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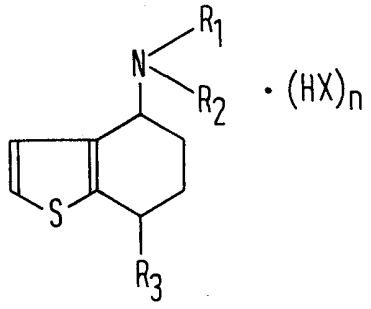
(71) We, AMERICAN CYANAMID COMPANY, a Corporation organized and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America,

do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

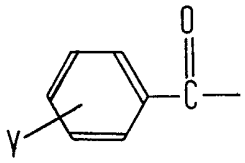
This invention relates to novel 4,5,6,7 - tetrahydro - 7 - oxo(oxy)benzo[*b*]-thiophen - 4 - amine compounds, to processes for their preparation, and to their use for improving feed efficiency and enhancing the growth rate of animals. The invention is a modification of or improvement in that forming the subject of our Patent No. 1,499,582.

The compounds of this invention have the formula:



(I)

wherein R_1 is hydrogen; R_2 is hydrogen, C_1—C_6 alkanoyl, halo-substituted C_1—C_6 alkanoyl or



wherein Y is hydrogen, 3,4-dichloro, chloro, methyl, methoxy or nitro; or R_1 and R_2 taken together with the associated nitrogen represent a cyclic imide selected from succinimido, maleimido, phthalimido and 1,2,3,6-tetrahydrophthalimido; R_3 is oxo or hydroxy, with the proviso that when R_3 is oxo then R_2 is not hydrogen or formyl; X is chlorine, bromine or iodine, and n is 0 except when R_1 and R_2 are both hydrogen when n is 0 or 1.

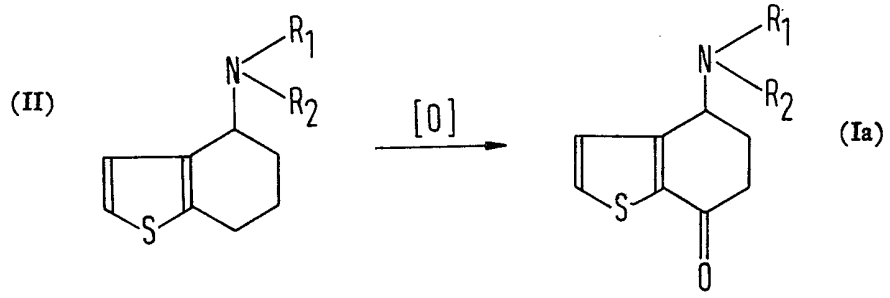
The invention includes the optical isomers of the compounds of formula I as well as racemic mixtures thereof, and when R_3 is hydroxyl the racemic mixture and optical isomers of the *cis* and *trans* isomers thereof, wherein the terms "*cis*" and "*trans*" refer to the configuration of the 7-hydroxy group with respect to the 4-amino group.

A preferred embodiment of the present invention consists of those compounds of formula (I) wherein R_1 is hydrogen; R_2 is C_1—C_6 alkanoyl or halo-substituted C_1—C_6 alkanoyl; and when R_1 and R_2 are taken together with the associated nitrogen they represent phthalimido.

Among the compounds of the invention are:
N-acetyl-4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-amine;
N-propionyl-4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-amine;
N-isobutyl-4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-amine;
N-pivaloyl-4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-amine;
N-trichloroacetyl-4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-amine; and
N-(4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-yl)phthalimide.

This invention further relates to methods of preparation of the above-described formula (I), 4,5,6,7 - tetrahydro - 7 - oxo(oxy)benzo[*b*]thiophen - 4 - amine compounds, hereinbelow described and exemplified in detail.

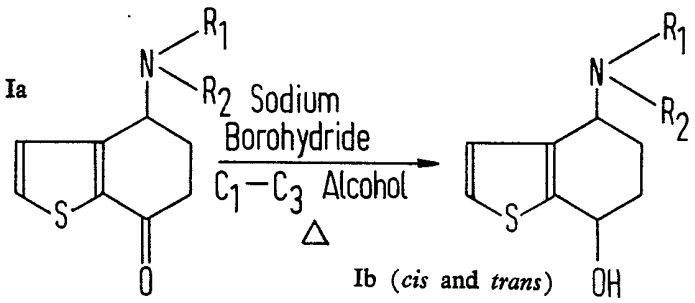
The novel formula (I) tetrahydro - 7 - oxobenzo - [*b*] thiophen - 4 - amine compounds of the present invention wherein R_3 is oxo may be prepared from the corresponding formula (II) 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4 - amines by an oxidation reaction which may be graphically illustrated as follows:



wherein R_1 and R_2 are as defined above.

In general, a formula (II) amine is reacted with a 2 to 8 mole equivalent, preferably with a 2 to 5 mole equivalent, of an oxidizing agent selected from ceric ammonium nitrate, ceric sulfate silver oxide, chromic anhydride and sodium bichromate at a temperature from 0°C. to 100°C., preferably 20°C., to 60°C., in a solvent selected from aqueous solutions of acetic acid, acetonitrile, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether, which may contain nitric acid, phosphoric acid or perchloric acid, or chromic anhydride — acetic anhydride, followed by hydrolysis. Other oxidizing agents, such as persulfates, may also be used in the above oxidation reaction if so desired.

The corresponding 7-hydroxy (*cis* and *trans* isomer, as defined above) analogues may be prepared from the corresponding type (Ia) compounds, by reduction with equimolar or excess amounts of sodium borohydride, at a temperature range from 0°C. to 75°C., preferably 20°C. to 40°C., in C_2—C_3 alcohols to afford a mixture of the *cis* and *trans* isomers. The above reaction may be graphically illustrated as follows:



wherein R_1 and R_2 are as defined above.

The novel 4,5,6,7 - tetrahydro - 7 - oxo(oxy)benzo[*b*]thiophen - 4 - amine compounds of formulae Ia and Ib, obtained by the procedures hereinabove described, are racemic mixtures.

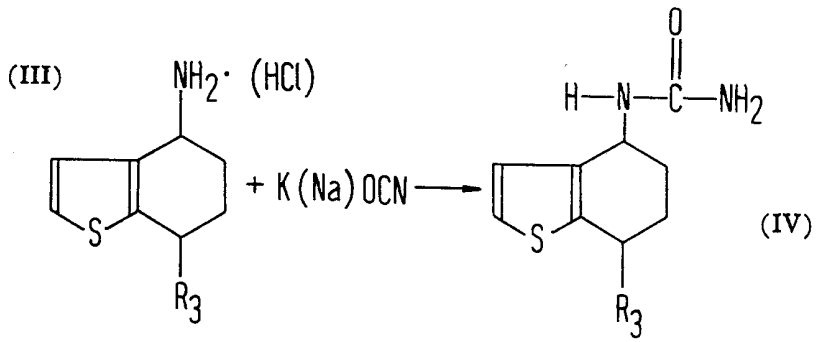
Should the optically active isomers of said compounds be desired, the racemic mixture of 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4 - amine (V) is initially treated with (R) - (+) - N - benzoylglutamic acid to afford a salt with the (+) - 4,5,6,7-tetrahydrobenzo[*b*]thiophen - 4 - amine. It is not necessary to employ more than one mole of the resolving acid for each 2 moles of the racemic amine, as a cheaper acid, preferably acetic acid, can be substituted for the balance of the required acid. The resolved salt, (+) - 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4 - ammonium (*R*) - N - benzoyl glutamate salt is then treated with alkali to liberate the (+)-amine, which is then isolated by standard means and converted to the (−)-N-acetyl derivative of structure (VI) by treatment with acetic anhydride. Corresponding, the remaining (−)-amine is resolved with (S) - (−) - N - benzoylglutamic acid and converted to the (+) acetamide of structure (VI). The above-mentioned reactions are then carried out to obtain the optically active keto isocyanates.

The compounds of this invention are useful as growth promoting agents for animals such as poultry, fur-bearing and farm animals and their use for this purpose has the added advantage of improving feed conversion for said animals. The term "feed conversion" means the ratio of unit weight of feed per unit weight of gain and "improvement in feed conversion" means increased weight gain from a given unit of feed consumed.

Thus, a growth-promoting amount of a formula (I) 4,5,6,7 - tetrahydro - 7 - oxo-(oxy)benzo[*b*]thiophen - 4 - amine or an optically active isomer thereof may be administered to a host animal in, or with, the animal's feed. In this connection, the invention provides an animal feed premix for improving feed efficiency and enhancing the growth rate of animals, which comprises from 70% to 99% by weight of an edible carrier and from 1% to 30% by weight of a compound of formula (I). Such compound may also be administered as a subcutaneous implant under the skin of said animal or as a parenteral injection. When administered in the feed of said animals, usually 0.0001% to 0.08% by weight, and preferably 0.001% to 0.04% by weight of formula (I) amine, is effective for increasing growth rate and improving feed conversion. When administered as a parenteral injection or subcutaneous implant, usually in amounts that will supply 0.005 mg., to 0.2 mg., preferably 0.001 mg. to 0.10 mg. per kg. of body weight per day of the active compound, it will produce the desired improvement in weight gain and enhance food conversion.

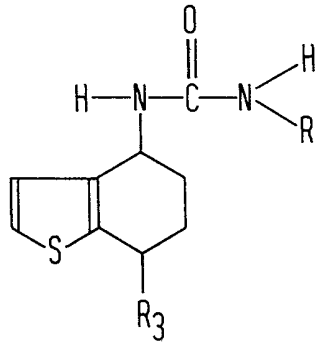
Compounds of the present invention are also useful for the preparation of animal growth regulating and herbicidal urea compounds by a number of alternative routes, as set forth in the following paragraphs.

A formula I amine, except when R_1 and R_2 are both hydrogen, is hydrolyzed in dilute mineral acid and the resulting 4,5,6,7 - tetrahydro - 7 - oxo(oxy)benzo[*b*]-thiophen - 4 - amine of formula (III) is reacted with an equimolar or excess (5% to 50%) amount of sodium or potassium cyanate at a temperature in the range of 0°C. to 100°C., preferably 0°C. to 70°C., in the presence of a solvent selected from water, C_1—C_3 alcohols, tetrahydrofuran, dioxane, ethylene glycol dimethyl ether, acetone, methyl ethyl ketone or mixtures thereof in the pH range of 5 to 7, and preferably at pH 6. The above reaction may be graphically illustrated as follows:



wherein R_3 represents oxo or hydroxy. The formula IV compounds obtained are the racemic mixtures and the *cis* and *trans* isomers thereof, wherein R_3 is hydroxyl.

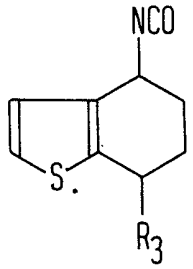
A formula III amine may also be reacted with an isocyanate of the formula: R—NCO under conditions similar to those described above to yield a formula IV substituted urea of the structure:



(IV)

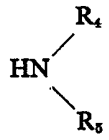
wherein R_3 is as defined above and R represents a substituent, such as alkyl, alkoxy, benzyl, phenyl and substituted phenyl, selected to enhance the biological activity and/or to impart suitable physical properties to said urea.

An amine of formula (III) where R_3 is oxo, may be reacted with phosgene, preferably under anhydrous conditions, under a blanket of inert gas such as nitrogen. The reaction is initially carried out at a temperature from 0°C. to 40°C., preferably 10°C. to 20°C., and then heated to from 50°C. to 100°C., preferably from 60°C. to 80°C. to yield the isocyanate of formula (V):

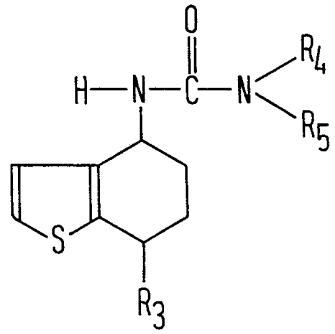


(V)

wherein R_3 is oxo. This reaction is usually conducted in the presence of an organic solvent such as benzene, toluene or xylene. The thus obtained isocyanate of formula (V) is then reacted with an equimolar or excess (5% to 50%) amount of an amine of the formula



to yield a formula IV urea of the structure:



(IV)

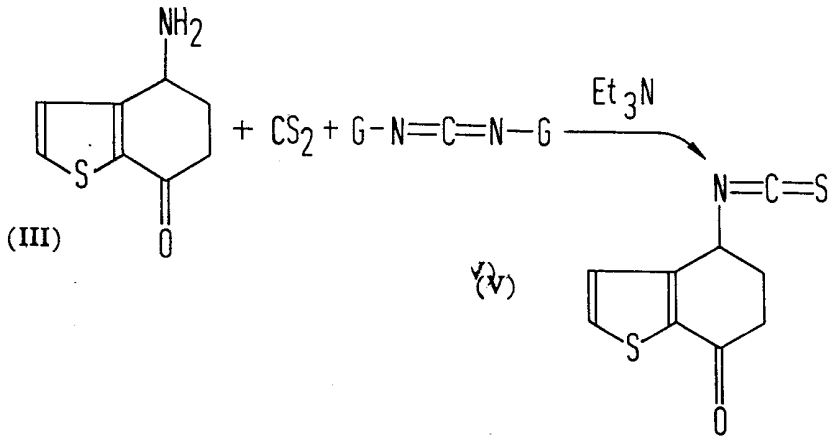
wherein R_3 is as defined above; R_4 and R_5 represent substituents, such as alkyl,

alkoxy, benzyl and aryl groups, selected to favorably enhance the biological activity and/or physical properties of said urea. For the preparation of compounds of formula IV, wherein R_3 is hydroxyl, the corresponding oxo compounds are conveniently reduced with sodium borohydride in C_1—C_3 alcohols.

An amine of formula (III) wherein R_3 is oxo, may also be reacted with equimolar amounts of carbon disulfide, triethylamine and a carbodiimide represented by the formula:

$$G—N=C=N—G$$

wherein G is cyclohexyl, cycloheptyl and C_4—C_6 alkyl to produce the corresponding thiophene (V). This reaction is generally conducted in the presence of a solvent such as tetrahydrofuran, ethyl acetate, or an ether such as diethyl ether, at a temperature from −10° to +80°C, and preferably from −10° to +50°C. The above reaction may be graphically illustrated as follows:



(III) (V)

wherein G is cyclohexyl, cycloheptyl or C_4—C_6 alkyl.

The thus obtained animal growth promoting urea compounds of formula IV are the racemic mixtures of the *cis* and *trans* isomers when R_3 is hydroxyl; unless, of course, the reaction sequence leading to said ureas is started with the resolved (*d* or *l*) formula (III) amines.

The invention is illustrated by the Examples set forth below. Examples 3 and 28 relate to the preparation of intermediates, while Example 27 illustrates the use of a compound of this invention in the preparation of a urea derivative thereof.

Example 1.

Preparation of N-Acetyl-4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-amine

A solution of 2.15 g of N - acetyl - 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4-amine in 12 ml of acetic acid is stirred and 3.04 g of chromium trioxide in 13.6 ml of acetic anhydride is added in 15 minutes at 10°C to 15°C. After an hour at 20°C, 20 ml of water is added and the mixture is allowed to stand overnight. Additional water (50 ml) is added, the mixture is saturated with sodium chloride and extracted with trichloromethane (100, 150 and 50 ml volumes). The combined extract is washed with brine and then with water. The water wash is extracted with trichloromethane and the extract is combined with the main trichloromethane extract. Evaporation of the extract affords a yellow-green residue, which after trituration with ether gives 1.32 g of the title compound, m.p. 160°C to 164°C.

Example 2.

Preparation of N-trichloroacetyl-4,5,6,7-tetrahydro-7-oxobenzo[*b*]thiophen-4-amine

Into 2 equivalents of trichloroacetic anhydride, 1 equivalent of 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4 - amine is added to afford the amide, which is collected and dried. The N - trichloroacetyl - 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4 - amine melts at 80°C to 86°C. This material is then oxidized in the general manner described in Example 1 but using ceric ammonium nitrate as oxidizing agent to afford the title product, m.p. 167°C to 171°C.

Example 3.

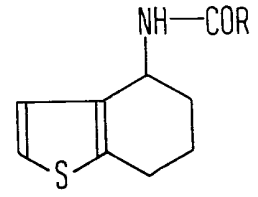
Preparation of N-chloroacetyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-amine

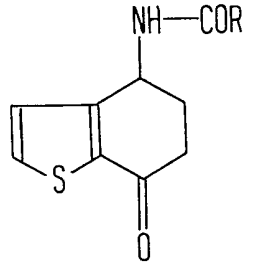
A mixture of 7.59 g of 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4 - amine hydrochloride is stirred in 60 ml of dry tetrahydrofuran and 10.1 g of triethylamine in 20 ml of dry tetrahydrofuran is added. After stirring under a nitrogen atmosphere for 15 minutes, 3.5 ml or 5.25 g of chloroacetyl chloride in 30 ml of dry tetrahydrofuran is added dropwise, while the temperature is maintained at 30°C to 40°C. After an hour of stirring, the mixture is filtered, the filter cake is washed with tetrahydrofuran, and the filtrate is evaporated to dryness. The residue is then triturated with water and the title compound, m.p. 115°C to 119°C, is collected and washed with water and hexane.

Example 4 to 25.

The following compounds, exemplified by structure *B*, are prepared by following the method of Example 2. The corresponding starting materials, exemplified by structure A, are prepared by the methods of either Example 2 or Example 3.

A





B

Example	R
4	CCl_3
5	CH_2Cl
6	$CHCl_2$
7	CF_3
8	CH_2CH_3
9	$CH(CH_3)_2$
10	$CH_2—C(CH_3)_3$
11	$(CH_2)_4CH_3$
12	$—C_6H_5$
13	4-chlorophenyl
14	2-chlorophenyl
15	3-chlorophenyl
16	4-nitrophenyl
17	3-nitrophenyl
18	2-nitrophenyl
19	4-methoxyphenyl
20	2-methoxylphenyl
21	3-methoxylphenyl
22	2-methylphenyl
23	3-methylphenyl
24	4-methylphenyl
25	3,4-dichlorophenyl

Example 26.

Preparation of N-(4,5,6,7-tetrahydro-7-oxobenzo[*b*]thien-4-yl)phthalimide

In 50 ml of toluene, 5 g of 4,5,6,7 - tetrahydrobenzo[*b*]thiophen -4 - ylamine, 4.84 g of phthalic anhydride, and 0.5 ml of triethylamine are heated at reflux to azeotropically remove water. After the distillation of water is completed, the mixture is cooled, the crystals are collected and washed with ether to afford N - (4,5,6,7 - tetrahydrobenzo[*b*]thien - 4 - yl) phthalimide, m.p. 166°C to 167.5°C. Oxidation of this compound by the method of Example 2 affords the title compound, m.p. 163°C to 166°C.

Similarly, use of maleic anhydride, *cis* - 1,2,3,6 - tetrahydrophthalic anhydride, and succinic anhydride in place of phthalic anhydride affords N - (4,5,6,7 - tetrahydro-7 - oxobenzo[*b*]thien - 4 - yl) maleimide, -*cis* - 1,2,3,6 - tetrahydrophthalimide and -succinimide, respectively.

Example 27.

Preparation of 4,5,6,7-Tetrahydro-7-oxobenzo[*b*]thien-4-ylurea

A sample of 18.95 g. of N - acetyl - 4,5,6,7 - tetrahydro - 7 - oxobenzo[*b*]-thiophen - 4 - amine is heated to reflux temperature with 6N hydrochloric acid for 4 hours. The mixture is cooled, filtered through glass wool to remove tars and the tars are washed twice with 75 ml of water. The combined washes and filtrate is washed with dichloromethane and then evaporated to dryness *in vacuo*. The residue is dissolved in 75 ml of water and a solution of 12.5 g of potassium cyanate in 35 ml of water is added rapidly. After stirring overnight, the product is collected by filtration and washed with water and then with methanol. This affords 7.7 g of the title compound, m.p. 231°C to 234°C dec.

Example 28.

Preparation of (−) N-acetyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4-amine

A solution in toluene of (+) 4,5,6,7 - tetrahydrobenzo[*b*]thiophen - 4 - amine is stirred under a nitrogen atmosphere and acetic anhydride is added. The mixture is then heated to reflux and water is removed by azetroping. After water no longer is distilled over, the mixture is cooled and the title compound is collected and washed with toluene.

Example 29.

Preparation of (−) N-acetyl-4,5,6,7-tetrahydro-7-oxobenzo-[*b*]-thiophen-4-amine

The ceric ammonium nitrate oxidation of (−) N - acetyl - 4,5,6,7 - tetrahydro-benzo[*b*]thiophen - 4 - amine by the method of Example 2 affords the title compound. m.p. 130°C to 136°C, $[\alpha]_D^{24} = -144.4°C$, C=0.514 in acetic acid.

Example 30.

Mouse Growth Regulant Tests

CFI female mice from Carworth Farm are received when they are 6 weeks old. They are housed 10 to a cage in air-conditioned rooms (72°F to 76°F) with automatically controlled lights, 14 hours on and 10 hours off. The basal diet used in these studies is Purina Laboratory Chow (see description below), which is supplied *ad libitum*. Water is also allowed *ad libitum*.

Thirteen days after arrival, the mice are weighed in groups of 10 and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following Table. Twelve days later the mice are weighed again and the experiment terminated. At least 3 cages (30 mice) of untreated controls are included in each test. Test data are provided in the Table below wherein data are reported as percent weight gain over controls. The following is a description of the diet to which the growth promoting compounds are added.

DIET

Guaranteed Analysis

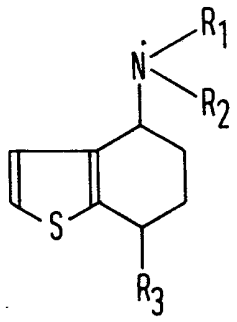
Crude protein not less than 23.0%
Crude fat not less than 4.5%
Crude fiber not more than 6.0%
Ash not more than 9.0%

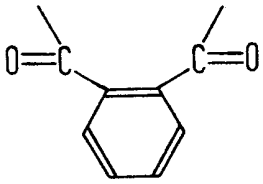
Ingredients

Meat and bone meal, dried skimmed milk, wheat germ meal, fish meal, animal liver meal, dried beet pulp, ground extruded corn, ground oat groats, soybean meal, dehydrated alfalfa meal, cane molasses, animal fat preserved with BHA, vitamin B_{12} supplement, calcium pantothenate, choline chloride, folic acid, riboflavin supplement, brewers' dried yeast, thiamin, niacin, vitamin A supplement, D activated plant sterol, vitamin E supplement, calcium carbonate, dicalcium phosphate, iodized salt, ferric ammonium citrate, iron oxide, manganous oxide, cobalt carbonate, copper oxide, zinc oxide,

TABLE

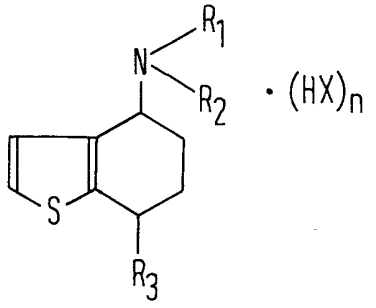
Effectiveness of 4,5,6,7-Tetrahydro-7-oxo(oxy)benzo[*b*]thiophen-4-amines As Animal Growth Promoting Agents Reported as Percent Weight Over Controls Using Mice as the Test Animal



Rate ppm in diet	R_1	R_2	R_3	% Weight Gain Over Controls
400	H	CH_3CO	oxo	38.5
400	H	CH_3CO	hydroxyl	18.5
400			oxo	9.5

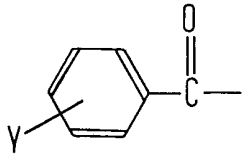
WHAT WE CLAIM IS:—

1. A compound of the formula:



(I)

wherein R_1 is hydrogen; R_2 is hydrogen, C_1—C_6 alkanoyl, halo-substituted C_1—C_6 alkanoyl or



wherein Y is hydrogen, 3,4-dichloro, chloro, methyl, methoxy or nitro; or R_1 and R_2 taken together with the associated nitrogen represent a cyclic amide selected from succinimodo, maleimido, phthalimido and 1,2,3,6 - tetrahydrophthalimido; R_3 is oxo or hydroxy, with the proviso that when R_3 is oxo then R_2 is not hydrogen or formyl; X is chlorine, bromine or iodine; and n is 0 except when R_1 and R_2 are both hydrogen when n is 0 or 1.

2. N - Acetyl - 4,5,6,7 - tetrahydro - 7 - oxobenzo[*b*]thiophen - 4 - amine.

3. N - Propionyl - 4,5,6,7 -tetrahydro - 7 - oxobenzo[*b*]thiophen - 4 - amine.

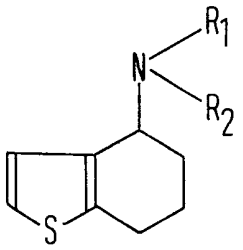
4. N - Isobutyryl - 4,5,6,7 - tetrahydro - 7 - oxobenzo[*b*]thiophen - 4 - amine.

5. N - Pivaloyl - 4,5,6,7 - tetrahydro - 7 - oxobenzo[*b*]thiophen - 4 - amine.

6. N - Trichloroacetyl - 4,5,6,7 - tetrahydro - 7 - oxobenzo[*b*]thiophen - 4 - amine.

7. N - (4,5,6,7 - Tetrahydro - 7 - oxobenzo[*b*]thien - 4 - yl)phthalamide.

8. A process for the preparation of a compound as defined in Claim 1, which comprises oxidizing 1 mole equivalent of a compound of the formula:



wherein R_1 and R_2 are as defined in Claim 1 with from 2 to 8 mole equivalents of an oxidizing agent selected from ceric ammonium nitrate, ceric sulfate, silver oxide, chromic anhydride and sodium dichromate in the presence of an aqueous solution of a solvent selected from acetic acid, acetonitrile, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether, wherein said solutions may contain nitric acid, phosphoric acid, perchloric acid or chromic anhydride in acetic anhydride at a temperature of from 0°C to 100°C for a period of time sufficient for a substantial degree of oxidation to take place.

9. A process according to Claim 8, wherein 2 to 5 mole equivalents of an oxidizing agent is used at a temperature range of 20°C to 60°C.

10. A method for improving feed efficiency and enhancing the growth rate of animals, which comprises administering to said animals an effective amount of a compound according to any one of Claims 1—7.

11. A method according to Claim 10, wherein said compound is administered to said animals in an amount equivalent to from 0.0001% to 0.08% by weight of the animal feed.

12. A method according to Claim 10, wherein said compound is parenterally administered as one or more subcutaneous implants beneath the skin of said animal and said implants being sufficient to provide a daily drug release of from 0.0005 mg to 0.2 mg of said compound per kg of animal body weight.

13. An animal feed composition for improving feed efficiency and enhancing the growth rate of animals, which comprises a nutrionally balanced animal feed containing from 0.0001% to 0.08% by weight of a compound according to any one of Claims 1—7.

14. An animal feed premix for improving feed efficiency and enhancing the growth rate of animals, which comprises from 70% to 99% by weight of an edible carrier and from 1% to 30% by weight of a compound according to any one of Claims 1—7.

15. A compound according to Claim 1 and substantially as described in any one of Examples 1, 2, 4—26 and 29 herein.

16. A process for preparing a compound according to Claim 1, substantially as described in any one of Examples 1, 2, 4—26 and 29 herein.

17. A compound according to Claim 1, whenever prepared by a process according to any one of Claims 8, 9 or 16.

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