

SYNTHESIS OF 2- AND 4-CARBOXYLIC ACID DERIVATIVES OF LORATADINE AND DESLORATADINE

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ABSTRACT

A process for the synthesis of 2- and 4-carboxylic acid derivatives of Loratadine (**1**) and Desloratadine (**2**) has been described. The process comprises the N-oxide formation of (**1**)&(**2**) using hydrogen peroxide and acetic acid followed by cyanation with sodium cyanide and then dry hydrolysis by Mathew's method using phthalic acid in presence of microwave without adding any solvent or water. Various spectroscopic methods have been used for identification and characterization.

Keywords: Loratadine, Desloratadine, NMR, Infrared studies, TLC, HPLC & chemical shift.

INTRODUCTION

Loratadine¹, [Ethyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate] (**1**) and Desloratadine², [8-Chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine] (**2**) are non-sedating antihistamine drugs used to treat allergic disorders, especially rhinitis and urticaria. Both are long-acting tricyclic antihistamine with selective peripheral histamine H₁-receptor antagonistic activity. Both of these do not normally cause drowsiness because it does not readily enter the central nervous system. Loratadine is a white to off-white powder not soluble in water, but very soluble in acetone, alcohol, and chloroform. Desloratadine is a white to off-white powder and is slightly soluble in water, but very soluble in ethanol and propylene glycol. Desloratadine is also an active metabolite of Loratadine. According to the literature desloratadine is 2.5–4 times more active orally than loratadine and antihistaminic activity lasts for 24 hrs³⁻⁴. Various degradation products⁵⁻⁸ have been reported for both of these drugs.

The present research relates to a process for the synthesis of 2- and 4-carboxylic acid derivatives of compounds (**1**) & (**2**). Both of these are degradation products, which may retain as an impurity in the final drug in a very small quantity. The preparation of both contaminants has been necessary to prepare references for quality control analysis and validation. IR, NMR, MS spectral studies⁹ have been also discussed for these contaminants.

EXPERIMENTAL

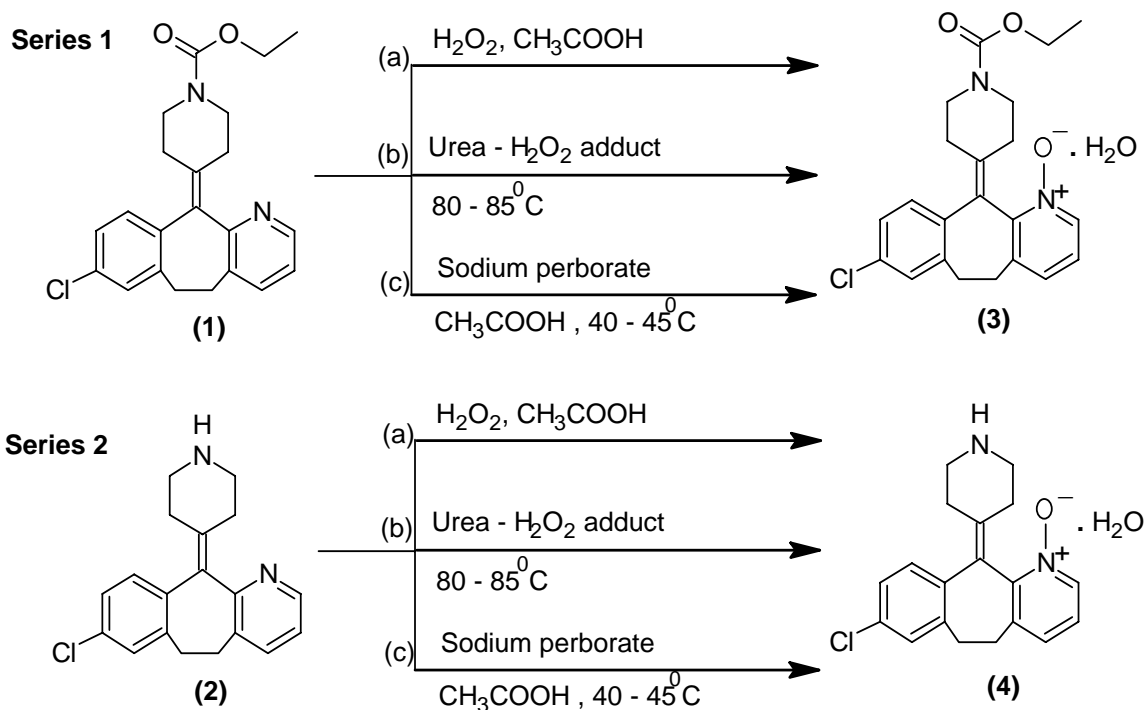
Both the starting compounds (**1**)&(**2**) were of pharmaceutical grade having HPLC purity of >99.0%. All the other chemicals used were of AR grade. All reactions were carried out using AR grade solvents after drying by routine procedures. In the present paper, **Series-1** and **Series-2** are mentioned in schemes, which represent the reactions for compound (**1**) & (**2**) respectively.

Synthesis of Ethyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene-N-oxide)piperidine-1-carboxylate (3**):**

Various methods for the preparation of N-oxide have been reported¹⁰⁻¹¹. In Scheme-1, three different

routes are mentioned for reference. In the present study, route-(a) was followed because of the good yield and quality of the product and it was also an easily handled reaction.

In a 100ml round bottom flask adapted with condenser, 5.0gm (13.0mmol) of Loratadine (**1**) was taken followed by the addition of 40% hydrogen peroxide solution 12.0gm (353.0mmol) and glacial acetic acid 7.0gm (116.6mmol). Stir the reaction mass for 2hrs at 30-40°C and again 20-25hrs at 65-75°C. Check the reaction completion on TLC (mobile phase: Isopropylalcohol/Ethylacetate/Triethylamine, 8:2:0.5). Transfer the reaction mass into 50ml chilled water. Adjust pH 8-9 by 15-20% ammonium hydroxide solution and stir for 1hr at 5-10°C. Add 25ml Ethyl acetate (EA) and separate layers. Again add 25ml EA into aqueous layer and separate layers. Dry both the EA layers with sodium sulphate and recover EA completely under vacuum, which results the compound (**3**). Use it as such in the next step. (4.5gm, reddish-yellow semi-solid).



Scheme 1

Synthesis of Ethyl 4-(8-chloro-2-cyano-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b] pyridin-11-ylidene)piperidine-1-carboxylate (**5**) :

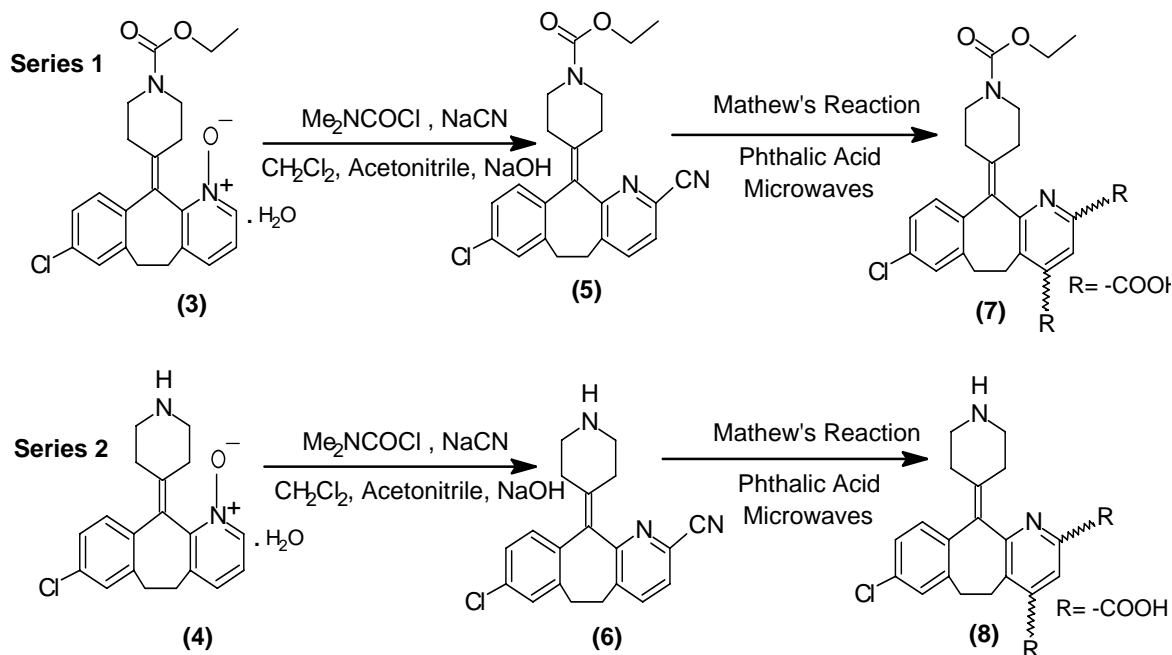
Dissolve the compound (**3**), as prepared above, in 10ml acetonitrile then add dimethyl carbamoyl chloride (Me_2NCOCl) 5.06gm (47.06mmol) and stir for 2-3hrs at 35-40°C. Transfer this reaction mass into aqueous Sodium cyanide solution (34.7mmol, 1.7gm in 10ml) at -5 to +5°C and stir for 3hrs. Check reaction completion on HPLC. Then add 10ml 50% aqueous K_2CO_3 solution and NaOH solution (2.3gm in 15ml water) into the reaction mass. Separate organic layer and after drying in sodium sulphate, recover the solvent completely under vacuum to get compound (**5**). Use it as such in the next hydrolysis step. (3.5gm, light brown colored semi-solid). (Scheme 2)

Synthesis of Ethyl 4-(8-chloro-2-carboxylic acid-5,6-dihydro-11H-benzo[5,6]cyclohepta [1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (**7**):

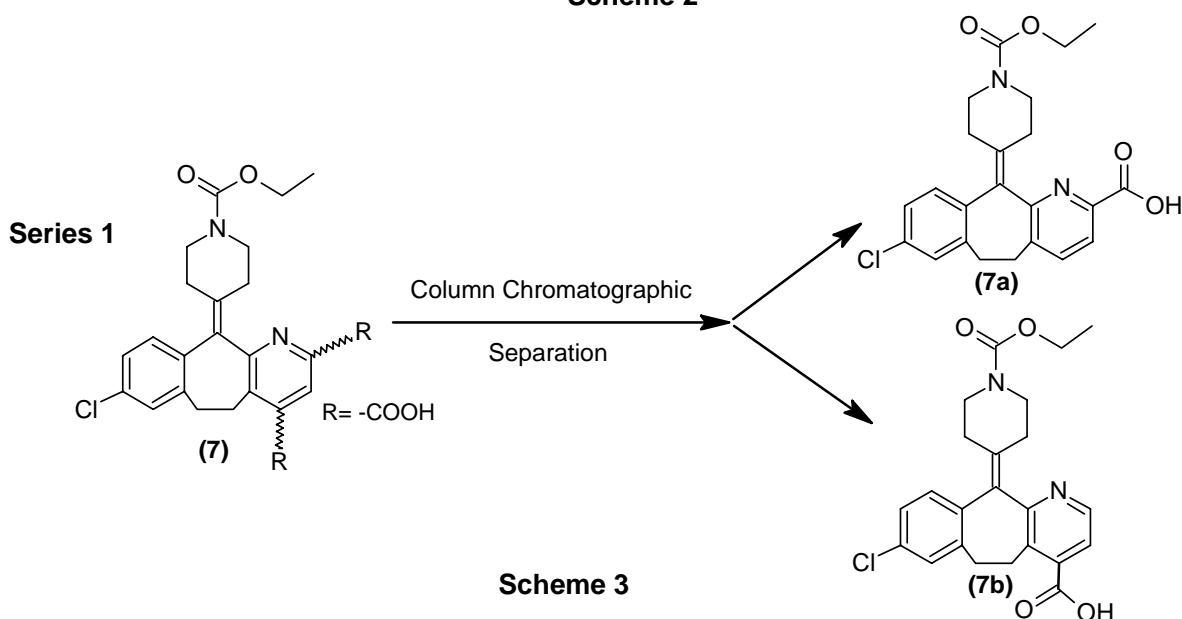
Take the previous step compound (**5**) in a 50ml round bottom flask and add phthalic acid 5.2gm (31.3mmol), heat the reaction mass in microwave oven for 5-8min without adding any solvent or water¹²⁻

¹³. Check the reaction completion on TLC (mobile phase: Isopropyl alcohol/Methanol/ Triethylamine, 5:5:0.5). Quench this reaction mass into water and ethyl acetate mixture (1:1, 50ml). Separate organic layer and after drying in sodium sulphate, recover the solvent completely under vacuum to get compound (7) (5.5gm, cream colored solid) in crude form. (Scheme 2)

HPLC analysis of above prepared compound (7) shows two major close peaks having 45% and 36% of total peak area. TLC of the said compound also shows two adjacent spots. On the basis of TLC and HPLC analysis, compound (7) (mixture of 2- & 4- isomers) was purified through column chromatographic technique and characterized, which results 1.2gm of 2-isomer (7a) and 0.8gm of 4-isomer (7b). The observed melting points were 186-188°C and 116-118°C for compound (7a) and (7b) respectively. (Scheme 3)



Scheme 2



Scheme 3

By the help of above reported procedures, Series-2 compounds i.e. 8-Chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-*N*-oxide (**4**), 8-chloro-2-cyano-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (**6**), and 8-chloro-11-(piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine-(2-/4-) carboxylic acid (**8**) (mixture of 2- & 4- isomers) were also prepared by slight modifications and the said isomers were separated by column chromatography. In the present paper, we report results of only final compounds of Series-1, i.e. compound (**5**), (**7a**) & (**7b**).

PHYSICAL MEASUREMENTS

Melting points of the synthesized compounds were determined in open glass capillaries using melting point apparatus. Percentage of C, N and H were determined on a Perkin Elmer 2400 CHN analyser at RSIC, Punjab Univ. Chandigarh. IR spectra were recorded using KBr pellets on 'Perkin Elmer-Spectrum BX FTIR' spectrometer in the region ~ 4000 -200 cm^{-1} at Parabolic Labs Ltd. The NMR spectra were recorded on Bruker Avance-II Ultrashield-400 MHz FT-NMR spectrometer at Punjab Univ. Chandigarh. Chemical shifts (δ) were determined using TMS as internal standard, and multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) is indicated for every signal. MS spectra were recorded on Waters Micromass Q-ToF micro spectrometer at Punjab Univ. Chandigarh. Column chromatography was performed using silica gel (100–200 mesh size) as the stationary phase. Mobile phase for column chromatography was 1-10% ethyl acetate in hexane. Reaction monitoring by HPLC was recorded on 'Waters 2695 alliance' gradient system using phosphate buffer with methanol and acetonitrile as mobile phase at 254nm wavelength and 1.5ml/min flow rate. Hypercil BDS 250x4.6mm HPLC column was used.

RESULTS AND DISCUSSION

C, H, N Elemental Analysis

(**5**): Anal Calcd.=C(67.73%), H(5.44%), N(10.30%) / Found C(67.70%), H(5.53%), N(10.27%)

(**7a**): Anal Calcd.=C(64.71%) H(5.43%) N(6.56%) / Found C(64.75%) H(5.40%) N(6.59%)

(**7b**): Anal Calcd.=C(64.71%) H(5.43%) N(6.56%) / Found C(64.69%) H(5.42%) N(6.62%)

Mass spectral studies

(**5**): MS m/z 408 (M+1), m/z 382 (M-C \equiv N), m/z 334 (M-COOC $_2$ H $_5$)

(**7a**): MS m/z 426 (M+1), m/z 382 (M-COOH), m/z 353 (M-COOC $_2$ H $_5$)

(**7b**): MS m/z 427 (M+1), m/z 382 (M-COOH), m/z 354 (M-COOC $_2$ H $_5$)

^1H NMR (CDCl $_3$, 400MHz)

In the ^1H NMR spectrum of (**7a**) & (**7b**), a sharp singlet at δ 5.75 & δ 5.68 assigned as carboxylic proton respectively. The chemical shift range of δ 8.28- δ 8.30 & δ 7.21-7.30 in (**7b**) is due to the presence of proton at 2- & 3- position respectively. Chemical shift at around δ 7.2-7.35 is absent in (**7b**), which shows the absence of proton at 4-position.

The chemical shift range of δ 7.35-7.38 in (**7a**) is due to the presence of a single proton at 3- & 4- position respectively. Chemical shift at around δ 8.2-8.35 is absent in (**7a**), which shows that there is no proton at 2-position. These results suggest that (**7a**) & (**7b**) are 2- and 4-carboxylic acid derivatives of (**1**) respectively. Other Chemical shifts are:

(**7a**) : [t,3H, δ 1.24-1.26]; [m,4H, δ 2.27-2.90]; [m,2H, δ 2.93-3.12]; [m,2H, δ 3.19-3.31]; [m,4H, δ 3.50-3.75]; [q,2H, δ 4.08-4.11]; [s,1H, δ 5.75]; [m,3H, δ 6.98-7.11]; [d,2H, δ 7.35-7.38].

(7b) : [t,3H, δ 1.24-1.28]; [m,4H, δ 2.35-2.95]; [m,2H, δ 2.98-3.17]; [m,2H, δ 3.23-3.38]; [m,4H, δ 3.60-3.89]; [q,2H, δ 4.12-4.17]; [s,1H, δ 5.68]; [m,3H, δ 6.91-7.03]; [d,1H, δ 7.21-7.30]; [d,1H, δ 8.28-8.30].
[Multiplicity, Proton Intensity, Chemical Shift (δ) in ppm].

Infrared spectral Studies

IR spectra of (5) show major peaks at 3449, 2233, 1689, 1560, 1436, 1229, 952, 842, 769 cm^{-1} . Among these peaks, peak at 2233 cm^{-1} represent the C \equiv N linkage.

In the spectra of (7a) peaks are at 1703, 1561, 1480, 1225, 982, 826, 764 cm^{-1} and for (7b) these are at 1704, 1559, 1486, 1231, 986, 832, 765 cm^{-1} . In both of these spectra, a very broad peak in the region 2800-3300 cm^{-1} is also present, which is due to the O-H stretching. Peak in the region 2200-2300 cm^{-1} is also absent in both of these spectra, which shows the absence of C \equiv N linkage.

CONCLUSIONS

The analytical and spectral results from the study demonstrated the identification and characterization of 2- and 4-carboxylic acid derivatives of Loratadine.

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The means by which we live have outdistanced the ends for which we live. Our scientific power has outrun our spiritual power. We have guided missiles and misguided men.

-Martin Luther King, Jr.