INTRODUCTION

Bridgehead nitrogen heterocyclic compounds are of interest because they constitute an important class of natural as well as synthetic products, many of which exhibit useful biological activity, particularly in the treatment of neurodegenerative disorders such as Parkinson’s disease [1], antianxiety disorders [2] and depression [3]. Heterofused pyrimidines exhibit promising antiviral [4], antibacterial [5], anti AIDS [6], and antinoiceptive [7] activities. Fused pyrimidines are selective inhibitors for multidrug resistance (MDR) [8]. A review on the synthesis, chemical and biological properties of pyrido[1,2-a]pyrimidines is described [9]. Pyridin-1,2-alpyrimidin-4-one derivatives as a novel class of selective aldose reductase inhibitors exhibiting antioxidant activity has been reported [10]. Some bridgehead nitrogen heterocycles are key intermediates for the synthesis of rutaecarpine alkaloids, some have characteristic pharmacological properties such as analgesic antiallergic, antiasthmatic and antipsychotic agents, and some are neutral hydrogen chloride acceptors in organic synthesis [11]. Acid catalyzed interaction of hetaryl amines viz., aminopyridines and aminopicolines, with 1,3-difunctional compounds e.g., β-ketoesters, malonates or 2-alkoxymethylene malonates, is a commonly employed reaction for preparation of bridgehead and other related N-heterocycles [12, 13]. The interaction is known to proceed through the intermediacy of enamines which are cyclized to the desired products e.g., pyridopyrimidines, naphthyridines.

In the present study, we report the synthesis and X-ray studies of 2,8-dimethyl-3-chloro-4H-pyrido[1,2-a]pyrimidin-4-one. The first detailed paper in the field of the pharmacology of the pyrido[1,2-a]pyrimidines was a study on the histamine-liberating and nonspecific spasmylic activity of 2-(2-dimethylaminoethyl)-3-(4-methoxyphenylmethyl)-4-oxo-4H-pyrido[1,2-a]pyrimidine [14]. Certain pyrido[1,2-alpyrimidin-ium salts [15] and 4-oxo-4H-pyrido[1,2-alpyrimidine derivatives [16–18] have been patented as dyes sensitizing photographic silver halide emulsions and photoconducting layers.

EXPERIMENTAL

Synthesis of 2,8-dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one. 2,8-Dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one, was synthesized by reported procedure [12, 13]. 2-Amino-4-picoline (1.08 gm, 10 mM) and ethyl acetoacetate (1.95 gm, 15 mM) were taken in a round-bottom flask fitted with a reflux condenser and a CaCl2 guard tube. To the reactants, PPA was added and progress of the reaction was monitored on Merck precoated TLC Silica gel 60 F254 plates (CHCl3 : MeOH = 98 : 2). Reaction was completed in 24 hrs. Then the reaction mixture was poured into water, basified with aq. ammonia and extracted with CHCl3. The extract was dried over anhydrous Na2SO4 and distilled under reduced pressure to obtain the title compound. It was crystallized from acetone-petroleum ether. Spectral data was observed to be identical with the reported data [19].

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Synthesis of 2,8-dimethyl-3-chloro-4H-pyrido[1,2-a]pyrimidin-4-one. 2,8-Dimethyl-4H-pyrido[1,2-a]pyrimidin-4-one (870 mg, 5 mM) was taken in a round-bottom flask fitted with reflux condenser and a guard tube. Carbon tetrachloride (50 mL) was added into the flask. N-Chlorosuccinimide (665 mg, 5 mM) and catalytic amount of benzoyl peroxide was added to the clear solution. The reaction mixture was refluxed on steam bath and progress of reaction was monitored on Merck precoated TLC Silica gel 60 F254 plates (CHCl3: MeOH = 98:2). Reaction was complete in 2 hrs. After the completion of the reaction, liberated succinimide was filtered off; the filtrate was distilled under reduced pressure to obtain the title compound. It was crystallized from acetone under refrigerated conditions. The reaction scheme and chemical structure of the title compound is shown in Fig. 1.

Crystal structure determination. The crystallographic data are summarized in Table 1. The structure was solved by direct methods. All non-hydrogen atoms were located in the best E-map. All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-H atoms with C–H distances of 0.93–0.96 Å; and with $U_{	ext{iso}}(H) = 1.2U_{	ext{eq}}(C)$, except for the methyl groups where $U_{	ext{iso}}(H) = 1.5U_{	ext{eq}}(C)$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4).

Crystallographic information has been deposited with Cambridge Crystallographic Data Centre, CCDC number 840262. These data can be obtained free of charge at Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

An ORTEP [21] view of the title compound with atomic labeling is shown in Fig. 2. The geometry of the molecule was calculated using the PLATON [22] and PARST [23] softwares. The asymmetric unit contains two independent molecules, A and B. The molecules consist of a pyridine ring fused to a substituted pyrimidine ring via the common atoms N5 and C10 creating a planar ring system. The overall molecular parameters of the title compound, including bond distances and angles, have a normal values [24] and are in good agreement with related structures [25–28]. The sum of the angles around N5 in both the molecules is 360.0(2)° indicating sp2–

Table 1. Crystallographic characteristics and the X-ray-data collection and structure-refinement parameters for C10H9ClN2O
hybridization. The C4=O4 bond length is found to be 1.235(3) Å in molecule A and 1.232(3) Å in molecule B. These values are in good agreement with those observed in pipemidic acid [1.237(3) Å] [29] and in cinoxacin [1.248(3) Å] [30]. In both molecules, the pyrido-pyrimidine moiety is planar with a dihedral angle of 3.53(9)° for molecule A and 1.61(9)° for molecule B. These values are in good agreement with those observed between the molecules A and B. In molecule A, the observed C–H···π interactions are given in Tables 3 and 4, respectively.

A packing of the molecules in the unit cell viewed down the a-axis is shown in Fig. 3. Three intermolecular C–H···O hydrogen bonds link the molecules A and B into layers. One C–H···Cl interaction was also observed between the H atom of the methyl group at C6 and Cl atom at C3. π–π Interactions were also observed between the molecules A and B. The pyrido-pyrimidine moiety is involved only in π–π stacking interactions in the structure and not in any C–H···π contacts. Details of C–H···O, C–H···Cl and π–π interactions are given in Tables 3 and 4, respectively.

**Table 2.** Selected bond lengths, d, Å and bond angles, ω, deg for nonhydrogen atoms (e.s.d.’s are given in parentheses)

|     | A       | B       |
|-----|---------|---------|
| N1A–C10A | 1.328(4) | N1B–C10B | 1.328(4) |
| N1A–C2A   | 1.354(4) | N1B–C2B   | 1.350(4) |
| C4A–O4A   | 1.235(3) | C4B–O4B   | 1.232(3) |
| C4A–N5A   | 1.432(4) | C4B–N5B   | 1.434(4) |
| N5A–C6A   | 1.382(4) | N5B–C6B   | 1.380(4) |
| N5A–C10A  | 1.392(4) | N5B–C10B  | 1.400(3) |
| C10A–N1A–C2A | 118.8(2) | C10B–N1B–C2B | 119.3(2) |
| N1A–C2A–C3A | 121.3(3) | N1B–C2B–C3B | 121.2(3) |
| N1A–C2A–C11A | 116.3(2) | N1B–C2B–C11B | 116.7(2) |
| O4A–C4A–C3A | 127.8(3) | O4B–C4B–C3B | 128.1(3) |
| O4A–C4A–N5A | 119.4(3) | O4B–C4B–N5B | 119.3(3) |
| C3A–C4A–N5A | 112.8(2) | C3B–C4B–N5B | 112.6(2) |
| C6A–N5A–C10A | 120.5(2) | C6B–N5B–C10B | 120.2(2) |
| C6A–N5A–C4A | 118.0(2) | C6B–N5B–C4B | 118.0(2) |
| C10A–N5A–C4A | 121.5(2) | C10B–N5B–C4B | 121.7(2) |
| C7A–C6A–N5A | 122.1(3) | C7B–C6B–N5B | 121.8(3) |
| N1A–C10A–N5A | 122.3(3) | N1B–C10B–N5B | 121.9(3) |
| N1A–C10A–C9A | 121.1(3) | N1B–C10B–C9B | 121.5(2) |
| N5A–C10A–C9A | 116.6(3) | N5B–C10B–C9B | 116.6(2) |
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CONCLUSIONS

Synthesis of 2,8-dimethyl-3-chloro-4H-pyrido[1,2-a]pyrimidin-4-one was achieved by two step reaction starting from 2-amino-4-methyl pyridine. The second step was accomplished in 2 hrs in high yield. The molecular and crystal structure of title compound was determined using single crystal X-ray diffraction data collected at 100 K. The pyrido-pyrimidine moiety is planar in both independent molecules. The planarity of this moiety confirms the aromatic character of the system. Weak interactions (C–H⋯O, C–H⋯Cl and π–π) play a crucial part in assembling the molecules into an organized supramolecular structure.

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