A Novel Synthesis of the Enantiomers of an Antihistamine Drug by Piperazine Formation from a Primary Amine

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An enantioselective synthesis of each enantiomer of the antihistamine drug 2-(2-{4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl}ethoxy)acetic acid dihydrochloride (1) is described, involving the preparation of the benzhydrylpiperazine portion of the molecule from reaction of each enantiomer of 4-chlorobenzhydrylamine with *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide. A modification of standard toluenesulfonamide deprotection with hydrogen bromide in acetic acid was introduced, substituting 4-hydroxybenzoic acid for phenol.

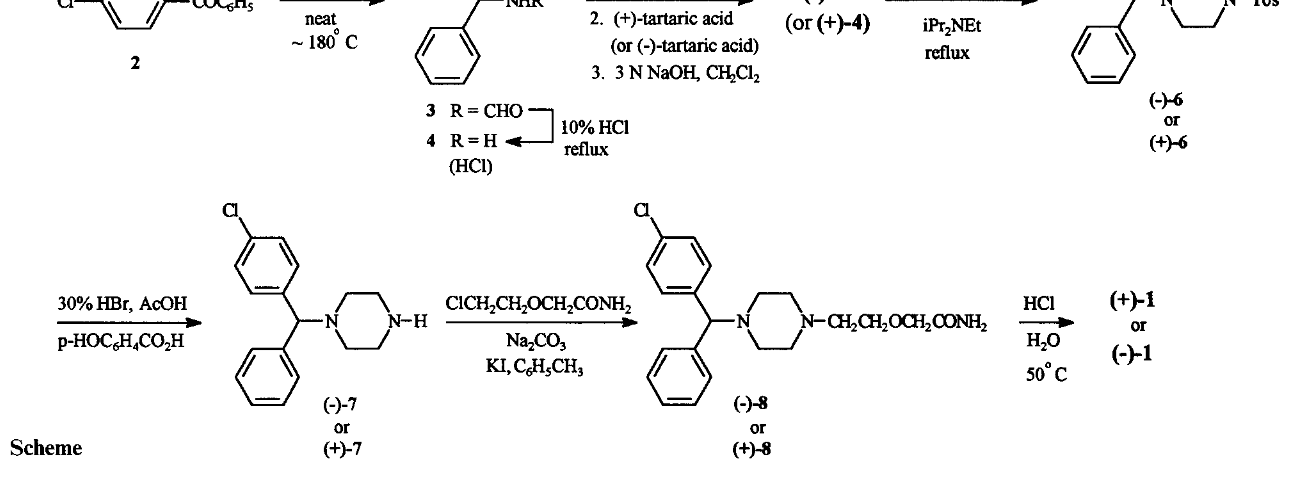
The compound 2-(2-{4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl}ethoxy)acetic acid dihydrochloride (**1**), designated by the generic name of *cetirizine hydrochloride* (USAN), is a second generation antihistamine agent.[2,3] It is prescribed for the treatment of allergic syndromes, such as chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria, etc. The presence of a 4-chloro substituent on only one of the aromatic rings of **1** confers a center of asymmetry at the benzhydryl position.

A process for the preparation of the enantiomers of **1** has been described.[4] Because of limitations to this process we developed and describe herein an alternate process to prepare each enantiomer of **1**, by procedures which can potentially be adapted to industrial scale, and yielding material of high (> 99 %) optical purity.

Although the separation of the enantiomers of **7** by classical resolution with (+)- or (−)-tartaric acid was low yielding and afforded insufficient enantiomeric enrichment,[4] the corresponding crystallization of 4-chlorobenzhydrylamine (**4**) with enantiomerically pure tartaric acid provided good yields of **4** of high optical purity.[5] We reasoned that the piperazine of **7** could be constructed from optically pure **4**,[6] by reaction with an appropriate nitrogen-containing bis-alkylating agent (nitrogen mustard).[7,8] Because of past interest in "mustard analogs" as anticancer agents, many such bis-alkylating agents have been prepared.[7,9] Our initial attempts to convert **4** to **7** were not successful, despite many variations of bis-alkylating agent, solvent(s), base, and temperature.

We had anticipated that a carboxamide-protected bis-alkylating agent would meet our requirements for this transformation, due to a deactivation of the amine lone pair. Simple acyl derivatives of bis(2-chloroethyl)amine, however, did not yield any evidence of piperazine product. Since results of probe experiments with carboxamide-type bis-alkylating agents were not encouraging, we shifted our attention to the corresponding toluenesulfonamide reagent. This reagent was found to work well for this transformation. By careful selection of conditions, **6** could be obtained in high yield. For example, refluxing a homogeneous solution of the free base of either (−)-**4** or (+)-**4** with a slight excess of *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (**5**)[10] in three volumes (w/v) of diisopropylethylamine for 3 hours afforded the tosyl derivatives (−)-**6** or (+)-**6**, respectively (Scheme), which were easily crystallized from ethanol. On larger scales, the volume of diisopropylethylamine to **4** was brought to nearly 1:1 (v/w), and 75–80 % yields were reproducibly obtained.

Although use of Vitride®[11] with **6** afforded the deprotected target **7** in good yield, it soon became apparent



Scheme

that some epimerization (5–8 %) at the benzhydryl position was occurring, as determined by enantiomeric HPLC analysis of the resulting product. In evaluating other conditions for removal of an *N*-tosyl protecting group, it was found that stirring **6** with hydrogen bromide and phenol in acetic acid[12] at room temperature was effective [62 % yield of (−)-**7** (> 99 % enantiomerically pure on a 1.7 kg scale)], and no epimerization was produced. For this transformation, the volume of hydrogen bromide in acetic acid could be substantially reduced relative to literature procedures. The (−)-**7** obtained was then converted to optically pure (+)-**1** by standard procedures (Scheme). In a similar fashion, (+)-**6** was converted to (+)-**7**, and then to (−)-**1** by this sequence.

The use of hydrogen bromide and phenol for reductive removal of the *N*-tosyl group was successful for providing initial quantities of **7** of high optical purity. The extensive workup and multiple extractions to remove phenolic byproducts from the crude product, however, were not conditions well suited for synthesizing larger quantities. Because of these difficulties, we developed an improved procedure for conducting this reaction, substituting 4-hydroxybenzoic acid for phenol. After the deprotection reaction is complete, the mixture is simply poured into water, whereupon most of the hydroxybenzoic acid derivatives precipitate out. Basification of the aqueous filtrate and extraction affords very clean, crude **7**. Although we have not evaluated the use of 4-hydroxybenzoic acid in the deprotection of other *p*-toluenesulfonamides with hydrogen bromide, it is speculated that this modification may have broad applications, and improve the usefulness of this reaction.

In summary, we have developed a novel procedure to prepare the enantiomers of the key intermediate **7** and thus the enantiomers of the antihistamine drug **1** in large quantities and in high optical purity. In developing this process, an improved sequence of piperazine formation from an optically pure benzhydrylamine was developed. In addition to providing large scale quantities of the optically pure enantiomers of **1**, these procedures may have general use in the synthesis of related structures.

^{1}H NMR spectra were measured at 200 MHz on a Varian XL-200 instrument using $CDCl_3$ or DMSO-d_6 as solvent. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter in a Perkin-Elmer 10 mm microcell. Elemental analyses were performed by Quantitative Technologies of Whitehouse, New Jersey USA. HPLC determinations of the enantiomeric purity of **7** and **4** were made using a Daicel CHIRALCEL OD column (Chiral Technologies, Exton, PA). The mobile phase for both compounds was the same: hexane/2-propanol (99 : 1) with the hexane spiked with 0.02 % diethylamine, at a flow rate of 0.9 mL/min. For **4** this system provided average retention times of 25.5 min for the (+)-enantiomer and 35 min for the (−)-enantiomer. For **7** average retention times were 21 min for the (+)-enantiomer and 24 min for the (−)-enantiomer. Satisfactory microanalyses were obtained for all new compounds: C ± 0.37, H ± 0.06, N ± 0.16.

(−)-1-[(4-Chlorophenyl)phenylmethyl]-4-[(4-methylphenyl)-sulfonyl]piperazine [(−)-6]:

To the free base of (−)-4-chlorobenzhydrylamine generated from the (+)-tartaric acid salt (1.8 kg, 4.9 mol) was added *N,N*-diisopropylethylamine (700 mL). To this mixture was added **5** (1.4 kg, 4.7 mol) carefully in portions, and additional *N,N*-diisopropylethylamine was added in portions to ensure mixing. After the addition of the bis-alkylating agent was complete, the remaining *N,N*-diisopropylamine was added, totaling 1.4 L. The flask was then equipped with a reflux condenser and drying tube and the mixture was refluxed for 3.5 h, whereupon TLC analysis (i-$PrNH_2$/MeOH/$CHCl_3$, 3 : 3 : 94) showed a significantly less polar spot with respect to **4**, as well as a loss of **4**. The reaction mixture had become dark orange. This mixture was allowed to cool to 70 °C, then MeCN (3.2 L) was added and the mixture stirred overnight. A precipitate formed, which was collected and washed with MeOH to afford 1.13 kg (59 %) of a white solid. The filtrate was concentrated at reduced pressure. The yellow residue was treated with MeOH and stirred in an ice bath. The resulting solid was collected and was washed with MeOH to afford 0.34 kg (total yield of 77 %) of white solid; mp 166–168 °C; $[\alpha]_D$ − 40.95° (c = 1, toluene).

*(+)-1-[(4-Chlorophenyl)phenylmethyl]-4-[(4-methylphenyl)sulfonyl]piperazine [(+)-***6***]:*

This compound was prepared from (+)-**4** in an analogous manner; mp 164–168 °C, $[\alpha]_D$ + 41.67 (c = 1, toluene).

*(−)-1-[(-4-Chlorophenyl)phenylmethyl]piperazine (Using 4-Hydroxybenzoic Acid) [(−)-***7***]:*

To a slurry of 4-hydroxybenzoic acid (2.22 kg, 16.6 mol) in 30 % HBr/AcOH (8.65 L) at ice-bath temperature was added (−)-**6** (2.21 kg, 5.02 mol). The mixture was stirred at r. t. for 2 d. TLC analysis ($CHCl_3$) indicated that the reaction was complete. The mixture was diluted with H_2O (10 L) with stirring. The resulting solids were washed with H_2O (2 × 2 L). The combined aqueous was washed with toluene (2 L). The aqueous phase was separated and made basic with 50 % NaOH solution. The product was extracted with toluene (3 × 2 L). The organic extracts were combined, washed with H_2O (2 L) and brine (2 L) dried ($MgSO_4$), filtered and concentrated in vacuo to afford 1255 g of a white solid. Recrystallization from hexane (6 L) after treatment with Darco G-60 (100 g) afforded 851.8 g (59 %) of a white solid; mp 94–96 °C; $[\alpha]_D$ − 21.72° (c = 1, toluene). By enantiomeric HPLC analysis this material was determined to be a 99.7 to 0.3 mixture of enantiomers.

*(+)-1-[(-4-Chlorophenyl)phenylmethyl]piperazine [(+)-***7***]:*

The dextro enantiomer was similarly prepared; mp 82–85 °C; $[\alpha]_D$ + 20.02° (c = 1, toluene).

*(−)-2-(2-{4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl}ethoxy)acetamide [(−)-***8***]:*

An analytical sample was prepared by recrystallization from diisopropyl ether; mp 94 °C; $[\alpha]_{365}$ − 23.5° (c = 1, MeOH).

*(+)-2-(2-{4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl}-ethoxy)acetic Acid Dihydrochloride [(+)-***1***]:*

After workup the product was crystallized as a dihydrochloride from acetone, yielding 820 g (71 %) of a white solid; mp 215–219 °C; $[\alpha]_{365}$ + 11.12° (c = 1, H_2O).

*(−)-2-(2-{(4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl}ethoxy)-acetic Acid Dihydrochloride [(−)-***1***]:*

This enantiomer was similarly prepared; mp 216–220 °C; $[\alpha]_{365}$ − 11.07° (c = 1, H_2O).

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