Carcinogenesis Abstracts Vol. 8, No. 1, July 1970, Item No. 0187, RC 261 Al C.3

Primary Examiner—Alan L. Rotman
Attorney—Gerald A. Hapka

ABSTRACT

This invention relates to a novel class of ethanopyridinothienopyrimidines which possess antiviral activity against viruses having a core of double stranded D.N.A. Specifically, the compounds of the invention exhibit antiviral activity against Herpes simplex/H4 virus, Herpes simplex/2 Ala./SM virus, pseudorabies virus, vaccinia virus, vesicular stomatis and adenovirus based on experimental data in warm-blooded animals and birds, (animals possessing the homeostatic mechanism).

3 Claims, No Drawings
CERTAIN 5,6,7,8-TETRAHYDRO-5,8-ETHANO-
PYRIDINO[2,3-b]THIENO[5,4-d] PYRIMIDINES

SUMMARY OF THE INVENTION

This invention relates to compounds of the formulas:

(I)

where

R₁ is hydrogen, —OH, —SH of

where

R₂ is hydrogen, alkyl of one to six carbon atoms, alky or propargyl;

R₃ is hydrogen, alkyl of one to four carbon atoms, —OH, —SH or —NH₂; and the pharmaceutically acceptable salts of said compounds; and

(II)

where

R₄ is alkyl of one to four carbon atoms, phenyl of —NH₂; R₅ is hydrogen alkyl of one to four carbon atoms, —OH, —SH, or —NHR₆ where R₆ is hydrogen, alkyl of one to six carbon atoms, alky or propargyl; and the pharmaceutically acceptable salts of said compounds.

This invention also relates to a method for controlling virus infections of warm-blooded animals which comprises administering to said animal an antiviral effective amount of a compound of this invention prior to and/or during the period of exposure to said infection or after said animal has become infected.

This invention further relates to pharmaceutical compositions which contain an antiviral effective amount of a compound of this invention in combination with suitable pharmaceutical adjuvants.

DESCRIPTION OF THE INVENTION

As summarized above, this invention relates to antiviral active compounds of formulas (I) and (II) and the non-toxic acid addition salts of said compounds.

It will be understood that the term non-toxic acid addition salts includes those salts of the compounds of formulas (I) and (II) which are suitable for administration to warm-blooded animals. Representative of such salts are the hydrochloride, hydrobromide, sulfate, phosphate, acetate, nitrate, succinate, adipate, propionate, tartrate, cyclohexylsulfamate, citrate, bicarbonate and pamoate salts of said compounds. Of these, the most preferred is the hydrochloride.

The compounds of this invention are primarily active against infections caused by DNA type viruses such as herpesvirus and poxvirus strains, although preliminary tests indicate that the compounds of this invention also possess some antiviral activity against infections caused by RNA type viruses, such as arbovirus.

Illustrative of the compounds of this invention are the following:

5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amino
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-ol
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-thiol
N-methyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amino
N-allyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amino
N-propargyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amino
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-amino
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-ol
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-thiol
N-ethyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-amino
N-isopropyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-amino
5,6,7,8-tetrahydro-2-methyl-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amino
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2,4-diamine
2-amino-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-ol
4-amino-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-ol
2-amino-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-thiol
3,4,5,6,7,8-hexahydro-4-imino-3-methyl-5,8-
ethanopyridino[5,4-d]thieno[4,5-b]pyrimidine
3,4,5,6,7,8-hexahydro-4-imino-3-phenyl-5,8-
ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine
3,4,5,6,7,8-hexahydro-4-imino-5,8-
ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-3-amino
3,4,5,6,7,8-hexahydro-4-imino-2-methyl-5,8-
ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-3-amino
3,4,5,6,7,8-hexahydro-4-imino-3-methyl-5,8-
ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-amino
3,4,5,6,7,8-hexahydro-4-imino-3-phenyl-5,8-
ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-amino
N-ethyl-3,4,5,6,7,8-hexahydro-4-imino-3-ethyl-5,8-
ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-amino
Of the above compounds the following are preferred:
5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amino
N-methyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amino
3,4,5,6,7,8-hexahydro-4-imino-3-methyl-5,8-
ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine
It will be understood that the pharmaceutically acceptable salts of the above named compounds are also included within the scope of this invention. The term “pharmaceutically acceptable salts” as used herein means non-toxic acid addition salts of the compounds of this invention suitable for administration to warm-blooded animals. Representative of such salts are the hydrochloride, hydrobromide, sulfate, phosphate, acetate, nitrate, succinate, adipate, propionate, tartrate, cyclohexylsulfamate, citrate, bicarbonate, and pamoate salts. Of these, the hydrochloride salt is preferred.

**PREPARATION**

The compounds of this invention can be prepared by treating 2-amino-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile with triethyl orthoformate to give 2-(ethoxymethyleneamino)-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile. The 2-(ethoxymethyleneamino)-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile is treated with ammonia or an appropriate secondary amine to obtain, respectively, 5,6,7,8-tetrahydro-5,8-ethanopyridine[2,3-b]thieno-[5,4-d]pyrimidine-4-amine or the corresponding 3-substituted 3,4,5,6,7,8-hexahydro-4-amin-5,8-ethanopyridino[2,3-b]-thieno/[5,4-d]pyrimidine.

Those compounds of this invention where R₁ is hydroxyl, can be prepared by treating an ester of 2-amino-4,5,6,7-tetrahydro-4,7-ethano[2,3-b]pyridine-3-carboxylic acid first with triethyl orthoformate and then with ammonia.

The 4-hydroxy derivatives may be converted to the corresponding 4-mercapto, 4-chloro and 4-alkylamino compounds by conventional chemical techniques known to the art.

The 4-alkylamino compounds can also be prepared by rearrangement of the 3-alkyl-3,4,5,6,7,8-hexahydro-4-amin-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidines in aqueous solution.

The 2,4-diamino- and 2-amino-4-hydroxy-pyrimidines, respectively, can be prepared from the corresponding 2-amino-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile or a 2-amino-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carboxylate ester by treating said carbonitrile or ester with guanidine.

Treatment of the 2-amino-4-hydroxy-pyrimidines with phosphorus oxychloride followed by catalytic hydrogenation furnishes the 4,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-2-amine.

The 2-amino-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine carbonitrile starting material can be prepared by reacting malonitrile, 3-quinuclidinone, sulfur and morpholine at a temperature of about 50°C. under a nitrogen atmosphere and can be isolated by conventional techniques.

The酰基 2-amino-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carboxylate starting material can be prepared by reacting an alkyl cyanoacetate, 3-quinuclidinone, sulfur and morpholine at a temperature of about 40°C., cooling the reaction mixture, filtering and treating the filtrate with glacial acetic oxide to give a semi-solid product which can be purified if desired.

The following Examples are presented to illustrate the method of preparing the compounds of this invention.

**EXAMPLE 1**

5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine

A solution of 0.1 mole of 2-amino-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile in 200 ml. of triethyl orthoformate is refluxed for 4 hours under an atmosphere of nitrogen. The excess triethyl orthoformate is removed in vacuo to give a solid residue which is recrystallized from aqueous ethanol to yield 2-(ethoxymethyleneamino)-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile, m.p. 99°-100°C.

A solution of 0.1 mole of this carbonitrile in 200 ml. of ethanol is added with stirring to 300 ml. of ethanol saturated with ammonia gas. The reaction mixture is cooled to 10° C. and ammonia gas is bubbled through the solution for 30 minutes. The mixture is then allowed to stir overnight at room temperature. Removal of the ethanol in vacuo yields a solid residue which is recrystallized from DMF to give 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine, m.p. 268°-284°C.

The dihydrochloride of this compound is prepared by passing dry hydrogen chloride gas into an ethanolic solution of the base. The salt is recrystallized from ethanol/water to give 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine dihydrochloride, m.p. 282°-284°C.

**EXAMPLE 2**

5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine 4-ol

A solution of 0.1 mole of ethyl 2-amino-4,5,6,7-tetrahydro-4,7-ethano[2,3-b]pyridine-3-carboxylate in 200 ml. of triethyl orthoformate is refluxed for 4 hours under an atmosphere of nitrogen. The excess triethyl orthoformate is removed in vacuo to yield ethyl 2-(ethoxymethyleneamino)-4,5,6,7-tetrahydro-4,7-ethanethieno[2,3-b]pyridine-3-carboxylate.

A solution of 0.1 mole of this ester in 200 ml. of ethanol is added with stirring to 300 ml. of ethanol saturated with ammonia gas. The reaction mixture is cooled to 10° C. and ammonia gas is bubbled through the solution for 30 minutes. The mixture is then allowed to stir overnight at room temperature. Removal of the ethanol in vacuo yields 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-ol.

**EXAMPLE 3**

N-isopropyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine

A mixture of 0.1 mole of 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[4,5-d]pyrimidine-4-ol in 100 ml. of phosphorus oxychloride is warmed at 40°C. for 3 hours. The clear solution is cooled and poured into 400 ml. of ice and water, and the resulting solution is made basic with concentrated ammonium hydroxide solution to give a solid precipitate. The solid material is
extracted into benzene, dried over magnesium sulfate and the solvent removed to give 4-chloro-5,6,7,8-
tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine.

A solution of 0.1 mole of this chloro compound and 0.1 mole of isopropylamine in 120 ml of toluene is
refluxed for 6 hours. After cooling, the precipitate is removed by filtration, dissolved in the minimum
amount of water and the solution made basic with concentrated potassium carbonate to give a precipitate.
This product is filtered off, dried and dissolved in ethanol and the solution saturated with dry hydrogen
chloride gas to give N-isopropyl-5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-
amine dihydrochloride.

**EXAMPLES 4-6**

The procedure of Example 3 is repeated, substituting the indicated "amine" for the isopropylamine of Example 3 to obtain the indicated product.

<table>
<thead>
<tr>
<th>Example</th>
<th>Amine</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>ethylamine</td>
<td>N-ethyl-5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-amine.</td>
</tr>
<tr>
<td>5</td>
<td>hexylamine</td>
<td>N-hexyl-5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-amine.</td>
</tr>
<tr>
<td>6</td>
<td>allylamine</td>
<td>N-allyl-5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-amine.</td>
</tr>
</tbody>
</table>

**EXAMPLE 7**

5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-thiol

A mixture of 0.1 mole of 5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[4,5-b]-pyrimidine-4-ol
and 20.0 gm. of phosphorus pentasulfide in 250 ml of xylene is stirred vigorously and refluxed for 2 hours.
The mixture is then cooled in an ice-bath and an excess of 10 percent sodium hydroxide solution is added drop-
wise. The mixture is stirred for an additional 15 minutes and then filtered to give a residue of 5,6,7,8-
tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-thiol.

**EXAMPLE 8**

5,6,7,8-tetrahydro-2-methyl-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-amine

A solution of 0.1 mole of 2-amino-5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-amine in 200 ml. of triethyl orthoacetate is refluxed for 4 hours under an atmosphere of nitrogen. The ex-
cess triethyl orthoacetate is removed in vacuo to give a solid residue which is recrystallized from pentane to yield
2-(1-ethoxycarbonylaminomethyl)-4,5,6,7-tetrahydro-4,7-ethanothieno-[2,3-b]-pyrimidine-3-carbonitrile, m.p.
87°-88°C.

A solution of 0.1 mole of this carbonitrile in 200 ml of ethanol is added with stirring to 300 ml of ethanol
saturated with ammonia. The reaction mixture is cooled to 10°C and ammonia gas is bubbled through the
solution for 30 minutes. The mixture is then allowed to stir overnight at room temperature. Removal
of the ethanol in vacuo yields a solid residue which is recrystallized from DMF to give 5,6,7,8-tetrahydro-2-
methyl-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-amine, m.p. 261°-262°C.

The dihydrochloride of this compound is prepared by passing dry hydrogen chloride gas into an ethanolic
solution of the base. The salt is recrystallized from ethanol/water to give 5,6,7,8-tetrahydro-2-methyl-5,8-
ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-amine dihydrochloride, m.p. 279°-280°C.

**EXAMPLE 9**

5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-2,4-diamine

A solution of sodium methoxide in methanol is prepared by dissolving 0.10 g-atom of sodium in 150
ml. of methanol. To this solution is added 0.11 mole of guanidine hydrochloride and the mixture is refluxed for
30 minutes. The mixture is filtered and 0.03 mole of 2-
amino-4,5,6,7-tetrahydro-4,7-ethanothieno-[2,3-b]
pyrimidine-3-carbonitrile is added to the filtrate and the mixture is then refluxed for 30 minutes. On cooling, a precipitate is formed which is removed by filtration and dried to yield 5,6,7,8-tetrahydro-5,8-ethanopyridino-
[2,3-b]thieno-[5,4-d]-pyrimidine-2,4-diamine.

**EXAMPLE 10**

2-amino-5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-ol

By substituting ethyl 2-amino-4,5,6,7-tetrahydro-4,7-
ethano-[2,3-b]-pyridine-3-carboxylic compound for the 2-
amino-4,5,6,7-tetrahydro-4,7-ethano-[2,3-b]-pyridine-
3-carbonitrile employed in Example 9, the corresponding
2-amino-5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-ol is obtained.

**EXAMPLE 11**

5,6,7,8-tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-2-amine

A mixture of 0.1 mole of 2-amino-5,6,7,8-
tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-4-ol in 100 ml. of phosphorus oxychloride is
warmed at 40° C. for 3 hours. The clear solution is cooled and poured into 400 ml. of ice and water, and the
resulting solution is made basic with concentrated ammonium hydroxide solution to give a solid
precipitate. This solid material is removed by filtration and dried to give 4-chloro-5,6,7,8-tetrahydro-5,8-
ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-2-amine.

To a solution of 0.1 mole of this chloro compound in 400 ml. of methanol is added 10.0 gm. of potassium
hydroxide, 5.0 gm. of 5 percent palladium -on-calcium carbonate catalyst and a trace of 5 percent palladium
-on-carbon catalyst. This mixture is hydrogenated at 40
p.s.i. for 2 hours, the catalysts are removed by filtration and the filtrate is concentrated to a volume of 100 ml.
The addition of 50 ml. of water precipitates a solid which is removed by filtration and dried to give 5,6,7,8-
tetrahydro-5,8-ethanopyridino-[2,3-b]thieno-[5,4-d]-pyrimidine-2-amine.
EXAMPLE 7
A solution of 0.1 mole of 2-(ethoxymethyleneamino)-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile in 200 ml of ethanol is added with stirring to 300 ml of ethanol saturated with methylamine gas. The reaction mixture is cooled to 10°C and methylamine gas is bubbled through the solution for 30 minutes. The mixture is then allowed to stir overnight at room temperature. Removal of the ethanol in vacuo yields a solid residue which is recrystallized from acetonitrile to give 3,4,5,6,7,8-hexahydro-4-imino-3-methyl-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine, m.p. 178°-180°C.

EXAMPLE 13
3,4,5,6,7,8-hexahydro-4-imino-3-phenyl-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine

By substituting aniline for the methylamine employed in Example 12, the corresponding 3,4,5,6,7,8-hexahydro-4-imino-3-phenyl-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine is obtained.

EXAMPLE 14
3,4,5,6,7,8-hexahydro-4-imino-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-3-amine

A solution of 0.1 mole of 2-(ethoxymethyleneamino)-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbo-nitrile in 200 ml of ethanol is added with stirring to 20 ml of 95 percent hydrazine hydrate. After 10 minutes a precipitate is formed and the mixture is stirred for two hours at room temperature.

The precipitate is removed by filtration and recrystallized from ethanol to give 3,4,5,6,7,8-hexahydro-4-imino-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-3-amine, m.p. 202°-204°C.

EXAMPLE 15
N-methyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine

A solution of 0.1 mole of 3,4,5,6,7,8-hexahydro-4-imino-3-methyl-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine in 250 ml of water is stirred and refluxed for 2 hours. After this time, a white precipitate has formed. The solid product is removed by filtration and recrystallized from acetonitrile to give N-methyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine, m.p. 211°-212°C.

EXAMPLE 16
3,4,5,6,7,8-hexahydro-4-imino-2-methyl-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-3-amine

A solution of 0.1 mole of 2-(1-ethoxymethyleneamino)-4,5,6,7-tetrahydro-4,7-ethanothieno[2,3-b]pyridine-3-carbonitrile in 200 ml of ethanol is added with stirring to 20 ml of 95 percent hydrazine hydrate. After 10 minutes a precipitate is formed and the mixture is stirred for 2 hours at room temperature.

The precipitate is removed by filtration and recrystallized from acetonitrile to give 3,4,5,6,7,8-hexahydro-4-imino-2-methyl-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-3-amine, m.p. 210-212°C.
It will be understood that pharmaceutical compositions for parenteral administration include sterile solutions, suspensions, powders for solution or suspension, pellets for implantation and the like.

It will be understood that pharmaceutical compositions for topical application include solutions, suspensions, ointments, jellies and the like.

One embodiment of a pharmaceutical composition of this invention is a gelatin capsule for oral administration containing from about 1 to 50 percent of a compound of this invention, such as 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine, and from about 99 to 50 percent of a suitable pharmaceutical carrier. In another embodiment, the active ingredient is tableted with or without adjuvants. In yet another embodiment, the active ingredient is formulated as a divided powder and employed. In these capsules, tablets and powders, the active ingredient will generally constitute from about 5 percent to about 99 percent by weight and preferably from 25 percent to 90 percent by weight of the finished formulation.

Another embodiment of a pharmaceutical composition of this invention is a sterile solution for parenteral administration containing from 0.05 percent to 10 percent by weight, and preferably from 0.1 to 1 percent by weight of a compound of this invention such as 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-aminehydrochloride dissolved in sterile water. Alternatively, the pharmaceutical carrier can be a sterile oil such as peanut oil, soybean oil, mineral oil, sesame oil and the like.

In general, water, saline, aqueous dextrose and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are the preferred liquid carriers for injectable solutions when the salts of the active ingredient are to be administered. When a parenteral dosage form of the free base, especially those compounds of this invention that do not readily form pharmaceutically acceptable salts, is desired, those oils hereinbefore enumerated are the most preferred pharmaceutical carriers.

The active ingredient can be prepared for oral administration in a suitable suspension or syrup, in which the active ingredient ordinarily will constitute from about 0.5 percent to 10 percent and preferably 2 percent to 10 percent by weight. The pharmaceutical carrier in such composition can be a watery vehicle such as an aromatic water, a syrup or a pharmaceutical mullucilage.

The active ingredient can be prepared for topical administration in a suitable solution, suspension, liquid emulsion, ointment, paste or jelly in which the active ingredient ordinarily will constitute from about 0.5 to 10 percent by weight. The pharmaceutical carrier in such topical compositions can be water; an organic solvent such as glycerin; a suitable emulsion or a suitable ointment base such as petrolatum, hydrophilic ointment, a jelly or the like.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, a well known reference text in this field.

In addition to the exemplary illustrations above, the following examples further explain one aspect of the present invention.

EXAMPLE 19

A large number of unit capsules are prepared for oral administration by filling standard two-piece hard gelatin capsules with 50 milligrams of powdered N-propargyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine hydrochloride, 125 milligrams of lactose and 1 milligram of "Cab-o-sil" finely divided silica.

EXAMPLE 20

A large number of compressed tablets are prepared by conventional procedures so that the dosage unit is 5 milligrams of 3,4,5,6,7,8-hexahydro-4-imino-3-methyl-5,8-ethano-3,4-pyridino[2,3-b]thieno[5,4-d]pyrimidine, 5 milligrams of gelatin, 1.5 milligrams of magnesium stearate and 100 milligrams of lactose.

EXAMPLE 21

A parenteral composition suitable for administration by injection is prepared by mixing 0.25 percent by weight of N-propargyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimid-dine-4-amine with sterile soybean oil.

EXAMPLE 22

A composition for topical application is prepared by triturating 10 percent by weight of 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine in hydrophilic ointment, U.S.P.

A large variety of compositions according to this invention can thus readily be made by substituting other compounds of this invention, and including specifically but not limited to compounds of this invention that have specifically been named hereinbefore. The compounds will be used in the amounts indicated in accordance with procedures well known and described in the Martin text mentioned above.

The compounds of this invention have been found to possess antiviral activity against viruses having a core of double-stranded DNA. Specifically, the compounds exhibit antiviral activity against virus types such as herpes virus infections, poxvirus infections and adenovirus infections.

The compounds of this invention can be used for the prevention, treatment of mitigation of virus infections of warm-blooded animals such as caused by Herpes simplex/H4 virus, Herpes simplex/2/Ala./SM virus, pseudorabies virus, vaccinia virus, vesicular stomatitis and adenovirus.

It will be understood that a "warm-blooded animal" is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The compounds of this invention can be administered in the antiviral treatment according to this invention by any means that effects contact of the active ingredient compound with the site of virus infection in the body of a warm-blooded animal. It will be understood that this includes the site prior to infection setting in as well as after. For example, administration can be by the parenteral, topical or oral route.

The antiviral effectiveness of the compounds of this invention can be demonstrated against Herpes virus
when a medium containing at least 10 mcg/ml of 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine is applied to rabbit kidney cells which have been infected with 200 plaque forming units of Herpes simplex/H4/virus with the result that complete inhibition of the cytopathic effect of the virus is noted.

In another test for antiviral activity, chick embryo cells were grown to confluency (+ 24 hours). The growth media above the monolayer was removed and replaced with 5 ml of new media containing 60 mcg/ml of 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine. This preparation was incubated for 24 hours, after which 200 plaque forming units of vesicular stomatitis virus are added. The media containing virus and compound is stirred moderately and incubated an additional 72 hours. At the conclusion of the incubation period, monolayers in the presence of test compound plus virus appear completely normal, while the monolayers incubated with virus but with no test compound present, appear totally destroyed by virus. The result demonstrates that the test compound effectively inhibits the cytopathic effect of the virus on chick embryo cells.

In yet another test for antiviral activity, it has been observed that guinea pigs infected subcutaneously with herpes virus hominis develop skin lesions. It has also been observed that the number of lesions is significantly lowered when 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine is applied topically once a day for four days after infection when compared to the number of lesions observed in similarly infected guinea pigs which received no drug.

I claim:
1. A compound of the formula

```
  R1
  / \   /
 R2 --N--C--R3
  \ /   \ /
    S   N
```

where

- R1 is hydrogen, —OH, —SH, or —NHR3 where R3 is hydrogen, alkyl of one through six carbon atoms, allyl or propargyl;
- R2 is hydrogen, alkyl of one through four carbon atoms, —OH, —SH or —NH2; and
- the pharmaceutically acceptable salts of said compounds.

2. The compound of claim 1 which is 5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine and a pharmaceutically acceptable salt of said compound.

3. The compound of claim 1 which is N-methyl-5,6,7,8-tetrahydro-5,8-ethanopyridino[2,3-b]thieno[5,4-d]pyrimidine-4-amine and a pharmaceutically acceptable salt of said compound.

* * * *