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Research Paper

Synthesis and Characterization of Some New α-Hydroxy-β-acetamido Substituted Tryptamine Derivatives

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Abstract- *Novel α-Hydroxy-β-acetamido substituted tryptamines were synthesized by the trimolecular condensation between N-Phthalimido-α-hydroxy acetaldehyde, Meldrum's acid and various substituted indoles followed by aminolysis, and careful deprotection. N-Phthalimido-α-hydroxy acetaldehyde was prepared by the reaction between Phthalimide and Glyoxalic acid followed by direct reduction with hexamine in acetic acid medium.*

Keywords: Synthesis, Tricondensation, Tryptamines, Deprotection, Aminolysis.

Introduction

Tryptamines(3-minoethylindoles) are important biologically active compounds. By acting on various receptors they participate in the regulation of biological processes, and they are widely used in medicine and medical chemistry[1]. Also Tryptamine still remains an useful starting material toward 1,2,3,4-tetrahydro- or 3,4-dihydro-β-carbolines of biological interest via pictet-spengler[2-6] and Bischler-Napieralski[7-10] condensation reactions.

In this connection there is currently increased interest in tryptamines and methods for their synthesis. A large number of different approaches to the synthesis of tryptamines have been described in the literature. However, to the best of our knowledge, no reports have appeared concerning the synthesis of α-Hydroxy-β-acetamido substituted tryptamines. Thus it was deemed of interest to find a facile and efficient methodology to synthesize this biologically significant compounds.

This paper describes work aimed at preparing a series of new α-Hydroxy-β-acetamido substituted tryptamines derivatives. All the compounds were characterized through various spectral and analytical techniques.

Material and Methods

All chemicals were of analytical grade and solvents were distilled before use. Melting points are determined in open capillaries and are uncorrected. All the compounds were routinely checked for their homogeneity by TLC. The 1H NMR and 13C NMR were recorded on Bruker AMX-500 spectrometer operating at 400 MHz using CDCl3 as solvent.

Synthesis of N-Phthalimido-α-hydroxy acetic acid (1)

Phthalimide (10 g, 68 mmol) was dissolved in THF (200 cm^3) at room temperature with stirring. 50 wt% Glyoxalic acid (30.20 g, 0,204 mol) was added to this solution. The reaction mixture was heated to reflux for 3 Hr. Evaporation to dryness under reduced pressure produced a cream solid.This was recrystallised from ethyl acetate yielding NPHA.(Scheme-I).

1:Yield:87%,White powder**,**m.p 190^O C-191^O C PMR Spectra (CDCl3): δ (ppm) 7.72-8.3 (1H, aromatic),6.32 (-CH), 2.3 (-OH);11.2(-COOH) CMR Spectra (CDCl3): δ (ppm) 127.2-133(benzene), 80.5 (- CH,aliphatic), 177.2(-COOH), 166.1 (C=O of amide)

Direct reduction of N-Phthalimido-α-hydroxy acetic acid in to N-Phthalimido-α-hydroxy acetaldehyde (2)

N-Phthalimido-α-hydroxy acetic acid (0.01 mole) was dissolved in dilute acetic acid. To this an equimolar amount of Hexamine (0.01 mole) was added and refluxed in water bath for 2 hrs. The crude N-Phthalimido-α-hydroxy acetaldehyde was isolated and crystallized from ethyl acetate.

2: Yield:84%,White powder M.P. 156^{o}C-158^{o}C :PMR

Spectra (CDCl3): δ (ppm) 7.65-8.2 (1H, aromatic),6.12 (-CH), 2.3 (-OH);9.7(-CHO) CMR Spectra (CDCl3): δ (ppm) 127.2-132.7(benzene), 86.5 (-CH,aliphatic), 200.2(-CHO),166.3 (C=O of amide)

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1-hydroxy-2-(5-hydroxy-1H-indol-3-yl)-ethyl]-isoindole 1,3-dione 3b($C_{24}H_{20}N_2O_8$)

General procedure for the synthesis of 2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1-hydroxy-2-(1H-indol-3-yl)-ethyl]-isoindole-1,3-diones(3a - c)

N-Phthalimido-α-hydroxy acetaldehyde (47.15mmol) was dissolved in 250 cm^3 of CH_3CN and to this solution appropriate indole(47.15mmol),Meldrum's acid and D,L-proline (2.36 mmol) were added under N_2 atmosphere.The reaction mixture was stirred at room temperature for 48 Hrs. The resulting solution was evaporated to dryness under reduced pressure yielded crude product. Purification of the crude product was done by Column chromatography on silica geL.

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1 hydroxy-2-(1H-indol-3-yl)-ethyl]-isoindole-1,3-dione 3a ($C_{24}H_{20}N_2O_7$)

:Yield:87%,yellow solid,mp 180^{o}C-182^{O}C PMRSpectra (CDCl3): δ (ppm) 6.7-8.3 (1H, aromatic),10.1 (-NH), 2.2 (-OH),3.5-5.8(- CH,aliphatic),1.8(CH_3) CMR Spectra (CDCl3): δ (ppm) 112.2-137.3(aromatic), 35.3-74.4 (- CH,aliphatic), 173(-COO),166.2 (C=O of amide) ,25.7(CH_3),

: Yield:85%,pale yellow solid, mp 232^{o}C -234^{o}C PMR Spectra (CDCl3): δ (ppm) 5.7-8.1 (1H, aromatic),10.3 (-NH), 2.1 (-OH),3.5-5.8(- CH,aliphatic),1.78(CH_3) CMR Spectra (CDCl3): δ (ppm) 108.2-150.3(aromatic), 34.4-73.4 (- CH,aliphatic), 172.3(-COO),167.2 (C=O of amide) ,26.1(CH_3),

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1-hydroxy-2-(5-methoxy-1H-indol-3-yl)-ethyl]-isoindole-1,3-dione 3c($C_{25}H_{22}N_2O_8$)

: Yield:87%,orange solid, mp 189^{o}C-191^{O}C PMR Spectra (CDCl3): δ (ppm) 6.8-7.1 (1H, aromatic),10.1 (-NH), 2.2 (-OH,aliphatic),3.5-5.7(-CH,aliphatic),1.8(CH_3) CMR Spectra (CDCl3): δ (ppm) 108.2-153.3(aromatic), 35.5-74.2 (- CH,aliphatic), 173.3(-COO),165.8 (C=O of amide) ,26.3(CH_3),

General procedure for the synthesis of 4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-hydroxy-3-(1H-indol-3-yl)-butyramides (4a - c)

The appropriate trimolecular adduct (1 mmol) was dissolved in 20 cm^3 of CH_3CN.To this an equimolar amount of NH_3 solution in THF (1 mmol) was added**.**

The reaction mixture was stirred under N_2 at 70^{o}C.The solvent was evaporated under reduced pressure yielded the crude product. Purification was done by column chromatography on silica gel.

4-(3-Allylidene-2,5-dioxo-pyrrolidin-1-yl)-4-hydroxy-3-(1H-indol-3-yl)-butyramide

4a ($C_{20}H_{17}N_3O_4$)

: Yield:82%,brown solid , mp 267^{o}C -269^{o}C PMR Spectra (CDCl3): δ (ppm) 7.1-8.2 (1H, aromatic),10.1 (-NH), 2.1 (-OH),2.5-5.7(CH,aliphatic),5.8(amide) CMR Spectra (CDCl3): δ (ppm) 111.2-133.2(aromatic), 35.1-75.3 (- CH,aliphatic), 165.6(-C=O),176.7 (amide)

4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4 hydroxy-3-(5-hydroxy-1H-indol-3-yl)-butyramide 4b($C_{20}H_{17}N_3O_5$)

: Yield:84%,brown solid , mp 310^{o}C-312^{O}C PMR Spectra (CDCl3): δ (ppm) 5.7-8.1 (1H, aromatic),10.3 (-NH), 5.1(-OH,aromatic)

2.0(-OH,aliphatic)2.4.5-5.8(-CH,aliphatic) ,5.8(amide) CMR Spectra (CDCl3): δ (ppm) 106.2-150.5(aromatic), 35.4-75.2 (-CH,aliphatic), 166.2(-C=O),176.2 (amide)

4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-hydroxy-3-(5-methoxy-1H-indol-3-yl)-butyramide 4c($C_{21}H_{19}N_3O_5$)

: Yield:82%,brown solid , mp 283^{o}C- 285^{o}C PMR Spectra (CDCl3): δ (ppm) 5.7-7.2(1H,aromatic),10.2(-NH), 2.1 (-OH,aliphatic)2.5-5.8

(-CH,aliphatic)),5.9(amide) ,3.7(CH_3)CMR Spectra (CDCl3): δ (ppm) 106.2-132.5(aromatic), 38.4-76.1 (- CH,aliphatic), 166.2 (-C=O),175.8 (amide)

General procedure for the synthesis of α-Hydroxy-β-acetamido substituted tryptamines(5a -c)

The corresponding 4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-hydroxy-3-(1H-indol-3-yl)-butyramides(1 mmol) were dissolved in 20 cm^3 and stirred at 50^o C for 24 Hrs under N_2. The solvent was evaporated and the residue was purified by column chromatography on silica gel.

4-Amino-4-hydroxy-3-(1H-indol-3-yl)-butyramide 5a($C_{12}H_{15}N_3O_2$)

:Yield:86%,brown solid , mp 205-207^{o}C PMR Spectra (CDCl3): δ (ppm) 6.8-7.2 (1H, aromatic), 2.0 (-OH), 10.1 (-NH), 2.5-4.8(CH,aliphatic),6.1(amide),2.1(-NH_2) CMR Spectra (CDCl3): δ (ppm) 111.4-136.2(aromatic), 43.1-82.5 (- CH,aliphatic), 35.2(-CH_2) ,176.4 (amide)

4-Amino-4-hydroxy-3-(5-hydroxy-1H-indol-3-yl)-butyramide 5b($C_{12}H_{15}N_3O_3$)

: Yield:88%,brown solid , mp 252-254^{o}C :PMR Spectra (CDCl3): δ (ppm) 6.8-7.0 (1H, aromatic),2.2 (-NH_2), 10.1(-NH), 2.1 (-OH,aliphatic), 5.2 (-OH,aromatic),2.4-4.8(CH,aliphatic),6.2(amide),2.0(-NH_2) CMR Spectra (CDCl3): δ (ppm) 107.4-133.2(aromatic), 43.3-82.1 (- CH,aliphatic), 35.2(-CH_2) , 176.2 (amide)

4-Amino-4-hydroxy-3-(5-methoxy-1H-indol-3-yl)-butyramide5c($C_{13}H_{17}N_3O_3$)

4.8(CH,aliphatic),6.1(amide),3.69(CH_3) CMR Spectra (CDCl3): δ (ppm) 111.4-131.2(aromatic), 43.1-82.3 (-CH,aliphatic), 35.1(-CH_2) , 176.4 (amide),56.2(CH_3)

Results and Discussion

N-Phthalimido-α-hydroxy acetic acid[11] **1** was conveniently prepared by the reaction between Phthalimide and Glyoxalic acid(scheme 1).The acid was then reduced to the corresponding aldehyde **2** by reduction with hexamine in aqueous acetic acid medium(scheme 2). Condensation of N-Phthalimido-α-hydroxy acetaldehyde with indole and Meldrum's acid smoothly gave the trimolecular adduct[12] **3,** in good yield (scheme 3).Transformation of **3** in to amide **4** through Nucleophilic cleavage of the Meldrum's ring was achieved by aminolysis. Deprotection of the phthalimido group of 4 yielded the corresponding α-Hydroxy-β-acetamido substituted tryptamine derivatives[13-16].Their structures were confirmed by analytical and spectral data. The proton magnetic resonance spectra of the prepared compounds (5a-c) shows signal at 6 δ for amide proton at β-positionof the tryptamine chain ,a signal at10 δ for -NH protons in the pyrrole ring and a signal at 2 δ confirms the presence of hydroxyl group at the α-positionof the tryptamine. All other signals are at their respective positions in the PMR spectrum. The CMR spectra of the compounds also show the signal at 176 δ for amide proton at β-positionof the tryptamine chain, a signal at35 δ for $-CH_2$ protons. All other signals appeared at their respective positions.

Conclusion

All the experiments reported here together with the previous studies of others have left no room for doubt that the compounds (3a,3b,3c,4a,4b,4c,5a,5b,5c) reported in this study are newly designed compounds. This study may provide a route for designing 1,2,3,4-tetrahydro- or 3,4-dihydro-β-carbolines having pyrrole moiety via pictet-spengler and Bischler-Napieralski condensation reactions.

Acknowledgement

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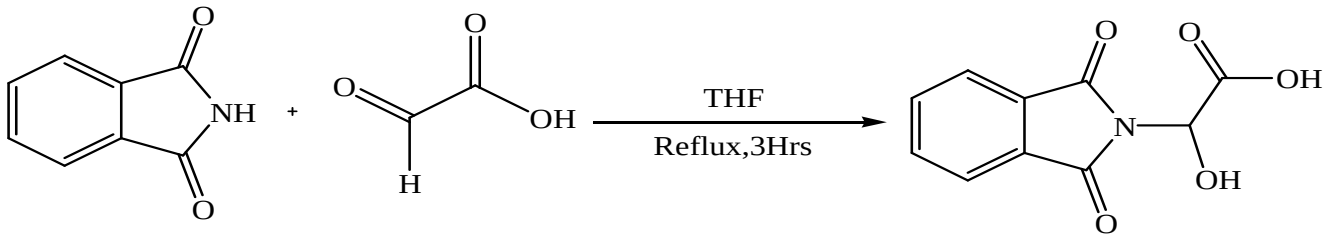
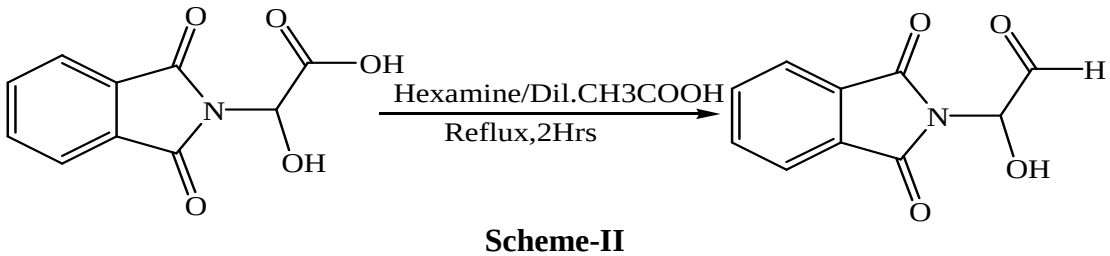
Reaction Scheme



Scheme-I

1



Scheme-II

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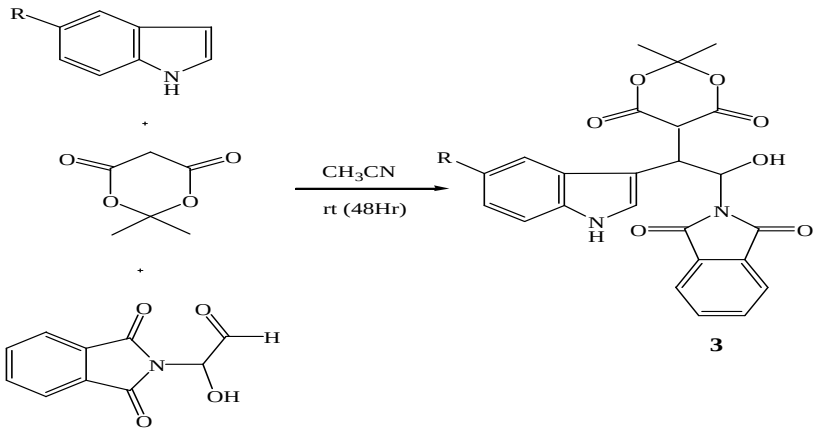
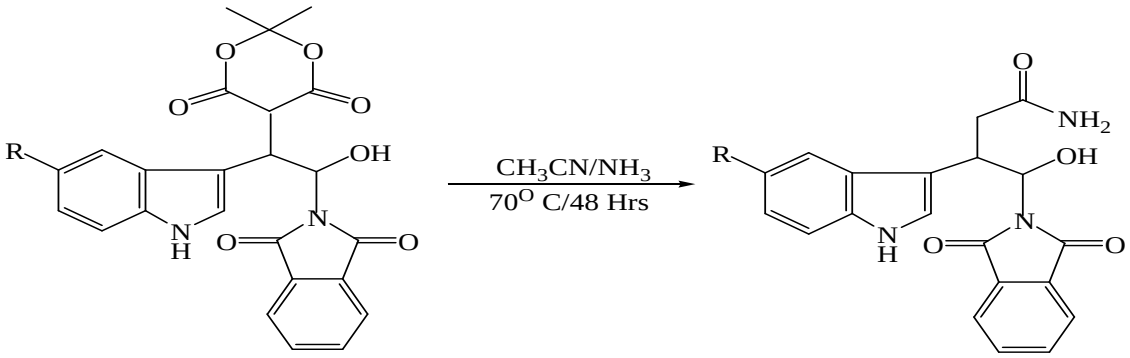
2



R = H,OH,OCH_3

R=H , 3a
R=OH , 3b
R=OCH_3 , 3c

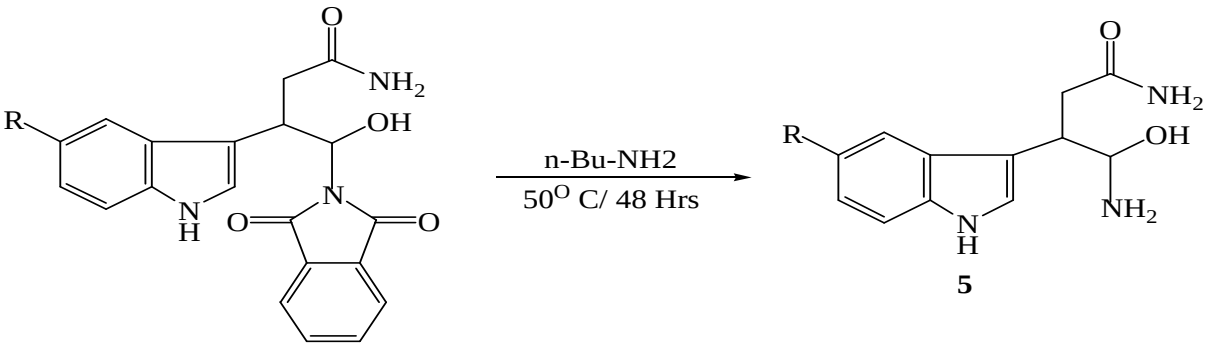
Scheme-III



R = H,OH,OCH_3

R=H , 4a
R=OH , 4b
R=OCH_3 , 4c

Scheme-IV



R = H,OH,OCH_3

Scheme-V

R=H , 5a
R=OH , 5b
R=OCH_3 , 5c