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(54) Title: RUMEN PROTECTED ESSENTIAL AMINO ACIDS

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Use of essential amino acid imines and compositions containing them as a source of rumen protected essential amino acids for ruminant animals. Preferred are histidine and methionine.

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(54) Title: RUMEN PROTECTED ESSENTIAL AMINO ACIDS

(57) Abstract: Use of essential amino acid imines and compositions containing them as a source of rumen protected essential amino acids for ruminant animals. Preferred are histidine and methionine.

TITLE: RUMEN PROTECTED ESSENTIAL AMINO ACIDS**FIELD OF THE INVENTION**

5 This invention relates to a rumen stable bioavailable dietary supplement for ruminant animals to provide in bioavailable form essential amino acids, preferably histidine and methionine. It represents a specific improvement over the bypass rumen product of prior U.S. Patent No. 5,885,610 to Anderson, owned by the common Assignee.

10 BACKGROUND OF THE INVENTION

It is well known that ruminants are in need of bioavailable essential amino acids in order to perform well as domesticated livestock. In this regard, if the animal, for example a dairy cow, does not have its minimum requirements of essential amino acids such as lysine and methionine, the animal will not produce milk at optimum yield, and its health may be 15 in general decline.

Providing essential amino acids to ruminants is not as simple as it sounds. For example, the bacteria in the rumen of a cow are known to routinely degrade amino acid sources, like lysine and methionine. Put another way, the bacteria in the rumen metabolize the amino acid source and thus "rob" the animal of the benefit of the amino acid. By the 20 time metabolized byproduct passes from the rumen into the intestine, the amino acid is gone. The challenge, therefore, is to develop products which will allow the amino acid to be stable in the rumen, but capable of absorption when it passes from the rumen into the intestine. In other words, the essential amino acids, such as lysine and methionine, need to be bioavailable only in the intestine, and remain stable and therefore not metabolized in the 25 rumen.

In the past, this problem has been recognized, and feed developers have used fats, minerals, carbohydrates and binders to protect amino acids from rumen degradation. This technology involves simple coating of the material in hopes that the coated amino acid is rumen stable. Recently, Rhone Poulenc has provided a pH-sensitive polymer coating. The 30 theory of a pH-sensitive polymer coating for the amino acid revolves around the pH differential between the rumen and the intestine. The rumen, for example, typically has a

pH of 5.5 to 7.0, and the intestine a pH of 2-3. The theory of polymer-coated essential amino acids is that something which is stable as a coating at 5.5 to 7.0 (the rumen pH), but will solubilize at more acid pH's of the intestine (pH 2-3), should be stable in the rumen, but available in the intestine.

5 Both technologies used in the past, i.e. coatings, such as fat coatings, and the more recently developed pH-sensitive polymer coatings, have met with limited success and have some problems. The primary problem with any product relying upon coatings of any kind for rumen stability is that the coating can become abraded during handling and during chewing by the animal. If the process handler disturbs the coating, then the amino acid
10 becomes available to microbes in the rumen and consumed, and therefore wasted by the animal. Likewise, if the animal abrades the coating during chewing, it then becomes available in the rumen for rumen bacteria to metabolize, and is therefore also wasted to the animal. Additionally, fat-protected or coated essential amino acids rely upon the fat
15 resistance to enzymes in the rumen that are capable of digesting the protective fat coat, and, on the other hand, the ability of digestion by enzymes post-rumenally. However, if there is not a proper balance between resistance to attack in the rumen and digestion in the intestine, then the amino acid benefit to the animal may be lost.

From the above description, it can be seen that there is a real and continuing need for the development of products for delivery of essential amino acids to ruminant animals
20 in a form that allows the material to be rumen stable, i.e. resistant to degradation in the rumen, but yet after delivery from the rumen to the intestine, highly absorbable and bioavailable in the intestine. It is a primary objective of this invention to improve upon available products to fulfill this need safely, effectively, efficiently and at low cost.

In the prior Zinpro Corporation patent by Michael Anderson, it was discovered that
25 calcium or magnesium complexed salts of certain amino acids could be used to prepare a bypass rumen product. This invention takes a different attack on the problem with specificity of improving the availability of essential amino acids in ruminants.

Lysine is an essential amino acid in the diet of mammals. That is, lysine cannot be synthesized by mammals at a rate adequate to meet metabolic requirements and so must be
30 supplied in the diet. Corn (*Zea mays L.*) is notoriously low in lysine and, if used in a single grain ration, requires lysine supplementation both to maintain animal health and to achieve

economical animal growth. Protected lysine imine derivatives are disclosed in copending, concurrently filed, commonly assigned case, Stark et al. entitled RUMEN PROTECTED LYSINE.

The present invention extends the above referenced technology to other limiting and/or essential amino acids, by forming compounds which are essentially immune to attack by the microbes in the rumen but can still be digested and absorbed through the intestine wall to allow a highly bioavailable form of essential amino acids that are surprisingly immune from rumen organism attack. Structures of the compounds prepared are centered around the imine of the essential amino acids (Schiff's base).

10 In the past, there have been some alpha imine and epsilon imine derivatives of lysine investigated for biologically available active derivatives for rats. See for example, Finot, *N-Substituted Lysines As Sources of Lysine in Nutrition*, Adv. Exp. Med. Bio. 1978; 105:549-570; Nutritional Improvement of Food and Feed Proteins, edited by Friedman, published at Plenum, New York, and Finot et al., *Availability of the true Schiff's bases of lysine. Chemical Evaluation of the Schiff's Base Between Lysine and Lactose in Milk*, Adv. Exp. Med. Biol. 1977; 86B:343-365. The first Finot article concludes that the biological availability of derivatives were four to seven times less reactive than free lysine in the Maillard reaction and could therefore be subjected to heat. The second article deals with chemical evaluation of the Schiff's base between lysine and the lactose in milk. There 20 is no teaching in either article of any compounds having usefulness of providing stability of lysine derivatives in the rumen or providing compounds which can be successfully absorbed through the intestine after passing through the rumen to assure that lysine will be available to the animal for diet supplementation of this important essential amino acid. There is also no teaching relating to other essential amino acids beyond lysine.

25 It is therefore another primary objective to provide diet supplements of ruminants to provide essential amino acid supplementation for animals that often use as a major grain ration corn (known to be notoriously low in lysine and methionine). As a result, overall economic growth of the animal can be enhanced, and enhanced in a manner which assures that the expense of essential amino acid supplementation will go to the animal and not be 30 "robbed" (so to speak) by the microbes in the rumen as the material passes through the rumen.

The method of achieving the above objectives with certain chemical structures premised around imine (Schiff's base) of the essential amino acids is another primary objective of the invention.

Yet another objective of the present invention is to provide compounds which can 5 be utilized to achieve successfully a rumen bypass an essential amino acid supplement that does not rely upon encapsulation and one which employs compounds that are easily processible in feed forms.

A still further objective is to provide methionine and histidine and other essential amino acid supplements that are rumen protected.

10

BRIEF SUMMARY OF THE INVENTION

Use of essential amino acid imines and compositions containing them as a source of rumen protected essential amino acids for ruminant animals. Especially preferred embodiments are methionine and histidine.

15

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The basic concept in preferred form relates to the imine (Schiff's base) of essential amino acids and some of their derivatives and salts. It could be the imine variety produced from aldehydes or ketones, and any one of the essential amino acids. It could be the imines 20 produced from aldehydes or ketones and the amino acid methionine or histidine. It could also be the imines from aldehydes or ketones and salts, ester or complexes of these essential amino acids. In other words, the invention recognizes the imines of the alpha amino group as rumen resistant sources of the essential amino acids, and modification of other functional groups can be made, if one wishes, or not made if one wishes.

25 In the ruminant animal, ingested feed first passes into the rumen where it is partially broken down by bacterial fermentation. During rumen fermentation, rumen microbes utilize nitrogen from nitrogen compounds that they have degraded to form microbial protein. Nitrogen sources for rumen microbes include rumen degradable protein and peptides, free amino acids and urea. Microbial protein and undegraded feed protein pass to 30 the abomasum and small intestine where hydrochloric acid and mammalian enzymes degrade microbial protein and undegraded feed protein to free amino acids and short

peptides. The amino acids and short peptides are absorbed in the intestine, and the ruminant animals utilize the amino acids for synthesis of protein to sustain life, grow, reproduce and produce milk. However, if the amino acid, such as lysine or methionine or histidine, has been metabolized by rumen microbes, its value to the host animal is lost.

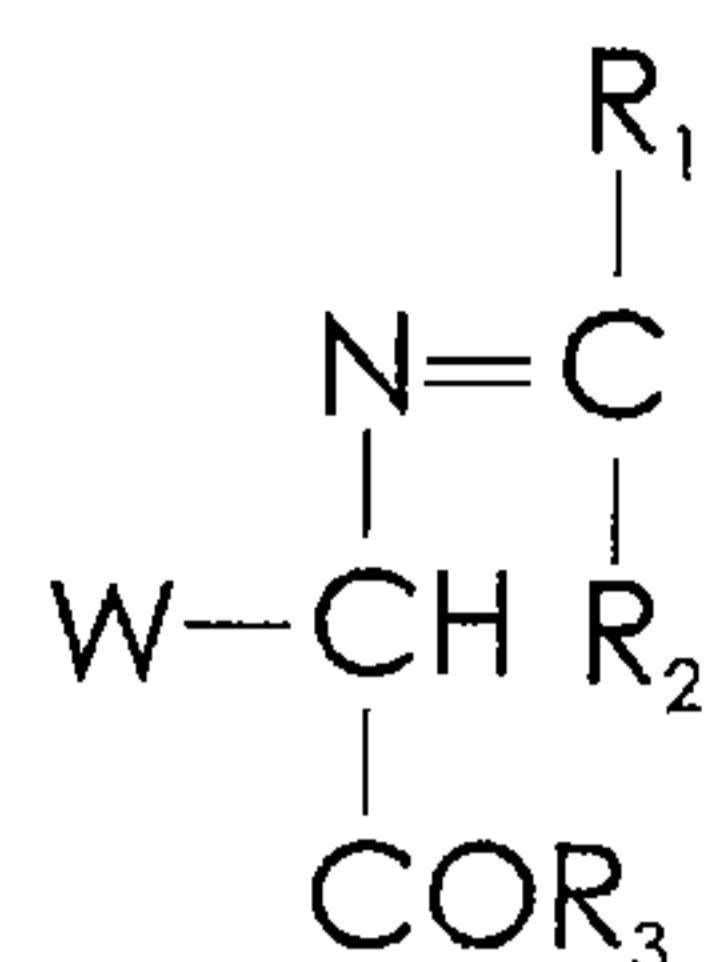
5 Of the twenty or more amino acids utilized by the animal to synthesize proteins, nine are considered to be essential. Examples of the essential amino acids include leucine, isoleucine, valine, methionine, threonine, lysine, histidine, phenylalanine and tryptophan. Essential amino acids are those amino acids which are required in quantities exceeding amounts produced by the animal, and must be supplied by microbial protein or rumen
10 undegraded protein. Amino acids supplied in excess are degraded by the animal and excreted in the form of urea. The process of synthesizing urea from ammonia is a process requiring energy input from the animal. If certain essential amino acids are not provided in adequate amounts, the animal will be limited on the amount and types of protein it can produce, thus limiting animal performance. Supplying the proper amounts of essential
15 amino acids therefore maximizes animal performance while enhancing efficiency of energy utilization by the animal.

Lysine and methionine are two of the most limiting essential amino acids when corn-based rations are fed. Results from studies also indicate that milk protein content is the most sensitive of the production variables (yield of milk, fat-corrected milk, milk
20 protein, milk fat, and content of milk fat and protein) to alterations in amino acid content of duodenal digesta. Researchers have determined, by infusing incremental amounts of the limiting amino acids into the duodenum of lactating dairy cows, that the required contribution of lysine and methionine to total essential amino acids in duodenal digesta for maximum milk protein content approximated 15% and 5.2%, respectively.

25 This present invention relates to essential amino acid imines as the most preferred, including some of the essential amino acids such as methionine and histidine. While this case preferably deals with methionine and histidine and their derivatives and salts, other alpha amino acids containing an alpha amino group may also be employed.

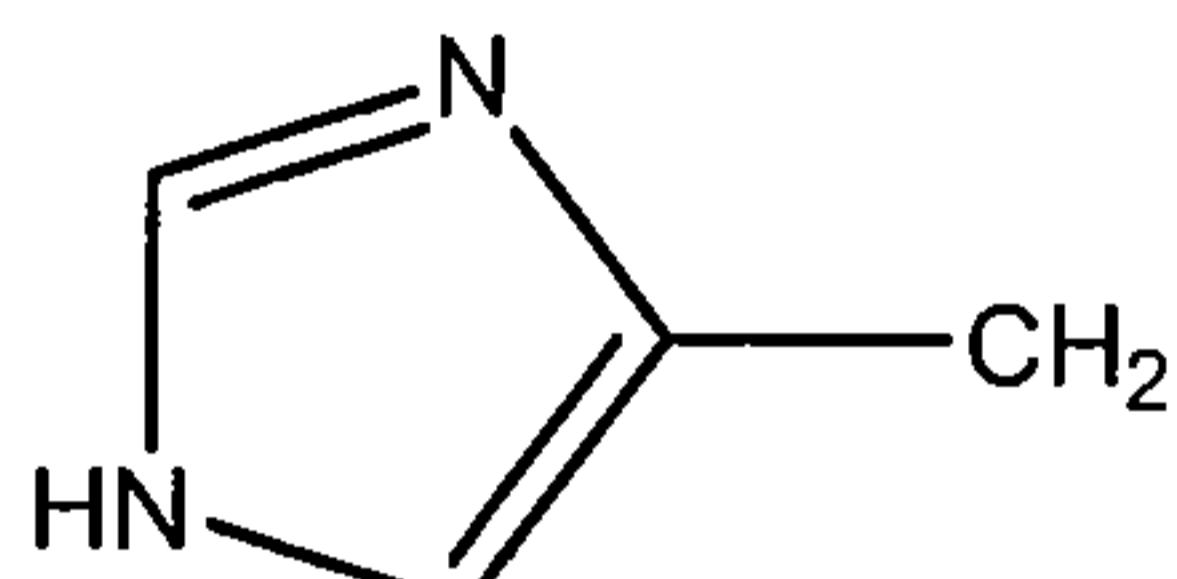
Compositions of the present invention which are rumen stable but intestine soluble
30 for supplementing the diet of ruminants with a source of rumen protected essential amino acids can generally be described as dietary supplement compositions that are imines

(Schiff's base) of the alpha amine moiety. They can be an imine from a variety of aldehydes or ketones as evidenced by the examples below. The amino acid portion of the molecule could also be salts or esters or amides of the carboxylate group. Generally speaking, the composition will contain a diet supplementing effective amount of an imine 5 of the formula:



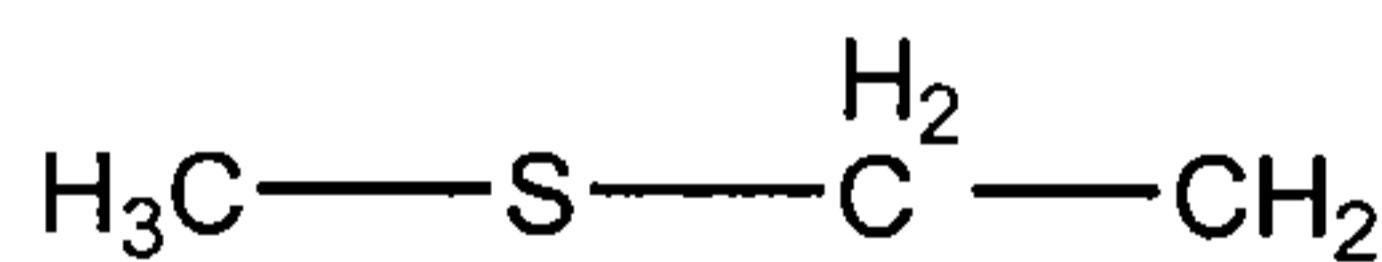
(STRUCTURE 1)

W represents the remaining portion of an essential amino acid and can be selected 10 from the group derived from leucine, isoleucine, valine, methionine, threonine, lysine, histidine, phenylalanine and tryptophan. It preferably is from histidine or methionine in which case W is:



(histidine)

15 or



(methionine)

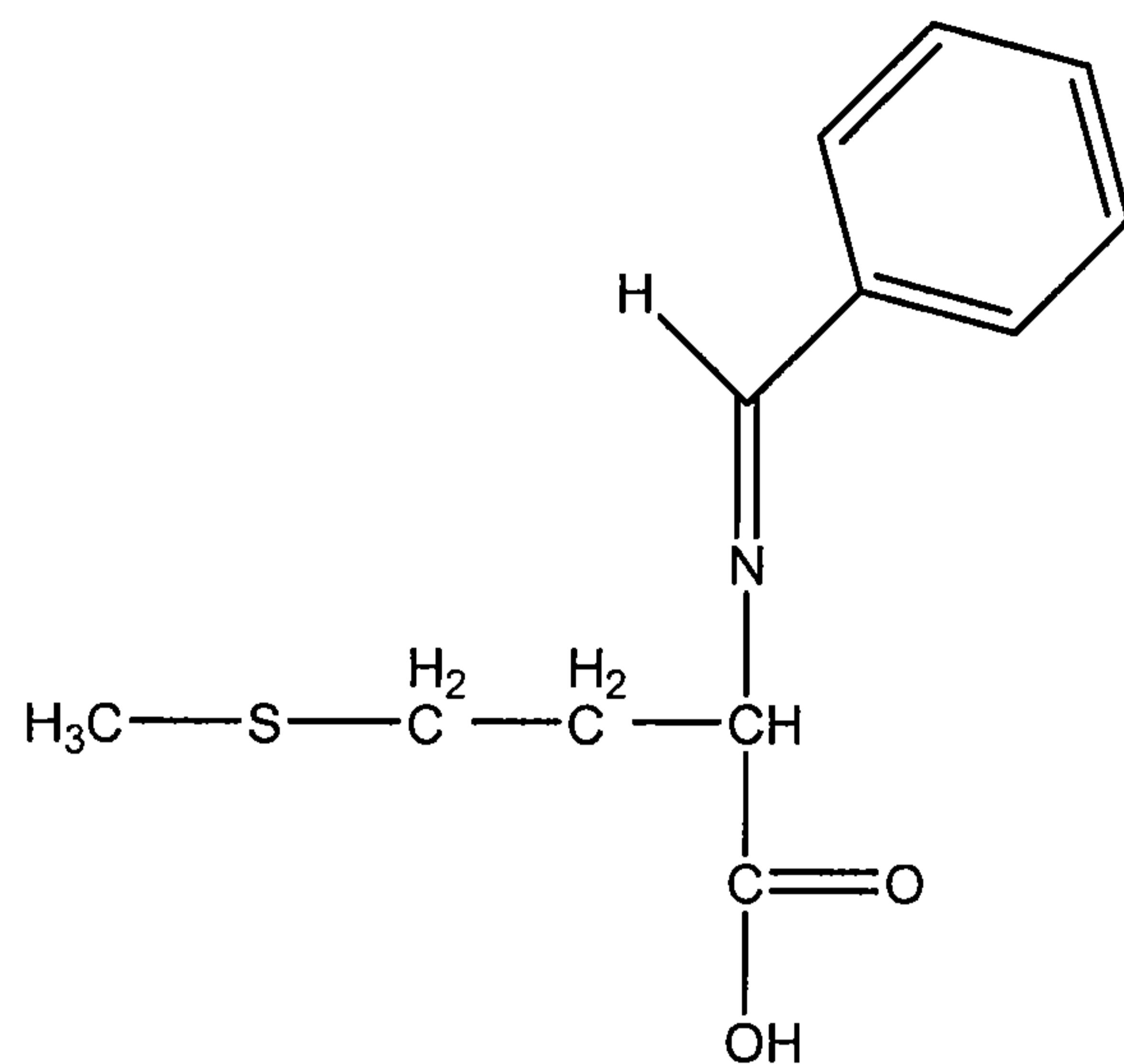
It goes without saying that the carboxylic acid moiety can be the acid itself or functional 20 substituted derivatives such as salts, amides, esters, etc.

In the formula, the R₁ and R₂ moiety can be the same or different and can be selected from the group consisting of hydrogen, aliphatics, aromatics, and cyclic moieties. R₃ can be -OH, or as previously indicated an ester producing moiety or a salt producing moiety or an amide producing moiety or a complex producing moiety, etc. The preferred 25 structures are those wherein R₁ is hydrogen and R₂ is an aromatic, and R₃ is -OH. As R₃ -

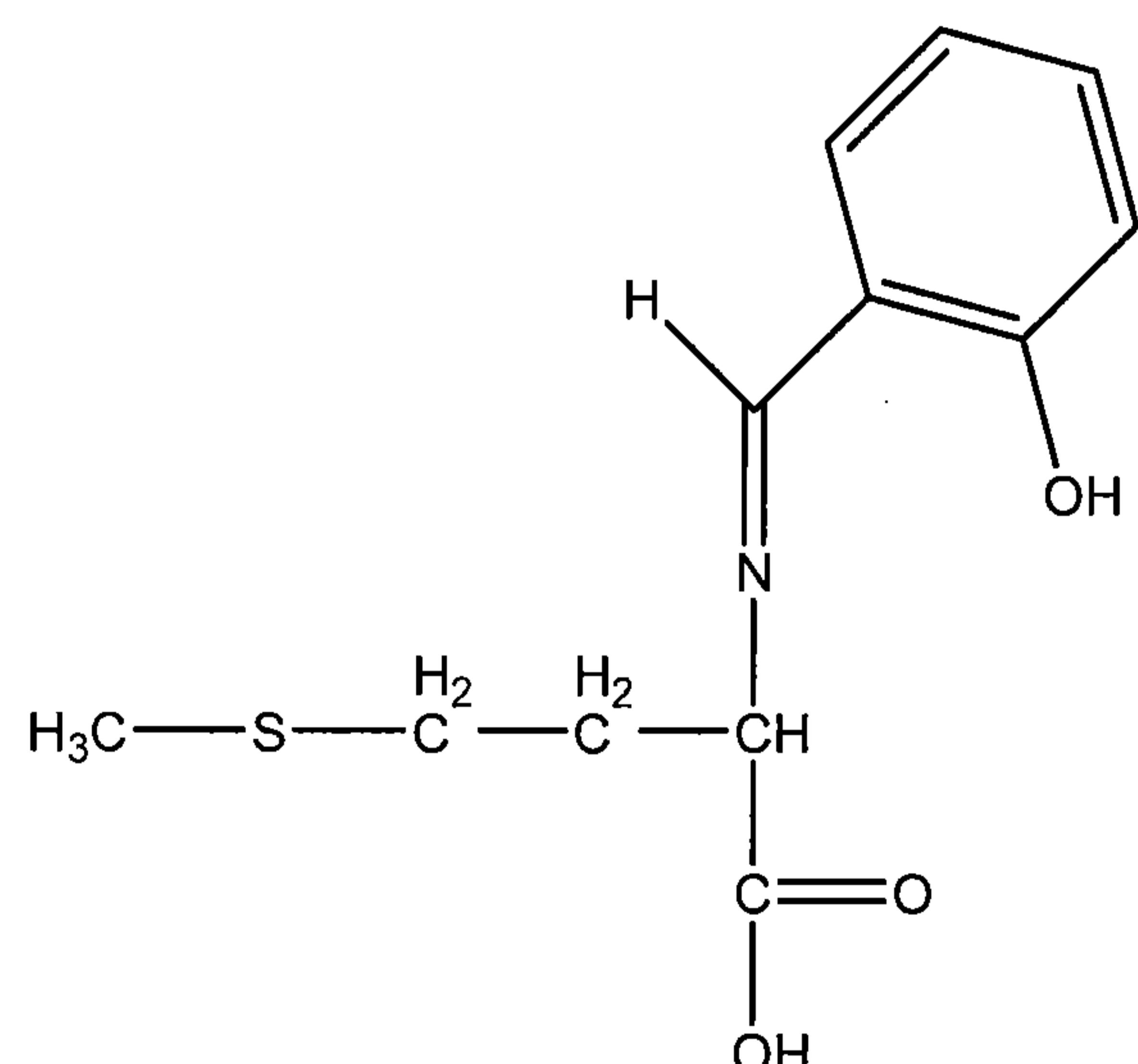
OH is preferred, but it is mentioned herein that the scope of the invention includes other moieties as listed, primarily so that someone simply cannot substitute essentially any other moiety and still achieve the benefit of the invention and argue non-infringement.

The preferred moieties at the R₁ and/or R₂ position are those formed from use as a reactant Benzaldehyde, Salicylaldehyde, cinnamaldehyde, or vanillin to prepare the most preferred compounds falling within the generic formula of structure 1 as herein set forth. These are shown below.

For Methionine:

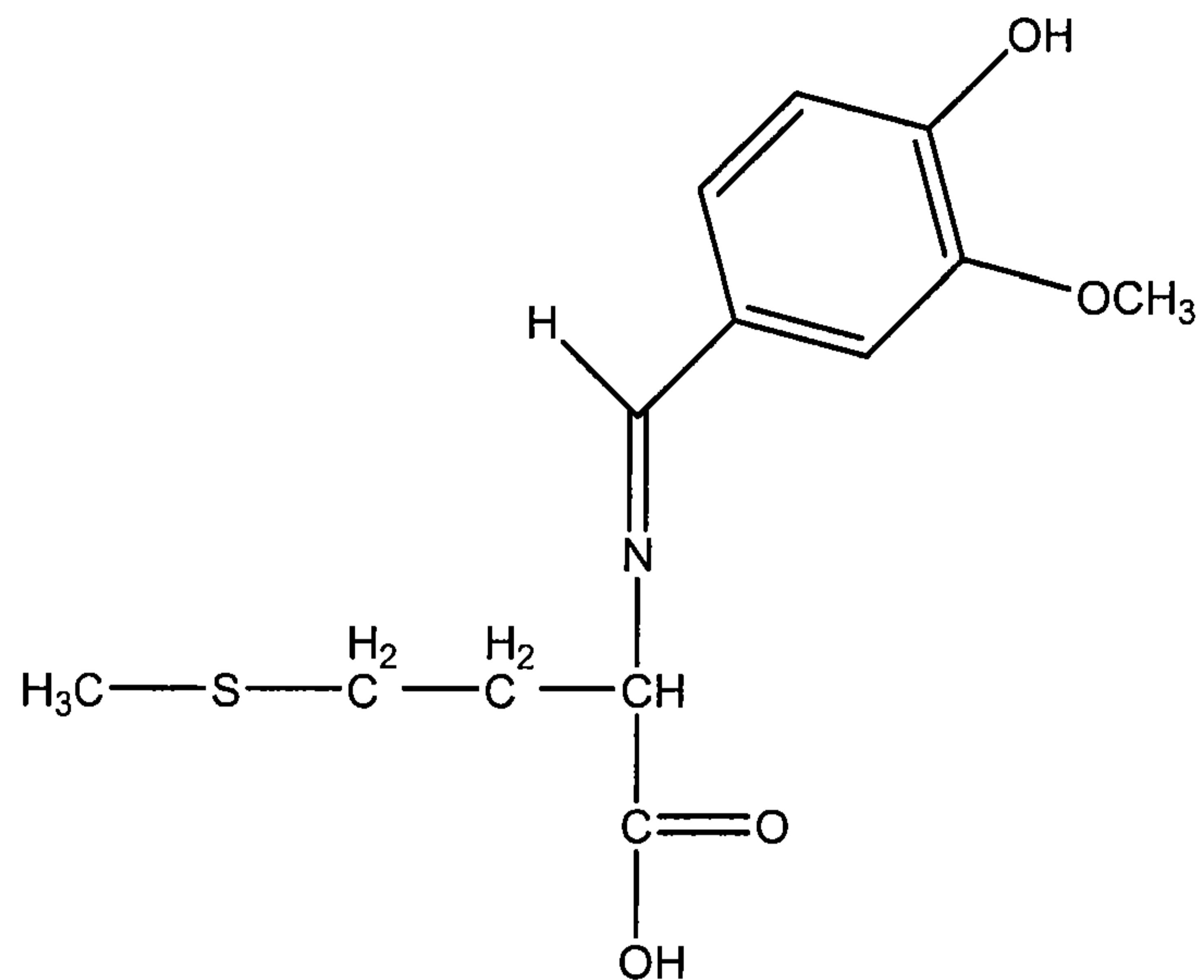


From Benzaldehyde

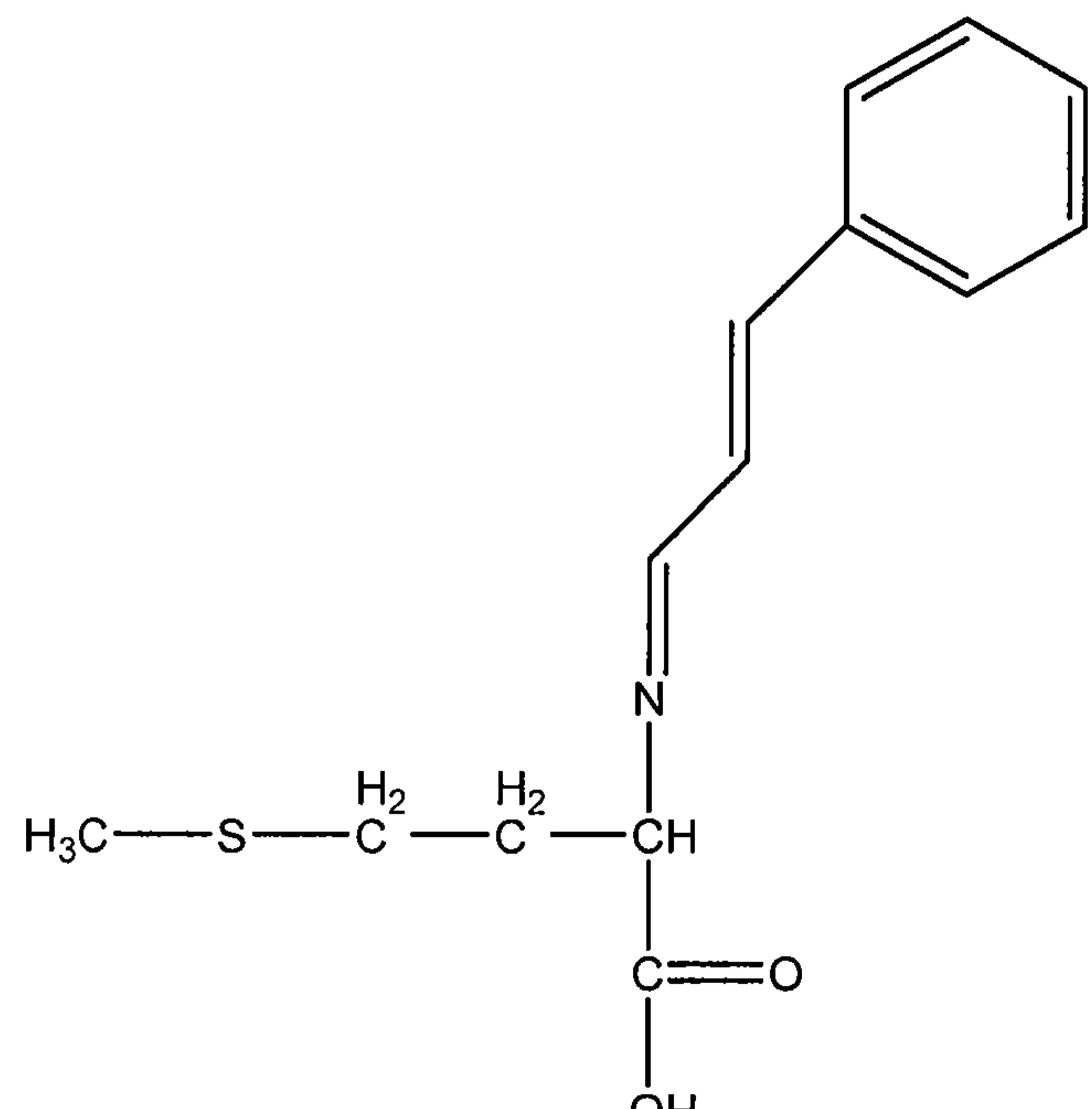


5

From Salicylaldehyde



From Vanillin

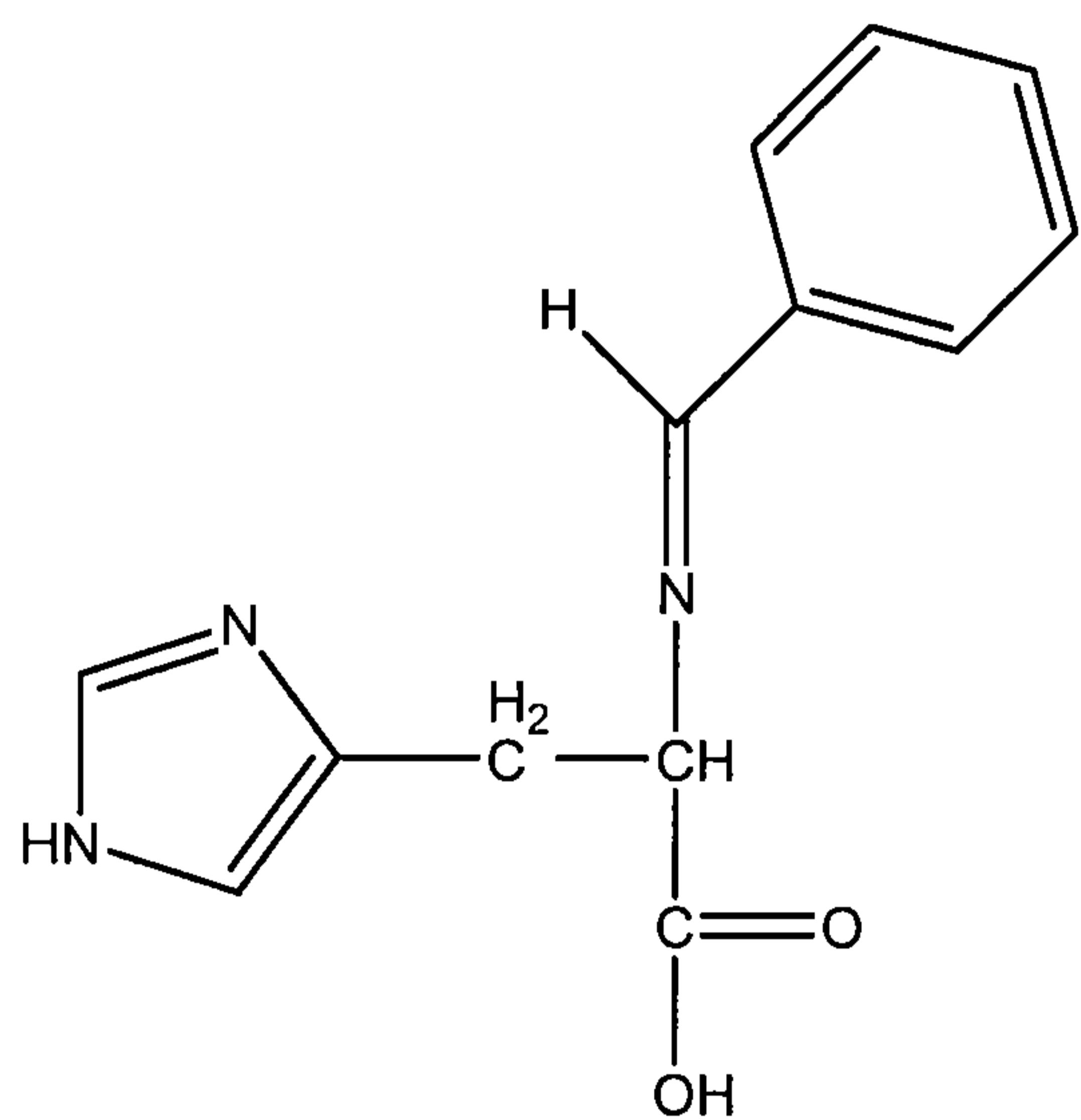


5

From Cinnamaldehyde

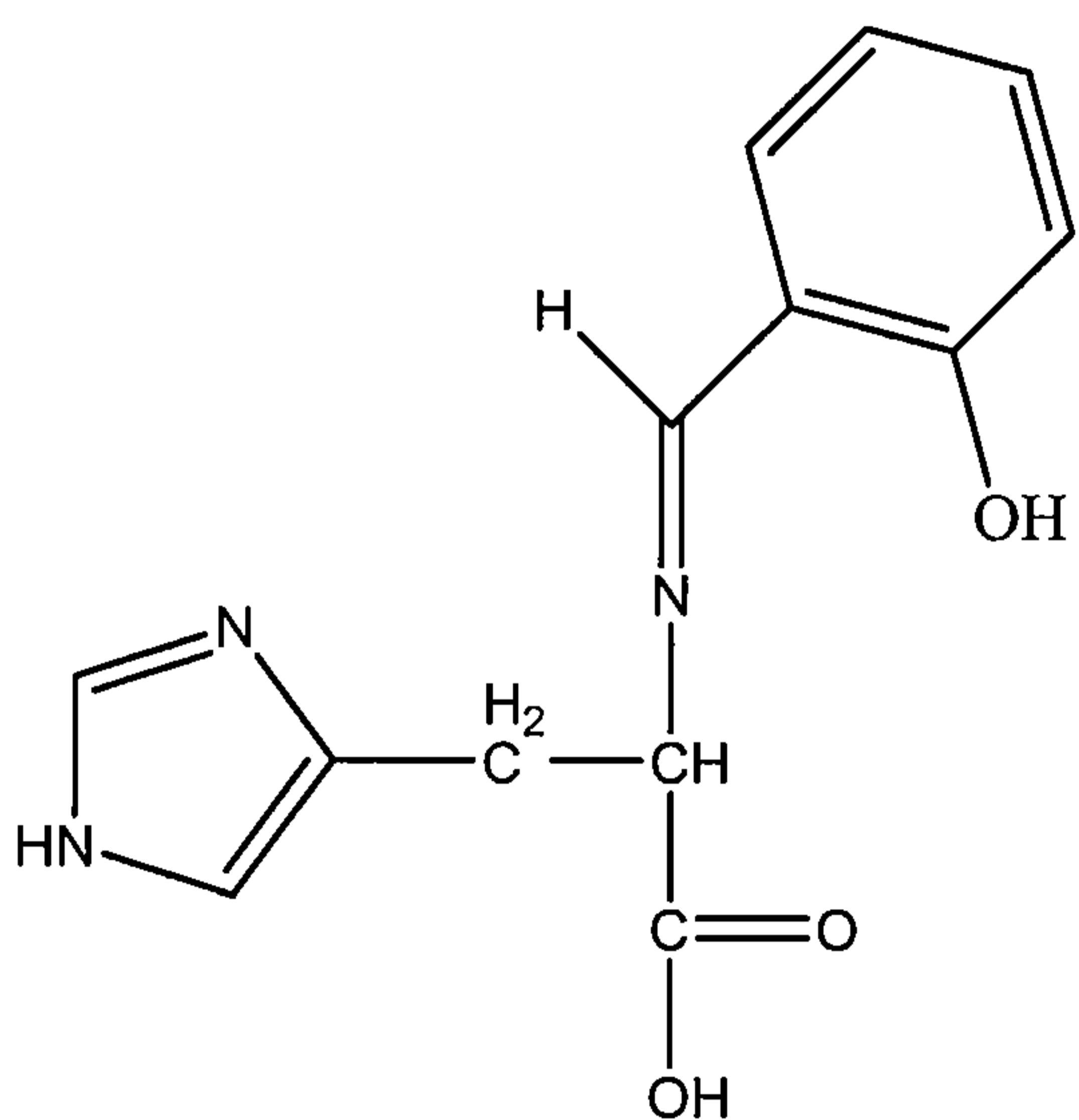
10

For Histidine:



From Benzaldehyde

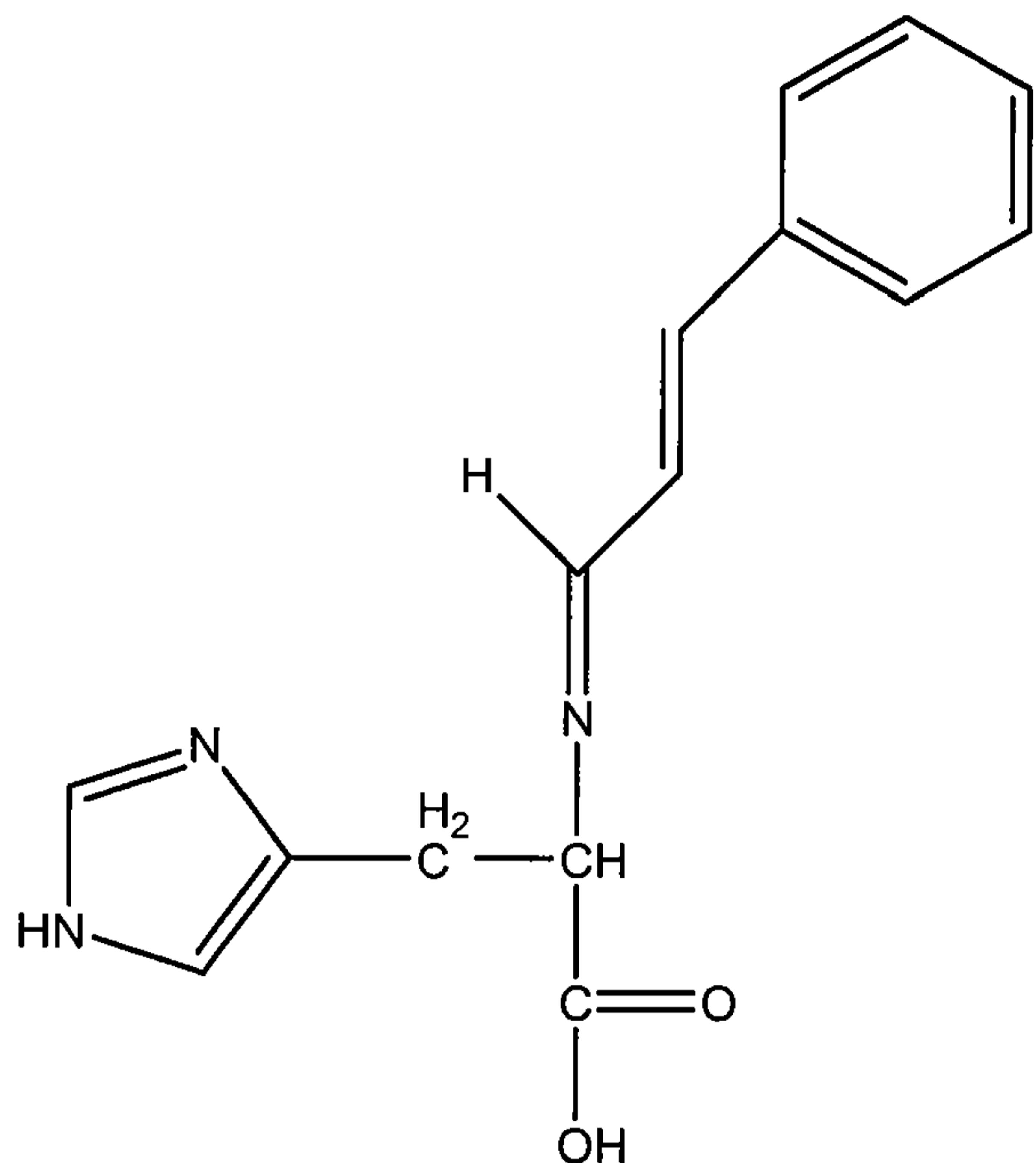
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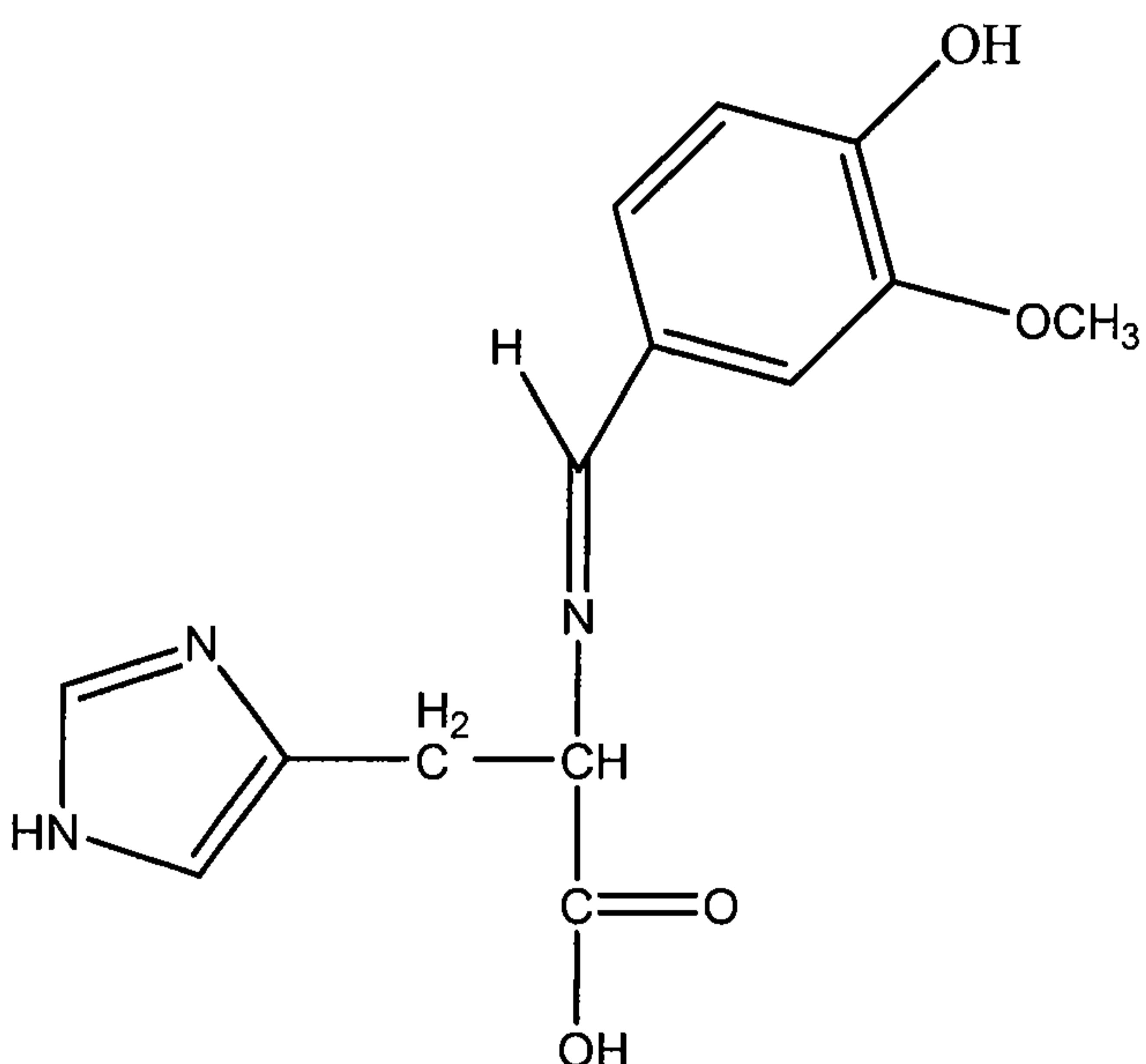
From Salicylaldehyde

10

10



From Cinnamaldehyde



From Vanillin

The compounds prepared above and especially those listed as preferred are easily processable. They can be sold and subdivided as a supplementing additive or they can be mixed with carriers to improve packaging, processability, and taste. Preferred carriers are, for example, powdered sugar which significantly improves taste for the ruminants that 5 ingest the same. For example, the Benzaldehyde derivatives have an almond taste which can be masked with powdered sugar.

While it is preferred that the compounds of the present invention be added without additional carriers or filler material, as heretofore mentioned flavorants can be used as or with the carrier. If carriers are employed, the carrier can be suitable carriers such as 10 distillers fermentation solubles, feed grains, corn cob flour, whey, or other cellulosic carrier materials. They can also be added at the same time as trace mineral preparations are added. In other words, they can be mixed with other nutritional ingredients.

The amount of supplement added to the feed ration will vary, of course, depending on whether one is using the pure compositions or the composition with a carrier. Basically 15 the supplement will simply mix with the feed ration, as sold.

Generally the imines should be added at a level to provide sufficient essential amino acid for the animals daily nutritional needs, i.e., within the range of about 1 gram to about 50 grams per animal per day.

The following examples illustrate the preparation of the imine (Schiff's base) of 20 lysine, methionine and histidine of the present invention and illustrate a variety of different moieties that may be attached at the R₁ through R₃ position.

EXAMPLE 1:

Preparation of N-Benzylidene-L-Lysine from lysine hydrochloride and benzaldehyde.

25 Lysine hydrochloride (4.8 gr, 26.3 mmol) was dissolved in 35 mL of water. NaOH (1 gr, 26.3 mmol) was added to the mixture which was cooled with an ice batch. To this mixture was added benzaldehyde (2.8 gr, 26.3 mmol) and the product precipitated in about 10 minutes. The mixture was filtered and washed with water. The solid was dried to yield 30 about 5.2 gr of a white solid.

EXAMPLE 2:**Preparation of 2-amino-6-((E)-3-phenylallylideneamino)hexanoic from lysine hydrochloride and trans cinnamaldehyde.**

5 Lysine hydrochloride (4.2 gr, 23 mmol) was dissolved in 30 mL of water. NaOH (0.91 gr, 23 mmol) was added to the mixture which was cooled with an ice batch. To this mixture was added trans cinnamaldehyde (3.0 gr 23 mmol) and the product precipitated in about 10 minutes. The mixture was filtered and washed with water. The solid was dried to yield about 4.9 gr.

10

EXAMPLE 3:**Preparation of 2-amino-6-(4-methoxybenzylideneamino)hexanoic acid from lysine hydrochloride and 4-hydroxy-3-methoxybenzaldehyde.**

15 Lysine hydrochloride (2.2 gr, 12 mmol) was dissolved in 25 mL of water. NaOH (0.48 gr, 12 mmol) was added to the mixture which was cooled with an ice batch. To this mixture was added 4-methoxybenzaldehyde (1.6 gr, 12 mmol) and the product precipitated in about 10 minutes. The mixture was filtered and washed with water. The solid was dried to yield about 2.6 gr.

20

EXAMPLE 4:**Preparation of 2-amino-6-(octylideneamino)hexanoic acid from lysine hydrochloride and octylaldehyde**

25 Lysine hydrochloride (2.7 gr, 14.8 mmol) was dissolved in 100 mL of water. NaOH (0.59 gr, 14.8 mmol) was added to the mixture which was cooled with an ice batch. The pH was adjusted to between 4-5 by the addition of acetic acid. To this mixture was added octylaldehyde (1.9 gr, 14.8 mmol) and the product precipitated in about 10 minutes. The precipitate agglomerated as an oil. The solvent was decanted off and the oil residue dried under vacuum. This yielded 2.5 gr as an oil.

30

EXAMPLE 5**Evaluation of Feeding N-Benzylidene-L-Lysine Using Lactating Holstein Dairy Cows**

35 **TREATMENT DURATION:** 14 days

TREATMENTS:

- 1) Control
- 2) Control plus 40 g Lys from N-Benzylidene-L-Lysine

40

All cows received the same base diet. Cows were assigned to one of two treatments: (1) control, (2) control + N-Benzylidene-L-Lysine (TrTA). N-Benzylidene-L-Lysine was supplemented at a rate to supply 40 g of Lys when cows consumed 53.0 lb dry matter/d. The control diet was formulated to be deficient of lysine. The lactation response to the control diet as well as the diet supplemented with N-benzylidene -L-lysine is shown in Table 1. "P" refers to the probability value (p-value).

45

Table 1. Lactation responses to N-Benzylidene-L-Lysine

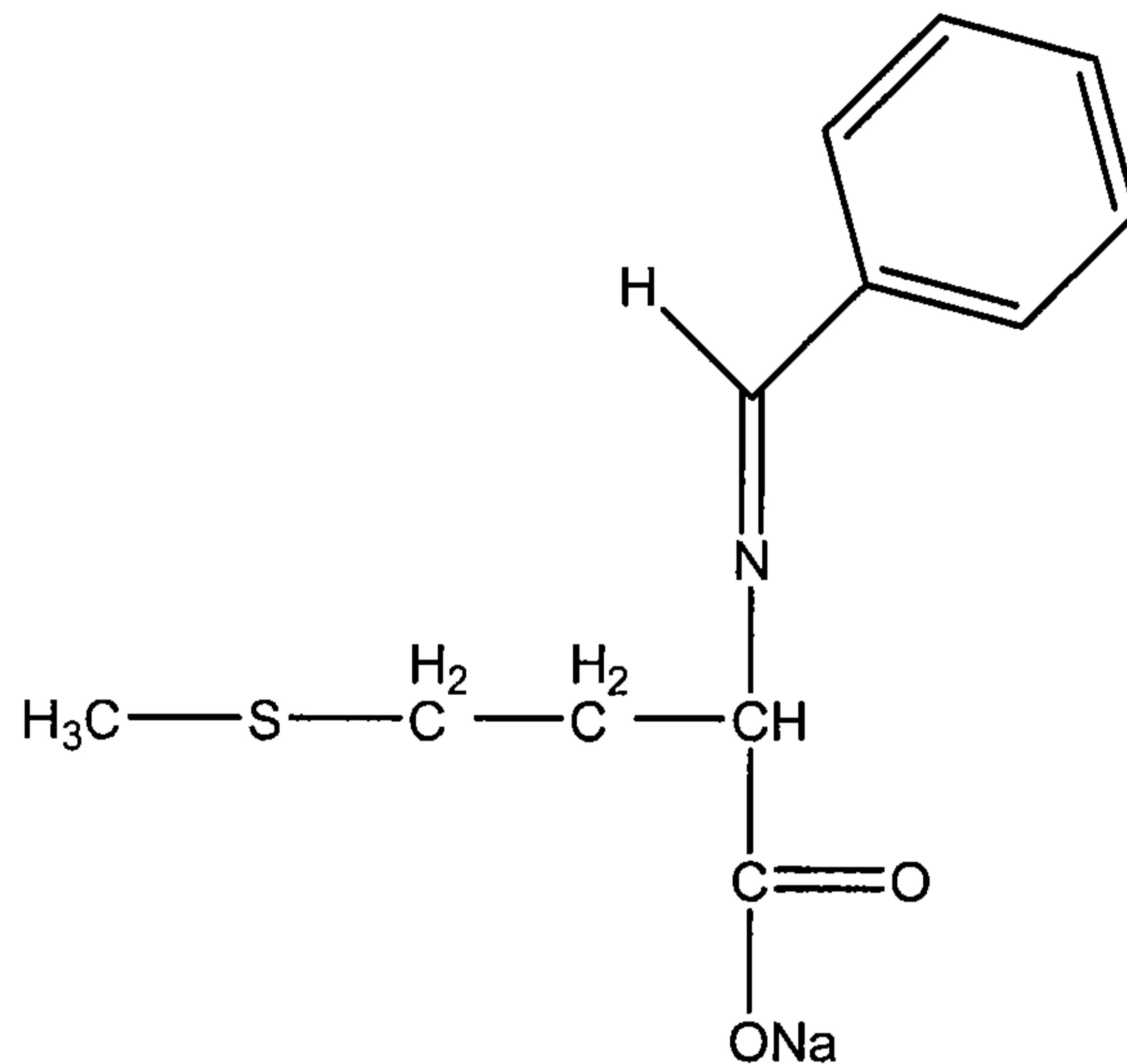
Item	Control	Trt A	P
Milk ,lbs/d	73.7	77.3	.1743
FCM, lbs/d	76.0	81.2	.1074
ECM, lbs/d	75.9	81.3	.0698
Fat, %	3.71	3.81	.5358
Fat, lbs/d	2.72	2.94	.1420
Protein, %	3.06	3.14	.1478
Protein, lbs/d	2.25	2.41	.0344
SCC	230.9	239.3	.5014
DMI, lbs/d	53.5	53.1	.8487
ECM/Feed	1.45	1.53	.2562

From the Table 1 data, it can be concluded that the imine supplement composition produced more milk, more protein and more fat, and that the differences were significant as 5 indicated by the P value. In contrast, if one were to simply add lysine to the diet, one would see no differences such as these, since microbes in the rumen would simply consume the lysine never allowing it to effectively supplement the animal and produce any different or enhanced result.

It therefore can be seen that the invention accomplishes at least all of its stated 10 objectives.

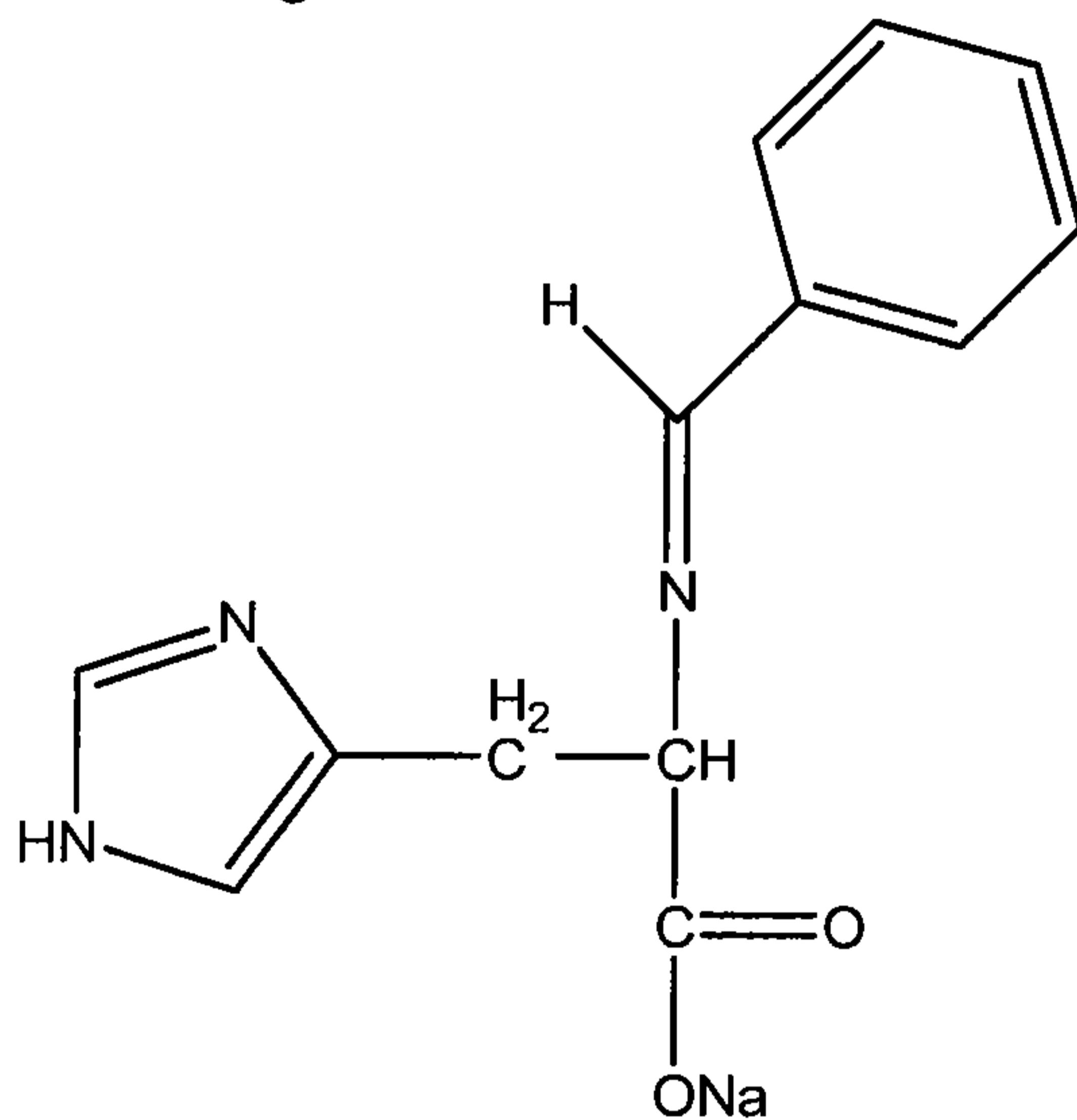
EXAMPLE 6**Preparation of sodium 2-(benzylideneamino)-4-(methylthio)butanoate from methionine and benzaldehyde.**

5 Methionine (2.2 gr, 14.7 mmol) was added to 100 mL of MeOH. NaOH (0.59 gr, 14.7 mmol) was added to the mixture and stirred until all components dissolved. To this mixture was added benzaldehyde (1.9 gr, 17.9 mmol) and the mixture was stirred for about 10 minutes. The mixture was then concentrated under vacuum and the residue was added to EtOH. The product crystallized from this solution. It was filtered and washed with 10 EtOH. The solid was dried to yield about 1.5 gr. The product was white solid and analyzed for percent nitrogen and compared to theoretical. Theoretical 5.9% nitrogen, actual 5.9%.



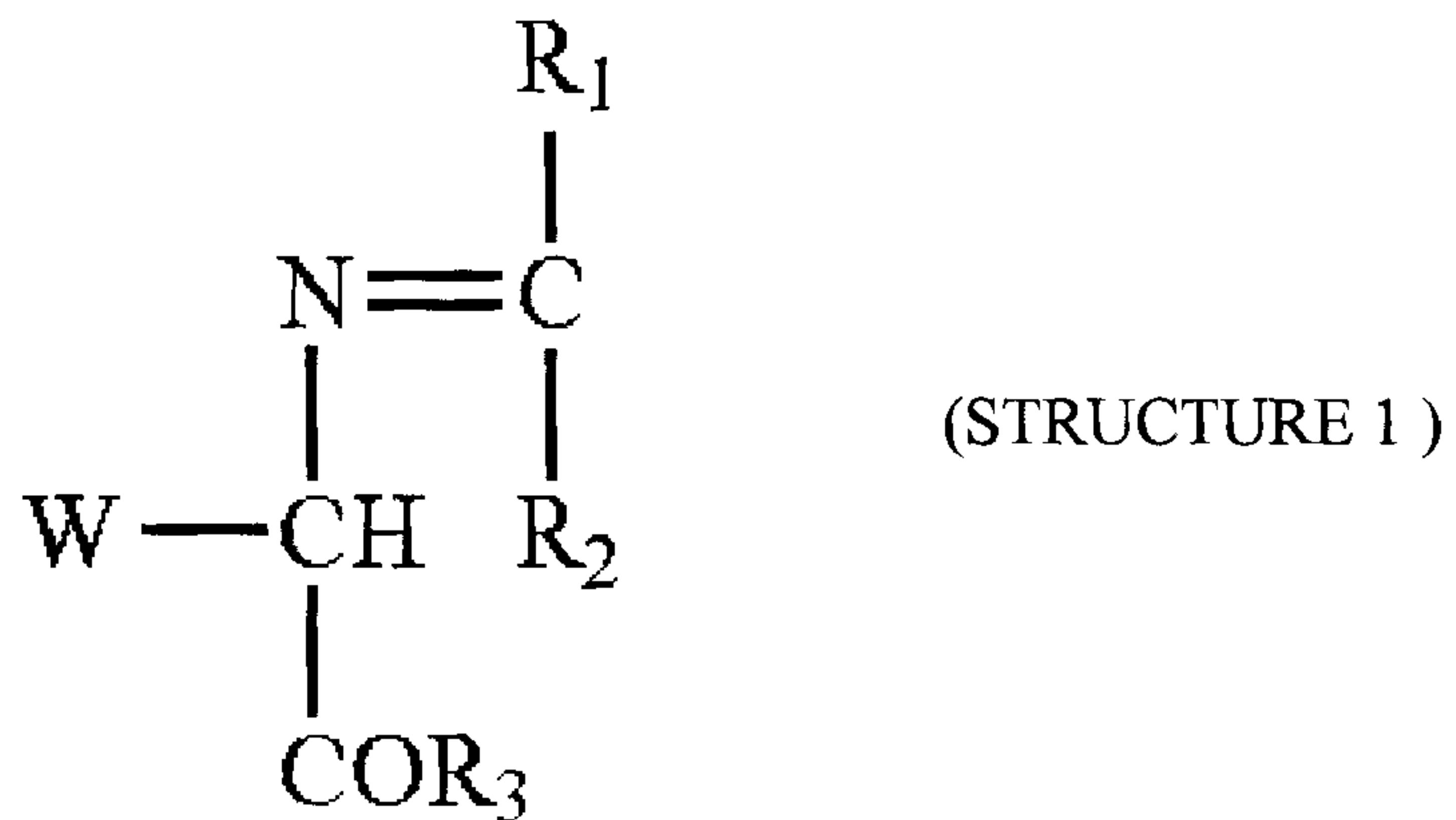
EXAMPLE 7**Preparation of sodium 2-(benzylideneamino)-3-(1H-imidazol-4-yl)propanoic acid from histidine hydrochloride and benzaldehyde.**

5 Histidine monohydrochloride monohydrate (5.3 gr, 25.3 mmol) was added to 100 mL of MeOH. NaOH (2.0 gr, 50 mmol) was added to the mixture and stirred. The histidine did not completely dissolve so water was added until all components dissolved. To this mixture was added benaldehyde (2.6 gr, 25 mmol) and the mixture was stirred for about 10 minutes. The mixture was then concentrated under vacuum and the residue was added to 10 EtOH. The product was filtered and washed with EtOH. The solid was dried to yield about 3.7 gr and was a white solid.



Claims:

1. A composition for supplementing the diet of ruminants with a source of rumen protected essential amino acid comprising:
a non toxic carrier; and
a diet supplementing effective amount of an imine derivative of an essential amino acid of the formula:



wherein R_1 and R_2 can be the same or different and are selected from the group consisting of hydrogen, aliphatic, aromatics, and cyclic moieties, W represents the remaining portion of an essential amino acid selected from the group consisting of leucine, isoleucine, valine, methionine, threonine, lysine, histidine, phenylalanine and tryptophan, and R_3 can be $-\text{OH}$, an ester producing moiety, or an inorganic salt producing moiety or amide producing moiety.

2. The composition of claim 1 wherein W is an organic moiety of methionine or histidine.
3. The composition of claim 1 wherein R_1 is hydrogen and R_2 is formed from use as a reactant Benzaldehyde, Salicylaldehyde, Cinnamaldehyde or Vanillin and R_3 is $-\text{OH}$.
4. The composition of claim 1 wherein R_1 is hydrogen and R_2 is formed from use as a reactant butyraldehyde, isobutyrylaldehyde, propionaldehyde or octylaldehyde and R_3 is $-\text{OH}$.

5. The composition of claim 1 wherein R_1 and R_2 are the same and are formed from use as a reactant Cyclohexanone, propiophenone, diethylketone, octanone, decanone or acetone.

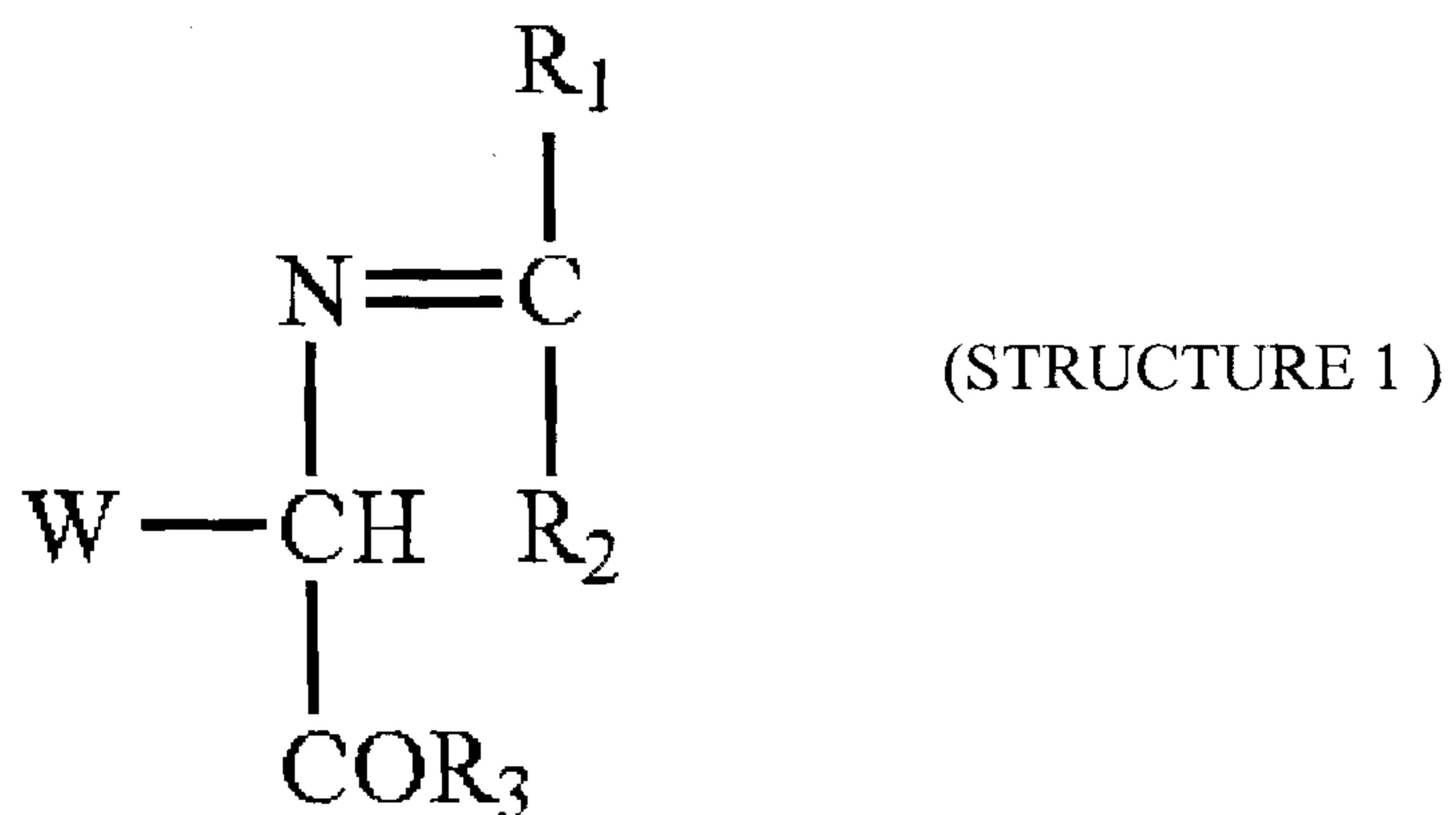
6. The composition of claim 1 wherein R_3 is either an organic moiety to form an ester or an inorganic salt moiety.

7. The composition of claim 1 wherein the non-toxic carrier is a flavorant.

8. The composition of claim 1 wherein the nontoxic carrier is selected from the group consisting of sugars, fermentations solubles, feed grains, corn cob flour, whey, and other cellulosic carrier materials.

9. The composition of claim 1 wherein the diet supplementing effective amount is an amount sufficient to provide a level of from about 1 gram to about 50 grams of amino acid used per animal per day.

10. The method of providing rumen protected essential amino acid for dietary supplementation of ruminants, said method comprising:
selecting at least one essential amino acid imine to be used as a source of rumen protected essential amino acid of the formula:



wherein R_1 and R_2 can be the same or different and are selected from the group consisting of hydrogen, aliphatic, aromatics, and cyclic moieties, W represents the remaining portion of an essential amino acid selected from the group consisting of leucine, isoleucine, valine, methionine, threonine, lysine, histidine, phenylalanine and tryptophan, and R_3 can be the same or different and are selected from the group consisting of hydrogen, aliphatic, aromatic and carbonyl moieties, and where R_3 is carbonyl, R_4 is not present and R_3 can be -OH, an ester producing moiety, or an inorganic salt moiety or an amide moiety; and feeding the rumen protected amino acid to a ruminant animal.

11. The method of claim 10 wherein W is either a histidine or methionine moiety.
12. The method of claim 10 wherein R_1 is hydrogen and R_2 is formed from use as a reactant Benzaldehyde, Salicylaldehyde, Cinnamaldehyde or Vanillin and R_3 is -OH.
13. The method of claim 10 wherein R_1 is hydrogen and R_2 is formed from use as a reactant butyraldehyde, isobutyrylaldehyde, propionaldehyde or octylaldehyde and R_3 is -OH.
14. The method of claim 10 wherein R_3 is either an organic moiety to form an ester or an inorganic moiety to form a salt.
15. The method of claim 10 wherein an additional step includes mixing the essential amino acid imine with a non-toxic carrier as a flavorant.
16. The method of claim 15 wherein the nontoxic carrier is selected from the group consisting of sugars, fermentations solubles, feed grains, corn cob flour, whey, and other cellulosic carrier materials.

17. The method of claim 16 wherein a diet supplementing effective amount of said amino acid imine is used and is an amount sufficient to provide a level of from about 1 gram to about 50 grams of amino acid used per animal per day.