6)), 2.908ppm (1H, d, H (7eq)), 3.002ppm (1H, d, H (2)), 3.076-3.111ppm (2H, m, H (4ax) and H (4eq)), 3.324ppm (1H, t, H (7ax)), 7.567ppm (1H, s, -NH), 7.726ppm (1H, s, -NH).

F. X-ray Structure Determinations

Colorless crystal suitable for X-ray was obtained by solvent evaporation in ethanol slowly at room temperature. Single crystals of $C_7H_{10}N_2O_2$ were measured using an Oxford Gemini E diffract meter for data collection (graphite-monochromated MoKα radiation λ=0.71073, ωs can mode). The crystal was kept at 293.15 K during data collection. Using Olex2 [7], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimisation. The non-hydrogen atoms were refined anisotropically by full-matrix least-aquares calculations on F2. The hydrogen atoms were placed in geometric positions and refined isotropically.

III. RESULTS AND DISCUSSION

Cis-perhydropyrrolo[3,4-c]pyridine-3,4-dione was synthesized by five steps, the above mentioned reactions could take place under mild conditions, the yields were high, and the products were purified easily. In [2], the reductive cyclization reaction was conducted under hydrogen at 100 ℃ and 100 atm pressure for 48h by one-pot method. We have the work coming from two steps: the reductive experiment should be made under hydrogen at 60 ℃ and 45 atm pressure for 12 h and after filtration and stripping of the solvent, the final cyclization step was conducted in toluene at 120 ℃ in the same autoclave to avoid high pressure.

The bond lengths and bond angles for compound 5 are listed in Fig. 3 and the relevant information in the literature is given in Fig. 2, the crystal datas are reported in Table I and the relevant tordion angles computered are shown in Table II, while perspective views of compound 5 are reported in Fig. 4. In the structure of compound 5, the six-membered ring and five-membered ring are connected by C2-C6 bond length of 1.530Å. The six-membered ring assumes a half-chair conformation, all atoms are not coplanar in both rings, and the dihedral Angles between two planes are shown in Table Ⅲ.

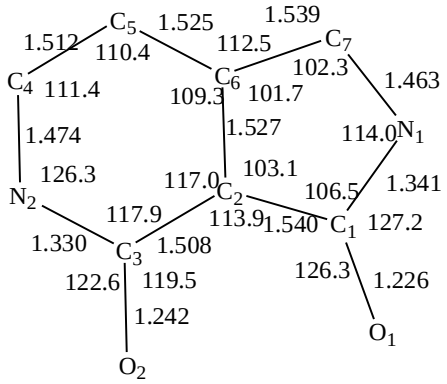

Figure 2. Bond angles and bond lengths in [8]

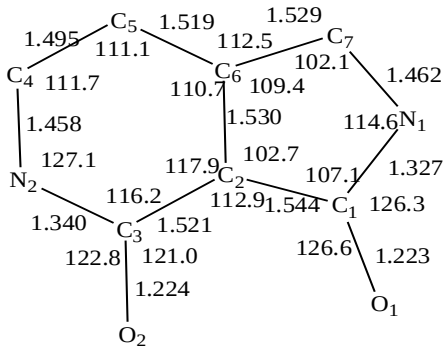

Figure 3. Bond angles and bond lengths for compound 5

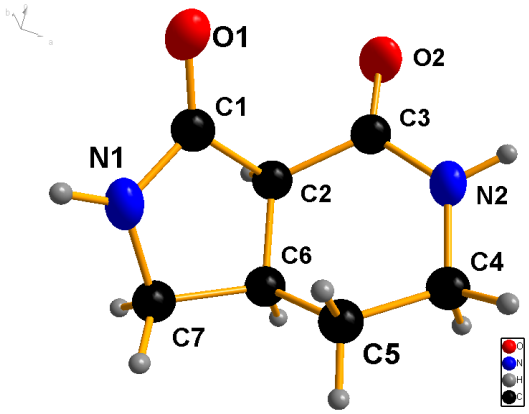

Figure 4. Perspective views of the crystals of 5 measured

TABLE I. CRYSTAL DATA FOR CIS-PERHYDROPYRROLO[3,4-C]PYRIDINE-3,4-DIONE (5) AND CIS-PERHYDROPYRROLO[3,4-C]PYRIDINE-3,4-DIONE IN [8]

Compound	5	5·H_2O
Empirical formula	$C_7H_{10}N_2O_2$	$C_7H_{10}N_2O_2.H_2O$
Formula weight	154.17	172.2
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a/Å	12.9862(8)	10.693(6)
b/Å	6.4081(3)	6.159(3)
c/Å	9.1138(6)	12.805(9)
β/°	109.583(7)	91.32(5)
Volume/$Å^3$	714.54(7)	843.1(8)
Z	4	4
F(000)	328.0	368
Crystal size/mm^3	0.42 ×0.36 ×0.28	0.5 ×0.4 ×0.2

TABLE II.. THE DIFFERENCE IN RELEVANT TORSION ANGLES FOR COMPOUND (5) AND COMPOUND IN [8]

	Five –Membered Ring	
	Compound (5)	5·H_2O
C7-N1-C1-C2	-0.4	-1.0
N1-C1-C2-C6	-19.6	22.4
C1-C2-C6-C7	30.7	33.5
C2-C6-C7-N1	-30.7	32.7
C6-C7-N1-C1	20.2	-20.6
	Six –Membered Ring	
C3-N2-C4-C5	-26.3	24.6
N2-C4-C5-C6	51.3	-50.7
C4-C5-C6-C2	-57.0	58.7
C5-C6-C2-C3	37.7	-40.3
C6-C2-C3-N2	-12.5	13.7
C2-C3-N2-C4	6.3	-5.4
C4-C5-C6-7	-169.7	170.8
N2-C3-C2-C1	107.1	-106.5
	others	
C1-C2-C6-C5	-87.1	
C3-C2-C6-C7	155.4	
N1-C1-C2-C3	-147.6	
C4-N2-C3-O2	-174.6	
N1-C7-C6-C5	86.1	
O1-C1-N1-C7	-179.3	
O1-C1-C2-C3	31.3	
O1-C1-C2-C6	159.3	
O2-C3-C2-C1	-71.9	
O2-C3-C2-C6	168.5	

TABLE III. THE DIHEDRAL ANGLES OF PLANES IN BOTH RINGS

Plane 1	Plane 2	dihedral Angle
C1-N1-C7	C2-C6-C7	32.421(320)°
C4-C5-C6	C6-C2-C3	52.962(290)°
C4-C6-C5	C4-N2-C3	46.417(297)°
C6-C2-C3	C4-N2-C3	11.175(236)°

The crystal packing of compound 5, which is shown in Fig.5, is characterized by intermolecular hydrogen bonds. The two amide groups formed intermolecular hydrogen bonds (N1-H1···O1 and N2-H2…O2), the H(7A) of C(7) is also attractive to O(1) atom forming intermolecular hydrogen bond. The hydrogen bond information about compound 5 is shown in Table Ⅳ. In the [8], the water molecules are engaged in three hydrogen bonds, one as acceptor, with the six-membered ring NH group, the others as donor, with the CO groups of the same ring [8]

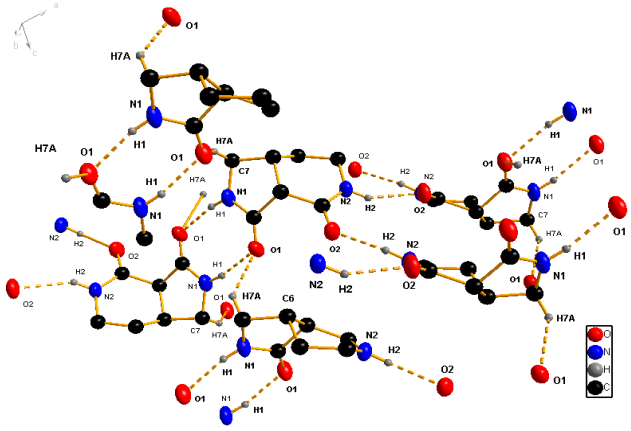

Figure 5. The hydrogen-bond interaction of compound 5

TABLE Ⅳ. THE HYDROGEN BOND INFORMATION ABOUT COMPOUND 5

D-H···A	d(H···A)/ Å	d(D-A)/ Å	∠(D-H···A)/°
N(1)-H(1)···O(1)	2.07	2.922(4)	169
N(2)-H(2)···O(2)	2.20	2.971(4)	149
C(7)-H(7A)···O(1)	2.55	3.322(5)	137

IV. CONCLUSIONS

The nootropic drug had been successfully synthesized by a mild route. The compound 5 was dissolved in ethanol at room temperature and colorless crystal was obtained by solvent evaporation. The formula of colorless crystal was $C_7H_{10}N_2O_2$, the crystal was packed by intermolecular hydrogen bond and other information on crystal 5 also was reported.

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