

CYCLOBUTENE COMPOUND

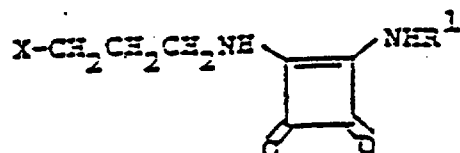
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BACKGROUND

The present invention provides novel compounds useful as intermediates in the preparation of certain histamine H₂-antagonists which are useful in the treatment of peptic ulcers and other conditions caused or exacerbated by gastric acidity.

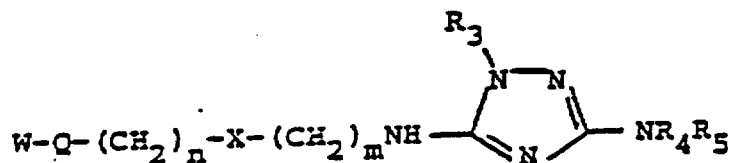
Our colleagues A.A. Algieri and R.R. Crenshaw disclose histamine H₂-receptor antagonists in U.S. Patents 4,390,701 issued June 28, 1983, 4,395,553 issued July 26, 1983, 4,552,943 issued June 11, 1985 and 4,526,973 issued July 2, 1985 which are substantially the same as those mentioned above.

United States Patent 4,521,625 issued June 4, 1985 to T.H. Brown and R.C. Young discloses compounds of the formula



wherein R¹ is hydrogen or a C₁₋₆ alkyl group and X is hydroxy or a group displaceable by hydroxy or the equivalent thereof which are used in a process for the preparation of compounds which are substantially the same as those described in the above-mentioned U.S. patents.

United Kingdom Patent Application GB 2,023,133 published December 28, 1979 discloses inter alia intermediates of the formula.



in which W represents the group -CHO or -(CH₂)_pCONR₁R₂ and Q, n, X, m, R₃, R₄, R₅, R₁ and R₂ correspond to a large number of substituents.

The novel compounds provided in the present invention are useful in an improved process for the preparation of histamine H₂-antagonists.

SUMMARY OF THE INVENTION

A novel compound ~~of the formula~~ 1-Amino-2-butoxy-1-cyclobutene-3, 4-dione is disclosed as well as a process
5 for preparing this compound including a one pot process for such preparation.

The compound is useful as an intermediate in the preparation of certain histamine H₂-antagonists which are used in the treatment of peptic ulcers or other conditions
10 caused or exacerbated by gastric acidity.

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DESCRIPTION OF THE INVENTION

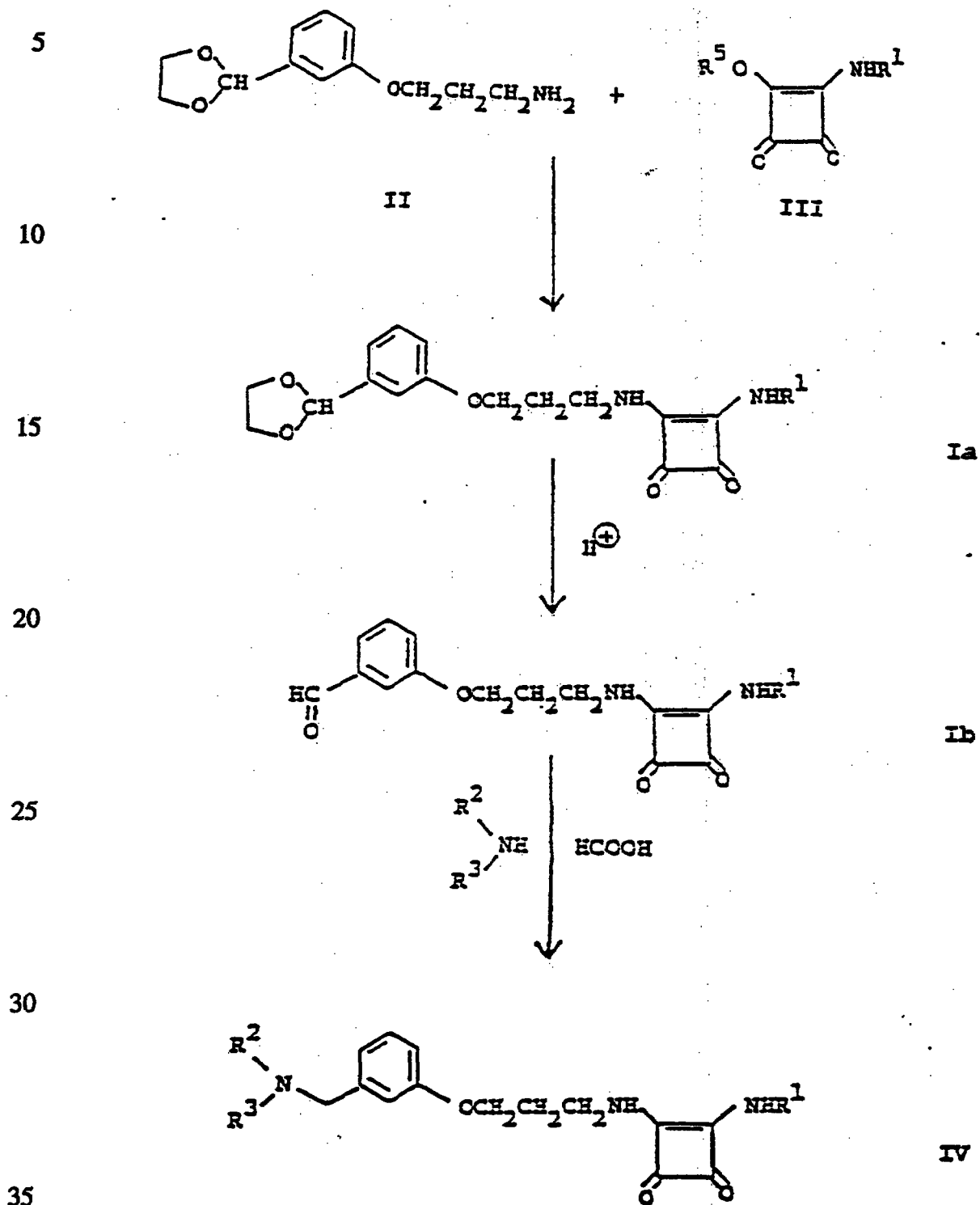
The present invention which is a divisional application of U.K. Patent Application No. 8811456.6 relates to ^anovel compounds which ^{is}are useful in the preparation of certain histamine H₂-antagonists which are described herein. Accordingly, the present invention provides ^{the}compounds of ~~the formula~~ 1-Amino-2-butoxy-1-cyclobutene-3, 4-dione.

10 In the present invention, as used herein and in the claims, the term "lower alkyl" means straight or branched chain alkyl containing from 1 to 6 carbon atoms. Preferably they contain from 1 to 4 atoms and, most; preferably, they contain 1 to 2 carbon atoms. Unless
15 otherwise specified in the particular instance, the terms "butyl" and "butoxy" as used herein and in the claims is intended to mean n-butyl and n-butoxy and other C₄ alkyl and alkyloxy groups.

The compounds of formula IV may be prepared from the
20 compound of formula II by reaction with a compound of formula III. The acetal of formula Ia thereby produced is hydrolyzed to an aldehyde of formula Ib followed by reaction with a secondary amine in the presence of formic acid to produce the desired histamine H₂-antagonist of the
25 formula IV as illustrated in Scheme 1.

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Scheme 1



The compound of formula II may be prepared by the procedures described in United Kingdom Patent Application GB 2,023,133 published December 28, 1979.

the compounds of formula III may be prepared by the
5 reaction of ammonia or a primary lower alkyl amine with a 1,2-dialkoxy-1-cyclobutene-3,4-dione which is itself prepared from squaric acid according to the general procedures described by G. Maahs, Justus Liebigs Ann. Chem. 686, 55 (1965) and A. H. Schmidt, Synthesis, 869 (1978).
10 The compounds of formula III may be prepared in a two-step process from squaric acid, however, in another aspect of the present invention, we have found that the novel compound of formula III wherein R^1 is hydrogen and R^5 is butyl may be prepared in a stepwise manner in a "one pot"
15 reaction. Furthermore, we have found that the preferred 1-amino-2-butoxy-1-cyclobutene-3,4-dione as described herein may readily be prepared in high yield and purity on a manufacturing scale in a "one pot" reaction from squaric acid which is especially useful for the preparation of the
20 compounds of the present invention and certain histamine H_2 -antagonists thereof.

In reaction Scheme 1, R^1 is hydrogen or lower alkyl and, preferably, hydrogen. Preferably R^5 is cyclohexyl or lower alkyl for example, methyl, ethyl, propyl, isopropyl,
25 butyl, sec-butyl, tertiary-butyl, neopentyl, pentyl and the like. Most preferably, R^5 is butyl, sec-butyl or neopentyl. For the compounds of formula IV or a non-toxic pharmaceutically acceptable salt thereof, R^2 and R^3 are lower alkyl, or R^2 and R^3 , taken together with the nitrogen
30 to which they are attached, may be pyrrolidino, methylpyrrolidino, piperidino, methylpiperidino, homopiperidino,

heptamethyleneimino or octamethyleneimino. Most preferably, R^2 and R^3 are joined together with the nitrogen atom to form a piperidino group.

5 The compounds of formula Ia may be prepared by the reaction of the compound of formula II with a compound of formula III in a non-reactive solvent such as methanol, ethanol, acetonitrile, tetrahydrofuran and the like at a temperature from about 0°C to the reflux temperature of the solvent. For convenience, we prefer to conduct the reaction at about ambient temperature. The aldehydes of the formula Ib may be prepared by acid hydrolysis of the acetals of formula Ia. The
10 hydrolysis reaction may be conducted in a non-reactive solvent such as methanol, ethanol, tetrahydrofuran and aqueous mixtures thereof in the presence of an organic or inorganic acid for example, hydrochloric acid, sulfuric acid, formic acid and p-toluenesulfonic acid.

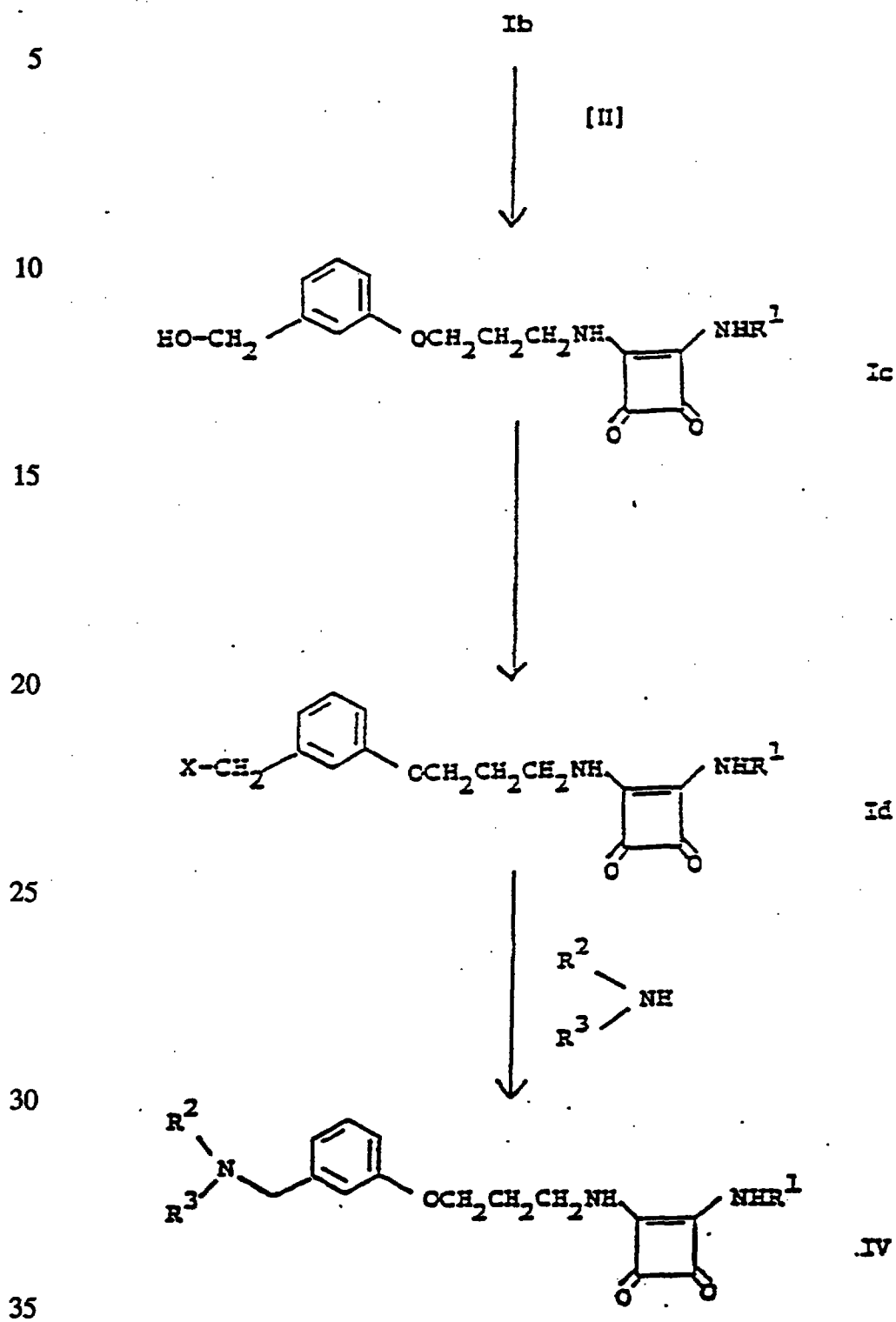
15 The histamine H_2 -antagonist compounds of formula IV may then be prepared by the reaction of a compound of formula Ib with a secondary amine of the formula R^2R^3NH in the presence of at least one equivalent of formic acid as reducing agent. The reductive amination may be conducted in an excess of formic acid wherein the formic acid is also used as solvent. Preferably the reaction is conducted in a non-
20 reactive solvent such as benzene, toluene, xylene and n-propanol with at least one equivalent of formic acid and, preferably, two to three equivalents. It is also preferred to azeotropically remove the water which is thereby produced at about the reflux temperature of the solvent employed.

25 The compounds of formula IV may also be prepared from the compounds of formula Ib as illustrated in Scheme 2.

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Scheme 2



In reaction Scheme 2, a compound of formula Ib is reduced to an alcohol of formula Ic which is then converted by conventional techniques to a compound of formula Id. The conventional leaving group is then displaced by an amine of the formula R^2R^3NH to produce the desired histamine H_2 -antagonist of the formula IV wherein R^1 , R^2 and R^3 are as previously defined.

The compounds of formula Ic may be prepared from the aldehydes of formula Ib by catalytic hydrogenation or reducing metal hydrides according to methods well-known in the art. The conversion of the hydroxy radical in formula Ic to a conventional leaving group may be carried out with suitable halogenating agents or sulfonating agents. Suitable halogenating agents such as thionyl chloride and thionyl bromide may be employed neat or in a non-reactive solvent and, preferably, in the presence of a base such as a tertiary amine (e.g., triethylamine, pyridine and lutidine) or inorganic base (e.g., sodium carbonate and potassium carbonate) at a temperature of $0^\circ C$ to about the reflux temperature of the solvent. Suitable sulfonating agents such as methanesulfonyl chloride, benzenesulfonyl chloride, p-toluenesulfonyl chloride, p-bromobenzenesulfonyl chloride and p-nitrobenzenesulfonyl chloride may be employed in a non-reactive solvent, for example, dichloromethane, acetonitrile, tetrahydrofuran, and dimethylformamide and, preferably, in the presence of a tertiary amine or inorganic base to remove the acid which is produced.

The compounds of formula IV may then be prepared by the reaction of a compound of formula Id with the appropriate amine of formula R^2R^3NH in a non-reactive solvent and preferably in the presence of a base to remove the acid which is thereby produced.

DESCRIPTION OF SPECIFIC EMBODIMENTS

In the following examples, all temperatures are given in degrees Centigrade and melting points and boiling points are uncorrected. All evaporations of solvents were performed under reduced pressure. As used herein, the term Skellysolve B is a petroleum solvent fraction having a bp range of 60-68°C consisting essentially of n-hexane.

Example 1

1-Amino-2-butoxy-1-cyclobutene-3,4-dione

Preparation A: A solution of 1,2-dibutoxy-1-cyclobutene-3,4-dione (6.09, 0.027 mole) in 40 mL of tetrahydrofuran was cooled to 5°C in an ice-water bath and treated dropwise over a period of 9 minutes with a solution of 1.8 mL of concentrated ammonium hydroxide in a mixture of 8 mL of tetrahydrofuran and 1 mL of methanol. After stirring at 5°C for 30 minutes and at ambient temperature for 90 minutes the mixture was concentrated under reduced pressure to a slurry. A small amount of Skellysolve B was added and the product was collected by filtration after 16 hours of standing at 0°C to give 3.26 g of the title compound. A sample (8.54 g) was partly dissolved in acetone, filtered and cooled to give 4.51 g of purified title compound; mp=165.5-168°C (clear melt).

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.79; H, 6.56; N, 8.28

Found: C, 56.46; H, 6.19; N, 8.56.

Preparation B: A solution of 1,2-dibutoxy-1-cyclobutene-3,4-dione (30.0 g, 0.123 mole, 92.5 area % pure by glc assay) in 300 mL of tetrahydrofuran was cooled to 5°C and treated dropwise, over 30 minutes, with a solution of concentrated NH₄OH (8.18 mL, 0.123 mole) in a mixture of 40 mL of tetrahydrofuran and 5 mL of methanol. The resultant solution was stirred in the ice-water bath for 30 minutes followed by 5.5 hours at ambient temperature.

The hazy solution was filtered through diatomaceous earth to remove a small amount of bright yellow solid and the filtrate was concentrated under reduced pressure to near dryness. The solid residue was rubbed under a small amount of Skellysolve B and diethyl ether and cooled at 0°C. The mixture was filtered and dried to give 17.9 g (86%) of the title compound as white solid; mp=165-167.5°C (clear melt).

Preparation C: In a 5-Liter flask equipped with stirrer and nitrogen inlet/outlet tubes was placed 1,2-dihydroxy-1-cyclobutene-3,4-dione (400.0 g, 3.506 moles), 1-butanol (1.2 L) and toluene (800 mL). The mixture was stirred and heated under reflux with a Dean-Stark water trap until water stopped passing over (136 mL water collected, about 5.5 hours). The clear reaction mixture was heated under reflux for a further one hour, then cooled under nitrogen to 0-5°C. The cooled stirred solution was treated dropwise at such a rate that the reaction remains at or below 10°C (2.5 hours required) with a solution containing 14 M ammonium hydroxide (240 mL, 3.37 moles), 1-butanol (960 mL) and methanol (40 mL). Stirring was continued at ambient temperature for 2 hours, then the mixture was cooled to 0-5°C for 1.5 hours and filtered. The product was washed with toluene (800 mL) and dried to give 492.4 g (88.0%) of the title compound; mp=165-168°C.

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CLAIMS

1. The compound 1-Amino-2 butoxy-1-cyclobutene-3, 4-dione.

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2. A process for preparing the compound of claim 1 comprising the steps of reacting squaric acid with butanol, and then the resulting product with one equivalent of ammonia.

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3. The process of claim 2 which is a one pot process.

as claimed in claim 1

4. The compound substantially as hereinbefore described with particular reference to the Example.

as claimed in claim 2

5. A process substantially as hereinbefore described with particular reference to the Example.
