This invention relates to antihistaminic agents and to a new class of compounds having highly effective antihistaminic properties.

It is only in comparatively recent years that medical science has succeeded in developing drugs which could be used satisfactorily in countering the painful, irritating and sometimes fatal effects of various types of allergic and similar disturbances such as food allergy, serum sickness, hayfever, asthma, migraine, urticaria, etc.

As a result of work carried out by numerous researchers, it has been rather definitely shown that occurrence of the above and similar disturbances may in practically all cases be traced, at least in part, to the liberation of histamine from a fixed state in certain of the body cells and the subsequent reaction of the liberated histamine upon other body cells as the histamine diffuses into surrounding tissues. It is believed that the histamine is released from its fixed state in the cells in which it is contained by the action upon such cells of various compounds which in many cases appear to be of a protein nature and which are usually referred to as allergens. These allergens are found in substances such as the pollen of various weeds, in foods such as strawberries, eggs, etc., in serums used in treating various diseases, etc.

At first it was believed that by injecting histamine into persons who were subject to allergies and similar disturbances a tolerance to histamine could be developed; however, it was found that such was not the case. Thereafter various researchers directed their efforts along the lines of developing drugs which would either destroy histamine or in some manner or other alleviate its ill effects. In recent years several drugs have been developed which have been found to be rather effective antihistaminic agents. All of the effective antihistaminic compounds so far developed seem to counteract the effect of histamine by, in some manner or other, attaching themselves to the various body cells which would be affected by the liberated histamine and either preventing such histamine from itself attaching to such receptor cells or displacing the histamine if it is already attached to such cells.

In the Journal of The American Medical Association, 132, 702 (1946), there is an excellent article by Feinberg in which he discusses the antihistaminic agents known at that time and the various results which have been obtained from the use thereof. According to his article...
Another compound which has recently been found to have antihistaminic properties is the hydrochloride salt of 
N,N-dimethyl-N-(2-thienyl)-N'-{(2-pyridyl)-ethylenediamine

From the comparison of the above formulae it will be seen that each of these eight compounds contains one or the other of two rather similar groups. Thus it will be seen that six of the eight compounds contain the group 

and that the other two compounds contain the group 

Feinberg stated in his article that as far as was known at that time, the antihistaminic agents operate by competing with liberated histamine in attaching to receptor cells. Since all of the effective antihistaminic agents to date contain one or the other of two similar chemical groups, it is reasonable to assume that one or the other of these groups must be present for any compound to be an efficient antihistaminic agent, and that the antihistaminic agents herefore known attach to the receptor cells through or by means of one of these two groups.

It is the object of this invention to provide an entirely new class of antihistaminic agents.

Other objects of the invention will in part be obvious and in part appear hereinafter.

We have discovered that a new class of compounds having the general formula:

wherein R is an alkyl group containing from 1 to 4 carbon atoms, i.e., methyl, ethyl, propyl, and butyl and propyl and butyl isomers, and hydrohalide salts of such compounds are highly effective antihistaminic agents. The preferred antihistaminic compounds of our invention are 1-methyl-piperidyl-4-benzhydryl ether

and the hydrohalide salts thereof.

The compounds of our invention may be prepared by reacting a 1-alkyl-4-piperidinol where-
reaction mixture to neutralize any hydrogen halide which is formed.

The reaction should preferably be carried out under substantially anhydrous conditions in order to obtain the most favorable yields and therefore it is preferable to employ only substantially anhydrous reactants and solvents. After the reaction medium has been heated for a sufficient length of time to give substantially complete reaction between the two reacting compounds, it will be found that the reaction mass will separate into two layers if an excess of a piperidinol or similar basic compound has been employed, the upper phase containing the desired benzhydryl ether compound. If an inert solvent such as xylene, toluene or one of the other aromatic or aliphatic hydrocarbon solvents has been employed, it will also be found in the upper phase. The lower phase of the reaction mixture will be made up of the excess piperidinol or similar basic compound, if any. If no inert solvent was utilized in the carrying out of the reaction, a volume of such a solvent equal to about the volume of the reaction mixture may be added thereto so as to aid in separating the desired benzhydryl ether compound from the rest of the reaction mixture. After separating the upper phase from the other components of the reaction mixture, if the reaction mixture has separated into two phases, any inert solvent in that phase is removed therefrom, e.g., by distillation under reduced pressure. The crude benzhydryl ether may then be purified by dissolving it in an excess of an aqueous solution of medium strength, e.g., 20% hydrochloric acid, and the aqueous acid solution then washed with some solvent such as ethyl ether to remove any non-basic impurities therefrom. If the reaction mixture does not separate into two phases, any inert solvent therein may be removed as by distillation under reduced pressure and the remainder of the reaction mixture then admixed with an aqueous acid solution and the resulting mixture washed with a solvent such as ethyl ether to remove any non-basic impurities. The aqueous acid solution of the desired benzhydryl ether compound may be decolorized with activated carbon and the acid solution neutralized with a base such as aqueous ammonia. The free benzhydryl ether compound will separate from the aqueous solution as an oily material and may be readily recovered by extraction with a solvent such as ethyl ether or a similar solvent. The oily product may then be converted to a crystalline hydrohalide salt by dissolving the oily product in a solvent such as isopropanol and adding thereto an alcoholic, e.g., methanolic, ethanolic, etc., halide. Ethyl ether may then be added to the acidified solution until a faint turbidity is observed. The crystalline hydrohalide salt of the benzhydryl ether will soon separate and after recovery from the solution may be further purified by recrystallization from a small amount of a solvent such as isopropanol if desired.

For a fuller understanding of the nature and objects of our invention, reference may be had to the following example which is given merely to illustrate the production of the compounds of our invention and such example is not to be construed in a limiting sense.

**Example**

A mixture of 46 gm. of 1-methyl-4-piperidinol (0.4 mol), 49.4 gm. of benzhydryl bromide (0.2 mol) and 100 ml. of xylene was refluxed for approximately 24 hours. The reaction mixture separated into two phases with the upper phase containing the desired ether compound dissolved in xylene. The lower phase consisted of the hydrobromide salt of the excess 1-methyl-4-piperidinol. The upper phase was separated from the lower phase and the desired benzhydryl ether recovered in the crude state by distilling off the xylene under reduced pressure. The crude benzhydryl ether was a clear reddish oil. It was dissolved in 75 ml. of 20% hydrochloric acid and the aqueous acid solution then washed three times with 50 ml. portions each of ethyl ether. The aqueous acid solution was then decolorized with activated carbon and thereafter slowly admixed with 75 ml. of 28% aqueous ammonia. The benzhydryl ether separated as an oily material and was removed from the aqueous mixture by extraction with three 50 ml. portions of ethyl ether. On evaporation of the ethyl ether from the ethyl ether solution, the benzhydryl ether was recovered as a pale yellow oil. The benzhydryl ether was dissolved in 60 ml. of isopropanol and the isopropanol solution acidified to a pH of 3 with dry hydrogen chloride-methanol solution. The acidic propanol solution was then diluted with ethyl ether until a faint turbidity was observed. In a short time, the crystalline hydrochloride salt of the benzhydryl ether separated from the propanol solution. The crystallized salt was recrystallized once from 75 ml. of isopropanol with the aid of ethyl ether in order to further purify the material. A yield of the pure hydrochloride salt of 1-methylpiperidyl-4-benzhydryl ether of 24.5 gm. was obtained. This was 39% of the theoretical yield. The pure material had a melting point of 206° C.

Calc. for C16H24ONCi: C, 71.81; H, 7.61; N, 4.40; Cl, 11.15. Found: C, 71.25; H, 7.32; N, 4.07; Cl, 11.32.

The new compounds of our invention when tested physiologically have been found to have very good antihistaminic properties with a very low order of undesirable side effects.

It will be noted that the chemical structure of our new antihistaminic agents is entirely different from the chemical structure of any of the previously known antihistaminic compounds. Thus it is quite apparent that we have provided an entirely new class of antihistaminic agents.

In addition to their antihistaminic properties, the compounds of our invention manifest antianaphylactic action when tested on animals.

Having described our invention, what we claim as new and desire to secure by Letters Patent is:

1. The class of compounds consisting of compounds having the structural formula

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\[
\text{N-R} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{C} \quad \text{C} \\
\text{O} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H}
\]
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wherein R is an alkyl group containing from 1 to 4 carbon atoms and the hydrohalide salts of such compounds.

2. The compound having the formula
3. The compound having the formula
\[ \text{XI C-C d-o-o/ Y-ch-HC1} \]

4. The compound having the formula
\[ \text{H C-O-C} \]

5. A process for preparing a new class of anti-histaminic agents which comprises heating a benzhydryl halide with a 1-alkyl-4-piperidinol wherein the alkyl group contains from 1 to 4 carbon atoms.

6. A process for preparing a new anti-histaminic agent which comprises heating a benzhydryl halide with 1-methyl-4-piperidinol.

7. A process in accordance with the process of claim 5 wherein the reaction is carried out in the presence of an inert solvent selected from the class consisting of aliphatic and aromatic hydrocarbons and aliphatic ethers having boiling points of at least 80°C, and the reaction mixture is heated at the reflux temperature of the inert solvent.

8. A process in accordance with the process of claim 6 wherein the reaction is carried out in the presence of an inert solvent selected from the class consisting of aliphatic and aromatic hydrocarbons and aliphatic ethers having boiling points of at least 80°C, and the reaction mixture is heated at the reflux temperature of the inert solvent.

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