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ANTI-INFLAMMATORY AGENTS

Bruce E. Witzel, Westfield, N.J., assignor to Merck & Co., Inc., Rahway, N.J.

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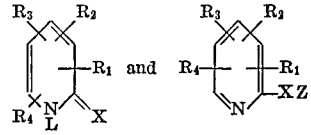
ABSTRACT OF THE DISCLOSURE

The treatment of inflammation, pain and fever utilizing compositions containing alkyl substituted pyridones, thiopyridones and pyridines.

This application is a continuation-in-part of U.S. application Ser. No. 879,925, filed Nov. 25, 1969.

This invention relates to a method of treating inflammation in its varying manifestations, utilizing novel anti-inflammatory compositions containing alkyl pyridones and pyridines. In addition, these novel compositions exhibit potent analgesic and antipyretic activity and, therefore, this invention also relates to analgesic and antipyretic methods and compositions. More particularly, this invention is concerned with compositions containing alkyl pyridones and pyridines for use in the treatment of inflammation and associated pain and fever. Furthermore, this invention is directed to analgesic and antipyretic methods for the relief and treatment of pain and fever not symptomatically related to an inflammatory indication and compositions utilized therefore.

The alkyl pyridones and pyridines employed in the treatment of a condition symptomatically evidenced by pain, fever and inflammation, either as an essential or concommitant phenomena of the condition are represented by the following formulas:



(I) (II)

in which X is O, S; R_1, R_2, R_3 and R_4 is hydrogen, alkyl (preferably lower alkyl such as methyl, ethyl, propyl, butyl and pentyl, etc.), cycloalkyl (preferably cyclolower-alkyl such as cycolpropyl, cyclobutyl, cyclopentyl, etc.) with the proviso that at least one of the R's is alkyl or cycloalkyl; Z is H, alkyl (preferably lower alkyl such as ethyl and propyl); aryl such as naphthyl, and phenyl including substituted phenyl such as tolyl, halophenyl, hydroxyphenyl, anisyl, etc., acyl such as formyl, acetyl, propionyl, butyryl, etc. and benzoyl; L may be hydrogen; alkyl (preferably loweralkyl such as methyl, ethyl, propyl, etc.); alkenyl (preferably lower alkenyl such as vinyl, allyl, methallyl, etc.); alkynyl (preferably lower alkynyl such as ethynyl, methylbutynyl, propynyl, etc.); aralkyl (preferably arloweralkyl such as benzyl and substituted benzyl, phenethyl, phenylhexyl, etc.); aryl (preferably phenyl) or

substituted phenyl (such as tolyl, halophenyl, hydroxyphenyl, anisyl, etc.); hydroxyalkyl (preferably hydroxyloweralkyl such as hydroxyethyl, hydroxypropyl, etc.); amino, dialkylamino (preferably diloweralkylamino, methylethylamino, etc.); dialkylaminoalkyl (preferably diloweralkylamino loweralkyl such as diethylaminoethyl, etc.); alkylaminoalkyl (preferably loweralkylaminoloweralkyl); alkylamino (preferably loweralkylamino such as methylamino, ethylamino, etc.); carboxyalkyl (preferably carboxyloweralkyl such as carboxymethyl, carboxyethyl, carboxypropyl, etc.); haloalkyl (preferably halolower-alkyl such as trifluoromethyl, etc.); hydroxy; alkoxy; alkylamidoalkyl (preferably loweralkylamidoloweralkyl such as acetamidoethyl, etc.); alkoxyalkyl; N-alkanoyl-alkylaminoalkyl such as N-acetylmethylaminoethyl; N-alkyl-N-alkyl-aminoalkyl such as N-ethyl-N-methylamino-propyl; aralkenyl (preferably arloweralkenyl such as styryl, phenylpropylenyl, phenylbutylenyl, etc.); heterocyclic such as furyl, tetrahydropyranyl, thienyl, thiazolyl, imidazolyl, oxazolyl, pyridyl and substituted derivatives thereof, etc.

In its preferred aspects this invention relates to the class of chemical compounds of Formula I wherein L is hydrogen, alkyl or aryl, X=oxygen and at least one R is lower alkyl.

Representative of the preferred compounds of the invention include the following:

4-methyl-2[1H]-pyridone
3-methyl-2[1H]-pyridone
5-methyl-2[1H]-pyridone
4-ethyl-2[1H]-pyridone
4-t-butyl-2[1H]-pyridone
5-t-butyl-2[1H]-pyridone
6-methyl-2[1H]-pyridone
3,4-dimethyl-2[1H]-pyridone
6-i-butyl-2[1H]-pyridone
4,5-dimethyl-2[1H]-pyridone
5-t-butyl-4-methyl-2[1H]-pyridone
5-n-butyl-2[1H]-pyridone
5-i-propyl-2[1H]-pyridone
5-cyclohexyl-2[1H]-pyridone
6-butyl-5-methyl-2[1H]-pyridone
6-pentyl-2[1H]-pyridone
5-butyl-6-methyl-2[1H]-pyridone
3-ethyl-4-methyl-2[1H]-pyridone
5-ethyl-4-methyl-2[1H]-pyridone
5-i-propyl-6-methyl-2[1H]-pyridone

Other illustrative alkyl pyridines and pyridones within the scope of the invention include:

1-methyl-4-butyl-2[1H]-pyridone
4-t-butyl-2[1H]-thiopyridone
5-cyclopentyl-2[1H]-thiopyridone
5-ethyl-4-methyl-2[1H]-thiopyridone
1-phenyl-4-t-butyl-2[1H]-pyridone
4,5,6-trimethyl-2[1H]-pyridone
4-ethyl-5-cyclopropyl-2[1H]-pyridone
1-allyl-6-methyl-2[1H]-pyridone
1-ethoxy-4-t-butyl-2[1H]-thiopyridone
3-ethyl-1-hydroxy-2[1H]-pyridone
1-amino-4-cyclohexyl-2[1H]-pyridone
1-dimethylamino-4-t-butyl-2[1H]-pyridone
1-aminoethyl-6-butyl-5-methyl-2[1H]pyridone
1-ethoxymethyl-3,4-dimethyl-2[1H]-pyridone
4-ethyl-1-propylaminomethyl-2[1H]-pyridone

1-carboxymethyl-4-t-butyl-2[1H]-pyridone
4-t-butyl-2[1H]-thiopyridone
3-methyl-1-phenyl-2[1H]-pyridone
2-ethoxy-4-ethylpyridine
4-methyl-2-phenoxypyridine
2-acetoxy-4-t-butylpyridine
4-methyl-2-propionyloxypyridine
4-methyl-2[1H]-thiopyridone
3-methyl-2[1H]-thiopyridone
5-methyl-2[1H]-thiopyridone
4-ethyl-2[1H]-thiopyridone
4-t-butyl-2[1H]-thiopyridone
5-t-butyl-2[1H]-thiopyridone
6-methyl-2[1H]-thiopyridone
3,4-dimethyl-2[1H]-thiopyridone
6-i-butyl-2[1H]-thiopyridone
4,5-dimethyl-2[1H]-thiopyridone
5-t-butyl-4-methyl-2[1H]-thiopyridone
5-n-butyl-2[1H]-thiopyridone
5-i-propyl-2[1H]-thiopyridone
5-cyclohexyl-2[1H]-thiopyridone
6-butyl-5-methyl-2[1H]-thiopyridone
6-pentyl-2[1H]-thiopyridone
5-butyl-6-methyl-2[1H]-thiopyridone
3-ethyl-4-methyl-2[1H]-thiopyridone
5-ethyl-4-methyl-2[1H]-thiopyridone
5-i-propyl-6-methyl-2[1H]-thiopyridone
1-methyl-4-butyl-2[1H]-thiopyridone
5-cyclopentyl-2[1H]-thiopyridone
1-phenyl-4-t-butyl-2[1H]-thiopyridone
4,5,6-trimethyl-2[1H]-thiopyridone
4-ethyl-5-cyclopropyl-2[1H]thiopyridone
1-allyl-6-methyl-2[1H]-thiopyridone
1-ethoxy-4-t-butyl-2[1H]-thiopyridone
3-ethyl-1-hydroxy-2[1H]-thiopyridone
1-amino-4-cyclohexyl-2[1H]-thiopyridone
1-dimethylamino-4-t-butyl-2[1H]-thiopyridone
1-aminoethyl-6-butyl-5-methyl-2[1H]-thiopyridone
1-ethoxymethyl-3,4-dimethyl-2[1H]-thiopyridone
4-ethyl-1-propylaminomethyl-2[1H]-thiopyridone
1-carboxymethyl-4-t-butyl-2[1H]-thiopyridone
3-methyl-1-phenyl-2[1H]-thiopyridone
4-methyl-2-ethoxypyridine
3-methyl-2-methoxypyridine
5-methyl-2-propoxypyridine
4-ethyl-2-phenoxypyridine
4-t-butyl-2-naphthoxypyridine
5-t-butyl-2-tolyloxypyridine
6-methyl-2-acetoxypyridine
3,4-dimethyl-2-propionyloxypyridine
6-i-butyl-2-acetoxypyridine
4,5-dimethyl-2-propoxypyridine
5-t-butyl-4-methyl-2-methoxypyridine
5-n-butyl-2-phenoxypyridine
5-i-propyl-2-ethoxypyridine
5-cyclohexyl-2-methoxypyridine
6-butyl-5-methyl-2-propoxypyridine
6-pentyl-2-p-chlorophenoxypyridine
5-butyl-6-methyl-propionyloxypyridine
3-ethyl-4-methyl-2-butoxypyridine
5-ethyl-4-methyl-2-acetoxypyridine
5-i-propyl-6-methyl-2-naphthoxypyridine
4-butyl-2-methoxypyridine
5-cyclopentyl-2-phenoxypyridine
5-ethyl-4-methyl-2-acetoxypyridine
4-t-butyl-2-propionoxypyridine
4,5,6-trimethyl-2-methoxypyridine
4-ethyl-5-cyclopropyl-2-ethoxypyridine
6-methyl-2-propoxypyridine
4-t-butyl-2-phenoxypyridine
3-ethyl-2-acetoxypyridine
4-cyclohexyl-2-ethoxypyridine
4-t-butyl-2-methoxypyridine
6-butyl-5-methyl-2-phenoxypyridine
3,4-dimethyl-2-methoxypyridine

4-ethyl-2-ethoxypyridine
4-t-butyl-2-propoxypyridine
4-t-butyl-2-phenoxypyridine
3-methyl-2-methoxypyridine
2-ethoxy-4-ethylpyridine
4-methyl-2-phenoxypyridine
2-acetoxy-4-t-butylpyridine
4-methyl-2-propionyloxypyridine
4-methyl-2-methylthiopyridine
3-methyl-2-ethylthiopyridine
5-methyl-2-propylthiopyridine
4-ethyl-2-butylthiopyridine
4-t-butyl-2-pentylthiopyridine
5-t-butyl-2-phenylthiopyridine
6-methyl-2-naphthylthiopyridine
3,4-dimethyl-2-tolylthiopyridine
6-i-butyl-2-formylthiopyridine
4,5-dimethyl-2-acetylthiopyridine
5-t-butyl-4-methyl-2-propionylthiopyridine
5-n-butyl-2-benzoylthiopyridine
5-i-propyl-2-methylthiopyridine
5-cyclohexyl-2-ethylthiopyridine
6-butyl-5-methyl-2-propylthiopyridine
6-pentyl-2-butylthiopyridine
5-butyl-6-methyl-2-pentylthiopyridine
3-ethyl-4-methyl-2-phenylthiopyridine
5-ethyl-4-methyl-2-naphthylthiopyridine
5-i-propyl-6-methyl-2-tolylthiopyridine
4-butyl-2-formylthiopyridine
4-t-butyl-2-acetylthiopyridine
5-cyclopentyl-2-propionylthiopyridine
5-ethyl-4-methyl-2-methylthiopyridine
4--t-butyl-2-ethylthiopyridine
4,5,6-trimethyl-2-propylthiopyridine
4-ethyl-5-cyclopropyl-2-butylthiopyridine
6-methyl-2-pentylthiopyridine
4-t-butyl-2-phenylthiopyridine
3-ethyl-2-naphthylthiopyridine
4-cyclohexyl-2-tolylthiopyridine
4-t-butyl-2-anisylthiopyridine
6-butyl-5-methyl-2-formylthiopyridine
3,4-dimethyl-2-acetylthiopyridine
4-ethyl-2-propionylthiopyridine
4-t-butyl-2-benzoylthiopyridine
4-t-butyl-2-methylthiopyridine
3-methyl-2-ethylthiopyridine.

The alkyl-2[1H]-pyridones and pyridines utilized in the practice of this invention are well known in and are readily made by procedures disclosed in the chemical literature. For example, diazotization of a 2-amino-alkylpyridine yields the corresponding pyridone [see Takahashi and Kariyone, Chem. and Pharm. Bull. vol. 8, 1960), page 1106, or Adams and Schrecker, J. Am. Chem. Soc., vol. 71, (1949), page 1188]. Rearrangement of a pyridine-N-oxide with acetic anhydride yields a 2-acetoxypyridine, which on gentle hydrolysis yields the pyridone [see Bain and Saxton, Chem. and Ind., page 402, (1960) or C.A. 63, 13202e]. Ring closure procedures are well known [e.g., see Prelog, et al., Helv. Chim. Acta, Vol. 25, page 1654 (1942) or Perez-Medina, et al., J. Am. Chem. Soc., Vol. 69, (1947), page 2574 (followed by hydrolysis and decarboxylation of the resultant cyano compound)]. Direct oxidation of pyridinium salts yield N-substituted alkyl pyridones directly [Org. Syn. Coll. Vol. II, page 419]. Other well known procedures may be employed in preparing the compounds of the invention, such as hydrolysis of 2-halo or 2-sulfopyridines or conversion of the corresponding alkyl pyrone to the pyridone with ammonia or equivalent.

The pyridones and pyridines of the invention possess a high degree of anti-inflammatory, analgesic and antipyretic activity. They are of value in the treatment of arthritic and dermatological disorders of like conditions responsive to anti-inflammatory drugs. In general they

are indicated for a wide variety of conditions where one or more of the symptoms of inflammation, fever and pain are manifested. Included within this category are diseases such as rheumatoid arthritis, osteo arthritis, gout, infectious arthritis and rheumatic fever. As indicated above the compounds utilized in the practice of the invention also possess a useful degree of analgesic and antipyretic activity.

For these purposes the compounds of the invention may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions in for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide a pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example maize starch, or alginic acid; binding agents, for example starch, gelatine or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate above or with a wax may be employed.

Formulations for oral use may also be presented as hard gelatine capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatine capsules wherein the active ingredient is mixed with water or an oil medium, for example arachis oil, peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan mono-oleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectibles.

The compounds of this invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions etc. containing the anti-inflammatory agents are employed.

Dosage levels of the order of 20 mg. to 7 grams per day are useful in the treatment of the above indicated conditions. For example, inflammation is effectively treated and anti-pyretic and analgesic activity manifested by the administration from about .3 to 100 milligrams of the compound per kilogram of body weight per day. Advantageously from about 2 mg. to about 50 mg. per kilogram of body weight and especially from about 4 mg. to about 20 mg./kg. per daily dosage produce highly effective results.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the partic-

ular mode of administration. For example a formulation intended for the oral administration of humans may contain from 5 mg. to 5 grams of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 25 mg. to about 500 mg. of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The following are illustrative of the techniques that may be employed in the preparation of pharmaceutical formulations to be utilized in the practice of the invention:

EXAMPLE 1

A mixture of 250 parts of 4-t-butyl-2[1H]-pyridone and 25 parts of lactose is granulated with suitable water, and to this is added 100 parts of maize starch. The mass is passed through a 16 mesh screen. The granules are dried at a temperature below 60° C. The dry granules are passed through a 16 mesh screen, and mixed with 3.8 parts of magnesium stearate. They are then compressed into tablets suitable for oral administration.

The 4-t-butyl-2[1H]-pyridone used in the foregoing example may be replaced by 25, 100, 250, or 500 parts of other pyridones of this invention to produce tablets suitable for oral administration as an anti-inflammatory, antipyretic and/or analgesic according to the method of this invention.

EXAMPLE 2

A mixture of 50 parts of 4-methyl-2[1H]-pyridone, 3 parts of the calcium salt of lignin sulphonic acid, and 237 parts of water is ball-milled until the size of substantially all of the particles of 4-methyl-2[1H]-pyridone is less than 10 microns. The suspension is diluted with a solution containing 3 parts of sodium carboxymethylcellulose and 0.9 part of the butyl ester of p-hydroxybenzoic acid in 300 parts of water. There is thus obtained an aqueous suspension suitable for oral administration for therapetutic purposes.

EXAMPLE 3

A mixture of 250 parts of 5-methyl-2[1H]-pyridone, 200 parts of maize starch and 30 parts of alginic acid is mixed with a sufficient quantity of a 10% aqueous paste of maize starch, and granulated. The granules are dried in a current of warm air and the dry granules are then passed through a 16-mesh screen, mixed with 6 parts of magnesium stearate and compressed into tablet form to obtain tablets suitable for oral administration.

EXAMPLE 4

A mixture of 500 parts 4-ethyl-2[1H]-pyridone, 60 parts maize starch and 20 parts of gum acacia is granulated with a sufficient quantity of water. The mass is passed through a 12-mesh screen and the granules are dried in a current of warm air. The dry granules are passed through a 16-mesh screen, mixed with 5 parts of magnesium stearate and compressed into tablet form suitable for oral administration.

EXAMPLE 5

(1) Tablets.—10,000 scored tablets for oral use, each containing 500 mg. of pyridone, are prepared from the following ingredients:

	Gm.
3,4-dimethyl-2[1H]-pyridone	5000
Starch, U.S.P.	350
Talc, U.S.P.	250
Calcium stearate	35

The powdered pyridone is granulated with a 4% w./v. aqueous solution of methylcellulose U.S.P. (1500 cps.). To the dried granules is added a mixture of the remainder of the ingredients and the final mixture compressed into tablets of proper weight.

(2) Capsules.—10,000 two-piece hard gelatine capsules for oral use, each containing 250 mg. of pyridone are prepared from the following ingredients:

	Gm.
3-methyl-2[1H]-pyridone	2500
Lactose, U.S.P.	1000
Starch, U.S.P.	300
Talc, U.S.P.	65
Calcium stearate	25

The powdered pyridone is mixed with the starch-lactose mixture followed by the talc and calcium stearate. The final mixture is then encapsulated in the usual manner. Capsules containing 10, 25, 50, and 100 mg. of pyridone are also prepared by substituting 100, 250, 500 and 1000 gm. for 2500 gm. in the above formulation.

(3) Soft elastic capsules.—One-piece soft elastic capsules for oral use, each containing 200 mg. of 6-methyl-2[1H]-pyridone, are prepared in the usual manner by first dispersing the powdered active material in sufficient corn oil to render the material capsulatable.

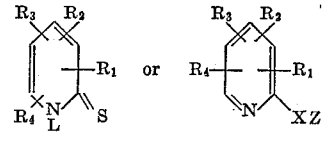
(4) Aqueous suspension.—An aqueous suspension for oral use containing in each 5 ml., 1 gram of pyridone is prepared from the following ingredients:

4-t-butyl-2[1H]-pyridone	gm..	2000
Methylparaben, U.S.P.	gm..	7.5
Propylparaben, U.S.P.	gm..	2.5
Saccharin sodium	gm..	12.5
Glycerin	ml..	3000
Tragacanth powder	gm..	10
Orange oil flavor	gm..	10
F. D. and C. orange dye	gm..	7.5

Deionized water, q.s. to 10,000 mg.

What is claimed is:

1. A method of treating a condition exhibiting at least one of the symptoms of pain, fever and inflammation which comprises the administration to humans and animals of a therapeutically effective amount of a compound having the formula:



(I) (II)

in which

R_1, R_2, R_3 and R_4 are each hydrogen, alkyl or cycloalkyl with the proviso that at least one of the R's is alkyl or cycloalkyl;

Z is H, alkyl, aryl, or acyl;

X is O or S;

L is hydrogen, loweralkyl, loweralkenyl, loweralkylnyl, arloweralkyl, aryl, hydroxyloweralkyl, amino, diloweralkylamino, diloweralkylaminoloweralkyl, loweralkylaminoloweralkyl, loweralkylamino, carboxyloweralkyl, haloloweralkyl, hydroxy, loweralkoxy, loweralkylamidoloweralkyl, loweralkoxyloweralkyl, N - loweralkanoyl - loweralkylaminoloweralkyl, N-loweralkyl-N-loweralkyl - aminoloweralkyl, arloweralkenyl or heterocyclic selected from the group consisting of furyl, tetrahydropyranyl, thienyl, thiazolyl, imidazolyl, oxazolyl and pyridyl.

2. The method of claim **1** wherein the compound is of Formula I wherein at least one R is lower alkyl or cycloloweralkyl the remaining R's being hydrogen; L is hydrogen, loweralkyl or aryl.

3. The method of claim 2 wherein L is hydrogen and at least one R is lower alkyl, the remaining R's being hydrogen.

4. The method of claim 3 wherein the compound is
4-methyl-2[1H]-thiopyridone,
3-methyl-2[1H]-thiopyridone,
5-methyl-2[1H]-thiopyridone,
4-ethyl-2[1H]-thiopyridone,
4-t-butyl-2[1H]-thiopyridone,
5-t-butyl-2[1H]-thiopyridone,
6-methyl-2[1H]-thiopyridone,
3,4-dimethyl-2[1H]-thiopyridone,
6-i-butyl-2[1H]-thiopyridone,
4,5-dimethyl-2[1H]-thiopyridone,
5-t-butyl-4-methyl-2[1H]-thiopyridone,
5-n-butyl-2[1H]-thiopyridone,
5-i-propyl-2[1H]-thiopyridone,
6-butyl-5-methyl-2[1H]-thiopyridone,
6-pentyl-2[1H]-thiopyridone,
5-butyl-6-methyl-2[1H]-thiopyridone,
3-ethyl-4-methyl-2[1H]-thiopyridone,
5-ethyl-4-methyl-2[1H]-thiopyridone, or
5-i-propyl-6-methyl-2[1H]-thiopyridone.

5. The method of claim 4 wherein the compound is 4-t-butyl-2[1H]-thiopyridone.

6. The method of claim 4 wherein the compound is 4-ethyl-2[1H]-thiopyridone.

7. The method of claim 4 wherein the compound is 4-methyl-2[1H]-thiopyridone.

8. The method of claim 4 wherein the compound is 3,4-dimethyl-2[1H]-thiopyridone.

9. The method of claim 4 wherein the compound is 5-methyl-2[1H]-thiopyridone.

10. The method of claim 1 wherein the compound is of Formula II.

11. The method of claim 10 wherein the compound is
4-t-butyl-2-methoxypyridine,
2-ethoxy-4-ethylpyridine,
4-methyl-2-phenoxypyridine,
4-methyl-2-methoxypyridine,
2-acetoxy-4-t-butylpyridine,
4-methyl-2-propionyloxypyridine,
4-methyl-2-ethoxypyridine,
3-methyl-2-methoxypyridine,
4-ethyl-2-phenoxypyridine,
4,5-dimethyl-2-methoxypyridine,
4,5,6-trimethyl-2-methoxypyridine,
4-ethyl-5-cyclopropyl-2-ethoxypyridine,
4-t-butyl-2-methylthiopyridine,
4-methyl-2-methylthiopyridine,
3-methyl-2-ethylthiopyridine,
5-t-butyl-2-phenylthiopyridine,
5-ethyl-4-methyl-2-methylthiopyridine, or
4,5,6-trimethyl-2-methylthiopyridine.

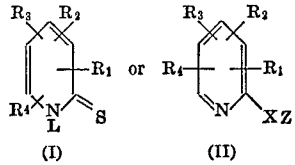
12. The method of claim 11 wherein the compound is 4-t-butyl-2-methoxypyridine.

13. The method of claim 11 wherein the compound is 4-t-butyl-2-methylthiopyridine.

14. The method of claim 11 wherein the compound is 4-methyl-2-methylthiopyridine.

15. The method of claim 11 wherein the compound is 4-methyl-2-methoxypyridine.

16. A pharmaceutical tablet or capsule comprising a pharmaceutical carrier and an antiinflammatory, antipyretic and analgesic effective non-toxic amount within the range from about 5 milligrams to about 5 grams of a compound of the formula:



(I) (II)

in which
R_1, R_2, R_3 and R_4 are each hydrogen, alkyl or cycloalkyl with the proviso that at least one of the R's is alkyl or cycloalkyl;
Z is H, alkyl, aryl, or acyl;
X is O or S;
L is hydrogen, loweralkyl, loweralkenyl, loweralkynyl, arloweralkyl, aryl, hydroxyloweralkyl, amino, diloweralkylamino, diloweralkylaminoloweralkyl, loweralkylaminoloweralkyl, loweralkylamino, carboxyloweralkyl, halooweralkyl, hydroxy, loweralkoxy, loweralkylamidoloweralkyl, loweralkoxyloweralkyl, N - loweralkanoyl - loweralkylaminoloweralkyl, N-loweralkyl-N-loweralkyl - aminoloweralkyl, arloweralkyl or heterocyclic selected from the group consisting of furyl, tetrahydropyranyl, thienyl, thiazolyl, imidazolyl, oxazolyl and pyridyl.

17. The composition of claim 16 wherein the compound is of Formula I wherein at least one R is lower alkyl or cycloloweralkyl the remaining R's being hydrogen; L is hydrogen, loweralkyl or aryl.

18. The composition of claim 17 wherein L is hydrogen and at least one R is lower alkyl, the remaining R's being hydrogen.

19. The composition of claim 18 wherein the compound is
4-methyl-2[1H]-thiopyridone,
3-methyl-2[1H]-thiopyridone,
5-methyl-2[1H]-thiopyridone,
4-ethyl-2[1H]-thiopyridone,
4-t-butyl-2[1H]-thiopyridone,
5-t-butyl-2[1H]-thiopyridone,
6-methyl-2[1H]-thiopyridone,
3,4-dimethyl-2[1H]-thiopyridone,
6-i-butyl-2[1H]-thiopyridone,
4,5-dimethyl-2[1H]-thiopyridone,
5-t-butyl-4-methyl-2[1H]-thiopyridone,
5-n-butyl-2[1H]-thiopyridone,
5-i-propyl-2[1H]-thiopyridone,
6-butyl-5-methyl-2[1H]-thiopyridone,
6-pentyl-2[1H]-thiopyridone,
5-butyl-6-methyl-2[1H]-thiopyridone,
3-ethyl-4-methyl-2[1H]-thiopyridone,
5-ethyl-4-methyl-2[1H]-thiopyridone, or
5-i-propyl-6-methyl-2[1H]-thiopyridone.

20. The composition of claim 19 wherein the compound is 4-t-butyl-2[1H]-thiopyridone.

21. The composition of claim 19 wherein the compound is 4-ethyl-2[1H]-thiopyridone.

22. The composition of claim 19 wherein the compound is 4-methyl-2[1H]-thiopyridone.

23. The composition of claim 19 wherein the compound is 3,4-dimethyl-2[1H]-thiopyridone.

24. The composition of claim 19 wherein the compound is 5-methyl-2[1H]-thiopyridone.

25. The composition of claim 16 wherein the compound is of Formula II.

26. The composition of claim 25 wherein the compound is
4-t-butyl-2-methoxypyridine,
2-ethoxy-4-ethylpyridine,
4-methyl-2-phenoxypyridine,
4-methyl-2-methoxypyridine,
2-acetoxy-4-t-butylpyridine,
4-methyl-2-propionyloxypyridine,
4-methyl-2-ethoxypyridine,
3-methyl-2-methoxypyridine,
4-ethyl-2-phenoxypyridine,
4,5-dimethyl-2-methoxypyridine,
4,5,6-trimethyl-2-methoxypyridine,
4-ethyl-5-cyclopropyl-2-ethoxypyridine,
4-t-butyl-2-methylthiopyridine,
4-methyl-2-methylthiopyridine,
3-methyl-2-ethylthiopyridine,
5-t-butyl-2-phenylthiopyridine,

5-ethyl-4-methyl-2-methylthiopyridine, or 4,5,6-trimethyl-2-methylthiopyridine.

27. The composition of claim **26** wherein the compound is 4-t-butyl-2-methoxypyridone.

28. The composition of claim **26** wherein the compound is 4-t-butyl-2-methylthiopyridine.

29. The composition of claim **26** wherein the compound is 4-methyl-2-methylthiopyridine.

30. The composition of claim **26** wherein the compound is 4-methyl-2-methoxypyridine.

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STANLEY J. FRIEDMAN, Primary Examiner

U.S. Cl. X.R.

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