United States Patent

[11] 3,624,216

[72] Inventors **Herman Hal Stein**
Skokie;
Elizabeth Goodsell, Waukegan, both of Ill.

[21] Appl. No. **49,919**
[22] Filed **June 25, 1970**
[45] Patented **Nov. 30, 1971**

[73] Assignee **Abbott Laboratories**
North Chicago, Ill.

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[54] 8-SUBSTITUTED THEOPHYLLINES AS ANTI-INFLAMMATORY AGENTS

3 Claims, No Drawings

[52] **U.S. Cl.** **424/253**

[51] **Int. Cl.** **A61k 27/00**
[50] **Field of Search** 424/253

[56] **References Cited**

OTHER REFERENCES

Quevauviller, Actualitis Pharmacol., 8:106– 152 (1955)

Primary Examiner—Stanley J. Friedman
Attorney—Robert L. Niblack

ABSTRACT: A method of relieving inflammation and its concomittant swelling, tenderness and pain by administering therapeutically effective amounts of an 8-substituted theophylline to a patient in need of such treatment.

8-SUBSTITUTED THEOPHYLLINES AS ANTI-INFLAMMATORY AGENTS

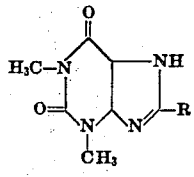
DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a method of treating inflammation in mammals and more particularly relates to the use of 8-substituted theophyllines as anti-inflammatory agents.

Numerous humans and animals are known to suffer from various rheumatic conditions involving inflammation, swelling, tenderness, decreased mobility, pain and fever. While there are a number of currently available anti-inflammatory agents which have been found to be effective in the symptomatic treatment of conditions such as rheumatoid arthritis, rheumatoid spondylitis, degenerative joint disease (osteoarthritis) of the hip, and the like, such agents have a number of undesirable side effects. Thus, the search for improved anti-inflammatory agents continues.

Accordingly, it is a primary object of this invention to provide method for treating inflammation in mammalian patients.

Theophylline and various 8-substituted theophyllines have previously been reported as central nervous system stimulants and as diuretics. [See, for example, Quevauviller, "Actualitis Pharmacol.," 8: 106–52 (1955)]. It has been found that certain 8-substituted theophylline derivatives of the formula



wherein R is C_3 to C_5 alkyl or cycloalkyl, are effective, orally active anti-inflammatory agents when administered to mammals in need of such treatment in dosages of from 5 to 100 mg./kg. of body weight daily.

As used herein, the term "C_3—C_5 alkyl" refers to straight and branched chain alkyls including n-propyl, iso-propyl, n-butyl, sec-butyl, n-pentyl, and the like.

The anti-inflammatory activity of the 8-substituted theophyllines useful in the practice of this invention was established in the Rat and Mouse Paw Edema test carried out according to the method described by Winter et al., "Proc. Soc. Exp. Biol. Med.," 111:544 (1962) and L. Levy, Carrageenan Paw Edema in the Mouse, "Life Sci.," 8, p. 1 (1969).

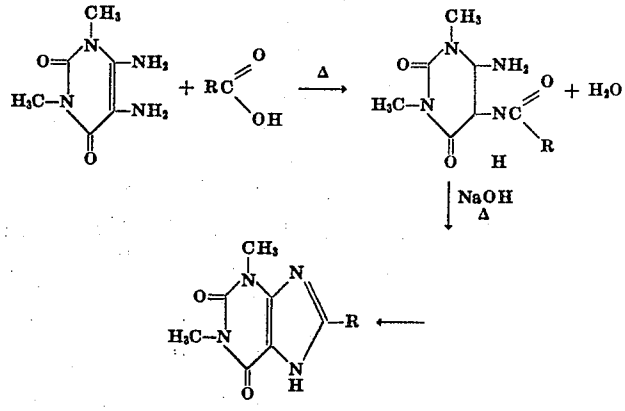
In the practice of this invention the compounds are administered to patients in need of such treatment in dosages of from 5 to 100 mg./kg. daily either in single or divided doses. It is preferred, however, that the anti-inflammatory agents be administered in divided doses, i.e., every 4 to 6 hours. The compounds can be administered in a variety of dosage forms comprising as an active ingredient at least one of the compounds useful in the practice of this invention in association with a pharmaceutically acceptable carrier or diluent. However, in the case of filled capsules, for example, the active agent may be the sole ingredient in the capsule. The compounds exhibit both oral and parenteral activity, however, the preferred route of administration is the oral route.

Representative compounds useful in the practice of this invention include the following:

8-n-Propyltheophylline
8-Cyclopropyltheophylline
8-iso-Propyltheophylline
8-n-Butyltheophylline
8-sec-Butyltheophylline
8-Cyclobutyltheophylline
8-n-Pentyltheophylline

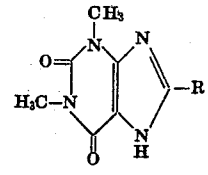
The 8-substituted theophyllines useful in the practice of this invention can be prepared according to the methods described by Hager et al., "J. Am. Pharm. Associ.," 43, 152 (1954) and by Furst and Ebert, "J. Chem. Ber.," 93, p. 99 (1960). Generally speaking, the compounds useful in the practice of this invention are conveniently prepared by reacting 5,6-diamino-1,3-dimethyl-uracil (commercially available from Aldridge Chemical Co., Milwaukee, Wis.) with an acid of the formula

wherein R is C_3—C_5 alkyl or cycloalkyl according to the following reaction scheme.



We claim:

1. A method of relieving inflammation and the concommitant pain, fever, swelling, and tenderness in mammals by administering from 5 to 100 mg./kg. of a compound of the formula



wherein R is C_3 to C_5 alkyl or cycloalkyl.

2. A method in accordance with claim 1 wherein the compound is 8-cyclobutyl theophylline.

3. A method in accordance with claim 1 wherein the compound is 8-n-butyl theophylline.

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