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New Manufacturing Procedure of Cetirizine

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ABSTRACT: A new procedure for the manufacture of cetirizine dihydrochloride via the new intermediate 2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)-*N*,*N*-dimethylacetamide dihydrochloride, synthesized by O-alkylation of 2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethanol with 2-chloro-*N*,*N*-dimethylacetamide, is elaborated. Hydrolysis of the resulting amide and subsequent salification provided cetirizine dihydrochloride.

INTRODUCTION

Cetirizine dihydrochloride (**1**) is a nonsedating (second generation) antihistamine, widely used in the treatment of allergic syndromes. Its pharmacological properties and therapeutic indications are summarized in the literature.[1,2]

Several methods have been described for the synthesis of compound **1** (Scheme 1). The procedures mentioned in the basic patent[3] led to required product **1** by alkaline hydrolysis of the corresponding amide (**2a**) or ester (**2b**), followed by salt formation. The synthesis of intermediates **2a** and **2b** was carried out by N-alkylation of 1-[(4-chlorophenyl)(phenyl)-methyl]piperazine (**3**) with 2-(2-chloroethoxy)acetamide (**4a**) or methyl 2-(2-chloroethoxy)acetate (**4b**) in 47% and 27.8% yield, respectively. The overall yields of the procedures starting from piperazine **3** are moderate (34%, via **2a**) or low (10%, via **2b**). The presumably more economical synthesis of intermediates **2a** and **2b** by O-alkylation of 2-{4-[(4-chlorophenyl)-(phenyl)methyl]piperazin-1-yl}ethanol (**5**) with the easier accessible alkylating agents chloroacetamide (**6a**) or methyl chloroacetate (**6b**) is mentioned in the introductory part of the basic patent and is claimed as well; however, the synthesis is not illustrated by examples.

In a later patent application[4] alkylation of piperazine **3** with 2-(2-chloroethoxy)acetonitrile (**7**) is described (Scheme 1). Although both the N-alkylation reaction and the subsequent alkaline or acidic hydrolysis gave the products in good yields, intermediate **8** could only be purified and isolated by column chromatography, thus rendering the procedure inapplicable for industrial purposes.

According to another invention,[5] cetirizine (**2d**) was obtained in 55.5% yield by treating alcohol **5** with sodium chloroacetate (**6c**) in the presence of potassium *tert*-butoxide and subsequent cautious acidification of **2c** with hydrochloric acid (Scheme 1). Cetirizine dihydrochloride (**1**) was obtained in a separate step by repeated treatment with hydrochloric acid in 88% yield. A Polish patent[6] discloses an improved implementation of the same synthesis by treating alcohol **5** with chloroacetic acid (**6d**) in the presence of an alkali metal hydroxide and a phase transfer catalyst in a two-phase system. The yield of the target compound **1** is reported to be 67%. The execution of the procedure is extremely complicated, obviously because of the capability of the alkali metal chloroacetate to react with itself.[7]

O-Alkylation of compound **5** in the presence of a base and a phase transfer catalyst, followed by hydrolysis of the resulting ester of type **2** and subsequent salt formation, was patented a few years later.[8] The nature of the alkylating agent, which is claimed to result in an improved yield when compared with earlier processes, is not evident from the text, nor is the purity of **1** disclosed in the patent. From a technological point of view, the obvious disadvantage of this procedure is having to perform more reaction steps (alkylation, hydrolysis, salt formation) without isolation of an intermediate. This renders it difficult to ensure the very strict quality requirements of the drug substance.

The patent EP 0927173[9] provides alternative synthetic routes to the target compound **1**, characterized by the aliphatic side chain being introduced into the piperazine ring prior to the benzhydryl group (Scheme 2). A 2-(2-chloroethoxy)acetic acid derivative (**4** or the corresponding iodo compounds) was reacted with piperazine or N-protected piperazine, to afford (after removal of the protecting group, if required) piperazines **9**. After alkylation with benzhydryl chloride **10**, the corresponding acid derivatives **2** were transformed to cetirizine dihydrochloride (**1**) by methods described in earlier patents. The use of type **4** alkylating agents, partially suitable for head–tail reactions,[10] and that of protected piperazine, necessitating additional reaction steps, are the drawbacks of this approach.

RESULTS AND DISCUSSION

We undertook studies with the aim of developing a new, noninfringing manufacturing synthesis of cetirizine dihydrochloride (**1**), which would make it possible to obtain this product from reasonable commercially available precursors with the least synthetic steps possible and would avoid drawbacks of the published methods. We decided to pass through 2-{4-[(4-chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethanol (**5**) and to apply a simple, chemoselective O-alkylating agent, resulting in an intermediate in high yield, which can easily be transformed to cetirizine dihydrochloride (**1**)[11] (Scheme 3). The synthesis of *N*,*N*′-disubstituted piperazine **5** is described in the literature[12] by N-alkylation of the commercially available *N*-(2-hydroxyethyl)piperazine (**11**) with 4-chlorobenzhydryl

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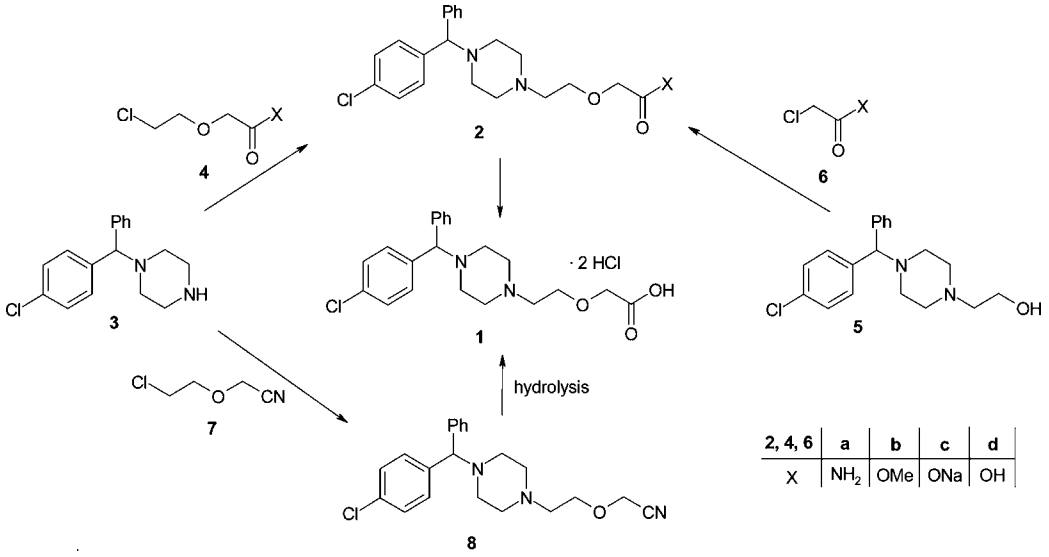
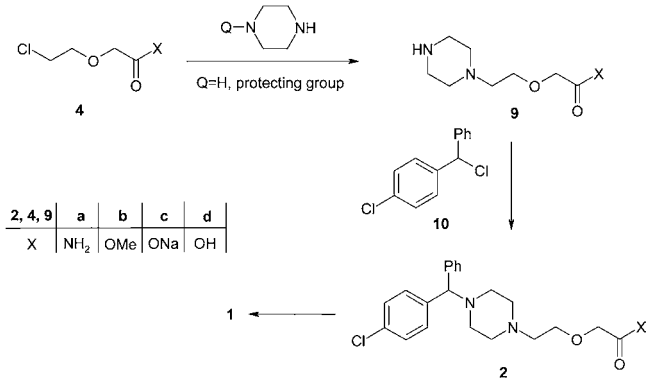
Scheme 1



Scheme 2



chloride (**10**). In our manufacturing process a solution of 4-chlorobenzhydryl chloride (**10**) in toluene was prepared starting from purchased 4-chlorobenzophenone (**12**). It is important to note that the starting material **12** had to meet very strict purity requirements: no quantity of its characteristic impurities (benzophenone, 2- or 3-chlorobenzophenone, or any dichlorobenzophenone isomer) should exceed 0.1%; otherwise final product **1** will fall short of the required purity.

4-Chlorobenzophenone (**12**) was reduced with sodium borohydride under phase transfer catalytic conditions in a toluene–water mixture. The solution of benzhydrol **13** in toluene thus obtained was treated with thionyl chloride to afford 4-chlorobenzhydryl chloride (**10**), which was also used without isolation. The solution of compound **10** in toluene was introduced into the N-alkylation reaction of *N*-(2-hydroxyethyl)piperazine (**11**). According to the literature,[12] compound **5** is an oil with an extremely high boiling point even under reduced pressure (205–208 °C at 0.1 Hgmm), which was later characterized also in the form of its dihydrochloride salt.[5] We succeeded in developing a simple and productive technology, avoiding the purification of intermediate **5** by distillation. In our hands, the dihydrochloride monohydrate of the compound (**5**·2HCl·H_2O) proved to be a conveniently isolable new form, with its water content proved by Karl Fischer titration. Best yields of **5**·2HCl·H_2O (60–68%, based on 4-chlorobenzophenone **12**) were achieved by using an excess (2–3 equiv) of piperazine **11**.

Alcohol **5** liberated from its dihydrochloride monohydrate was deprotonated and alkylated with the commercially available *N*,*N*-dimethyl-2-chloroacetamide (**14**) to produce the new *N*,*N*-dimethylamide derivative isolated as the dihydrochloride salt (**15**) in 82–90% yield. At first we applied sodium amide for deprotonation of alcohol **5**. In the course of the process development we succeeded in replacing sodium amide with the more favorable sodium methoxide, conducting the deprotonation in toluene with continuous removal of the methanol formed.

Preparation of amide **15** is the key factor of our manufacturing process. It meets the most important requirements set out for the last intermediate of a manufacturing procedure: (i) it is readily isolable and easily purified due to its increased hydrolytic stability as compared to that of the corresponding esters; (ii) nevertheless, it can be hydrolyzed to the final product under relatively mild conditions when compared with conditions for the corresponding nitriles.

Alkaline hydrolysis of dimethylamide **15** and subsequent salification with hydrochloric acid afforded cetirizine dihydrochloride (**1**) in 64–66% yield. The product meets the severe HPLC purity requirements (total impurity not more than 0.3%) of the *European Pharmacopoeia*.[13]

■ CONCLUSION

A new and efficient synthesis of cetirizine dihydrochloride (**1**) was elaborated. An improved manufacturing technology was developed for the preparation of intermediate *N*-benzhydryl-*N*′-(2-hydroxyethyl)piperazine (**5**). Deprotonation with sodium methoxide followed by alkylation with 2-chloro-*N*,*N*-dimethylacetamide afforded the new key intermediate *N*,*N*-dimethylamide **15**. Alkaline hydrolysis of amide **15** and subsequent salification gave the target compound **1** at industrial scale, in high overall yield and in excellent quality.

■ EXPERIMENTAL SECTION

General Remarks. All melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS-113v

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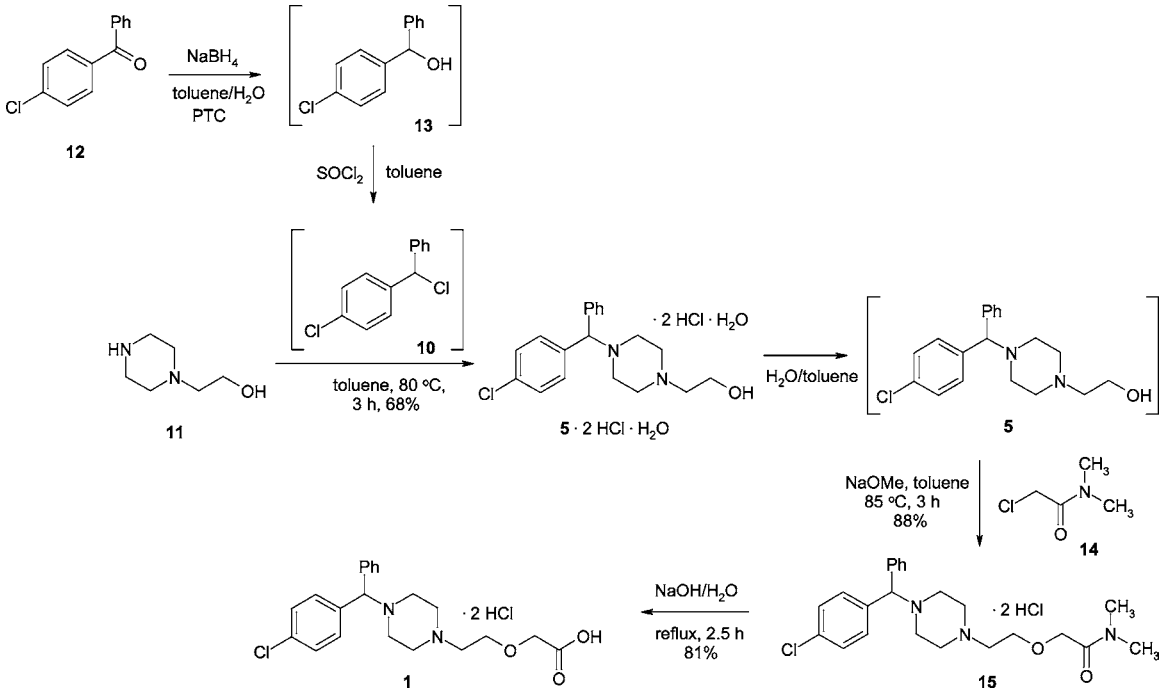
Scheme 3



FT spectrometer in KBr pellets. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer. ^{1}H and ^{13}C NMR spectra were recorded in D_2O, DMSO-d_6, or $CDCl_3$ on a Varian Unity Inova 400 spectrometer (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively), using TMS as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. All reagents were from commercial sources.

2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}-ethanol Dihydrochloride Hydrate (5·2 HCl·H_2O). To a solution of 4-chlorobenzophenone (**12**, 150 kg, 690 mol) in toluene (250 L) were added at 20 °C phase transfer catalyst methyltrioctylammonium chloride (2.5 kg) and water (55 L). While the mixture was stirred intensely, sodium borohydride (10 kg, 264 mol) was added in three portions, over a period of 1 h, while keeping the temperature below 50 °C. After 4 h the layers were separated, the organic layer was washed with a 15 w/w% NaCl solution (50 L) and dried over $MgSO_4$ and partly evaporated to a volume of 150 L.

To the solution obtained, thionyl chloride (63 L, 870 mol) was added, while keeping the temperature below 50 °C. The reaction mixture was heated to 85−90 °C for 1 h. The solution was evaporated to dryness, toluene (75 L) was added and the solvent was removed again in vacuo. This treatment with toluene was repeated once again.

The residue was dissolved in toluene (50 L), and the solution of 4-chlorobenzhydryl chloride (**10**) thus obtained was added to a solution of *N*-(2-hydroxyethyl)piperazine (**11**, 200 kg, 1540 mol) in toluene (50 L). The temperature was kept between 70 and 82 °C during the addition. The reaction mixture was stirred for 3 h at 80 °C; then toluene (400 L) was added, and the mixture was extracted with aqueous NaCl solution (15 w/w%, 400, then 200 L). The organic layer was evaporated, the residue was dissolved in 2-propanol (150 L), acidified with concentrated aqueous hydrochloric acid until pH = 1, and evaporated. The partly crystalline residue was stirred with acetone (800 L) for 4 h at 5−10 °C, and the resulting crystals were centrifuged, washed with acetone (60 L), and dried at 45−55 °C. Yield: 170−210 kg (60−68%, based on 4-chlorobenzophenone). HPLC purity >99.7%. Mp 190−194 °C dec. Karl Fischer water titration, calcd: 4.27%, found: 4.12%. IR (KBr, cm^{-1}): 3339, 1600, 1495, 1092, 758. ^{1}H NMR (D_2O, 400 MHz): δ 7.97 (m, 2H), 7.88 (~d, J = 8.6 Hz, 2H), 7.82 (m, 2H), 7.76 (m, 1H), 7.64 (~d, J = 8.5 Hz, 2H), 5.77 (s, 1H), 4.34 (m, 2H), 4.11 (m, 4H), 3.86 (m, 6H). ^{13}C NMR (D_2O, 100 MHz): δ 137.1, 135.9, 134.9, 132.1, 132.1, 131.9, 131.7, 130.2, 76.8, 60.2, 57.1, 51.2, 50.5. Anal. Calcd for $C_{19}H_{27}Cl_3N_2O_2$ (421.80): C, 54.10; H, 6.45; N, 6.64; Cl, 25.22. Found: C, 54.42; H, 6.52; N, 6.55; Cl, 25.46.

2-(2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)-*N*,*N*-dimethylacetamide Dihydrochloride (15). 2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}-ethanol dihydrochloride hydrate (**5**·2HCl·H_2O, 200 kg, 470 mol) was dissolved in water (660 L). Toluene (340 L) was added, and the two-phase system was cooled to 10−15 °C. While the mixture stirred, the pH was adjusted to 9 with aqueous sodium hydroxide solution (40 w/w%). The layers were separated, and the aqueous layer was extracted with toluene (100 L). The combined organic layers were extracted with aqueous sodium chloride solution (120 L, 15 w/w%). A part of the toluene (100−120 L) was evaporated in vacuo, and the remaining solution was dried over $MgSO_4$ (10 kg).

This solution was added under argon atmosphere to a refluxing suspension of sodium methoxide (50 kg, 930 mol) in toluene (300 L). In order to remove the methanol formed in the reaction, toluene (700 L) was continuously added into the reactor over a period of 3 h, under atmospheric distillation conditions.

The mixture was cooled to 50−55 °C, 2-chloro-*N*,*N*-dimethylacetamide (**14**, 100 L, 118 kg, 970 mol) was added over a period of 1 h, and the reaction mixture was stirred further for 1 h at 55−60 °C. Then, it was added to the cooled solution (0−10 °C) of concentrated aqueous hydrochloric acid (40 L) in water (320 L) under vigorous stirring. The pH of the

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mixture was adjusted to 4.0−4.5 by the addition of concentrated aqueous hydrochloric acid (∼10 L), and the layers were separated.

Dichloromethane (520 L) was added to the aqueous layer, and the pH was adjusted to 7.5 by the addition of 40 w/w% aqueous sodium hydroxide solution (∼43 L). After separation, the organic layer was stirred with a NaCl solution (15 w/w%, 120 L) and dried over $MgSO_4$ (20 kg). The solution was evaporated, the residue was dissolved in 2-propanol (200 L), and the pH was adjusted to 1.0−1.5 with a solution of hydrochloric acid in 2-propanol (20 w/w%). After partial evaporation of 2-propanol (∼150 L), acetone (1000 L) was added, and the mixture was cooled. The precipitate was centrifuged, washed with acetone, and dried in vacuo at 50−60 °C. Average yield: 190−210 kg (82−90%). Mp 185−190 °C dec. IR (KBr, cm^{-1}): 1644, 1495, 1121. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37−7.15 (m, 9H), 4.20 (s, 1H), 4.14 (s, 2H), 3.63 (t, J = 7.0 Hz, 2H), 2.98 (s, 3H), 2.92 (s, 3H), 2.62 (t, J = 7.0 Hz, 2H), 2.53 (t, J = 5.8 Hz, 4H), 2.41 (br s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 169.1, 136.9, 133.5, 130.3, 129.5, 128.9, 128.4, 72.5, 68.3, 64.9, 55.1, 48.2, 35.5, 35.1. Anal. Calcd for $C_{23}H_{32}Cl_3N_3O_2$ (488.88): C, 56.50; H, 6.60; N, 8.60; Cl, 21.76. Found: C, 56.32; H, 6.63; N, 8.40; Cl, 21.67.

(2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)acetic Acid Dihydrochloride (1). 2-(2-{4-[(4-Chlorophenyl)(phenyl)methyl]piperazin-1-yl}ethoxy)-*N*,*N*-dimethylacetamide dihydrochloride (**15**, 100 kg, 200 mol) was dissolved in water (300 L), and aqueous sodium hydroxide solution (40 w/w%, 60 L) was added. The reaction mixture was refluxed for 3 h, water (400 L) was added, and the pH was adjusted to 9.5−11.5 with concentrated aqueous hydrochloric acid. The mixture was cooled to 5−10 °C, and it was extracted with ethyl acetate (300 L, then 5 × 150 L) and finally with diethyl ether (2 × 200 L).

The pH of the aqueous solution was adjusted to 3.5−4.5 with concentrated aqueous hydrochloric acid. After removal of the residual ether in vacuo, the solution was extracted with dichloromethane (350 L), and the organic layer was separated.

Water (200 L) was added, and the pH was adjusted to 1.3−1.6 by the addition of concentrated aqueous hydrochloric acid under vigorous stirring. The aqueous layer containing cetirizine dihydrochloride (**1**) was separated, filtered, and evaporated in vacuo. Acetone (600 L) was added to the residue, and then the solid was filtered and dried in vacuo.

Crude product **1** thus obtained was dissolved in purified water (150 L) at 60−75 °C and filtered. The solution was evaporated in vacuo at a maximum temperature of 55 °C. Acetone (450 L) was added to the honey-like residue, and the resulting slurry was cooled to 5−10 °C and centrifuged. The filter cake was dried in vacuo at 55 °C for 24 h to give cetirizine dihydrochloride (**1**, 60−62 kg, 64−66%). Mp 226−228 °C dec. The purity of the product (>99.7%, as determined by HPLC) corresponds to the quality requirements of the European Pharmacopoeia (individual impurities <0.10%).[13] IR (KBr, cm^{-1}): 3424, 2374, 1746, 1320, 1137.[14] ^1H NMR (D_2O, 400 MHz): δ 7.82 (m, 2H), 7.76 (∼d, J = 8.7 Hz, 2H), 7.69 (m, 2H), 7.64 (m, 1H), 7.58 (∼d, J = 8.7 Hz, 2H), 5.57 (s, 1H), 4.47 (s, 2H), 4.16 (t, J = 4.8 Hz, 2H), 3.94 (m, 4H), 3.78 (t, J = 4.8 Hz, 2H), 3.69 (m, 4H).[15] ^{13}C NMR (D_2O, 100 MHz): δ 176.9, 137.4, 136.4, 135.3, 132.4, 132.3, 132.2, 132.0, 130.4, 77.1, 69.9, 66.4, 58.4, 51.6, 50.8. Anal. Calcd for $C_{21}H_{27}Cl_3N_2O_3$ (461.82): C, 54.62; H, 5.89; N, 6.07; Cl, 23.03. Found: C, 54.73; H, 5.92; N, 6.06; Cl, 23.04.

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Notes

The authors declare no competing financial interest.

DEDICATION

Dedicated to the memory of Professor István Hermecz.

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