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3,154,546

METHENAMINE UNDECYLENATE AND
METHOD OF PREPARATION

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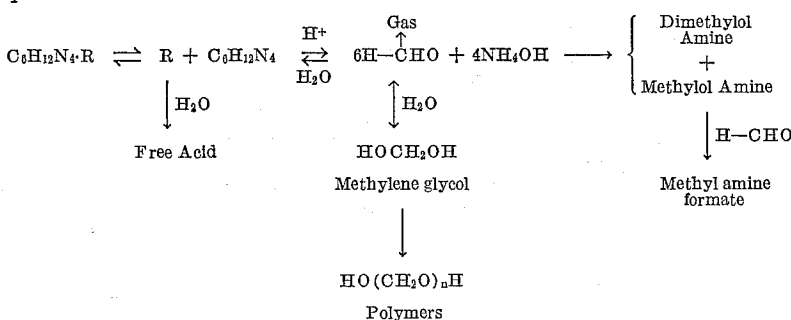
4 Claims. (Cl. 260-248.5)

The present invention relates to a new compound which has been found to be particularly suitable for use in treating fungal and bacterial dermatological infections. The invention also provides a process for preparing this new compound as well as a therapeutic method for its use in the treatment of topical infections. This application is a continuation-in-part of my copending application Serial No. 855,964, filed November 30, 1959, now abandoned.

In treating topical infections and especially those of fungal origin, an important problem results from the fact that the therapeutic agent which is active against relatively undifferentiated organisms is usually also a protoplasmic poison which in sufficient concentration itself serves to aggravate an already insulated area. Any mechanism therefore which will provide a controlled release of active agents will not only counteract the undesirable organisms but also enable more rapid healing. This consideration is particularly important when the patient has been rendered more susceptible to therapeutic trauma by reason of an underlying complication such as diabetes.

It has now been found that methenamine undecylenate, which is the new compound of the present invention, is capable of exerting a pronounced drying effect on a topically infected area and is therefore particularly well suited for the topical treatment of fungal or bacterial dermatological infections. Bound and inactive in the dry state, methenamine undecylenate is non-toxic, non-irritating and may be topically applied to sensitive skin.

In the presence of body moisture activation of methenamine undecylenate occurs with the hydrolytic liberation of undecylenic acid and methenamine. The alkaline portion of the molecule, methenamine, is further hydrolyzed with the gradual release of active therapeutic agents, as schematically illustrated in the following reaction sequence:



where R equals the undecylenate moiety. As the local hydrogen ion concentration of the skin varies, either toward the acid or alkaline side (in the presence of moisture) minute amounts of formaldehyde gas are released. Upon release, formaldehyde, in low concentration, has deodorant, bacteriostatic and fungistatic properties, and achieves an adhesive quality by virtue of a mild protein precipitation. The remaining hydrolytic products are all believed to function as active agents as well as sources of active agents to be released when attacked by nitrogen requiring organisms.

In general, formulations containing from 2 to 15 percent of methenamine undecylenate are preferred although concentrations of from about 0.1 to about 20 percent are useful.

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Methenamine undecylenate may be obtained by reacting methenamine with undecylenic acid, preferably in the presence of a solvent, and then recovering the methenamine undecylenate from the reaction product, such as by evaporating the solvent under vacuum or freeze drying. Alternatively, the methenamine undecylenate may be prepared merely by directly triturating methenamine with undecylenic acid, in the presence of ammonium hydroxide.

The antibacterial activity in vitro of methenamine undecylenate was established by the serial dilution method, in which methenamine undecylenate is solubilized in either ethanol or in broth and brought up to volume with tryptose phosphate broth. Starting concentrations were 5000 gamma per ml. and were diluted, appropriate controls being used. The resulting antibacterial inoculum may be described as 0.1 ml. of a 1:1000 dilution of an 18 hour tryptose phosphate broth culture of the test organism. Incubation was maintained at 37° C. for 48 hours. The resulting minimal inhibitory concentration (in gamma per ml.) follows:

TABLE I

Organism:	Methenamine undecylenate
<i>E. coli</i> -----	5,000
<i>S. aureus</i> -----	2,500
<i>P. vulgaris</i> -----	5,000
<i>Ps. aeruginosa</i> -----	2,500
<i>Str. fecalis</i> -----	2,500
<i>A. aerogenes</i> -----	1,250

The antifungal activity in vitro of methenamine undecylenate was established by plate tests, in which methenamine undecylenate was solubilized in either ethanol or broth and then incorporated into Sabourand's dextrose agar in the desired concentrations. The agar was allowed to solidify and was then streaked with a 10-15 day old test fungi culture. The inoculum streak was heavy. As before, the appropriate controls used in the effective test ranges were negative in antifungal activity.

The plates were incubated at room temperature and examined for the presence of growth after 72 hours and daily thereafter for a minimum observation period of 10 days.

The minimal inhibitory concentrations in gamma per ml. were as follows:

TABLE II

Organism:	Methenamine undecylenate
<i>M. andouini</i> -----	320
<i>T. mentagrophytes</i> -----	125
<i>A. fumigatus</i> -----	2,500
<i>E. floccosum</i> -----	1,250
<i>S. schenckii</i> -----	125
<i>P. ovale</i> -----	625
<i>M. canis</i> -----	5,000

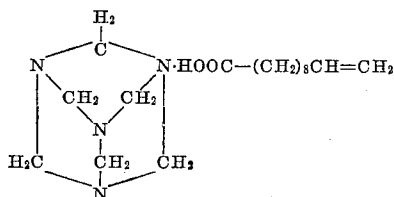
The following examples are presented in order to point out more clearly the manner of carrying out the invention,

but are not intended to limit its scope beyond that indicated in the claims.

Example I

184.27 grams (one mole) of undecylenic acid are dissolved in 500 ml. of a 28 percent solution of concentrated ammonium hydroxide, with agitation and at temperatures of between 0° C. and 25° C., it being preferred to carry out the reaction between 20° and 25° C. and the range of solution of concentrated ammonium hydroxide being 5 to 50 percent, with the higher percentage solutions of concentrated ammonium hydroxide being preferably employed at the lower portion of the temperature range above set forth. After the undecylenic acid is dissolved, there is added 140.19 grams (one mole) of solid methenamine and agitation continued until a clear solution is obtained. If all the methenamine has not been dissolved after two hours, there is added 25-ml. portions of water until the solution is obtained. It is then filtered to remove any extraneous materials. Water is removed by freeze-drying. The yield is 234 grams.

The structure of the resulting methenamine undecylenate is believed to be as follows:



The compound has the empirical formula $C_{17}H_{32}N_4O_2$ and analyzes to contain carbon 61.48%, hydrogen 10.05%, nitrogen 17.6% (calculated: carbon 62.91%, hydrogen 9.91%, nitrogen 17.27%). The compound appears as an off-white amorphous powder having an apricot odor.

Methenamine undecylenate is separate and distinct from its component moieties and present characteristics which are substantially different. A comparison follows:

TABLE III

	Mol. Wt.	M. P.	Appearance at room temp. (25° C.)	Odor	Solubility
Undecylenic acid.....	182.27	24.5° C.....	Yellow liquid.....	Suggestive of body perspiration.	Insol. in water.
Methenamine.....	140.19	Sublimes at 60° C. without melting and with partial decomposition.	White crystalline powder.	Practically orderless.....	Very soluble in water, alcohol, chloroform.
Methenamine undecylenate.....	323.46	Softens at 55-57° C.....	Off-white amorphous powder.	Apricot.....	Soluble in alcohol, chloroform, propylene glycol; moderate sol. in glycerine.

Therapeutically, methenamine undecylenate may be employed in a variety of forms employing known pharmaceutical carriers. They are applied topically to the site of bacterial or fungal infection. Examples of such formulations follow. In the following examples, all percentages are intended to refer to percentages by weight.

Example II

A 5 percent methenamine undecylenate powder may have the following formula:

	For 100 gms.
Methenamine undecylenate	5
Corn cellulose	12.5
Sodium lauryl sulfate	0.5
Perfume concentrate	0.5
Fine talc	81.5

The methenamine undecylenate is refrigerated prior to grinding and sifting (#60 mesh). The sifted powder is mixed intimately with the corn cellulose, sodium lauryl sulfate, and a portion of the talc in a mortar. The perfume oil is added gradually with trituration. An amount of talc equal in bulk to the mixture is added with tritura-

tion and the mixture is sifted (#20 mesh). The remaining talc is added and mixing is completed by shaking for a period of time. Before packing, additional sifting (#20 mesh) may be desirable.

Powders in useful form may contain from 0.5 to 20 percent by weight of methenamine undecylenate and from 99.5 to 80 percent by weight of talc. Instead of the pharmaceutical carriers mentioned, there may be used such inert carriers as starch, kaolin, wood filler, clay (such as bentonite), sodium carboxymethylcellulose, and zein.

Example III

An ointment with 5 percent by weight of methenamine undecylenate would have the following formula:

	For 100 gms.
Methenamine undecylenate	5
Perfume concentrate	0.5
"Polysorb" (sorbitan sesquieolate in a petrolatum-wax base "Morden Drug Encyclopedia," 7th Ed., p. 912)	94.5

The methenamine undecylenate, prepared as in the description for powders (Example II), is levigated with a portion of the "Polysorb." The perfume is added gradually to the ointment primary with levigation. The primary is completed in an ointment mill. Following the milling process, the remaining "Polysorb" is added with levigation.

Other pharmaceutical carriers by way of basis for the ointment formulation may be any one of the following:

- "Aquaphor" (99.5 to 80%) (group of alcohols and esters of cholesterol in aliphatic hydrocarbons, Mod. Drug Encyc., 7th Ed., p. 83)
- Petrolatum (94.5 to 75% with White Wax 5%)
- Polyethylene glycol ("Carbowax" 1580) (99.5 to 80%)
- Polyethylene glycol 300 (80% mixed with 20% "Carbowax" 4,000) (99.5 to 80%)
- Petrolatum (99.5 to 80%)

Example IV

A solution of methenamine undecylenate may employ the following formula:

	Percent
Propylene glycol	99.8 to 85
Methenamine undecylenate	0.2 to 15

Example V

For the propylene glycol there may be substituted any number of liquid pharmaceutical carriers among which may be included ethyl alcohol and glycerine, preferred formulations employing these liquid carriers consisting of 95 percent of the alcohol or glycerine, and 5 percent of methenamine undecylenate.

Example VI

Spray formulations may incorporate methenamine undecylenate as a 5 percent concentration together with isopropyl alcohol 5 percent, dichlorodifluoromethane 45 percent, and trichloromonofluoromethane 45 percent.

Example VII

To illustrate the ease and efficacy with which pharmaceutical preparations containing methenamine undecylenate may be used to treat fungal or bacterial dermatological infections in accordance with the invention, a series of clinical tests was conducted by a duly licensed physician to determine the effect of methenamine undecylenate (in both powder and ointment forms) in dermatological disorders commonly occurring in the diabetic patient and the patient with peripheral vascular disease.

A group of 73 patients was observed for periods of one to twelve months during the evaluation of the compound. The age range of the patients studied was from 17 to 76 years, and the group consisted of 38 females and 35 males. All of these patients were considered to be particularly vulnerable to dermatologic infection. The greater majority of the test group had previously been treated or maintained with other topical preparations including such common types as corn starch, talc and bland ointments, for dermatologic disorders associated with metabolic disorders (diabetes) or peripheral vascular disease. In this particular type of patient, the occurrence of symptoms such as excessive skin moisture, itching or burning discomfort, calls for immediate steps to prevent excoriation of the protective skin on the extremities.

After a thorough physical examination, each patient was instructed to use the powder or ointment of methenamine undecylenate to meet individual requirements. Since anhidrosis of the legs and feet in the diabetic patient is commonly observed, they were given the ointment form for application between the toes. Each patient was asked to report at regular follow-up visits when the therapeutic response would be evaluated.

Seventy-three patients were placed in two groups according to diagnosis as diabetic and non-diabetic. The diabetic group consisted of 53 patients, 27 female and 26 male, in an age range of from 17 to 76 years. Of these, 26 did not present active dermatologic lesions and were included for prophylactic therapy. Among the non-diabetic patients, there were 11 females and 9 males, with an age range of from 32 to 72 years. Most of the latter group were considered dermatologic "risks" due to the concomitant peripheral vascular disease and excessive moisture on the skin of the extremities. Experience has shown that such patients invariably require special care of the feet in order to prevent the more serious infections and ulceration of the extremities.

The criteria used in the evaluation of the response to therapy were as follows:

Complete clearing—rapid improvement of appearance resulting in an intact resilient skin.

Marked improvement—itching and burning relieved, drying of moist and excoriated areas.

Partial desquamation—considerable improvement, additional therapy required.

Slight improvement—slight change for better.

Aggravation—any irritation or excoriation due to drug.

Thirty-eight patients were treated with methenamine

undecylenate for various dermatoses. There was complete clearing in 12 patients (31.6%); marked improvement in 19 patients, (50%); partial desquamation in 5 patients, (13.2%) and little or no improvement in 2 patients, (5.2%). The drying effect of methenamine undecylenate was the remarkable feature of this type of therapy.

Among the 35 patients treated prophylactically with the ointment and/or powder, there was no complaint of undesirable side effects. An occasional patient observed a yellowish discoloration (superficial) after repeated applications of methenamine undecylenate. However, these discolorations promptly cleared when the test agent was discontinued. In all instances of prophylaxis, there was no infection of the extremities during the test period, which was from 2 to 12 months.

The results of these clinical tests conclusively demonstrate the unique drying effect exerted by methenamine undecylenate on topically infected areas. Formulations incorporating methenamine undecylenate in accordance with the present invention may be employed prophylactically for long periods without encountering either sensitization or irritation.

What is claimed is:

1. Methenamine undecylenate.
2. The method of preparing methenamine undecylenate which comprises combining equimolar quantities of undecylenic acid and methenamine in the presence of a solvent comprising an aqueous solution consisting of from 5 to 50 percent of concentrated ammonium hydroxide, and at a temperature of between 0° to 25° C. recovering methenamine undecylenate from the resultant reaction product.
3. The method of preparing methenamine undecylenate which comprises combining equimolar quantities of undecylenic acid and methenamine in the presence of a solvent comprising an aqueous solution consisting of from 5 to 50 percent of concentrated ammonium hydroxide, and at a temperature of between 0° to 25° C. recovering methenamine undecylenate from the resultant reaction product, and desiccating the resultant reaction product to recover methenamine undecylenate.
4. The method of claim 3, wherein the step of desiccating comprises freeze-drying.

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