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Short Note

(2,3-Dihydro-1*H*-indol-5-ylmethyl)amine

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Abstract: New (2,3-dihydro-1*H*-indol-5-ylmethyl)amine was synthesized from 2-((1-acetylindolin-5-yl)methyl)isoindoline-1,3-dione by simultaneous deprotection of phthalimide and acetyl groups. The structure of the newly synthesized compounds was established by elemental analysis, high resolution mass-spectrometry, ^{1}H, ^{13}C NMR and IR spectroscopy and mass-spectrometry. The resulting compound is a convenient intermediate for various disubstituted 1-(indolin-5-yl)methanamines, which may be of interest as substances with useful pharmacological properties.

Keywords: 2,3-dihydroindoles (indolines); (2,3-dihydro-1*H*-indol-5-ylmethyl)amine; deprotection; biological activity

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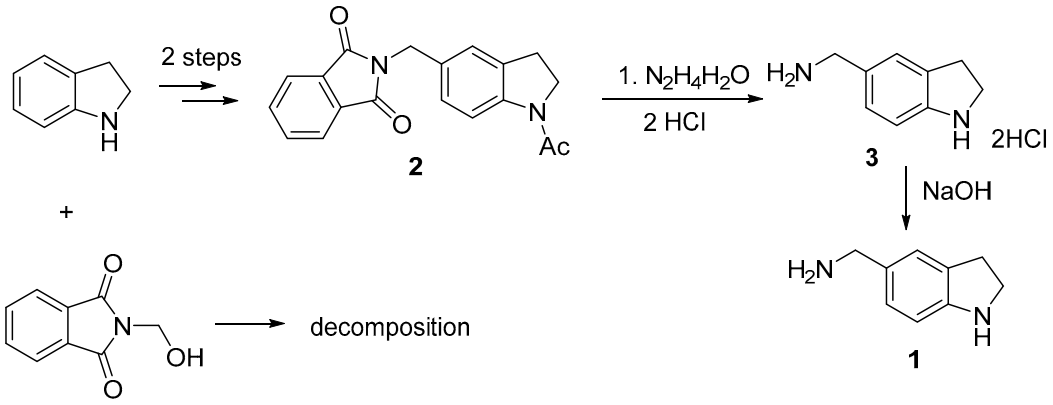
1. Introduction

2,3-Dihydroindoles (indolines) are important structural components presented in many natural products and biologically active compounds [1,2]. In this regard, di-N,1-substituted 1-(indolin-5-yl)methanamines are of a great interest. These compounds have been identified by targeted SAR studies as promising structures interacting with RCAR/(PYR/PYL) receptor proteins [3]. Some of indolinylmethyl sulfonamides showed a strong affinity for RCAR/(PYR/PYL) receptor proteins in wheat, and the binding affinity of several their representatives was at the same level or even better than that of the essential plant hormone abscisic acid (ABA) [3]. All of these heterocyclic compounds were obtained from commercially available indoline in several synthesis steps. (2,3-dihydro-1*H*-indol-5-ylmethyl)amine **1** can be considered as an important intermediate for the preparation of other disubstituted 1-(indolin-5-yl)methanamines. Herein, we report the synthesis of a previously unknown (2,3-dihydro-1*H*-indol-5-ylmethyl)amine **1** via its dihydrochloride salt **2**.

2. Results and Discussion

The most direct method for the preparation of (2,3-dihydro-1*H*-indol-5-ylmethyl)amine **1** is the Tscherniac-Einhorn reaction of indoline with commercially available 2-(hydroxymethyl) isoindoline-1,3-dione using concentrated sulfuric acid as a catalyst [4] followed by hydrolysis of phthalimido to amino group. We have shown that this reaction led to a difficult-to-separate mixture of compounds apparently due to the reaction with the unprotected NH indoline group. It has been described that acetyl-protected indoline reacted successfully with 2-(hydroxymethyl)isoindoline-1,3-dione giving compound **2** in good yield [5]. Refluxing compound **2** with hydrazine hydrate in MeOH, followed by treatment with conc. HCl led to the desired (2,3-dihydro-1*H*-indol-5-ylmethyl)amine dihydrochloride **3** in high yield (Scheme 1). The main feature of this procedure is that two protective (phthalimido and acetyl) groups were removed simultaneously with the formation of unsubstituted heterocycle **3**. The target (2,3-dihydro-1*H*-indol-5-ylmethyl)amine was obtained by alkalizing the disalt **3**.



Scheme 1. Synthesis of (2,3-dihydro-1*H*-indol-5-ylmethyl)amine **1**.

The structure of (2,3-dihydro-1*H*-indol-5-ylmethyl)amine **1** and its dihydrochoride salt **3** was confirmed by elemental analysis, high resolution mass-spectrometry, ^{1}H, ^{13}C NMR and IR spectroscopy, and mass-spectrometry. Compared with disubstituted compound **2**, the spectral data of compound **1** contain, in addition to signals characteristic of the indoline ring and CH_2 group, signals characteristic of the NH_2 and NH groups: in ^{1}H NMR spectrum—2.45 (2H) and 5.28 (1H) ppm, and in IR spectrum—3359, 3282, 3012 cm^{-1}.

In conclusion, the first representative of indolines containing a methylamine group—(2,3-dihydro-1*H*-indol-5-ylmethyl)amine **1**, was obtained. This compound opens up possibilities for the synthesis of various functional derivatives of disubstituted 1-(indolin-5-yl)methanamines, which may be of interest as compounds with useful pharmacological properties.

3. Materials and Methods

2-((1-Acetylindolin-5-yl)methyl)isoindoline-1,3-dione **2** was prepared according to the published method [5]. The solvents and reagents were purchased from commercial sources and used as received. Elemental analysis was performed on a 2400 Elemental Analyzer (Perkin ElmerInc., Waltham, MA, USA). Melting point was determined on a Kofler hot-stage apparatus and is uncorrected. ^{1}H and ^{13}C NMR spectra were taken with a Bruker AM-300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) (at frequencies of 300 and 75 MHz) with TMS as the standard. J values are given in Hz. MS spectrum (EI, 70 eV) was obtained with a Finnigan MAT INCOS 50 instrument (Hazlet, NJ, USA). IR spectrum was measured with a Bruker "Alpha-T" instrument in KBr pellet. High-resolution MS spectrum was measured on a Bruker micrOTOF II instrument (Bruker Daltonik Gmbh, Bremen, Germany) using electrospray ionization (ESI).

Synthesis of (2,3-dihydro-1*H*-indol-5-ylmethyl)amine dihydrochloride **3** (Supplementary Materials).

A mixture of 2-((1-acetylindolin-5-yl)methyl)isoindoline-1,3-dione **2** (2 g, 6.3 mmol) and hydrazine hydrate (1 mL, 31.6 mmol) in methanol (20 mL) was refluxed for 3 h. Excess of methanol was removed under reduced pressure. Water (10 mL) and concentrated HCl (10 mL) were added to the residue. The mixture was heated with stirring for 3 h at 70 °C. After filtration of the precipitate the aqueous layer was evaporated, the residue was washed with acetone and dried in air. Yield 1.15 g (83%), white solid, mp 211–213 °C. IR spectrum (KBr), ν, cm^{-1}: 3434, 3003, 2885, 2799 (all NH_2 and NH), 2705, 2598, 2466 (all C-H), 1591 and 1576 (N-H), 1508, 1495, 1388, 1294, 1092, 914, 838, 593, 573, 431. ^{1}H-NMR (DMSO-d_6 + CF_3COOH, ppm, *J*/Hz): δ 3.17 (2H, t, *J* = 7.7), 3.69 (2H, t, *J* = 8.1), 4.01 (2H, d, *J* = 5.1), 7.41 (1H, d, *J* = 8.1), 7.49 (1H, m), 7.58 (1H, s), 8.61 (3H, broad s). ^{13}C-NMR (DMSO-d_6, ppm): δ 28.9 (CH_2), 41.9 (CH_2-N), 44.9 (CH_2-N), 119.7 (CH-Ar), 126.7 (CH-Ar), 129.1 (CH-Ar), 135.3 (C-Ar), 136.1 (C-Ar) 136.9 (C-Ar). MS (EI, 70 Ev), *m*/*z* (I, %): 148 (M^+ − 2HCl, 100), 132 (M^+ − NH_2, 75), 118 (20), 91 (8), 36 (HCl, 33), 30 (16). HRMS (ESI-TOF): calcd for $C_9H_{12}N_2$

$[M + H]^+$ 149.1073; found *m*/*z* 149.1067. Anal. calcd. for $C_9H_{14}Cl_2N_2$: C, 48.88; H, 6.38; Cl 32.07; N, 12.67; found: C, 48.25; H, 6.43; Cl 31.96; N, 12.95%.

Synthesis of (2,3-dihydro-1*H*-indol-5-ylmethyl)amine **1** (Supplementary Materials).

Salt **3** (1 g, 4.56 mmol) was dissolved in water (8 mL). NaOH solution (40%) was added dropwise at room temperature until pH = 9. The solution was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Yield 0.52 g (77%), yellow oil. IR spectrum (KBr), ν, cm^{-1}: 3359, 3282 and 3012 (all NH_2 and NH), 2927, 2851 (C-H), 1615, 1496 (N-H), 1323, 1251, 1056, 943, 888, 816, 749, 623, 567, 420.^{1}H-NMR (DMSO-d_6, ppm, *J*/Hz): δ 2.45 (2H, broad s), 2.85 (2H, t, *J* = 8.4), 3.37 (2H, t, *J* = 8.4), 3.53 (2H, s), 5.28 (1H, broad s), 6.41 (1H, d, *J* = 8.1), 6.82 (1H, d, *J* = 7.3), 6.98 (1H s). ^{13}C-NMR (DMSO-d_6, ppm): δ 29.3 (CH_2), 45.7 (CH_2-N), 46.7 (CH_2-N), 108.0 (CH-Ar), 123.4 (CH-Ar), 125.8 (CH-Ar), 128.8 (C-Ar), 132.9 (C-Ar) 151.1 (C-Ar). Mass spectrum (EI, 70 Ev), *m*/*z* (I, %): 148 (100), 132 ($M^+ - NH_2$, 79), 118 (25), 91 (12), 30 (13). HRMS (ESI-TOF): calcd. for $C_9H_{12}N_2$ $[M + H]^+$ 149.1073; found m/z 149.1068. Anal. calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90; found: C, 72.31; H, 8.23; N, 19.01%.

Supplementary Materials: The following are available online, copies of ^{1}H, ^{13}C NMR, IR, HRMS and mass-spectra for the compounds **3** and **1** (Figure S1–Figure S10).

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