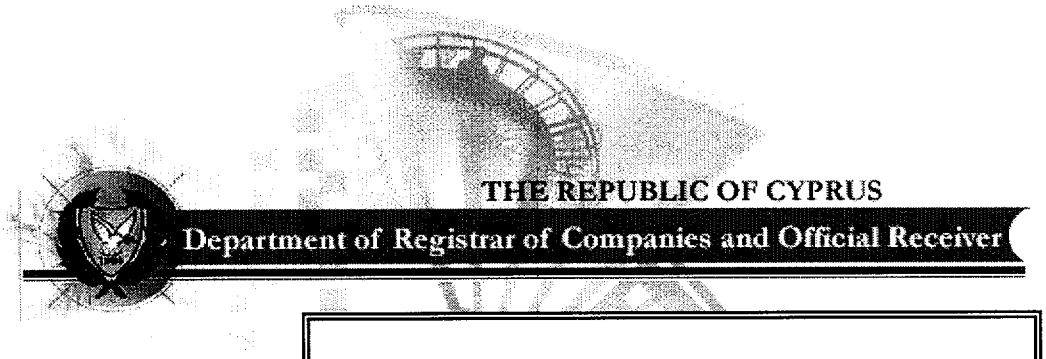

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

THE PATENT OFFICE OF CYPRUS

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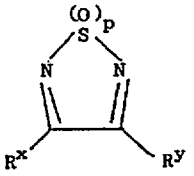
(54) Thiadiazole oxides and dioxides

(57) Thiadiazole oxides are provided of the formula



I

wherein;
p is 1 or 2;
R^x and R^y can be the same or different and can be R^7, R^{12} or $-NH(CH_2)_nHS$ or NR^2R^3;
R^7 is a leaving group;
R^{12} is $A(CH_2)_mZ(CH_2)_nNH-$, R^2R^3N- or $HS(CH_2)_nNH-$; R^2 and R^3 each are independently groups such as hydrogen and (lower)alkyl,
m is 0 to 2;
n is 2 to 4;
Z and Z′ each are independently sulfur, oxygen or methylene;
A and A′ each are independently groups such as phenyl, imidazolyl, or other heterocyclic groups. These compounds are useful as intermediates for pharmaceutically active compounds.

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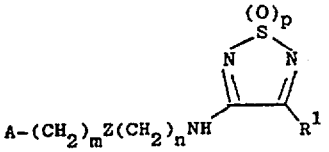
SPECIFICATION

Thiadiazole oxides and dioxides

This invention relates to thiadiazole oxides and dioxides.

In Patent Application 8028326 (A-2067987) there are described and claimed compounds of the formula



wherein p is 1 or 2

R^1 is hydroxy or NR^2R^3;

R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)alkyl, pyridyl(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; provided that R^2 and R^3 may not both be cyclo(lower) alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'-(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is a methylene, sulfur, oxygen or $N-R^4$, provided that, when r is 1, X is methylene;

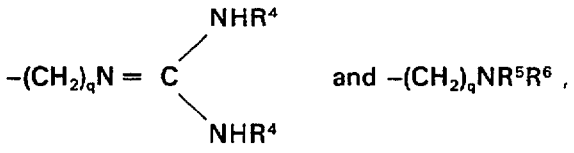
R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, isothiazoyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,



and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive; each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N-methylpiperazino or homopiperidino;

or a nontoxic, pharmaceutically acceptable salt, hydrate, solvate or N-oxide thereof.

These compounds are useful as gastric acid secretion inhibitors. There is also described the preparation of these compounds.

The present invention relates to the certain thiadiazole oxides which are useful as starting materials for the preparation of said compounds.

According to the invention there is provided a compound of the formula

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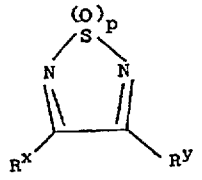

I

wherein:

p is 1 or 2 and

(a) when p is 1

(i) R^x and R^y are the same and are R^7, or

(ii) R^x is R^{12} and R^y is R^7, or

(iii) R^x is $-NH(CH_2)_nHS$ and R^y is NR^2R^3, and

(b) when p is 2

(i) R^x is R^{12} and R^y is R^7, or

(ii) R^x is $-NH(CH_2)_nHS$ and R^y is $-NR^2R^3$;

R^7 is a leaving group selected from halogen, (lower)alkoxy, (lower)alkylthio, phenoxy, phenylthio, substituted phenoxy and substituted phenylthio wherein the phenyl ring may contain 1 or 2 substituents selected from halogen(lower)alkyl, (lower)alkoxy and nitro;

R^{12} is $A(CH_2)_mZ(CH_2)_nNH-$, R^2R^3N- or $HS(CH_2)_nNH-$; R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)aklyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)alkyl, pyridyl(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'-(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino but further provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$,

provided that, when p is 2 and R^7 is methoxy, R^2 and R^3 taken together with the nitrogen to which they are attached, may not be morpholino, and that, when r is 1, X is methylene;

R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

$$-(CH_2)_qN=C\begin{matrix}NHR^4\\ \diagdown\\ \diagup\\ NHR^4\end{matrix} \quad \text{and} \quad -(CH_2)_qNR^5R^6$$

and the second substituent being selected from (lower)alkyl, hydroxy, trifluormethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive;

each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N-methylpiperazino or homopiperidino;

or a salt, hydrate, solvate or N-oxide thereof.

The present invention includes within its scope all possible tautomeric forms, geometric isomers, optical isomers and zwitterionic forms of the compounds of Formula I as well as

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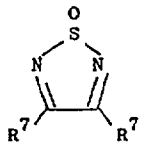
mixtures thereof. As used herein and in the claims, the terms "(lower)alkyl," "(lower)alkenyl," "(lower)alkynyl," "(lower)alkoxy" and "(lower)alkylthio" mean, in their broadest sense, straight or branched chain alkyl, alkenyl, alkynyl, alkoxy and alkylthio groups containing from 1 to 12 carbon atoms providing that where the structure so mandates the minimum number of carbon atoms may be greater than 1 (e.g. alkenyl). Preferably, these groups contain from 1 to 8 carbon atoms and, most preferably, from 1 to 6 carbon atoms.

In the compounds of Formula I, A and A', independently, are preferably optionally substituted phenyl, imidazolyl, thiazolyl, oxazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl rings. Most preferably, A and A', independently, are optionally substituted phenyl, imidazolyl, thiazolyl, furyl, thienyl, or pyridyl rings. Particularly preferred A and A' groups are guanidino-substituted thiazolyl, di(lower)alkylamino(lower)alkyl-substituted (and especially dimethylaminomethyl-substituted) furyl, (lower)alkyl-substituted (and especially methyl-substituted) imidazolyl, di(lower)alkylamino(lower)alkyl-substituted (and especially dimethylaminomethyl-substituted) thiazolyl, di(lower)alkylamino(lower)alkyl-substituted (and especially dimethylaminomethyl-substituted) phenyl and di(lower)alkylamino(lower)alkyl-substituted (and especially dimethylaminomethyl-substituted) thienyl moieties.

It is preferred that m is zero or 1 and n is 2 or 3. Preferably, X is sulfur, oxygen or methylene (and most preferably sulfur or oxygen). R^2 and R^3 preferably are each independently selected from hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$. In particularly preferred embodiments, R^2 and R^3 are both hydrogen or methyl. In other particularly preferred embodiments R^2 is hydrogen and R^3 is hydrogen, (lower)alkyl (especially methyl, ethyl or propyl), (lower)alkenyl (especially 2-propenyl), (lower)alkynyl (especially 2-propynyl) or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$ in which m' is preferably zero or 1, n' is preferably 2 or 3, Z' is preferably sulfur or oxygen, and A' is preferably a substituted thiazolyl, phenyl or furly ring (and especially guanidino-substituted thiazolyl or dimethylaminomethyl-substituted phenyl or furyl).

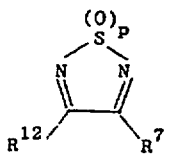
Thus in one aspect, this invention relates to novel compounds having the formula



II

in which each R^7 is a leaving group selected from halogen, (lower)alkoxy, (lower)alkylthio and phenoxy or phenylthio which optionally contain 1 or 2 substituents selected from halogen, (lower)alkyl, (lower)alkoxy and nitro. In a preferred embodiment of the compounds of Formula IIa, each R^7 is (lower)alkoxy, phenoxy or substituted phenoxy; most preferably, each R^7 is methoxy.

In another aspect, this invention relates to novel compounds of the formula



wherein p is 1 or 2;

R^7 is a leaving group selected from halogen, (lower)alkoxy, (lower)alkylthio, phenoxy, phenylthio, substituted phenoxy and substituted phenylthio wherein the phenyl ring may contain 1 or 2 substituents selected from halogen, (lower)alkyl, (lower)alkoxy and nitro; and

R^{12} is $A(CH_2)_mZ(CH_2)_nNH-$, R^2R^3N- or $HS(CH_2)_nNH-$; in which R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)pyridyl(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

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X is methylene, sulfur, oxygen or N–R^4, provided that, when p is 2 and R^7 is methoxy, R^2 and R^3 taken together with the nitrogen to which they are attached, may not be morpholino, and that, when r is 1, X is methylene;

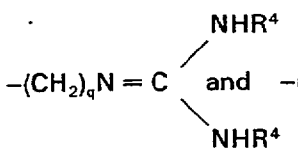
R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m and m′ each are independently an integer of from zero to 2 inclusive;

n and n′ each are independently an integer of from 2 to 4, inclusive;

Z and Z′ each are independently sulfur, oxygen or methylene;

A and A′ each are independently phenyl, imidazolyl, thiazolyl, isothizolyl, oxaxolyl, isoxazolyl, trizolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A′ independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,



and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

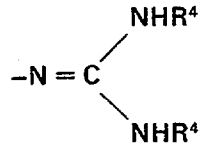
q is an integer of from 0 to 6, inclusive;

each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N–methylpiperazino or homopiperidino;

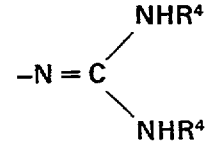
or a salt, hydrate, solvate or N-oxide thereof.

In a more preferred embodiment of the compounds of Formula XI, R^{12} is $A(CH_2)_mZ(CH_2)_nNH–$ in which A is phenyl, imidazolyl, thiazolyl, furyl, thienyl or pyridyl, each of which may contain one or two substituents, the first substituent being selected from (lower) alkyl,



and the second substituent being selected from (lower)alkyl; z is sulfur, oxygen or methylene; m is zero or one; n is two or three; each R^4 independently is hydrogen or (lower)alkyl, or the two R^4 groups, taken together, may be ethylene; R^5 and R^6 each are independently hydrogen or (lower)alkyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N–methylpiperazino or homopiperidino; and R^7 is (lower)alkoxy.

In another more preferred embodiment of the compounds of Formula XI, R^{12} is $R^2R^3N–$ in which R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl(lower)alkyl, pyridyl(lower)alkyl, $A'–(CH_2)_{m'}Z'(CH_2)_{n'}–$, phenyl(lower)alkyl or 3,4-methylenedioxybenzyl; provided that R^2 and R^3 may not both be $A'–(CH_2)_{m'}Z'(CH_2)_{n'}–$; m′ is zero or one; n′ is two or three; Z′ is sulfur, oxygen or methylene; A′ is phenyl, imidazolyl, thiazolyl, furyl, thienyl or pyridyl, each of which may contain one or two substituents, the first substituent being selected from (lower)alkyl,



each R^4 independently is hydrogen or (lower)alkyl, or the two R^4 groups, taken together, may be ethylene; R^5 and R^6 each are independently hydrogen or (lower)alkyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N–methylpiperazino or homopiperidino; and R^7 is (lower)alkoxy.

In another more preferred embodiment of the compounds of Formula XI, R^{12} is $HS(CH_2)_nNH–$; in which n is an integer of from two to four and R^7 is (lower)alkoxy.

In a particular preferred embodiment of the compounds of Formula XI, R^{12} is

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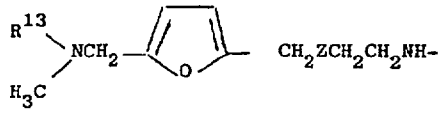
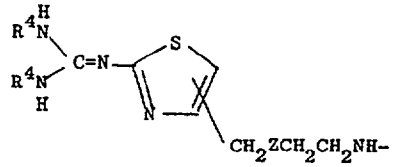


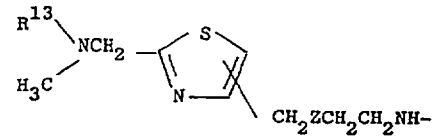
wherein Z is sulfur or methylene and R^{13} is hydrogen or methyl; and R^7 is (lower)alkoxy.

In another particularly preferred embodiment of the compounds of Formula XI, R^{12} is



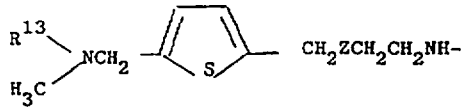
in which Z is sulfur or methylene; each R^4 is independently hydrogen or methyl, or the two R^4 groups, taken together, may be ethylene; and R^7 is (lower)alkoxy.

In another particularly preferred embodiment of the compounds of Formula XI, R^{12} is



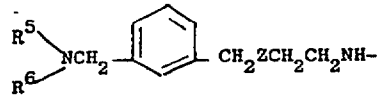
in which R^{13} is hydrogen or methyl; Z is sulfur or methylene; and R^7 is (lower)alkoxy.

In another particularly preferred embodiment of the compounds of Formula XI, R^{12} is



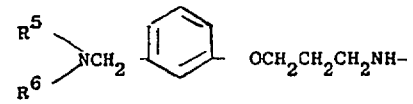
in which R^{13} is hydrogen or methyl; Z is sulfur or methylene; and R^7 is (lower)alkoxy.

In another particularly preferred embodiment of the compounds of Formula XI, R^{12} is



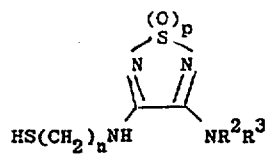
in which R^5 and R^6 each are independently hydrogen or (lower)alkyl; Z is sulfur or methylene; and R^7 is (lower) alkoxy.

In another particularly preferred embodiment of the compounds of Formula XI, R^{12} is



in which R^5 and R^6 each are independently hydrogen or (lower)alkyl, or, when R^5 is hydrogen, R^6 also may be (lower) alkenyl or (lower)alkynyl; or R^5 and R^6, taken together with the nitrogen to which they are attached, may be pyrrolidino, morpholino, piperidino or homopiperidino; and. R^7 is (lower)alkoxy.

In still another aspect, this invention relates to novel compounds of the formula



XII

wherein p is 1 or 2;

n is an integer of from 2 to 4 inclusive;

R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(-lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(low-

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er)alkyl, pyridy(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxty, trifluoromethyl and di(lower)alkylamino; provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'-(CH_2)_{n'}-$; or R^2 and R^3, taken together may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$, provided that, when r is 1, X is methylene;

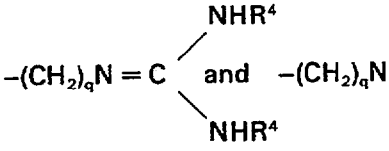
R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m' is an integer of from zero to 2, inclusive;

n' is an integer of from 2 to 4, inclusive;

Z' is sulfur, oxygen or methylene;

A' is phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A' may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,



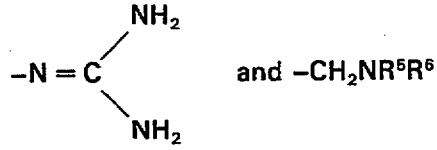
and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive;

each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

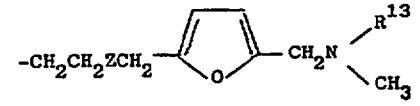
R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N-methylpiperazino or homopiperidino; or a salt, hydrate, solvate or N-oxide thereof.

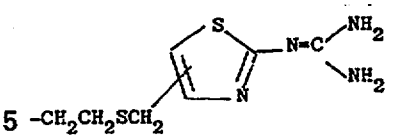
In a more preferred embodiment of the compounds of Formula XII, R^2 and R^3 each are independently selected from hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl(lower)alkyl, phenyl(lower)alkyl, pyridyl(lower)alkyl, 3,4-methylenedioxybenzyl or $A'(CH_2)_{m'}Z'(-CH_2)_{n'}-$; provided that R^2 and R^3 may not both be $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; m' is an integer of from zero to two inclusive; n and n' each are independently an integer of from 2 to 4, inclusive; Z' is sulfur, oxygen or methylene; A' is phenyl, imidazolyl, thiazolyl, furly, thienyl or pyridyl, each of which may contain one or two substituents, the first substituent being selected from (lower)alkyl,



and the second substituent being selected from (lower)alkyl; and R^5 and R^6 each are independently hydrogen or (lower)alkyl.

In another more preferred embodiment of the compounds of Formula XII, n is 2; R^2 and R^3 each are independently selected from hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl and phenyl (lower)alkyl, or, when R^2 is hydrogen, R^3 may be





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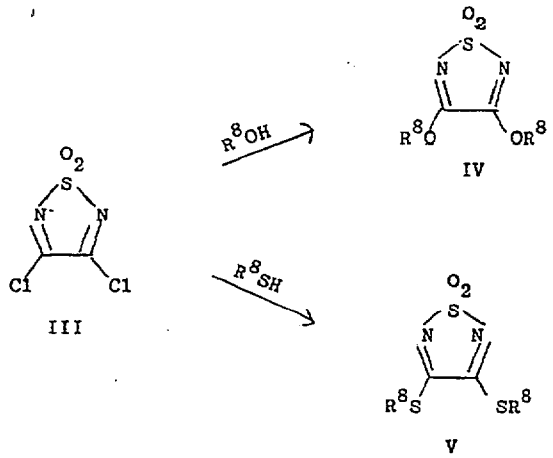
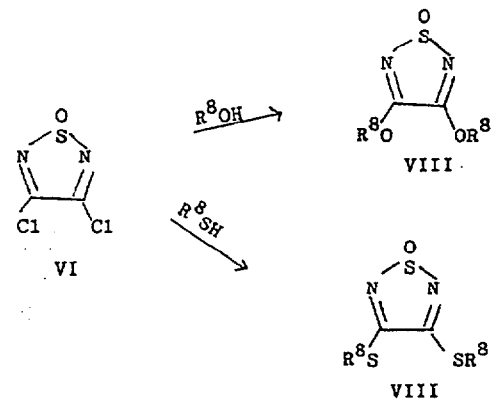
Compounds of Formula II in whcih p is 2 and each R^7 is chloro, methoxy or ethoxy are known, their preparation being described in *J.Org.Chem.40*,2743 (1975). Starting materials of formula II in which p is 2 and each R^7 is alkoxy, alkylthio, phenoxy, phenylthio, substituted phenoxy or substituted phenylthio (compounds of Formula IV and V) may be prepared by reacting the dichloro compound of Formula III with the appropriate alkanol, alkylthiol, phenol, thiophenol, substituted phenol or substituted thiophenol to produce the corresponding compound of Formula IV or V in which R^8 is alkyl, phenyl or substituted phenyl, as follows:

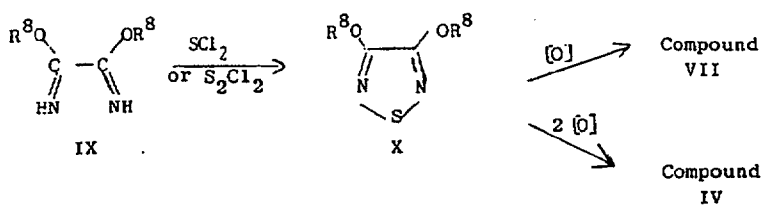


The reaction is conducted in an inert organic solvent such as ether, dimethylformamide or the like. When reactant R^8OH or R^8SH is a liquid, e.g. methanol, ethanol, ethylmercaptan or thiophenol, the reaction may be conducted in an excess of that reactant as a solvent. Corresponding starting materials of Formula II in which p is 1 (compounds of Formula VII and VIII) may be prepared in the same manner from a compound of Formula II in which each R^7 is chloro (compound VI).



Compound VI is a novel compound but it may be prepared from the known compound 3,4-dihydroxy-1,2,5-thiadiazole 1-oxide [itself prepared according to the procedure of *Org. Prep. Proced., 1,* 255 (1969)] by the same procedure utilized for preparing the compound of Formula III from 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide [see *J. Org. Chem., 40*,2743 (1975)]. The compounds Formulae VII and VIII are novel compounds not previously described in the literature.

Alternatively, the compounds of Formulae IV and VII may be prepared by reaction of an appropriately substituted oxaldiimidate ester of Formula IX with SCl_2 or S_2Cl_2 in an inert solvent such as dimethylformamide to form the corresponding 3,4-disubstituted 1,2,5-thiadiazole of Formula X which is then oxidized to the corresponding 1-oxide of Formula VII or 1,1-dioxide of Formula IV.



Oxaldiimidate esters of Formula IX in which R^8 is methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and

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n-pentyl are known and their preparation is described in *Chem. Ber., 107,* 3121 (1974). Corresponding compounds in which R^8 is phenyl, optionally substituted by (lower)alkyl, (lower)alkoxy, halogen or nitro may be prepared by a similar procedure. Compounds of Formula X in which R^8 is methyl or ethyl are described in *J. Org. Chem., 40,* 2749 (1975).

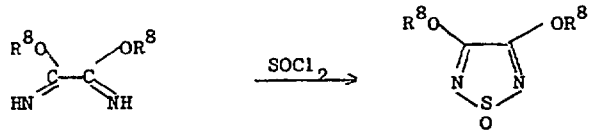
The literature reports that the 1,2,5-thiadiazole nucleus is sensitive to oxidation, that oxidation of thiadiazoles with peracids is usually accompanied by ring destruction and formation of sulfate ion, and that attempts to prepare 1,2,5-thiadiazole 1,1-dioxide by peracetic acid oxidation of the parent ring resulted in ring cleavage. Surprisingly, we have found that the 3,4-disubstituted-1,2,5-thiadiazole 1-oxides of Formula VII and 1,1-dioxides of Formula IV may readily be prepared in good yield by oxidation of the correspondingly 3,4-disubstituted-1,2,5-thiadiazole of Formula X with a peracid such a *m*-chloroperbenzoic acid, in an inert solvent such as chloroform. The preparation of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide is shown in Example 2; the preparation of the corresponding 1,1-dioxide is shown s below.

Illustrative Procedure No. 1
3,4-Dimethoxy-1,2,5-thiadiazole 1,1-dioxide

A solution of 3,4-dimethoxy-1,2,5-thiadiazole (1.48g; 10.1 mmoles) [prepared according to the procedure described in *J. Org. Chem., 40,* 2749 (1975)] in 20 ml of chloroform was added over a period of 1 minute to a stirred solution of *m*-chloroperbenzoic acid (4.11 g; 20.3 mmoles; 85% assay) in 60 ml of chloroform. After stirring at ambient temperature for 1 hour, the mixture was heated at reflux temperature for 8 hours and then stirred at ambient temperature for 1 hour. The reaction mixture was extracted with aqueous sodium bicarbonate and water, and the organic phase was dried over sodium sulfate, filtered and evaporated under reduced pressure. The residue was treated with methanol and filtered to give 1.03 g of product. Recrystallization from methanol yielded the title compound, mp 200–202°.

Anal. Calcd. for $C_4H_6N_2O_4S$: C, 26.97; H,3.39; N, 15.72; S, 18.00.
Found: C, 26.82; H, 3.18; N, 16.09; S, 18.00.

We have now found a particularly elegant procedure by which a compound of Formula VII may be prepared in a one-step reaction directly from a compound of Formula IX, by reaction of the latter with thionyl chloride. This



IX VII

reaction is conducted in an inert organic solvent such as methylene chloride, chloroform, or the like. Although the reaction may be conducted without the addition of a base as an acid scavenger, we prefer to add about two equivalents of a base to remove the HCl which is formed in the reaction. Higher yields of Compound VII are thereby obtained. Suitable bases include inorganic bases such as sodium carbonate, potassium carbonate, sodium bicarbonate and potassium bicarbonate, and organic bases such as triethylamine, pyridine and the like. This process not only eliminates one step, but is much more economical in that it avoids the use of expensive oxidizing agents such as *m*-chloroperbenzoic acid. The reaction may be conducted at a temperature of from about − 20° to about 25°, and preferably at about 0° to about 10°. Illustrative Procedure No. 2 shows the preparation, by this process, of the compound of Formula VII in which R^8 is methyl.

Illustrative Procedure No. 2
3,4-Dimethoxy-1,2,5-thiadiazole 1-oxide

A solution of dimethyl oxaldiimidate (4.p gm; 34.5 mmole) and pyridine (5.71 ml, 5:58 gm; 70.6 mmole) in 8 ml of Ch_2Cl_2 was added dropwise to a cold solution of thionyl chloride (2.61 ml, 4.25 gm; 34.7 mmole) in 18 ml of CH_2Cl_2 under a stream of nitrogen, at such a rate that the reaction temperature remained between 0 and 15°. After stirring at ambient temperature for 20 minutes, the reaction mixture was washed with two 11 ml portions of aqueous 0.055 N HCl. The aqueous phase was extracted with two 20 ml portions of CH_2Cl_2 and the combined organic phase was dried and evaporated to dryness under reduced pressure. The solid residue was recrystalized from isopropyl alcohol to give 3.0 gm of the title compound, mp 137–139°.

The use of the compounds of the present invention in the preparation of active compounds is fully described in Specification A-2067987

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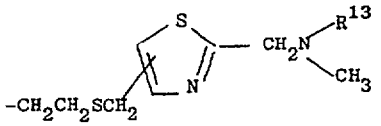
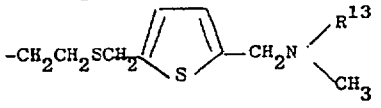
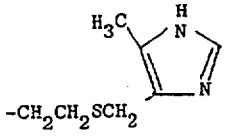
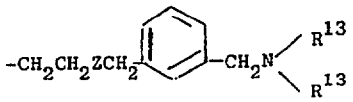






or



in which Z is sulfur or methylene and R^{13} is hydrogen or methyl.

In the following examples, all temperatures are given in degrees Centrigrade.

Example 1

3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]-ethylamine}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

To a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) [prepared according to the procedure described in *J. Org. Chem., 40,* 2743 (1975)] in 200 ml of methanol at ambient temperature was added a solution of 2-[(5-methyl-1H-imidazol-4-yl)-methylthio] ethylamine (from the dihydrochloride, 2.73 g; 11.2 mmoles) [prepared according to Belgian Patent 779,775] in 25 ml of methanol. After stirring for 30 minutes, a methanolic solution of the title compound was produced. The TLC (Silica/CH_2Cl_2:CH_3OH (90:10)] gave Rf = 0.44.

Example 2

3,4-Dimethoxy-1,2,5-thiadiazole 1-oxide

A solution of 3,4-dimethoxy-1,2,5-thiadiazole (35.2 g; 24.1 mmoles) [prepared according to the procedure described in *J. Org. Chem., 40,* 2749 (1975)] in 100 ml of chloroform was added over a period of 3 minutes to a stirred solution of *m*-chloroperbenzoic acid (50.7 g; 25.0 mmoles; 85% assay) in 900 ml of chloroform at 20°, using a cooling bath to keep the exothermic reaction from rising above 32°. After stirring for 3 hours at ambient temperature, the excess peracid was reacted with an additional 2.0 g of 3,4-dimethoxy-1,2,5-thiadiazole and stirred for 1 hour.

The organic solution was extracted with two-300 ml portions of a 1% solution of $NaHCO_3$, washed with 250 ml of water, dried and evaporated under reduced pressure to give 47.0 g of produce. Recrystallization from isopropyl alcohol gave the title compound (34.0 g). An additional recrystallization from isopropyl alchol gave an analytical sample, mp 135–137°.

Anal. Calcd for $C_4H_6N_2O_3S$: C, 29.63; H, 3.72; N, 17.27; S, 19.77.
Found: C, 29.53; H, 3.75; N, 17.26; S, 19.83.

Example 3

3-{2-[(5-Dimethylaminoethyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (2.41 g; 11.2 mmoles) [prepared according to the procedure described in Belgian Patent 857,388] in 20 ml of dry methanol was added all at once to a well stirred, cold (8°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (2.0 g; 11.2 mmoles) in 200 ml of methanol. After stirring at 3–10° for 15 minutes, a methanolic solution of the title compound is produced.

Example 4

3-{2-[(5-Dimethylaminomethyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-[(5-dimethylaminomethyl-2-furylmethylthio]ethylamine (2.14 g; 10.0 mmoles) in 25 ml of dry methanol was added dropwise over 35 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (1.78 g; 10.0 mmoles) in 180 ml of dry methanol

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that had been cooled to 1° in an ice-water bath. After 15 Minutes at 0° a methanol solution of the title compound is produced. A TLC [silica/CH_2Cl_2:CH_3OH (9.1)] gave RF = 0.48.

A 2.0 ml aliquot of the solution was made acidic with 6.0 N HCl and evaporated under reduced pressure without heating to yield the title compound as the hydrochloride salt. The NMR spectrum (100 MHz) in D_2O gave the following resonances δ: 6.45 (d,1H); 6.19 (d, 1H); 4.14 (s, 2H); 4.0 (s, 3H); 3.64 (s, 2H); 3.37 (t, 2H); 2.65 (s, 6H); 2.61 (t, 2H).

Example 5

3-{2-[(5-Dimethylmaninomethyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide

A solution of 2-[(5-dimethylaminomethyl-2-furyl)-methylthio]ethylamine (3.30 g; 15.4 mmoles) in 25 ml of methanol was added dropwise over a period of 14 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide (2.50 g; 15.4 mmoles) [prepared according to the procedure in Example 2] that was cooled to 12–15° in an ice-water bath. The solution was stirred at ambient temperature for 1.5 hours to yield a methanolic solution of the title compound.

Example 6

3-Methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1,1-dioxide

A solution of 2-aminoethanethiol (from the hydrochloride 1.91 g; 16.8 mmoles) in 20 ml of methanol was added dropwise over a period of 15 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (3.0 g; 16.8 mmoles) in 250 ml of methanol that had been cooled to 1° in an ice-water bath. After 10 minutes at 2–4°, methylamine was bubbled into the cooled solution for 6 minutes and stirring was continued for an additional 30 minutes at ambient temperature. The reaction mixture was evaporated under reduced pressure and the residue placed on 45 g of silica gel and chromatographed using a gradient elution of methylene chloride-methanol. The appropriate fractions were combined and evaporated, and the product (2.43 g) was crystallized from absolute ethanol. Recrystallization from absolute ethanol yielded the title compound, mp 259–260° (dec).

Anal. Calcd for $C_5H_{10}N_4O_2S_2$: C, 27.03; H, 4.54; N, 25.20.
Found: C, 27.13; H, 4.55; N, 24.86.

Example 7

3-Methylamino-4-(2-mercaptoethyl)-1,2,5-thiadiazole 1-oxide

A solution of 2-aminoethanethiol (from the hydrochloride, 2.04 g; 18.0 mmoles) in 25 ml of methanol was added dropwise over a period of 30 minutes to a well stirred suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1-dioxide (2.92 g; 18.0 mmoles) [prepared in Example 2] in 150 ml of methanol that had been cooled to 3° in an ice-water bath. After 10 minutes, anhydrous methylamine was bubbled into the solution for 6 minutes and stirring was continued at ambient temperature for an additional 20 minutes. The reaction mixture was evaporated under reduced pressure and the residue placed on 45 g of silica gel and chromatographed using a gradient elution of methylene chloride methanol. The appropriate fractions were combined and evaporated to give 2.74 g of product. Recrystallization from methanol and then 95% ethanol yielded the title compound, mp 191–193°.

Example 8

3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio] ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide

A. *3,4-Dimethoxy-1,2,5-thiadiazole 1-oxide*

A solution of 3,4-dimethoxy-1,2,5-thiadiazole (35.2 g; 24.1 mmoles) [prepared according to the procedure described in *J. Org. Chem., 40,* 2749 (1975)] in 100 ml of chloroform was added over a period of 3 minutes to a stirred solution of *m*-chloroperbenzoic acid (50.7 g; 25.0 mmoles; 85% assay) in 900 ml of chloroform at 20°, using a cooling bath to keep the exothermic reaction from rising above 32°. After stirring for 3 hours at ambient temperature, the excess peracid was reacted with an additional 2.0g of 3,4-dimethoxy-1,2,5-thiadiazole and stirred for 1 hour.

The organic solution was extracted with two-300 ml portions of a 1% solution of $NaHCO_3$, washed with 250 ml of water, dried and evaporated under reduced pressure to give 47.0 g of product. Recrystallization from isopropyl alcohol gave the title compound (34.0 g). An additional recrystallization from isopropyl alcohol gave an analytical sample, mp 135-137°.

Anal. Calcd for $C_4H_6N_2O_3S$: C, 29.63; H, 3.72; N, 17.27; S, 19.77.
Found: C, 29.53; H, 3.75; N, 17.26; S, 19.83.

B. *3-{2-[(5-Methyl-1H-imidazol-4-yl)methylthio]-ethylamino}-4-methoxy-1,2,5-thiadiazole 1-oxide*

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A solution of 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide obtained from the above Step A is reacted with an equimolar amount of 2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethylamine to produce 3- 2-[5-methyl-1H-imadazol-4-yl)methylthio]ethylamino -4-methoxy-1,2,5-thiadiazole 1-oxide.

Example 9

3-{2-[(5-Dimethylaminomethyl-3-methyl-2-furyl)methylthio]-ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

A. *5-Dimethylaminomethyl-3-methyl-2-furanmethanol*

A mixture containing 3-methyl-2-furfuryl alcohol (11.2 g; 0.1 mole [prepared according to the procedure described in *J. Am. Chem. Soc., 72,* 2195 (1950)], dimethylamine hydrochloride (12.23 g; 0.15 mole) and 37% aqueous formaldehyde (12 ml, 0.15 mole) was stirred for 2.5 hours at approximately 5°, and then at ambient temperature overnight. The solution was heated for 10 minutes on a steam bath, diluted with 12 ml of water and basified with sodium carbonate. The mixture was extracted with ethyl acetate, and the organic phase dried, filtered and evaporated under reduced pressure to yield the title compound, bp 88–96/0.05–0.08 mm Hg.

B. *2-[(5-Dimethylaminomethyl-3-methyl-2-furyl)-methylthio]ethylamine*

To a solution of 2-aminoethanethiol hydrochloride (2.27 g; 20.0 mmoles) in 20 ml of concentrated HCl that was cooled in an ice-salt bath to − 10° was added dropwise 5-dimethylaminomethyl-3-methyl-2-furanmethanol (3.38 g; 20.0 mmoles) [prepared in Step A], and the mixture stirred for 15 minutes then allowed to stand in the cold (0°) overnight. After 17 hours the cold solution was made strongly basic with aqueous KOH solution and then extracted with five portions of methylene chloride. The combined organic phase was dried, filtered and evaporated under reduced pressure to yield the title compound (4.16 g), bp 110–120°/0.1 mm Hg.

C. *3-{2-[(5-Dimethylaminomethyl-3-methyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide*

A methanol suspension of 3,4-dimenthoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-3-methyl-2-furyl)methylthio]ethylamine [prepared in Step B] to produce 3-{2-[(5-dimethylaminomethyl-3-methyl-2-furyl)methylthio]-ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide.

Example 10

3-{2-[(5-Dimethylaminomethyl-4-methyl-2-furyl)methylthio]-ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

A. *2-Dimethylaminomethyl-3-methylfuran*

A stirred solution of 3-methyl-2-furfuryl alcohol (25.2 g; 22.5 mmoles) and triethylamine (27.3 g; 27.0 mmoles) in 200 ml of methylene chloride was cooled to − 15° in an ice-salt bath and a solution of thionyl chloride (18.0 ml, 24.8) mmoles in 30 ml of methylene chloride was added dropwise, keeping the temperature between − 10 to − 15°. After 15 minutes, the mixture was poured into ice-water and the organic layer was separated. The methylene chloride phase containing 3-methyl-2-chloromethylfuran was added to a stirred solution, at 0°, of dimethylamine (137.0 g; 3.04 moles) in 400 ml of absolute ethanol and the resulting solution was stirred at ambient temperature for 17 hours. The reaction mixture was evaporated under reduced pressure and the residue was mixed with 400 ml of water, made strongly basic with 40% aqueous NaOH and extracted with five portions of methylene chloride. The combined extracts were dried, filtered and evaporated under reduced pressure to yield 26.0 g of the title compound, bp 64–70°/20 mm Hg. A TLC [Silica/$CHCl_3$:CH_3OH (85.15)] gave RF = 0.50.

B. *2-Chloromethyl-5-dimethylaminomethyl-3-methylfuran*

To a solution of 2-dimethylaminomethyl-3-methylfuran (6.5 g; 37.0 mmoles) [prepared in Step A] in 250 ml of chloroform was added paraformaldehyde (1.67 g; 55.7 mmoles) and zinc chloride (312 mg), and a slow stream of HCl gas was bubbled through while stirring at ambient temperature for 15 minutes. Stirring was continued for 2 hours, then HCl gas was bubbled through for 15 minutes and the mixture stirred for 1 hour. At this time additional paraformaldehyde (1.67 g; 55.7 mmoles) was added to the reaction mixture and a slow stream of HCl gas was passed through for 15 minutes. After stirring at ambient temperature for 18 hours, the reaction mixture was filtered through Celite and the filtrate evaporated under reduced pressure to yield the title compound (4.97 g) which crystallized upon standing and was without further purification in Step C.

The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 6.33 (s, 1H); 4.55 (s, 2H); 4.30 (d, 2H); 2.83 (d, 6H); 2.13, (s, 3H)

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C. *2-[(5-Dimethylaminomethyl-4-methyl-2-furyl)-methylthio)ethylamine*

To a solution of 2-chloromethyl-5-dimethylamino-methyl-3-methylfuran (773 mg, 3.45 mmoles) [prepared in Step B] in 20 ml of concentrated hydrochloric acid that was cooled in an ice-water bath was added 2-aminoethanethiol hydrochloride (392 mg, 3.45 mmoles), and the mixture was stirred for 30 minutes. The solution was allowed to stand at 0° for 3 days, then made strongly basic with 50% aqueous KOH, diluted with water and extracted with five portions of methylene chloride. The combined extract was dried, filtered and evaporated under reduced pressure to yield the title compound as an oil.

The product was dissolved in absolute ethanol, treated with anhydrous hydrogen chloride and evaporated under reduced pressure. The residue was dissolved in hot isopropyl alcohol, treated with charcoal, filtered and concentrated to crystallize the hydrochloride salt. Recrystallization from isopropyl alcohol yielded the title compound as the dihydrochloride salt, mp 185–190° (dec).

D. *3-{2-[(5-Dimethylaminomethyl-4-methyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide*

A methanol suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide is reacted with an equimolar amount of 2-[(5-dimethylaminomethyl-4-methyl-2-furyl)methylthio]ethylamine [prepared in Step C] to produce 3-{[(5-dimethylaminomethyl-4-methyl-2-furyl)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide.

Example 11

3-{2-[(2-Dimethylaminomethyl-4-thiazoly)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide

A. *N-Carbophenoxy-N-methylaminoacetonitrille*

To a suspension of methylaminoacetonitrile hydrochloride (100 g; 0.94 mole) in 1 liter of methylene chloride (cooled in an ice-water bath) was added triethylamine (269 ml, 1.88 moles) and a solution of phenyl chloroformate (155.0 g; 0.99 mole) in 500 ml of methylene chloride. The reaction mixture was heated at reflux temperature for 18 hours, then evaporated under reduced pressure to give a semi-solid which was triturated with 1 liter of diethyl ether and filtered. The filtrate was evaporated under reduced pressure and the residual oil was vacuum distilled to yield the title compound (123 g), bp 111–113°/0.25 mm Hg; the NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.23 (m, 5H); 4.30 (s, 2H); 3.13 (s, 3H).

B. *(N-Carbophenoxy-N-methylamino)thioacetamide*

A solution of N-carbophenoxy-N-methylaminoacetonitrile (131.0 g; 0.69 mole) [prepared in Step A] and thioacetamide (57.1 g; 0.71 mole) in 917 ml of dry DMF was treated with HCl gas until an exothermic reaction took place, and then heated on a steam bath for 20 minutes. The reaction mixture was partially evaporated under reduced pressure to remove some of the solvent, then made basic with saturated aqueous $NaHCO_3$ solution and partitioned between ether and water. The aqueous phase was extracted with ether and the combined ether phase was washed with water, saturated aqueous NaCl solution and dried. Filtration and evaporation of the solvent gave an oil which was triturated with methylcyclohexane to give the produce as a solid. Recrystallization from isopropyl alcohol yielded the title compound, mp 101–103°.

Anal. Calcd $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.40; N, 12.49; S, 14.30.
Found: C, 53.65; H, 5.51; N, 12.69; S, 14.41.

C. *4-Chloromethyl-2-(N-carbophenoxy-N-methylamine)methylthiazole*

To a cooled solution of (N-carbophenoxy-N-methylamino)thioacetamide (1.0 g; 4.46 mmoles) and dry pyridine (0.36 mo, 4.46 mmoles) in 6 ml of absolute ethanol was added a solution of 1,3-dichloropropanone (0.57 g; 4.49 mmoles) in 3 ml of absolute ethanol. The mixture was heated at reflux temperature for 1.5 hours, then evaporated under reduced pressure and the oil residue partitioned between ether and water. The aqueous layer was extracted with ether and the combined ether phase was washed with water, saturated aqueous sodium chloride solution and dried. Filtration and evaporation yielded 1.02 g of the title compound as a viscous oil; TLC [silica/CH_2Cl_2:CH_3CN (85:15)]gave Rf = 0.82. The NMR spectrum (60 MHz) in $CDCl_3$ gave the following resonances δ: 7.16 (m, 6H); 4.77 (broad s, 2H); 4.60 (s, 2H); 3.07 (broad s, 3H).

D. *2-{[2-(N-Carbophenoxy-N-methylamino)methyl-4-thiazolyl]methylthio}ethylamine*

To a solution of sodium methoxide (26.1 g; 0.48 mole) in 290 ml of absolute ethanol at 0° under a nitrogen atmosphere was added cysteamine hydrochloride (27.6 g; 0.24 mole) and an additional 218 ml of absolute ethanol. After stirring at 0° for 1 hour a solution of 4-chloromethyl-2-(N-carbophenoxy-N-methylamino)methylthiazole (72.5 g; 0.24 mole) in 218 ml

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of absolute ethanol was added over a 15 minute period. The reaction mixture was stirred at ambient temperature for 18 hours, filtered and evaporated under reduced pressure to give an oil which was partitioned between methylene chloride and water. The aqueous phase was extracted with methylene chloride and the combined organic phase was washed with water, dried, filtered and evaporated under reduced pressure to give the product (68.5 g) as an oil which was treated with fumaric acid (23.6 g) in n-propanol to give the salt (47.0 g). Recrystallization from absolute ethanol yielded the title compound as the fumarate salt, mp 145–146°.

Anal. Calcd for $C_{15}H_{19}N_3O_2S_2.C_4H_4O_4$: C, 50.31; H, 5.11; N, 9.27; S, 14.14.
Found: C, 50.02; H, 5.16; N, 9.47; S, 14.22.

E. *2-[(2-Dimethylaminomethyl-4-thiazolyl)-methylthio]ethylamine*

To a solution of 2-{[2-(N-Carbophenoxy-N-methylamino)methyl-4-thiazolyl]methylthio}ethylamine (0.50 g; 1.48 mmoles) [prepared in Step D] in 10 ml of dry tetrahydrofuran under a nitrogen atmosphere was added lithium aluminum hydride (0.17 g; 4.48 mmoles) and the mixture was heated at reflux temperature for 0.5 hour. An additional 10 ml of tetrahydrofuran was added and heating was continued for 3 hours. The reaction mixture was treated with 0.17 ml of H_2O, 0.17 ml of 15% aqueous NaOH and 0.51 ml of H_2O, and filtered through Celite and dried. The filtrate was filtered and evaporated under reduced pressure to give an oil which was dissolved in absolute ethanol, diluted with diethyl ether and acidified with dry HCl. The hydroscopic hydrochloride salt of the title compound was collected and partitioned between aqueous 2.5N NaOH and methylene chloride. The organic phase was washed with water, dried and filtered. The filtrate was evaporated under reduced pressure to give the free base of the title compound as an oil (0.22 g; 0.95 mmole) which was combined with anhydrous oxalic acid (0.24 g; 1.90 mmole) in 30 ml of hot acetonitrile. The mixture was evaporated from hot absolute ethanol to yield the title compound the *bis*-oxalate, mp 168–171°.

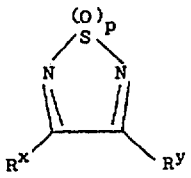
Anal. Calcd for $C_9H_{17}N_3O_4S_2.2C_2H_2O_4$: C, 37.95; H, 5.15; N, 10.21; S, 15.59.
Found: C, 37.95; H, 5.04; N, 9.81; S, 15.27.

F. *3-{2-[(2-Dimethylaminomethyl-4-thiazolyl)-methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide*

To a cooled (6°) suspension of 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (0.74 g; 4.17 mmoles) in 80 ml of methanol was added dropwise over a period of 45 minutes a solution of 2-[(2-dimethylaminomethyl-4-thiazolyl)methylthio]ethylamine (0.96 g; 4.17 mmoles) [prepared in Step E] to give 3-{2-[(2-dimethylaminomethyl-4-thiazoly)methylthio]ethylamino}-4-methoxy-1,2,5-thiadiazole 1,1-dioxide, Rf = 0.64 [Silica/CH_2Cl_2:CH_3OH (9:1)].

CLAIMS

1. A compound of the formula



I

wherein:
p is 1 or 2 and
(a) when p is 1
(i) R^x and R^y are the same and are R^7, or
(ii) R^x is R^{12} and R^y is R^7, or
(iii) R^x is $-NH(CH_2)_nHS$ and R^y is NR^2R^3, and
(b) when p is 2
(i) R^x is R^{12} and R^y is R^7, or
(ii) R^x is $-NH(CH_2)_nHS$ and R^y is $-NR^2R^3$;

R^7 is a leaving group selected from halogen, (lower)alkoxy, (lower)alkylthio, phenoxy, phenylthio, substituted phenoxy and substituted phenylthio wherein the phenyl ring may contain 1 or 2 substituents selected from halogen, (lower)alkyl, (lower)alkoxy and nitro;

R^{12} is $A(CH_2)_mZ(CH_2)_nNH-$, R^2R^3N- or $HS(CH_2)_nNH-$; R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(-lower)alkyl, morpholino(lower)alkyl, piperazino(lower)alkyl, pyridyl(lower)alkyl, amino, (lower)al-

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kylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'-(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxy, trifluoromethyl and di(loweralkylamino but further provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$, provided that, when p is 2 and R^7 is methoxy, R^2 and R^3 taken together with the nitrogen to which they are attached, may not be morpholino, and that, when r is 1,X is methylene;

R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive.

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

$$-(CH_2)_qN=C\begin{matrix}NHR^4\\ \diagup\\ \diagdown\\ NHR^4\end{matrix} \quad \text{and} \quad -(CH_2)_qNR^5R^6$$

and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

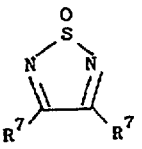
q is an integer of from 0 to 6, inclusive;

each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N-methylpiperazino or homopiperidino;

or a salt, hydrate, solvate or N-oxide thereof.

2. A compound of the formula

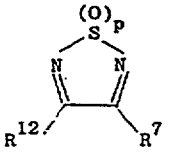


II

wherein each R^7 is halogen, (lower)alkoxy or (lower)alkylthio, or phenoxy or phenylthio which may contain 1 or 2 substituents selected from halogen, (lower)alkyl, (lower)alkoxy and nitro.

3. 3,4-Dimethoxy-1,2,5-thiadiazole 1-oxide.

4. A compound of the formula



XI

wherein p is 1 or 2;

R^7 is a leaving group selected from halogen, (lower)alkoxy, (lower)alkylthio, phenoxy, phenylthio, substituted phenoxy and substituted phenylthio wherein the phenyl ring may contain 1 or 2 substituents selected from halogen, (lower)alkyl, (lower)alkoxy and nitro; and

R^{12} is $A(CH_2)_mZ(CH_2)_nNH-$, R^2R^3N- or $HS(CH_2)_nNH-$; in which R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, pi-

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peridino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)alkyl, pyridyl(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$, provided that, when p is 2 and R^7 is methoxy, R^2 and R^3 taken together with the nitrogen to which they are attached, may not be morpholino, and that, when r is 1, X is methylene;

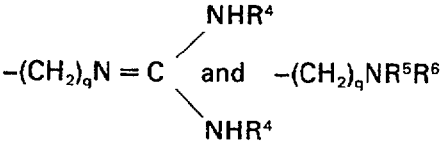
R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m and m' each are independently an integer of from zero to 2, inclusive;

n and n' each are independently an integer of from 2 to 4, inclusive;

Z and Z' each are independently sulfur, oxygen or methylene;

A and A' each are independently phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A' independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,



and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

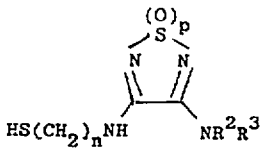
q is an integer of from 0 to 6, inclusive;

each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

R^5 and R^6 each are inependently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower) alkyl or phenyl, provided that R^5 and R^6 may not be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N-methylpiperazino or homopiperidino;

or a salt, hydrate, solvate or N-oxide thereof.

5. A compound of the formula



XII

wherein p is 1 or 2;

n is an integer of from 2 to 4 inclusive;

R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkyl amino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, morpholino(lower)alkyl, piperazino(lower)alkyl, pyridyl(lower)alkyl, amino,2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected for methylenedioxy, trifluoromethyl and di(lower)alkylamino; provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$, provided that, when r is 1, X is methylene;

R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m' is an integer of from zero to 2, inclusive;

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n′ is an integer of from 2 to 4, inclusive;
Z′ is sulfur, oxygen or methylene;
A′ is phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazoly, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A′ may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

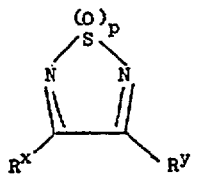
$$-(CH_2)_qN=C\begin{matrix}NHR^4\\ \diagup\\ \diagdown\\ NHR^4\end{matrix} \quad \text{and} \quad -(CH_2)_qNR^5R^6$$

and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;
q is an integer of from 0 to 6, inclusive;
each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and
R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, morpholino, piperidino, methylpiperidino, N-methylpiperazino or homopiperidino; or a salt, hydrate, solvate or N-oxide thereof.

6. A compound according to claim 1 substantially as hereinbefore described with particular reference to the Examples.

CLAIMS (1 Dec 1983 and 8 Feb 1984)

1. A compound of the formula



I

wherein:
p is 1 or 2 and
(a) when p is 1
(i) R^x and R^y are the same and are R^7, or
(ii) R^x is R^{12} and R^y is R^7, or
(iii) R^x is $-NH(CH_2)_nHS$ and R^y is NR^2R^3, and
(b) when p is 2
(i) R^x is R^{12} and R^y is R^7, or
(ii) R^x is $-NH(CH_2)_nHS$ and $R^y$is $-NR^2R^3$;
R^7 is a leaving group selected from halogen, (lower)alkoxy, (lower)alkylthio, phenoxy, phenylthio, substituted phenoxy and substituted phenylthio wherein the phenyl ring may contain 1 or 2 substituents selected from halogen, (lower)alkyl, (lower)alkoxy and nitro;
R^{12} is $A(CH_2)_mZ(CH_2)_nNH-$, R^2R^3N- or $HS(CH_2)_nNH-$; R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, piperazino(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}(CH_2)_{n'}-$, phenyl, phenyl–(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino but further provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;
r is an integer of from 1 to 3, inclusive;
X is methylene, sulfur, oxygen or $N-R^4$, provided that, when p is 2 and R^7 is methoxy, R^2 and R^3 taken together with the nitrogen to which they are attached, may not be morpholino, and that, when r is 1,X is methylene;

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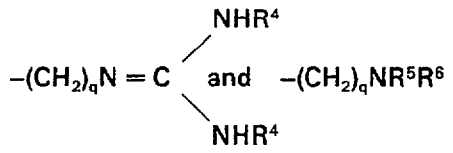
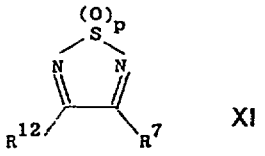
R^4 is hydrogen, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;
m and m′ each are independently an integer of from zero to 2, inclusive;
n and n′ each are independently an integer of from 2 to 4, inclusive.
Z and Z′ each are independently sulfur, oxygen or methylene;
A and A′ each are independently phenyl, imidazoyly, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A′ independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethy, halogen, amino, hydroxymethyl, (lower)alkoxy,



and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;
q is an integer of from 0 to 6, inclusive;
each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and
R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, piperidino, methylpiperidino, or homopiperidino;
or a salt, hydrate, solvate or N-oxide thereof.

4. A compund of the formula



XI

wherein p is 1 or 2;
R^7 is a leaving group selected from halogen, (lower)alkoxy, (lower)alkylthio, phenoxy, phenylthio, substituted phenoxy and substituted phenylthio wherein the phenyl ring may contain 1 or 2 substituents selected from halogen, (lower)alkyl, (lower)alkoxy and nitro; and
R^{12} is $A(CH_2)_mZ(CH_2)_nNH-$, R^2R^3N- or $HS(CH_2)_nNH-$; in which R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkylamino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, piperazino(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoromethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;
r is an integer of from 1 to 3, inclusive;
X is methylene, sulfur, oxygen or $N-R^4$, provided that, when p is 2 and R^7 is methoxy, R^2 and R^3 taken together with the nitrogen to which they are attached, may not be morpholino, and that, when r is 1, X is methylene;
R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;
m and m′ each are independently an integer of from zero to 2, inclusive;
n and n′ each are independently an integer of from 2 to 4, inclusive;
Z and Z′ each are independently sulfur, oxygen or methylene;
A and A′ each are independently phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazoly, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A and A′ independently may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,

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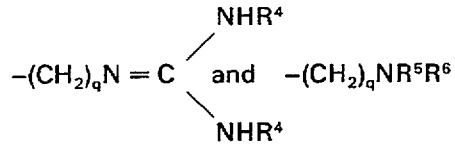


and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

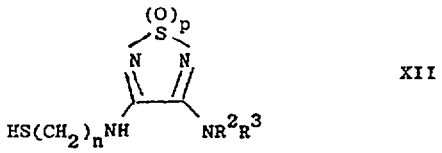
q is an integer of from 0 to 6, inclusive;

each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

R^5 and R^6 each are inependently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower) alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be pyrrolidino, piperidino, methylpiperidino, or homopiperidino;

or a salt, hydrate, solvate or N-oxide thereof.

5. A compound of the formula



XII

wherein p is 1 or 2;

n is a integer of from 2 to 4 inclusive;

R^2 and R^3 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkyl, cyclo(lower)alkyl, cyclo(lower)alkyl(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxy(lower)alkyl, (lower)alkylthio(lower)alkyl, amino(lower)alkyl, (lower)alkylamino(lower)alkyl, di(lower)alkyl amino(lower)alkyl, pyrrolidino(lower)alkyl, piperidino(lower)alkyl, piperazino(lower)alkyl, amino, (lower)alkylamino, di(lower)alkylamino, 2,2,2-trifluoroethyl, 2-fluoroethyl, hydroxy, (lower)alkoxy, 2,3-dihydroxypropyl, cyano, cyano(lower)alkyl, amidino, (lower)alkylamidino, $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$, phenyl, phenyl(lower)alkyl, substituted phenyl or substituted phenyl(lower)alkyl, wherein the phenyl ring may contain one or two substituents independently selected from (lower)alkyl, hydroxy, (lower)alkoxy and halogen, or one substituent selected from methylenedioxy, trifluoromethyl and di(lower)alkylamino; provided that R^2 and R^3 may not both be cyclo(lower)alkyl, phenyl, substituted phenyl, amino, (lower)alkylamino, di(lower)alkylamino, hydroxy, (lower)alkoxy, cyano, amidino, (lower)alkylamidino or $A'-(CH_2)_{m'}Z'(CH_2)_{n'}-$; or R^2 and R^3, taken together, may be $-CH_2CH_2X(CH_2)_r-$;

r is an integer of from 1 to 3, inclusive;

X is methylene, sulfur, oxygen or $N-R^4$, provided that, when r is 1, X is methylene;

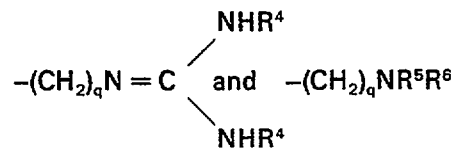
R^4 is hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, (lower)alkanoyl or benzoyl;

m' is an integer of from zero to 2, inclusive;

n' is an integer of from 2 to 4, inclusive;

Z' is sulfur, oxygen or methylene;

A' is phenyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, furyl, thienyl or pyridyl; provided that A' may contain one or two substituents, the first substituent being selected from (lower)alkyl, hydroxy trifluoromethyl, halogen, amino, hydroxymethyl, (lower)alkoxy,



and the second substituent being selected from (lower)alkyl, hydroxy, trifluoromethyl, halogen, amino, hydroxymethyl and (lower)alkoxy;

q is an integer of from 0 to 6, inclusive;

each R^4 independently is as defined above, or the two R^4 groups, taken together, may be ethylene; and

R^5 and R^6 each are independently hydrogen, (lower)alkyl, (lower)alkenyl, (lower)alkynyl, cyclo(lower)alkyl or phenyl, provided that R^5 and R^6 may not both be cyclo(lower)alkyl or phenyl; or R^5 and R^6, taken together with the nitrogen atom to which they are attached, may be

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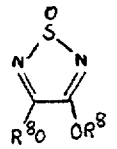
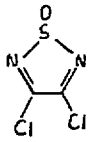
pyrrolidino, piperidino, methylpiperidino, or homopiperidino; or a salt, hydrate, solvate or N-oxide thereof.

7. A method for the preparation of a compound of formula

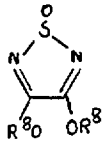


in which



is reacted with R^8OH
wherein R^8 is methyl, or ethyl
and R^8OH is methanol or ethanol.

8. A compound of formula



produced by a process according to claim 7.

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