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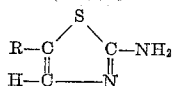
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ANALGESIC 5-LOWER ALKYL-2-AMINO THIAZOLES

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This invention relates to therapeutic compositions. More specifically, this invention relates to compositions containing certain thiazole derivatives which exhibit various pharmacological activities such as that of analgesic activity, antipyretic activity, motor depressant activity, tranquilizing activity and anti-inflammatory activity.

The therapeutic compositions of this invention comprise, as the therapeutically active agent, a 2-amino-5-alkyl thiazole having the following generic formula:



wherein R is an alkyl radical having from 1 to 4 carbon atoms, e.g., methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like.

The 2-amino-5-alkyl thiazoles or their pharmaceutically acceptable non-toxic acid addition salts can be administered to humans and animals by the conventional methods, the conventional types of unit dosages or with the conventional pharmaceutical carriers to produce a therapeutic effect such as the pharmacological activities mentioned above, e.g. analgesic activity etc. Oral administration by the use of tablets, capsules or in liquid form such as suspensions, solutions or emulsions is preferred. When formed into tablets, the conventional binding and disintegrating agents used in therapeutic unit dosages can be employed. Illustrative of binding agents there can be mentioned glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate and talc. Illustrative of disintegrating agents there can be mentioned corn starch, keratin, colloidal silica and potato starch.

The acid addition salts are formed by the conventional techniques of neutralizing the amine portion of a compound with either an organic or inorganic acid. Illustrative of the acids there can be mentioned hydrochloric, sulfuric, citric, acetic, malic, maleic, and phosphoric acids.

The unit dosage or therapeutically effective quantity of the 2-amino-5-alkyl thiazoles for human beings for the therapeutic uses of the invention can vary over wide limits such as that of less than 6 milligrams (mg.) to more than 1,500 mg. For oral administration it is preferable to employ from about 65 to about 650 milligrams of the therapeutic agent per unit dosage. Of course, the dosage of the particular therapeutic agent used can vary considerably, such as the age of the patient and the degree of therapeutic effect desired. Each unit dosage form of the novel therapeutic compounds can contain from about 5% to about 95% and preferably from about 10% to about 80% of the novel therapeutic agents by weight of the entire composition with the remainder comprising conventional pharmaceutical carriers. By the term pharmaceutical carriers we intend to include non-therapeutic materials which are conventionally used with unit dosages and includes fillers, diluents, binders, lubri-

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cants, disintegrating agents and solvents. Of course, it is possible to administer the novel therapeutics, i.e., the pure compounds, or their acid addition salts without the use of a pharmaceutical carrier. The therapeutic agents of this invention can be administered either prior to or after the onset of the condition to be treated, such as when they are used as: analgesics for the amelioration of pain such as the common headache, mild rheumatism and the like; anti-pyretics to reduce fever or simply to lower the body temperature; motor depressants or tranquilizers to relieve nervous tension, hyperexcitability and induce sedation; or anti-inflammatory agents for edematous conditions such as are caused by arthritis.

The invention is illustrated by the following examples of suitable therapeutic compositions in unit dosage form, although it is not intended that the compositions or dosages be limited by any of the proportions, amounts, types of carriers, or dosage units set forth therein.

EXAMPLE 1

A suitable formulation of tablets consists of:

	Grams
(1) 2-amino-5-methyl thiazole.....	10
(2) Lactose	80
(3) Starch	5
(4) Magnesium stearate.....	2

The thiazole derivative, lactose and starch are thoroughly mixed and granulated. For tableting, the magnesium stearate is added, mixed with the granules, and the mixture tableted on a rotary press. Use of this procedure produces 200 tablets each containing 50 mg. of the active therapeutic agent.

EXAMPLE 2

Another suitable formulation of tablets consists of:

	Grams
(1) 2-amino-5-methyl thiazole.....	25
(2) Mannitol	160
(3) Starch	10
(4) Magnesium stearate.....	4

The 2-amino-5-methyl thiazole, mannitol and starch are thoroughly mixed and granulated. For tableting, the magnesium stearate is added, mixed with the granules, and the mixture is tableted on a rotary press. Use of this procedure produces 100 tablets each containing 250 mg. of the active therapeutic agent.

EXAMPLE 3

Another suitable formulation of tablets consists of:

	Grams
(1) 2-amino-5-methyl thiazole.....	25
(2) b-Lactose	70
(3) Dextrin	10
(4) Hydrogenated vegetable oil.....	0.5
(5) Talc	2

The thiazole derivative, b-lactose, and dextrin are thoroughly mixed and granulated. For tableting, the hydrogenated vegetable oil and talc are added, mixed with the granules, and the mixture tableted on a rotary press. Use of this procedure can produce 200 tablets with each tablet containing 125 mg. of active therapeutic agent.

EXAMPLE 4

This example shows the analgesic effect of 2-amino-5-

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methyl thiazole on rats. This test was performed by uniformly blackening the tails of rats, administering orally 100 mg. per kg. of animal weight of the thiazole derivative to 30 rats and subsequently focusing a beam of light on the animals' tails at various intervals of time after administration of the analgesic. For comparative purposes a number of rats were treated in the same manner but were fed aspirin instead of the thiazole derivative. The time required for an animal to flick its tail after the beam of light is applied determines the analgesic effect of the material being tested. The longer the interval for the tail flick after the application of the concentrated beam of light, the more effective is the analgesic. Table 1 shows the results of the analgesic tests. The results are given in seconds above the time required for the animals to give the pain response when no analgesic was administered and which is about 4.1 seconds.

Table 1

Times in minutes after administration of analgesic.....	20	40	60
Time, in seconds, for pain response of animals which had ingested the 2-amino-5-methyl thiazole.....	1.0	1.3	1.5
Time, in seconds, for pain response of animals which had ingested aspirin.....	0.3	0.2	-0.3

EXAMPLE 5

This example shows the antipyretic activity of 2-amino-5-methyl thiazole on rats. The method employed for this example is that which is reported by Eagle and Carlson, *Journal of Pharmacology and Experimental Therapy*, vol. 99, page 450 (1950), and which is often referred to as the brewer's yeast method. Separate tests were conducted with two different doses of the thiazole derivative and also with aspirin. The results of the experiment which show the drop in temperature at different time periods from an induced fever of approximately 102° F. is shown in Table 2.

Table 2

	One Hour, ° F.	Three Hours, ° F.
Aspirin at 100 mg. per kg. of animal weight.....	2.3	3.2
2-amino-5-methyl thiazole at 100 mg. per kg. of animal weight.....	4.4	6.0
2-amino-5-methyl thiazole at 200 mg. per kg. of animal weight.....	7.0	7.0

EXAMPLE 6

This example shows anti-inflammatory activity of 2-amino-5-methyl thiazole. The method employed was that of R. Domenjo and W. Theobald, "Antimalarials in Rheumatoid Arthritis," *Experientia*, vol. 14, page 33 (January 15, 1958). Essentially, the method comprises the steps of: (a) orally administering to a rat a material to be tested for anti-inflammatory activity; (b) inflaming the animal's right hind paw with a subcutaneous injection of 0.1 ml. of a 3% aqueous formalin solution 30 minutes after administration of the material to be tested; (c) sacrificing the animal at a predetermined time after the formalin injection (a two hour period was used in this example); (d) amputating the animal's right hind paw; and (e) comparing the volume of the amputated paw of the animal which was given the test material with the amputated right paw of a similar rat which had not received the test material but which was treated in the same manner in all other respects. The method is conducted by using ten rats for the test material and ten rats as controls and the total difference in volume of the paws of treated and untreated animals is compared. The results of this example are given in Table 3.

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Table 3

	Reduction in swelling, cc.
Animals treated with 500 mg. of 2-amino-5-methyl thiazole per kg. of animal weight.....	3.2
Animals treated with 500 mg. of aspirin per kg. of animal weight.....	2.2

EXAMPLE 7

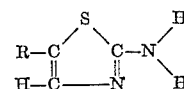
This example shows the decrease in spontaneous activity (motor depressant) of 2-amino-5-methyl thiazole. The example was performed by orally administering to ten mice a predetermined quantity of 2-amino-5-methyl thiazole. Ten mice which had not received the thiazole derivative were used as controls. Ten minutes after administration of the thiazole derivative the treated and untreated mice were individually and in alternate sequence placed in a circular chamber having a plurality of photoelectric cells and cooperating beams of light with means to count the number of times the beam of light is broken. Each animal remained in the chamber for four minutes. The results of this example are shown in Table 4 which shows the percent decrease in activity of three sets of ten mice in each set which received various dosage levels of the thiazole derivative as compared with three sets of ten mice in each set which were used as controls for testing each of the dosage levels. The percent decrease represents the numerical average for each set of animals.

Table 4

	Decrease in activity below controls, percent
2-amino-5-methyl thiazole at:	
(a) 100 mg. per kg. of animal weight.....	41
(b) 50 mg. per kg. of animal weight.....	37
(c) 25 mg. per kg. of animal weight.....	7

What is claimed is:

1. A method for relieving an edematous condition in a human being which comprises administering to a human being suffering from edema, from about 65 milligrams to about 650 milligrams of a member selected from the group consisting of 2-amino-5-methyl thiazole and a pharmaceutically acceptable non-toxic acid addition salt thereof.
2. A method for relieving fever in a human being which comprises administering to a human being suffering from fever, from about 65 milligrams to about 650 milligrams of a member selected from the group consisting of 2-amino-5-methyl thiazole and a pharmaceutically acceptable non-toxic acid addition salt thereof.
3. An analgesic composition in unit dosage form comprising a significant quantity of a pharmaceutical carrier and from about 6 milligrams to about 1,500 milligrams of a member selected from the group consisting of a thiazole derivative having the following generic formula:

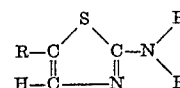


wherein R is an alkyl radical having from 1 to 4 carbon atoms and a pharmaceutically acceptable non-toxic acid addition salt of said thiazole derivative.

4. The analgesic composition of claim 3 wherein R of the generic formula is the methyl radical.

5. An analgesic tablet comprising a significant quantity of a pharmaceutical carrier and from about 65 to about 650 milligrams of 2-amino-5-methyl thiazole.

6. A method for inducing analgesia which comprises administering to an animal, including a human, an analgesically effective quantity of a member selected from the group consisting of a thiazole derivative having the following generic formula:



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wherein R is an alkyl radical having from 1 to 4 carbon atoms and a pharmaceutically acceptable non-toxic acid addition salt of said thiazole derivative.

7. The method of claim 6 wherein R of the generic formula is the methyl radical.

8. A method for inducing analgesia which comprises administering to a human being suffering from pain, from about 65 milligrams to about 650 milligrams of a member selected from the group consisting of 2-amino-5-methyl thiazole and a pharmaceutically acceptable non-toxic acid addition salt thereof.

9. A method for inducing sedation which comprises

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administering to a human being suffering from nervous excitement from about 65 milligrams to about 650 milligrams of a member selected from the group consisting of 2-amino-5-methyl thiazole and a pharmaceutically acceptable non-toxic acid addition salt thereof.

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