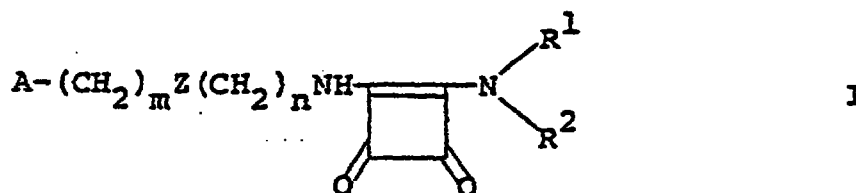


DESCRIPTIONChemical Intermediates derived from Cyclobutene

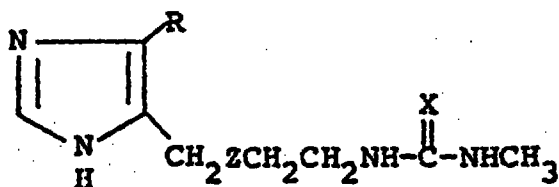
The present Application has been divided out of Application No.82.14351 (2098988), referred to below as our "primary" Application.

As disclosed in our primary Application, certain substituted 1,2-diaminocyclobutene-3,4-diones of the formula



wherein A is substituted phenyl, furyl, thienyl or pyridyl, Z is sulfur, oxygen or methylene, m is 0-2, n is 2-5 and R^1 and R^2 are as defined below, are potent histamine H_2 -antagonists, inhibit gastric acid secretion and are useful in the treatment of peptic ulcers.

Burimamide (IIa) was the first clinically effective H_2 -receptor antagonist. It inhibits gastric secretion in animals, including man, but oral absorption is poor.

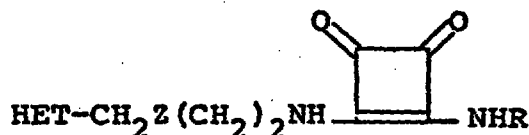


- IIa; R=H, Z=CH₂, X=S Burimamide
 b; R=CH₃, Z=S, X=S Metiamide
 c; R=CH₃, Z=S, X=NCN Cimetidine

Metiamide (IIb), a subsequently evaluated H₂-antagonist, is more potent than burimamide and is orally active in man. Clinical utility was limited, however, owing to toxicity (agranulocytosis). Cimetidine (IIc) is as effective an H₂-antagonist as metiamide, without producing agranulocytosis, and has recently been marketed as an anti-ulcer drug.

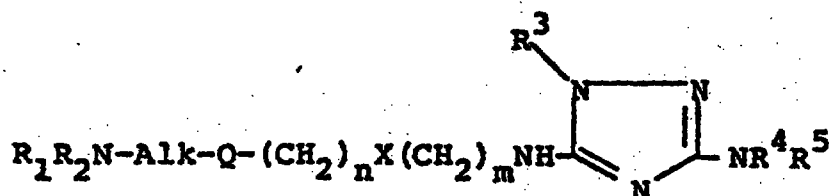
Reviews on the development of H₂-antagonists, including those discussed in the preceding paragraph, may be found in C. R. Ganellin, et al., Federation Proceedings, 35, 1924 (1976), in Drugs of the Future, 1, 13 (1976) and in references cited therein.

U.S. Patent 4,062,863 discloses histamine H₂-antagonists of the formula



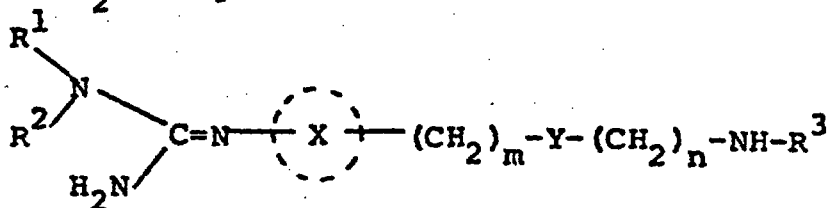
wherein R is hydrogen, (lower)alkyl or (CH₂)₂Z'CH₂-HET'; Z and Z' each are sulfur or methylene; and HET and HET' each are an imidazole ring optionally substituted by methyl or bromo, a pyridine ring optionally substituted by hydroxy, methoxy, chloro or bromo, a thiazole ring or an isothiazole ring, and pharmaceutically acceptable acid addition salts thereof. U.S. Patents 4,120,968, 4,120,973 and 4,166,857 are divisionals thereof which have substantially the same disclosure.

U.K. Published Patent Application 2,023,133 discloses histamine H₂-antagonists of the formula



wherein R_1 and R_2 are independently hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, trifluoroalkyl or alkyl substituted by hydroxy, alkoxy, amino, alkylamino, dialkylamino or cycloalkyl, or R_1 and R_2 , taken together with the nitrogen to which they are attached, may be a 5- to 10-membered alicyclic heterocyclic ring which may be saturated or may contain at least one double bond, which may be substituted by one or more alkyl groups or a hydroxy group and/or which may contain another heteroatom; Alk is a straight or branched alkylene chain of 1-6 carbon atoms; Q is a furan or thiophene ring incorporated into the molecule via the 2- and 5-positions, the furan ring optionally bearing a further substituent R_7 adjacent the $R_1R_2N-Alk-$ group, or Q is a benzene ring incorporated into the molecule via its 1- and 3- or 1- and 4-positions; R_7 is halogen, alkyl (which may be substituted by hydroxy or alkoxy); X is methylene, oxygen, sulfur or $>N-R^6$ in which R^6 is hydrogen or methyl; n is 0, 1 or 2; m is 2, 3 or 4; R_3 is hydrogen, alkyl, alkenyl, aralkyl, hydroxyalkyl having at least two carbon atoms, alkoxyalkyl or aryl; and R_4 and R^5 are independently hydrogen, alkyl, alkyl substituted by hydroxy or C_{1-3} alkoxy, alkenyl, aralkyl or heteroaralkyl, or R_4 and R_5 taken together with the nitrogen to which they are attached, may be a 5- to 7-membered saturated heterocyclic ring which may contain another heteroatom or the group $>NR^6$, or R_4 and R_5 taken together may be the group $>CR_8R_9$ wherein R_8 is aryl or heteroaryl and R_9 is hydrogen or alkyl; and physiologically acceptable salts and hydrates thereof.

Published European Patent Application No. 30,092 discloses histamine H₂-antagonists of the formula



in which R¹ and R² are hydrogen or optionally halogen-substituted alkyl, cycloalkyl or cycloalkylalkyl, provided that at least one of R¹ and R² is halogen-substituted alkyl, cycloalkyl or cycloalkylalkyl;

X is a phenyl ring with 1 or 2 optional substituents or a 5- or 6-membered heterocyclic aromatic ring containing 1, 2 or 3 heteroatoms selected from O, N and S, the heterocyclic ring, where possible, having 1 optional substituent, which optional substituents are halogen, alkyl, alkoxy, alkylthio, trifluoromethyl, hydroxy and amino;

Y is O, S, a direct bond, methylene, cis or trans vinylene, sulfinyl or NR⁴ in which R⁴ is H or alkyl;

m is 0 to 4 and n is 1 to 5;

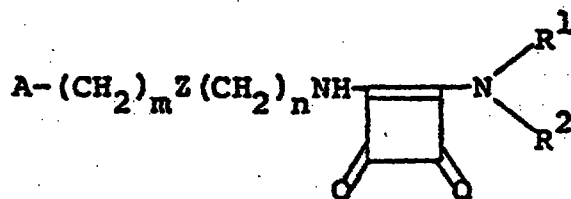
R³ is inter alia AB in which A is inter alia a 3,4-dioxocyclobuten-1,2-diyl radical and B is inter alia the radical NR⁷R⁸ in which R⁷ and R⁸ are inter alia hydrogen, alkyl, haloalkyl, alkoxy carbonyl, alkenyl, alkynyl, (primary hydroxy)alkyl or (primary amino)alkyl, or R⁸ and R⁹, together with the nitrogen atom to which they are attached, may be a 5- or 6-membered ring which optionally contains O or NR⁹ in which R⁹ is H or alkyl.

Complete Disclosure

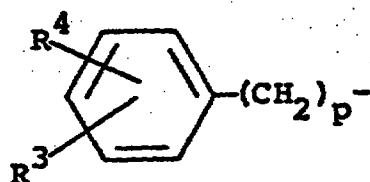
This application relates to intermediates useful for preparing certain histamine H₂-antagonists

which are effective inhibitors of gastric acid secretion in animals, including man, which are useful in the treatment of peptic ulcers and other conditions caused or exacerbated by

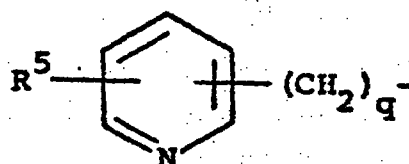
gastric acidity, and which have the formula



wherein R^1 and R^2 each are independently hydrogen or (lower) alkyl, and, when R^1 is hydrogen, R^2 also may be allyl, propargyl, cyclo(lower)alkyl(lower)alkyl, cyclo(lower)alkyl, cyano(lower)alkyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, hydroxy, 2,3-dihydroxypropyl,



or



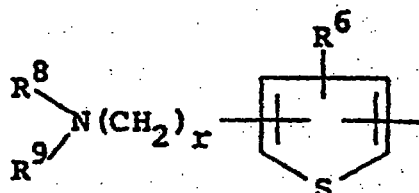
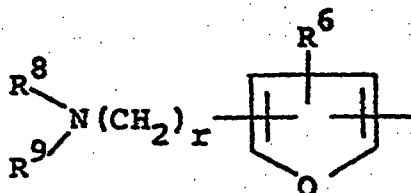
in which p is an integer of from 1 to 6, q is an integer of from 1 to 6, R^3 and R^4 each are independently hydrogen, (lower)alkyl, hydroxy, (lower)alkoxy or halogen, and, when R^3 is hydrogen, R^4 also may be trifluoromethyl, or R^3 and R^4 , taken together, may be methylenedioxy, R^5 is hydrogen, (lower)alkyl, (lower)alkoxy, hydroxy, amino or halogen;

m is an integer of from 0 to 2;

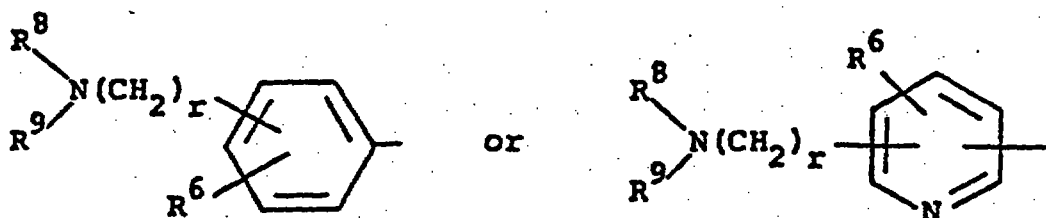
n is an integer of from 2 to 5;

Z is sulfur, oxygen or methylene; and

A is



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in which R^6 is hydrogen, (lower)alkyl, (lower)alkoxy or halogen;
 r is an integer of from 1 to 4; and
 R^8 and R^9 each are independently hydrogen, (lower)-alkyl, allyl, propargyl, (lower)alkoxy(lower)alkyl in which the (lower)alkoxy moiety is at least two carbon atoms removed from the nitrogen atom, cyclo(lower)alkyl, or phenyl(lower)alkyl, provided that R^8 and R^9 may not both be cyclo(lower)alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, 3-pyrrolino, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane;

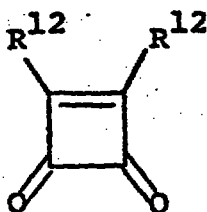
or a nontoxic, pharmaceutically acceptable salt, hydrate or solvate thereof.

The foregoing definition of the compounds which may be prepared from the intermediates of the present invention, the said compounds being the compounds of the Formula I initially set forth herein, is to be understood to include within its scope all

possible tautomeric forms, geometric isomers, optical isomers and zwitterionic forms of the compounds of Formula I, as well as mixtures thereof. As used herein and in the claims, the terms "(lower)alkyl" and "(lower)alkoxy" mean straight or branched chain alkyl or alkoxy groups containing from 1 to 6 carbon atoms. Preferably these groups contain from 1 to 4 carbon atoms and, most preferably, they contain 1 or 2 carbon atoms. The term "cyclo(lower)alkyl", as used herein and in the claims, means a cycloalkyl ring containing from 3 to 7 carbon atoms and preferably from 3 to 6 carbon atoms. Unless otherwise

specified in the particular instance, the term "halogen" as used herein and in the claims is intended to include chloride, fluorine, bromine and iodine. The term "nontoxic pharmaceutically acceptable salts" is intended to include salts of the compounds of Formula I with any nontoxic pharmaceutically acceptable acid. Such acids are well-known and include hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, maleic, fumaric, succinic, oxalic, benzoic, methanesulfonic, tartaric, citric, camphorsulfonic, and levulinic. The salts are made by methods known in the art.

The compounds of Formula I may be prepared by certain procedures utilizing as a starting material a compound of the formula



II

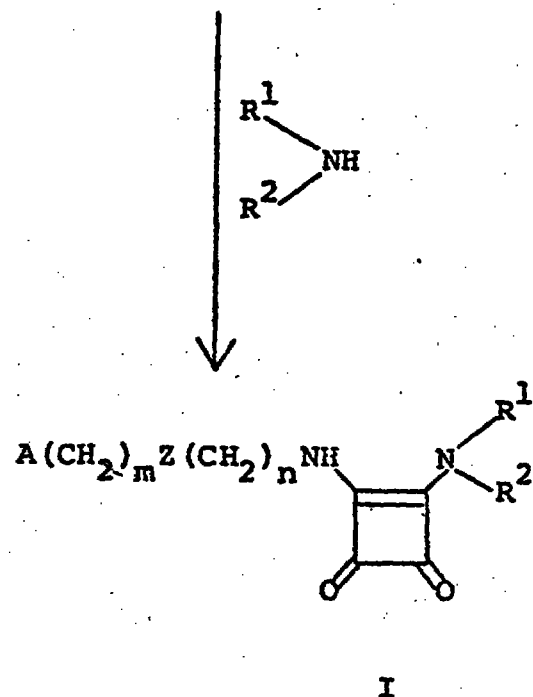
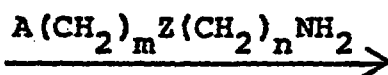
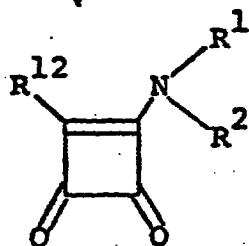
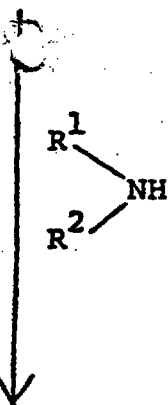
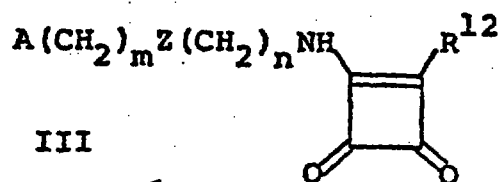
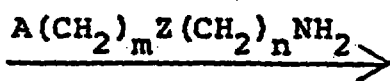
in which R^{12} is a good leaving group such as halogen, phenoxy, substituted phenoxy, or alkoxy. Suitable leaving groups are well-known to those skilled in the art. Preferably, R^{12} is (lower)alkoxy, and especially methoxy and ethoxy.

Of the two routes from a compound of the Formula II to a compound of the Formula I which are represented in the Reaction Scheme set forth below, that which is of interest in connection with the present Application is the route passing through a compound of the Formula III.



Reaction Scheme

Compound
II



The reactions are conducted in an inert organic solvent; we find methanol to be a convenient and readily available solvent. The reaction temperature is not critical. Most starting materials are quite reactive and we prefer to conduct the reaction at a temperature below room temperature, e.g. 0-10°C. With some less reactive compounds it is convenient to conduct the reaction at room temperature. Sometimes it is desirable to subsequently raise the temperature of the reaction mixture (e.g. to 50-60°C) to complete the reaction.

According to the present invention, there are provided intermediates of the formula



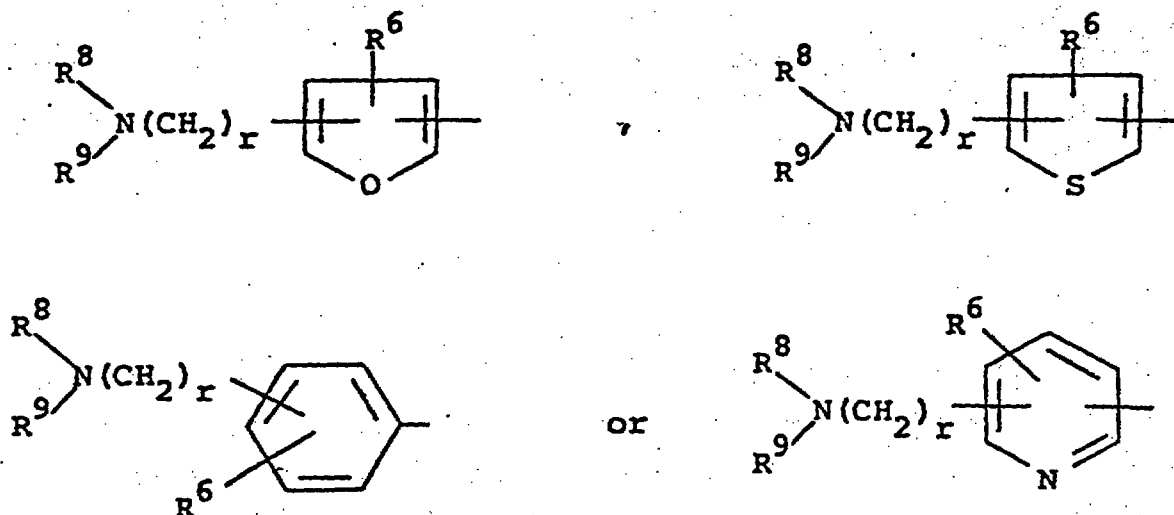
wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and alkoxy;

m is an integer of from 0 to 2;

n is an integer of from 2 to 5;

Z is sulfur, oxygen or methylene; and

A is



in which R^6 is (lower)alkyl, (lower)alkoxy or halogen, provided that, in the second, third or fourth of the four values of A specified above, R^6 may alternatively be hydrogen;

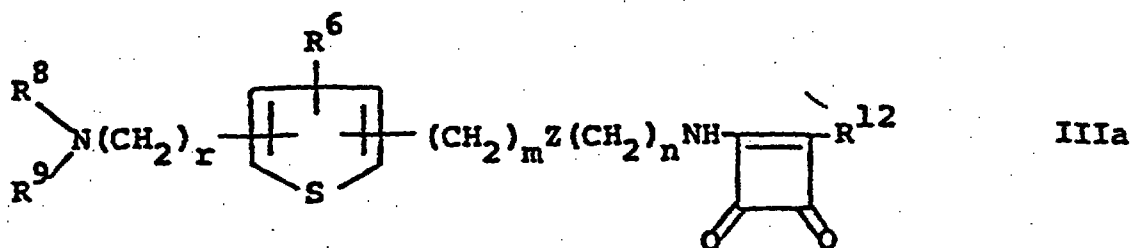
r is an integer of from 1 to 4; and

R^8 and R^9 each are independently hydrogen, (lower)alkyl, allyl, propargyl, (lower)alkoxy(lower)-alkyl in which the

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(lower)alkoxy moiety is at least two carbon atoms removed from the nitrogen atom, cyclo(lower)alkyl, or phenyl(lower)alkyl, provided that R^8 and R^9 may not both be cyclo(lower)alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, 3-pyrrolino, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

A preferred embodiment of the intermediates of Formula III are those having the structure



wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2;

n is an integer of from 2 to 5;

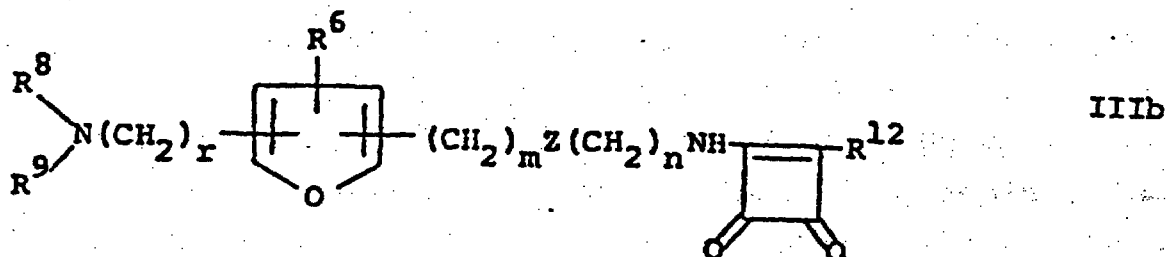
Z is sulfur, oxygen or methylene;

R^6 is hydrogen or (lower)alkyl;

r is an integer of from 1 to 4; and

R^8 and R^9 each are independently hydrogen or (lower)-alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

Another preferred embodiment of the intermediates of Formula III are those having the structure



wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2 ;

n is an integer of from 2 to 5 ;

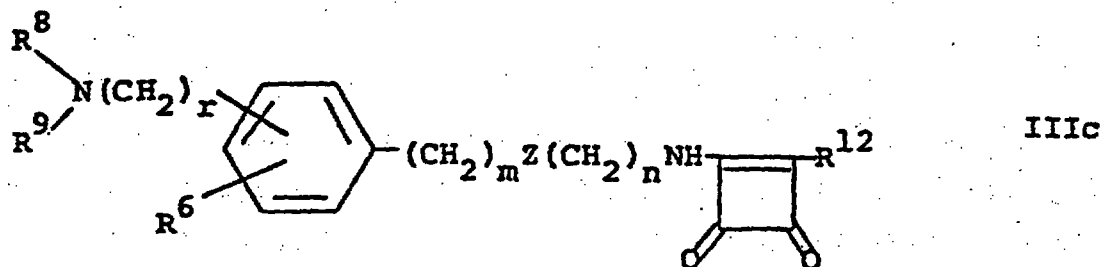
Z is sulfur, oxygen or methylene;

R^6 is (lower)alkyl;

r is an integer of from 1 to 4; and

R^8 and R^9 each are independently hydrogen or (lower)-alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

Another preferred embodiment of the intermediates of Formula III are those having the structure



wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2;

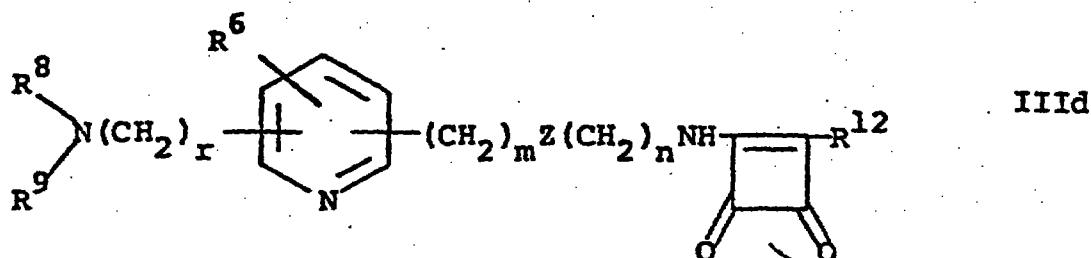
n is an integer of from 2 to 5;

Z is sulfur, oxygen or methylene;

R^6 is hydrogen or (lower)alkyl;

r is an integer of from 1 to 4; and
 R^8 and R^9 each are independently hydrogen or (lower)-alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

Another preferred embodiment of the intermediates of Formula III are those having the structure



wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2;

n is an integer of from 2 to 5;

Z is sulfur, oxygen or methylene;

R^6 is hydrogen or (lower)alkyl;

r is an integer of from 1 to 4; and

R^8 and R^9 each are independently hydrogen or (lower)-alkyl; or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

As presently envisaged, the most preferred intermediates of Formula III are



- a) 1-Methoxy-2-[3-(3-piperidinomethylphenoxy)propylamino]-cyclobutene-3,4-dione.
- b) 1-Methoxy-2-{2-[(5-dimethylaminomethyl-3-thienyl)-methylthio]ethylamino}cyclobutene-3,4-dione.
- c) 1-Methoxy-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}cyclobutene-3,4-dione.
- d) 1-Methoxy-2-[3-(3-dimethylaminomethylphenoxy)propylamino]-cyclobutene-3,4-dione.
- e) 1-Methoxy-2-[3-(3-pyrrolidinomethylphenoxy)propylamino]-cyclobutene-3,4-dione.
- f) 1-Methoxy-2-{3-[3-(3-methylpyrrolidino)methylphenoxy]-propylamino}cyclobutene-3,4-dione.
- g) 1-Methoxy-2-[3-(3-hexamethyleneiminomethylphenoxy)-propylamino]cyclobutene-3,4-dione.
- h) 1-Methoxy-2-[3-(3-piperidinomethylthiophenoxy)propylamino]cyclobutene-3,4-dione.
- i) 1-Methoxy-2-[3-(3-heptamethyleneiminomethylphenoxy)-propylamino]cyclobutene-3,4-dione.
- j) 1-Methoxy-2-[3-(3-octamethyleneiminomethylphenoxy)-propylamino]cyclobutene-3,4-dione.

The invention is illustrated by the following examples, in which all temperatures are given in degrees Centigrade, and in which the word "Celite" is a registered Trade Mark and refers to a diatomaceous earth.

Examples dealing with additional preparations of compounds of the Formula I set forth above, from intermediates of the Formula III, are to be seen in the specification of our primary Application.

Example 1

1-Amino-2-[3-(3-piperidinomethylphenoxy)propylamino]cyclobutene-3,4-dione

A solution of 3-(3-piperidinomethylphenoxy)propylamine (from the dihydrochloride, 4.46 g; 13.9 mmoles) [prepared according to published U.K. Patent Application 2,023,133] in 40 mL of methanol was added all at once to a solution of 1,2-dimethoxycyclobutene-3,4-dione (1.97 g; 13.9 mmoles) in 40 mL of methanol that had been cooled to 5° in an ice-water bath. After 2 hours at ambient temperature, the solution was cooled to 5° and excess anhydrous ammonia was bubbled into the solution for 5 minutes. The mixture was stirred at ambient temperature for 18 hours and then filtered to give 4.35 g of product.

The product (4.20 g; 12.2 mmoles) was suspended in 40 mL of 95% aqueous ethanol and 6.11 mL (12.2 mmoles) of aqueous 2.0 N HCl was added with stirring. The solution was filtered through Celite, cooled at 0° for 17 hours, and then filtered to give 4.33 g of the title compound as its hydrochloride salt, mp 254-257°.

Anal. Calc'd. for $C_{19}H_{26}ClN_3O_3$: C, 60.08; H, 6.90, N, 11.06; Cl, 9.33.

Found (corr. for 0.28% H_2O): C, 59.73; H, 6.97; N, 11.14; Cl, 9.36.

Example 2

1-Amino-2-{2-[(5-dimethylaminomethyl-2-thienyl)methylthio]ethylamino}cyclobutene-3,4-dione

A solution of 2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamine (2.06 g; 8.94 mmoles) [prepared according to the procedure described in Belgian Patent 867,105] in 20 mL of methanol was added all at once to a cold (5°) solution of 1,2-dimethoxycyclobutene-3,4-dione (1.27 g; 8.94 mmoles) in 20 mL of methanol. After 3.5 hours at ambient temperature, the solution was cooled to 5° and excess anhydrous ammonia was bubbled into the solution for 5 minutes. The mixture was stirred for 18 hours at ambient temperature and then filtered to give 2.66 g of product. Recrystallization from 95% aqueous ethanol yielded the title compound, mp 240-243° (dec.).

Anal. Calc'd. for $C_{14}H_{19}N_3O_2S_2$: C, 51.67; H, 5.88; N, 12.91; S, 19.70.

Found: C, 51.60; H, 5.76; N, 12.97; S, 19.69.

Example 3

2-{2-[(5-Dimethylaminomethyl-2-thienyl)methylthio]ethylamino}-1-methylaminocyclobutene-3,4-dione

A solution of 2-[(5-dimethylaminomethyl-2-thienyl)-methylthio]ethylamine (1.32 g; 5.73 mmoles) in 20 mL of methanol was added to a cold (5°) solution of 1,2-dimethoxycyclobutene-3,4-dione (814 mg; 5.73 mmoles) in 15 mL of methanol. After 3.5 hours at ambient temperature, the solution was cooled to 5° and excess anhydrous methylamine was bubbled into the

solution for 5 minutes. The mixture was stirred for 70 hours at ambient temperature and then filtered to give 1.38 g of product. Recrystallization from ethanol yielded the title compound, m.p. 185-187°.

Anal. Calc'd for $C_{15}H_{21}N_3O_2S_2$: C, 53.07; H, 6.23; N, 12.38;
S, 18.89

Found: C, 53.18; H, 6.21; N, 12.25;
S, 18.94

Example 4

1-Methylamino-2-[3-(3-piperidinomethylphenoxy)propylamino]cyclo-
butene-3,4-dione

A solution of 3-(3-piperidinomethylphenoxy)propylamine (from the dihydrochloride, 3.21 g; 10.0 mmols) in 40 mL of methanol was added to a solution of 1,2-dimethoxycyclobutene-3,4-dione (1.42 g; 10.0 mmols) in 40 mL of methanol. After 1 hour at 10° and 30 minutes at ambient temperature, the solution was cooled to 5° and excess anhydrous methylamine was bubbled into the solution for 5 minutes. The mixture was stirred for 17 hours at ambient temperature and then filtered to give 2.77 g of product.

The product (2.77 g) was suspended in 40 mL of ethanol and 4.07 mL (8.1 mmols) of aqueous 2N HCl was added with stirring to yield the hydrochloride salt of the title compound,

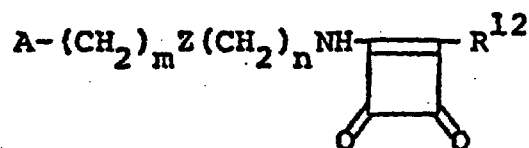
m.p. 194-198°.

Anal. Calc'd for $C_{20}H_{27}N_3O_3 \cdot HCl$: C, 60.99; H, 7.16; N, 10.67
Found (corr. for 1.35% H_2O): C, 60.63; H, 6.96; N, 10.71



CLAIMS

1. A compound of the formula



III

wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and alkoxy;

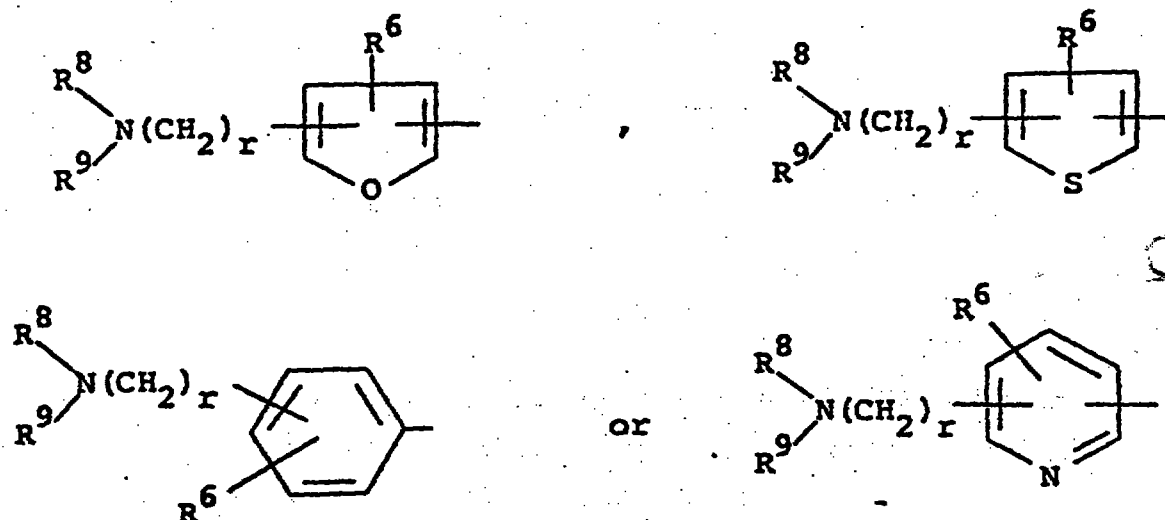
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m is an integer of from 0 to 2 inclusive;

n is an integer of from 2 to 5 inclusive;

Z is sulfur, oxygen or methylene; and

A is

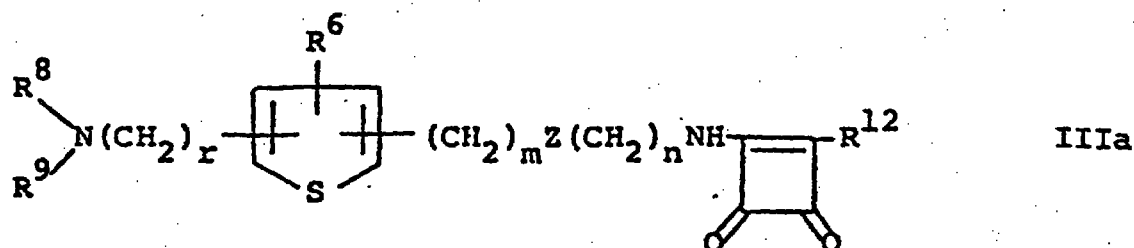


in which R^6 is (lower)alkyl, (lower)alkoxy or halogen, provided that, in the second, third or fourth of the four values of A specified above, R^6 may alternatively be hydrogen;

r is an integer of from 1 to 4 inclusive; and

R^8 and R^9 each are independently hydrogen, (lower)-alkyl, allyl, propargyl, (lower)alkoxy(lower)alkyl in which the (lower)alkoxy moiety is at least two carbon atoms removed from the nitrogen atom, cyclo(lower)alkyl, or phenyl(lower)alkyl, provided that R^8 and R^9 may not both be cyclo(lower)alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, dimethylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, dimethylpiperidino, hydroxypiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, 3-pyrrolino, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

2. A compound of Claim 1 having the formula





(32)

wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2 inclusive;

n is an integer of from 2 to 5 inclusive;

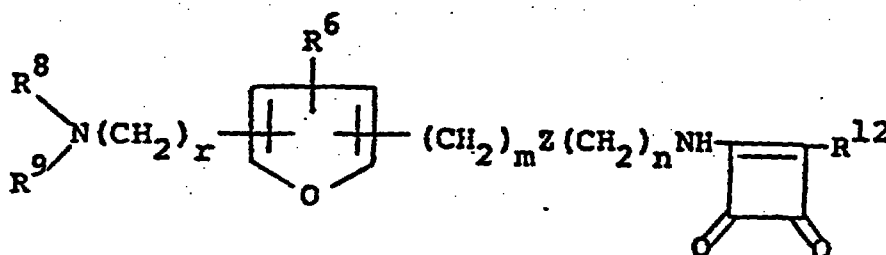
Z is sulfur, oxygen or methylene;

R^6 is hydrogen or (lower)alkyl;

r is an integer of from 1 to 4 inclusive; and

R^8 and R^9 each are independently hydrogen or (lower)-alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

3. A compound of Claim 1 having the formula



IIIb

wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2 inclusive;

n is an integer of from 2 to 5 inclusive;

Z is sulfur, oxygen or methylene;

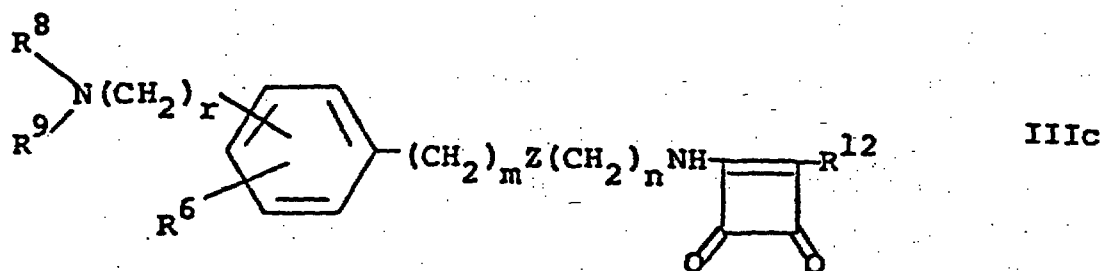
R^6 is (lower)alkyl;

r is an integer of from 1 to 4 inclusive; and

R^8 and R^9 each are independently hydrogen or (lower)-alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.



4. A compound of Claim 1 having the formula



wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2 inclusive;

n is an integer of from 2 to 5 inclusive;

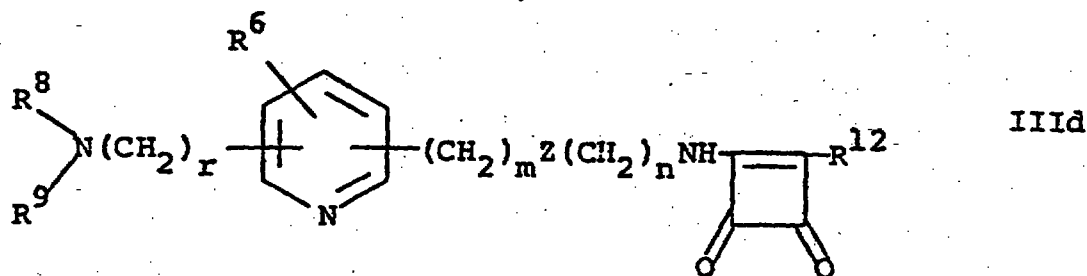
Z is sulfur, oxygen or methylene;

R^6 is hydrogen or (lower)alkyl;

r is an integer of from 1 to 4 inclusive; and

R^8 and R^9 each are independently hydrogen or (lower)-alkyl, or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]-nonane.

5. A compound of Claim 1 having the formula



wherein R^{12} is a conventional leaving group selected from halogen, phenoxy, substituted phenoxy and (lower)alkoxy;

m is an integer of from 0 to 2 inclusive;

n is an integer of from 2 to 5 inclusive;

Z is sulfur, oxygen or methylene;

R^6 is hydrogen or (lower)alkyl;



r is an integer of from 1 to 4 inclusive; and R^8 and R^9 each are independently hydrogen or (lower)-alkyl; or R^8 and R^9 , taken together with the nitrogen atom to which they are attached, may be pyrrolidino, methylpyrrolidino, morpholino, thiomorpholino, piperidino, methylpiperidino, N-methylpiperazino, 1,2,3,6-tetrahydropyridyl, homopiperidino, heptamethyleneimino, octamethyleneimino or 3-azabicyclo[3.2.2]nonane.

6. 1-Methoxy-2-[3-(3-piperidinomethylphenoxy)propylamino]-cyclobutene-3,4-dione.
7. 1-Methoxy-2-{2-[(5-dimethylaminomethyl-3-thienyl)-methylthio]ethylamino}cyclobutene-3,4-dione.
8. 1-Methoxy-2-{2-[(5-piperidinomethyl-3-thienyl)methylthio]ethylamino}cyclobutene-3,4-dione.
9. 1-Methoxy-2-[3-(3-dimethylaminomethylphenoxy)propylamino]-cyclobutene-3,4-dione.
10. 1-Methoxy-2-[3-(3-pyrrolidinomethylphenoxy)propylamino]-cyclobutene-3,4-dione.
11. 1-Methoxy-2-{3-[3-(3-methylpyrrolidino)methylphenoxy]-propylamino}cyclobutene-3,4-dione.
12. 1-Methoxy-2-[3-(3-hexamethyleneiminomethylphenoxy)-propylamino]cyclobutene-3,4-dione.
13. 1-Methoxy-2-[3-(3-piperidinomethylthiophenoxy)propylamino]cyclobutene-3,4-dione.
14. 1-Methoxy-2-[3-(3-heptamethyleneiminomethylphenoxy)-propylamino]cyclobutene-3,4-dione.



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15. 1-Methoxy-2-[3-(3-octamethyleneiminomethylphenoxy)-
propylamino] cyclobutene-3,4-dione.
