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A New Addition Compound of Desloratadine with Carbon Dioxide

Tibor Mezei,† Balázs Volk,*,† Imre Király,‡ and Gyula Simig†

Chemical Research Division, EGIS Pharmaceuticals Plc., P.O. Box 100, H-1475 Budapest, Hungary, and Pilot Plant for API, EGIS Pharmaceuticals Plc., P.O. Box 100, H-1475 Budapest, Hungary

Abstract:

The addition compound of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (descarboethoxyloratadine, desloratadine) with CO_2, in molar ratio 2:1, is described. This unique form of desloratadine drug substance can be prepared in exceedingly high purity by a simple process from crude desloratadine. The addition compound is a useful intermediate in the manufacturing process of desloratadine Form I polymorph. An improved, environmental friendly manufacturing process for the synthesis of desloratadine starting from loratadine is also disclosed here.

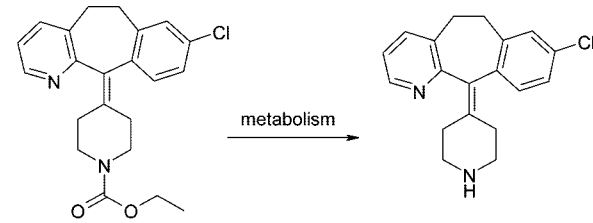
Introduction

Histamine H1 receptor antagonists represent the most widely used class of drugs for the treatment of allergic disorders, especially rhinitis and urticaria. The significant side effects of the early drugs in this therapeutic field were first eliminated by the widely marketed non-sedating antihistamine loratadine (**1**), which was initially launched in 1988 as Claritin by Schering-Plough.

Nevertheless, **1** undergoes extensive first-pass metabolism (Scheme 1) to yield the active metabolite desloratadine (**2**),[1] which was identified as having increased potency and improved safety as compared to **1**.[2−5] It displayed radioligand binding to cloned H1 human receptors with significantly greater potency than **1**, while showing negligible affinity for H2 and H3 subtype receptors. Also, desloratadine (**2**) was 20 times more potent in antagonizing histamine-induced contractions in isolated guinea pig ileum strips.[6] Therefore, **2** was selected for further development and was finally launched in 2001 as Neoclarityn, as Form I polymorph.[7]

Essentially, two different synthetic pathways are described in the literature for the synthesis of **2**. According to the first method, demethylation of key intermediate **3** was carried out by treatment with highly toxic cyanogen bromide (Scheme 2, route A, von Braun reaction) affording cyanamide **4**, which was hydrolyzed and decarboxylated in one step by refluxing (20 h) in a mixture of acetic acid and concentrated HCl. After alkalization of the reaction mixture, **2** was prepared and finally purified by multiple recrystallization from hexane.[8] This procedure is obviously inappropriate for scale-up.

Scheme 1. **Conversion of loratadine (1) to desloratadine (2)**



loratadine (**1**) desloratadine (**2**)

The second literature procedure (Scheme 2, route B) for the synthesis of desloratadine (**2**) proceeds via loratadine (**1**), which was obtained by the reaction of *N*-methyl derivative **3** with ethyl chloroformate.[9] Several methods have been described for the removal of the ethoxycarbonyl group of loratadine under basic and acidic conditions. For example, desethoxycarbonylation of loratadine (**1**) was performed by long refluxing (64 h) with potassium hydroxide in aqueous ethanol affording desloratadine (**2**) in 77% yield, after recrystallization from toluene.[9] In another procedure, treatment of loratadine (**1**) with sodium hydroxide in aqueous ethanol for 24 h at reflux temperature, followed by acidification with glacial acetic acid, provided the acetate salt of **2**, which was converted into the free base, and then purified by multiple recrystallization from a benzene−hexane mixture.[8,10] Use of solvents with higher boiling points led to a decreased reaction time. A recent patent application[11] disclosed the hydrolysis of **1** with sodium hydroxide, in a mixture of toluene and polyethylene glycol 400. After a 2-h reaction time and a multistep purification procedure, the process furnished **2** in only 48% yield, as a mixture of polymorphs, Form I and Form II. A process leading to a similar polymorphic mixture was described by Sriraman et al. in aqueous alcohols, using potassium hydroxide.[12] Suri et al. published the transformation of loratadine to desloratadine in methanol with 10.5 mol equiv of sodium hydroxide.[13] The reaction was complete in 2 h; however, the

* To whom correspondence should be addressed. Telephone: +36 1 2655874. Fax: +36 1 2655613. E-mail: volk.balazs@egis.hu..

† Chemical Research Division.

‡ Pilot Plant for API.

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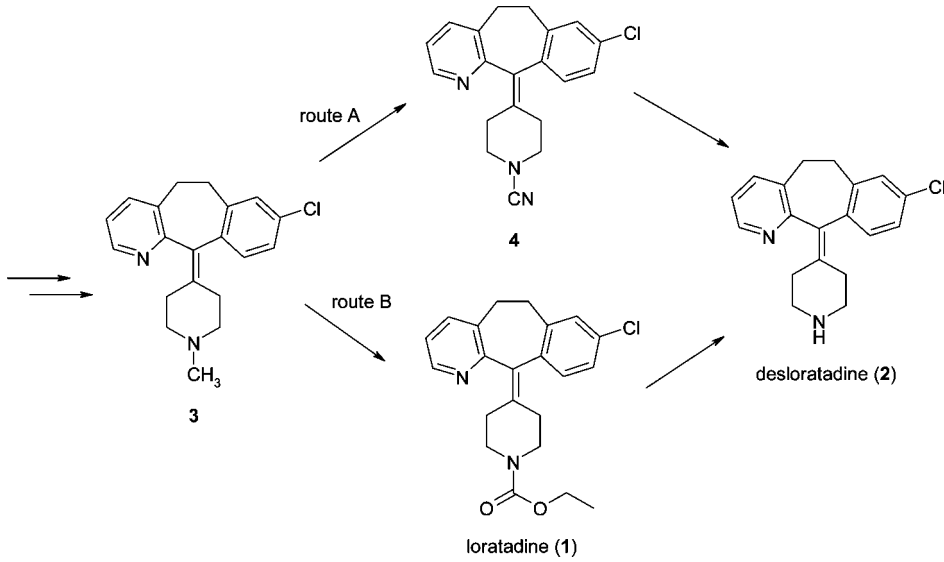
Scheme 2. **Synthetic procedures leading to desloratadine (2)**



high excess of sodium hydroxide caused difficulties during the workup. A slight reduction of the amount of base to 8.8 mol equiv led to a significant increase of the reaction time (8 h), most probably because of the lower reflux temperature of the reaction mixture.

Acidic removal of the ethoxycarbonyl moiety of loratadine (**1**) is also described. After treatment of **1** in sulfuric acid (60−80 w/w%) at 120 °C for 6−8 h, the disulfate salt of desloratadine (**2**) was obtained.[14,15] A similar process in 50 w/w % sulfuric acid (3 h, 100−105 °C) is also known from the patent literature.[16] Acidic desethoxycarbonylation can also be accomplished in 70% aqueous HCl (12 h at reflux), followed by basic treatment.[17] Nevertheless, the quality of the product obtained after acidic treatments was unsatisfactory.

The procedures mentioned above, in our hands, gave products contaminated with coloured impurities, which could be removed only by laborious recrystallizations resulting in low yields. Due to the rich polymorphism (Form I,[7,18−20] II,[18] III,[21] V,[21] and the amorphous form[22]) of desloratadine (**2**), the purity of the primary product is a very important factor in the efficient production of the active substance. The last recrystallization of the manufacturing procedure should be focused rather on the formation of the required polymorph than on further purification of the active substance.

Results and Discussion

Herein we report a new, stable addition compound of desloratadine with CO_2 as well as the application of this new substance for the purification of crude desloratadine and its conversion into crystalline Form I desloratadine.

First, an improved version of the desethoxycarbonylation of loratadine under basic conditions has been elaborated in our laboratory. We carried out the reaction in a laboratory autoclave, in ethanol at 105 °C, with 3.75 mol equiv of sodium hydroxide. After 5 h reaction time, **2** was obtained in high yield and high purity.

Our next target was to develop the amorphous form of desloratadine active substance. It is known that amines form addition compounds with CO_2, however, mostly with undefined molar composition,[23] low stability, and sometimes with very limited shelf life.[24−27] We expected that evaporation of a desloratadine solution saturated with CO_2 may afford such an undefined addition compound, which may then result in amorphous desloratadine by decomposition upon heating.

To our great surprise, during the addition of a solution of desloratadine in ethanol into ethyl acetate saturated with CO_2,

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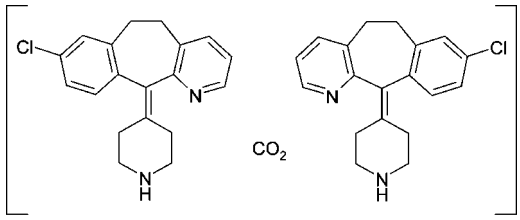

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Figure 1. **Addition compound of desloratadine with CO_2 (2:1).**

a crystalline product precipitated immediately. The NMR (^1H, ^{13}C) and MS spectra of the product were identical with those of desloratadine. However, the IR and XRPD data were significantly different from those of crystalline Forms I−III and V, published in the literature.[18,21] Elemental analysis and DTG measurements unambigously proved that the product is a 2:1 addition compound (**5**, Figure 1) of desloratadine and CO_2. According to the DTG and DSC measurements, addition compound **5** is stable up to 120 °C, and its crystal structure remains also unchanged, as shown by XRPD measurements. At 140 °C **5** decomposes, losing about 6.6% of its weight, which corresponds to the CO_2 content of the 2:1 addition compound. Nevertheless, despite all our efforts, we could not obtain single crystals from **5**, the reason being that the primarily precipitating fine solid was not appropriate for X-ray measurements. Moreover, since the dissolution of **5** in any solvent led immediately to the loss of CO_2, the compound could not be recrystallized.

In order to characterize **5** more thoroughly, comparative solid-state ^{13}C NMR studies with Form I polymorph of desloratadine were carried out. Although a significant difference between the ^{13}C ssNMR spectra of the two forms was observed, the presence of CO_2 in **5** could not be convincingly proved, due to the weak signal of the quaternery carbon atom of CO_2 and to the disturbance caused by the atmospheric CO_2. When using $^{13}CO_2$, an analogous $^{13}CO_2$ addition compound (**6**) was synthesised. As expected, the product (**6**) exhibited a strong signal in ^{13}C ssNMR at 164.6 ppm, unambiguously indicating the presence of $^{13}CO_2$ in the substance.

The literature abundance of crystalline CO_2 addition compounds of amines with integral molecular ratio is very scarce.[28] To the best of our knowledge, **5** is the first CO_2 addition compound of a drug substance. The HPLC purity of **5** is exceedingly high, almost independently from the quality of the crude desloratadine starting material. Even when starting from desloratadine base (**2**) of only 99.1% purity, the precipitated **5** exhibited an HPLC purity over 99.9%. This is probably due to the fact that the impurities present in the solution do not form insoluble addition compounds with CO_2.

During drying at 80 °C and the forced stability studies (40 °C, 75% relative humidity, 6 weeks) of **5** we encountered an unexpected problem: formation and continuous increase of an impurity was observed quickly exceeding 0.10%, as determined by HPLC. HPLC/MS measurements suggested that the impurity is the *N*-acetyl derivative of desloratadine (**7**, Figure 2). The structure assignment was confirmed by the synthesis of an authentic sample. The formation of impurity **7** can be explained by the presence of residual ethyl acetate in the product, which acetylates desloratadine upon heating.

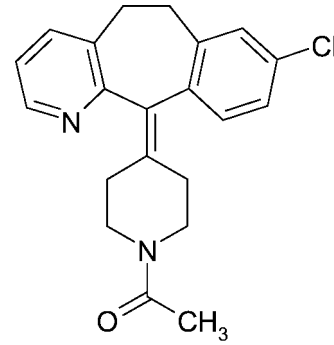

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Figure 2. ***N*****-acetyl desloratadine (7).**

In order to avoid the problem caused by ethyl acetate we had to find an alternative solvent for the preparation of **5**. Acetone proved to be the appropriate choice.[29] When the ethanol solution of **2** was added at 45 °C to acetone saturated with CO_2, **5** precipitated in similarly high yield and purity as with ethyl acetate. The substance obtained from acetone kept its high purity after drying, and during subsequent stability tests performed under various conditions. Thus, **5** synthesised by this method proved to be an appropriate drug substance. Furthermore, it served as an ideal intermediate for the preparation of desloratadine Form I polymorph. After dissolution of **5** in ethanol and subsequent evaporation, the resulting desloratadine base was recrystallized from a mixture of methanol and acetone to give Form I base in good yield and excellent purity.

The improved procedure described above represents a green chemistry approach for the manufacure of desloratadine. In contrast with the majority of known methods, the improved desethoxycarbonylation procedure does not necessitate long (12−64 h) boiling of the reaction mixture. It applies a decreased excess of alkali hydroxide, and only environmental friendly (Class III) solvents are used. The new purification procedure via the CO_2 addition compound results directly in a drug substance of outstanding purity, thereby eliminating the need of laborious, low-yielding recrystallization steps from toxic

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solvents (e.g., hexane, benzene). The robustness of the improved desethoxycarbonylation and CO_2 addition procedure is demonstrated by the fact that the process was successfully scaled up in our pilot plant in good yields.

Conclusion

The search for new patentable polymorphs, solvates, hydrates, and salts of promising drugs is a continuous effort in the pharmaceutical industry. In our laboratory, an addition compound of desloratadine with CO_2, in molar ratio 2:1, has been developed. It is interesting to note that no drug substance has ever been described in the form of an addition compound with CO_2. According to our experience, isolation of addition compound **5** is the most efficient tool of purification of crude desloratadine (**2**) obtained after desethoxycarbonylation of loratadine (**1**). Moreover, **5** is a new, patentable[30] form of desloratadine, which is an appropriate drug substance itself, or alternatively, it can also be applied as a useful intermediate in the manufacturing process of Form I polymorph.

Experimental Section

General Remarks. All melting points were determined on a Buchi 535 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer. ^1H and ^{13}C NMR spectra were recorded in CD_3OD or DMSO-d_6 on a Varian Unity Inova 500 spectrometer (500 and 125 MHz for ^1H and ^{13}C NMR spectra, respectively), using TMS as internal standard. Solid state ^{13}C NMR measurements were performed on a Varian Unity 300 (7 T) spectrometer, at 293 K, with glycine as external standard, using CP/MAS (xpolar) and direct MAS experiments (rotation speeds: 4000−11000 Hz; rotors: zirkonia 5 mm, thin wall, N_2 flow; contact time: 2−3 ms; relaxation delay: 5−7 s). Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. HPLC measurements were run on a Kromasil 100-5 C-18 column (150 mm × 4.6 mm, 5 μm) with the following eluent: 725 mL of buffer (4.14 g NaH_2PO4 + 14.20 g of sodium dodecyl sulfate in 1000 mL of water, pH = 3.0) + 1775 mL of methanol. Column temperature was 45 °C, UV detection occurred at $\lambda = 220$ nm. TG measurements were run on a Perkin-Elmer Pyris 1 TG apparatus at a heating rate of 10 °C/min, with a 10 mg sample, Al sample holder, and N_2 as flushing gas. DSC was performed with a Perkin-Elmer DSC 7 calorimeter at a heating rate of 10 °C/min, with a 2 mg sample, Al sample holder, without flushing gas. XRPD measurements were performed on a Bruker D8 Advance diffractometer [radiation: Cu Kα_1 ($\lambda = 1.54060$ Å) and Cu Kα_2 ($\lambda = 1.54439$ Å), voltage: 40 kV, zero-signal current: 30 mA, accessories: Gödel mirror and Soller slot, standard reference: SRM 640c silicon powder, continuous measurement Θ/Θ scan 5.00°−35.00° 2Θ, step scale: 0.04°, room temperature]. Some reactions were carried out in autoclaves (volume: 70 or 850 mL, depending on the amount of reagents used), which were equipped with a temperature controller, a manometer (60 bar), a valve for gas inlet and a magnetic stirrer. All reactions were followed by TLC on silica gel 60 F_{254}. $^{13}CO_2$ (99 atom % ^{13}C) was purchased from Fluka in a 250 mL cylinder.

Desloratadine (2). *Laboratory Process.* In a laboratory autoclave, loratadine (**1**, 75.0 g, 0.20 mol) was added to a mixture of ethanol (500 mL) and 40 w/w% NaOH (75 mL) under stirring. The reaction mixture was heated to 105 °C for 5 h. Ethanol was distilled off, the residual off-white crystals were dissolved at 50 °C in a mixture of water (100 mL) and toluene (350 mL). The layers were separated, and the organic layer was extracted with brine (50 mL) and dried over K_2CO_3. Charcoal (3.5 g) was added, and the suspension was filtered through a pad of perlite (2.0 g). The filtrate was evaporated in vacuo to give 57.4 g (94%) of off-white crystals. The product was used without further purification.

Pilot-Plant Process. A 20-L stainless steel autoclave was equipped with a turbine stirrer, baffles, a pressure gauge, a thermometer, a thermostat (oil heating jacket), a valve for inert gas inlet, and a flush-out valve. Into the autoclave were introduced loratadine (**1**, 1.5 kg, 3.92 mol), a solution of NaOH pellets (0.85 kg, 21.25 mol) in purified water (1.25 L), and finally ethanol (10.0 L). The autoclave was purged with nitrogen three times, and the stirred (600 min^{-1}) mixture was heated to 100−105 °C for 4−5 h. The end-point of the reaction (<0.25% of remaining **1**) was determined by TLC. The autoclave was cooled to ambient temperature, the mixture was transferred into a glass autoclave, and the solvent was evaporated. To the solid residue, toluene (7.0 L) and purified water (2.0 L) were added at 50−55 °C. After complete dissolution, a 40 w/w% NaOH solution (0.4 L) was introduced, and the two-phase system was stirred at 50−55 °C for 30 min. The organic layer was washed first with brine (1.1 L) and then with purified water (1.0 L). The solution was dried over K_2CO_3 and treated with charcoal at 60−65 °C. It was filtered off on a 25-L Nutsche filter under moderate argon pressure (1.0−1.5 bar). The filter cake was washed with toluene (0.5 L), and the filtrate was concentrated in vacuo to give 1.17 kg (96%) of pale-pink crystals. The product was used without further purification.

Desloratadine CO_2 Addition Compound 2:1 (5). *Laboratory Method A.* Dry ice (100 g, 2.27 mol) was placed into a flask, and the CO_2 gas formed was led into another flask, which was filled with ethyl acetate (700 mL). A solution of desloratadine (**2**, 57.4 g, 0.185 mol) in ethanol (80 mL) was added into the ethyl acetate flask at 60 °C under intense stirring. Bubbling of CO_2 was continued until the end of the addition. The crystallization of the CO_2 addition compound began approximately after the addition of one-fifth of the volume. After the additon was complete (1−1.5 h), the suspension was cooled to 5 °C and stirred for 1 h further, under continuous CO_2 bubbling. The solid was filtered, washed with ethyl acetate (100 mL), and dried at 80 °C to give 59.3 g (91%) of white crystals. HPLC purity >99.97%. Mp 144−158 °C (under decomposition to **2**). IR (KBr): 2927, 1560, 1468, 1421, 1279. ^1H NMR (CD_3OD, 500 MHz): δ 8.31 (dd, 1H, $J = 4.9$, 1.6 Hz), 7.63 (dd, 1H, $J = 7.8$, 0.9 Hz), 7.23 (dd, 1H, $J = 7.7$, 4.9 Hz), 7.21 (d, 1H, $J = 2.0$ Hz), 7.16 (dd, 1H, $J = 7.8$, 2.2 Hz), 7.13 (d, 1H, $J = 8.2$ Hz), 3.41 (m, 2H), 3.03 (m, 2H), 2.85 (m, 2H), 2.75 (m, 2H), 2.39 (m, 2H), 2.35 (m, 1H), 2.22 (m, 1H). ^{13}C

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NMR (CD_3OD, 125 MHz): δ 158.7, 147.1, 141.3, 139.7, 139.5, 138.6, 136.0, 134.3, 134.0, 131.9, 130.5, 127.2, 124.2, 48.0, 47.9, 32.8, 32.4, 32.4, 32.1. Anal. Calcd. for 2 $C_{19}H_{19}ClN_2 \cdot CO_2$: C, 70.37; H, 5.75; N, 8.42; Cl, 10.65. Found: C, 70.23; H, 5.69; N, 8.34; Cl, 10.48. For XRPD data, see ref 30.

Laboratory Method B. Dry ice (100 g, 2.27 mol) was placed into a flask, and the CO_2 gas formed was bubbled through another flask, which was filled with acetone (1200 mL). A solution of desloratadine (**2**, 80.0 g, 0.257 mol) in ethanol (40 mL) was added into the acetone flask at 45 °C under intense stirring. Bubbling of CO_2 was continued until the end of addition. The crystallization of the CO_2 addition compound began approximately after the addition of half of the volume. After the additon was complete (30 min), the suspension was cooled to 20 °C over a period of 1 h, and stirred for 1 h further, under continuous CO_2 bubbling. The solid was filtered, washed with cold (5 °C) acetone (150 mL), and dried at 25 °C for 3 h to give 80.7 g (94%) of white crystals. HPLC purity >99.97%. Mp, IR, ^{1}H NMR, ^{13}C NMR and XRPD were identical to those of the product synthesised by Method A.

Pilot-Plant Process. A 20-L glass autoclave was equipped with an impeller stirrer, a condenser, a dropping funnel, and a gas injection tube. The vessel was filled with acetone (17.5 L), and CO_2 gas was injected into the solvent ~20 cm below its surface at 45 °C and dispersed by intense stirring (250 min^{-1}). Inlet of CO_2 was maintained until the end of the process. In a separate vessel, desloratadine (**2**, 1.15 kg, 3.7 mol) was dissolved in ethanol (2.0 L) at 70−75 °C. This solution was added dropwise into the CO_2−acetone vessel during 1 h. The temperature of the ethanolic solution was kept above 60 °C during the addition. After the addition was completed, the white suspension was cooled to room temperature and stirred for 1 h. Then it was cooled to 0−5 °C and kept at this temperature for 1 h further. It was filtered on a 25-L Nutsche filter under moderate argon pressure (1.0−1.5 bar). The equipment was rinsed, and the filter cake was washed twice with acetone (2 × 1.0 L). The white solid was dried in a tray dryer at 45−50 °C for 2−4 h, under smooth air flow, to yield 1.1 kg (84%) of the title compound. HPLC purity: 99.96%.

Desloratadine $^{13}CO_2$ Addition Compound 2:1 (6). Desloratadine CO_2 addition compound (**5**, 1.5 g, 2.25 mmol) was dissolved in a mixture of EtOAc (24 mL) and EtOH (3 mL) under boiling. The solution was cooled to ambient temperature, and it was poured into a laboratory autoclave. The autoclave was placed under vacuum, and it was filled with $^{13}CO_2$ gas. The reaction mixture was stirred for 16 h in the vessel, and then the precipitated solid was filtered, washed with EtOAc (20 mL), and dried under vacuum to give 1.38 g (92%) of white crystals. HPLC purity: 99.95%. Mp 144−158 °C (under decomposition to **2**). IR (KBr): 2928, 2394, 1559, 1437, 1408, 1262, 1242. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.31 (d, 1H, J = 4.9 Hz, H-2), 7.63 (d, 1H, J = 7.8 Hz, H-4), 7.23 (dd, 1H, J = 7.8, 4.9 Hz, H-3), 7.21 (d, 1H, J = 2.1 Hz, H-7), 7.16 (dd, 1H, J = 8.2, 2.1 Hz, H-9), 7.13 (d, 1H, J = 8.2 Hz, H-10), 3.40 (m, 2H, 5-CH_2+6-CH_2), 3.06 (m, 2H, C$\underline{H}_2$-NH-C$\underline{H}_2$), 2.85 (m, 2H, 5-CH_2+6-CH_2), 2.76 (m, 2H, C$\underline{H}_2$-NH-C$\underline{H}_2$), 2.41 (m, 2H, NH-CH_2−C$\underline{H}_2$), 2.35 (m, 1H, NH-CH_2−C$\underline{H}$H), 2.23 (m, 1H, NH-CH_2−C$\underline{H}$H).^{13}C NMR (CD_3OD, 125 MHz): δ 164.0, 161.5 ($^{13}CO_2$), 158.5 (C-11a), 147.0 (C-2), 141.2 (C-6a), 139.6 (C-4), 139.1 [(C-11)=$\underline{C}$], 138.5 (C-10a), 135.9 (C-4a), 134.2 (C-11), 134.0 (C-8), 131.7 (C-10), 130.4 (C-7), 127.1 (C-9), 124.1 (C-3), 47.8 (NH-CH_2), 47.7 (NH-CH_2), 32.6 (C-6), 32.1 (C-5), 32.0 (NH-CH_2-$\underline{C}H_2$). Anal. Calcd for 2 $C_{19}H_{19}ClN_2 \cdot {}^{13}CO_2$: C, 70.41; H, 5.74; N, 8.41; Cl, 10.63. Found: C, 70.21; H, 5.88; N, 8.50; Cl, 10.35.

4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-acetyl-piperidine (7). To desloratadine (**2**, 2.0 g, 6.4 mmol), acetic acid (10 mL), and acetic anhydride (3.0 mL, 31.8 mmol) were added. The reaction mixture was stirred at ambient temperature for 2 h, and then it was poured onto ice−water (50 mL). After extraction with toluene (50 mL), the organic layer was dried over $MgSO_4$ and evaporated to give 1.81 g (80%) of the title compound as pale-yellow oil. IR (neat): 2919, 1718, 1645, 1439, 1234.^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.42 (d, 1H, H-2, J = 4.7 Hz), 7.45 (d, 1H, H-4, J = 6.0 Hz), 7.24 (t, 1H, H-3, J = 7.4 Hz), 7.17 (m, 1H, H-7), 7.13 (m, 1H, H-9), 7.12 (m, 1H, H-10), 4.04 (m, 1H, NH-C$\underline{H}_2$), 3.65 (m, 1H, NH-C$\underline{H}_2$), 3.36 (m, 2H, 5-CH_2+6-CH_2), 3.26 (m, 1H, N-CH_2−C$\underline{H}_2$), 3.19 (m, 1H, NH-C$\underline{H}_2$), 2.82 (m, 2H, 5-CH_2+6-CH_2), 2.51 (m, 1H, NH-C$\underline{H}_2$), 2.39 (m, 2H, NH-CH_2−C$\underline{H}_2$), 2.32 (m, 1H, NH-CH_2−C$\underline{H}_2$), 2.10 (s, 3H, CH_3). Anal. Calcd for $C_{21}H_{21}ClN_2O$: C, 71.48; H, 6.00; N, 7.94; Cl, 10.05. Found: C, 71.19; H, 6.08; N, 7.75; Cl, 9.98.

Desloratadine (2), Polymorph Form I. Desloratadine CO_2 addition compound 2:1 (**5**, 40.0 g, 60 mmol) was added to ethanol (120 mL), and the suspension was heated to reflux temperature. While the suspension changed to a clear, colourless solution, the evolution of CO_2 stopped. After 0.5 h at reflux temperature, ethanol was distilled off. To the residue were added acetone (200 mL) and methanol (18 mL), and the solution was heated to reflux for 15 min. The solution was filtered while hot, and then it was cooled to ambient temperature. The suspension was stirred for 1 h at room temperature and for 4 h further at −10 °C. The solid was filtered, washed with acetone (25 mL), and dried at 50 °C for 3 h to give 32.5 g (87%) of the title product as white crystals, mp 257−258 °C. HPLC purity >99.97%. Mp, IR and XRPD were in accordance with the literature data of the Form I polymorph.[7,18]

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