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ANTI-INFLAMMATORY TREATMENT

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U.S. Cl. 424—330 5 Claims

ABSTRACT OF THE DISCLOSURE

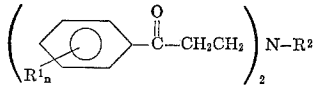
A process for treatment of inflammatory conditions preferably employing pharmaceutical compositions comprising as active ingredient an optionally substituted N,N-bis[2-(benzoyl)ethyl]lower alkylamine in the form of a pharmaceutically acceptable salt.

BACKGROUND OF THE INVENTION

The compounds employed in the method of the invention, which have now been found to be active anti-inflammatory and antipyretic agents, are generally known to the art. Mannich and Heilner [Berichte, 55, 356 (1922)] report the preparation of N,N-bis[2-(benzoyl)ethyl]methylamine hydrochloride. Draper (U.S. Pat. 3,272,838) describes halogen and alkoxy substituted derivatives. Plati and Wenner [J. Org. Chem., 14, 543 (1949)] describe an improved process of the Mannich and Heilner type for synthesis of these compounds. However, the physiological activity of the compounds and their utility in the process of the invention have so far as is known not been heretofore described.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to processes or methods of treatment, and to pharmaceutical compositions and their use as anti-inflammatory and antipyretic agents. More particularly, there is described a method in which compounds of the formula



wherein R^1 is fluorine, chlorine, bromine, lower alkyl or lower alkoxy, n is zero, one or two and R^2 is lower alkyl, and pharmaceutically acceptable salts thereof are used as anti-inflammatory and antipyretic agents.

It is presently preferred that for this method of the invention the compounds be used as their pharmaceutically acceptable salts.

Suitable salts are formed with organic or inorganic acids and include (although not limited to) the hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, citrate, tartrate, malate, maleate and the like. These salts are representative of the pharmaceutically acceptable salts of physiologically active bases, as is well known to the art.

Evaluation of the anti-inflammatory and antipyretic activity of the compounds useful in the method of the present invention is carried out according to recognized pharmacological methods for the detection of anti-inflammatory and antipyretic activity. The compounds are found to be active in one or more of these test methods, some of which are described in more detail hereinafter. The assays used include the rat foot edema test, which measures the inhibition of carrageenin-induced hyperthermia [as described by Smith et al., J. Pharm. Expt. Ther., 54, 346 (1935)], and the like.

The terms "lower alkyl" or "lower alkoxy" as used herein refer to alkyl or alkoxy substituents containing one to six atoms, which may be straight or branched chain, including methyl, ethyl, isopropyl, *n*-butyl, isobutyl, *n*-hexyl and the like. When R^1 is lower alkyl or lower alkoxy, the substituent is presently preferred to contain one carbon atom. Compounds wherein R^1 is fluorine, chlorine or methoxy are presently preferred, and most preferred are those in which R^1 is fluorine and/or chlorine. It is presently preferred that n be one.

Accordingly, presently preferred compounds of the invention are N,N-bis[2-(4-fluorobenzoyl)ethyl]methylamine, N,N-bis[2-(4-chlorobenzoyl)ethyl]methylamine and their pharmaceutically acceptable salts, particularly the hydrochloride salts.

In carrying out the method of the invention a daily dose of from about 25 to 2000 mg. of the active compound, depending on the age, weight and physical condition of the subject and the route of administration is administered. The individual unit dosage and frequency of administration is determined by the physician after consideration of the nature and severity of the inflammatory condition for which relief is desired.

In the method of the present invention, pharmaceutical compositions are preferably used in the treatment of inflammatory conditions in human and veterinary medicine for palliation and temporary relief of symtoms accompanying inflammatory processes. Antipyretic effects are commonly noted. The pharmaceutical compositions used are prepared and used in a conventional manner, excipients and other formulating agents being employed as desired, with or without supplementary or adjuvant medicinal agents. Preferably the composition is in unit dosage form containing 5 to 250 mg. of the active ingredient, e.g. tablets, pills or capsules.

The carrier or diluent may be a solid or liquid. If the carrier is a solid, the selected compound may be incorporated into capsules, suppositories or tablets which may include binders or lubricants and may be coated, e.g. with an exterior coating. If the carrier is a liquid, the selected compound may be incorporated into aqueous solution in ampoules for parenteral administration, or solutions or suspensions in soft gelatin capsules for oral administration, or solutions or suspensions for oral administration can be prepared.

It is preferred to administer the pharmaceutical compositions of the invention by the oral route.

It is presently preferred to administer the compounds of the invention orally in admixture with a solid carrier and with a pharmaceutically acceptable pill or capsule coating to facilitate the release of the compound in the gastrointestinal tract and to prevent release of the compound in the mouth.

The preparation of the compounds used in the process of the invention and typical pharmaceutical compositions and their uses are illustrated in the following examples for the purpose of describing the best mode presently contemplated for practicing the invention. Since these examples are merely illustrative, they should not be construed as limiting the invention.

EXAMPLE 1

4-fluoroacetophenone (150 g., 1.09 mole), paraformaldehyde (36 g., 1.2 mole) and methylamine hydrochloride (36.8 g., 0.55 mole) are stirred and heated on an oil bath for five minutes at 150° C. Ethanol (250 ml.) is added with stirring, and the mixture is cooled to about 5° C. and allowed to stand for two hours. The crystalline product, N,N-bis[2-(4-fluorobenzoyl)ethyl]methylamine hydrochloride, is isolated by filtration, washed with ethanol and diethyl ether and then dried. Its melting point is 150° C.

The method described is used to prepare

N,N-bis[2-(4-chlorobenzoyl)ethyl]methylamine;
N,N,-bis[2-(fluorobenzoyl)ethyl]-*n*-butylamine hydrochloride;
N,N-bis[2-(2,4-dimethoxy-benzoyl)ethyl]methylamine hydrochloride; and
N,N-bis[2-(4-methylbenzoyl)ethyl]ethylamine hydrochloride.

EXAMPLE 2

The comparative effect on an inflammatory condition known as adjuvant-induced polyarthritis in rats was determined for N,N-bis[2-(4-fluorobenzoyl)ethyl]methylamine hydrochloride. The test method used was that described by Ward and Cloud, J. Pharm. Exptl. Therap., 152:116–121 (1966).

The arthritic syndrome was induced by intradermal injection into the plantar surface of one hind paw of a rat of 0.1 ml. of a fine suspension of dead tubercular bacilli in mineral oil. The rats used were Holtzman males of approximately 200 g. body weight. Each group, including an untreated control group, consisted of six animals. The drug was administered orally in the diet in admixture with the food, beginning on the day of adjuvant injection.

In this method paw size is measured by immersion of the injected hind paw into a pool of mercury. The pressure increase caused by the slight rise in mercury level is transmitted to a venous-pressure transducer designed to transmit a signal to a recording polygraph. The polygraph is calibrated by introduction of known volumes into the mercury and measuring pen excursion in millimeters, this being converted to milliliters to indicate mercury displacement and, hence, volume of edematous fluid in the immersed limb. The measurement method together with equipment typically employed is described by Van Arman et al., J. Pharm. Exptl. Therap., 150:328–344 (1965).

In the control animals, swelling and redness in the injected hind limb comprises an inflammatory reaction that subsides somewhat after about eight to nine days and then increases with the appearance of disseminated arthritis. In experimental animals the inflammatory reaction is characterized by the same pattern of swelling and redness followed by subsidence and subsequent increase, but the reaction at all stages is considerably inhibited in direct relationship to the anti-inflammatory activity of the drug administered.

The drug was mixed with the food of the rats at a ratio of about 100 mg./kg. of body weight. This was adjusted by daily noting the food intake of the rats and adjusting the ratio of drug to food to achieve the desired dosage.

When administered at a dose of 100 mg. per kg., the compound of this example showed 30 percent control (treated vs. control animals) of the swelling.

EXAMPLE 3

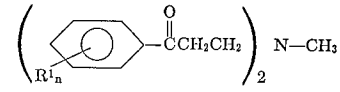
The comparative effect on carrageenin-induced edema in the hind paw of the rat was also determined for N,N - bis[2 - (4 - fluorobenzoyl)ethyl]methylamine hydrochloride. The method used was that described by Winter et al., Proc. Soc. Exptl. Biol. & Med., 111:544–547 (1962).

The edema is induced by injection into the plantar surface of the right hind paw of a male rat, of carrageenin, prepared as a 1 percent suspension in sterile 0.9 percent sodium chloride solution. The volume injected is 0.05 ml. The volume of the paw is measured immediately after injection with carrageenin and again three hours later. The difference in volume between the two measurements indicates the increase due to swelling caused by edematous fluid. Volume measurements are made as described in Example 2.

One hour before injection with carrageenin a dose of 50 mg./kg. of N,N-bis[2-(3-fluorobenzoyl)ethyl]methylamine hydrochloride contained in 5.0 ml. of aqueous 4 percent by weight of gum acacia is administered by intubation orally to each of the treated animals. The control anima's similarly receive 5.0 ml. of water by intubation. The percentage of inhibition of swelling was 57 percent when compared to the control animals.

What is claimed is:

1. A method of treating inflammatory conditions in mammals which comprises administering to said mammal an effective amount of a compound of the formula



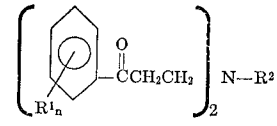
wherein R_1 is fluorine or chlorine and n is one, or a pharmaceutically acceptable salt thereof.

2. A method according to claim **1** wherein the compound is N,N-bis[2-(4-fluorobenzoyl)ethyl]methylamine hydrochloride.

3. A method according to claim **1** wherein the compound is N,N-bis[2-(4-chlorobenzoyl)ethyl]methylamine hydrochloride.

4. A method according to claim **1** in which the method of administration is oral.

5. A composition effective for symptomatic relief of inflammatory conditions, which comprises as the active component 5 to 250 milligrams of a compound of the formula



wherein R^1 is fluorine or chlorine, n is one and R^2 is methyl, and any pharmaceutically acceptable salt thereof in unit dosage form in admixture with a solid pharmaceutical carrier, and a pharmaceutically acceptable substance covering said unit dosage form effective to prevent release of the said active ingredient in the mouth and permitting release in the gastrointestinal tract.

References Cited

UNITED STATES PATENTS

3,272,838 9/1966 Draper et al. ------ 260—297 R

OTHER REFERENCES

Berichte, *55* (1922), pp. 356–359.

STANLEY J. FRIEDMAN, Primary Examiner