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PHARMACEUTICAL PREPARATIONS AND METHODS OF USING SAME

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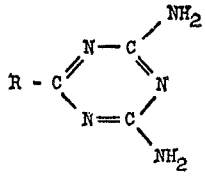
ABSTRACT OF THE DISCLOSURE

Preparations containing 2,4-diamino-6-substituted-s-triazines and methods of using same whereby a host, including man, to whom such preparations are administered, is provided with anti-inflammatory relief while avoiding the unwanted side effects of steroid therapy.

The triazine compounds of this invention have the structure



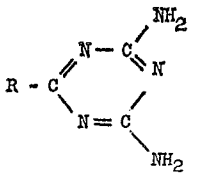
wherein R is selected from the group consisting of primary alkyl, secondary alkyl, tertiary alkyl, said alkyls having from one to 15 carbon atoms, and $R'(CH)_n$ wherein R' is selected from the group consisting of phenyl, diphenyl, chlorophenyl or methoxyphenyl, and "*n*" is a cardinal number having a value of from 1 to 4.

DISCLOSURE OF INVENTION

This invention relates to pharmaceutical preparations and their use and more particularly to the unexpected benefits obtained when a preparation containing certain 2,4-diamino-6-substituted-s-triazine is administered to a host afflicted with an inflammatory condition.

The properties of these compounds and particularly their lack of steroid side effects, make this a highly valuable discovery since, as used, it provides relief for patients who, suffering from inflammatory conditions, cannot tolerate steroid therapy in the treatment thereof.

The compounds of this invention have the structural formula



wherein R is selected from the group consisting of primary alkyl, secondary alkyl, tertiary alkyl in which the alkyl has from one to 15 carbon atoms and $R'(CH)_n$ wherein said R' is selected from the group consisting of phenyl, diphenyl, chlorophenyl and methoxyphenyl, and "*n*" is a cardinal number having a value of from one to 4.

Representative of compounds useful in the preparation and methods of the present invention are:

2,4-diamino-6-methyl-s-triazine;
2,4-diamino-6-ethyl-s-triazine;
2,4-diamino-6-propyl-s-triazine;
2,4-diamino-6-iso-propyl-s-triazine;
2,4-diamino-6-butyl-s-triazine;
2,4-diamino-6-iso-butyl-s-triazine;
2,4-diamino-6-secondary butyl-s-triazine;
2,4-diamino-6-tertiary butyl-s-triazine;
2,4-diamino-6-pentyl-s-triazine;
2,4-diamino-6-hexyl-s-triazine;
2,4-diamino-6-heptyl-s-triazine;
2,4-diamino-6-octyl-s-triazine;
2,4-diamino-6-nonyl-s-triazine;
2,4-diamino-6-decyl-s-triazine;
2,4-diamino-6-undecyl-s-triazine;
2,4-diamino-6-dodecyl-s-triazine;
2,4-diamino-6-tridecyl-s-triazine;
2,4-diamino-6-tetradecyl-s-triazine;
2,4-diamino-6-pentadecyl-s-triazine;
2,4-diamino-6-[2-phenylvinyl]-s-triazine;
2,4-diamino-6-phenylmethyl-s-triazine;
2,4-diamino-6-methoxyphenylmethyl-s-triazine;
2,4-diamino-6-chlorophenylmethyl-s-triazine;
2,4-diamino-6-biphenylmethyl-s-triazine;
2,4-diamino-6-phenethyl-s-triazine;
2,4-diamino-6-phenylpropyl-s-triazine;
2,4-diamino-6-phenylbutyl-s-triazine;
2,4-diamino-6-chlorophenylethyl-s-triazine;
2,4-diamino-6-biphenylethyl-s-triazine;
2,4-diamino-6-chlorophenylpropyl-s-triazine;
2,4-diamino-6-methoxyphenylethyl-s-triazine;
2,4-diamino-6-methoxyphenylpropyl-s-triazine;
2,4-diamino-6-methoxyphenylbutyl-s-triazine;
2,4-diamino-6-chlorophenylbutyl-s-triazine;
2,4-diamino-6-biphenylpropyl-s-triazine;
2,4-diamino-6-biphenylbutyl-s-triazine; and
2,4-diamino-6-cyclopentylmethyl-s-triazine.

Our entire group of compounds, for ease of expression shall, from time to time, hereinafter be referred to as "2,4-diamino - 6 - alkyl-s-triazine and selected derivatives thereof" even though, in certain instances the more correct nomenclature should be "6-alkyl-2,4-diamino-s-triazine." The beneficial effects obtained when these compounds are formulated into pharmaceutically acceptable dosage forms and administered to a host requiring anti-inflammatory therapy is new and totally unexpected.

Thus, the present invention is predicated upon our discovery that beneficial effects are obtainable when 2,4-diamino-6-alkyl-s-triazine and selected derivatives thereof are employed in pharmaceutically acceptable forms to effectively disseminate the compound within the host to which it is administered to the benefit of the host.

"Inflammatory conditions" as that term is used herein, refers to those physical conditions exhibiting one or more of the symptoms, redness, pain, heat and swelling. In the past, inflammatory conditions have been treated with various analgesics, antipyretics, narcotics, hormones, and steroids, alone or in combination. In some inflammatory conditions, such as the rheumatoid diseases, particularly rheumatoid arthritis, the generally accepted approach has been treatment by the administration of adrenocorticosteroids, if and when the subject can assimilate and tolerate the drug. However, extreme care must be exercised in administering steroids so as to avoid or minimize the various undesirable side effects which, as is well known in the art, are frequently encountered with such drugs.

The present invention is based upon our discovery of the remarkably unexpected anti-inflammatory action obtained when preparations containing 2,4-diamino-6-aklyl-

s-triazine and selected derivatives thereof as herein defined, are administered to a host having an "inflammatory condition" as defined.

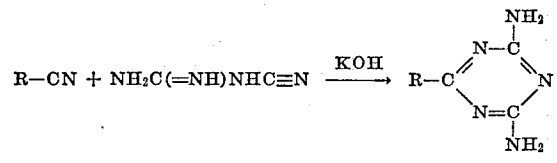
Accordingly, a prime object of the present invention is to provide a new and useful pharmaceutical preparation containing, as its principal active ingredient, the compound 2,4-diamino-6-alkyl-s-triazine or selected derivatives thereof as herein defined.

Another object of the present invention is to provide a new pharmaceutical preparation which is a potent anti-inflammatory agent.

A still further object of the present invention is to provide an anti-inflammatory agent which substantially precludes the onerous side effects accompanying exogenous steroid therapy of inflammatory conditions.

These and still further objects as shall hereinafter appear are fulfilled by the present invention in a remarkably unexpected manner as will be readily discerned from a careful consideration of the following detailed description of exemplary embodiments thereof.

In one practice of the present invention, 2,4-diamino-6-methyl-s-triazine is prepared by condensing acetonitrile with dicyandiamide in the presence of potassium hydroxide according to the reaction:



The reagents are heated with stirring in the presence of a suitable solvent, such as 2-methoxyethanol, and after about 2 hours, the slurry is cooled to about 25° C. and filtered. The crude product is then reslurried with hot water, refiltered and washed. The washed product is thereafter dried to constant weight to eliminate excessive moisture therefrom and is 2,4-diamino-6-methyl-s-triazine.

Of course, in the foregoing practice, the methyl derivative is described as illustrative only and the procedure can be followed to prepare the other derivatives using the appropriate nitrile as a starting material.

Another known method of preparing such compounds comprises reacting the appropriate ethyl (substituted) acetate with biguanide sulfate in methanolic sodium hydroxide.

The finished compound may thereafter be formulated into pharmaceutical unit dosage forms using the known procedures of mixing, granulating, compressing, suspending or dissolving and adding suitable pharmaceutical carriers or non-toxic excipients thereto.

In one embodiment of our invention, the principal active ingredient of our pharmaceutical preparation is 2,4-diamino-6-substituted-s-triazine as herein defined or a pharmaceutically acceptable salt thereof, e.g., a non-toxic salt of sulfuric, nitric, phosphoric, citric, acetic, lactic, tartaric, sulfamic, succinic, fumaric, maleic, ethanedisulfonic, hydrobromic, benzoic or a similar acid. The acceptable salts may be formed by reacting the triazine base with excess acid in a suitable solvent such as ethanol, ether, acetone, water or mixtures thereof. The mixture is heated to facilitate solution and the salts crystallize therefrom on cooling.

The preferred dosage forms for this invention contain our principal active ingredient associated with an acceptable pharmaceutical carrier. The carrier, a nontoxic pharmaceutical grade substance, may be either solid or liquid. Suitable flavors or sweeteners may also be added, if desired, to those forms for oral administration. The routes by which our preparation may be administered are subcutaneous, intramuscular, and intravenous injection, pancaval, including oral, and topical.

Suitable solid carriers for use herewith include lactose, magnesium stearate, starch, sucrose, mannitol, sorbitol, cellulose powder, dicalcium phosphate, talc, stearic acid, gelatin, agar pectin, acacia and the like. Suitable liquid carries include glycols, polyglycols, peanut oil, olive oil, sesame oil, alcohols, water and the like. If desired, the carrier may include a time delay material such as glycerol monostearate, shellac or glycerol distearate, either alone or with wax.

Our composition preferbly is provided in unit dosage forms for accuracy and convenience in administration. When appropriate, oral administration is effective and preferred and dosage units suitable for oral administration are provided. Such dosage forms which employ solid carriers include tablets, filled capsules, packets, lozenges, troches and the like. The amount of solid carrier per dosage unit may vary widely, e.g., from 25 mg. to 1 gram, depending upon the form selected. The choice of an appropriate amount is well within the skill of an artisan once confronted with this disclosure.

Our compounds and their salts may also be compounded with semi-solid and liquid carriers in solutions, suspensions, emulsions, ointments, suppositories and soft gelatin capsules, for example. Such compositions may be administered pancavally, i.e., via natural and artificial openings in the body such as the mouth, the anus, the vagina, the nares, and the stoma of colostomy patients; intravenously; intramuscularly; or topically; employing the appropriate composition having a suitable concentration of active ingredient according to the desired route of administration.

An inflammatory condition is treated in accordance with the invention by administering the preparation of this invention in an amount sufficient to alleviate the symptoms of the condition. The compound will be administered at a daily dosage of from 25 mg. to 2000 mg. of the active ingredient disposed in a pharmaceutical carrier. A preferred daily amount of from 100 to 1000 mg. of the drug gives satisfactory results when oral administration is desired. When routes of administration such as topical and intramuscular are desired so as to place the drug directly at the site of inflammation, the dosage level may be substantially reduced.

The dosage level, and frequency of administration will vary to a great extent between conditions and between patients. It is therefore required that the doctor take into consideration the cause of the condition, the case history of the patient, the reaction of the subject, the preferred route of administration, and the like in prescribing dosages. The daily dosage may be administered during one or more times during the day. Tablets and hard gelatin capsules are especially well suited when oral administration is selected for the practice of this invention.

To further aid in the appreciation and comprehension of the present invention, and not to limit its scope, the following examples are presented.

EXAMPLE I

To prepare 2.4 - diamino - 6 - p - chlorobenzyl - s-triazine, 1.16 gms. of potassium hydroxide was dissolved in 100 ml. of 2-methoxyethanol. Stirring was started and 16.7 gms. of p-chlorophenylacetonitrile and 11.7 gms. of dicyandiamide were added. The temperature was raised to reflux (ca. 123° C.). After 5 hours the slurry was cooled to 25° C. and 200 ml. of water was added. The crude product was filtered and the cake collected. The cake was washed with 2 liters water and dried under vacuum to yield 23.0 gms. of white crystals, M.P. 249–50° C. The material was then recrystallized from 700 ml. of 50% aqueous acetic acid to yield 19.0 gms. of product, M.P. 249–50° C.

EXAMPLE II

Several dosage forms were prepared embodying the present invention. They are shown as Compositions A through K below, with the notation "active ingredient" signifying a compound of this invention and including the non-toxic pharmaceutically active salts thereof.

Composition A

Tablets suitable for oral administration and having the following composition per tablet are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	200
Sorbitol	15
Mannitol	85
Gelatin, as a 10% aqueous solution	6
Corn starch	30
Magnesium stearate	4

The first three ingredients are milled together to a uniform powder and granulated into the gelatin solution. The mixture is screened onto trays and dried at 60° C. The dried granules are sized, mixed with the corn starch and the magnesium stearate, and compressed into tablets.

Composition B

Tablets suitable for oral administration and having the following composition per tablet are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	200
Microcrystalline cellulose [1]	150
Polyvinyl pyrrolidone	5
Magnesium stearate	4

[1] Avicel (FMC Corporation, U.S. Pat. No. 2,978,446), average particle size 38 microns.

The first three ingredients are mixed to uniformity and lubricated with a portion of the magnesium stearate. The mixture is compressed into slugs, and the slugs are granulated. The granules are lubricated with the remainder of the magnesium stearate and compressed into tablets.

Composition C

Filled gelatin capsules suitable for oral administration and containing the following composition in each capsule are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	200
Lactose	175
Magnesium stearate	5

The above ingredients are screened through a #40 U.S. mesh screen to a uniform powder, transferred to a mixer, mixed well, and filled into No. 1 hard gelatin capsules.

Composition D

Filled soft gelatin capsules suitable for oral administration and containing the following composition in each capsule are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	50
Sesame oil	50

The ingredients are mixed to form a thick slurry, and the slurry is filled into soft gelatin capsules.

Composition E

Filled soft gelatin capsules suitable for oral administration and containing the following composition in each capsule are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	300
Polyethylene glycol 400	240

The ingredients are mixed to form a thick slurry, and the slurry is filled into soft gelatin capsules.

Composition F

Tablets used for oral administration and having the following composition per tablet are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	200
Dicalcium phosphate	180
Corn starch	60
Polyvinylpyrrolidone	5
Magnesium stearate	4

The active ingredient, dicalcium phosphate and a portion of the starch and magnesium stearate are mixed, granulated with an alcoholic solution of the polyvinylpyrrolidone, dried, and sized. The remainder of the starch and the magnesium stearate are added and mixed. This mixture then is compressed into tablets.

Composition G

Tablets used for oral administration and having the following composition per tablet are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	200
Lactose	200
Microcrystalline cellulose	30
Polyvinylpyrrolidone	5
Amberlite XE-88 [1]	5
Magnesium stearate	4

[1] Potassium salt of a carboxylic acid cation exchange resin available at Rohm & Haas, Philadelphia, Pa.

Composition H

Tablets useful for oral administration and having the following composition per tablet are produced by compounding the ingredients in the relative proportions indicated:

Ingredients:	Amount, mg.
Active ingredient	50
Microcrystalline cellulose	79
Magnesium stearate	1

Tablets may be white or colored with appropriate food, drug and cosmetic or drug and cosmetic dyes.

Composition I

The following ingredients are compounded to provide a solution suitable for intramuscular administration.

Ingredients:	Amount, g.
Active ingredient	20
Polyethylene glycol 200, q.s. up to 1 liter.	

The ingredients are mixed and warmed to about 50–60° C. with stirring to effect solution. The solution is sterile filtered, cooled to room temperature and packaged in sterile vials.

Composition J

Suppositories melting at about 60° F. and each having the following composition are produced by compounding the ingredients in the same relative proportions:

Ingredients:	Amount, mg.
Active ingredient	200
Polyethylene glycol 600	200
Polyethylene glycol 4000	800

The ingredients are mixed and heated to about 60° C. to effect solution. The solution is poured into cooled molds and allowed to cool and solidify.

Composition K

An ointment suitable for topical administration has the following composition, in parts by weight:

Ingredients:	Amount
Active ingredient	200
Polyethylene glycol 1540	500
Polyethylene glycol 4000	80
Propylene glycol	200
Cetyl alcohol	20

The polyethylene glycols and cetyl alcohol are mixed and warmed to about 60° C. The active triazine ingredient then is stirred into the mixture to effect solution. The propylene glycol is added to the solution with stirring until cool. The cool ointment is filled into jars.

EXAMPLE III

2,4-diamino-6-benzyl-s-triazine was prepared by refluxing a stirred mixture of 16.4 g. (0.14 mole) of phenylacetonitrile, 11.7 g. (0.14 mole) of dicyandiamide, 1.16 g. of potassium hydroxide and 100 ml. of 2-methoxyethanol (methyl cellosolve) for 5 hours. The mixture was cooled to room temperature and 200 ml. of water was added. The precipitate was collected by filtration in a Büchner funnel, washed with water and dried under vacuum to yield white crystals. The material was then recrystallized from 700 ml. of 50% aqueous acetic acid to yield a product, M.P. 248–50° C. which is 2,4-diamino-6-benzyl-s-triazine.

EXAMPLE IV

A mixture of 16.2 g. (0.11 mole) of p-methoxyphenylacetonitrile, 11.7 g. (0.14 mole) of dicyandiamide, 1.16 g. of potassium hydroxide and 100 ml. of methyl Cellosolve was refluxed with stirring for 5 hours. The solvent was removed by distillation under vacuum, and the solid residue was washed with 100 ml. of water and collected in a Büchner funnel by filtration. This material was recrystallized from 500 ml. of 50% aqueous acetic acid to yield 25.8 g. of material, M.P. 128–30° C. This was dissolved in 260 ml. of 0.5 N hydrochloric acid and filtered. The filtrate was neutralized with concentrated ammonium hydroxide, and the precipitate was collected by filtration, washed with water and dried to yield 17.4 g. of 2,4-diamino-6-p-methoxybenzyl-s-triazine, M.P. 207–9° C.

Analysis.—Calculated for $C_{11}H_{13}N_5O$ (percent): C, 57.11; H, 5.67; N, 30.29. Found (percent): C, 57.12; H, 5.82; N, 30.24.

EXAMPLE V

A mixture of 10.1 g. (0.22 mole) of acetonitrile, 9.24 g. (0.11 mole) of dicyandiamide, 1.16 g. of potassium hydroxide and 100 ml. of methyl Cellosolve was refluxed with stirring for 5 hours. The solvent was removed by distillation under vacuum and 50 ml. of water was added to the solid residue. The precipitate was collected by filtration in a Büchner funnel and recrystallized from 100 ml. of 50% aqueous methanol to yield 8.68 g. of 2,4-diamino-6-methyl-s-triazine, M.P. 277–9° C.

Analysis.—Calculated for $C_4H_7N_5$ (percent): C, 38.41; H, 5.63; N, 56.00. Found (percent): C, 38.60; H, 5.90; N, 55.75.

EXAMPLE VI

A mixture of 6.06 g. (0.11 mole) of propionitrile, 23.4 g. (0.28 mole) of dicyandiamide, 1.16 g. of potassium hydroxide and 100 ml. of ethyl Cellosolve was refluxed with stirring for 5 hours. The solvent was removed by distillation under vacuum and to the residue was added 50 ml. of water. The precipitate was collected by filtration in a Büchner funnel and dissolved in 200 ml. of 1 N hydrochloric acid. The solution was filtered and the filtrate was neutralized with concentrated amomnium hydroxide. The precipitate was collected by filtration, washed with water and dried in a vacuum oven to yield 14.8 g. of 2,4-diamino-6-ethyl-s-triazine, M.P. 292–3° C., dec.

EXAMPLE VII

A mixture of 15.2 g. (0.22 mole) of butyronitrile, 9.24 g. (0.11 mole) of dicyandiamide, 1.16 g. of potassium hydroxide and 100 ml. of ethyl Cellosolve was refluxed with stirring for 5 hours. The solvent was removed by distillation under vacuum, and washed with 50 ml. of water. The precipitate was collected by filtration in a Büchner funnel and recrystallized from 200 ml. of 50% aqueous methanol to yield 12.77 g. of 2,4-diamino-6-propyl-s-triazine, M.P. 196–8° C.

Analysis.—Calculated for $C_6H_{11}N_5$ (percent): C, 47.03; H, 7.24; N, 45.72. Found (percent): C, 46.90; H, 7.09; N, 46.00.

EXAMPLE VIII

The following compounds were prepared using the procedure of Example VII and an equivalent amount (0.22 mole) of the appropriate nitrile. The corresponding melting points and recrystallization solvents are listed.

	M.P., °C.	Recrystallization solvent
2,4-diamino-6-isobutyl-s-triazine	176–9	50% aqueous methanol.
2,4-diamino-6-n-butyl-s-triazine	213–15	Do.
2,4-diamino-6-n-amyl-s-triazine	180–3	Do.
2,4-diamino-6-n-hexyl-s-triazine	159–61	Do.
2,4-diamino-6-n-heptyl-s-triazine	173–5	Do.
2,4-diamino-6-n-octyl-s-triazine	142–50	Do.
2,4-diamino-6-n-nonyl-s-triazine	103–6	n-Hexane.
2,4-diamino-6-n-decyl-s-triazine	116–18	Acetone.
2,4-diamino-6-n-dodecyl-s-triazine	117–19	Do.
2,4-diamino-6-n-pentadecyl-s-triazine	111–15	Do.

EXAMPLE IX

A mixture of 15.2 g. (0.22 mole) of isobutyronitrile, 9.25 g. (0.11 mole) of dicyandiamide, 1.16 g. of potassium hydroxide and methyl Cellosolve was refluxed with stirring for 6 hours. The solvent was removed by distillation under vacuum and 100 ml. of water was added to the residue. The precipitate was collected by filtration in a Büchner funnel and recrystallized from aqueous methanol to yield 8.2 g. of 2,4-diamino-6-isopropyl-s-triazine, M.P. 263–5° C.

Analysis.—Calculated for $C_6H_{11}N_5$ (percent): C, 47.03; H, 7.24; N, 45.72. Found (percent): C, 46.86; H, 7.12; N, 45.60.

EXAMPLE X

2,4-diamino-6-sec-butyl-s-triazine was prepared using the procedure of Example IX and 18.3 g. (0.22 mole) of 2-methylbutyronitrile. The crude product was recrystallized from hot water to yield 6.8 g. of white crystals, M.P. 176–8° C.

Analysis.—Calculated for $C_7H_{13}N_5$ (percent): C, 50.28; H, 7.84; N, 41.88. Found (percent): C, 50.13; H, 7.73; N, 41.66.

EXAMPLE XI

2,4-diamino-6-tert-butyl-s-triazine was prepared using the procedure of Example IX and starting with 18.3 g. (0.22 mole) of tert-butyl cyanide. Recrystallization from hot water yielded 6.1 g. of final product, M.P. 169–71° C.

Analysis.—Calculated for $C_7H_{13}N_5$ (percent): C, 50.28; H, 7.84; N, 41.88. Found (percent): C, 50.50; H, 7.84; N, 41.77.

EXAMPLE XII

2,4-diamino-6-(γ-phenylpropyl)-s-triazine was prepared using the procedure of Example IX and starting with 32.0 g. (0.22 mole) of γ-phenylbutyronitrile. Recrystallization from acetone yielded 13.7 g. of product, M.P. 151–2° C.

Analysis.—Calculated for $C_{12}H_{15}N_5$ (percent): C, 62.86; H, 6.59; N, 30.54. Found (percent): C, 62.65; H, 6.61; N, 30.50.

EXAMPLE XIII

2,4-diamino-6-phenethyl-s-triazine was prepared using the procedure of Example IX and starting with 29.0 g. (0.22 mole) of freshly distilled phenethyl cyanide. Recrystallization from methanol yielded 10.9 g. of product, M.P. 184–6° C.

EXAMPLE XIV

2,4-diamino-6-(p-phenylbenzyl)-s-triazine was prepared by the same procedure using 42.5 g. (0.22 mole) of 4-phenylbenzyl cyanide. Recrystallization from dimethyl formamide yielded 20.9 g. of product, M.P. 278–81° C., dec.

Analysis.—Calculated for $C_{16}H_{15}N_5$ (percent): C, 69.29; H, 5.45; N, 25.25. Found (percent): C, 69.16; H, 5.46; N, 25.40.

EXAMPLE XV

To a stirred solution of 5.06 g. (0.050 mole) of biguanide in 70 ml. of methanol was added a solution of 9.87 g. (0.056 mole) of ethyl cinnamate. After 1 hour of stirring, a white precipitate began to separate. Stirring was continued for a total of 24 hours. The precipitate was collected by filtration in a Büchner funnel and dried in a vacuum oven at 50° C. to yield 6.52 g. of material, M.P. 275–8° C. Recrystallization from 1-butanol yielded 5.09 g. of 2,4-diamino-6-cinnamyl-s-triazine, M.P. 275.5–6.5° C.

EXAMPLE XVI

To a solution of 8.0 g. (0.2 mole) of sodium hydroxide in 150 ml. of methanol was added with stirring, 19.9 g. (0.1 mole) of biguanide sulfate. After 2 hours of stirring, 15.6 g. (0.1 mole) of ethyl cyclopentyl acetate was added. Stirring was continued overnight, and the precipitate was collected by filtration in a Büchner funnel. The solids were resuspended in 50 ml. of water, collected by filtration and dried to yield 10.5 g. of material, M.P. 180–2° C. The crude product was recrystallized twice from ethanol to yield 6.86 g. of 2,4-diamino-6-cyclopentylmethyl-s-triazine, M.P. 180–2° C.

A sample for analysis was prepared by precipitation from 1 N hydrochloric acid solution with ammonium hydroxide, followed by two recrystallizations from 50% aqueous ethanol, M.P. 181–3° C.

Analysis.—Calculated for $C_9H_{15}N_5$ (percent): C, 55.92; H, 7.83; N, 36.25. Found (percent): C, 55.68; H, 8.11; N, 36.17.

EXAMPLE XVII

Selected compounds of this invention were tested for anti-inflammatory activity in rats using the Selye Granuloma Pouch assay described in Arch. Int. Pharmacodyn. 97, 379 (1954).

In this assay, 25 ml. of air is injected subcutaneously to form an air pouch on the dorsal side of the rats. An injection is made into each pouch, of 0.5 ml. of corn oil containing 1% of croton oil as an irritant. The irritant action causes the formation of an inflammatory exudate which averages 7 to 9 ml. at the end of 4 days.

The effect of administering the test compounds to groups of 6 rats was compared to the effect obtained in a similar group which received no test compound. Male rats obtained from Holtzman Company, Madison, Wisc., and weighing 220 to 240 grams each, were used throughout the assay. The dorsal area of each animal was shaved with an electric clipper and the animals were placed under light ether anesthesia. The shaved regions were wiped with 70% ethanol, and 25 ml. of air was injected at the approximate center of each animal's shaved portion using a syringe and a 24 gauge needle.

The phlogistic agent was suspended to provide 0.125 mg. of agent in 0.5 ml. sesame oil. This suspension was then injected, using a 22 gauge needle, into the formed air pouch at a situs different from that of the air injection. All syringe needles were cleaned thoroughly with 70% ethanol between uses in successive animals. To insure accurate dosage, the phlogistic-agent suspension was continuously mixed with a magnetic stirrer. In all instances, air was removed 48 hours after formation of the pouch.

The compounds were administered orally in 1% aqueous pectin, initially at the time of introduction of the irritant and thrice subsequently at 24 hour intervals. The aqueous composition was administered to the animals at a constant volume of 1 ml. per 100 grams of body weight, and the triazine concentration was adjusted to provide the desired dosage level.

The animals were sacrificed 24 hours after the last administration, i.e., 4 days from the start of the test. The exudate formed in the pouch of each animal was removed and its volume measured. The percent inhibition of inflammation was determined as the quotient of: the average volume of exude of the control minus the average exudate volumeof the group of animals treated divided by the average volume of exudate of the control group of animals, multiplied by 100. The anti-inflammatory activities of a number of the compounds determined in this manner are shown in Table A. below. The higher the value of "Percent Inhibition," the more effective the test compound is as an anti-inflammatory agent. A "Percent Inhibition" value of 30% or greater indicates the presence of anti-inflammatory activity.

TABLE A.—ANTI-INFLAMMATORY ACTIVITIES OF 2,4-DIAMINO-6-(R)-s-TRIAZINE USING SEYLE POUCH ASSAY

Compound No.	R	Dose, mg./kg.	Percent inhibition
1	Methyl	100	58
		200	97
2	Ethyl	100	79
		50	7
3	Propyl	200	94
		50	73
		200	98
4	Iso-propyl	100	91
		50	49
		20	6
		200	98
5	Butyl	50	66
		20	21
		200	92
6	Iso-butyl	100	90
		50	58
		20	62
7	Secondary butyl	200	95
8	Tertiary butyl	200	92
9	Pentyl	200	94
		50	13
10	Hexyl	200	63
11	Heptyl	200	47
12	Octyl	200	42
13	Nonyl	200	32
		200	35
14	Decyl	100	21
		50	26
15	Undecyl	200	56
16	Pentadecyl	200	33
17	[2-phenylvinyl]	200	56
		200	86
18	Phenylmethyl	100	61
		100	40
19	p-Methoxyphenylmethyl	200	50
		200	98
20	p-Chlorophenylmethyl	100	91
		50	50
21	p-Biphenylmethyl	200	49
22	Phenethyl	200	24
23	Phenylpropyl	200	72

EXAMPLE XVIII

The compounds of this invention were tested for anti-inflammatory activity by a cotton pellet assay.

In this assay, cotton pellets weighing 10.0 mg. ±0.1 mg. are implanted in the lateral dorsal regions of adrenalectomized rats. An untreated control pellet is implanted on one side while the treated pellet is implanted on the other. The treated pellet contains 0.5 mg. of the test compound suspended in an aqueous medium containing, in grams per liter, 10 gm. of carboxymethylcellulose No. 70, 1 gram of polysorbate 80 U.S.P. (available as Tween 80 from Atlas Chemical Company). 1.8 grams of methyl-p-hydroxybenzoate, 0.2 gram of propyl-p-hydroxy-benzoate, and 0.15 gram of Methocel. At least 4 to 10 animals are included in each of the test and control groups.

After 4 days, the pellets were removed, dried in vacuo at atmospheric temperature and weighed. Reduction or inhibition of the formation of granulation tissue in the test pellets was determined as the difference between the weight of the control pellet and the weight of the test pellet in each case. The results were averaged for the respective groups and are reported in Table B below, using the compound identification code set forth in Table A. A reduction of granulation of at least about 1 mg. is an accepted indication of anti-inflammatory activity in this assay.

TABLE B

Anti-inflammatory activity as shown by cotton pellet assay

Compound No.:	Reduction in granulation (mg.)
1	1.5
2	0.0
3	—1.1
4	0.9
5	0.9
6	4.0
7	1.5
8	1.1
9	0.5
10	3.32
11	4.26
12	0.88
13	1.0
14	1.5
15	1.1
16	1.9
17	--
18	0.7
19	—0.48
20	—0.92
21	1.9
22	1.4
23	0.8

EXAMPLE XIX

Selected compounds of this invention were tested again for anti-inflammatory activity using the carrageenin edema test described by Winter et al. [Proc. Soc. Exp. Biol. Med., 111, 544 (1962)].

The compounds were administered in pectin suspension by gavage at a dosage of 100 mg./kg. to adult male Holtzman rats 1 hour before injection of 0.05 ml. of 1% suspension of carrageenin in sterile 0.9% sodium chloride solution into the plantar tissue of the right hind paw. Each drug was administered to a group of 6 rats. The volume of the injected foot was measured immediately and then again 3 hours later. The average increase in volume was calculated and compared with that of control animals which received pectin only before injection with 0.05 ml. of the 1% carrageenin suspension. The percent inhibition was then calculated for each drug in the manner described in Example XVII. A value of 20% or greater is indicative of anti-inflammatory activity in this assay.

TABLE C.—ANTI-INFLAMMATORY ACTIVITY AS SHOWN BY CARRAGEENIN ASSAY

	Dose, mg./kg.	Percent inhibition
Compound No.:		
4	100	24
5	200	22
6	100	48
9	100	24
14	200	28
15	100	39

Evaluation of the results of this particular assay are based on percent inhibition and it comprises: very active, 40% or greater; moderately active, 20–40%; relatively inactive, less than 20%.

EXAMPLE XX

2,4-diamino - 6 - cyclopentylmethyl-s-triazine prepared according to Example XVI was assayed for anti-inflammatory effect using the adjuvant air pouch protocol of Example XVII and the carrageenin foot edema protocol of Example XIX. In both assays, the compound was found to have significant anti-inflammatory activity. The results are shown in Table D.

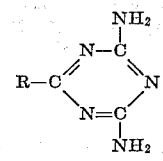
TABLE D

Assay	Dose, mg./kg.	Percent inhibition
Air pouch	200	98
Foot edema	200	39

From the foregoing, it becomes apparent that new and quite remarkable pharmaceutical preparations have been herein described and illustrated which have the surprising ability when administered to a host to relieve inflammatory conditions while avoiding steroid side effects. It is, of course, understood that the artisan confronted with this disclosure will contemplate various alterations, modifications and applications all of which are intended to be encompassed within the spirit of this invention especially as it is defined by the scope of the claims appended hereto.

What we claim is:

1. A pharmaceutical preparation in unit dosage form selected from the group consisting of tablets, filled capsules, packets, lozenges, troches, solutions, suspensions, emulsions, ointments, suppositories and soft gelatin capsules and having, when administered to a host with an inflammatory condition, an anti-inflammatory activity, said preparation comprising a pharmaceutically acceptable carrier and from about 1 mg. to about 2000 mg. of a member selected from the group consisting of a triazine compound having the structure shown below and a non-toxic pharmaceutically acceptable acid salt thereof said structure being



wherein R is selected from the group consisting of primary alkyl, secondary alkyl, tertiary alkyl, in which each of said alkyl has from 1 to 15 carbon atoms, and $R'(CH)_n$ wherein R' is selected from the group consisting of phenyl, diphenyl, chlorophenyl, and methoxyphenyl, and *n* is a cardinal number having a value of from 1 to 4.

2. A preparation according to claim 1 in dosage form for topical administration.

3. A preparation according to claim 2 containing from about 50 mg. to about 1000 mg. of said triazine compound or its non-toxic pharmaceutically acceptable acid salt.

4. A preparation according to claim 3 in dosage form for administration by a route selected from the group consisting of intramuscular, intravenous, subcutaneous, and pancaval, including oral.

5. A preparation according to claim 1 in which said compound is 2,4-diamino-6-iso-butyl-s-triazine.

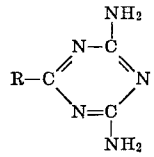
6. A preparation according to claim 1 in which said compound is 2,4-diamino-6-methyl-s-triazine.

7. A preparation according to claim 1 in which said compound is 2,4-diamino-6-cyclopentylmethyl-s-triazine.

8. A preparation according to claim 1 in which said compound is 2,4-diamino-6-ethyl-s-triazine.

9. A preparation according to claim 1 in which said compound is 2,4-diamino-6-propyl-s-triazine.

10. The method of treating inflammatory condition of a host including man comprising administering to said host from about 1 mg. to about 2000 mg. of a compound having the structure



wherein R is selected from the group consisting of primary, secondary and tertiary in which said alkyl has from 1 to 15 carbon atoms, and $R'(CH)_n$ wherein R' is selected from the group consisting of phenyl, diphenyl, chlorophenyl, and methoxyphenyl, and *n* is a cardinal number having a value of from 1 to 4.

11. The method of claim **10** in which said compound is administered subcutaneously, pancavally, intromuscularly or intravenously in an amount of from about 50 mg. to about 1000 mg. per day.

12. The method of claim **10** in which said compound is administered topically in an amount of at least 1 mg. per day.

13. The method of claim **10** in which said compound is 2,4-diamino-6-alkyl-s-triazine wherein said alkyl is primary, secondary or tertiary and contains from 1 to 15 carbon atoms.

14. The method of claim **13** in which said compound is 2,4-diamino-6-isobutyl-s-triazine.

15. The method of claim **13** in which said compound is 2,4-diamino-6-cyclopentylmethyl-s-triazine.

16. The method of claim **13** in which said compound is 2,4-diamino-6-methyl-s-triazine.

17. The method of claim **13** in which said compound is 2,4-diamino-6-ethyl-s-triazine.

18. The method of claim **13** in which said compound is 2,4-diamino-6-propyl-s-triazine.

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