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N-SECONDARY ALKYL ALKANEDIAMINES AND DERIVATIVES THEREOF AS ANTI-INFLAMMATORY AGENTS

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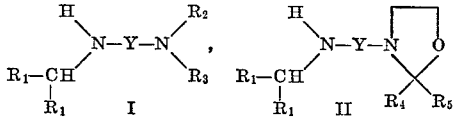
ABSTRACT OF THE DISCLOSURE

A series of N-secondary alkyl alkanediamines, and pro-drug forms thereof; namely, 3-[(ω-secondary alkylamino) alkyl]oxazolidines; 1,3-dialkyl-1,3-diazacycloalkanes; and the non-toxic acid addition salts thereof having the formulae below are useful as anti-inflammatory and immunosuppressive agents:



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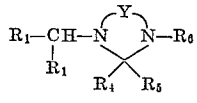


III

wherein

Y is alkylene of from 2 to 5 carbon atoms;
R_1 is alkyl of from 4 to 13 carbon atoms;
R_2 is hydrogen, 2-hydroxyethyl or ethyl;
R_3 is 2-hydroxyethyl or R_6 wherein R_6 is alkyl of from 1 to 20 carbon atoms;
R_4 is hydrogen, alkyl of from 1 to 20 carbon atoms; cycloalkyl of from 3 to 7 carbon atoms; phenyl or substituted phenyl wherein the substituent is halogen, lower alkyl, lower alkoxy, cyano or trifluoromethyl;
R_5 is R_4, thienyl, pyridyl or furyl; and
R_4 and R_5 when taken together with the carbon atom to which they are attached are cycloalkyl of from 3 to 7 carbon atoms.

BACKGROUND OF THE INVENTION

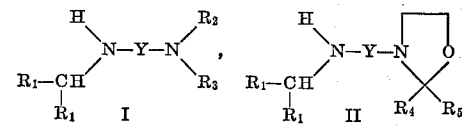
This invention relates to novel 3-[(ω-secondary alkylamino)alkyl]oxazolidines; 1,3 - dialkyl - 1,3-diazacycloalkanes and N-secondary alkyl alkanediamines for which the aforenamed compounds serve as pro-drugs; and the non-toxic acid addition salts thereof, which are useful as anti-inflammatory agents and immunosuppressants.

The high incidence of rheumatoid arthritis and an awareness of the chronic disability and crippling deformity associated with this disease has within recent years given rise to major projects aimed at determining its etiology and developing methods for treating and eliminating, or at least minimizing, its effects. A wide variety of drugs have been used for the treatment of rheumatoid arthritis. The most commonly used are anti-inflammatory agents such as salicylates, phenylbutazone, phenacetin, acetophenetidine, cinchophen, neocinchophen and corticosteroids. Other drugs, the therapeutic value and mechanism of action of which are debatable, gold salts, chloroquines, indomethacin and, more recently, alkylating agents such as N,N',N''-triethylenephosphoramide, cyclophosphamide, tris(chloroethyl)amine; urea derivatives and antilymphocyte serum. However, such drugs suffer from

various shortcomings such as limited efficacy, toxic side-effects, short-term response and narrow therapeutic index.

SUMMARY OF THE INVENTION

It has now been discovered that novel 3-[(ω-secondary alkylamino)alkyl]oxazolidines; 1,3-dialkyl-1,3-diazacycloalkanes; and N-secondary alkyl alkanediamines, the compounds for which the aforementioned heterocyclic products serve as pro-drugs; and the non-toxic acid addition salts of all these compounds having the formulae below are useful as anti-inflammatory and immunosuppressive agents:



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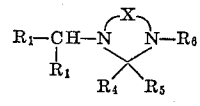


III

wherein

Y is alkylene of from 2 to 5 carbon atoms and is selected from the group consisting of ethylene, trimethylene, tetramethylene and pentamethylene;
R_1 is selected from the group consisting of alkyl of from 4 to 13 carbon atoms;
R_2 is selected from the group consisting of hydrogen, 2-hydroxyethyl and ethyl;
R_3 is selected from the group consisting of 2-hydroxyethyl and R_6 wherein R_6 is alkyl of from 1 to 20 carbon atoms;
R_4 is selected from the group consisting of hydrogen, alkyl of from 1 to 20 carbon atoms, cycloalkyl of from 3 to 7 carbon atoms, phenyl and substituted phenyl wherein the substituent is selected from the group consisting of halogen, lower alkyl, lower alkoxy, cyano and trifluoromethyl;
R_5 is selected from the group consisting of R_4, thienyl, pyridyl and furyl;
R_4 and R_5 when taken together with the carbon atom to which they are attached are selected from the group consisting of cycloalkyl of from 3 to 7 carbon atoms.

By the terms "lower alkyl" and "lower alkoxy" is meant those alkyl and alkoxy groups having from 1 to 4 carbon atoms, since such materials are generally more readily available than are compounds having larger alkyl or alkoxy groups.

By "non-toxic acid addition salts" is meant those acid addition salts which are non-toxic at the dosages administered for the purposes of this invention. Representative non-toxic acid addition salts of the above-mentioned bases which may be employed are the water soluble and water insoluble salts such as the hydrochloride, hydrobromide, phosphate, nitrate, sulfate, acetate, hexafluorophosphate, citrate, gluconate, benzoate, propionate, butyrate, sulfosalicylate, maleate, laurate, malate, fumarate, succinate, oxalate, tartrate, amsonate (4,4' - diaminostilbene - 2,2'-disulfonate), pamoate (1,1'-methylene - bis-2-hydroxy-3-naphthoate), stearate, 3-hydroxy-2-naphthoate, p-toluenesulfonate, picrate, lactate and suramin salt.

Also included within the scope of this application are the toxic acid addition salts. Such salts, while not suitable for therapy, are useful for isolation and purification of the compounds described herein as well as for the preparation of the non-toxic acid addition salts. Toxic acid addition salts include hydrofluoride, oxalate and picrate.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention of Formula I are prepared by the known reductive alkylation reaction of a ketone and an alkanediamine ($H_2N—Y—NR_2R_3$) as is described in U.S. 3,197,510, issued July 27, 1965. The reductive alkylation is normally carried out using equimolar proportions of the appropriate ketone and diamine reactant although an excess of one or the other reactant can be used to insure complete reaction. The use of an excess of one reactant is frequently employed in cases wherein the other reactant is not readily available. The reaction can be carried out as a one-step or two-step process.

It is preferred to conduct the reaction as a two-step process since it permits isolation of the intermediate Schiff's base resulting in a more easily purified end-product than does the one-step process. The first step comprises formation of the Schiff's base by reaction of the appropriate ketone and alkanediamine ($H_2N—Y—NR_2R_3$) usually in the presence of a solvent and at an elevated temperature to permit removal of by-product water. Any suitable solvent can be used, but it is advantageous to use a solvent which forms an azeotrope with by-product water and thus facilitates its removal and completion of the reaction. The reaction is conducted at a temperature of from about 50° C. to about 200° C. and is normally conducted at the boiling point of the solvent system used.

As an alternative to removal of the water azeotropically or by simple distillation, molecular sieves can be used as adsorbents for the water. Suitable adsorbents are the natural and synthetic crystalline aluminosilicates. The latter adsorbents are favored because of their greater water-loading capacity relative to the natural crystalline aluminosilicates. Included among such adsorbents are chabazite, gmelinite and analcite, naturally-occurring materials, the synthetic "Linde Molecular Sieves" produced and distributed by the Linde Company, such as Types 4A, 5A and 13X, and the "Microtraps" produced by the Davison Company. Such materials sorb and thus effectively remove water from the reaction medium. The exhausted or partially exhausted aluminosilicate is separated from the reaction mixture by filtration or decantation. The adsorbent is regenerated by heating to an elevated temperature, e.g., about 150° to 350° C., with simultaneous purging with air or nitrogen to desorb the water.

When using a molecular sieve to effectively remove by-product water, it is necessary to use a reaction-inert solvent such as benzene, toluene, dimethyl sulfoxide, ethanol or propanol.

The Schiff's base thus produced is isolated by methods well known to those skilled in the art such as filtration in cases wherein the Schiff's base precipitates as a solid and/or by concentration of the solvent. It is then reduced in any suitable manner. The reduction can be accomplished by sodium and alcohol, by aluminum amalgam, by alkali metal hydrides, by catalytic hydrogenation in the presence of a catalyst such as nickel, palladium, platinum, rhodium, etc., and by other methods known to those skilled in the art. For convenience when catalytic hydrogenation is used, the catalyst is composited with a suitable support such as alumina or charcoal. The reduction is normally conducted at greater than atmospheric pressure at a temperature of from about 100° C. to 300° C. Pressures of from about 50 to 3000 p.s.i. are advantageously used to effect reduction. It is preferred to use sodium borohydride reduction since the reaction can be conducted at atmospheric pressure in the original reaction vessel under relatively mild conditions.

The reductive alkylation process when conducted as a one-step reaction is affected in the presence of a suitable catalyst and hydrogen. A favored catalyst for the one-step process, because of the satisfactory yields produced, is platinum. Other catalysts which can be used are copper oxide, barium oxide, copper chromite, chromium oxide, etc. The reaction conditions for the one-step process are essentially the same as those for the two-step process.

Compounds of Formula II above are readily prepared from compounds of Formula I wherein R_2 is hydrogen and R_3 is 2-hydroxyethyl and an appropriate aldehyde or ketone. The reaction, a condensation, is easily reversible and is, therefore, conducted under conditions which remove by-product water and usually with an excess of the carbonyl reactant. The condensation is generally carried out in a suitable solvent such as ether, benzene, a lower alkanol, (e.g., ethanol, butanol) with continuous separation of water. A catalyst such as potassium carbonate, p-toluene sulfonic acid is sometimes used but is not necessary. Here also, as in the reductive alkylation procedure discussed above, a molecular sieve can be used to effect removal of water. The products are recovered by removal of the solvent and purified by distillation in vacuo or recrystallization.

Compounds of Formula III are also conveniently prepared by condensation of an N,N'-disubstituted alkanediamine $H—N(CHR_1R_1)—Y—NHR_6$ with an appropriate aldehyde or ketone. The reaction conditions are similar to those described above for formation of the oxazolidine derivatives of Formula II.

Acid addition salts of the compounds described herein are prepared by conventional procedures as by mixing the amine compound in a suitable solvent with the required acid and recovering the salt by evaporation or by precipitation by addition of a non-solvent for the salt. Hydrochloride salts are readily prepared by passing dry hydrogen chloride through a solution of the basic compound in an organic solvent such as ether.

The compounds of this invention are, as noted, valuable non-steroidal anti-inflammatory agents for animals, including humans. Their anti-inflammatory activity is determined by measuring their ability to suppress the reversed passive Arthus reaction. N-(2-hydroxyethyl)-N'-(8-pentadecyl)-1,3-propanediamine is twenty times more active in this experimental model of inflammation induced by antigen-antibody complex than is indomethacin.

Many of the compounds described herein are highly potent suppressors of canine synovites (Chang et al., Arthritis and Rheumatism 11, 145–150, 1968). N-(2-hydroxyethyl) - N' - (8 - pentadecyl) - 1,3 - propanediamine is more potent in this test than all known anti-inflammatory agents with the exception of colchicine.

Compounds of Formulae II and III serve as pro-drugs for Formula I compounds since they are readily decomposed by hydrolysis with elimination of the $>CR_4R_5$ moiety to give Formula I compounds both in vivo and in vitro. The term "pro-drug" as used herein is, therefore, intended to include the biological conversion as well as the chemical conversion of the compounds of Formulae II and III to those of Formula I. The nature of the R_4 and R_5 groups is immaterial for the purposes of this invention. The only requirement relates to those pro-drugs which are used as such or are converted to the drug prior to administration without separation of the drug from the aldehyde or ketone degradation product. In such instances, the by-product aldehyde or ketone should be one which is non-toxic at the levels at which it is administered along with the drug.

The immunosuppressant activity is determined by the lymphocyte-target cell interaction in vitro according to the procedure of Canty et al., J. Natl. Cancer Institute 45, 761–72 (1970). These compounds are thus found to be of value in suppressing the immune response which is a defensive mechanism in the animal broadly against foreign bodies. They can, therefore, be used to prevent rejection of organ transplants such as renal transplants and skin grafts in lower animals and, on the basis of experience, is extrapolatable to humans.

The herein-described compounds are effective via the oral and parenteral routes of administration. When administered parenterally, the materials of this invention

are used at a level of from about 1 mg./kg. of body weight to about 50 mg./kg. of body weight. The favored range is from about 5 mg./kg. to about 50 mg./kg. of bdoy weight, and the preferred range from about 5 mg./kg. to about 33 mg./kg. of body weight. When administered orally they are used at a level of from about 5 mg./kg. to about 300 mg./kg. of body weight. Intraarticular administration permits dosages as low as 0.1 mg./kg. of body weight. The dosage, of course, is dependent upon the animal being treated and the particular compound involved and is to be determined by the individual responsible for its administration. Generally, small doses will be administered initially with gradual increase in dosage until the optimal dosage level is determined for the particular subject under treatment.

Intraperitoneal injections are the preferred method of parenteral injection for several reasons: simplicity, convenience and lower toxicity. Vehicles suitable for parenteral injection may be either aqueous such as water, isotonic saline, isotonic dextrose. Ringer's solution, or non-aqueous such as fatty oils of vegetable origin (cottonseed, peanut oil, corn, sesame) and other non-aqueous vehicles which will not interfere with the efficacy of the preparation and are non-toxic in the volume or proportion used (glycerol, ethanol, propylene glycol, sorbitol). Additionally, compositions suitable for extemporaneous preparation of solutions prior to administration may advantageously be made. Such compositions may include liquid diluents, for example, propylene glycol, diethyl carbonate, glycerol, sorbitol.

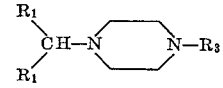
When the materials of this invention are administered, they are most easily and economically used in a dispersed form in an acceptable carrier. When it is said that this material is dispersed, it means that the particles may be molecular in size and held in true solution in a suitable solvent or that the particles may be colloidal in size and dispersed through a liquid phase in the form of a suspension or an emulsion. The term "dispersed" also means that the particles may be mixed with and spread throughout a solid carrier so that the mixture is in the form of a powder or dust. This term is also meant to encompass mixtures which are suitable for use as sprays, including solutions, suspensions, or emulsions or the agents of this invention.

The compounds employed in this invention may be employed alone, i.e., without other medicinals, as mixtures of more than one of the herein-described compounds, or in combination with other medicinal agents such as analgesics, anesthetics, antiseptics, decongestants, antibiotics, vaccines, buffering agents and inorganic salts to afford desirable pharmacological properties. Further, they may be administered in combination with hyaluronidase to avoid, or at least, to minimize local irritation and to increase the rate of absorption of the compound. Hyaluronidase levels of at least about 150 (U.S.P.) units are effective in this respect although higher or lower levels can, of course, be used.

Those materials of this invention which are water soluble, including those which are of low and/or difficult solubility in water, are, for optimum results, administered in formulations, e.g., suspensions, emulsions, which permit formation of particle sizes of less than about 20μ. The particle sizes of the formulations influence their biological activity apparently through better absorption of the active materials. In formulating these materials, various surface active agents and protective colloids are used. Suitable surface active agents are the partial esters of common fatty acids, such as lauric, oleic, stearic, with hexitol anhydrides derived from sorbitol; and the polyoxyethylene derivatives of such ester products. Such products are sold under the trademarks "Spans" and "Tweens," respectively, and are available from the Atlas Powder Co., Wilmington, Del. Cellulose ethers, especially cellulose methyl ether (Methocel, available from the Dow Chemical Co., Midland, Mich.) are highly efficient as protective colloids for use in emulsions containing the materials of this invention. The water soluble materials described herein are administered for optimum results in aqueous solution.

In addition to the compounds described above, homologous and analogous compounds wherein R_2 and R_3 are 2-mercaptoethyl or hydroxyalkyl or mercaptoalkyl groups of from 3 to 8 carbon atoms and such compounds, as well as those of the above formulae, wherein Y is alkylene of 6 carbon atoms are also effective anti-inflammatory and immunosuppressant agents. Further, homologs of Formula II compounds wherein the 3-oxazolidino moiety is replaced by a 3-(5-alkyl substituted)oxazolidino, a 3-tetrahydro-1,3-oxazino or a 3-(6-alkyl substituted)-tetrahydro-1,3-oxazino moiety, or the corresponding sulfur-containing heterocyclic moieties, are valuable anti-inflammatory and immunosuppressant agents. Such compounds are prepared from compounds of Formula I wherein at least one of R_2 and R_3 is a β-hydroxyalkyl, a γ-hydroxyalkyl, or corresponding mercaptoalkyl moiety and an appropriate aldehyde or ketone in the same manner as is described above for the preparation of compounds of Formula II.

Still further, compounds analogous to those described herein wherein the symmetrical secondary alkyl moiety ($—CHR_1R_1$) is replaced by an unsymmetrical secondary alkyl moiety, such as 2-pentadecyl-, 3-octadecyl- and 5-octadecyl-, or by phenyl or substituted phenyl (halo, lower alkyl, lower alkoxy, CF_3, etc.); and compounds of the formula



are also effective antibacterial and immunosuppressant agents.

EXAMPLE I

N-(2-hydroxyethyl)-N'-(8-pentadecyl)-1,3-propanediamine

A mixture of N-(2-hydroxyethyl)-1,3-propanediamine (0.2 mole), di-n-heptyl ketone (0.21 mole) and benzene (200 ml.) is refluxed for forty-eight hours with continuous removal and collection of water in a Dean-Stark apparatus. Approximately 150 ml. of benzene are distilled off and the remaining mixture added dropwise over a period of one hour to a suspension of sodium borohydride (0.2 mole) in isopropanol (150 ml.). The reaction is exothermic and reaches a temperature of 45° to 50° C. The mixture is refluxed for one and one-half hours, then cooled and the solvent removed under reduced pressure. The residue is partitioned between ether (200 ml.) and 3 N aqueous sodium hydroxide (200 ml.) and the ether layer then separated. It is extracted with 3 N hydrochloric acid (150 ml.), and the acid solution extracted twice with ether. The acid solution is then made alkaline, extracted with ether and the ethereal solution dried over anhydrous sodium sulfate and evaporated. The residue is distilled in vacuo to give the product as an oil in 61 percent yield. B.P.=190–191° C. at 0.02 mm.

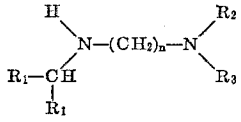
EXAMPLE II

N,N-bis-(2-hydroxyethyl)-N'-(8-pentadecyl)-1,2-ethanediamine

A solution of N,N-bis-(2-hydroxyethyl)ethanediamine (95 mm.) and di-n-heptyl ketone (87 mm.) in benzene (150 ml.) is heated at reflux in a 500 ml. round-bottomed flask equipped with a condenser, magnetic stirrer and a Dean-Stark trap. After eighteen hours, 1.45 ml. of water is collected. The mixture is cooled to room temperature, sodium borohydride (175 mm.) added and the mixture refluxed for four hours. The reaction is worked up by addition of 5 N sodium hydroxide (160 ml.) and stirred for two hours to decompose the borohydride-amine complex. Thereafter, water (160 ml.) is added and the ben-

zene layer separated. The aqueous solution is extracted twice more with benzene (150 ml. each). The benzene extracts are dried with sodium sulfate, filtered through Super-Cel, and concentrated to give an oily residue (37.3 g.). The residue is dissolved in ethanol (200 ml.) and an excess of phosphoric acid added. The precipitate is filtered and recrystallized twice from methanol-ethyl acetate to give the triphosphate salt (20.6 g.), 36.4 percent yield, M.P. 212° C. (dec.).

The following compounds are prepared from appropriate reactants by the procedures of Examples I or II:

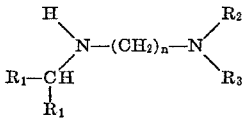


R_1	R_2	R_3	n.	B.P. (° C.)	P (mm. Hg)
C_8H_{17}	H	CH_2CH_2OH	2	185–8	0.02
C_6H_{13}	H	CH_2CH_2OH	3	155–70	0.02
C_7H_{15}	CH_2CH_2OH	CH_2CH_2OH	3	185	0.025
C_5H_{11}	H	CH_2CH_2OH	3	142–5	0.05
C_5H_{11}	CH_2CH_2OH	CH_2CH_2OH	3	[1] 241	
C_7H_{15}	H	C_2H_5	3	147	0.1
C_6H_{13}	CH_2CH_2OH	CH_2CH_2OH	3	185	0.05
C_9H_{19}	CH_2CH_2OH	CH_2CH_2OH	3	240	0.05
C_8H_{17}	CH_2CH_2OH	CH_2CH_2OH	3	210	0.05
C_6H_{13}	H	CH_2CH_2OH	2	155–213	0.02
C_6H_{13}	H	C_2H_5	3	130–2	0.1

[1] M.P. of tripposphate salt.

EXAMPLE III

Repetition of the procedures of Examples I and II but using appropriate reactants in place of N-(2-hydroxyethyl)-1,3-propanediamine, N,N-bis-(2 - hydroxyethyl)-ethanediamine and di-n-heptyl ketone produces the following compounds:



R_1	R_2	R_3	n
C_4H_9	H	CH_2CH_2OH	2
C_4H_9	CH_2CH_2OH	CH_2CH_2OH	2
C_4H_9	C_2H_5	CH_2CH_2OH	2
C_2H_9	H	CH_3	2
C_4H_9	H	n-C_4H_9	2
C_4H_9	H	$C_{12}H_{25}$	2
C_4H_9	H	$C_{20}H_{41}$	2
C_4H_9	H	$C_{18}H_{37}$	3
C_4H_9	H	$C_{18}H_{37}$	3
C_4H_9	H	$C_{12}H_{25}$	3
C_4H_9	C_2H_5	$C_{12}H_{25}$	3
C_4H_9	C_2H_5	CH_2CH_2OH	3
C_4H_9	H	CH_2CH_2OH	3
C_4H_9	CH_2CH_2OH	CH_2CH_2OH	4
C_4H_9	CH_2CH_2OH	C_6H_{13}	4
C_4H_9	CH_2CH_2OH	$C_{16}H_{33}$	4
C_4H_9	C_2H_5	CH_2CH_2OH	4
C_4H_9	H	CH_2CH_2OH	5
C_7H_{15}	H	C_4H_9	3
C_7H_{15}	H	$C_{12}H_{25}$	3
C_7H_{15}	H	$C_{18}H_{37}$	3
C_7H_{15}	CH_2CH_2OH	$C_{18}H_{37}$	3
C_7H_{15}	CH_2CH_2OH	$C_{12}H_{25}$	3
C_7H_{15}	H	C_2H_5	4
C_7H_{15}	H	$C_{18}H_{37}$	4
C_7H_{15}	H	CH_2CH_2OH	4
C_7H_{15}	CH_2CH_2OH	CH_2CH_2OH	4
C_7H_{15}	CH_2CH_2OH	CH_3	4
C_7H_{15}	CH_2CH_2OH	C_6H_{13}	4
C_7H_{15}	CH_2CH_2OH	$C_{18}H_{37}$	4
C_7H_{15}	H	CH_2CH_2OH	5
C_7H_{15}	CH_2CH_2OH	CH_2CH_2OH	5
C_7H_{15}	CH_2CH_2OH	C_4H_9	5
C_7H_{15}	CH_2CH_2OH	$C_{14}H_{29}$	5
C_7H_{15}	C_2H_5	$C_{14}H_{29}$	5
C_7H_{15}	H	$C_{12}H_{25}$	5
C_8H_{17}	H	CH_2CH_2OH	2
C_8H_{17}	CH_2CH_2OH	CH_2CH_2OH	2
C_8H_{17}	H	C_2H_5	2
C_8H_{17}	CH_2CH_2OH	C_9H_{17}	2
C_8H_{17}	H	CH_2CH_2OH	3
C_8H_{17}	CH_2CH_2OH	$C_{18}H_{37}$	3
C_8H_{17}	C_2H_5	$C_{18}H_{37}$	3
C_8H_{17}	CH_2CH_2OH	CH_3	3
C_8H_{17}	H	CH_2CH_2OH	4

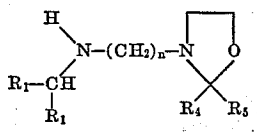
R_1	R_2	R_3	n
C_8H_{17}	H	CH_3	4
C_8H_{17}	H	C_6H_{13}	4
$C_{12}H_{25}$	H	CH_2CH_2OH	3
$C_{12}H_{25}$	H	C_3H_7	3
$C_{12}H_{25}$	H	$C_{12}H_{25}$	3
$C_{12}H_{25}$	H	$C_{18}H_{37}$	3
$C_{12}H_{25}$	CH_2CH_2OH	CH_2CH_2OH	3
$C_{12}H_{25}$	CH_2CH_2OH	C_6H_{13}	3
$C_{12}H_{25}$	CH_2CH_2OH	$C_{14}H_{29}$	3
$C_{12}H_{25}$	H	CH_2CH_2OH	4
$C_{12}H_{25}$	C_2H_5	CH_2CH_2OH	4
$C_{12}H_{25}$	CH_2CH_2OH	CH_2CH_2OH	4
$C_{12}H_{25}$	CH_2CH_2OH	C_6H_{13}	4
$C_{12}H_{25}$	C_2H_5	C_6H_{13}	5
$C_{12}H_{25}$	CH_2CH_2OH	CH_2CH_2OH	5
$C_{12}H_{25}$	CH_2CH_2OH	$C_{12}H_{25}$	5
$C_{13}H_{27}$	H	CH_2CH_2OH	3
$C_{13}H_{27}$	H	CH_3	2
$C_{13}H_{27}$	H	C_7H_{15}	2
$C_{13}H_{27}$	H	$C_{16}H_{33}$	2
$C_{13}H_{27}$	CH_2CH_2OH	$C_{16}H_{33}$	2
$C_{13}H_{27}$	H	CH_2CH_2OH	3
$C_{13}H_{27}$	H	C_6H_{13}	3
$C_{13}H_{27}$	H	$C_{18}H_{37}$	3
$C_{13}H_{27}$	CH_2CH_2OH	$C_{18}H_{37}$	3
$C_{13}H_{27}$	CH_2CH_2OH	CH_2CH_2OH	3
$C_{13}H_{27}$	C_2H_5	CH_2CH_2OH	3
$C_{13}H_{27}$	C_2H_5	CH_2CH_2OH	4
$C_{13}H_{27}$	H	CH_2CH_2OH	4
$C_{13}H_{27}$	CH_2CH_2OH	CH_2CH_2OH	4
$C_{13}H_{27}$	CH_2CH_2OH	C_4H_9	4
C_4H_9	CH_2CH_2OH	$C_{12}H_{25}$	5
C_4H_9	H	C_6H_{13}	5
C_6H_{13}	H	C_6H_{13}	2
C_6H_{13}	H	C_2H_5	2
C_6H_{13}	H	CH_2CH_2OH	2
C_6H_{13}	H	$C_{18}H_{33}$	3
C_6H_{13}	CH_2CH_2OH	$C_{18}H_{33}$	3
C_6H_{13}	H	$C_{18}H_{37}$	3
C_6H_{13}	H	$C_{18}H_{37}$	4
C_6H_{13}	CH_2CH_2OH	C_6H_{13}	4
C_6H_{13}	C_2H_5	CH_2CH_2OH	5
C_6H_{13}	CH_2CH_2OH	CH_2CH_2OH	5
C_6H_{13}	C_2H_5	C_2H_5	5
C_7H_{15}	C_2H_5	$C_{12}H_{25}$	2
C_7H_{15}	CH_2CH_2OH	$C_{12}H_{25}$	2
C_7H_{15}	C_2H_5	$C_{12}H_{25}$	3
C_7H_{15}	C_2H_5	CH_2CH_2OH	3
C_7H_{15}	C_2H_5	$C_{18}H_{37}$	3
C_8H_{17}	H	$C_{18}H_{33}$	4
C_8H_{17}	C_2H_5	$C_{16}H_{33}$	4
C_8H_{17}	CH_2CH_2OH	CH_2CH_2OH	4
C_8H_{17}	CH_2CH_2OH	C_3H_7	4
C_8H_{17}	CH_2CH_2OH	CH_2CH_2OH	5
C_8H_{17}	H	CH_2CH_2OH	5
C_8H_{17}	C_2H_5	CH_2CH_2OH	5
C_8H_{17}	CH_2CH_2OH	C_9H_{17}	5
C_8H_{17}	CH_2CH_2OH	$C_{18}H_{37}$	5
C_9H_{19}	H	CH_2CH_2OH	3
C_9H_{19}	H	CH_2CH_2OH	5
$C_{11}H_{23}$	H	CH_1CH_2OH	2
$C_{11}H_{23}$	C_2H_5	CH_2CH_2OH	2
$C_{11}H_{23}$	H	CH_2CH_2OH	2
$C_{11}H_{23}$	H	C_6H_{13}	2
$C_{11}H_{23}$	CH_2CH_2OH	CH_2CH_2OH	3
$C_{11}H_{23}$	H	CH_2CH_2OH	3
$C_{11}H_{23}$	H	C_2H_5	3
$C_{11}H_{23}$	H	$C_{10}H_{21}$	3
$C_{11}H_{23}$	H	CH_2CH_2OH	4
$C_{11}H_{23}$	CH_2CH_2OH	CH_3	4
$C_{11}H_{23}$	CH_2CH_2OH	C_7H_{15}	4
$C_{11}H_{23}$	CH_2CH_2OH	$C_{16}H_{33}$	4
$C_{11}H_{23}$	CH_2CH_2OH	CH_2CH_2OH	5
$C_{12}H_{25}$	H	CH_2CH_2OH	2
$C_{12}H_{25}$	C_2H_5	CH_2CH_2OH	2
$C_{12}H_{25}$	CH_2CH_2OH	$C_{16}H_{33}$	2
$C_{12}H_{25}$	CH_2CH_2OH	C_2H_5	2
$C_{12}H_{25}$	H	C_2H_5	2
$C_{13}H_{27}$	CH_2CH_2OH	$C_{20}CH_{41}OH$	4
$C_{13}H_{27}$	CH_2CH_2OH	CH_2CH_2OH	5
$C_{13}H_{27}$	H	C_3H_7	5
$C_{13}H_{27}$	CH_2CH_2OH	$C_{14}H_{29}$	5
$C_{13}H_{27}$	H	CH_2CH_2OH	5
$C_{13}H_{27}$	C_2H_5	CH_2CH_2OH	5
$C_{13}H_{27}$	H	C_6H_{13}	5
$C_{13}H_{27}$	H	$C_{18}H_{37}$	5
C_5H_{11}	C_2H_5	CH_2CH_2OH	2
C_5H_{11}	CH_2CH_2OH	C_6H_{13}	2
C_5H_{11}	CH_2CH_2OH	C_6H_{13}	3
C_5H_{11}	H	CH_2CH_2OH	4
C_5H_{11}	H	CH_2CH_2OH	5
C_5H_{11}	C_2H_5	CH_2CH_2OH	5
$C_{10}H_{21}$	H	CH_2CH_2OH	2
$C_{10}H_{21}$	H	CH_2CH_2OH	3

EXAMPLE IV

2-methyl-3-[3-(8-pentadecylamino)propyl]oxazolidine

A mixture of N-(2-hydroxyethyl)-N'-(8-pentadecyl)-1,3 - propanediamine (0.01 mole), acetaldehyde (0.02 mole) and benzene (25 ml.) is refluxed overnight and by-product water collected azeotropically in a Dean-Stark apparatus. The benzene is then removed by evaporation and the residue distilled in vacuo. B.P.=173–178° C. at 0.02 mm.; yield—64.2 percent.

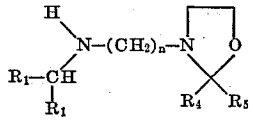
The following are similarly prepared from appropriate reactants:



R_1	n	R_4	R_5	B.P. (° C.)	Mm. Hg
C_7H_{15}	3	C_6H_5	H	195-9	0.02
C_7H_{15}	3	H	2-thienyl	205-9	0.02
C_5H_{11}	3	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		156-8	0.05
C_5H_{11}	3	C_6H_5	H	164-6	0.02
C_5H_{11}	3	C_6H_{11}	H	191-3	5
C_7H_{15}	3	C_6H_{11}	H	201-8	0.02
C_7H_{15}	3	C_6H_{15}	H	195-9	0.02
C_7H_{15}	3	$C_{11}H_{33}$	H	230-2	0.02
C_7H_{15}	3	C_6H_{13}	H	190-200	0.02
C_7H_{15}	3	H	2-pyridyl	200-5	0.01
C_7H_{15}	3	H	3-pyridyl	203-5	0.01
C_7H_{15}	3	H	H	169-70	0.02
C_6H_{13}	3	H	2-pyridyl	178-82	0.01
C_6H_{13}	2	H	3-pyridyl	181-4	0.01
C_6H_{13}	2	H	C_6H_5	170-9	0.02
C_5H_{11}	3	H	2-thienyl	175-8	0.02
C_6H_{13}	3	H	CH_3	138-43	0.05

EXAMPLE V

The following compounds are prepared from the products of Examples I through III wherein R_3 is hydroxyethyl and R_2 is hydrogen and appropriate aldehydes and ketones by the procedure of Example IV:



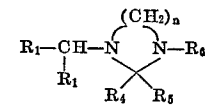
R_1	n	R_4	R_5
C_7H_{15}	3	C_3H_7	H
C_7H_{15}	3	C_8H_{17}	H
C_7H_{15}	3	$C_{17}H_{35}$	H
C_7H_{15}	3	$2\text{-}CH_3\text{-}C_6H_4$	H
C_7H_{15}	3	$4\text{-}t\text{-}C_4H_9\text{-}C_6H_4$	H
C_7H_{15}	3	$3\text{-}ClC_6H_4$	H
C_7H_{15}	3	CH_3	CH_3
C_7H_{15}	3	C_6H_5	CH_3
C_7H_{15}	3	C_6H_5	C_6H_5
C_7H_{15}	3	$4\text{-}BrC_6H_4$	CH_3
C_7H_{15}	3	$3\text{-}(CF_3)C_6H_4$	CH_3
C_7H_{15}	3	CH_3	$4\text{-}(CH_3O)C_6H_4$
C_7H_{15}	3	CH_3	$4\text{-}CNC_6H_4$
C_7H_{15}	3	C_3H_5	H
C_7H_{15}	3	H	C_7H_{13}
C_7H_{15}	3	C_5H_9	C_5H_9
C_7H_{15}	3	CH_2-CH_2	
C_7H_{15}	3	H	H
C_8H_{17}	3	CH_3	H
C_8H_{17}	3	$C_{20}H_{41}$	H
C_8H_{17}	3	C_6H_5	H
C_8H_{17}	3	H	C_4H_7
C_8H_{17}	3	H	4-pyridyl.
C_8H_{17}	3	H	2-furyl.
C_8H_{17}	3	$4\text{-}(CH_3)C_6H_4$	C_6H_5
C_6H_{13}	3	H	H
C_6H_{13}	3	C_3H_5	C_3H_5
C_6H_{13}	3	C_6H_5	$4\text{-}ClC_6H_4$
C_6H_{13}	3	$-CH_2CH_2CH_2CH_2CH_2-$	
C_5H_{11}	3	H	H
C_5H_{11}	3	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$
C_5H_{11}	3	C_6H_{13}	C_6H_{13}
C_5H_{11}	3	C_4H_7	C_4H_7
C_5H_{11}	3	$-CH_2CH_2CH_2CH_2-$	
C_5H_{11}	3	$4\text{-}(CH_3)C_6H_4$	$4\text{-}(CH_3)C_6H_4$
C_5H_{11}	3	$2\text{-}CF_3\text{-}C_6H_4$	H
C_5H_{11}	3	$C_{11}H_{23}$	C_6H_5
C_5H_{11}	3	H	2-thienyl
C_4H_9	2	C_6H_5	H
C_4H_9	2	C_6H_{11}	H
C_4H_9	2	$-CH_2CH_2CH_2CH_2CH_2CH_2-$	
C_4H_9	2	C_6H_5	H
C_4H_9	2	C_6H_{11}	H
C_4H_9	2	$-CH_2CH_2CH_2CH_2CH_2CH_2-$	
C_4H_9	2	$C_{10}H_{21}$	H
C_4H_9	2	C_2H_5	C_2H_5
C_4H_9	2	$4\text{-}(CH_3)C_6H_5$	CH_3
C_4H_9	2	$-CH_2CH_2CH_2-$	
C_4H_9	3	CH_3	CH_3
C_4H_9	3	H	H
C_4H_9	3	C_5H_9	C_5H_9
C_4H_9	3	C_6H_5	C_6H_5
C_4H_9	4	$C_{20}H_{41}$	H
C_4H_9	4	$2\text{-}ClC_6H_4$	H
C_4H_9	4	$i\text{-}C_3H_7$	$i\text{-}C_3H_7$
C_4H_9	5	H	H
C_4H_9	5	CH_3	$i\text{-}C_4H_9$
C_4H_9	5	H	2-pyridyl.
C_4H_9	5	$-CH_2CH_2-$	
C_5H_{11}	2	H	H
C_5H_{11}	2	$3\text{-}IC_6H_4$	H
C_5H_{11}	2	H	C_6H_{13}
C_5H_{11}	2	$2\text{-}(CF_3)C_6H_4$	H
C_5H_{11}	2	$-CH_2CH_2CH_2CH_2CH_2-$	
C_5H_{11}	3	$-CH_2CH_2CH_2CH_2CH_2-$	
C_5H_{11}	4	C_3H_5	C_3H_5
C_5H_{11}	5	C_6H_{11}	H
C_6H_{13}	2	H	H
C_6H_{13}	2	C_3H_7	C_3H_7
C_6H_{13}	2	$-CH_2CH_2CH_2-$	
C_6H_{13}	3	C_4H_7	H
C_6H_{13}	3	C_6H_{13}	C_6H_{13}
C_8H_{17}	2	H	2-thienyl.
C_8H_{17}	2	C_6H_5	H
C_8H_{17}	2	$-CH_2CH_2CH_2-$	
C_8H_{17}	3	H	H
C_8H_{17}	3	CH_3	C_6H_{11}
C_8H_{17}	3	$-CH_2CH_2CH_2CH_2CH_2-$	
C_8H_{17}	4	CH_3	C_2H_5
C_8H_{17}	4	C_4H_7	H
C_8H_{17}	4	$2\text{-}FC_6H_4$	H
C_8H_{17}	5	H	H
C_8H_{17}	5	$C_{18}H_{37}$	$C_{18}H_{37}$
C_8H_{17}	5	C_2H_5	C_2H_5
C_8H_{17}	5	C_6H_5	H
C_9H_{19}	3	C_6H_{11}	H
C_9H_{19}	5	C_6H_{11}	H
$C_{10}H_{21}$	2	C_6H_5	H
$C_{10}H_{21}$	3	C_6H_5	C_6H_5
$C_{11}H_{23}$	3	$C_{12}H_{25}$	$C_{12}H_{25}$
$C_{11}H_{23}$	3	C_6H_{13}	H
$C_{12}H_{25}$	2	H	H
$C_{12}H_{25}$	2	$3\text{-}ClC_6H_4$	H
$C_{12}H_{25}$	2	C_7H_{13}	H
$C_{12}H_{25}$	3	CH_3	$C_{10}H_{21}$
$C_{12}H_{25}$	3	C_6H_5	C_6H_5
$C_{12}H_{25}$	3	C_6H_{11}	C_6H_{11}
$C_{12}H_{25}$	4	C_6H_5	H
$C_{13}H_{27}$	2	CH_3	H
$C_{13}H_{27}$	2	H	C_7H_{15}
$C_{13}H_{27}$	2	C_8H_{17}	C_8H_{17}
$C_{13}H_{27}$	3	$C_{12}H_{25}$	CH_3
$C_{13}H_{27}$	3	$C_{20}H_{41}$	$C_{20}H_{41}$
$C_{13}H_{27}$	3	$-CH_2CH_2CH_2CH_2-$	
$C_{13}H_{27}$	3	H	2-pyridyl.
$C_{13}H_{27}$	3	CH_3	2-furyl.
$C_{13}H_{27}$	3	C_3H_5	2-thienyl.
$C_{13}H_{27}$	4	CH_3	CH_3
$C_{13}H_{27}$	4	C_6H_{11}	CH_3
$C_{13}H_{27}$	4	C_5H_9	$i\text{-}C_3H_7$
$C_{13}H_{27}$	5	$C_{17}H_{35}$	$C_{17}H_{35}$
$C_{13}H_{27}$	5	C_6H_5	$n\text{-}C_4H_9$

EXAMPLE VI

1-(8-pentadecyl)-2-phenyl-3-ethyl-1,3-hexahydropyrimidine

The procedure of Example IV is repeated but using N-ethyl-N'-(8-pentadecyl)1,3-propanediamine and benzaldehyde as reactants to give the title compound; B.P.=140–159° C. at 0.02 mm.

The following compounds are similarly prepared from appropriate reactants:

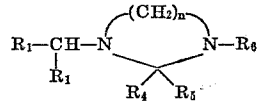


R_1	n	R_4	R_5	R_6	B.P. (° C.)	P (mm. Hg)
C_7H_{15}	3	C_6H_{11}	H	C_2H_5	180-95	0.02
C_7H_{15}	3	C_6H_{13}	H	C_2H_5	180-4	0.02
C_6H_{13}	3	C_6H_5	H	C_2H_5	151	1.02
C_5H_{11}	3	C_6H_5	H	C_2H_5	155-58	0.05

EXAMPLE VII

The procedure of Example VI is repeated but using the appropriate N,N'-dialkylalkanediamines of Examples II

and III and the appropriate aldehydes or ketones to produce the following compounds:

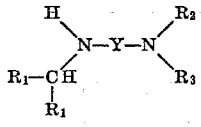


R_1	n	R_4	R_5	R_6
C_4H_9	2	CH_3	H	CH_3
C_4H_9	2	C_6H_{11}	H	n-C_4H_9
C_4H_9	2	CH_3	i-C_4H_9	$C_{12}H_{25}$
C_4H_9	2	C_6H_5	H	$C_{20}H_{41}$
C_4H_9	3	H	H	$C_{18}H_{37}$
C_4H_9	3	C_2H_5	C_2H_5	$C_{18}H_{37}$
C_4H_9	3	$-CH_2CH_2CH_2CH_2-$		$C_{18}H_{37}$
C_4H_9	3	H	2-thienyl	$C_{18}H_{37}$
C_4H_9	3	C_6H_5	CH_3	$C_{18}H_{37}$
C_4H_9	5	C_4H_7	H	C_6H_{13}
C_4H_9	5	C_4H_9	C_4H_9	C_6H_{13}
C_6H_{13}	2	CH_3	i-C_4H_9	C_6H_{13}
C_6H_{13}	2	4-ClC_6H_4	CH_3	C_6H_{13}
C_6H_{13}	2	CH_3	2-pyridyl	C_6H_{13}
C_6H_{13}	2	2-(CH_3)C_6H_4	H	C_2H_5
C_6H_{13}	2	$-CH_2CH_2-$		C_2H_5
C_6H_{13}	3	$C_{17}H_{35}$	$C_{17}H_{35}$	C_2H_5
C_6H_{13}	3	CH_3	C_6H_{11}	C_2H_5
C_6H_{13}	3	4-(CF_3)C_6H_4	H	C_2H_5
C_6H_{13}	3	C_6H_9	C_6H_9	$C_{18}H_{37}$
C_6H_{13}	4	C_7H_{13}	H	$C_{18}H_{37}$
C_6H_{13}	4	$-CH_2CH_2CH_2CH_2-$		$C_{18}H_{37}$
C_6H_{13}	4	4-$C_2H_5O$$C_6H_4$	H	$C_{18}H_{37}$
C_7H_{15}	3	C_6H_5	C_6H_5	C_4H_9
C_7H_{15}	3	C_6H_5	C_6H_5	$C_{12}H_{25}$
C_7H_{15}	3	C_6H_5	C_6H_5	$C_{18}H_{37}$
C_7H_{15}	3	C_6H_{11}	H	C_4H_9
C_7H_{15}	3	CH_3	2-furyl	C_4H_9
C_7H_{15}	4	CH_3	CH_3	C_2H_5
C_7H_{15}	4	4-CNC_6H_4	H	C_2H_5
C_7H_{15}	4	H	H	$C_{18}H_{37}$
C_7H_{15}	5	$C_{20}H_{41}$	H	$C_{12}H_{25}$
C_7H_{15}	5	H	3-pyridyl	$C_{12}H_{25}$
C_7H_{15}	5	$C_{18}H_{37}$	CH_3	$C_{12}H_{25}$
C_8H_{17}	2	CH_3	C_6H_5	C_2H_5
C_8H_{17}	2	C_6H_{13}	C_6H_5	C_2H_5
C_8H_{17}	4	CH_3	C_6H_{11}	CH_3
C_8H_{17}	4	C_2H_5	4-(C_3H_7)C_6H_4	CH_3
C_8H_{17}	4	i-C_3H_7	i-C_3H_7	C_6H_{13}
C_8H_{17}	4	H	C_6H_5	$C_{16}H_{33}$
C_8H_{17}	4	CH_3	3-BrC_6H_4	$C_{16}H_{33}$
$C_{11}H_{23}$	2	CH_3	3-pyridyl	C_6H_{13}
$C_{11}H_{23}$	2	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		C_6H_{13}
$C_{11}H_{23}$	2	C_7H_{13}	C_7H_{13}	C_6H_{13}
$C_{11}H_{23}$	2	4-(C_3H_7O)C_6H_4	H	C_6H_{13}
$C_{11}H_{23}$	3	H	H	C_2H_5
$C_{11}H_{23}$	3	CH_3	2-thienyl	C_2H_5
$C_{11}H_{23}$	3	C_3H_5	C_3H_5	C_2H_5
$C_{11}H_{23}$	3	$C_{16}H_{33}$	$C_{16}H_{33}$	$C_{10}H_{21}$
$C_{11}H_{23}$	3	H	C_6H_5	$C_{10}H_{21}$
$C_{11}H_{23}$	3	C_6H_{11}	H	$C_{10}H_{21}$
$C_{12}H_{25}$	2	H	2-furyl	C_2H_5
$C_{12}H_{25}$	2	C_6H_5	H	C_2H_5
$C_{12}H_{25}$	2	C_6H_{13}	C_6H_{13}	C_2H_5
$C_{12}H_{25}$	3	H	H	C_3H_7
$C_{12}H_{25}$	3	$-CH_2CH_2CH_2CH_2-$		C_3H_7
$C_{12}H_{25}$	3	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		C_3H_7
$C_{12}H_{25}$	3	2-(CH_3O)C_6H_4	CH_3	C_3H_7
$C_{12}H_{25}$	3	C_6H_5	H	$C_{12}H_{25}$
$C_{12}H_{25}$	3	H	H	$C_{18}H_{37}$
$C_{12}H_{25}$	3	$C_{20}H_{41}$	H	$C_{18}H_{37}$
$C_{13}H_{27}$	2	C_6H_{11}	H	CH_3

R_1	n	R_4	R_5	R_6
$C_{13}H_{27}$	2	H	H	CH_3
$C_{13}H_{27}$	2	C_3H_5	C_3H_5	CH_3
$C_{13}H_{27}$	2	H	H	C_7H_{15}
$C_{13}H_{27}$	2	H	H	$C_{16}H_{33}$
$C_{13}H_{27}$	2	C_6H_5	H	$C_{16}H_{33}$
$C_{13}H_{27}$	2	H	2-pyridyl	$C_{16}H_{33}$
$C_{13}H_{27}$	3	C_6H_{11}	CH_3	C_6H_{13}
$C_{13}H_{27}$	3	CH_3	H	C_6H_{13}
$C_{13}H_{27}$	3	3-(C_2H_5)C_6H_4	3-(C_2H_5)C_6H_4	C_6H_{13}
$C_{13}H_{27}$	3	C_4H_7	C_4H_7	C_6H_{13}
$C_{13}H_{27}$	3	$C_{12}H_{25}$	$C_{12}H_{25}$	$C_{18}H_{37}$
$C_{13}H_{27}$	3	H	H	$C_{18}H_{37}$
$C_{13}H_{27}$	3	C_6H_5	C_6H_5	$C_{18}H_{37}$
$C_{13}H_{27}$	5	CH_3	C_6H_5	C_3H_7
$C_{13}H_{27}$	5	$-CH_2CH_2CH_2CH_2CH_2-$		C_3H_7
$C_{13}H_{27}$	5	H	H	C_6H_{13}
$C_{13}H_{27}$	5	H	H	$C_{18}H_{37}$
$C_{13}H_{27}$	5	CH_3	H	$C_{18}H_{37}$
$C_{13}H_{27}$	5	C_6H_5	H	$C_{18}H_{37}$

What is claimed is:

1. A method of reducing inflammation in animals which comprises internally administering to the animals an antiinflammatory effective amount of a compound selected from the group consisting of those having the formula:



and the non-toxic acid addition salts thereof wherein

Y is selected from the group consisting of ethylene, trimethylene, tetramethylene and pentamethylene;

R_1 is alkyl of from 4 to 13 carbon atoms;

R_2 is selected from the group consisting of hydrogen, 2-hydroxyethyl and ethyl and

R_3 is selected from the group consisting of 2-hydroxyethyl and alkyl of from 1 to 20 carbon atoms.

2. The method of claim 1 wherein R_2 is hydrogen, R_3 is 2-hydroxyethyl and Y is trimethylene.

3. The method of claim 1 wherein the compound is N-(2 - hydroxyethyl) - N' - (8-pentadecyl)-1,3-propanediamine.

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U.S. Cl. X.R.

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