

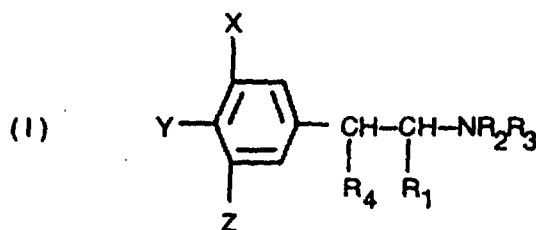
Description

Substitution products of 1-(amino-dihalophenyl)-2-aminoethanes, and the acid addition salts thereof, are disclosed in United States Patent 3,536,712. Specifically, methods for the synthesis of said compounds are disclosed as useful for enhancing the blood circulation, and as bronchodilators, analgesics, sedatives, diuretics, antiphlogistics and antitussives in warm-blooded animals. However, only the analgesic utility is exemplified. The preparation of other related 1-(amino-dihalophenyl)-2-aminoethanols and their derivatives are disclosed in JP-A 77 83,619 (Chemical Abstracts, 87, 201061r), German Offenlegungsschrift 2,804,625 (1979), German Offenlegungsschrift 2,157,040 (1973), German Offenlegungsschrift 2,261,914 (1974), European Patent Application 8,715 (1980), Netherlands Patent Application 7,303,612 (1973) and German Offenlegungsschrift 28 04 625. These applications disclose uses selected from analgesics, broncholytic, antiinflammatory, uterine spasmolytic, β -blocking activities, antispasmodic activity on cross-striated muscle structure, for tocology, reducing blood pressure by peripheral vasodilation and mobilizing body fat, and for treating allergies. There is no indication or suggestion in any of these disclosures that said compounds are effective as growth-promoting agents for meat-producing animals, such as poultry, cattle, sheep or the like; nor is there any suggestion that said compounds improve the efficiency of feed utilization by said meat-producing animals or the ratio of lean meat to fat.

US-A-3818101 describes a method for increasing the feed intake of meat producing animals beyond satiation by administering hydroxphenethanolamines with one or two hydroxyl groups attached to the phenyl group. These compounds lead to an accelerated growth rate. These compounds do not reduce the ratio of fat to lean meat or the even increase said ratio.

Therefore, it is the problem of the present invention to provide a method for increasing the ratio of lean meat to fat of meat producing animals.

In accordance with the process of the invention, it has been found that the growth rate of meat-producing animals such as chickens, turkeys, rabbits, sheep, swine, goats and cattle, including calves, can be increased, the efficiency of feed utilization thereby measurably improved, and the lean meat to fat ratio improved by the oral or parenteral administration to said animals of an effective amount of a compound of the following formula at selected levels of administration



wherein

X is hydrogen or halogen;

Y is hydrogen, NR_5R_6 or NHCOR_5 ;

Z is halogen, CN, CF_3 , COOR_1 , CONH_2 , methyl, methoxy or NO_2 ;

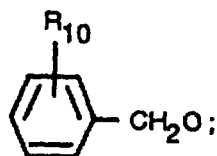
R_1 is hydrogen, C_1 - C_4 alkyl;

R_2 is hydrogen, C_1 - C_6 alkyl or C_3 - C_4 alkenyl;

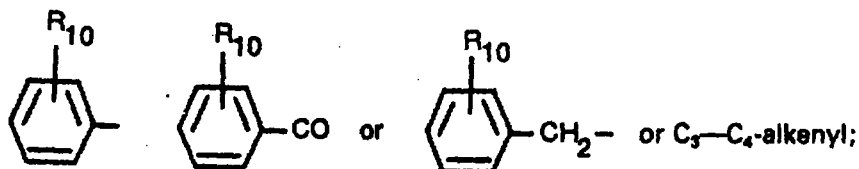
R_3 is hydrogen C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_4 alkenyl, phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl or benzyl;

R_4 is OH, OR_5 or SR_{11} ;

R_5 is hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy or



R_6 is C_1 - C_6 alkyl, C_2 - C_6 alkanoyl,



R_1 is hydrogen, C_1-C_4 -alkyl or C_3-C_4 -alkenyl;

R_2 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl or C_3-C_4 alkenyl;

R_3 is chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro;

R_4 is C_1-C_6 -alkyl, phenyl, or benzyl;

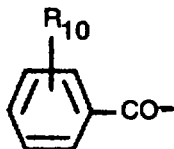
with the proviso that

when R_3 is phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl, C_3-C_6 cycloalkyl or benzyl R_2 is hydrogen;

and

when R_3 is 2-hydroxyethyl, R_4 is hydroxyl; and

when R_6 is alkanoyl or



R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or a substituted alkyl group which contains a tertiary carbon attached to the nitrogen; and

when Y is hydrogen, X and Z are halogen, and R_2 is hydrogen and R_3 is isopropyl, 2-butyl or *t*-butyl.

and

When R_6 is C_1-C_4 alkyl or C_3-C_4 alkenyl, R_9 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl; and

that at least one of X and Y represents a substituent other than hydrogen; and

when Z is a group other than halogen, Y is NR_5R_6 or $NHCO-R_6$; and

further provided that when Y is hydrogen, NH_2 or $NHCO-R_6$, and Z is halogen then R_4 cannot be OH or OR_6 , wherein R_6 is C_1-C_6 alkyl;

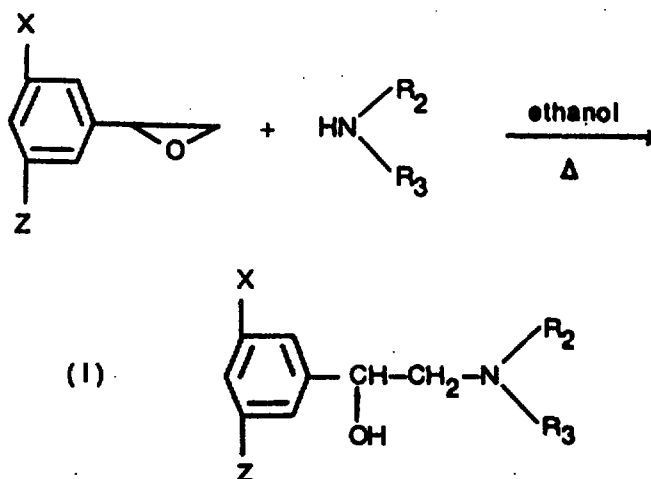
racemic mixtures of the above identified compounds and the optically active isomers, and non-toxic, pharmacologically acceptable acid addition salts thereof.

Applicants prior European patent application 80 10 46 19.4 describes similar compounds for use in a method for improving the ratio of lean meat to fat. These compounds and the compounds used in the present invention do not only enhance the growth rate but also increase the ratio of lean meat to fat and improve the feed utilization efficiency of meat producing animals.

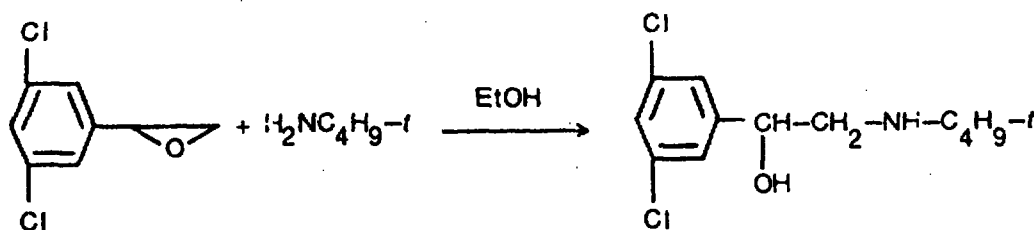
A preferred group of compounds for use in the method of this invention have the above formula I structure wherein X is hydrogen, chlorine, or bromine; Y is hydrogen or NR_5R_6 ; Z is chlorine, bromine, CN, CF_3 ; R_1 is hydrogen or methyl; R_4 is OH, OR_6 , SR_{11} ; R_6 is C_1-C_4 alkyl, or C_2-C_6 alkanoyl, or a non-toxic, pharmacologically acceptable acid addition salt thereof.

The most preferred compounds for use in this invention are: N - *tert* - butyl - 3,5 - dichloro - β - methoxy - 4 - methylaminophenethylamine; α - [(*tert* - butylamino)methyl] - 3,5 - dichloro - 4 - isopropylaminobenzyl alcohol; 5 - [2 - (*tert* - butylamino) - 1 - hydroxyethyl] - 3 - chloroanthranilic nitrile; 5 - [2 - (*tert* - butylamino) - 1 - hydroxyethyl]anthranilic nitrile; methyl - 5 - [2 - (*tert* - butylamino) - 1 - hydroxyethyl] - 3 - chloroanthranilate; 4 - amino - N - *tert* - butyl - 3,5 - dichloro - β - (methylthio)phenethylamine; α - [(*tert* - butylamino) - methyl] - 3,5 - dichloro-4-methylaminobenzyl alcohol; α - [(*tert* - butylamino)methyl - 3,5 - dichloro - 4 - dimethylaminobenzyl alcohol; methyl - 4 - [2 - (*tert* - butylamino) - 1 - hydroxyethyl] - 2,6 - dichlorocarbonyl; and the non-toxic, pharmacologically acceptable acid addition salts thereof.

It is found, that formula (I) compounds below (wherein Y is hydrogen) can be prepared by the condensation of an appropriately substituted styrene oxide with the appropriately substituted amine in the presence of an inert solvent, such as a lower alcohol at or near the boiling point of same, as shown below

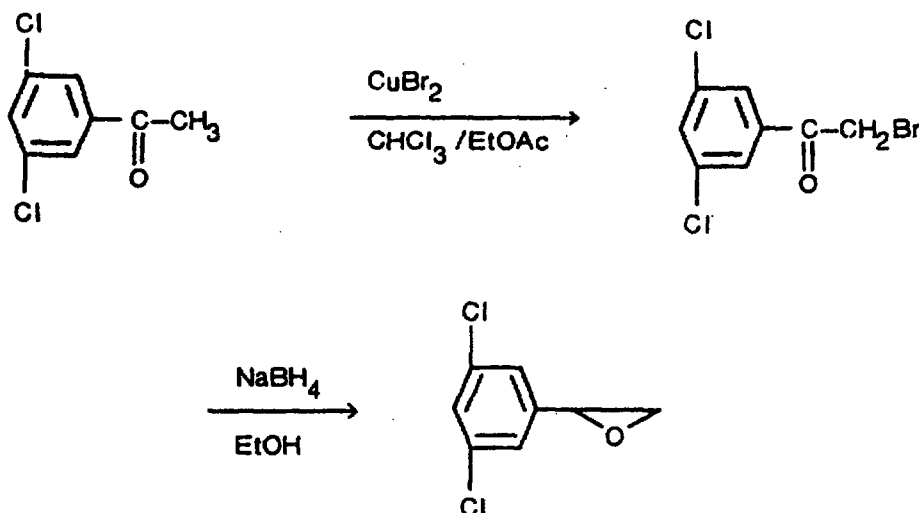


wherein X and Z are halogen, R_2 and R_3 are as hereinabove defined and Y is hydrogen. Thus, 3,5-dichlorostyrene oxide can be reacted with an equimolar or molar excess of *t*-butylamine in ethanol at reflux from about one to about eight hours, or until the reaction is essentially complete and the desired α -[(*t*-butylamino)methyl]-3,5-dichlorobenzyl alcohol is obtained as illustrated below:



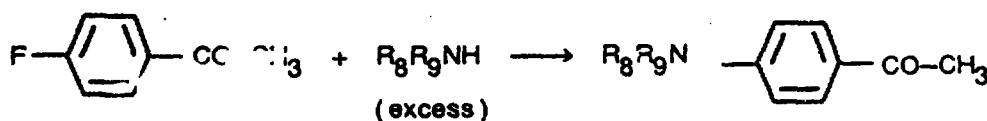
The thus obtained product can be purified by known procedures, such as chromatography or recrystallization of salts thereof.

The above styrene oxide is made by reducing the corresponding phenacyl bromide with $NaBH_4$ at or below $5^\circ C$ in the presence of an anhydrous lower alcohol, such as ethanol. The phenacyl bromide intermediate is prepared by brominating the appropriately substituted acetophenone with $CuBr_2$ in the presence of chloroform and ethyl acetate. The above sequence may be graphically illustrated as follows:



Alternatively, a formula (I) compound wherein Y is hydrogen may be prepared from the corresponding formula (I) compound wherein Y is amino, via a deamination reaction, by dissolving the amine in 50—52% aqueous hypophosphorous acid (H_3PO_2). The solution is chilled below $10^\circ C$, and an equimolar or excess amount of sodium nitrite is added to an aqueous solution with stirring over a period of time. On completion of the addition, the reaction mixture is warmed to room temperature and stirred for an additional period of time. The product is then recovered from the reaction mixture by standard laboratory procedures and purified if so desired.

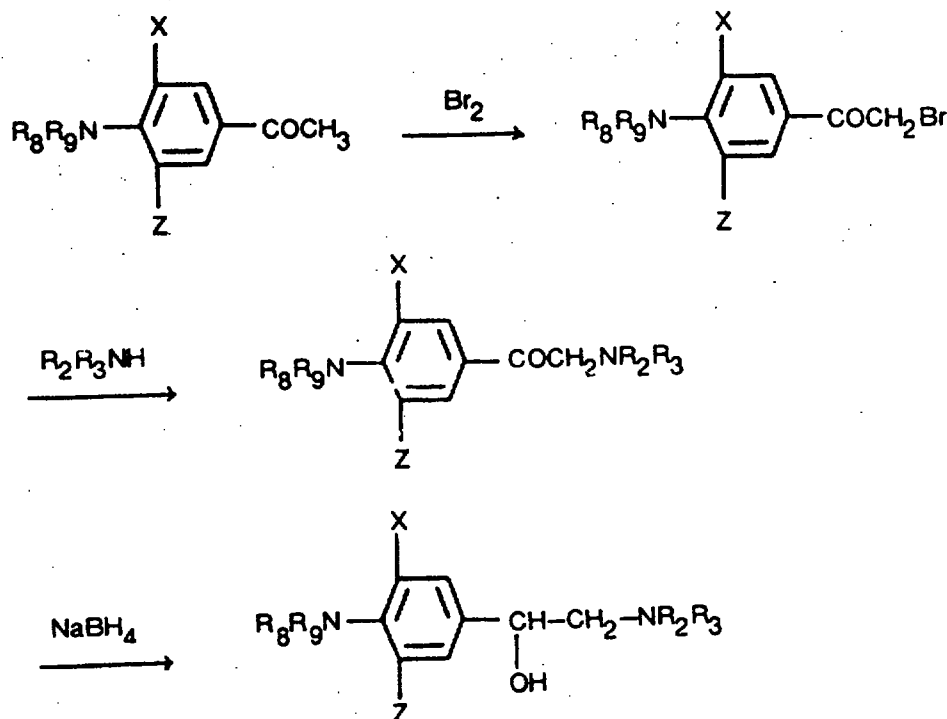
The preparation of 4-substituted aminoacetophenones required for the preparation of 4-substituted phenylethane derivatives which are now found to be useful for raising meat-producing animals, is exemplified as follows:



The fluorine displacement is carried out with excess amine in the presence or absence of a solvent; and, if a solvent is required, water appears to be the most useful. With volatile amines, the reaction is conducted in a sealed vessel and generally temperatures of $50-100^\circ C$ are sufficient to complete the reaction.

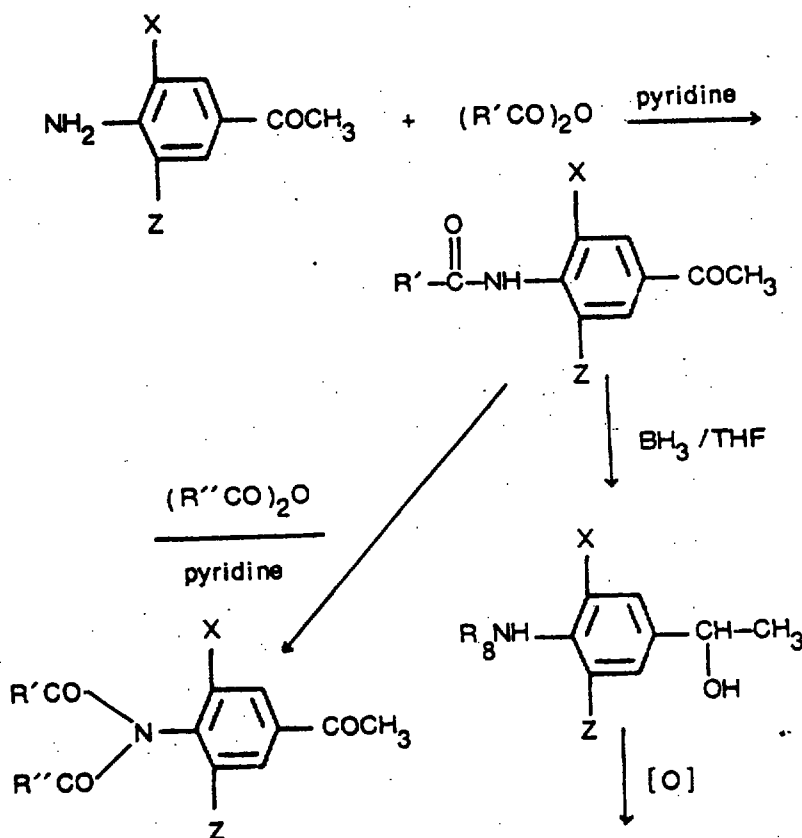
Chlorination and bromination of these aminoacetophenones may be conducted with *N*-chlorosuccinimide and *N*-bromosuccinimide in toluene, chlorobenzene or dichlorobenzene at $90-100^\circ C$. Iodination may be conducted with $NaI/N,N$ -dichlorobenzenesulfonamide or iodine monochloride in acetic acid.

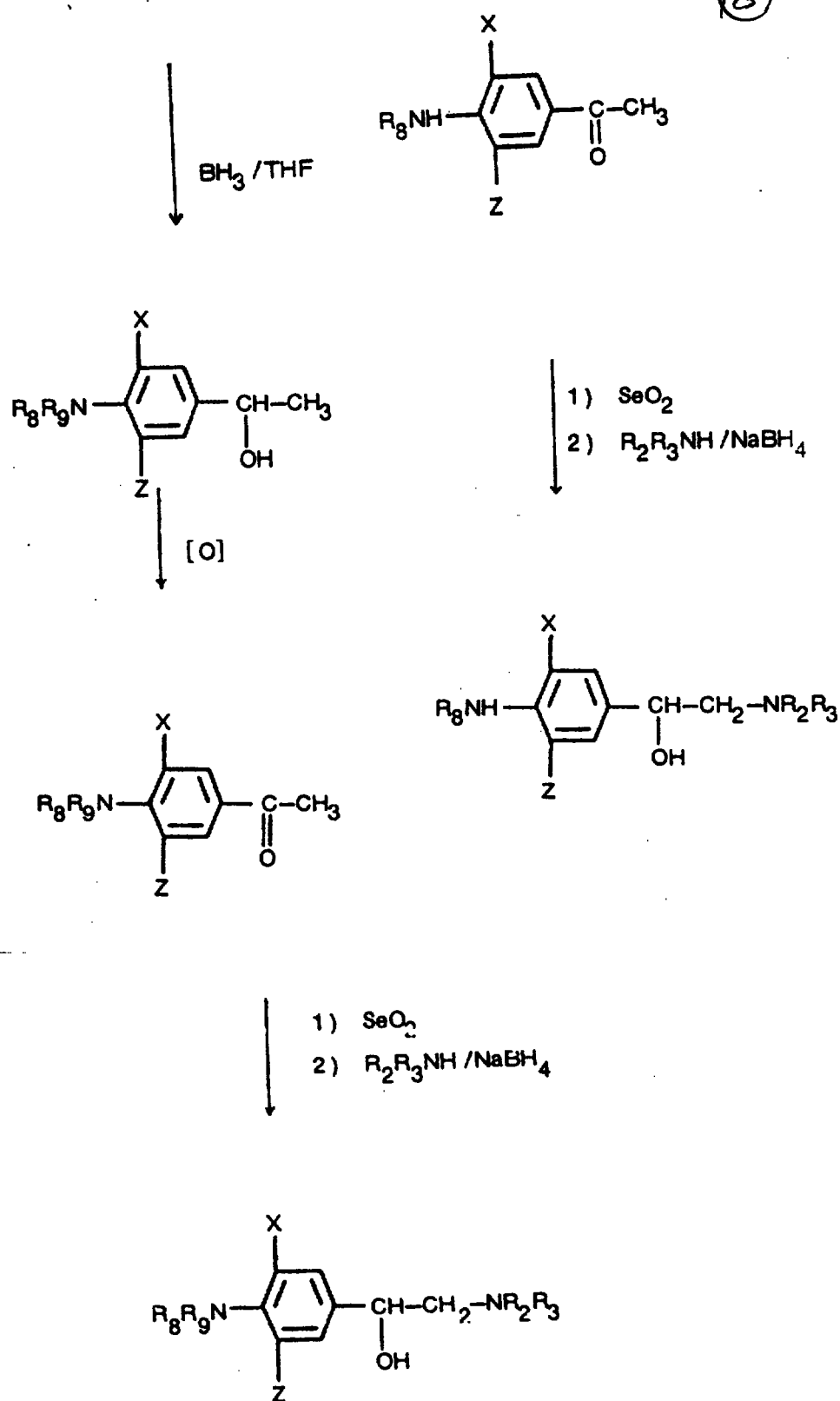
By reacting these acetophenones with bromine in chloroform or methylene chloride, the corresponding phenacyl bromides are prepared. These phenacyl bromides are then reacted with R_2R_3N amines and the aminoketones are reduced with $NaBH_4$ or $NaCNBH_3$ by conventional techniques described in reference cited hereinbefore. Naturally, compounds which contain groups reactive to halogen, such as when R_8 is alkenyl, require other approaches that are discussed below.



wherein X and Z are hydrogen, chlorine, or bromine and R_2 and R_3 are hydrogen, C_1-C_4 alkyl, or C_2-C_3 alkenyl groups.

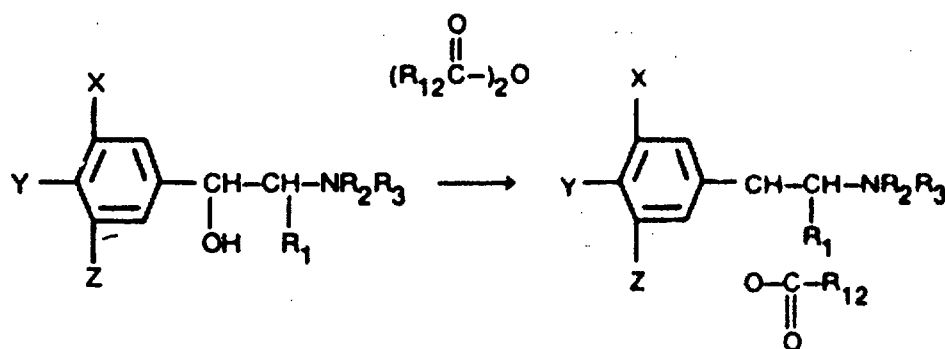
The compounds of formula I, wherein R_8 and R_9 are groups other than both being hydrogen are also prepared by the following general scheme:



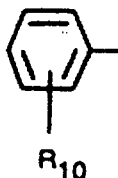


The methods utilized in the above scheme are either reported in references cited thereinbefore or by conventional methods. Oxidation of the alcohol may be conducted with chromic acid (Jones Reagent), MnO_2 , pyridinium chlorochromate, or other oxidizing agents. Where X or Z are the BH_3 -reducible groups, CN, COOR, or CONH_2 , the appropriate acetophenones are prepared by displacement of X or Z represented by bromine with CuCN/DMF at $100\text{--}160^\circ\text{C}$ by the conventional method, after reduction of the acylated aminoacetophenones in the first step followed by re-oxidation in the second step of the above procedure. The cyano substituted-amino-acetophenones are then converted to their corresponding ethanolamines, which are then converted to the desired esters, acids, and amides by conventional methods, such as $\text{R}_1\text{OH}/\text{acid} \rightarrow \text{esters}$, $\text{hydrolyses} \rightarrow \text{acids}$ and $\text{partial hydrolyses} \rightarrow \text{amides}$.

Furthermore, compounds of the following structure are prepared by allowing the corresponding ethanolamines to react with an equivalent or slight excess of the acid anhydrides with or without organic bases such as tertiary amines or pyridine.

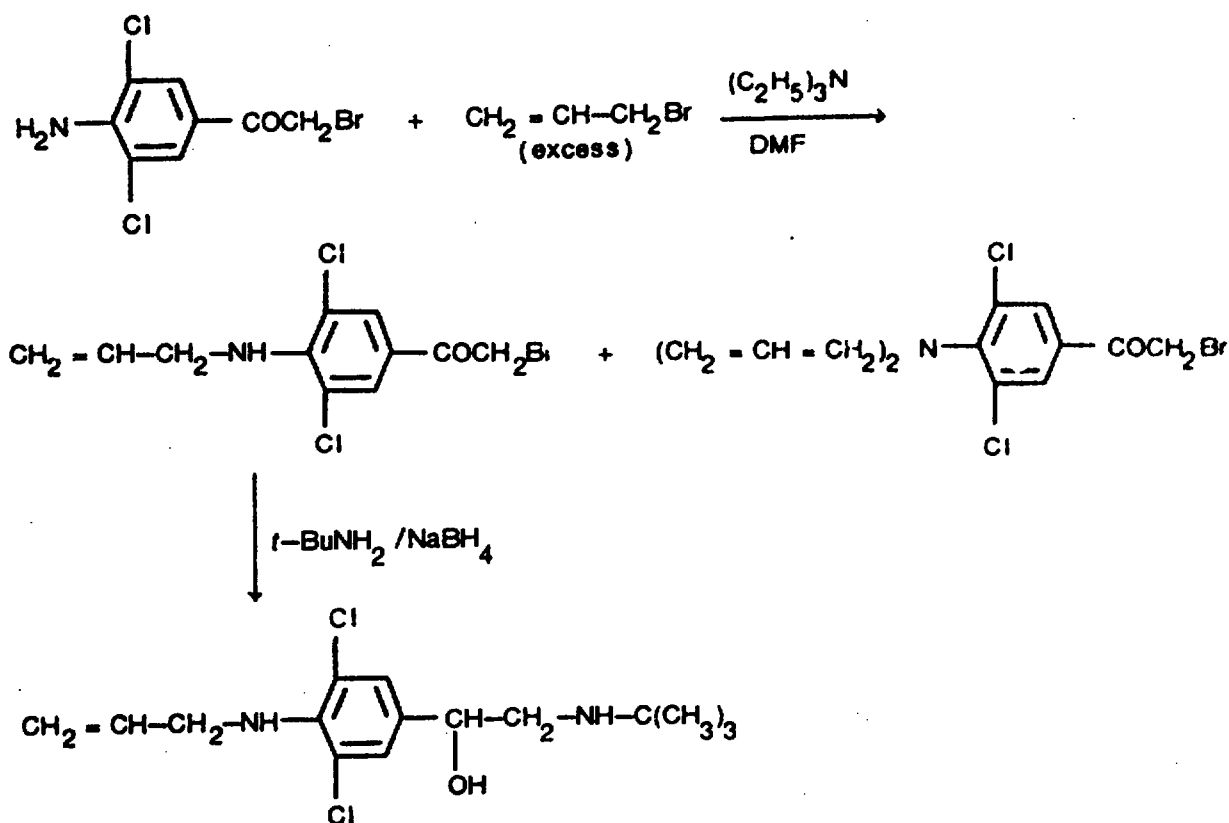


wherein R_{12} is C_1 — C_4 -alkyl or

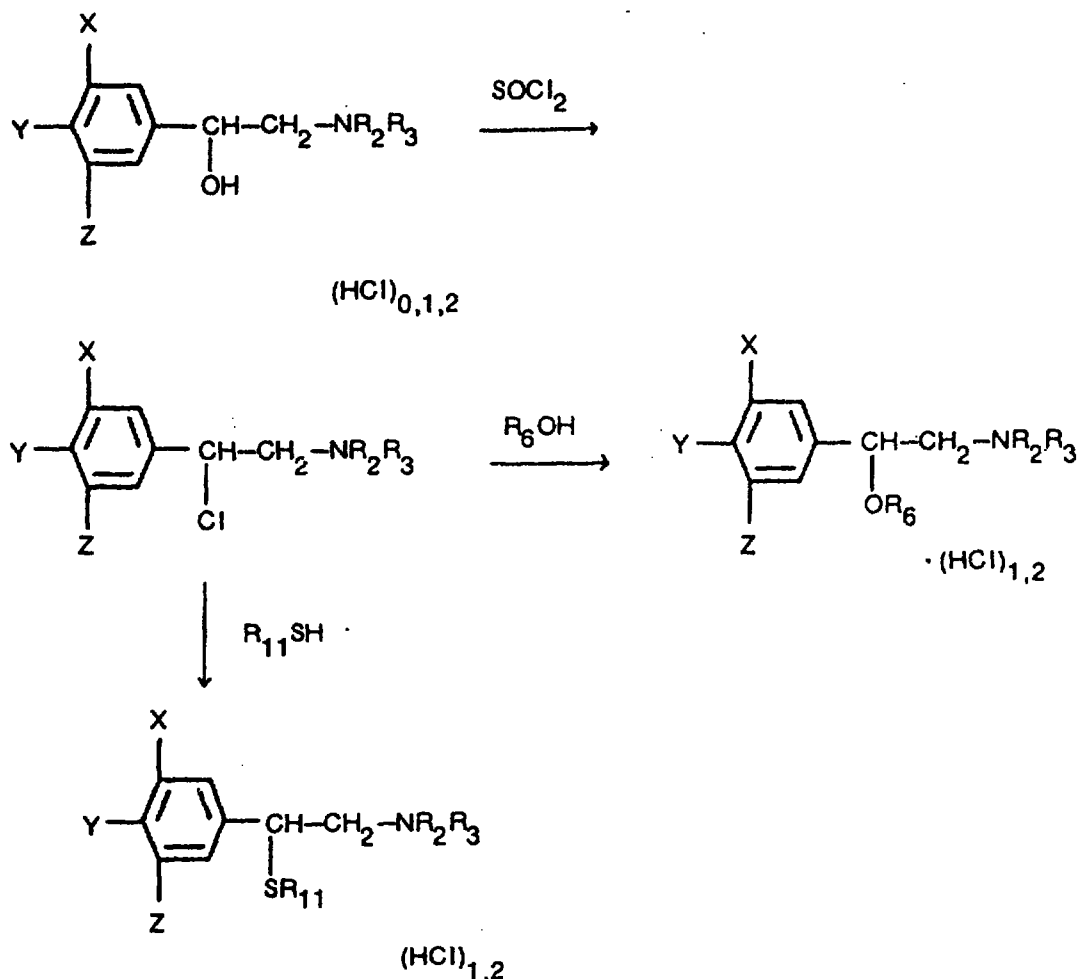


Reactions are conducted in inert solvents such as chlorinated hydrocarbons, or aromatic solvents at -25°C . Reaction of the anhydride at the hydroxyl group proceeds well provided R_1 and R_2 are groups other than hydrogen and when R_2 is hydrogen, R_1 is a substituent containing a tertiary carbon attached to nitrogen.

Additionally, Formula I compounds, wherein R_8 and R_9 are selected from hydrogen and C_2 — C_4 alkenyl, are prepared by alkenylation of 4-amino-3,5-disubstituted phenacyl bromides in dimethylformamide (DMF) in the presence of an acid acceptor, such as triethylamine or sodium carbonate, at 70 — 100°C to afford mono and dialkenylated products which are separated and converted to I by conventional methods. The following scheme illustrates above-described general method:



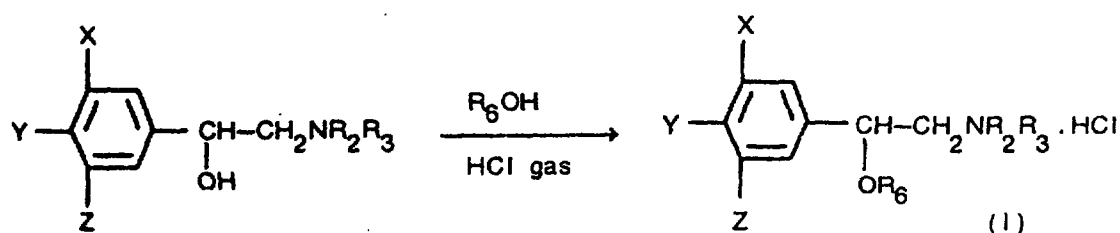
Formula (I) compounds wherein R_4 is OR_6 and SR_{11} , wherein R_6 and R_{11} are as hereinabove defined, may be prepared by converting the alcohol (R_4-OH) with thionyl chloride under an inert blanket of gas such as nitrogen at a temperature range of from about 0 to 10°C and preferably at 0 to 5°C for a reaction period sufficient to essentially complete the reaction. The thus obtained halo compound is isolated by conventional methods and is then reacted with the appropriate alcohol or mercaptan, under an inert blanket of gas, such as nitrogen at a temperature range of from about 0 to 50°C. The formula (I) product thus obtained is then isolated by standard laboratory methods and purified, if so desired. The above reaction sequence may be graphically illustrated as follows:



wherein X, Y, Z, R_2 , R_3 , R_6 and R_{11} are as hereinabove defined.

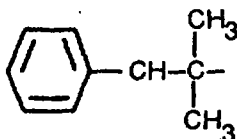
These displacement reactions may also be performed by using an excess of alkoxide (R_6O^-) or mercaptide ($R_{11}S^-$) in an inert solvent such as tetrahydrofuran to afford the above esters and thioesters in a similar manner.

Alternatively, a formula (I) compound wherein R_4 is OR_6 may be prepared by dissolving the corresponding formula (I) compound wherein R_4 is OH in the corresponding R_6OH alcohol and saturating the thus obtained solution with dry HCl gas. The reaction mixture is then stirred at room temperature for a period of time sufficient to essentially complete the reaction and the product is then isolated by standard laboratory procedures and purified, if so desired. This reaction sequence may be illustrated as follows:



wherein X, Y, Z, R₂, R₃ and R₄ are as hereinabove defined.

In the present specification and claims, the term α,α -dimethylphenethyl means a structure having the following configuration:



When orally administered in the feed, generally about 0.01 to 300 grams per ton of feed of the above-identified phenylethane derivative or acid addition salt thereof, is effective for enhancing the growth rate and improving the efficiency of feed utilization by the above-mentioned meat-producing animals.

Since the effective and preferred dietary levels of the active ingredient vary somewhat from species to species in the above-mentioned animals, said levels for each animal species are listed in Table I below on a gram per ton feed basis:

TABLE I

Compound	Effective Feed Level g/1.100 kg	Preferred Level g/1.100 kg	Animal Animal
Formula (I)	0.1—200	1—100	Sheep, Goats
	0.01—50	0.1—10	Chickens, Rabbits
	0.01—50	0.1—10	Turkeys
	0.1—300	1—100	Cattle & Swine

Animal feed compositions which will provide the desired group promotion and feed efficiency in the above-mentioned animals can be prepared by admixing the phenylethane derivative or acid addition salt thereof, or an animal feed supplement containing said compound, with a sufficient quantity of an appropriate animal feed to provide the desired level of active compound in said feed.

Animal feed supplements can be prepared by admixing about 10% to 75% by weight of the phenylethane derivative or acid addition salt thereof, with about 90% to 25% by weight of a suitable carrier or diluent. Carriers suitable for use to make up the feed supplement compositions include the following: alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal sodium chloride, cornmeal, can molasses, urea, bone meal, corncob meal and the like. The carrier promotes a uniform distribution of the active ingredient in the finished feed into which the supplement is blended. It thus performs an important function by ensuring proper distribution of the active ingredient throughout the feed.

If the supplement is used as a top dressing for feed, it likewise helps to ensure uniformity of distribution of the active material across the top of the dressed feed.

For parenteral administration, the phenylethane derivative may be prepared in the form of a paste or pellet and administered as an implant, usually under the skin of the head or ear of the animal in which enhanced growth rate and/or improved efficiency of feed utilization is sought.

In practice, parenteral administration generally involves injection of a sufficient amount of the above-said phenylethane derivative to provide the animal with from 0.001 to 50 mg/kg of body weight of the active ingredient. The preferred dosage level for cattle is the range of from 0.001 to 25 mg/kg of body weight of the active phenylethane derivative. The preferred dose level of said phenylethane derivative for poultry is about 0.001 to 35 mg/kg of animal body weight and the preferred dose level of said phenylethane derivative for sheep and goat is 0.001 to 40 mg/kg of animal body weight. The preferred dose level for rabbits is 0.001 to 35 mg/kg of animal body weight.

Paste formulations can be prepared by dispersing the active phenylethane derivative in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing an effective level of the phenylethane derivative can be prepared by admixing the above-said active ingredient with a diluent such as carbowax, biodegradable polymers, carnauba wax, or the like. A lubricant, such as magnesium stearate or calcium stearate may be added to improved the pelleting process if desired.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increased growth rate and/or improve efficiency of feed utilization by said animal. Moreover, it has been found that additional implants may also be introduced periodically during the treatment period in order to maintain the proper drug release rate in the animal's body.



In addition to enhanced growth promotion and improved efficiency of feed utilization by meat-producing animals, the compounds of the present invention have the added advantage that, at selected levels of administration, they increase the deposition of lean meat (i.e., muscle or protein) in said animals and improve the carcass quality thereof by increasing the ratio of lean meat to fat in the animals receiving them. This biological response has substantial advantage to poultrymen, cattlemen, and swine, sheep and goat producers since administration of said compounds at selected levels yields leaner animals which command premium prices from the meat industry.

These and other advantages of the present invention will become apparent from the examples set forth below.

Example 1

Evaluation of Test Compounds as Animal Growth Promoters

GFI female mice from Carworth Farms are received when they are six weeks old. They are housed ten to a cage in air-conditioned rooms 22, 2—24.4°C (72°F—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 allowed *ad libitum*.

Thirteen days after arrival, the mice are weighed in groups of ten and assigned at random to the different treatments. The concentration of the different compounds in the diet is indicated in the following tables. Twelve days later the mice are weighed again, and the experiment terminated. Test data are provided in Table II below wherein data are reported as percentage gain over controls. Different control animals are used for each test. The following is a description of the diet to which the growth promoting compounds were added.

DIET

Guaranteed Analysis

Crude protein not less than	23.0%
Crude fat not less than	4.0%
Crude fiber not more than	0.5%
Ash not more than	9.0%

Ingredients

Meat and bone meal, dried skimmed milk, wheat germ meal, fish meal, animal liver meal, dried yeast pulp, ground extruded corn, ground oat groats, soybean meal, dehydrated alfalfa meal, animal fat preserved with BHA, vitamin B₁ supplement, calcium pantothenate, choline chloride, rutin, riboflavin supplement, brewer's dried yeast, thiamin, niacin, vitamin A supplement, D-activated plant sterol, vitamin E supplement, calcium carbonate, dicalcium phosphate, killed salt, ferric pyrophosphate citrate, iron oxide, manganous oxide, cobalt carbonate, copper oxide, zinc oxide

TABLE II
Evaluation of Test Compounds as Anticarcinogenic Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
α -[2-(<i>Tert</i> -butylamino)methyl]-3,5-dichloro-4-dimethylaminobenzyl alcohol	200	16.0	0
	50	21.9	+36.9
α -[2-(<i>Tert</i> -butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol	200	19.4	+21.3
	50	24.4	+52.5
Methyl-4-[2-(<i>Tert</i> -butylamino)-1-hydroxyethyl]-2,6-dichlorocarbaniolate	50	27.9	+40.8
5-[2-(<i>Tert</i> -butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile	200	27.3	+90.9
	50	26.2	+83.2
α -[2-(<i>Tert</i> -butylamino)methyl]-3,5-dichloro-4-isopropylaminobenzyl alcohol	200	24.6	+72.0
	50	24.3	+69.9
	12	28.0	+95.8
	3	27.3	+90.8
5-[2-(<i>Tert</i> -butylamino)-1-hydroxyethyl]-anthranilonitrile	200	29.6	+79.4
	50	29.9	+81.2
Methyl-5-[2-(<i>Tert</i> -butylamino)-1-hydroxyethyl]-3-chloroanthranilate hydrochloride	200	24.4	+47.9
	50	20.1	+21.8
4-Amino-N- <i>Tert</i> -butyl-3,5-dichloro- β -(methylthio)-phenethylamine hydrochloride	200	25.4	+55.8
	50	25.3	+55.2

TABLE II (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
3-Bromo-5-[2-(<i>tert</i> -butylamino)-1-hydroxyethyl]-anthranilonitrile	200	16.	+50.5
	50	24.2	+126.2
4-Amino- α -[(<i>tert</i> -butylamino)methyl]-3-methylbenzyl alcohol	100	20.8	+94.5
4-(Butylamino)- α -[(<i>tert</i> -butylamino)methyl]-3,5-dichlorobenzyl alcohol	200	19.3	+80.4
	50	19.4	+ 81.3
2-Amino-3-bromo-5-[2-(<i>tert</i> -butylamino)-1-hydroxyethyl]benzamide	200	17.4	+62.6
	50	19.8	+85.0
4-Amino- α -[(<i>tert</i> -butylamino)methyl]-3,5-dichlorobenzyl alcohol acetate (ester)	200	14.6	+36.4
	50	19.1	+78.5
3-Bromo-5-[2-(<i>tert</i> -butylamino)-1-hydroxyethyl]-anthranilic acid	200	18.2	+70.1
	50	13.6	+27.1
N- <i>tert</i> -butyl-3,5-dichloro-8-methoxy-4-methylaminophenethylamine hydrochloride	200	18.0	+68.2
	50	23.1	+115.9
α -[(<i>tert</i> -butylamino)methyl]-3,5-dichloro-4-(hexylamino)benzyl alcohol	200	19.6	+83.2
	50	20.7	+93.5
4-Amino- α -[(<i>tert</i> -butylamino)methyl]-3,5-dichlorobenzyl alcohol acetate, acetic acid salt	200	14.4	+34.6
	50	18.7	+74.8

TABLE II (Continued)

Evaluation of Test Compounds as Animal Growth Promoters

Compound	Dosage (ppm)	Gain (grams)	% Gain Over Controls
3-Bromo-5-[2- <i>tert</i> -butylamino)-1-hydroxyethyl]- anthranilic acid	200 50	18.2 13.6	+70.1 +27.1
N- <i>tert</i> -butyl-3,5-dichloro-8-methoxy-4-methyl- aminophenethylamine hydrochloride	200 50	18.0 23.1	+68.2 +115.9
α -[<i>(tert</i> -butylamino)methyl]-3,5-dichloro-4- (hexylamino)benzyl alcohol	200 50	19.6 20.7	+83.2 +93.5
4-Amino- α -[<i>(tert</i> -butylamino)methyl]-3,5-dichloro- benzyl alcohol acetate	200 50	14.4 18.7	+34.6 +74.8
β -(allyloxy)-4-amino-N- <i>tert</i> -butyl-3,5- dichlorophenethylamine	200 50	21.5 19.6	+100.9 +83.2
4-(allylamino)- α -[<i>(tert</i> -butylamino)methyl]-3,5- dichlorobenzyl alcohol	200 50	20.2 21.9	+88.8 +104.7
4'-[3-(<i>tert</i> -butylamino)-1-hydroxyethyl]-2',6'- dichloroacetanilide acetate (ester), hydrochloride	200 50	25.8 16.2	+141.1 +51.4
α -[<i>(tert</i> -Butylamino)methyl]-3,5-dichloro-4- cyclohexylaminobenzyl alcohol	100	23.0	+115.0
α -[<i>(tert</i> -Butylamino)methyl]-4-amino-3-chloro-5- methylbenzyl alcohol, hydrochloride	200 50	16.5 19.7	+54.2 +84.1

(25)



Example 2

Antilipogenic Evaluation of Test Compounds — Mouse Study

CFI female mice, 55 days old, are weighed in groups of 10 and allotted to cages to minimize variation among cages. Treatments are randomly assigned to cages.

Each of the treatments are tested in 3 replicates, i.e., in 3 cages of 10 mice each. There are 10 cages of 10 control mice each. Drugs are mixed in the diet at the dosage level indicated. Feed and water are offered ad libitum for 12-day test period. Feed spilled is collected during the test period. At the end of the period, the collected feed is weighed and the mean feed consumption per cage of ten mice is determined for each treatment. The mice are weighed as a group of 10 and the weight gain determined. The mice are sacrificed by cervical dislocation. The right uterine fat pad of each mouse is removed. The fat pads for each cage of 10 mice are weighed as a unit.

Data obtained are reported in Table III. Data are reported as percent reduction in fat pad weight. Reduction in fat pad weights of animals is generally indicative of reduction of total body fat of the treated animals.

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TABLE III

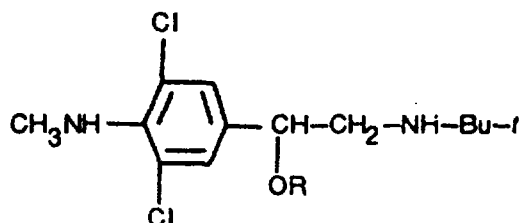
Antitlipogenic Evaluation of Test Compounds — Mouse Study

Compound	Dosage (ppm)	% Reduction in Fat Pad Weight vs Controls
α -[(<i>tert</i> -butylamino)methyl]-3,5-dichloro-4-dimethylamino benzyl alcohol	200 50	-46.1 -14.8
Methyl-4-[2-(<i>tert</i> -butylamino)-1-hydroxyethyl]-2,6-dichlorocarbonilate	50	-23.5
α -[(<i>tert</i> -butylamino)methyl]-3,5-dichloro-4-methylamino-benzyl alcohol	200 50	-51.0 -41.9
5-[2- <i>tert</i> -butylamino-1-hydroxyethyl]-3-chloroanthranilonitrile	200 50	-45.9 -10.4
α -[(<i>tert</i> -butylamino)methyl]-1,3-dichloro-4-isopropylamino-benzyl alcohol	200 50 12 3	-52.5 -22.6 -6.3 -25.5
Methyl-5-[2-(<i>tert</i> -butylamino)-1-hydroxyethyl]-3-chloro-anthranilate hydrochloride	200 50	-5.9 -5.8
5-[2-(<i>tert</i> -butylamino)-1-hydroxyethyl] anthranilonitrile	200 50	-41.5 -10.3
4-Amino-N- <i>tert</i> -butyl-3,5-dichloro- β -(methylthio) phenethylamine hydrochloride	200 50	-28.9 -16.2

Example 3

N-tert-butyl-3,5-dichloro-β-methoxy-4-methylaminophenethylamine hydrochloride

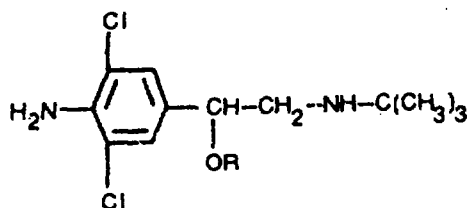
A 7 g sample of α-[(*tert*-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol is added to 70 ml of thionyl chloride under N₂ atmosphere and the mixture is stirred for two hours. Excess thionyl chloride is removed *in vacuo*, and the glassy residue is dissolved in 50 ml of methanol. The solution is stirred for 1.5 hours and evaporated to dryness. The residue is dissolved in 100 ml of H₂O and extracted with 2 × 50 ml of CH₂Cl₂. The aqueous layer is neutralized with solid NaHCO₃ and extracted with CH₂Cl₂. The extract is dried (MgSO₄) and evaporated to dryness *in vacuo* to give 4.1 g of semi-solid, which after trituration with ethyl ether affords 1.07 g of the title compound, mp 220—221°C. Similarly, the following ethers are prepared:



<u>Alcohol</u>	<u>R</u>
ethanol	C ₂ H ₅
1-propanol	1-C ₃ H ₇
2-propanol	2-C ₃ H ₇
1-butanol	1-C ₄ H ₉
2-butanol	2-C ₄ H ₉
1-hexanol	<i>n</i> -C ₆ H ₁₃
allyl alcohol	allyl
4-methoxybenzyl alcohol	4-methoxybenzyl
4-chlorobenzyl alcohol	4-chlorobenzyl
4-nitrobenzyl alcohol	4-nitrobenzyl
4-methylbenzyl alcohol	4-methylbenzyl
3,4-dimethylbenzyl alcohol	3,4-dimethylbenzyl
3,4-dimethoxybenzyl alcohol	3,4-dimethoxybenzyl
3,4-dichlorobenzyl alcohol	3,4-dichlorobenzyl
2-chlorobenzyl alcohol	2-chlorobenzyl
2-methylbenzyl alcohol	2-methylbenzyl

Example 4

In the manner described in Example 3, the following ethers are prepared by substituting the corresponding alcohols for methanol.

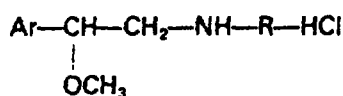


<u>R</u>	<u>mp°C</u>
allyl	57—59
4-methoxybenzyl	
4-chlorobenzyl	
4-nitrobenzyl	
4-methylbenzyl	
3,4-dimethylbenzyl	
3,4-dimethoxybenzyl	
3,4-dichlorophenyl	
4-chlorophenyl	
4-methoxyphenyl	
4-methoxyphenyl	
2-chlorophenyl	
4-nitrophenyl	

Example 5

N-tert-Butyl-3-chloro-5-cyano-β-methoxy-4-aminophenethylamine hydrochloride

In the manner described in Example 3, α-(tert-butylamino)methyl-4-amino-3-chloro-5-cyanobenzyl alcohol is converted into the title compound, and, similarly, the following are also prepared:



<u>Ar</u>	<u>R</u>
4-amino-3-chloro-5-trifluoromethylphenyl	<i>t</i> -butyl
4-amino-3-chloro-5-trifluoromethylphenyl	<i>i</i> -propyl
4-amino-3-chloro-5-H ₂ N—CO—phenyl	<i>t</i> -butyl
4-amino-3-chloro-5-HO—CO—phenyl	<i>t</i> -butyl
4-amino-3-chloro-5-methylphenyl	<i>t</i> -butyl
4-amino-3-chloro-5-methoxyphenyl	<i>t</i> -butyl
4-amino-3-chloro-5-nitrophenyl	<i>t</i> -butyl
4-amino-3-chloro-5-CH ₃ O—CO—phenyl	<i>t</i> -butyl
4-amino-5-cyano-phenyl	<i>t</i> -butyl

Example 6

4-Amino- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol acetate

A mixture containing 1 g of 4-amino- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol in 35 ml of CH_2Cl_2 at 10–15°C is stirred, and 0.37 g of Ac_2O and 0.5 ml of Et_3N are added dropwise. The reaction mixture is then allowed to warm to room temperature, and the reaction is followed by thin-layer chromatography to completion. The mixture is evaporated to dryness *in vacuo*, and the yellow viscous liquid (1.5 g) is stirred with 50 ml of ethyl ether to afford a yellow solid (0.84 g), mp 128–131°C. This material is shown by nuclear magnetic resonance spectroscopy and by neutralization with alkali to be the acetic acid salt. On treating 100 mg of this salt in 30 ml of CH_2Cl_2 with 30 ml of 10% aqueous NaOH , the salt is neutralized. The CH_2Cl_2 solution is dried (MgSO_4) and evaporated to dryness *in vacuo* to afford the viscous title compound.

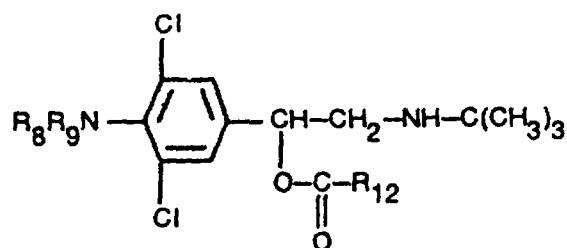
Analysis:

Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2\text{N}_2\text{Cl}_2$: C, 52.67; H, 6.32; N, 8.78;
Found: C, 52.38; H, 6.51; N, 8.88.

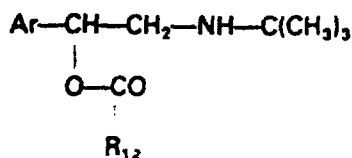
In the same manner, propionic anhydride, butyric anhydride, are allowed to react with 4-amino- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol (A) and α -[(*tert*-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol (B) respectively, to afford the propionate, butyrate and pivalate of A and B.

Example 7

The following esters are prepared by the method of Example 6 by using the appropriate acid anhydride.



$\underline{R_8}$	$\underline{R_9}$	$\underline{R_{12}}$
H	CH_3	CH_3
H	C_2H_5	CH_3
H	$n\text{-C}_3\text{H}_7$	CH_3
H	$2\text{-C}_3\text{H}_7$	CH_3
H	allyl	CH_3
CH_3	CH_3	CH_3
H	CH_3	C_2H_5
H	$\text{CH}_3\text{O}-\text{CO}-$	CH_3
H	CH_3	$n\text{-C}_4\text{H}_9$
C_2H_5	C_2H_5	CH_3
$n\text{-C}_4\text{H}_9$	$n\text{-C}_4\text{H}_9$	CH_3



(31)

<u>Ar</u>	<u>R₁₂</u>
3,5-dichlorophenyl	2-C ₃ H ₇
4-amino-3-chloro-5-cyanophenyl	CH ₃
4-amino-3-chloro-5-trifluoromethylphenyl	CH ₃
4-amino-3-chloro-5-H ₂ NCO-phenyl	CH ₃
4-amino-3-chloro-5-HOOC-phenyl	CH ₃
4-amino-3-chloro-5-methylphenyl	CH ₃
4-amino-3-bromo-5-cyanophenyl	CH ₃
4-amino-3-chloro-5-CH ₃ OCO-phenyl	CH ₃
4-amino-5-cyanophenyl	<i>t</i> -C ₄ H ₉

Example 8

4-Acetamido- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol acetate

In 15 ml of CH₂Cl₂, 1.57 g of 4-acetamido- β -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol is suspended and stirred while 1.2 g of triethylamine in 30 ml of CH₂Cl₂ is added, followed by 0.7 g of acetic anhydride in 15 ml of CH₂Cl₂. The mixture is stirred for 20 hours and then is washed with 100 ml of 10% NaOH solution. The organic phase is separated, dried (Na₂SO₄) and evaporated to dryness *in vacuo*. The residue is dissolved in 30 ml of ethanol and a trace of H₂O is added, followed by 10% HCl to acidify. The mixture is evaporated to dryness *in vacuo* and the residue is crystallized from acetone/hexane (30 ml/5 ml). This affords 1.35 g, mp. 254–257°C dec., of the title compound.

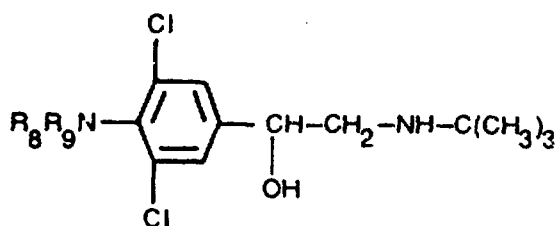
Similarly, by replacing acetic anhydride with propionic anhydride, butyric anhydride and pivalic anhydride, the corresponding propionate, butyrate and pivalate are prepared.

Example 9

 α -[(*tert*-butylamino)-methyl]3,5-dichloro-4-dimethylaminobenzyl alcohol

A mixture containing 50 g of *p*-fluoroacetophenone and 150 ml of 40% aqueous dimethylamine is warmed in a pressure bottle at 90–100°C. After two hours, a pale yellow oil is formed. The mixture is cooled, and the oil solidifies. The solid is collected and washed well with H₂O to give 54.93 g of *p*-dimethylaminoacetophenone, mp 101–103°C, after heptane recrystallization. A 72 g sample of this acetophenone is heated with 129 g of *N*-chlorosuccinimide in 700 ml of toluene to reflux temperature and maintained at this temperature for 35 minutes. The mixture is cooled and filtered. The filter cake is washed with 200 ml of toluene, and the filtrate and wash solution are evaporated to dryness *in vacuo* to afford 66 g of oil. This oil is chromatographed on SiO₂ with 40% hexane/CH₂Cl₂ to give 38.9 g of 3,5-dichloro-4-dimethylaminoacetophenone as a yellow oil. A 5.22 g sample of this oil is added portionwise to 2.75 g of SeO₂ in 20 ml of dioxane and 0.7 ml of H₂O at 55–60°C. This mixture is heated at reflux temperature for 4.5 hours, cooled and filtered through siliceous earth. The filter cake is washed with 20 ml of dioxane. The dioxane solutions are cooled to 15°C and 2.77 g of *t*-butylamine is added dropwise to afford a tan precipitate. After stirring 15 minutes at room temperature, the mixture is diluted with 200 ml of ethanol, cooled to 50°C and 7 g of NaBH₄ is added portionwise. After 15 hours, the mixture is treated with 300–400 g of ice and 200 ml of H₂O at below 10°C. The mixture is stirred to dissolve all solids and extracted with 300 ml of CH₂Cl₂. The CH₂Cl₂ layer is washed with 100 ml of H₂O, dried (MgSO₄) and evaporated to dryness *in vacuo* to give 5.6 g of orange oil. This oil is dissolved in ethyl ether, decolorized with activated carbon and concentrated to 15 ml. On cooling, crystals are obtained. The title product is collected as white crystals, mp 96–99°C.

The following compounds are prepared by the same method



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15

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R_8	R_9	mp °C
H	1-C ₄ H ₉	oil
H	1-C ₆ H ₁₃	62—64
H	C ₂ H ₅	209 (HCl salt)
H	cyclopentyl	oil
H	cyclohexyl	194—198 (HCl salt)

25

Example 10

α -[(*tert*-butylamino)methyl]-3,5-dichloro-4-methylaminobenzyl alcohol

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p-Methylaminoacetophenone is prepared and chlorinated by method described in Example 19 to give 3,5-dichloro-4-methylaminoacetophenone. This ketone (18 g) in 200 ml of CHCl₃ is stirred and 4.65 ml of Br₂ in 50 ml of CHCl₃ is added dropwise. After the addition is completed the mixture is stirred an additional 20 minutes and warmed to reflux temperature for 25 minutes. The mixture is cooled, 100 ml of H₂O is added and saturated Na₂CO₃ solution is added carefully until the mixture is neutral. The CHCl₃ layer is separated and the aqueous layer is further extracted with 100 ml of CH₂Cl₂. The combined extracts are dried (MgSO₄) and evaporated to dryness to afford 16.3 g of the phenacyl bromide. This material (16 g) in 80 ml of EtOH is stirred at 12—15°C and 40 ml of *t*-butylamine is added dropwise. After the addition is completed the mixture is stirred for 10 minutes at 12—15°C and then cooled to 5° and 4 g of NaBH₄ is carefully added. After stirring for 0.5 hours, the mixture is allowed to warm to room temperature and stirring is continued for 0.75 hours. The mixture is poured on 300 ml of ice with stirring and the resulting mixture is extracted with 300 ml of CH₂Cl₂. The CH₂Cl₂ extract is dried (MgSO₄) and evaporated to dryness *in vacuo* to give a yellow oil. Trituration of this residue with ethyl ether affords 7.45 g of the title compound, which melts at 98—101°C after recrystallization from ethyl ether.

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Example 11

5-[2-(*tert*-butylamino)-1-hydroxyethyl]anthranilonitrile

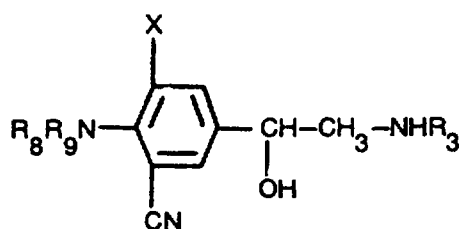
45

A mixture containing 48.86 g of *p*-aminoacetophenone in 490 ml of toluene is stirred while 64.5 g of *N*-bromosuccinimide is added in portions over 0.5 hours at below 40°C. After 15 minutes, the mixture is washed with H₂O (4 × 100 ml). The solution is dried (MgSO₄) and evaporated to dryness to afford 70.53 g of 4-amino-3-bromoacetophenone, mp 59—62°C. A 35 g sample of this material in 180 ml of dry dimethylformamide is stirred and heated at reflux with 17.57 g of Cu₂(CN)₂ for 6 hours under N₂ atmosphere. Subsequently, 180 ml of FeCl₃/HCl solution (40 g FeCl₃·6 H₂O/10 ml concentrated HCl/60 ml H₂) is added and the mixture is heated for 20 minutes at 60—70°C and poured into 350 ml of H₂O. The aqueous mixture is extracted with CH₂Cl₂ and the extracts are washed with H₂O, saturated NaHCO₃ solution and H₂O, respectively. The CH₂Cl₂ solution is evaporated to dryness *in vacuo* and the residue is recrystallized from 95% EtOH to afford 14.25 g, mp 155—15°C, of 4-amino-3-cyanoacetophenone. A 4.8 g sample of this product in 100 ml of EtOAc and 100 ml of CHCl₃ containing 13.32 g of CuBr₂ is heated at reflux temperature for 20 minutes. The mixture is further heated after 20 ml of EtOH is added and then filtered while still hot. The filter cake is washed with 50 ml of hot 20% MeOH/CH₂Cl₂ and the combined organic solutions are evaporated to dryness *in vacuo*. The residue is stirred in 25 ml of CH₂Cl₂ and the solid is collected and washed with CH₂Cl₂ to give 8.08 g of the phenacyl bromide. This material is added to 50 ml of *t*-BuNH₂ in 100 ml of EtOH at 5° under N₂ atmosphere. After 10 minutes of stirring, the mixture is allowed to warm to 30°C to give a solution. This solution is cooled to 10° and 4 g of NaBH₄ is added in portions. After 45 minutes, the mixture is allowed to warm (42°C) and kept at 20°C until the exotherm subsides. The mixture is then evaporated to dryness and the residue is washed with H₂O. The residue is dried and treated with 200 ml of boiling MeOH and the hot MeOH solution is filtered. The filter cake is further washed with hot MeOH and the combined filtrates are concentrated to afford crystals. This solid is recrystallized from MeOH/2-PrOH to afford 2.08 g, mp 184—186°C, of the title compound.

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In a similar manner, the following related compounds are prepared starting with the appropriate acetophenone:

(33)



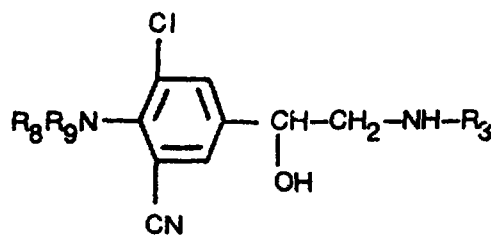
R_8	R_9	R_3	X
H	H	2-C ₃ H ₇	H
H	CH ₃	<i>t</i> -butyl	H
CH ₃	CH ₃	<i>t</i> -butyl	H
H	C ₂ H ₅	<i>t</i> -butyl	H
H	<i>n</i> -C ₃ H ₇	<i>t</i> -butyl	H
J	2-C ₃ H ₇	<i>t</i> -butyl	H
H	<i>n</i> -C ₄ H ₉	<i>t</i> -butyl	H
H	CH ₃	2-C ₃ H ₇	H
C ₂ H ₅	C ₂ H ₅	<i>t</i> -butyl	Cl
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	<i>t</i> -butyl	Cl
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	<i>t</i> -butyl	Cl

Example 12

3-chloro-5-[2-(*tert*-butylamino)-1-hydroxyethyl]anthranilonitrile

In 100 ml of toluene, 5 g of 4-amino-3-cyanoacetophenone is heated at reflux temperature for 20 minutes with 4.2 g of N-chlorosuccinimide. The mixture is cooled and filtered. The filtrate is further heated at reflux temperature for 2 hours. The precipitate is collected and washed with H₂O. The remaining solid is treated with 0.75 ml of Br₂/14 ml of CHCl₃ added to 75 ml of CHCl₃ and 4.9 ml of EtOH. The mixture is evaporated to dryness and the residue is slurried with CH₂Cl₂, collected and washed with CH₂Cl₂ to afford 2.84 g of the phenacyl bromide. This material is allowed to react with *t*-BuNH₂ and reduced with NaBH₄ by the procedure of Example 11 to afford the title compound, mp 128—138°C.

In a similar manner, the following compounds are prepared:



(34)

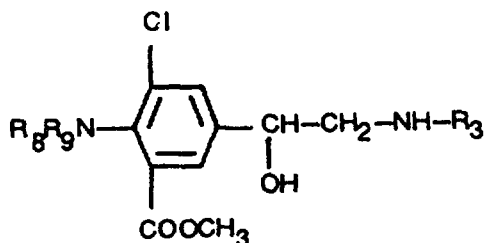
R_8	R_9	R_3
H	H	2-propyl
H	CH ₃	<i>t</i> -butyl
CH ₃	CH ₃	<i>t</i> -butyl
H	C ₂ H ₅	<i>t</i> -butyl
H	2-propyl	<i>t</i> -butyl
H	<i>n</i> -butyl	<i>t</i> -butyl

Example 13

5-[2-(*tert*-butylamino)-1-hydroxyethyl]-3-chloro-anthranilic acid, methyl ester, hydrochloride

A mixture containing 1.36 g of 5-[2-(*tert*-butylamino)-1-hydroxyethyl]-3-chloroanthranilonitrile in 21 ml of 50% aqueous NaOH and 21 ml of EtOH is stirred under N₂ for 0.5 hours. The mixture is evaporated to remove EtOH and acidified to pH 3 and further evaporated to dryness *in vacuo*. The residue treated several times with MeOH and evaporated to dryness. The solid is then treated with a solution which is prepared from 40 ml of MeOH and 2 ml of acetyl chloride. After allowing to stand overnight, the mixture is filtered and the filtrate is evaporated to dryness. The filter cake is also washed with MeOH and added to preceding filtrate. The residue is dissolved in acetone, filtered, and evaporated to dryness. The solid is triturated with Et₂O and filtered to give 1.49 g, mp 95–115°C, of the title compound.

In a similar manner, the following related esters are prepared:



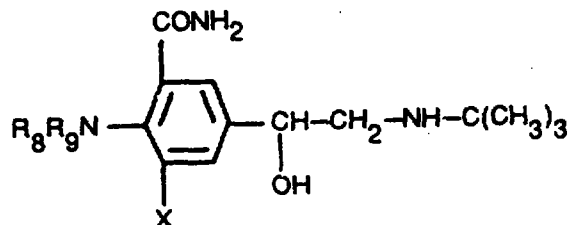
R_8	R_9	R_3
H	H	2-propyl
H	CH ₃	<i>t</i> -butyl
CH ₃	CH ₃	<i>t</i> -butyl
H	C ₂ H ₅	<i>t</i> -butyl
H	<i>n</i> -propyl	<i>t</i> -butyl
H	<i>n</i> -butyl	<i>t</i> -butyl
H	allyl	<i>t</i> -butyl
C ₂ H ₅	C ₂ H ₅	<i>t</i> -butyl
<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₉	<i>t</i> -butyl
<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	<i>t</i> -butyl

Example 14

2-Amino-3-bromo-5-[2-(*tert*-butylamino)-1-hydroxyethyl]benzamide

A mixture containing 1.02 g of 3-bromo-5-[2-(*tert*-butylamino)-1-hydroxyethyl]anthranilonitrile in 25 ml of H₂O, 5 ml of 50% NaOH and 30 ml of EtOH is stirred and heated at 55—65°C under N₂ atmosphere for 1.25 hours. The mixture is evaporated to remove EtOH and extracted with CHCl₃. The CHCl₃ extract is washed with 25 ml of 2% NaOH, dried (MgSO₄) and evaporated to dryness to afford 0.74 g. This solid is stirred with pentane and filtered to afford 0.6 g, mp 135—145°C, of the title compound.

Similarly, the following compounds are prepared:



<u>R₈</u>	<u>R₉</u>	<u>X</u>
H	CH ₃	Cl
H	C ₂ H ₅	Cl
CH ₃	CH ₃	Cl
H	2-C ₃ H ₇	Cl
H	n-C ₄ H ₉	Cl
H	CH ₃	Br
C ₂ H ₅	C ₂ H ₅	Cl
n-C ₃ H ₇	n-C ₃ H ₇	Cl
n-C ₄ H ₉	n-C ₄ H ₉	Cl

Example 15

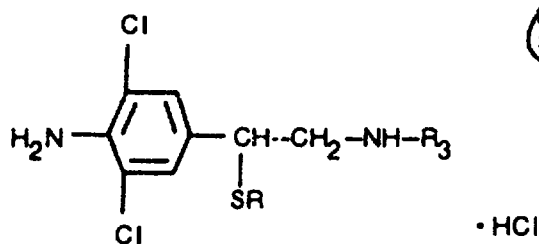
4-amino-N-*tert*-butyl-3,5-dichloro-β-(methylthio)phenethylamine hydrochloride

In the manner described in Example 3, N-*tert*-butyl-3,5-dichloro-β-chloro-4-aminophenethylamine hydrochloride is prepared. An 11 g sample of this product is portionwise added to 5 ml of methyl mercaptan in 100 ml of dry ethylenedichloride at +10°C to 0°C. The mixture is stirred and allowed to rise gradually to room temperature over a four day period. The mixture is filtered, the filter cake is washed with ethylenedichloride (2 × 500 ml). The solid is dispersed in 200 ml of H₂O, cooled to 5°C and basified with 6N NaOH solution to give a white oil, which is extracted with CH₂Cl₂ (3 × 100 ml). The CH₂Cl₂ (3 × 100 ml). The CH₂Cl₂ extract is dried (MgSO₄) and evaporated to dryness to give 6.41 g of dark green oil. This oil is stirred in HCl/isopropanol and the mixture is evaporated to dryness. The residue is stirred in 35 ml of ethyl ether for 16 hours and filtered to give 3.63 g, mp 178—181°C *c. ac.* This solid is heated in refluxing ethyl acetate and filtered to give 2.07 g, mp 188—193°C. Recrystallization from 75 ml of ethylenedichloride affords 1.45 g of the title compound, mp 191—196°C.

The title compound is also obtained by adding 5—10 fold excess of sodium mercaptide in tetrahydrofuran at 0—10°C and by following the above workup.

Example 16

In the same manner as described in Example 15, the following thioesters are prepared by substituting methyl mercaptan with the corresponding mercaptans:



<u>R</u>	<u>R₃</u>
methyl	2-propyl
ethyl	<i>t</i> -butyl
2-propyl	<i>t</i> -butyl
<i>n</i> -butyl	<i>t</i> -butyl
<i>t</i> -butyl	<i>t</i> -butyl
<i>n</i> -hexyl	<i>t</i> -butyl
phenyl	<i>t</i> -butyl
benzyl	2-propyl

Example 17

In the manner described in Example 15, substitution of corresponding chloro compound for *N*-butyl-3,5-dichloro- β -chloro-4-aminophenethylamine hydrochloride and adding the appropriate mercaptans afford the following thioethers:

$$\begin{array}{c}
 \text{Ar}-\text{CH}(\text{Cl})-\text{CH}_2-\text{NH}-\text{R}_3 + \text{RSH} \rightarrow \text{Ar}-\text{CH}(\text{SR})-\text{CH}_2-\text{NHR}_3
 \end{array}$$

<u>Ar</u>	<u>R</u>	<u>R₃</u>
4-amino-3-cyanophenyl	methyl	2-propyl
4-methylamino-3,5-dichlorophenyl	methyl	<i>t</i> -butyl
4-amino-3-chloro-5-trifluoromethyl	methyl	<i>t</i> -butyl
4-amino-3-chloro-5-cyanophenyl	methyl	<i>t</i> -butyl
4-amino-3-chloro-5-cyanophenyl	ethyl	<i>t</i> -butyl
4-acetamido-3,5-dichlorophenyl	methyl	<i>t</i> -butyl
4-amino-3-chloro-5-H ₂ NCO-phenyl	methyl	<i>t</i> -butyl
4-amino-3-chloro-5-HOCO-phenyl	methyl	<i>t</i> -butyl
4-amino-3-chloro-5-methylphenyl	ethyl	<i>t</i> -butyl
4-amino-3-chloro-5-methoxyphenyl	<i>n</i> -butyl	<i>t</i> -butyl
4-amino-3-chloro-5-nitrophenyl	methyl	<i>t</i> -butyl
4-amino-3-chloro-5-CH ₃ O-CO-phenyl	methyl	<i>t</i> -butyl

Example 18

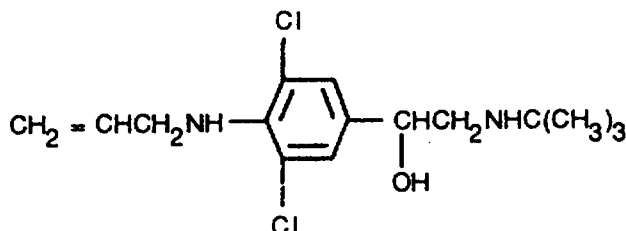
α -[(*tert*-butylamino)methyl]-3,5-dichloro-4-diethylaminobenzyl alcohol

In the manner described in Example 9, 3,5-dichloro-4-diethylaminoacetophenone is oxidized with SeO_2 and reductively alkylated with *t*-BuNH₂/NaBH₄ to afford the title compound, mp 93–96°C.

Similarly, α -[(*tert*-butylamino)methyl]-3,5-dichloro-4-(*n*-dipropyl)aminobenzyl alcohol and α -[(*tert*-butylamino)methyl]-3,5-dichloro-4-(*n*-dibutyl)aminobenzyl alcohol are prepared.

Example 19

4-(Allylamino)- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol



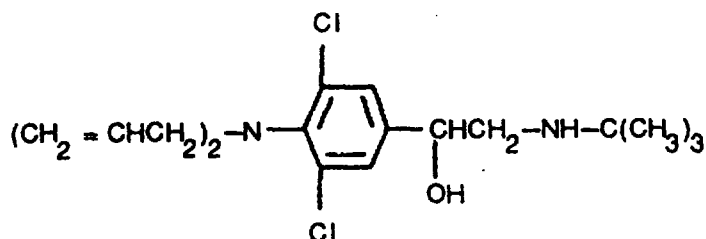
(a) Triethylamine (17.0 g, 0.168 mol) is added in one portion to allyl bromide (105.9 g, 0.875 mol) under a nitrogen atmosphere. The resulting white emulsion gives an exotherm to 70°C and becomes a thick white solid mass within 5 minutes. The solution formed with the addition of ~100 ml of DMF is stirred for 1 hour at 70–95°C. A solution of 4'-amino-2-bromo-3',5'-dichloroacetophenone (25.0 g, 0.088 mol) in 50 ml of DMF is added in one portion and the resulting brown reaction mixture is maintained at 80–90°C for 2 hours. The progress of the reaction is frequently checked by thin layer chromatography ($\text{SiO}_2/\text{CH}_2\text{Cl}_2/\text{hexanes}$ (1/1)) since prolonged heating results in the decomposition of both starting material and products. The reaction mixture is poured into 1.5 l of H_2O and is stirred for 0.5 hours. After a second aqueous trituration, the residual brown semi-solids are stirred with ~150 ml of CCl_4 for 0.5 hours to form a suspension. The yellowish-brown solids are collected by filtration and are air dried to give 14.9 g (59.6%) of recovered phenacyl bromide starting material. The CCl_4 filtrate is stirred with MgSO_4 , filtered and concentrated to yield 9.42 g of a brown syrup. Gradient elution ($\text{hexanes}/\text{CH}_2\text{Cl}_2$) (10/0 → 8/2 flash chromatography on a 9" x 2" column of Silica Gel 60 gives two major fractions:

(A) 1.82 g (5.7%) of a faster moving amber syrup, identified as 2-bromo-3',5'-dichloro-4'-diallylaminoacetophenone by IR (neat) 1680 cm^{-1} ; NMR (CDCl_3) δ 7.93 (s, 2, Ar-H), 6.25–5.55 (complex m, 2, CH=), 5.40–4.95 (complex m, 4, CH_2), 4.40 (s, 2, CH_2Br) and 3.87 (m resembling d, 4, $\text{J}=6\text{Hz}$, CH_2N); chemical ionization mass spectrum ($\text{M} + \text{H}$)⁺ = 362; and

(B) 3.49 g (12.2%) of a slower moving brown syrup, identified as 4'-(allylamino)-2-bromo-3',5'-dichloroacetophenone by IR (neat) 3330, 1670 cm^{-1} ; NMR (CDCl_3) δ 7.83 (s, 2, Ar-H), 6.35–5.65 (complex m, 1, CH=), 5.50–5.00 (complex m, 2, CH_2 =), 4.84 (br, t, 1, NH), 4.37 (s, 2, CH_2Br) and 4.20 (br, m, 2, CH_2N); chemical ionization mass spectrum ($\text{M} + \text{H}$)⁺ = 322.

(b) A solution of 4'-(allylamino)-2-bromo-3',5'-dichloroacetophenone (2.88 g, 8.92 mmol) in 10 ml is added dropwise over 1 hour to a stirred solution of *t*-butylamine (1.34 g, 18.3 mmol) in 29 ml of THF. The reaction temperature is maintained at –24°–13° by cooling a dry ice- CCl_4 bath. The resulting amber suspension is warmed to room temperature over 30 minutes and is stirred at 21–22°C for 1.5 hours. Sodium Cyanoborohydride (2.80 g, 44.6 mmol) is added in two portions over 5 minutes to give a thick tan suspension with an exotherm from 22–25°C. Glacial acetic acid (~10 ml) is added dropwise to gradually form a yellow solution which is stirred at room temperature for 3 days. The reaction mixture is poured into a solution of 100 ml of H_2O and 100 ml of saturated aqueous NaCl which is then adjusted to pH7 with 10% Na_2CO_3 and extracted three times with Et_2O . The combined extracts are shaken with two portions of diluted aqueous HCl which are combined, neutralized with 10% Na_2CO_3 to pH8 and extracted three times with Et_2O . After stirring the combined extracts with anh. K_2CO_3 , the pale yellow-green solution is filtered and concentrated to yield 2.04 g (72.1%) of pale yellow syrup, identified as 4-(allylamino)- α -[(*tert*-butylamino)methyl]-3,5-dichlorobenzyl alcohol by IR (neat) 3400 cm^{-1} ; NMR (CDCl_3) δ 7.32 (s, 2, Ar-H), 6.35–5.60 (complex m, 1, CH=), 5.45–4.95 (complex m, 2, CH_2 =), 4.52 (d of d, 1, Ar-CH), 3.97 (overlapping m, 3, Ar- NHCH_2), 3.03 (br s, 2, NH and OH), 2.68 (m, 2, CH_2N) and 1.13 (s, 9, $\text{C}(\text{CH}_3)_3$); chemical ionization mass spectrum ($\text{M} + \text{H}$)⁺ = 317. The $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{conc. NH}_4\text{OH}$ (80/19/1) shows one major spot ($R_f = 0.6$) with nine trace impurities. The syrup gradually crystallizes to a tan solid on standing.

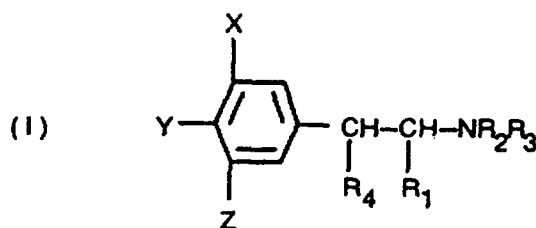
Example 20

 α -[(*tert*-butylamino)methyl]-3,5-dichloro-4-diallylaminobenzyl alcohol

The title compound is prepared using a starting material fraction (A) of Example 19 (a) and the procedure described in Example 19 (b). The pale yellow syrup, which gradually crystallizes on standing, is identified by IR (neat) 3300 and 1630 cm^{-1} ; NMR (CDCl_3) δ 7.26 (s, 2, Ar—H), 6.23—5.54 (complex m, 2, CH=), 5.32—4.87 (complex m, 4, CH_2 =), 4.48 (m, 1, Ar—CH), 3.78 (m resembling d, 4, J=6Hz, Ar— NCH_2), 3.4—2.0 (br, s, 2, NH and OH), 2.62 (m, 2, CH_2N) and 1.13 (s, 9, $\text{C}(\text{CH}_3)_3$); chemical ionization mass spectrum ($\text{M} + \text{H}^+$) = 357, corresponding to that expected of the title compound.

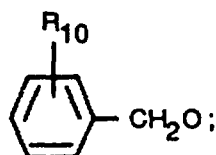
Claims

1. A method for enhancing the growth rate and for reducing the fat deposition in meat-producing animals by administering to said animals a compound of the following formula, at selected levels of administration,

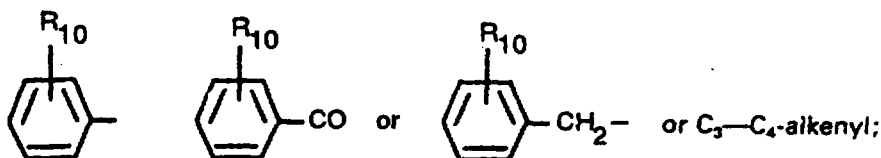


wherein

- X is hydrogen or halogen;
- Y is hydrogen, NR_8R_9 or NHCOR_5 ;
- Z is halogen, CN, CF_3 , COOR_{11} , CONH_2 , methyl, methoxy or NO_2 ;
- R_1 is hydrogen, C_1 — C_4 alkyl;
- R_2 is hydrogen, C_1 — C_8 alkyl or C_3 — C_4 alkenyl;
- R_3 is hydrogen C_1 — C_8 alkyl, C_3 — C_6 cycloalkyl, C_3 — C_4 alkenyl, phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl or benzyl;
- R_4 is OH, OR_6 or SR_{11} ;
- R_5 is hydrogen, C_1 — C_4 alkyl, C_1 — C_4 alkoxy or



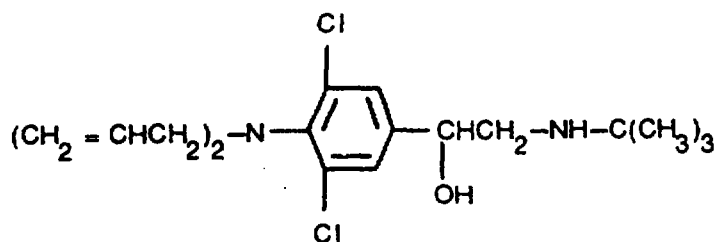
R_6 is C_1 — C_8 alkyl, C_2 — C_5 alkanoyl,





Example 20

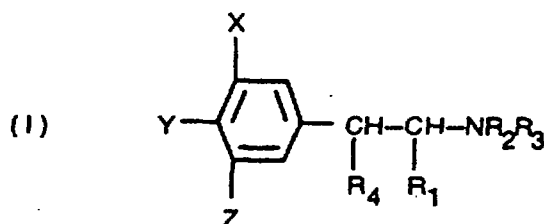
α -[(*tert*-butylamino)methyl]-3,5-dichloro-4-diallylaminobenzyl alcohol



The title compound is prepared using a starting material fraction (A) of Example 19 (a) and the procedure described in Example 19 (b). The pale yellow syrup, which gradually crystallizes on standing, is identified by IR (neat) 3300 and 1630 cm^{-1} ; NMR (CDCl_3) δ 7.26 (s, 2, Ar—H), 6.23—5.54 (complex m, 2, CH=), 5.32—4.87 (complex m, 4, CH_2 =), 4.48 (m, 1, Ar—CH), 3.78 (m resembling d, 4, J=6Hz, Ar— NCH_2), 3.4—2.0 (br, s, 2, NH and OH), 2.62 (m, 2, CH_2N) and 1.13 (s, 9, $\text{C}(\text{CH}_3)_3$); chemical ionization mass spectrum ($\text{M} + \text{H}$) $^+$ = 357, corresponding to that expected of the title compound.

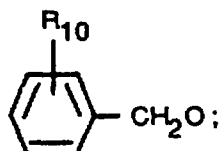
Claims

1. A method for enhancing the growth rate and for reducing the fat deposition in meat-producing animals by administering to said animals a compound of the following formula, at selected levels of administration,

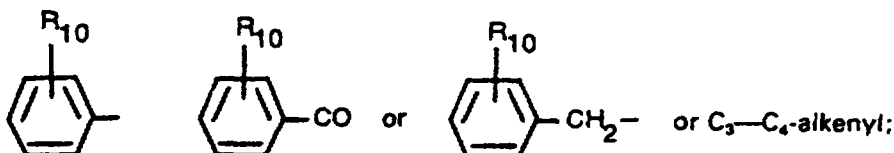


wherein

- X is hydrogen or halogen;
- Y is hydrogen, NR_5R_6 or NHCOR_5 ;
- Z is halogen, CN, CF_3 , COOR_1 , CONH_2 , methyl, methoxy or NO_2 ;
- R_1 is hydrogen, C_1 — C_4 alkyl;
- R_2 is hydrogen, C_1 — C_6 alkyl or C_3 — C_4 alkenyl;
- R_3 is hydrogen, C_1 — C_6 alkyl, C_3 — C_6 cycloalkyl, C_3 — C_4 alkenyl, phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl or benzyl;
- R_4 is OH, OR_6 or SR_{11} ;
- R_5 is hydrogen, C_1 — C_4 alkyl, C_1 — C_4 alkoxy or



R_6 is C_1 — C_6 alkyl, C_2 — C_5 alkanoyl,



R_2 is hydrogen, C_1-C_4 -alkyl or C_3-C_4 -alkenyl;

R_3 is hydrogen, C_1-C_6 alkyl, C_4-C_6 cycloalkyl or C_3-C_4 alkenyl;

R_{10} is chloro, dichloro, methyl, dimethyl, methoxy, dimethoxy or nitro;

R_{11} is C_1-C_6 -alkyl, phenyl, or benzyl;

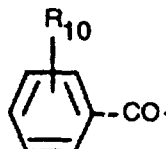
with the provisos that

when R_3 is phenyl, 2-hydroxyethyl, α,α -dimethylphenethyl, C_3-C_6 cycloalkyl or benzyl R_2 is hydrogen;

and

when R_3 is 2-hydroxyethyl, R_4 is hydroxyl; and

when R_6 is alkanoyl or



R_2 and R_3 are substituents other than hydrogen, except when R_3 is an alkyl or a substituted alkyl group which contains a tertiary carbon attached to the nitrogen; and

when Y is hydrogen, X and Z are halogen, and R_2 is hydrogen and R_3 is isopropyl, 2-butyl or *t*-butyl;

and

when R_6 is C_1-C_4 alkyl or C_3-C_4 alkenyl, R_9 is hydrogen, C_1-C_4 alkyl or C_3-C_4 alkenyl; and

that at least one of X and Y represents a substituent other than hydrogen; and

when Z is a group other than halogen, Y is NR_8R_9 or $NHCOR_5$; and

further provided that when Y is hydrogen, NH_2 or $NHCOR_5$, and Z is halogen then R_4 cannot be OH or OR_6 , wherein R_6 is C_1-C_6 alkyl;

racemic mixtures of the above identified compounds and the optically active isomers, and non-toxic, pharmacologically acceptable acid addition salts thereof.

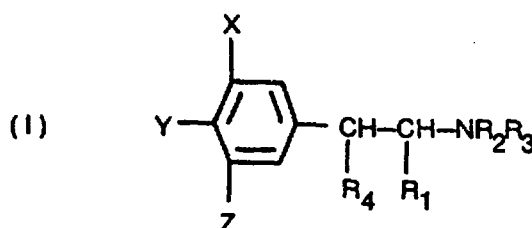
2. A method according to Claim 1, characterized in that 5-[1-hydroxy-2-(isopropylamino)ethyl] anthranilonitrile is administered.

3. A method according to Claim 1, characterized in that 5-[2-(*tert*-butylamino)-1-hydroxyethyl]-N-ethyl-anthranilotrile is administered.

4. A method according to Claim 1, characterized in that 5-[2-(*tert*-butylamino)-1-hydroxyethyl] anthranilonitrile is administered.

Patentansprüche

1. Verfahren zur Steigerung der Wachstumsrate und zur Reduzierung der Lagerung bei fleischerzeugenden Tieren durch Verabreichung einer Verbindung der folgenden Formel mit ausgewählten Verabreichungspegeln an die Tiere



wobei

X für Wasserstoff oder Halogen steht;

Y für Wasserstoff, NR_8R_9 oder $NHCOR_5$ steht;

Z für Halogen, CN, CF_2 , $COOR_{11}$, $CONH_2$, Methyl, Methoxy oder NO_2 steht;

R_1 für Wasserstoff, C_1-C_4 -Alkyl steht;

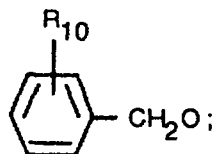
R_2 für Wasserstoff, C_1-C_6 -alkyl oder C_3-C_4 -Alkenyl steht;

R_3 für Wasserstoff, C_1-C_6 -Alkyl, C_3-C_6 -Cycloalkyl, C_3-C_4 -Alkenyl, Phenyl, 2-Hydroxyäthyl, α,α -Dimethylphenäthyl oder Benzyl steht;

R_4 für OH, OR_6 oder SR_{11} steht;

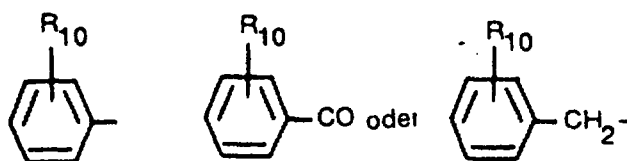


R_5 für Wasserstoff, C_1 - C_4 -Alkyl, C_1 - C_4 -Alkoxy oder



steht;

R_6 für C_1 - C_6 -Alkyl, C_2 - C_5 -Alkanoyl,



oder C_3 - C_4 -alkenyl;

R_8 für Wasserstoff, C_1 - C_4 -Alkyl oder C_3 - C_4 -Alkenyl steht;

R_9 für Wasserstoff, C_1 - C_6 -Alkyl, C_4 - C_6 -Cycloalkyl oder C_3 - C_4 -Alkenyl steht;

R_{10} für Chlor, Dichlor, Methyl, Dimethyl, Methoxy, Dimethoxy oder Nitro steht;

R_{11} für C_1 - C_6 -Alkyl, Phenyl oder Benzyl steht;

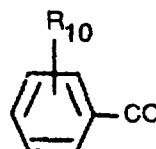
mit den Maßgaben, daß

falls R_2 für Phenyl, 2-Hydroxyäthyl, α,α -Dimethylphenäthyl, C_3 - C_6 -Cycloalkyl oder Benzyl steht, R_2 für

Wasserstoff steht; und

falls R_3 für 2-Hydroxyäthyl steht, R_4 für Hydroxyl steht, und

falls R_6 für Alkanoyl oder



steht, R_2 und R_3 für andere Substituenten als Wasserstoff stehen, ausgenommen den Fall, daß R_3 eine Alkyl- oder eine substituierte Alkylgruppe bedeutet, welche ein tertiäres Kohlenstoffatom, gebunden an den Stickstoff, enthält; und

falls Y für Wasserstoff steht, X und Z für Halogen stehen und R_2 für Wasserstoff steht und R_3 für Isopropyl, 2-Butyl oder t -Butyl steht; und

falls R_6 für C_1 - C_4 -Alkyl oder C_3 - C_4 -Alkenyl steht, R_9 für Wasserstoff, C_1 - C_4 -Alkyl oder C_3 - C_4 -Alkenyl steht; und

daß mindestens einer von X und Y für einen anderen Substituenten als Wasserstoff steht; und

falls Z für eine andere Gruppe als Halogen steht, Y für NR_8R_9 oder $NHCOR_5$ steht; und

mit der weiteren Maßgabe, daß falls Y für Wasserstoff, NH_2 oder $NHCOR_5$ steht, und Z für Halogen steht, R_4 nicht OH oder OR_6 sein kann, wobei R_6 für C_1 - C_6 -Alkyl steht;

racemische Mischungen der oben identifizierten Verbindungen und die optisch aktiven Isomeren und nichttoxische, pharmakologische akzeptable Säureadditionssalze derselben.

2. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß 5-[1-Hydroxy-2-(isopropylamino)äthyl]-anthranilonitril verabreicht.

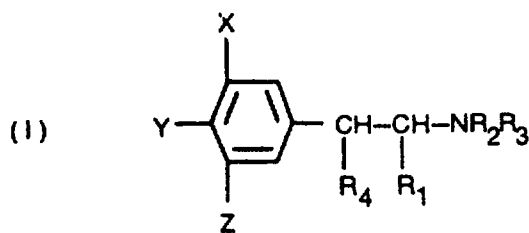
3. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß 5-[2-($tert$ -Butylamino)-1-hydroxyäthyl]- N -äthylanthranilonitril verabreicht.

4. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß 5-[2-($tert$ -Butylamino)-1-hydroxyethyl]-anthranilonitril verabreicht.

Revendications

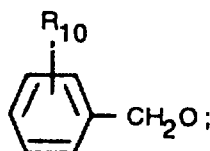
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1. Procédé pour accroître le taux de croissance et réduire le dépôt de graisses dans les animaux produisant de la viande par administration aux animaux, à des niveaux d'administration choisis, d'un composé de formule suivante:

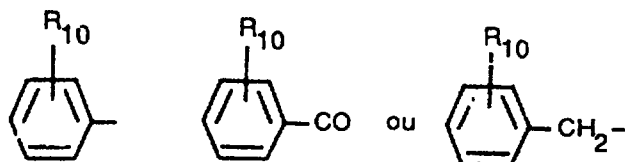


dans laquelle

- X est un hydrogène ou halogène;
 Y est un hydrogène, NR_6R_9 ou NHCOR_5 ;
 Z est un halogène, CN, CF_3 , COOR_1 , CONH_2 , méthyle, méthoxy ou NO_2 ;
 R_1 est un hydrogène, (C_1-C_4) alkyle;
 R_2 est un hydrogène, (C_1-C_6) alkyle ou (C_3-C_4) alcényle;
 R_3 est un hydrogène, (C_1-C_6) alkyle, (C_3-C_6) cycloalkyle, (C_3-C_4) alcényle, phényle, 2-hydroxyéthyle, α, α -diméthylphénéthyle ou benzyle;
 R_4 est OH, OR_6 ou SR_{11} ;
 R_5 est un hydrogène, (C_1-C_4) alkyle, (C_1-C_4) alkoxy ou



R_6 est un C_1-C_6 alkyle, (C_2-C_5) alcanoyle,

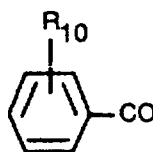


ou C_3-C_4 alcényle;

- R_6 est un hydrogène, (C_1-C_4) alkyle ou (C_3-C_4) alcényle;
 R_9 est un hydrogène, (C_1-C_6) alkyle, (C_4-C_6) cycloalkyle ou (C_3-C_4) alcényle;
 R_{10} est un chloro, dichloro, méthyle, diméthyle, méthoxy, diméthoxy ou nitro;
 R_{11} est (C_1-C_6) alkyle, phényle ou benzyle;

sous réserve que

- lorsque R_3 est un phényle, 2-hydroxyéthyle, α, α -diméthylphénéthyle, (C_3-C_6) cycloalkyle ou benzyle, R_2 est un hydrogène; et
 lorsque R_3 est 2-hydroxyéthyle, R_4 est hydroxyle, et
 lorsque R_6 est alcanoyle ou





R_2 et R_3 sont des substituants autres que l'hydrogène, excepté lorsque R_3 est un groupe alkyle ou un groupe alkyle substitué qui contient un carbone tertiaire attaché à l'azote; et

lorsque Y est un hydrogène, X et Z sont des halogènes et R_2 est un hydrogène et R_3 est un isopropyle, 2-butyle ou *t*-butyle; et

5 lorsque R_2 est un (C_1-C_4) alkyle ou (C_3-C_4) alcényle, R_3 est un hydrogène, (C_1-C_4) alkyle ou (C_3-C_4) alcényle; et

qu'au moins l'un de X et Y représente un substituant autre qu'un hydrogène, et

lorsque Z est un groupe autre qu'un halogène, Y est NR_6R_9 ou $NHCOR_5$; et

de plus sous réserve que lorsque Y est un hydrogène, NH_2 ou $NHCOR_5$, et Z est un halogène alors R_4 ne

10 peut être OH ou OR_6 , R_6 étant un (C_1-C_8) alkyle;

les mélanges racémiques de ces composés et leurs isomères optiquement actifs, et leurs sels d'addition à des acides pharmacologiquement acceptables.

2. Procédé selon la revendication 1, caractérisé en ce que l'on administre le 5-[1-hydroxy-2-(isopropilamino)éthyl] anthranilo-nitrile.

15 3. Procédé selon la revendication 1, caractérisé en ce que l'on administre le 5-[2-(*tert*-butylamino)-1-hydroxyéthyl]-N-éthylanthranilonitrile.

4. Procédé selon la revendication 1, caractérisé en ce que l'on administre le 5-[2-(*tert*-butylamino)-1-hydroxyéthyl] anthranilonitrile.

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