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**Bader et al.**

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(54) **POLYMORPHIC FORMS OF OLOPATADINE HYDROCHLORIDE AND METHODS FOR PRODUCING OLOPATADINE AND SALTS THEREOF**

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JP 07002733 1/1995  
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(51) **Int. Cl.**  
**C07D 313/10** (2006.01)

(52) **U.S. Cl.** ..... **549/354**

(58) **Field of Classification Search** ..... 549/354  
See application file for complete search history.

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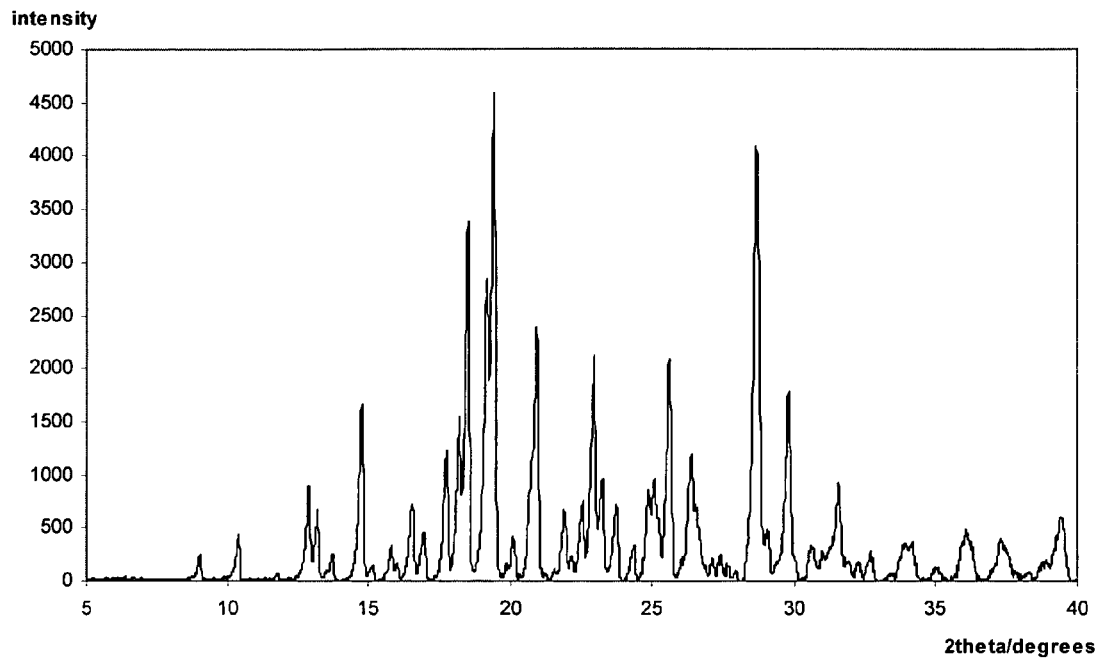
(57) **ABSTRACT**

The present invention provides a novel polymorphic form of olopatadine hydrochloride ((Z)-3-(dimethylamino)propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride), a selective histamine H1-receptor antagonist that is used for the treatment of ocular symptoms of seasonal allergic conjunctivitis. The present invention also provides novel methods for producing olopatadine on a large scale, and in a manner that is cost effective, provides a low level of impurities and eliminates the need to use the costly and dangerous base, butyllithium, which is used in prior art reactions for making olopatadine. The present invention further provides novel processes for carrying out a large scale production of 3-dimethylaminopropyltriphenylphosphonium bromide and its corresponding hydrobromide salt, which are employed in the production of olopatadine, and pharmaceutically acceptable salts of olopatadine.

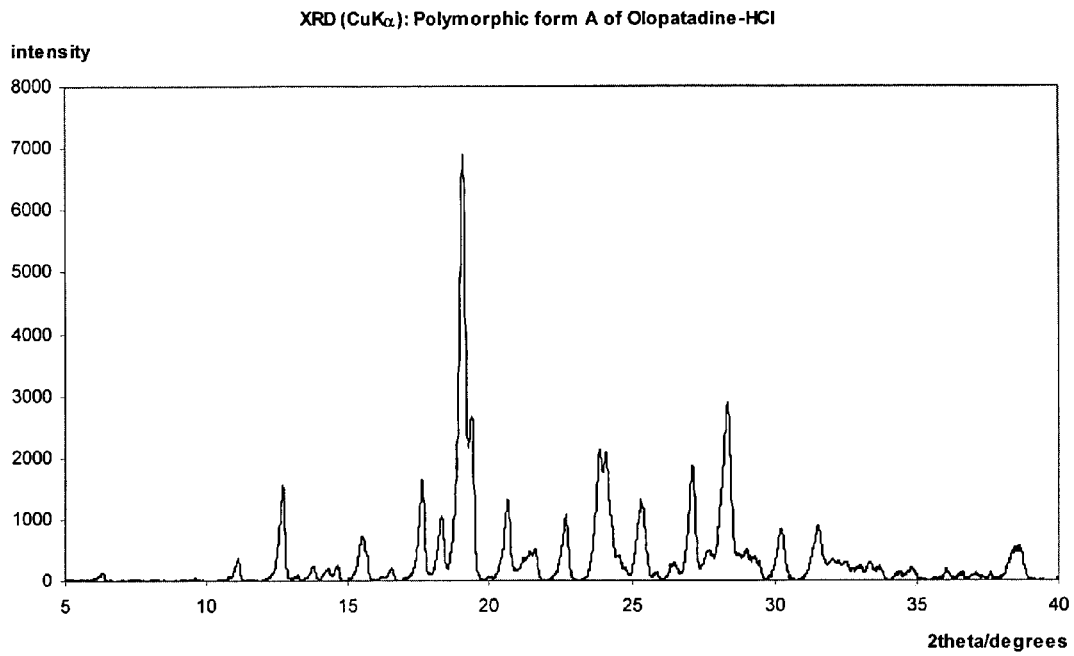
**45 Claims, 2 Drawing Sheets**

Fig. 1

XRD (CuKa): Polymorphic form B of Olopatadine-HCl



**Fig. 2**



**1**

**POLYMORPHIC FORMS OF OLOPATADINE  
HYDROCHLORIDE AND METHODS FOR  
PRODUCING OLOPATADINE AND SALTS  
THEREOF**

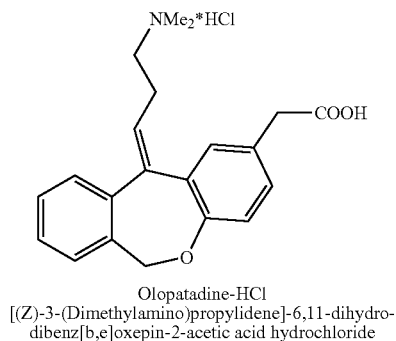
BACKGROUND OF THE INVENTION

1. Field of the Invention

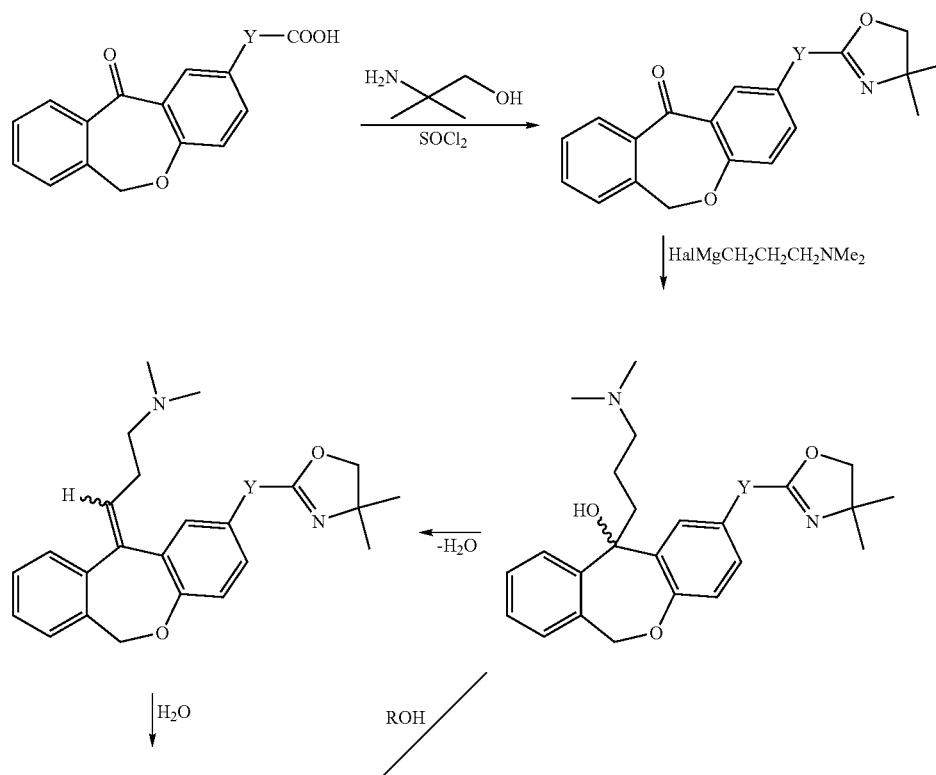
The present invention is directed to a novel polymorphic form of olopatadine hydrochloride, and to novel methods for producing olopatadine, and pharmaceutically acceptable salts thereof.

2. Background and Related Art

Olopatadine-HCl ((Z)-3-(dimethylamino)propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid hydrochloride) is a selective histamine H<sub>1</sub>-receptor antagonist that is used for the treatment of ocular symptoms of seasonal allergic conjunctivitis. The compound may be administered in a solid oral dosage form or as an ophthalmic solution.



Scheme 1:



**2**

Olopatadine is stated to be an effective treatment for symptoms of allergic rhinitis and urticaria (e.g., sneezing, nasal discharge and nasal congestion), as well as in the treatment of various skin diseases, such as eczema and dermatitis.

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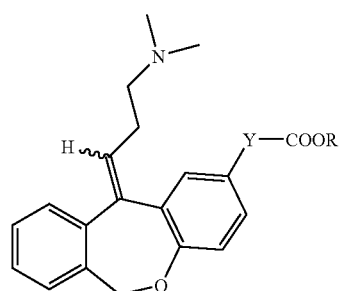
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Olopatadine and its pharmaceutically acceptable salts are disclosed in EP 0214779, U.S. Pat. No. 4,871,865, EP 0235796 and U.S. Pat. No. 5,116,863. There are two general routes for the preparation of olopatadine which are described in EP 0214779: One involves a Wittig reaction and the other involves a Grignard reaction followed by a dehydration step. A detailed description of the syntheses of olopatadine and its salts is also disclosed in Ohshima, E., et al., *J. Med. Chem.* 1992, 35, 2074-2084.

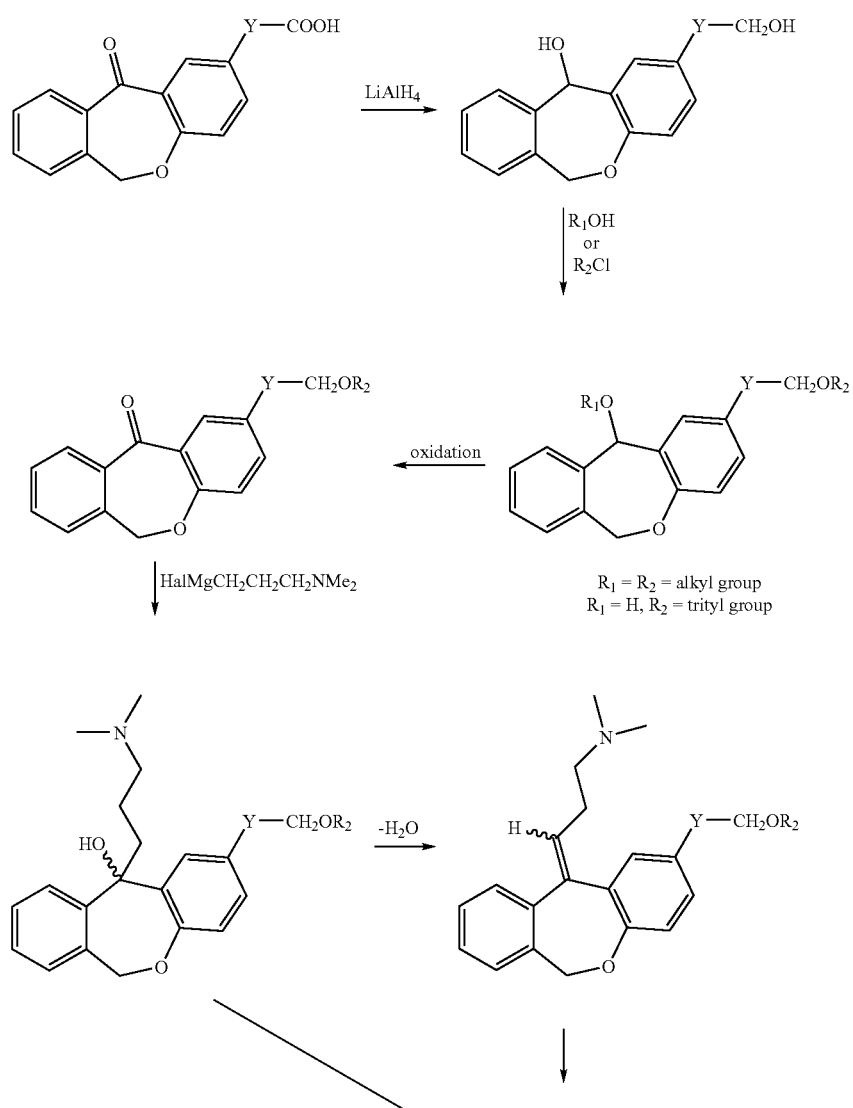
EP 0235796 describes a preparation of olopatadine derivatives starting from 11-oxo-6,11-dihydroxydibenz[b,e]oxepin-2-acetic acid, as well as the following three different synthetic routes for the preparation of corresponding dimethylaminopropylidene-dibenz[b,e]oxepin derivatives, as shown in schemes 1-3 below:

-continued



Y =  $-(CH_2)_m$   
 m = 0, 1, 2, 3, 4  
 R = H, alkyl group  
 Hal = halogen

Scheme 2:



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