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

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Abstract: New (2,3-dihydro-1H-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, 1H, 13C 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-1H-indol-5-ylmethyl)amine; deprotection; biological activity

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-1H-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-1H-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-1H-indol-5-ylmethyl)amine 1 is the Tschermic-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-1H-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-1H-indol-5-ylmethyl)amine was obtained by alkalizing the disalt 3.
Scheme 1. Synthesis of \(2,3\)-dihydro-1H-indol-5-ylmethyl)amine 1.

The structure of \(2,3\)-dihydro-1H-indol-5-ylmethyl)amine 1 and its dihydrochloride salt 3 was confirmed by elemental analysis, high resolution mass-spectrometry, \(\text{\(^1H\)}\), \(\text{\(^{13C}\)}\) 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 \(\text{\(^1H\)}\) 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-1H-indol-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. \(\text{\(^1H\)}\) and \(\text{\(^{13C}\)}\) 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 INCONS 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 microOTOF II instrument (Bruker Daltonik GmbH, Bremen, Germany) using electrospray ionization (ESI).

Synthesis of \(2,3\)-dihydro-1H-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 ν(KBr), 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. 1H-NMR (DMSO-\(d_6\) + CF\(_3\)COOH, 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). \(\text{\(^{13C}\)}\)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), \(m/z \) (%): 148 (M\(^+\) – 2HCl, 100), 132 (M\(^+\) – NH\(_2\), 75), 118 (20), 91 (8), 36 (HCl, 33), 30 (16). HRMS (ESI-TOF): calcd for C\(_9\)H\(_{12}\)N\(_2\)
Synthesis of (2,3-dihydro-1H-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 CH₂Cl₂ (2 × 10 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Yield 0.52 g (77%), yellow oil. IR spectrum (KBr), ν, cm⁻¹: 3359, 3282 and 3012 (all NH₂ and NH), 2927, 2851 (C-H), 1615, 1496 (N-H), 1323, 1251, 1056, 943, 888, 816, 749, 623, 567, 420.¹H-NMR (DMSO-d₆, 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).¹³C-NMR (DMSO-d₆, ppm): δ 29.3 (CH₂), 45.7 (CH₂-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⁻ + NH₂, 79), 118 (25), 91 (12), 30 (13). HRMS (ESI-TOF): calcd. for C₉H₁₂N₂ [M + H]⁺ 149.1073; found m/z 149.1068. Anal. calcd. for C₉H₁₂N₂: 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 ¹H, ¹³C NMR, IR, HRMS and mass-spectra for the compounds 3 and 1 (Figure S1–Figure S10).

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