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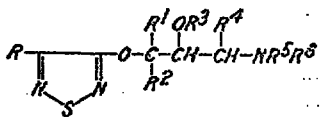
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(54) THIADIAZOLE DERIVATIVES

(71) We, CHARLES E. FROSST & Co., a corporation duly organised and existing under the laws of the Province of Quebec, Canada, of Westmount, Montreal, Quebec, Canada, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with 1,2,5-thiadiazole compounds. Compounds in accordance with the invention, particularly when substituted in the 3-position of the 1,2,5-thiadiazole nucleus, exhibit β-adrenergic blocking properties and have the marked advantages of a long duration of action and effectiveness at very low dosage levels.

The invention provides compounds of the formula:—



I

and their pharmacologically acceptable salts, where R is a hydrogen, chlorine or bromine atom, a straight or branched chain C_{1-5} alkyl group such as methyl, ethyl, propyl, isopropyl, *n*-butyl, iso-, secondary- or *tert*-butyl or amyl including all of its branched chain configurations, a C_{2-5} alkenyl group such as vinyl, allyl or methallyl, a group of the formula Y—X—Z— (where Y is a straight or branched chain C_{1-4} alkyl group optionally substituted with a phenyl group, or a phenyl group optionally having one or more substituents selected from halogen atoms, especially chlorine, bromine and fluorine atoms, and hydroxy, C_{1-3} alkyl and C_{1-3} alkoxy groups, X is an oxygen or sulphur atom, and Z is a C_{1-2} alkyl group, a group of the formula $R^{5'}HNCO$ (where $R^{5'}$ is a C_{1-3} alkyl group), a C_{3-6} cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, a straight or branched chain C_{1-5} alkoxy group, e.g. methoxy, ethoxy, propoxy, *iso*-propoxy, or straight or branched chain butoxy or pentoxy, a phenyl group optionally having one or more substituents selected from halogen atoms, preferably chlorine and fluorine atoms, and C_{1-3} alkyl and C_{1-3} alkoxy groups, a phenyl substituted straight or branched chain C_{1-4} alkyl group, optionally having one or more substituents selected from halogen atoms, preferably chlorine, fluorine and bromine atoms and C_{1-3} alkyl and C_{1-3} alkoxy groups attached to the phenyl ring, or a group of the formula $—NR'R^8$ (where R' is a hydrogen atom or a

[*Price 25p*]

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C_{1-4} alkyl or hydroxy C_{2-4} alkyl group and R^8 is a hydrogen atom or a C_{1-4} alkyl, hydroxy C_{2-4} alkyl or phenyl group, or R^7 and R^8 form, together with the nitrogen atom to which they are attached, a 3- to 7- membered ring, e.g. a aziridinyl, azetidinyl, pyrrolidyl, piperidyl, or hexahydroazepinyl ring, optionally having one or more substituents selected from hydroxy, C_{1-5} alkyl and hydroxy C_{1-3} alkyl groups, or R^7 and R^8 are joined together through an oxygen, nitrogen or sulphur atom to form a 5- or 6- membered ring, preferably a morpholino, hexahydropyrimidyl, thiazolidinyl, *p*-thiazinyl, or piperazinyl ring, optionally substituted by a C_{1-3} alkyl group, or a 5- or 6- membered heterocyclic ring linked through a carbon atom and having oxygen, nitrogen or sulphur as the hetero atom, preferably 2-furyl, 2- or 3-thienyl, 2-pyrryl or 2-, 3-, or 4-pyridyl, each of R^1, R^2 and R^4 is a hydrogen atom or a C_{1-3} alkyl group, R^1, R^2 and R^4 being similar or dissimilar, R^3 is preferably a hydrogen atom but may also be a benzoyl or C_{2-4} alkanoyl group, R^5 is a hydrogen atom, a straight or branched chain C_{1-5} alkyl group or a phenyl-C_{1-3} alkyl or C_{2-5} alkanoyl group, and R^6 is a straight or branched chain C_{1-20} alkyl, preferably branched chain C_{3-6} alkyl such as isopropyl, *tert*-butyl or 2,2-dimethylpropyl, C_{2-6} alkenyl such as allyl, or C_{2-6} alkynyl group, such as butynyl, propargyl or 1,1-dimethyl-2-propynyl, optionally having one or more substituents selected from halogen atoms, especially chlorine and bromine atoms, from hydroxy, carboxy, (C_{1-3} alkoxy) carbonyl, straight and branched chain C_{1-4} alkoxy and C_{1-4} alkylthio, di-C_{1-3} alkyl amino, pyrrolidinyl, piperazinyl, piperidinyl, morpholino, thiazolindinyl and thiazinyl groups, from 5- and 6- membered heterocyclic rings attached through a nuclear carbon and having oxygen, nitrogen or sulphur as the hetero atom, such as tetrahydrofuryl, furyl, thienyl, pyrrolidyl and piperidinyl, and from phenyl and phenoxy groups optionally having from one to three similar or dissimilar substituents selected from halogen atoms, preferably chlorine atoms, and hydroxy and C_{1-3} alkoxy groups; a phenyl group optionally substituted with a C_{1-3} alkyl pyrrolidyl or piperidinyl group; a C_{3-6} cycloalkyl group optionally substituted with a C_{1-3} alkyl group and being for example a cyclopropyl, cyclopentyl, cyclohexyl or 2-methylcyclohexyl group, or with a 5- or 6-membered N- or O- containing heterocyclic ring; or a 5- or 6- membered heterocyclic ring containing oxygen, nitrogen or sulphur as the hetero atom and being attached through a nuclear carbon, and optionally substituted with a C_{1-3} alkyl group or with a 5- or 6- membered N- or O- containing heterocyclic ring such as pyrrolidyl, 2-methylpyrrolidyl, morpholino, piperidino, pyridyl, morpholino-pyridyl or piperazinyl-pyridyl; or R^5 and R^6 together with the nitrogen atom to which they are attached form a 4- to 6- membered ring which may contain in addition to but not adjacent to said nitrogen atom, one or two different hetero atoms selected from oxygen, sulphur and nitrogen and which may be substituted by one or more C_{1-3} alkyl radicals, for example, pyrrolidyl, piperidino, morpholino, hexahydroazepinyl, pyrimidyl, *p*-thiazinyl, Δ^3- or Δ^2-piperideinyl or 1,2-dihydropyridyl.

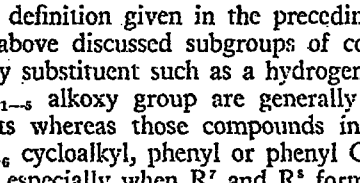
Suitable pharmacologically acceptable salts of the compounds of formula I are acid-addition salts derived from inorganic acids, for example, hydrochlorides, hydrobromides, phosphates and sulphates or salts derived from organic acids, for example, oxalates, lactates, malates, maleates, formates, acetates, succinates, tartrates, salicylates, citrates, phenylacetates, benzoates, *p*-toluenesulfonates and other salts such as those that provide relatively insoluble products that afford a slow release of the active material, for example, 1,1′-methylene-bis(2-hydroxy-3-naphthoate).

The compounds of formula I, as well as their intermediates that contain one asymmetric carbon atom in the propylene chain are obtained as racemic mixtures which can be separated into optically active isomers by known methods, for example, by forming a salt with an optically active acid, many of which are known to those skilled in the art, such as optically active tartaric, mandelic, cholic, O,O-di-*p*-toluoyl tartaric, or O,O-dibenzoyl tartaric acid, or another acid conventionally used for this purpose. Those products and intermediate compounds that contain two or more asymmetric carbons in the propylene chain are obtained as diastereoisomers, and each diastereoisomer is also obtained as a racemic mixture which can be separated into its optically active isomers by known methods such as described above. Resolution of certain representative intermediate and end products is described below in the Examples. All compounds of the invention can be similarly resolved and the invention braces these compounds in the form of racemic mixtures as well as in the form of the optically active isomers or diastereoisomers where appropriate.

Although the compounds of the invention generally possess β-adrenergic blocking properties compounds of formula I in which R^1, R^2, R^3, R^4 and R^5 are hydrogen atoms exhibit β-adrenergic blocking properties to a marked degree and, within this

subgroup, compounds in which R^6 is a branched chain C_{3-6} alkyl group, optionally having a hydroxy or C_{1-4} alkoxy substituent or a branched chain C_{3-6} alkynyl group have particularly good β-adrenergic blocking properties.

The preferred compounds of the invention are therefore illustrated by the formula:



I—a

where R^6 has the limited definition given in the preceding paragraph.

Within each of the above discussed subgroups of compounds, those compounds in which R is a non-bulky substituent such as a hydrogen or halogen atom or a C_{1-5} alkyl, C_{2-5} alkenyl or C_{1-5} alkoxy group are generally potent but short acting β-adrenergic blocking agents whereas those compounds in which R is a more bulky substituent such as a C_{3-6} cycloalkyl, phenyl or phenyl C_{1-4} alkyl group, or a group of the formula $—NR^7R^8$, especially when R^7 and R^8 form, together with the nitrogen atom to which they are attached, a 3- to 7- membered ring optionally having one or more substituents selected from hydroxy, C_{1-5} alkyl and hydroxy C_{1-3} alkyl groups, or R^7 and R^8 are joined together through an oxygen, nitrogen or sulphur atom to form a 5- or 6- membered ring together with the nitrogen atom to which they are attached, optionally substituted by a C_{1-3} alkyl group, or when R is a 5- or 6-membered heterocyclic ring linked through a carbon atom and having oxygen, nitrogen or sulphur as the heteroatom, generally exhibit potent and long-acting β-adrenergic blocking properties, and are generally substantially devoid of sympathomimetic properties.

Both the short-acting and long-acting β-adrenergic blocking agents are of value in therapy and each serves the need of certain patients requiring treatment with agents possessing this property.

The potential of a product as a β-adrenergic blocking agent is conventionally evaluated by the protocol used to assess the β-blocking properties of the thiadiazole compounds of this invention. The protocol comprises intravenous administration of graded doses of the selected compound to rats which are then challenged with a standard dose of isoproterenol, a product known to be a β-stimulant. The ED_{50} for representative compounds of this invention tested according to this protocol is included in certain of the examples that follow.

The clinical application of β-adrenergic blocking agents are well known to physicians. One use for the compounds of this invention, which constitutes the best mode for use of the compounds known to the applicants at this time, is for the control of tachycardia that may be drug induced (as by isoproterenol) or brought about by physiological conditions. In view of the considerable amount of literature that has accumulated concerning the use of β-adrenergic blocking agents, physicians would use compounds of this invention in any of the known conditions where a short-acting or long-acting agent is needed, such as in the management of angina pectoris.

The invention further provides pharmaceutical compositions comprising, as active ingredient, at least one of the compounds according to the invention together with a non-toxic pharmaceutically acceptable carried, diluent or coating or excipient. These compositions may be presented in a form suitable for oral, rectal or parenteral administration, e.g. in the form of a powder, syrup, elixir, pill, capsule or suppository, but preferably in the form of a tablet, solution, suspension or emulsion. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of pills, capsules, tablets, coated tablets or suspensions. Thus suitable tableting excipients include lactose, potato and maize starches, talc, gelatine, stearic acid, magnesium stearate, and polyvinyl pyrrolidone.

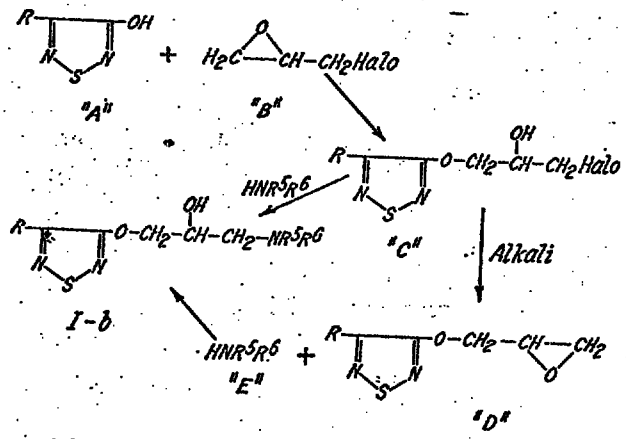
For parenteral administration, the carrier or excipient may be a sterile parenterally acceptable liquid, e.g., pyrogen-free water or an aqueous solution of polyvinyl pyrrolidone, or a parenterally acceptable oil, e.g., arachis oil, contained in ampoules.

In compositions for rectal administration, the carrier may comprise a suppository base, e.g., cocoa butter or a glyceride. The 1,2,5-thiadiazoles can be formulated in the form of the free base or in the form of their salts and may be used in conjunction or admixture with organic and/or inorganic solid or liquid pharmaceutical excipients. No special problems are involved in preparing suitable formulations of these products and methods generally used for this purpose, which are known to those skilled in this art, are suitable. If desired the compounds can be administered along with or formulated together with other active ingredients.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, ampoules and suppositories are examples of preferred dosage unit forms according to the invention. Each dosage unit adapted for oral administration may conveniently contain 1 to 20 mg., and preferably 2 to 10 mg., of the active ingredient; each dosage unit adapted for parenteral administration may conveniently contain 0.1 to 5 mg., and preferably 0.1 to 1 mg., of the active ingredient. Dosage units of from about 2 mg. to 10 mg. can be provided for the symptomatic adjustment of dosage by the physician depending upon the age and condition of the patient.

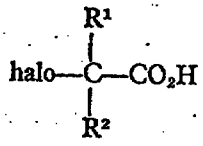
The compounds of the invention of Formula I can be prepared by one or more of the routes described below.

Route I

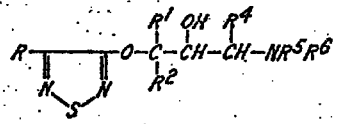


The 3-R-4-hydroxy-1,2,5-thiadiazole (A) is treated with epichlorhydrin or epibromhydrin (B) to provide product "C" which can be separated from the reaction mixture by extraction with ether. Ideally, the epihalohydrin is used in excess for its solvent properties and the reaction proceeds at room temperature or with heating up to about 90° C. with optimum results being obtained by heating at a temperature of from 55—70° C. The reaction of " A " and " B " is additionally facilitated by the presence of a trace of base which serves as a catalyst, preferred catalysts being piperidine, piperidine hydrochloride, pyridine and other heterocyclic bases. After extraction the intermediate product "C" is shaken with aqueous alkali to afford the epoxide (D). Aqueous sodium or potassium hydroxide is preferred at a concentration of about 20% for best yields. Treatment of the epoxide "D" with the amine "E" provides the desired thiadiazole product I—b. Advantageously an excess of the amine is used for its solvent properties; from 3 to 5 moles of the amine being adequate to give very good yields of the desired product. Larger quantities can be used if desired. This step can be carried out at a temperature between about ambient temperature and 90° C. although it is preferred to use temperatures of from 60—70° C. It has also been found that certain amines, particularly branched chain monoalkyl amines, such as neopentylamine, can be refluxed with the intermediate product "C" to give the desired product I—b directly.

When any one or more of the variables R^1, R^2 and R^4 in the desired product of Formula I is a C_{1-3} alkyl group, the product can be prepared by the reaction of starting substance "A" with an α-haloalkanoic acid of the structure

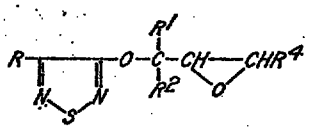


to provide a 3-R-4-α-carboxyalkoxy-1,2,5-thiadiazole which is converted by conventional methods to the acid chloride. Reaction of the acid chloride with a diazoalkane of the structure $R^4CH—N_2$ gives the 3-R-4-(3-chloro-3-R^4-2-oxo-1-R^1-1-R^2-propoxy)-1,2,5-thiadiazole which upon reduction, preferably with sodium borohydride, affords the intermediate " C ", which may be converted to the thiadiazole I—c by the procedures described above. This alternative method can, of course, be used for preparing products where R^1, R^2 and R^4 are hydrogen atoms.



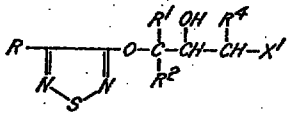
I—c

Accordingly the invention provides a process for preparing the compounds of the invention in which R^3 is a hydrogen atom, comprising reacting an epoxide of the formula:



where R, R^1, R^2 and R^4 are as defined above, with an amine of the formula HNR^5R^6 where R^5 and R^6 are as defined above.

Also in accordance with the invention compounds of the invention in which R^3 is a hydrogen atom are prepared by reacting a compound of the formula:

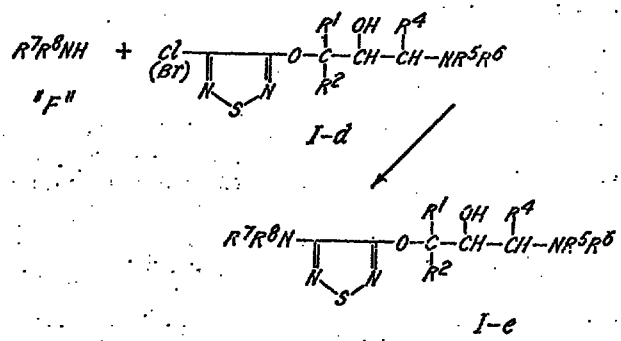


where R, R^1, R^2 and R^4 are as defined above and X^1 is a chlorine or bromine atom, with an amine of the formula R^5R^6NH where R^5 and R^6 are as defined above.

The compounds of the invention in which R^3 is a hydrogen atom may be reacted with a benzoyl acid halide or anhydride or a C_{2-4} alkanoic acid halide or anhydride to produce the corresponding compounds in which R^3 is a benzoyl or C_{2-4} alkanoyl group. This reaction is generally carried out at ambient temperature or with brief warming up to about 100° C.

Many of the thiadiazole starting materials, "A", are known compounds or can be made from known starting materials. In general, the process for making the thiadiazoles "A" comprises the reaction of an R—ClCH—$CONH_2$ with ammonium hydroxide to provide the corresponding α-R-α-amino-acetamide hydrochloride which product, when reacted with SCl_2, S_2Cl_2, $SOCl_2$ or thionylaniline, provides the desired thiadiazole "A". It is sometimes more convenient to prepare the α-amino-acetamide product from an α-amino acid such as an R—$CH(NH_2)$—CO_2H by treatment with acetyl chloride in methanol to form the ester which upon treatment with a large excess of ammonium hydroxide forms the desired α-amino-acetamide which can then be treated with SCl_2, S_2Cl_2, $SOCl_2$ or thionylaniline to provide the thiadiazole "A".

Route II



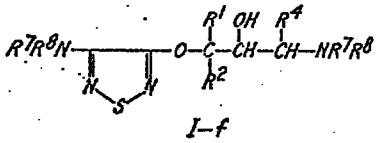
I-d

I-e

In the second route, the thiadiazole, I—d, (which may be prepared by the method described in Route I) is reacted with an amine, "F", to produce an appropriately 3-substituted product I—e. When the amine "F" is a primary or secondary amine, the reaction is advantageously carried out under pressure; however, when the amine is a heterocycle of the type defined hereinabove the reaction readily takes place without pressure by heating the reactants at a temperature of from 100—150° C. but pre-

ferably at a temperature of from 125—135° C. A slight excess of the amine "F" is generally used for its solvent properties and from about 3 to 5 moles of amine have been found to give optimum yields. Larger quantities can be used if desired.

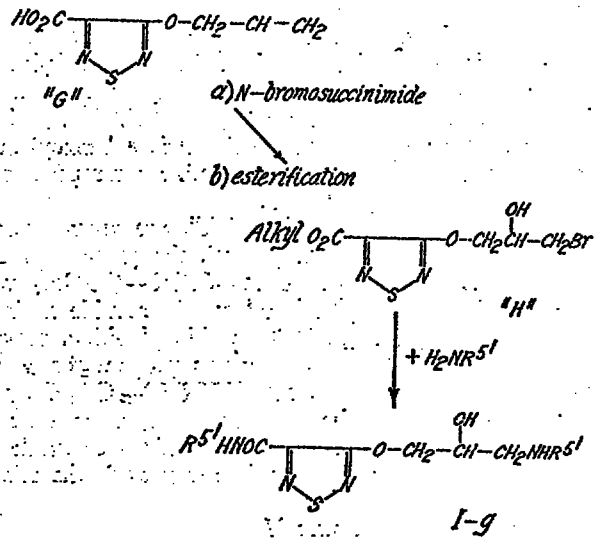
Various modifications can be made in the above preferred methods for preparing the compounds of this invention. For example, when starting material "A" in Route I is the 3-chloro(or bromo)-4-hydroxy-1,2,5-thiadiazole, it can be reacted with product "F" (see Route II) thereby introducing the desired —NR^7R^8 group in the 3-position of the thiadiazole nucleus. Also, when R in product "D" (see Route I) is chloro or bromo, product "D" can be reacted with the amine "F" whereupon the amine will first react with the epoxide portion of the product and then, by increasing the temperature, it will replace the chlorine or bromine atom thereby forming a product of the formula:



I–f

Obviously an amine of the structure HNR^5R^6 could be used in place of reactant "F". As is usual, the amine is used in excess for its solvent properties and the second stage of the reaction is advantageously carried out at a temperature of from 110—150° C. preferably from 125—135° C. to introduce the amino group into the 3-position. In some instances it may be advantageous to carry out this reaction in a sealed vessel.

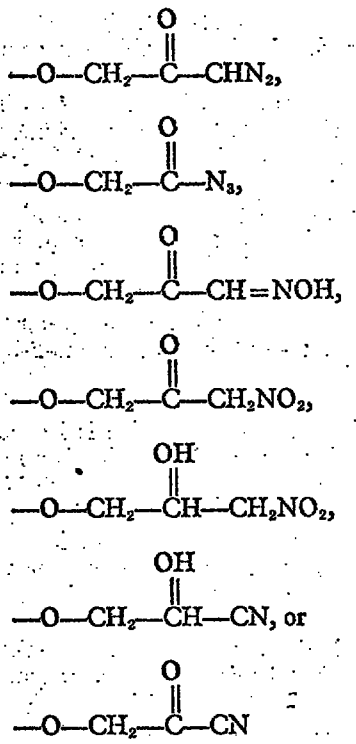
Route III



I–g

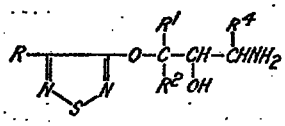
Route III is especially suitable for preparing compounds in accordance with the invention having a carbamoyl substituent in the 3-position. Treatment of the 4-allyloxy-1,2,5-thiadiazole-3-carboxylic acid "G" with N-bromosuccinimide followed by esterification gives the bromohydrin "H". An aqueous solution of N-bromosuccinimide is advantageously used and reaction takes place at about ambient temperature. As the reaction is exothermic, the reaction mixture is generally cooled to maintain the temperature from slightly below to slightly above ambient temperature for best results. Esterification can be effected with any alcohol, advantageously methanol or another C_{1-4} alkanol or a phenyl-C_{1-4} alkanol, for example, phenylethanol, and the reaction temperature is preferably maintained at a range from below to slightly above ambient temperature, such as in the range from about 10 to 30° C. The bromohydrin "H" which is obtained in good yields, is then reacted with an amine of the structure $H_2NR^{5'}$ to form the thiadiazole product I—g. The reaction with the amine is advantageously carried out at reflux or if desired it can be carried out under pressure at higher temperatures. The amine is generally used in excess for its solvent properties.

The invention further provides a process comprising reducing a 3-R-4-X^2-1,2,5-thiadiazole where X^2 is a



group, and R is as defined above, and then subjecting the resulting product to reductive alkylation with a ketone of the formula O=CYZ where Y^1 is a C_{1-5} alkyl, C_{2-5} alkenyl C_{2-5} alkynyl, hydroxy C_{2-5} alkyl, C_{3-5} cycloalkyl or phenyl group, and Z^1 is a C_{1-5} alkyl group or Y^1 and Z^1 are each C_{1-5} alkyl groups and are linked together to form with the carbon to which they are attached a 3- to 6-membered carbocyclic ring, to produce a compound of Formula I in which R^1, R^2, R^3, R^4 are hydrogen atoms and R^6 is a group of the formula $-CHY^1Z^1$ where Y^1 and Z^1 are as defined above.

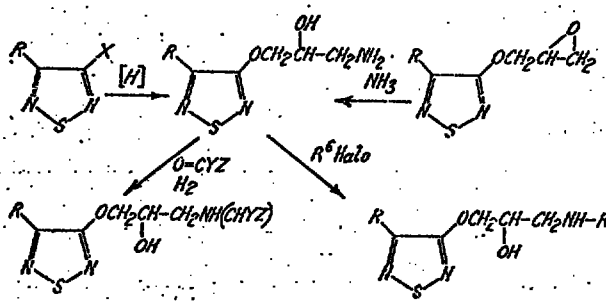
The compounds of Formula I in which R^3 and R^5 are hydrogen atoms may be prepared by reacting a compound of the formula:



where R, R^1, R^2 and R^4 are as defined above with an organic halide of the formula R^6X^1 where X^1 is a chlorine or bromine atom.

Route IV is illustrated in the following reaction scheme:

Route IV



Palladium-on-charcoal is advantageously used as a catalyst for the reduction while lithium aluminium hydride is advantageously used as reducing agent. The compound having the substituted amino group may be formed *in situ*.

The following examples illustrate representative compounds of this invention prepared by the above described procedures.

EXAMPLE 1

3-Chloro-4-(3-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

Step A: Preparation of 3-chloro-4-(2,3-epoxypropoxy)-1,2,5-thiadiazole

A mixture of 30 g. (0.22 mole) of 3-chloro-4-hydroxy-1,2,5-thiadiazole, 71 g. (0.77 mole) of epichlorohydrin, and 0.6 ml. of piperidine is maintained at 65—70° C. for two hours. Excess of epichlorohydrin is removed at about 95° C. using water-pump vacuum. The residual viscous gum, 55.5 g., is dissolved in diethyl ether and refrigerated. The supernatant ethereal liquor is drawn off and evaporated to dryness giving 20.2 g. of a viscous oil that is then stirred for about half an hour with 150 ml. of 10% sodium hydroxide solution. The mixture warms up slightly during this treatment. The mixture then is extracted with diethyl ether, washed with water, and evaporated to yield 20.2 g. of crude 3-chloro-4-(2,3-epoxypropoxy)-1,2,5-thiadiazole.

Step B: Preparation of 3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride

A mixture of 40.2 g. (0.21 mole) of 3-chloro-4-(2,3-epoxypropoxy)-1,2,5-thiadiazole and 76 g. (1.05 moles) of *tert*-butylamine is heated and stirred at 60—70° C. for two and one-half hours. Excess *tert*-butylamine is removed *in vacuo* giving 42.4 g. of residual crude product. The latter is dissolved by shaking with a mixture of diethyl ether and water containing 2.5 g. of sodium hydroxide. The ethereal phase is separated and the aqueous phase is extracted with several portions of diethyl ether. The ethereal extracts are combined, washed with small volumes of water and then treated with excess of 3N hydrochloric acid. The aqueous layer is separated, evaporated to dryness and the resulting residue is dried by azeotropic distillation of benzene ethanol. The crystalline solid is recrystallized from ethanol diethyl ether giving 31.3 g. (49.5%) of 3 - chloro - 4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole hydrochloride, m.p. 159—161° C. Recrystallizations from the same solvent mixture give a product melting at 161—163° C. (ED_{50}=0.093 mg./kg.).

Analysis calculated for $C_9H_{17}Cl_2N_3O_2S$:
C, 35.77; H, 5.67; Cl, 23.46; N, 13.90;
Found: C, 36.11; H, 5.37; Cl, 23.33; N, 13.82.

Step C: Preparation of 3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

The 3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride obtained in Step B is neutralized with aqueous sodium carbonate and the free base extracted with diethyl ether. After removal of the solvent, the residue is recrystallized from di-isopropyl ether giving the free base as colorless prisms, m.p. 78—79° C.

Analysis calculated for $C_9H_{16}ClN_3O_2S$:
C, 40.66; H, 6.07, Cl, 13.34; N, 15.81; S, 12.07;
Found: C, 40.80; H, 6.18; Cl, 13.80; N, 16.00; S, 11.80.

In the following Sections describing methods of resolving certain of the racemic products of this invention, no attempt has been made to assign an absolute configuration to the compounds. The (−)- and (+)-isomers of the resolving agents refer to the optical rotation of the parent (−) or (+) agent. All (−) and (+) values given throughout for the compounds refer to the actual rotation of the free base, i.e., in referring to the levorotatory salt, (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, the (+)- sign refers to the sign of rotation of the free base, (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole.

RESOLUTION OF EXAMPLE 1 PRODUCT

Section 1

Isolation of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole via the O,O-di-*p*-toluoyl-(−)-tartrate

Step A: A warmed solution of 26.5 g. (0.1 mole) of racemic 3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole from Example 1, Step C, in 100 ml. of ethanol is added to a warmed solution of 38.6 g. (0.1 mole) of O,O-di-*p*-toluoyl-(−)-tartaric acid in 225 ml. of ethanol and the mixture left overnight at 5° C. The precipitated solid is collected, washed with 25 ml. of ethanol and dried to give 49.8 g. of crystalline product, m.p. 160—2° C. (dec.), $([\alpha]_D^{22°}+77.5°$, c=2.9 in

CH_3OH)*. The crude salt is recrystallized five times from five volumes by weight of ethanol affording 21.0 g. of enriched (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen O,O-di-p-toluoyl-(−)-tartrate, m.p. 166.5—7.0° C. (dec.), ($[\alpha]_D^{22°}$+80.6°, c=2.5 in CH_3OH).

Step B: The above salt (21.0 g., 0.0323 mole) is shaken with a mixture of 100 ml. of water, 14 ml. (0.07 mole) of 5N sodium hydroxide solution, and 100 ml. of diethyl ether. Two further ether extractions (2×50 ml.) are performed and the combined ethereal extract is extracted once with 30 ml. (ca. 0.04 mole) of 1.38N hydrochloric acid. The acid layer is extracted once with a small amount of diethyl ether, and then basified with 10 ml. (0.05 mole) of 5N sodium hydroxide solution. The liberated base is extracted with 100 ml. of diethyl ether, followed by two 25 ml. portions of ether. The ethereal extracts are combined and washed with 20 ml. (2×10 ml.) of water, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give 7.9 g. of syrupy (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole ($[\alpha]_D^{20°}$+6.5°, c=2.4 in CH_3OH). The syrup (7.9 g.) is dissolved in 115 ml. of warm " Skellysolve B " (essentially, *n*-hexane, b. 60—68°) the solution allowed to cool to room temperature, seeded with a trace of racemic base, and left 18 hours at room temperature. The crystalline solids are collected, washed with a small volume of " Skellysolve B ", and dried to give 0.92 g. of (±)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole contaminated with a small amount of the (+) - enantiomer, m.p. 59—68° C. The filtrate afforded 5.6 g. of (+) - 3 - chloro - 4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - 1,2,5 - thiadiazole, m.p. 58.5—62.5° C. ($[\alpha]_D^{20°}$+6.7°, c=2.5 in CH_3OH). Further crystallization of the latter from "Skellysolve B" afforded the product melting at 58.5—60.0° C., ($[\alpha]_D^{20°}$+7.22°, c=2.5 in CH_3OH), (ED_{50}=0.023 mg./kg. tested as HCl salt).

Analysis calculated for $C_9H_{16}ClN_3O_2S$:
C, 40.68; H, 6.07; Cl, 13.34; N, 15.81; S, 12.06;
Found: C, 41.15; H, 6.08; Cl, 13.76; N, 16.13; S, 12.04.

Section 2

Preparation of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy-1,2,5-thiadiazole hydrochloride

A solution of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole (1.45 g., m.p. 59—60° C.) in 20 ml. of anhydrous diethyl ether is treated with an excess of ethanolic hydrogen chloride solution. The precipitated solid is collected and washed with anhydrous diethyl ether to give 1.43 g. of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride, m.p. 148—51° C. Precipitation of this material in ethanol with diethyl ether affords the product with m.p. 148—9.5° C., ($[\alpha]_D^{22°}$−7.65°, c=2.75 in CH_3OH).

Analysis Calculated for $C_9H_{16}ClN_3O_2S \cdot HCl$:
C, 35.77; H, 5.67; Cl, 23.46; N, 13.90; S, 10.60.
Found: C, 35.88; H, 5.74; Cl, 23.61; N, 14.06; S, 10.34.

Section 3

Isolation of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

All liquors and washes resulting from the isolation of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen O,O-di-p-toluoyl-(−)-tartrate (see Section 1) are combined, evaporated to dryness, and the residue treated with 5N sodium hydroxide solution as described in Section 1. The mixture then is extracted three times with diethyl ether. The combined ethereal extracts are washed with water, dried, and evaporated to dryness to give 14.3 g. of enriched (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 58—76° C. The crude material (14.3 g.) is dissolved in 210 ml. of " Skellysolve B ", allowed to cool to room temperature, seeded with a trace of racemic base, and left at room temperature for

* The legends used here and throughout the specification have the following significance. " $[\alpha]_D^{22}$+77.5 " signifies the specific rotation at 22° C. (or other given temperature), at the " D " line of sodium.
" c=2.9 in CH_3OH " signifies the concentration of the product (2.9% or other given concentration) in methanol (or other specified solvent).

24 hours. The crystals are collected and dried to give 5.9 g. of (±)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 78.5—9.5° C. $[\alpha]_D^{20°}$ 0°), and mother liquors afford further crops of crystalline racemic material. The remaining mother liquors upon evaporation then afford a total of 6.9 g. of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 57—60° C., $[\alpha]_D^{22°}$ −7.31°, c=2.5 in CH_3OH). Further purification gives (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 59—60° C., (ED_{50}=0.056 mg./kg., tested as hydrochloride salt.)

Analysis calculated for $C_9H_{16}ClN_3O_2S$:
C, 40.68; H, 6.07; Cl, 13.34; N, 15.81; S, 12.06.
Found: C, 40.46; H, 6.21; Cl, 13.31; N, 15.96; S, 11.90.

Section 4

Preparation of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride

A slight excess of ethanolic hydrogen chloride solution is added slowly to a stirred solution of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole (1.66 g., 6.26 millimoles, m.p. 59—60° C., obtained as in Section 3) in 50 ml. of dry diethyl ether. The resulting precipitated solid is collected, washed with anhydrous diethyl ether, and dried to give 1.8 g. of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride, m.p. 146—7° C. ($[\alpha]_D^{20°}$+7.9°, c=2.8 in CH_3OH).

Section 5

Isolation of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

Step A: The procedure set forth in Section 1 is repeated with the exception that O,O-di-*p*-toluoyl-(−)-tartaric acid is replaced by O,O-di-*p*-toluoyl)-(+)-tartaric acid. Thus solutions of 25.75 g. (0.0972 mole) of (±)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole in 100 ml. of anhydrous ethanol and 37.5 g. (0.0972 mole) of O,O-di-*p*-toluoyl-(+)-tartaric acid in 225 ml. of anhydrous ethanol are mixed and chilled for two hours at 5° C. to give 49.1g (77.6%) of the salt, m.p. 159—61° C. The crystalline product is recrystallized five times from anhydrous ethanol to give 24 g. of highly enriched (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen O,O-di-*p*-toluoyl-(+)-tartrate, m.p. 165—6° C. ($[\alpha]_D^{22°}$−80.1°, c=3 in CH_3OH).

Analysis calculated for $C_9H_{16}ClN_3O_2S \cdot C_{20}H_{18}O_6$:
C, 53.3; H, 5.25; Cl, 5.44; N, 6.44; S, 4.91.
Found: C, 53.1; H, 4.99; Cl, 5.86; N, 6.94; S, 4.93.

Step B: The procedure set forth in Step B of Section 1, is followed for the treatment of the salt to afford the free base. Thus treatment of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen O,O-di-p-toluoyl-(+)-tartrate, followed by extraction with diethyl ether, gave a free base that upon fractional crystallization from "Skellysolve B" to remove small amounts of racemic base affords 7 g. of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 59—60° C.

Analysis calculated for $C_9H_{16}ClN_3O_2S$:
C, 40.68; H, 6.07; Cl, 13.34; N, 15.81; S, 12.06.
Found: C, 40.50; H, 6.21; Cl, 13.30; N, 16.00; S, 11.90.

Section 6

Isolation of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

Following the procedure of Section 3, the mother liquors and washings from the isolation of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen O,O-di-*p*-toluoyl-(+)-tartrate (from Step A, Section 5) are treated with alkali, the free organic base extracted with diethyl ether, and the ether removed to afford the free base enriched with (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole. Careful fractional crystallization of this crude base from "Skellysolve B" removes (±)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 78—9° C. The remaining fractions are combined and recrystallized to afford (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 59—60° C

Section 7

Isolation of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

The procedure set forth in Section 1 is repeated with the exception that O,O-di-*p*-toluoyl-(−)-tartaric acid is replaced by (−)-tartaric acid. The resulting salt is recrystallized repeatedly from ethanol to give di-[(+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole]-(−)-tartrate, m.p. 130—2° C. ($[\alpha]_D^{22°}$ −15.3°, c=2.6 in CH_3OH). The tartrate is converted by the method described in Step B of Section 1 to the free base and the base subjected to fractional crystallization to afford (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole. Work up of the washings and mother liquors from di-[(+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole]-(−)-tartrate by the procedure given in Section 3 affords (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole.

Section 8

Isolation of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

Step A: The procedure set forth in Section 1 is repeated with the exception that O,O-di-*p*-toluoyl-(−)-tartaric acid is replaced by (+)-tartaric acid. The resulting salt upon repeated recrystallization affords di-[(−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole]-(+)-tartrate, m.p. 130—2° C. ($[\alpha]_D^{22°}$ +15.6°, c=2.3 in CH_3OH).

Analysis calculated for $(C_9H_{16}ClN_3O_2S)_2 . C_4H_6O_6$:
C, 38.7; H, 6.51; Cl, 10 4; N, 12.3; S, 9.39.
Found: C, 38.5; H, 5.70; Cl, 10.7; N, 12.2; S, 9.18.

Step B: The tartrate is converted by the procedure of Section 1, Step B, to the free base and the base recrystallized to afford (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 58—60° C.

Step C: Work up of the mother liquors and washings from di-[(−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole]-(+)-tartrate by the procedure described in Section 3 affords (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole.

Section 9

Isolation of (−) and (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole via O,O-dibenzoyl-(+)-tartaric acid

Step A: The procedure set forth in Section 1 is repeated with the exception that O,O-di-*p*-toluoyl-(−)-tartaric acid is replaced by O,O-dibenzoyl-(+)-tartaric acid. Thus, solutions of 5.3 g. (0.02 mole) of (±)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole in 20 ml. of anhydrous ethanol and 7.5 g. (0.02 mole) of O,O-dibenzoyl-(+)-tartaric acid in 45 ml. of anhydrous ethanol are mixed and left two days at room temperature to give 1.7 g. of product, m.p. 177—8° C. ($[\alpha]_D^{20°}$ −42.9°, c=1.55 in CH_3OH). Recrystallization of this material from anhydrous ethanol gives 1.35 g. of di-[(−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole)-O,O-dibenzoyl-(+)-tartrate, m.p. 177.7—178.2° C. (dec.). ($[\alpha]_D^{20°}$ −44.6°, c=1.24 in CH_3OH).

Step B: The salt is partitioned between 50 ml. of diethyl ether and 50 ml. of water containing 1 g. of sodium carbonate, the layers are separated after vigorous shaking and the aqueous phase extracted four times with diethyl ether. The combined ethereal extracts are washed with water and evaporated to give the free base. This product is recrystallized from " Skellysolve B " to give 600 mg. of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 59.5—60.5° C. ($[\alpha]_D^{20°}$ −7.16°, c=3.5 in CH_3OH). Work-up of the mother liquors from the dibenzoyl tartrate by the procedure of Section 3 affords (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, m.p. 59—60° C.

Section 10

Isolation of (−) and (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole via O,O-dibenzoyl-(+)-tartaric acid

Similarly, following the procedure set forth in Section 1 with the exception that the O,O-di-*p*-toluoyl-(−)-tartaric acid is replaced with O,O-dibenzoyl-(+)-tartaric acid there are obtained specimens of (−)- and (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole.

EXAMPLE 1A

3-Morpholino-4-(3-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate

A solution of 5.0 g. of 3-hydroxy-4-morpholino-1,2,5-thiadiazole (26.7 millimole) in 18.95 ml. of 1.41 *N* methanolic sodium methoxide is treated with 10.5 ml. of epichlorohydrin (134 millimole) and the mixture is stirred at 25° C. for 16 hours. The precipitated sodium chloride is filtered and washed with methanol. The filtrate is evaporated *in vacuo* to an oil residue. The residue is refluxed for 12 hours in 15 ml. *t*-butylamine and the excess amine evaporated *in vacuo*. The residue of crude 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole free base (6.1 g.) is converted to the maleate salt and recrystallized from ethanol, m.p. 214—215° C.

EXAMPLE 1B

3-Morpholino-4-(3-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, hydrogen maleate

A mixture of 0.22 mole of 3-morpholino-4-hydroxy-1,2,5-thiadiazole, 71 g. (0.77 mole) of epichlorohydrin, and 0.6 ml. of piperidine is maintained at 65—70° C. for 2 hours. Excess epichlorohydrin is removed at about 95° C. *in vacuo*. The residual gum is dissolved in diethyl ether and refrigerated. The supernatant ethereal liquor is separated and evaporated to a viscous oil. An excess of t-butylamine is added and the mixture is heated at 100° C. for 10 hours in a sealed vessel. The product is isolated by the method described in Example 1A to give 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, hydrogen maleate.

By following substantially the same procedure described in Example 1, 1A or 1B but replacing the 3-chloro-4-hydroxy-1,2,5-thiadiazole in Example 1, Step A, and the amine used in Example 1, Step B by the reactants "A" and "E" identified in the following table there are obtained thiadiazoles I—b which also are identified in Table I. The atoms and groups identified for the variable radicals R, R^5 and R^6 in the reagents "A" and "E" remain unchanged during the reaction and are the same R, R^5 and R^6 atoms and groups in the thiadiazole products I—b.

TABLE I

TABLE I

Ex. No.	R	R⁵	R⁶	Empirical Formula	M.P. in °C		C	H	Analysis Cl	N	ED_{50} mg/kg
2	H	H	$-C(CH_3)_2CH_2OH$	$C_9H_{17}N_3O_3S$	94—6	C:	43.70	6.93		16.99	4.8
						F:	43.21	7.13		16.66	
3	H		$-(CH_2)_2-O-(CH_2)_2-$	$C_9H_{15}N_3O_3S.HCl$	150—2	C:	38.86	5.72	12.58	14.91	3.1
						F:	38.55	6.02	12.78	14.88	
4	Cl	H	$-CH(CH_3)_2$	$C_8H_{14}ClN_3O_2S.HCl$	153—5	C:	32.65	5.25	24.60	14.58	0.12
						F:	33.20	5.65	24.56	14.43	
5	C_2H_5	H	$-CH(CH_3)_2$	$C_{10}H_{19}N_3O_2S.HCl$	144.5—145.5	C:	42.62	7.15	12.58	14.91	0.04
						F:	42.50	6.93	12.66	14.81	
6	C_2H_5	H	$-C(CH_3)_3$	$C_{11}H_{21}N_3O_2S.HCl$	137—8	C:	44.63	7.49	11.98	14.20	0.05
						F:	44.67	7.81	12.23	13.96	
7	C_2H_5	H	$-C(CH_3)_2CH_2OH$	$C_{11}H_{21}N_3O_3S.HCl$	125—7	C:	42.37	7.11	11.37	13.47	0.3
						F:	42.88	6.95	11.71	13.26	
8	C_2H_5O	H	$-CH(CH_3)_2$	$C_{10}H_{19}N_3O_3S.HCl$	167—70	C:	40.33	6.77		14.11	0.035
						F:	40.44	6.82		13.87	

TABLE I (Continued)

Ex. No.	R	R^5	R^6	Empirical Formula	M.P. in °C	Analysis				ED_{50} mg/kg
							C	H	Cl	N	
9	C_2H_5O	H	$-C(CH_3)_3$	$C_{11}H_{21}N_3O_3S.HCl$	147—9	C: 42.37 F: 42.60		7.11 7.08		13.47 13.02	0.057
10	C_2H_5O	H	$-CH_2C(CH_3)_3$	$C_{12}H_{23}N_3O_3S.HCl$	168—9	C: 44.23 F: 43.99		7.42 7.45	10.88 11.36	12.89 13.08	5.3
11	C_2H_5O	H	$-C(CH_3)_2C=CH$	$C_{12}H_{19}N_3O_3S.HCl$	130—1	C: 44.79 F: 44.79		6.26 6.65	11.02 11.33	13.06 12.98	0.08
12	C_2H_5O	$-(CH_2)_2-O-(CH_2)_2-$		$C_{11}H_{19}N_3O_4S.HCl$	124—6	C: 40.55 F: 41.13		6.19 6.17	10.88 11.24	12.90 12.28	1.95
13	C_6H_5	H	$-CH(CH_3)_2$	$C_{14}H_{19}N_3O_2S.HCl$	165—7	C: 50.98 F: 51.09		6.12 6.33	10.75 11.05	12.74 12.92	0.08
14	C_6H_5	H	$-C(CH_3)_3$	$C_{15}H_{21}N_3O_2S.HCl$	168—170.5	C: 52.39 F: 52.12		6.45 6.40	10.39 10.57	12.22 12.35	0.02
15	$C_6H_5CH_2$	H	$-C(CH_3)_3$	$C_{16}H_{23}N_3O_2S.HCl$	122—3	C: 53.42 F: 53.59		6.76 6.79	9.90 10.36	11.74 11.66	0.12

C = Calculated values.

F = Found values.

EXAMPLE 16

3-Morpholino-4-(3-tert-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

A mixture of 11.8 g. (39 millimoles) of 3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride from Example 1, Step B, and 65.5 ml. (752 millimoles) of morpholine is heated and stirred at 125—135° C. for four hours. This mixture is refrigerated overnight and the precipitated morpholine hydrochloride is collected and dried; yielding 8.55 g. (88.5%) m.p. 175—180° C. The excess morpholine is removed by distillation *in vacuo* to give 16.8 g. of residual oil. The residue is shaken with 10 ml. of water containing 1.6 g. of sodium hydroxide and extracted with diethyl ether. The combined ethereal extracts are washed sparingly with water and evaporated to dryness to give 11.7 g. of residue. The product is dissolved in anhydrous diethyl ether and treated with excess hydrogen chloride in diethyl ether to give 10.3 g. of crystalline product, m.p. 151—161° C. Recrystallization of this material from anhydrous acetone-diethyl ether gives 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride, m.p. 161—163° C., (ED_{50}=0.013 mg/kg).

Analysis calculated for $C_{13}H_{25}ClN_4O_3S$:
C, 44.25; H, 7.14; Cl, 10.05; N, 15.88; S, 9.08;
Found: C, 43.95; H, 7.50; Cl, 10.52; N, 15.82; S, 9.34.

In another preparation by the above procedure, the free base, 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, is isolated in 50.6% yield, m.p. 72—75° C. Recrystallization from diisopropyl ether gives the product melting at 71.5—72.5° C.

Analysis calculated for $C_{13}H_{24}N_4O_3S$:
C, 49.34; H, 7.64; N, 17.71; S, 10.13;
Found: C, 49.36; H, 7.51; N, 17.50; S, 10.11

Treatment of the mother liquors from the recrystallized free base with hydrogen chloride affords an additional 25% yield of 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride.

Resolution of Example 16 Product

Section 11

Preparation of optically active (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate

Racemic 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole from Example 16, (11.7 g., 0.038 mole), and 2.8 g. (0.0187 mole) of (+)-tartaric acid ($[\alpha]_D^{28°}$+12.9°, c=20 in H_2O) are dissolved in 200 ml. of hot acetone containing 20 ml. of water and aged with stirring at room temperature over a weekend. Filtration of the crystalline precipitate gives 9.6 g. of di-[3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole]-(+)-tartrate, m.p. 181—183° C. ($[\alpha]_D^{28°}$+12.9°, c=1.82 in CH_3OH). Recrystallization of 9.2 g. of this tartrate from 125 ml. of hot acetone containing 12.5 ml. of water gives 6.4 g. of solid material, m.p. 179.5—181° C. ($[\alpha]_D^{28°}$+13.5°, c=2.32 in CH_3OH). A 6.3 g. sample of this solid is shaken in a separatory funnel with 45 ml. N ammonium hydroxide and 100 ml. of ether for 10 minutes. The aqueous layer is extracted with 2×100 ml. portions of ether. The combined ethereal extracts are washed with 2×20 ml. aliquots of water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 5 g. of noncrystalline 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, ($[\alpha]_D^{28°}$−1.82°, c=2.45 in CH_3OH). A mixture of this base and 1.84 g. of maleic acid is dissolved in 240 ml. of hot ethyl alcohol and allowed to age at room temperature with stirring for 18 hours. Filtration of the crystalline solid yields 4.96 g. of 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, m.p. 211—214° C. ($[\alpha]_D^{28°}$+0.45°, c=2.8 in CH_3OH). The mother liquors are refluxed with 100 mg. of "Darco" ("Darco" is a registered trade mark) decolorizing charcoal for 5 minutes, filtered hot, and concentrated to 30 ml. This solution is aged at room temperature with stirring for 18 hours to give 1.029 g. of crystalline (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, m.p. 205—207° C., ($[\alpha]_D^{28°}$+4.17°, c=2.99 in CH_3OH). The mother liquors are diluted with 100 ml. of ether, from which is collected by filtration an additional 350 mg. of product, m.p. 203—204° C. A 321 mg. sample is recrystallized from 3 ml. of ethyl alcohol to give 270 mg. of (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxy-

propoxy)-1,2,5-thiadiazole hydrogen maleate, m.p. 202—203° C. ($[\alpha]_D^{28°}+5.0°$, c=3.02 in CH_3OH). The infrared spectrum of this sample is identical to that of the racemic hydrogen maleate.

Analysis calculated for $C_{17}H_{25}N_4O_7S$:
C, 47.21; H, 6.53; N, 12.95; S, 7.41;
Found: C, 47.57; H, 6.56; N, 12.86; S, 7.48

Section 12

Preparation of optically active (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole from its dextrorotatory hydrogen maleate salt

(−)-3-Morpholino-4-(3-*tert*-butylamino - 2 - hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, ($[\alpha]_D^{28°}+5.0°$, c=3.02 in CH_3OH), (100 mg. from Section 11), 100 ml. of ether and 20 ml. of N ammonium hydroxide is shaken in a separatory funnel for 5 minutes. The aqueous layer is extracted with an additional 50 ml. of ether, and the combined ethereal extracts are washed with 2×20 ml. of water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 70 mg. of oily (−) - 3 - morpholino - 4 - (3 - *tert* - butylamino - 2 - hydroxypropoxy) - 1,2,5-thiadiazole, ($[\alpha]_D^{28°}-4.32°$, c=5.13 in CH_3OH).

Section 13

Resolution with (−)-tartaric acid

By following the resolution procedure described in Section 11 above, but substituting an equal quantity of (−)-tartaric acid for the (+)-tartaric used in Section 11, the resolution of 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole affords the (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, ($[\alpha]_D^{28°}-4.4°$, c=2.56 in CH_3OH). Further fractional recrystallization gives rise to $[\alpha]_D^{28°}-5.0°$ for the hydrogen maleate salt.

Section 14

Preparation of (+)-3-morpholino-4-(*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole from its levorotatory hydrogen maleate salt

By replacing the (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate used in Section 12, with the (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate prepared as described in Section 13 above, and following the same procedure described in Section 12, there is obtained the (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, ($[\alpha]_D^{28°}+4.32°$, c=5.13 in CH_3OH).

ALTERNATIVE PREPARATION OF OPTICALLY ACTIVE ISOMERS OF EXAMPLE 16 PRODUCT

Conversion of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole to (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

Section 15

Preparation of (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

A mixture of 5.3 g. (20 millimoles of m.p. 58.5—62.5° C.) of (+)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole and 26.5 ml. of freshly distilled morpholine are heated for four hours at 135—40° C. The cooled mixture is refrigerated overnight and the precipitated solids collected, washed with anhydrous diethyl ether, and dried to give 2.18 g. (88.3%) of morpholine hydrochloride. The filtrate and washings are combined and evaporated to give an oily product. This material is dissolved in 150 ml. of diethyl ether, washed several times with water, and evaporated to dryness to give 5.7 g. of (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole as a slightly yellow oil.

Section 16

Preparation of (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate

A warm solution of 5.7 g. (18 millimoles) of (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole in 10 ml. of isopropanol is treated with a warm solution of 2.09 g. (18 millimoles) of maleic acid in 10 ml. of isopropanol. The solution is allowed to cool, left 2 hours at 5° C., and the solids collected to give 6.7

g. (86%) of (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, m.p. 192°—4° C. (dec.) ($[\alpha]_D^{20°}$ −4.3°, c=3.3 in CH_3OH). Crystallization of this product from anhydrous ethanol affords 385 g. of (+)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, m.p. 201—2° C., $[\alpha]_D^{20°}$ −5.57°, c=3.35 in CH_3OH), (ED_{50}=0.0066 mg/kg).

Conversion of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole to (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

Section 17

Preparation of (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

Following the procedure described in Section 15, a mixture of 6.9 g. (26 millimoles of material of m.p. 57—60°) of (−)-3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole and 34.5 ml. of freshly distilled morpholine is heated at 135—40° C. for four hours and the product isolated giving 7.2 g. of (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole as a slightly yellow oil.

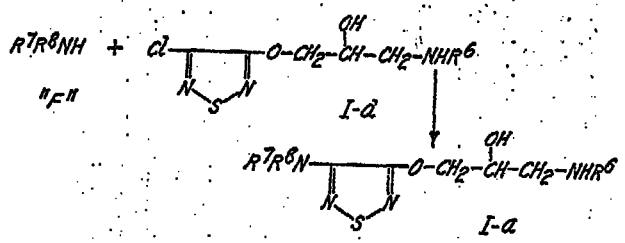
Section 18

Preparation of (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate

The oily (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole (7.2 g.) in 13 ml. of isopropanol is treated with a solution of 2.65 g. (22.8 millimoles) of maleic acid in 13 ml. of isopropanol to afford 9.04 g. (80%) of crude (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, m.p. 190—3.5° C. Careful fractional crystallization of this material from ethanol affords 5.0 g. of (−)-3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrogen maleate, m.p. 201.5—2.5° C. (dec.), $[\alpha]_D^{22°}$ +5.30°, c=3.3 in CH_3OH). A further recrystallization from the same solvent affords material, m.p. 201—2° C. (dec.), ($[\alpha]_D^{22°}$ +5.56°, c=3.2 in CH_3OH), (ED_{50}=0.088 mg/kg).

Additional products of this invention that advantageously are prepared by the procedure described in Example 16 are identified in Table II, below. These products are synthesized by following the procedure identified in Example 16 but replacing the 3-chloro-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride by the reactant I—d having the R^6 substituent identified in the Table and replacing the morpholine used in Example 16 by the amine reactant "F" having the substituents identified for this reactant in the following Table under the headings R^7 and R^8. The R^6, R^7 and R^8 groups identified for the starting materials "F" and I—d are retained in the end product I—a for which physical properties are provided.

TABLE II



Ex. No.	R^7	R^8	R^6	Empirical Formula	M.P. in °C	Analysis	C	H	Cl	N	S	ED_{50} mg/kg
17	$-(CH_2)_2-O-(CH_2)_2-$		$(CH_3)_2CH-$	$C_{12}H_{22}N_4O_3S.HCl$	168.5—170.5	C:	42.54	6.84	10.46	16.53	9.46	0.13
						F:	42.36	7.48	10.64	16.70	9.60	
18	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		$(CH_3)_3C-$	$C_{14}H_{27}N_5O_2S.2HCl.H_2O$	205	C:	40.00	7.43	16.87	16.75	7.63	
						F:	39.92	7.36	16.80	16.65	7.62	
19	$-(CH_2)_5-$		$(CH_3)_2CH-$	$C_{13}H_{24}N_4O_2S.HCl$	169—170.5	C:	46.35	7.48	10.52	16.63	9.52	0.13
						F:	46.71	7.32	10.58	16.40	9.42	
20	$-(CH_2)_5-$		$(CH_3)_3C-$	$C_{14}H_{26}N_4O_2S.HCl$	171—2	C:	47.92	7.76	10.10	15.97	9.14	0.03
						F:	48.06	8.29	10.29	16.04	9.40	
21	$-(CH_2)_2-CH(OH)-(CH_2)_2-$		$(CH_3)_3C-$	$C_{14}H_{26}N_4O_3S.C_4H_4O_4$	171—3	C:	48.42	6.77		12.55	7.18	0.033
						F:	48.33	6.83		12.34	7.21	

C = Calculated values.

F = Found values.

The preparation of Route 3 of products having a carbamoyl substituent in the 3-position of the thiadiazole is illustrated by the following two Examples:

EXAMPLE 22

*3-N-*tert-*butylcarbamoyl-4-(3-*tert-*butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole*

Step A: 4-Allyloxy-1,2,5-thiadiazole-3-carboxylic acid

A mixture of 1 mole of 4-allyloxy-3-cyano-1,2,5-thiadiazole in 10 parts (volume/grams) of 80% ethanol containing 4 equivalents of sodium hydroxide per equivalent of the thiadiazole is refluxed for 2 hours. The ethanol is removed *in vacuo* and the remaining residue dissolved in a minimum amount of water and made acidic (pH 2) with hydrochloric acid. The precipitated 4-allyloxy-1,2,5-thiadiazole-3-carboxylic acid is removed by filtration and washed with water to give a 90% yield of product, m.p. 138—139° C.

Step B: 4-(3-Bromo-2-hydroxypropoxy)-1,2,5-thiadiazole-3-carboxylic acid

A mixture of 9.3 g. (50 millimoles) of 4-allyloxy-1,2,5-thiadiazole-3-carboxylic acid and 8.9 g. (50 millimoles) of N-bromo-succinimide is suspended in 50 ml. of water. The mixture initially turns brown and evolves heat but after one minute a colorless solution results. The white crystals that deposit upon cooling are collected, washed with water, and dried giving 8.0 g. (56.5%) of 4-(3-bromo-2-hydroxypropoxy)-1,2,5-thiadiazole-3-carboxylic acid. Recrystallization of the product from ethyl acetate affords the purified bromohydrin, m.p. 175.0—177.5° C.

Analysis calculated for $C_6H_7BrN_2O_4S$:
C, 25.45; H, 2.49; Br, 28.23; N, 9.89; S, 11.32;
Found: C, 25.29; H, 2.38; Br, 28.14; N, 9.79; S, 11.28

Step C: 3-Carbomethoxy-4-(3-bromo-2-hydroxypropoxy)-1,2,5-thiadiazole

To a solution of 5 ml. (excess) of acetyl chloride in 40 ml. of anhydrous methanol is added 5.66 g. (20 millimoles) of 4-(3-bromo-2-hydroxypropoxy)-1,2,5-thiadiazole-3-carboxylic acid and the suspension is stirred for eighteen hours at room temperature. The resulting solution is evaporated to dryness to afford a colorless oil whose infrared spectrum is consistent with the proposed structure of 3-carbomethoxy-4-(3-bromo-2-hydroxypropoxy)-1,2,5-thiadiazole which is used without further purification in the following step.

Step D: 3-N-*tert*-butylcarbamoyl-4-(3-*tert*-butylamino-2-hydroxypropoxy)1,2,5-thiadiazole

A mixture of 1.49 g. (5 millimoles) of 3-carbomethoxy-4-(3-bromo-2-hydroxypropoxy)-1,2,5-thiadiazole in 6 ml. (excess) of *tert*-butylamine is refluxed for ninety hours. Considerable tertiary butylamine hydrobromide is precipitated by the addition of 100 ml. of diethyl ether. The salt is collected and the filtrate concentrated to remove diethyl ether and excess *tert*-butylamine. The resulting oil is dissolved in chloroform and washed sparingly with water. The chloroform layer is evaporated to give an oil that is dissolved in a mixture of methanol-diethyl ether and treated with a stream of hydrogen chloride until precipitation is complete. The solvent and excess hydrogen chloride are removed *in vacuo*. The residual oil is dissolved in hot ethyl acetate and cooled to give 1.2 g. of crystals. Further recrystallization of the product from ethyl acetate-diethyl ether and then methanol-diethyl ether affords pure 3-N-*tert*-butylcarbamoyl-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride, m.p. 145—147° C.

Analysis calculated for $C_{11}H_{27}ClN_4O_3S$:
Cl, 9.66; N, 15.27; S, 8.74
Found: Cl, 9.69; N, 15.61; S, 8.75

EXAMPLE 23

3-N-isopropylcarbamoyl-4-(3-isopropylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

A mixture of 1.49 g. (5 millimoles) of 3-carbomethoxy-4-(3-bromo-2-hydroxypropoxy)-1,2,5-thiadiazole (prepared as described in Example 22, Step B) and 10 ml. of isopropylamine is refluxed and stirred for seven days. The excess isopropylamine is removed *in vacuo*, and the residue is dissolved in diethyl ether. The ethereal solution is washed with water, dried, and evaporated to give 0.4 g. of oil. The oil is dissolved in methanol-diethyl ether and treated with excess hydrogen chloride. Evaporation of the solvent and treatment of the residue with ethyl acetate-methanol-diethyl ether gives 0.4 g. of crystalline product. Recrystallization of the product from ethyl acetate-

F = Found values.

methanol-diethyl ether gives 3-N-isopropylcarbamoyl-4-(3-isopropylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride, m.p. 96—99° C.

Analysis calculated for $C_{12}H_{23}ClN_4O_3S$:
Cl, 10.46; N, 16.53; S, 9.46;
Found: Cl, 10.46; N, 16.11; S, 9.25

The following Examples illustrate methods for the preparation of products of this invention illustrated by structure I above, in which R^1, R^2, R^3 and/or R^4 are other than hydrogen:

EXAMPLE 24

3-Morpholino-4-(3-tert-butylamino-2-hydroxybutoxy)-1,2,5-thiadiazole

Step A: Preparation of 3-chloro-4-(3-chloro-2-hydroxybutoxy)-1,2,5-thiadiazole

3-Chloro-4-hydroxy-1,2,5-thiadiazole is treated with 2-chloroacetic acid in the presence of ethanolic sodium hydroxide to give 3-chloro-4-carboxymethoxy-1,2,5-thiadiazole. Treatment of this acid with thionyl chloride or oxalyl chloride affords the acid chloride. The acid chloride (1 part) in 20 parts of diethyl ether is treated dropwise at −10° to −15° C. with a slight excess of diazoethane in 30 parts of diethyl ether and the mixture stirred one hour longer at −10° C. The solution is left at room temperature overnight, cooled to −10° to −15° C. and treated with anhydrous hydrogen chloride until evolution of nitrogen is complete. The solution is successively washed with water, a 5% sodium carbonate solution, and water. The dried solution is evaporated to a residue to give 3-chloro-4-(3-chloro-2-oxobutoxy)-1,2,5-thiadiazole. The crude 3-chloro-4-(3-chloro-2-oxobutoxy)-1,2,5-thiadiazole (1 part) in 5 parts of isopropanol is treated at 0—5° C. with a solution containing an excess of sodium borohydride in 5 parts of isopropanol. The mixture is left for 3 to 5 hours at room temperature, then poured onto a mixture of ice and acetic acid, the mixture is extracted with ether, and worked up to give 3-chloro-4-(3-chloro-2-hydroxybutoxy)-1,2,5-thiadiazole.

Step B: Preparation of 3-chloro-4-(3-butylamino-2-hydroxybutoxy)-1,2,5-thiadiazole hydrochloride

A mixture of 1 part of 3-chloro-4-(3-chloro-2-hydroxybutoxy)-1,2,5-thiadiazole and 7.5 parts of butylamine is heated for 10 hours at 100° C. in a sealed vessel. The product is isolated by the method described in Example 1, Step B, to give 3-chloro-4-(3-butylamino-2-hydroxybutoxy)-1,2,5-thiadiazole. The base is dissolved in anhydrous diethyl ether and treated with anhydrous hydrogen chloride to give 3-chloro-4-(3-butylamino-2-hydroxybutoxy)-1,2,5-thiadiazole hydrochloride.

Step C: Preparation of 3-morpholino-4-(3-butylamino-2-hydroxybutoxy)-1,2,5-thiadiazole

A mixture of 1 part of 3-chloro-4-(3-butylamino-2-hydroxybutoxy)-1,2,5-thiadiazole hydrochloride in 5 parts of freshly distilled morpholine is heated for four hours at 135—40° C. The product is isolated by the method described in Example 16 to give 3-morpholino-4-(3-butylamino-2-hydroxybutoxy)-1,2,5-thiadiazole which is converted to its hydrochloride salt.

EXAMPLE 25

3-Morpholino-4-(3-butylamino-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole

Step A: Preparation of 3-chloro-4-(3-chloro-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole

3-Chloro-4-(3-chloro-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole is prepared by a sequence of reactions similar to those described in Example 24, Step A. Thus 3-chloro-4-hydroxy-1,2,5-thiadiazole is condensed with 2-bromopropionic acid to give 3-chloro-4-(1-methylcarboxymethoxy)-1,2,5-thiadiazole. The acid is converted by conventional methods to the acid chloride and the acid chloride treated with diazomethane in diethyl ether at −10° to −15° C. The dried ethereal solution is treated with anhydrous hydrogen chloride and the resulting chloroketone reduced with sodium borohydride to give 3-chloro-4-(3-chloro-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole.

Step B: Preparation of 3-morpholino-4-(3-butylamino-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole

The procedure set forth in Example 24, Step B, is repeated with the exception that 3-chloro-4-(3-chloro-2-hydroxybutoxy)-1,2,5-thiadiazole is replaced by 3-chloro-4-(3-chloro-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole. Thus 3-chloro-4-(3-butylamino-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole is obtained and isolated as the hydrochloride salt. Treatment of either 3-chloro-4-(3-butylamino-2-hydroxy-1-methyl-

propoxy)-1,2,5-thiadiazole or its hydrochloride salt with morpholine as described in Example 16 gives 3-morpholino-4-(3-butylamino-2-hydroxy-1-methylpropoxy)-1,2,5-thiadiazole that is isolated as its hydrochloride salt.

EXAMPLE 26

3-Morpholino-4-(3-butylamino-2-acetoxypropoxy)-1,2,5-thiadiazole hydrochloride

A mixture of 1 part of 3-morpholino-4-(3-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole, 5 parts of acetic acid, and 1 part of acetic anhydride is left 24 hours at room temperature. The solution is poured on ice, made alkaline with ammonium hydroxide, extracted with ethyl ether, and the ethereal solution dried over anhydrous magnesium sulfate. The ethereal solution is treated with anhydrous hydrogen chloride and the precipitated product is recrystallized from ethanol-diethyl ether to give 3-morpholino-4-(3-butylamino-2-acetoxypropoxy)-1,2,5-thiadiazole hydrochloride.

EXAMPLE 27

3-Morpholino-4-(3-butylamino-2-benzoyloxypropoxy)-1,2,5-thiadiazole hydrochloride

A mixture of 1 part of 3-morpholino-4-(3-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride and 2.5 parts of benzoyl chloride is heated for 4—6 hours at 100° C. The mixture is cooled and added to 25 parts of diethyl ether. The ether is decanted, the remaining solid is slurried with a further 25 parts of diethyl ether, and the mixture is filtered. The collected product is washed several times with further amounts of diethyl ether. The solid is recrystallized from ethanol-diethyl ether to give 3-morpholino-4-(3-butylamino-2-benzoyloxypropoxy)-1,2,5-thiadiazole hydrochloride.

The compounds represented by those prepared in Examples 26 and 27, i.e., those in which the 2-hydroxy group of the side chain are esterified are readily converted back to the starting 2-hydroxy compounds by deesterification either with dilute alkali or acid, using standard experimental conditions.

EXAMPLE 28

3-Morpholino-4-(3-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole benzoate

A solution of 1 part of 3-morpholino-4-(3-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole in 50 parts of ethyl acetate is added to a solution of 1 part of benzoic acid in 40 parts of diethyl ether. The resulting solid is collected on a filter plate and washed several times with diethyl ether. The product is crystallized from ethanol-diethyl ether to give 3-morpholino-4-(3-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole benzoate.

Preparation of 3-R-4-hydroxy-1,2,5-thiadiazoles

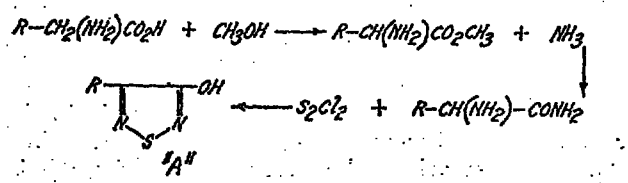
The novel 3-R-4-hydroxy-1,2,5-thiadiazole starting materials in Route I synthesis are made by esterification of the α-aminoacid, R—$CH(NH_2)CO_2H$, by reaction with a suitable C_{1-6} alkanol to produce the ester, R—$CH(NH_2)CO_2$-Alkyl, which when treated with ammonia is converted to the amide, R—$CH(NH_2)CONH_2$. Reaction of the amide with sulfur monochloride provides the desired 3-R-4-hydroxy-1,2,5-thiadiazole.

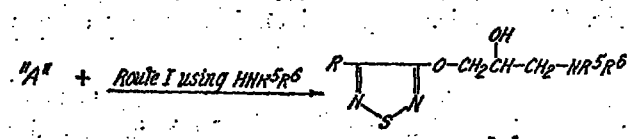
The following Table identifies additional 3-R-4-hydroxy-1,2,5-thiadiazoles that are representative of the starting materials that are and can be prepared by the procedure described above, using the α-aminoacid, R—$CH(NH_2)CO_2H$, having the R-group identified in the following Table, which are esterified with methanol (although other C_{1-6} alkanols can be used, e.g. ethanol, propanol or isopropanol) to provide the methyl or other C_{1-6} alkyl ester, which is then converted by treatment with ammonia to give the amide. Reaction of the amide with sulphur monochloride provides the 3-R-4-hydroxy-1,2,5-thiadiazole (product "A") having the group R attached to the carbon present at position 3 identified in the Table.

EXAMPLE 29

By substituting the thiadiazole products thus obtained in Route I, for example, by replacing the 3-chloro-4-hydroxy-1,2,5-thiadiazole of Example 1 by an equivalent quantity of the 3-R-4-hydroxy-1,2,5-thiadiazole identified in the following Table and using an excess of an amine of the structure HNR^5R^6 (also identified in the Table) for the tert-butylamine used in Step B of Example 1, but otherwise following substantially the same procedure there described, the thiadiazole products I—b are obtained having the R, R^5 and R^6 substituents identified in Table III.

TABLE III





I-b

R	R^5	R^6
$CH_3—S—CH_2—$	H	$(CH_3)_3C—$
$C_2H_5—S—CH_2—$	H	$(CH_3)_2CH—$
$C_3H_7—S—CH_2—$	H	$(CH_3)_2CH—$
$(CH_3)_2CH—S—CH_2—$	H	$(CH_3)_3C—$
$C_4H_9—S—CH_2—$	H	$(CH_3)_2CH—$
$C_6H_5—S—CH_2—$	H	$(CH_3)_3C—$
$C_6H_5CH_2—S—CH_2—$	H	$(CH_3)_3C—CH_2—$
$2—(CH_3—S)C_2H_4—$	H	$(CH_3)_3C—$
$2—(C_2H_5—S)C_2H_4—$	H	$CH\equiv C—C(CH_3)_2—$
$2—(C_3H_7—S)C_2H_4—$	H	$HO—CH_2—C(CH_3)_2—$
$2—[(CH_3)_2CH—S]C_2H_4—$	H	$HO—CH_2—C(CH_3)_2—$
$2—(C_4H_9—S)C_2H_4—$	$\vdash(CH_2)_2—O—(CH_2)_2\dashv$	
$2—[(CH_3)_2CHCH_2—S]C_2H_4—$	$\vdash(CH_2)_2—O—(CH_2)_2\dashv$	
$CH_3—O—CH_2—$	H	$(CH_3)_2CH—$
$C_2H_5—O—CH_2—$	H	$(CH_3)_3C—$
$(CH_3)_3C—O—CH_2—$	H	$(CH_3)_3C—$
$C_6H_5CH_2—O—CH_2—$	H	$(CH_3)_2CH—$
$2—(CH_3—O)C_2H_4—$	H	$(CH_3)_3C—$
$2—(C_2H_5—O)—C_2H_4—$	H	$(CH_3)_3C—$
$2—(C_3H_7—O)C_2H_4—$	H	$(CH_3)_3C—$
$2—(C_4H_9—O)C_2H_4—$	H	$(CH_3)_2CH—$
$2—[(CH_3)_3C—O]C_2H_4—$	H	$(CH_3)_3C—$
$2—(C_6H_5—O)C_2H_4—$	H	$HO—CH_2—C(CH_3)_2—$
$2—[(4—Cl—C_6H_4)—O]C_2H_4—$	H	$(CH_3)_2CH—$

TABLE III (Continued)

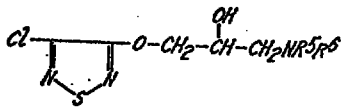
R	R^5	R^6
2—[(2,4—Cl_2—C_6H_3)—O]C_2H_4—	H	$(CH_3)_2CH$—
2—[(3—F—C_6H_4)—O]C_2H_4—	H	$(CH_3)_3C$—
2—[(4—CH_3—C_6H_4)—O]C_2H_4—	H	$(CH_3)_2CH$—
2—[(4—OH—C_6H_4)—O]C_2H_4—	H	$(CH_3)_2CH$—
2—{[3,4—$(OH)_2$—C_6H_3]—O}C_2H_4—	H	$(CH_3)_2CH$—
2—{[3,4—$(CH_3O)_2C_6H_3$]—O}C_2H_4—	H	$(CH_3)_3C$—
2—[(3—HO—4—CH_3O—C_6H_3)—O]C_2H_4—	H	$(CH_3)_2CH$—
2—[(4—CH_3O—C_6H_4)—O]C_2H_4—	H	$(CH_3)_2CH$—
2—(C_6H_5)C_2H_4—	H	$(CH_3)_3C$—
2—(4—Cl—C_6H_4)C_2H_4—	H	$(CH_3)_2CH$—
2—(2—Br—C_6H_4)C_2H_4—	H	$(CH_3)_3C$—
2—(4—HO—C_6H_4)C_2H_4—	H	$(CH_3)_2CH$—
2—(4—CH_3O—C_6H_4)C_2H_4—	H	$(CH_3)_2CH$—
2—[3,4,5—$(CH_3O)_3$—C_6H_2]C_2H_4—	H	$(CH_3)_3C$—CH_2—
3—C_6H_5—C_3H_6—	H	$(CH_3)_3C$—CH_2—
C_6H_5—CH(—C_2H_5)—	H	$(CH_3)_2CH$—
[3,4—$(HO)_2C_6H_3$]—CH(—C_2H_5)—	H	$(CH_3)_3C$—
[3,4—$(CH_3O)_2C_6H_3$]—CH(—C_2H_5)—	H	$(CH_3)_3C$—
3—(4—Cl—C_6H_4)—C_3H_6—	H	$(CH_3)_3C$—
3—(4—Br—C_6H_4)—C_3H_6—	H	$(CH_3)_2CH$—
3—(4—CH_3—C_6H_4)—C_3H_6—	H	$(CH_3)_3C$—
3—[2,4—$(Cl)_2$—C_6H_3]—C_3H_6—	H	$(CH_3)_3C$—
4—Cl—C_6H_4—	H	$(CH_3)_3C$—
4—CH_3—C_6H_4—	H	$(CH_3)_3C$—
4—CH_3O—C_6H_4—	H	$(CH_3)_3C$—

TABLE III (Continued)

R	R^5	R^6
2-furyl	H	$(CH_3)_3C$—
2-thienyl	H	$(CH_3)_3C$—
2-pyrrolyl		—$(CH_2)_2$—N(H)—(CH_2)—
4-pyridyl		—$(CH_2)_2$—N(H)—$(CH_2)_2$—
3-pyridyl		—$(CH_2)_2$—N(CH_3)—$(CH_2)_2$—
2-pyridyl		—$(CH_2)_2$—N(H)—$(CH_2)_2$—

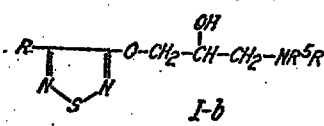
EXAMPLE 30

Additional compounds of this invention that are prepared by the procedures of Routes I and II and more particularly illustrated by Examples 1 and 16 are identified in the following table. The compounds identified in Table IV in which R is a group having the structure R^7R^8N- are advantageously prepared from the compound



synthesized by the process substantially as described in Example I and then replacing the 3-chloro by the R^7R^8N- group by reaction with the selected amine by substantially the procedure described in Example 16. The following products are prepared according to the procedures of Examples 1 and 16 except that the 3-R-4-hydroxy-1,2,5-thiadiazole starting substances, where necessary, can be prepared by the procedure described above for the products disclosed in Table III.

TABLE IV



I-b

R	R^5	R^6
Cl	H	$-C(CH_3)_2-C_7H_{15}$
Cl	H	$-C(CH_3)(CH(CH_3)_2)-C_7H_{15}$
C_2H_5-	H	$-CH(CH_3)-C_2H_5$
C_2H_5O-	H	$-CH_2-CH(CH_3)_2$
C_2H_5O-	H	$-CH(CH_3)-C_3H_7$
C_2H_5O-	H	$-C_6H_{13}$
$C_6H_5-CH_2-$	H	$-C_8H_{17}$
C_2H_5O-	H	$-CH(CH_3)-C_6H_{13}$
C_2H_5-	H	$-CH(C_2H_5)-C_2H_5$
C_2H_5O-	H	$-CH(C_2H_5)-C_3H_7$
morpholino	H	$-CH(CH_3)-CH(CH_3)-CH_3$
morpholino	H	$-CH(C_2H_5)-C_4H_9$
Cl	H	$-CH(CH_3)-C(CH_3)_2-CH_3$
piperidino	H	$-C_{10}H_{21}$
1-(4-methyl)-piperazinyl	H	$-CH(CH_3)-C_7H_{15}$
4-hydroxy-piperidino	H	$-CH(CH_3)-C_5H_{11}$
C_6H_5-	H	$-CH_2-CH=CH_2$
C_6H_5-	H	$-CH_2-C(CH_3)=CH_2$
piperidino	H	cyclopropyl

TABLE IV (Continued)

R	R^5	R^6
cyclohexyl	H	cyclopentyl
C_2H_5—	H	cyclohexyl
C_2H_5O—	H	cyclopentyl
morpholino	H	2-methyl-cyclohexyl
Cl	H	—$(CH_2)_3$—O—C_2H_5
C_2H_5—	H	—$(CH_2)_3$—O—CH_3
C_2H_5—	H	—$(CH_2)_2$—O—C_3H_7
Cl	H	—$(CH_2)_2$—O—$(CH_2)_2$—O—C_4H_9
morpholino	H	—$C(CH_3)_2$—CH_2—O—C_6H_5
C_2H_5—	H	—$CH(CH_3)$—CH_2—O—C_6H_5
C_2H_5O—	H	—$(CH_2)_2$—O—C_6H_5
piperidino		1-methyl-2-*p*-ethoxyphenoxyethyl
4-hydroxy-piperidino	H	2-*p*-methylphenoxyethyl
C_6H_5	H	—$CH(C_2H_5)$—CH_2—OH
morpholino	H	—$CH(CH_3)$—CH(OH)—CH_3
Cl	H	—$CH(CH_3)$—CH(OH)—C_6H_5
C_6H_5—	H	—$C(CH_3)_2$—CH(OH)—C_6H_5
4-hydroxy-piperidino	H	—$C(CH_2OH)_2$—C_2H_5
morpholino	H	—$CH(CH_3)$—$(CH_2)_2$—C_6H_5
Cl	H	—$CH(CH_3)$—CH_2—C_6H_5
C_6H_5	H	—$CH(C_2H_5)$—CH_2—C_6H_5
Br—	H	—CH_2—C_6H_5
C_4H_9—	H	—$(CH_2)_2$—C_6H_5
$CH_2 = CH$—	H	*p*-methoxybenzyl

TABLE IV (Continued)

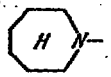
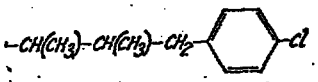
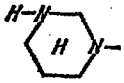
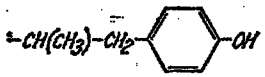
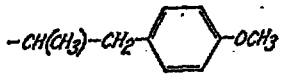
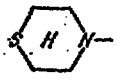
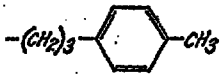
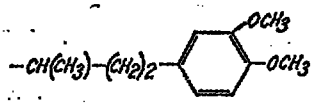
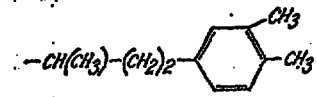
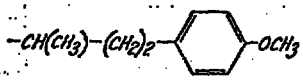
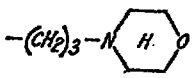
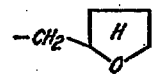
R	R^5	R^6
1-pyrrolidinyl	H	2-*m*,*p*-methoxy-phenethyl
	H	
	H	
	H	
	H	
morpholino	H	
C_2H_5O—	H	
C_2H_5O—	H	
Cl	H	—$C(CH_3)_2$—CH_2—Cl
piperidino	H	—$(CH_2)_3$—$N(CH_3)_2$
4-hydroxy-piperidino	H	—$(CH_2)_2$—$N(C_2H_5)_2$
morpholino	H	—$CH(CH_3)$—$(CH_2)_2$—$N(CH_3)_2$
morpholino	H	
C_6H_5—	H	
morpholino	H	—$(CH_2)_2$—S—CH_3
C_2H_5—	H	—$CH(CH_3)$—CH_2—$CO_2C_2H_5$

TABLE IV (Continued)

R	R^5	R]
C_2H_5—	H	
$(CH_3)_2CH$—	—$CH(CH_3)_2$	—$CH(CH_3)_2$
$(CH_3)_2CH$—	—CH_3	—$CH(CH_3)_2$
piperidino	—$CH(CH_3)_2$	—CH_2—C_4H_5
4-hydroxy-piperidino	—C_2H_5	—C_2H_5
morpholino	—C_4H_9	—C_4H_9
Cl	—CH_3	—CH_3
Cl	—C_2H_5	—C_4H_9
morpholino	—C_2H_5	2-*p*-chlorophenoxyethyl
CH_2=CH—	—CH_2—C_6H_5	—$CH(CH_3)$—C≡CH
C_6H_5—	—CH_2—C_6H_5	—$CH(CH_3)_2$
C_2H_5—	—$OCCH_3$	—$CH(CH_3)_2$
piperidino	⌊———	—$(CH_2)_5$———⌋
morpholino	⌊———	—$(CH_2)_2$—O—$(CH_2)_2$———⌋
1-pyrrolidinyl	⌊———	—$(CH_2)_4$———⌋
4-hydroxypiperidino	⌊———	—CH_2—CH=CH—$(CH_2)_2$———⌋
1-pyrrolidinyl	⌊———	—CH=CH—$(CH_2)_3$———⌋
C_2H_5O—	⌊———	—CH_2—CH=CH—CH=CH——⌋
	⌊———	—$(CH_2)_2$—S—$(CH_2)_2$ ———⌋
C_4H_8NH—	H	—$C(CH_3)_3$
$(C_2H_5)_2N$—	H	—$C(CH_3)_3$
$[(CH_3)_2CH]_2N$—	H	—$C(CH_3)_3$
$(HO—CH_2CH_2)_2N$—	H	—$C(CH_3)_3$
2-methylpiperidino	H	—$C(CH_3)_3$
4-methylpiperidino	H	—$CH(CH_3)_2$
2-ethylpiperidino	H	—$C(CH_3)_3$

(TABLE IV (Continued)

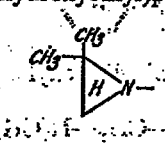
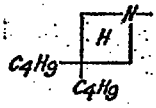
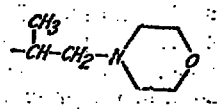
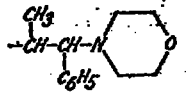
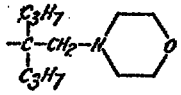
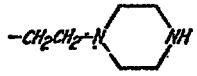
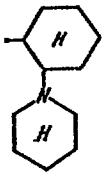
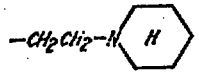
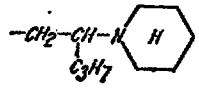
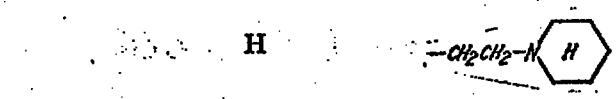
R	R⁵	R]
2-(2-hydroxyethyl)piperidino	H	—C(CH₃)₃
	H	—CH(CH₃)₂
	H	—CH(CH₃)₂
	H	—C(CH₃)₃
C₂H₅O—	H	
C₂H₅O—	H	3-(2-morpholino)pyridyl
C₂H₅O—	H	2-morpholinocyclohexyl
C₆H₅—	H	
C₂H₅—	H	
1-(4-methyl)piperazinyl	H	
morpholino	H	
piperidino	H	
piperidino	H	

TABLE IV (Continued)

R	R^5	R^6
piperidino	H	
C_6H_5—	H	*o*-(1-pyrrolidinyl)phenyl
morpholino	H	—$C(CH_3)_2$—CH_2—$N(CH_3)_2$
morpholino	H	—CH_2CH_2—$N(C_2H_5)_2$
morpholino	H	2-morpholinoethyl

Preparation of the novel products of this invention from the 3-R-4-(3-amino-2-hydroxypropoxy)-1,2,5-thiadiazole is described in the following examples.

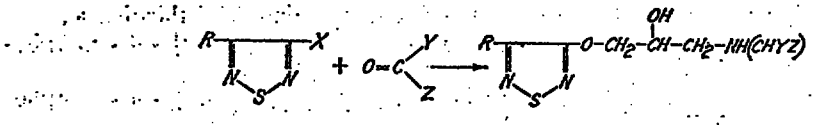
EXAMPLE 31

3-Chloro-4-(3-isopropylamino-2-hydroxypropoxy)-1,2,5-thiadiazole

The acid chloride, 3-chloro-4-chlorocarbonylmethoxy-1,2,5-thiadiazole, from Example 24, Step A, is treated with potassium cyanide by the usual method to give the cyanoketone, 3-chloro-4-cyanocarbonylmethoxy-1,2,5-thiadiazole. This product then is hydrogenated in the presence of a catalyst such as palladium on charcoal or reduced with lithium aluminium hydride to give 3-chloro-4-(3-amino-2-hydroxypropoxy)-1,2,5-thiadiazole. This amine, when reductively alkylated with acetone affords 3-chloro-4-(3-isopropylamino-2-hydroxypropoxy)-1,2,5-thiadiazole.

By replacing the cyanoketone and the acetone reactants used in Example 31 by the products identified in the following table, other 3-R-4-{3-[(CHYZ)NH]-2-hydroxypropoxy}-1,2,5-thiadiazole compounds are obtained in which the groupings R, X, Y and Z are those given.

TABLE V



R	X	Y	Z
C_2H_5	$-O-CH_2-C(=O)-CHN_2$	$-CH_2-C\equiv CH$	CH_3
morpholino	$-O-CH_2-C(=O)-CN_3$	$-CH_3$	CH_3
morpholino	$-O-CH_2-C(=O)-CH=NOH$	$-CH_2CH_2OH$	CH_3
morpholino	$-O-CH_2-C(=O)-CH_2NO_2$	$-C_6H_{11}$	CH_3
piperidino	$-O-CH_2-CH(OH)-CH_2NO_2$	$-C_6H_5$	CH_3
C_6H_5	$-O-CH_2-CH(OH)-CN$	$-C_2H_5$	C_2H_5
1-(4-methyl)-piperazinyl	$-O-CH_2-C(=O)-CN$	$-(CH_2)_5-$	

Preparation 1

3-(3-Amino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole

A solution of 5.0 g. of 3-hydroxy-4-morpholino-1,2,5-thiadiazole (26.7 millimole) in 18.95 ml. of 1.41 N methanolic sodium methoxide is treated with 10.5 ml. of epichlorohydrin (134 millimole) and the mixture is stirred at 25° C. for 16 hours. The precipitated sodium chloride is filtered and washed with methanol. The filtrate is evaporated *in vacuo* to an oil residue. The oil is taken up in 50 mls. of methanol and treated with 5 ml. of concentrated ammonium hydroxide solution. After standing for 48 hours, the solution was concentrated to dryness.

EXAMPLE 32

3-(3-t-Butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole

A solution of 260 g. (1 mole) of 3-(3-amino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole from Preparation 1 in dioxan is treated slowly with 0.4 mole of *t*-butyl chloride at 50—60° C. under vigorous stirring. A solution of 23 g. (0.4 mole) of potassium hydroxide in 20—25 ml. water is then added, and the precipitated salt is removed by filtration. The filtrate is concentrated to dryness and the product is purified by recrystallization, to give 3-(3-butylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole.

Using the method of Example 32 but substituting for the *t*-butyl chloride, an equivalent amount of

(1) isopropyl bromide,

(2) 1,1-dimethylpropyl chloride, or

(3) 2,2-dimetnylpropyl bromide

there is produced

(1) 3-(3-isopropylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole,

(2) 3 - [3 - (1,1 - dimethylpropyl)amino - 2 - hydroxy propoxy] - 4 - morpholino - 1,2,5 - thiadiazole, or

(3) 3 - [3 - (2,2 - dimethylpropyl)amino - 2 - hydroxypropoxy] - 4 - morpholino-1,2,5-thiadiazole, respectively.

In the following examples, pharmaceutical compositions according to the invention are illustrated; other acid addition salts, or other active compounds of the invention can be substituted for that named, if so desired.

The pharmaceutical compositions of the following examples contain 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride as active ingredient.

EXAMPLE 33

An injectable solution is prepared by conventional methods containing:

Active Compound	1 mg.
Sodium chloride	9 mg.
bidist. water q.s.	1.0 ml.

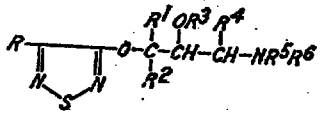
EXAMPLE 34

Capsules are prepared by conventional methods containing:

Active compound	5 mg.
Magnesium stearate	2.0 mg.
lactose U.S.P.	19.3 mg.

WHAT WE CLAIM IS:—

1. A 1,2,5-thiadiazole compound of the formula:



and its pharmacologically acceptable salts, where R is a hydrogen, chlorine or bromine atom, a straight or branched chain C_{1-5} alkyl or C_{1-5} alkoxy group, a C_{2-5} alkenyl or C_{3-6} cycloalkyl group, a group of the formula Y—X—Z— (where Y is a straight or branched chain C_{1-4} alkyl group optionally substituted with a phenyl group, or a phenyl group optionally having one or more substituents selected from halogen atoms, and hydroxy, C_{1-3} alkyl and C_{1-3} alkoxy groups, Z is a C_{1-2} alkyl group, and X is an oxygen or sulphur atom), a group of the formula $R^{5'}HNCO$ (where $R^{5'}$ is a C_{1-5} alkyl group), a phenyl or phenyl-substituted straight or branched chain C_{1-4} alkyl group optionally having one or more substituents selected from halogen atoms and C_{1-3} alkyl and C_{1-3} alkoxy groups attached to the phenyl ring, a group of the formula $-NR^7R^8$ (where R^7 is a hydrogen atom or a C_{1-4} alkyl or hydroxy C_{2-4} alkyl group, and R^8 is a hydrogen atom or a C_{1-4} alkyl, hydroxy C_{2-4} alkyl or phenyl group, or R^7 and R^8 form, together with the nitrogen atom to which they are attached, a 3- to 7-membered ring optionally having one or more substituents selected from hydroxy, C_{1-5} alkyl and hydroxy C_{1-3} alkyl groups, or R^7 and R^8 are joined together through an oxygen, nitrogen or sulphur atom to form a 5- or 6- membered ring together with the nitrogen atom to which they are attached, optionally substituted by a C_{1-3} alkyl group), or a 5- or 6- membered heterocyclic ring linked through a carbon atom and having oxygen, nitrogen or sulphur as the hetero atom, each of R^1, R^2 and R^4 is a hydrogen atom or a C_{1-3} alkyl group, R^1, R^2 and R^4 being similar or dissimilar; R^3 is a hydrogen atom or a benzoyl or C_{2-4} alkanoyl group, R^5 is a hydrogen atom, a straight or branched chain C_{1-5} alkyl group or a phenyl C_{1-3} alkyl or C_{2-5} alkanoyl group, and R^6 is a straight or branched chain C_{1-20} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl group optionally having one or more substituents selected from halogen atoms, from hydroxy, carboxy (C_{1-3} alkoxy)carbonyl, straight and branched chain C_{1-4} alkoxy

(3) 2,2-dimetnylpropyl bromide

there is produced

(1) 3-(3-isopropylamino-2-hydroxypropoxy)-4-morpholino-1,2,5-thiadiazole,

(2) 3 - [3 - (1,1 - dimethylpropyl)amino - 2 - hydroxy propoxy] - 4 - morpholino - 1,2,5 - thiadiazole, or

(3) 3 - [3 - (2,2 - dimethylpropyl)amino - 2 - hydroxypropoxy] - 4 - morpholino-1,2,5-thiadiazole, respectively.

In the following examples, pharmaceutical compositions according to the invention are illustrated; other acid addition salts, or other active compounds of the invention can be substituted for that named, if so desired.

The pharmaceutical compositions of the following examples contain 3-morpholino-4-(3-*tert*-butylamino-2-hydroxypropoxy)-1,2,5-thiadiazole hydrochloride as active ingredient.

EXAMPLE 33

An injectable solution is prepared by conventional methods containing:

Active Compound	1 mg.
Sodium chloride	9 mg.
bidist. water q.s.	1.0 ml.

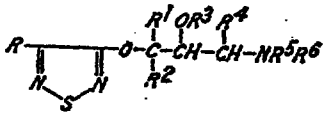
EXAMPLE 34

Capsules are prepared by conventional methods containing:

Active compound	5 mg.
Magnesium stearate	2.0 mg.
lactose U.S.P.	19.3 mg.

WHAT WE CLAIM IS:—

1. A 1,2,5-thiadiazole compound of the formula:



and its pharmacologically acceptable salts, where R is a hydrogen, chlorine or bromine atom, a straight or branched chain C_{1-5} alkyl or C_{1-5} alkoxy group, a C_{2-5} alkenyl or C_{3-6} cycloalkyl group, a group of the formula Y—X—Z— (where Y is a straight or branched chain C_{1-4} alkyl group optionally substituted with a phenyl group, or a phenyl group optionally having one or more substituents selected from halogen atoms, and hydroxy, C_{1-3} alkyl and C_{1-3} alkoxy groups, Z is a C_{1-2} alkyl group, and X is an oxygen or sulphur atom), a group of the formula $R^{5'}HNCO$ (where $R^{5'}$ is a C_{1-5} alkyl group), a phenyl or phenyl-substituted straight or branched chain C_{1-4} alkyl group optionally having one or more substituents selected from halogen atoms and C_{1-3} alkyl and C_{1-3} alkoxy groups attached to the phenyl ring, a group of the formula $—NR^7R^8$ (where R^7 is a hydrogen atom or a C_{1-4} alkyl or hydroxy C_{2-4} alkyl group, and R^8 is a hydrogen atom or a C_{1-4} alkyl, hydroxy C_{2-4} alkyl or phenyl group, or R^7 and R^8 form, together with the nitrogen atom to which they are attached, a 3- to 7-membered ring optionally having one or more substituents selected from hydroxy, C_{1-5} alkyl and hydroxy C_{1-3} alkyl groups, or R^7 and R^8 are joined together through an oxygen, nitrogen or sulphur atom to form a 5- or 6- membered ring together with the nitrogen atom to which they are attached, optionally substituted by a C_{1-3} alkyl group), or a 5- or 6- membered heterocyclic ring linked through a carbon atom and having oxygen, nitrogen or sulphur as the hetero atom, each of R^1, R^2 and R^4 is a hydrogen atom or a C_{1-3} alkyl group, R^1, R^2 and R^4 being similar or dissimilar; R^3 is a hydrogen atom or a benzoyl or C_{2-4} alkanoyl group, R^5 is a hydrogen atom, a straight or branched chain C_{1-5} alkyl group or a phenyl C_{1-3} alkyl or C_{2-5} alkanoyl group, and R^6 is a straight or branched chain C_{1-20} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl group optionally having one or more substituents selected from halogen atoms, from hydroxy, carboxy (C_{1-3} alkoxy)carbonyl, straight and branched chain C_{1-4} alkoxy

* C L M S *

and C_{1-4} alkylthio, di(C_{1-3} alkyl)amino, pyrrolidinyl, piperazinyl, piperidinyl, morpholino, thiazolidinyl and thiazinyl groups, from 5 and 6 membered heterocyclic rings attached through a nuclear carbon atom and having oxygen, nitrogen or sulphur as the heteroatom, and from phenyl and phenoxy groups optionally having from one to three similar or dissimilar substituents selected from halogen atoms and hydroxy and C_{1-3} alkoxy groups; a phenyl group optionally substituted with a C_{1-3} alkyl, pyrrolidinyl, or piperidinyl group; a C_{3-6} cycloalkyl group optionally substituted with a C_{1-3} alkyl group or with a 5- or 6- membered N- or O- containing heterocyclic ring; or a 5- or 6- membered heterocyclic ring containing oxygen, nitrogen or sulphur as the heteroatom and attached through a nuclear carbon atom, and optionally substituted with a C_{1-3} alkyl group or with a 5- or 6- membered N- or O- containing heterocyclic ring; or R^5 and R^6 together with the nitrogen atom to which they are attached from a 4- to 6- membered ring which may contain in addition to but not adjacent to said nitrogen atom, one or two different heteroatoms selected from oxygen, sulphur and nitrogen and which may be substituted by one or more C_{1-3} alkyl radicals.

2. A compound as claimed in claim 1, in which R^1, R^2, R^3, R^4 and R^5 are hydrogen atoms and R and R^6 are as defined in claim 1.

3. A compound as claimed in claim 1, in which R^1, R^2, R^3, R^4 and R^5 are hydrogen atoms, R is hydrogen, chlorine or bromine atom, a straight or branched chain C_{1-5} alkyl group or a C_{2-5} alkenyl or C_{1-5} alkoxy group, and R^6 is a branched chain C_{3-6} alkyl, hydroxy-substituted branched chain C_{3-6} alkyl, (C_{1-4} alkoxy) substituted branched chain C_{3-6} alkyl or branched chain C_{3-6} alkynyl group.

4. A compound as claimed in claim 3, in which R^6 is an isopropyl or *tert*-butyl group.

5. A compound as claimed in claim 1, in which R^1, R^2, R^3, R^4 and R^5 are hydrogen atoms, R is a C_{3-6} cycloalkyl, phenyl, phenyl C_{1-4} alkyl, morpholino, piperidyl, hydroxy-piperidino, 4-(C_{1-3} alkyl) piperazinyl, furyl, thienyl, pyrryl or pyridyl group; and R^6 is as defined in claim 4.

6. A compound as claimed in claim 5, in which R^6 is an isopropyl or *tert*-butyl group.

7. A compound as claimed in claim 2, in which R is a hydrogen atom.

8. A compound as claimed in claim 2, in which R is a hydrogen atom and R^6 is a branched chain C_{3-6} alkyl group.

9. A compound as claimed in claim 2, in which R is a hydrogen atom and R^6 is a hydroxy-substituted branched chain C_{3-6} alkyl group.

10. A compound as claimed in claim 1, in which R, R^1, R^2, R^3 and R^4 are hydrogen atoms and $—NR^5R^6$ is a morpholino group.

11. A compound as claimed in claim 2, in which R is a chlorine atom and R^6 is a branched chain C_{3-6} alkyl group.

12. A compound as claimed in claim 2, in which R is a chlorine atom and R^6 is a *tert*-butyl group.

13. The (+)-isomer of the compound claimed in claim 12.

14. The (−)-isomer of the compound claimed in claim 12.

15. A compound as claimed in claim 2 in which R is a chlorine atom and R^6 is an isopropyl group.

16. A compound as claimed in claim 2, in which R is a C_{1-5} alkyl group and R^6 is a branched chain C_{3-6} alkyl group.

17. A compound as claimed in claim 2, in which R is an ethyl group and R^6 is an isopropyl group.

18. A compound as claimed in claim 2, in which R is an ethyl group and R^6 is a *tert*-butyl group.

19. A compound as claimed in claim 2, in which R is a C_{1-5} alkoxy group and R^6 is a branched chain C_{3-6} alkyl group.

20. A compound as claimed in claim 2 in which R is an ethoxy group and R^6 is an isopropyl group.

21. A compound as claimed in claim 2 in which R is an ethoxy group and R^6 is a *tert*-butyl group.

22. A compound as claimed in claim 2, in which R is a C_{1-5} alkoxy group and R^6 is a branched chain C_{3-6} alkynyl group.



23. A compound as claimed in claim 2 in which R is an ethoxy group and R^6 is 1,1-dimethyl-2-propynyl.

24. A compound as claimed in claim 2, in which R is a morpholino group and R^6 is a branched chain C_{3-6} alkyl group.

25. A compound as claimed in claim 2, in which R is a morpholino group and R^6 is a *tert*-butyl group.

26. A compound as claimed in claim 2, in which R is a morpholino group and R^6 is an isopropyl group.

27. A compound as claimed in claim 2, in which R is a piperidyl group and R^6 is a branched chain C_{3-6} alkyl group.

28. A compound as claimed in claim 2, in which R is a piperidyl group and R^6 is a *tert*-butyl group.

29. A compound as claimed in claim 2, in which R is a piperidyl group and R^6 is an isopropyl group.

30. A compound as claimed in claim 2, in which R is a 4-hydroxypiperidino group and R^6 is a branched chain C_{3-6} alkyl group.

31. A compound as claimed in claim 2, in which R is a 4-hydroxypiperidino group and R^6 is a *tert*-butyl group.

32. A compound as claimed in claim 2, in which R is a phenyl group and R^6 is a branched chain C_{3-6} alkyl group.

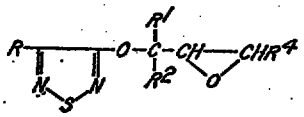
33. A compound as claimed in claim 2, in which R is a phenyl group and R^6 is an isopropyl group.

34. A compound as claimed in claim 2, in which R is a phenyl group and R^6 is a *tert*-butyl group.

35. The (+)-isomer of the compound claimed in claim 25.

36. The (−)-isomer of the compound claimed in claim 25.

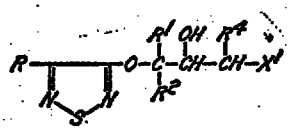
37. The process that comprises reacting an epoxide of the formula:



where R, R^1, R^2 and R^4 are as defined in claim 1, with an amine of the formula HNR^5R^6 where R^5 and R^6 are as defined in claim 1, to produce a compound as claimed in claim 1, in which R^3 is a hydrogen atom.

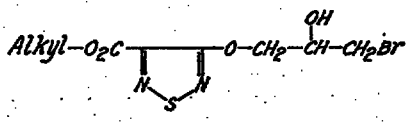
38. A process as claimed in claim 37, in which R is a chlorine or bromine atom, including the additional step of reacting the product with an amine of the formula NHR^7R^8 where R^7 and R^8 are as defined in claim 1, to produce a compound as claimed in claim 1, in which R^3 is a hydrogen atom and R is a group of the formula $—NR^7R^8$.

39. The process that comprises reacting a compound of the formula:



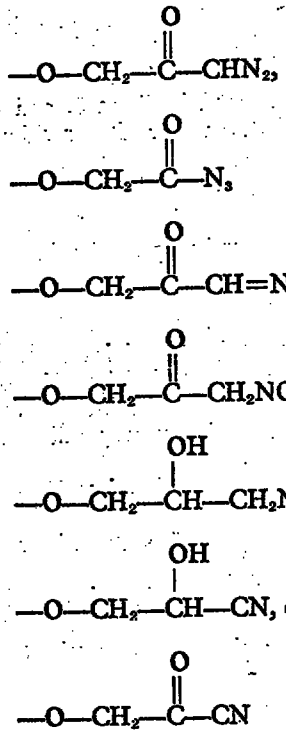
where R, R^1, R^2 and R^4 are as defined in claim 1 and X^1 is a chlorine or bromine atom, with an amine of the formula R^5R^6NH where R^5 and R^6 are as defined in claim 1, to produce a compound as claimed in claim 1, in which R^3 is a hydrogen atom.

40. The process that comprises reacting 4-allyloxy-3-carboxy-1,2,5-thiadiazole with N-bromosuccinimide and esterifying the resulting product to produce a bromohydrin compound of the formula:



and then reacting the bromohydrin compound with an amine of the formula $R^{5'}NH_2$ where $R^{5'}$ is a C_{1-5} alkyl group to produce a compound as claimed in claim 1, in which R^1, R^2, R^3, R^4 and R^5 are hydrogen atoms, R^6 is a C_{1-5} alkyl group and R is a group of the formula $R^{5'}HNOC$ where $R^{5'}$ is as defined above.

41. The process that comprises reducing a 3—R—4—X^2—1,2,5-thiadiazole where X^2 is a

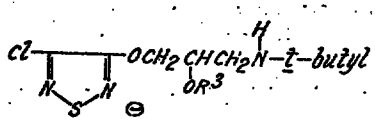


group, and R is as defined in claim 1, and then subjecting the resulting product to reductive alkylation with a ketone of the formula O=CYZ where Y^1 is a C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, hydroxy C_{2-5} alkyl, C_{3-6} cycloalkyl or phenyl group, and Z^1 is a C_{1-5} alkyl group, or Y^1 and Z^1 are each C_{1-5} alkyl groups and are linked together to form with the carbon to which they are attached a 3- to 6-membered carbocyclic ring, to produce a compound as claimed in claim 1, in which R^1, R^2, R^3, R^4 and R^5 are hydrogen atoms and R^6 is a group of the formula —CHY^1Z^1 where Y^1 and Z^1 are as defined above.

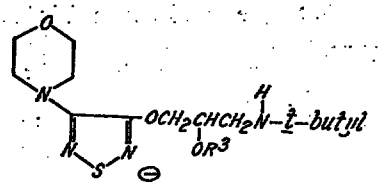
42. A process as claimed in claim 37, 38 or 41, in which R is a chlorine atom, R^1, R^2, R^4, and R^5 are hydrogen atoms and R^6 is an isopropyl or *tert*-butyl group.

43. A process as claimed in claim 37, 38 or 41 in which R is a morpholino group, R^1, R^2, R^4 and R^5 are hydrogen atoms and R^6 is an isopropyl or *tert*-butyl group.

44. The process that comprises reacting an optically active compound of the formula:

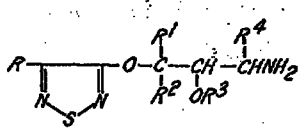


where R_3 is a hydrogen atom with morpholine to produce an optically active compound of the formula:

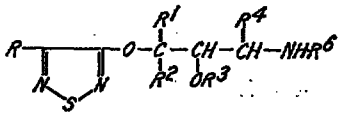


where R^5 is a hydrogen atom.

45. The process that comprises reacting a compound of the formula:



where R, R^1, R^2 and R^4 are as defined in claim 1, and R^3 is a hydrogen atom with an organic halide of the formula R^6X^1 where X^1 is a chlorine or bromine atom to produce a compound of the formula:



where R, R^1, R^2, R^4 and R^6 are as defined in claim 1 and R^3 is a hydrogen atom.

46. A process as claimed in any one of claims 37—45 including the further step of reacting the product with a benzoyl acid halide or anhydride or a C_{2-4} alkanoic acid halide or anhydride to produce the corresponding compound in which R^3 is a benzoyl or C_{2-4} alkanoyl group.

47. A process as claimed in any one of claims 37—46 including the further step of treating the product with an organic or inorganic acid to convert it to a salt.

48. A process as claimed in claim 37, substantially as hereinbefore described in any one of Examples 1, 2—15, 29 and 30.

49. A process as claimed in claim 39, substantially as hereinbefore described in any one of Examples 1A, 1B, 2—15, 24, 25, 29 and 30.

50. A process as claimed in claim 38, substantially as hereinbefore described in any one of Examples 16—21, 24—25 and 30.

51. A process as claimed in claim 40, substantially as hereinbefore described in Example 22 or 23.

52. A process as claimed in claim 41, substantially as hereinbefore described in Example 31.

53. A process as claimed in claim 45, substantially as hereinbefore described in Example 32.

54. A process as claimed in claim 46, substantially as hereinbefore described in Example 26 or 27.

55. A process as claimed in claim 47, substantially as hereinbefore described in Example 28.

56. A compound as claimed in claim 1, when prepared by a process as claimed in any one of claims 37—55 or an obvious chemical equivalent of such a process.

57. A pharmaceutical composition comprising a compound as claimed in any one of claims 1—36 and 56, together with a non-toxic pharmaceutically acceptable diluent, carrier, coating or excipient.

58. A pharmaceutical composition as claimed in claim 57, in unit dosage form and comprising from 1 to 20 mg of the 1,2,5-thiadiazole compound per unit dose.

59. A composition as claimed in claim 57 or 58, in the form of a tablet, pill, capsule, powder, syrup, elixir, emulsion, suppository or sterile injectable solution or suspension.

60. A composition as claimed in claim 57, substantially as hereinbefore described in Example 33 or 34.

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