

PATENT SPECIFICATION

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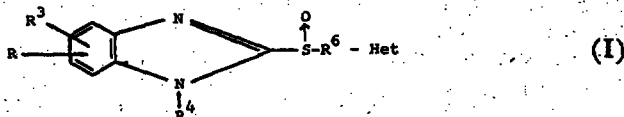
(54) 2-[HETEROCYCLIC SUBSTITUTED ALKYL-SULPHINYL]- BENZIMIDAZOLES AND THEIR PHARMACEUTICAL COMPOSITIONS

(71) We, AB HASSLE, a Swedish Body Corporate of Fack, S-431 20
 Molndal 1, Sweden, do hereby declare the invention, for which we pray that a patent
 may be granted to us, and the method by which it is to be performed, to be particularly
 described in and by the following statement:—

The present invention relates to new compounds having valuable properties in
 affecting gastric acid secretion in mammals, as well as processes for their preparation,
 method of affecting gastric acid secretion and pharmaceutical preparations containing
 said novel compounds.

The compounds of the present invention affect gastric acid secretion, and inhibit
 exogenously or endogenously stimulated gastric acid secretion. These compounds can
 be used in the treatment of peptic ulcer disease.

The compounds of the present invention are those of the general formula I



or a therapeutically acceptable salt thereof in which R and R³, which are the same
 or different, each is hydrogen, alkyl, halogen, cyano, carboxy, carboxyalkyl, carbo-
 alkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl,
 trifluoromethyl or acyl derived from a carboxylic acid, R⁴ is hydrogen, alkyl, acyl
 derived from carboxylic acid, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkyl-
 carbamoyl, alkylcarbonylmethyl, alkoxy carbonylmethyl or alkylsulfonyl, R⁶ is a
 straight or branched alkylene group having 1 to 4 carbon atoms, and only one carbon
 atom in the chain linking S and Het and Het is 2-quinolyl, or 2-pyridyl, the Het
 groups being unsubstituted or substituted by a C₁ to C₄ alkyl group or halogen.

Alkyl groups R and R³ are preferably those having up to 7 carbon atoms,
 particularly up to 4 carbon atoms. Thus, alkyl groups R and R³ can be methyl, ethyl,
 n-propyl, isopropyl, n-butyl, or isobutyl.

Halo groups R and R³ are fluoro, iodo, bromo, and chloro, preferably bromo and
 chloro.

Carboxy groups R and R³ are the group HOOC—.

Carboxyalkyl groups R and R³ are the group HOOC-alkyl- wherein the alkyl group preferably has up to 4 carbon atoms, particularly up to 2 carbon atoms, e.g. carboxymethyl and carboxyethyl.

Carboalkoxy groups R and R³ are the group alkyl—O—OC—, wherein the alkyl group preferably has up to 4 carbon atoms, particularly up to 2 carbon atoms, e.g. carbomethoxy (CH₃OOC—), carboethoxy (C₂H₅OOC—).

Carboalkoxyalkyl groups R and R³ are the group alkyl-OOC-alkyl¹-, wherein the alkyl group preferably has up to 4 carbon atoms, particularly up to 2 carbon atoms, and alkyl¹ group preferably has up to 4 carbon atoms, particularly up to 2 carbon atoms, e.g. carbomethoxymethyl (CH₃OOCCH₂—), carbomethoxyethyl (CH₃OOCCH₂CH₂—), carboethoxymethyl (C₂H₅OOCCH₂—) and carboethoxyethyl (C₂H₅OOCCH₂CH₂—).

Carbamoyl groups R and R³ are the group H₂NCO.

Carbamoylalkyl groups R and R³ are the groups H₂NCO alkyl, wherein the alkyl group preferably has up to 4 carbon atoms, particularly up to 2 carbon atoms, e.g. carbamoylmethyl (H₂NCOCH₂—), or carbamoylethyl (H₂NCOCH₂CH₂—).

Alkoxy groups R and R³ are preferably those having up to 5 carbon atoms, particularly up to 3 carbon atoms e.g. methoxy, ethoxy, n-propoxy, or isopropoxy.

Hydroxyalkyl groups R and R³ preferably have up to 7 carbon atoms, particularly up to 4 carbon atoms and may be straight or branched, e.g. hydroxymethyl, 1-hydroxy-propyl-2, 1-hydroxy-ethyl-2, or 1-hydroxy-2-methyl-propyl-2.

Carboxylic acid acyl R and R³ preferably have up to 4 carbon atoms, e.g. formyl, acetyl, or propionyl.

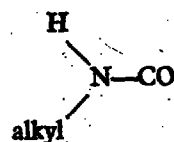
Alkyl group R⁴ may be straight or branched preferably having up to 5 carbon atoms particularly up to 3 carbon atoms, e.g. methyl, ethyl, or n-propyl.

Carboxylic acid acyl R⁴ preferably has up to 4 carbon atoms, e.g. formyl, acetyl or propionyl.

Carboalkoxy group R⁴ is the group alkyl—O—OC—, wherein the alkyl group preferably has up to 4 carbon atoms, particularly up to 2 carbon atoms, e.g. carbomethoxy (CH₃OOC—) or carboethoxy (C₂H₅OOC—).

Carbamoyl group R⁴ is the group H₂NCO—.

Alkylcarbamoyl group R⁴ is the group



wherein the alkyl group may be straight or branched and preferably has up to 4 carbon atoms, e.g. methylcarbamoyl, ethylcarbamoyl or isopropylcarbamoyl.

Dialkylcarbamoyl group R⁴ is the group (alkyl)₂NCO wherein each alkyl group preferably has up to 4 carbon atoms, e.g. dimethylcarbamoyl, diethylcarbamoyl or N-methyl-N-ethyl-carbamoyl.

Alkylcarbonylmethyl group R⁴ is the group alkyl—CO—CH₂—, wherein the alkyl group preferably has up to 4 carbon atoms, e.g. acetylmethyl, propionylmethyl.

Alkoxycarbonylmethyl group R⁴ is the group alkyl—O—CO—CH₂—, wherein the alkyl group preferably has up to 4 carbon atoms, e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl or propoxycarbonylmethyl.

Alkylsulphonyl group R⁴ is the group alkyl—SO₂— wherein the alkyl group preferably has up to 4 carbon atoms e.g. methylsulphonyl, ethylsulphonyl or isopropylsulphonyl.

Alkylene group R⁶ is a CH₂ or straight or branched alkylidene group having up to 4 carbon atoms e.g. ethylidene (CH₃CH), propylidene (C₂H₅CH), isobutylidene ((CH₃)₂CHCH) or isopropylidene ((CH₃)₂CH).

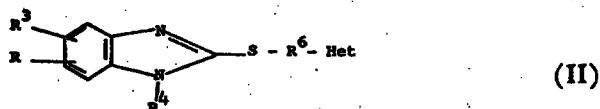
The heterocyclic group Het, may be further substituted by C₁—C₄ alkyl or halogeno, preferably in the 3 and/or 5 positions. Such alkyl groups are preferably methyl, ethyl, or propyl and the halogeno groups are preferably chloro or bromo.

In the compounds of the invention it is preferable that R is hydrogen, hydroxy, cyano, methyl, ethyl, n-propyl, isopropyl, t-butyl, trifluoromethyl, methoxy, acetyl, carboxy, or carbethoxy, R³ is hydrogen, methyl or chloro, R⁴ is hydrogen methyl, acetyl, carbomethoxy, carbamoyl, methylcarbamoyl, methylcarbonylmethyl, ethoxycarbonylmethyl or methylsulfonyl and R⁶ is CH₂. It is particularly preferred that R

and R^3 are hydrogen, methyl, ethyl, trifluoromethyl, cyano or chloro, R^4 is hydrogen, and Het is 2-pyridyl.

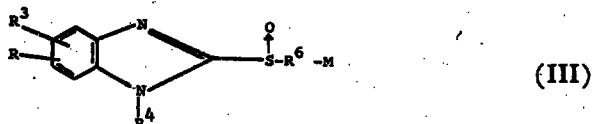
Compounds of formula I above may be prepared according to the following methods:

a) oxidizing a compound of formula II



wherein R, R^3 , R^4 , R^6 and Het have the meanings given above to form a compound of formula I.

b) reacting a compound of formula III

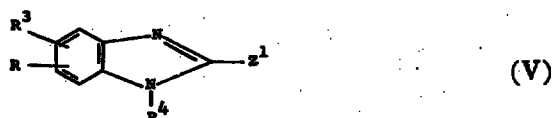


wherein R, R^3 , R^4 , R^6 have the meanings given above and M is K, Na, or Li, with a compound of formula IV



wherein Het has the same meaning as given above, Z is a reactive esterified hydroxy group to form a compound of formula I;

c) reacting a compound of the formula V



with a compound of the formula VI



wherein R, R^3 , R^4 , R^6 and Het have the meanings given above and one of Z^1 and Z^2 is SH and the other Z^1 and Z^2 is a reactive esterified hydroxy group to form an intermediate of formula II above, which is then oxidized to give a compound of formula I;

d) reacting a compound of the formula VII

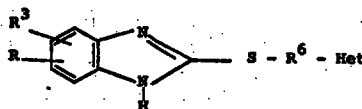


wherein R, and R^3 have the same meanings as given above with a compound of the formula VIII



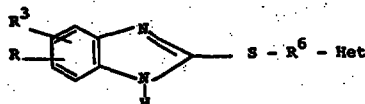
wherein Het and R^6 have the same meaning as given above, to form an intermediate of formula II above, which then is oxidized to give a compound of formula I,

e) reacting a compound of the formula



wherein R, R³, R⁴ and Het have the meanings given above with a compound Z—R⁷, wherein R⁷ is alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxy carbonylmethyl, and alkylsulphonyl, to give a compound of formula II wherein R⁴ has the meaning given for R⁷, which compound is further oxidized to give a compound of formula I.

f) reacting a compound of the formula



wherein R, R³, R⁴, and Het have the meanings given above with an alkylisocyanate to give a compound of formula II wherein R⁴ is alkylcarbamoyl, which compound is further oxidized to give a compound of formula I

The reactions e) and f) normally take place in a solvent such as acetonitrile.

In the reactions above Z, Z¹, and Z² may be a reactive, esterified hydroxy group which is a hydroxy group esterified with strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, also sulfuric acid or a strong organic sulfonic acid as a strong aromatic acid, e.g. benzenesulfonic acid, 4-bromo-benzenesulfonic acid or 4-toluenesulfonic acid.

The oxidation of the sulfur atom in the chains above to sulfinyl (S→O) is carried out using an oxidizing agent such as nitric acid, hydrogen peroxide, a peracid, a perester, ozone, dinitrogen tetroxide, iodosobenzene, N-halosuccinimide, 1-chloro-benzotriazole, t-butylhypochlorite, diazobicyclo-[2,2,2] octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate, or sulfur chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

Depending on the process conditions and the starting materials, the end product is obtained either as the free base or in the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or mixed salts may be obtained as well as hemiamino, sesqui- or polyhydrates. The acid addition salts of the new compounds may be transformed into free base in a manner known *per se* using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may be converted into salts with organic or inorganic acids. In the preparation of acid addition salts preferably acids are used which form therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic or heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, *p*-aminobenzoic, anthranilic, *p*-hydroxybenzoic, salicylic or *p*-aminosalicylic acid, embonic, methane-sulfonic, ethanesulfonic, hydroxyethane-sulfonic, ethylene-sulfonic, halogenbenzene-sulfonic, toluenesulfonic, naphthylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, e.g. picrates, may serve as purifying agents for the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from the salt in a purer state. In this specification and claims, references to the free base form includes references to the corresponding salts unless the context requires otherwise.

Some of the new compounds may, depending on the choice of starting materials and process, be prepared as optical isomers or racemates, or if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

The isomer mixtures (racemate mixtures) obtained may be separated into two stereoisomeric (diastereomeric) pure racemates by chromatography or fractional crystallization.

The racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active solvent, use of micro organisms, reactions with optically active acids forming salts which can be separated, separation based on different solubilities of the diastereomers. Suitable optically active acids are the L- and D-forms of tartaric acid, di-*o*-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid. Preferably, the more active part of the two antipodes is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known *per se*.

In clinical use, the compounds of the invention can be administered orally, rectally or by injection, in the form of a pharmaceutical preparation which contains an active component either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, such as hydrochloride, lactate, acetate, sulfamate, in combination with a pharmaceutically acceptable carrier or diluent. The carrier or diluent may be in the form of a solid, semi-solid or liquid, or a capsule. Usually, the amount of active compound is between 0.1 to 95% by weight of the preparation, preferably 0.5 to 20% by weight in preparations for injection and 2 to 50% by weight in preparations for oral administration.

In the formulation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration, the compound selected may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an anti-friction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide or with a lacquer dissolved in a volatile organic solvent or mixture of solvents. To this coating, various dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared which contain a mixture of the active compound or compounds of the invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharin and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as an aqueous solution of a water soluble pharmaceutically acceptable salt of the active compound, preferably in a concentration of 0.5% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured as different dosage unit ampoules.

Pharmaceutical tablets for oral use are prepared in the following manner: The solid substances are ground or sieved to a selected particle size, and the binding agent is homogenized and suspended in a suitable solvent. The therapeutically active compounds and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of approximately 1 mm. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, anti-friction and anti-adhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and its ability to dissolve in water. The compression pressure used should be in the range 0.5 to 5 tons. Tablets are manufactured at the rate of 20,000 to 200,000 per hour. The tablets, especially those which are rough or bitter may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices. The different types of packages consist of glass or plastic gallipots, boxes, tubes and specific dosage adapted packages.

The typical daily dose of the active substance varies according to the individuals needs and the manner of administration. In general, oral dosages range from 100 to 400 mg/day of active substance and intravenous dosages range from 5 to 20 mg/day. The following Examples are given to illustrate the invention. Temperatures are given in degrees Centigrade.

The starting materials in the Examples below were prepared in accordance with

(15)

the following methods: (1) a 1,2-diamino compound, such as *o*-phenylenediamine was reacted with potassium ethylxanthate (according to Org. Synth. Vol. 30 p. 56) to form a 2-mercaptobenzimidazole; (2) the compound 2-chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. Vol. 26, pp. 448—451 (1956)); (3) the compound 2-chloromethylbenzimidazole was prepared by condensing *o*-phenylenediamine with chloroacetic acid.

Example 1.

28.9 g of 2-[2-pyridylmethylthio]-benzimidazole were dissolved in 160 ml of CHCl_3 . 24.4 g of *m*-chloroperbenzoic acid were added in portions while stirring and cooling to 5°C. After 10 minutes, the precipitated *m*-chlorobenzoic acid was filtered. The filtrate was diluted with CH_2Cl_2 , washed with a Na_2CO_3 solution, dried over Na_2SO_4 and evaporated *in vacuo*. The residue crystallized when diluted with CH_3CN , and 2-[2-pyridylmethylsulfinyl]-benzimidazole was recrystallized from CH_3CN . Yield 22.3 g; m.p. 150—154°C.

Examples 2—28.

The preparation of compounds of formula I labelled 2—30 was carried out in accordance with Example 1 above. The compounds prepared are listed in Table 1 which identifies the substituents for these compounds.

Example 29 (method c).

0.1 moles of 4-methyl-2-mercaptobenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloro-methylpyridine hydrochloride were added and the mixture was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated *in vacuo*. The residue was dissolved in acetone and was treated with active carbon. An equivalent amount of concentrated hydrochloric acid was added, whereupon the mono-hydrochloride of 2-[2-pyridylmethylthio]-(4-methyl)-benzimidazole was isolated. Yield 0.05 moles; melting point 137°C.

This compound was then oxidized in accordance with Example 1 above.

Example 30 (method b).

0.1 mole Li-methylsulfinylbenzimidazole were dissolved in 150 mls of benzene, 0.1 mole 2-chloropyridine was added and the mixture was refluxed for two hours. The lithium chloride formed was filtered off, and the solution was evaporated *in vacuo*. The residue was crystallized from CH_3CN , and recrystallized from the same solvent. Yield 0.82 moles of 2-[2-pyridylmethylsulfinyl]-benzimidazole melting at 151—154°C.

Example 31 (method d).

18.3 g of 2-[(2-pyridine)methylthio] formic acid and 10.8 g of *o*-phenylenediamine were boiled for 40 minutes in 100 ml of 4N HCl. The mixture was cooled and neutralized with ammonia. The neutral solution was then extracted with ethyl acetate. The organic phase was treated with active carbon and evaporated *in vacuo*. The residue was dissolved in acetone, whereupon an equivalent of concentrated HCl was added. The precipitated hydrochloride was filtered off after cooling and the salt was recrystallized from absolute ethanol and some ether. Yield of 2-[2-(pyridyl)-methylthio]-benzimidazole hydrochloride was 4.3 g.

The compound was then oxidized in accordance with Example 1 above.

Example 32 (method e).

13.5 g (0.05 moles) of 2-[2-pyridylmethylthio]-benzimidazole hydrochloride, 3.9 g (0.05 moles) of acetylchloride, and 10.1 g (0.1 moles) of triethylamine were dissolved in 100 ml of acetonitrile. The mixture was heated in a 40°C. waterbath for 30 minutes. After cooling, the crystals formed were filtered off and were suspended in water in order to dissolve the triethylamine hydrochloride. The residue, 2-[2-pyridylmethylthio]-N-acetylbenzimidazole was filtered off. Yield 7.2 g (51%); m.p. 119—24°C. as base.

This compound was then oxidized in accordance with Example 1 above.

Example 33.

2-[2-pyridylmethylthio]-N-methoxycarbonylbenzimidazole was prepared in accordance with Example 34 above. Mp. 78°C.

This compound was then oxidized in accordance with Example 1 above Mp. 135°C.

Example 34 (method c).

16.2 g of 2-mercaptobenzimidazole and 16.4 g of chloromethylpyridine hydrochloride were dissolved in 200 ml of 95% ethanol. 8 g of sodium hydroxide in 20 ml of water were added, whereupon the solution was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated *in vacuo*. The residue, 2-[2-pyridylmethylthio]benzimidazole, was recrystallized from 70% ethanol. Yield 9 g.

This compound was then oxidized in accordance with Example 1 above.

Example 35.

2-[2-pyridylmethylsulfinyl]-(N-carbamoyl)-benzimidazole was prepared by reaction of 2-[2-pyridylmethylthio]-benzimidazole and carbamoylchloride followed by oxidation of the thio-compound obtained in accordance with Example 1. Mp. 164°C.

Example 36 (method f).

4.82 g (0.02 moles) of 2-[2-pyridylmethylthio]-benzimidazole and 1.5 g of methylisocyanate were refluxed in 150 mls of toluene for 2 hrs. The mixture was cooled, the precipitate formed filtered off and recrystallized from toluene. Yield of 2-[2-pyridylmethylthio]-(N-methylcarbamoyl)-benzimidazole was 4.5 g. Mp. 135°C. The thio-compound was oxidized to the corresponding sulphinyl-compound in accordance with Example 1 above. Mp. of 2-[2-pyridylmethylsulfinyl]-(N-methylcarbamoyl)-benzimidazole was 140°C.

Example 37.

12.0 g (0.05 moles) of 2-[2-pyridylmethylthio]-benzimidazole, 8.0 g (0.058 moles) of K_2CO_3 and 5.5 g (0.059 moles) of 1-chloro-2-propanone were refluxed in 200 mls of acetonitrile for 2 hrs. The solution was then filtered and evaporated. The residue, 2-[2-pyridylmethylthio]-(N-acetylmethyl)-benzimidazole was recrystallized from carbon tetrachloride. Yield 8 g. Mp. 113°C.

The thio-compound was oxidized to the corresponding sulphinyl-compound in accordance with Example 1 above.

Example 38.

2-[2-pyridylmethylthio]-(N-ethoxycarbonylmethyl)benzimidazole was prepared from 2-[2-pyridylmethylthio]-benzimidazole and chloroacetic acid ethyl ester.

The thio-compound was then oxidized to the corresponding sulphinyl compound.

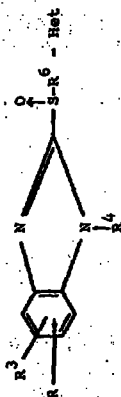
Example 39.

4.82 g (0.02 moles) of 2-[2-pyridylmethylthio]-benzimidazole and 4.05 g (0.04 moles) of triethylamine were dissolved in 200 mls of acetonitrile. 2.52 g (0.022 moles) of methylsulphonic chloride in 20 mls of acetonitrile were added dropwise, whereupon the solution was left to stand overnight. The mixture was poured into ice, whereby the product crystallized. Recrystallization of 2-[2-pyridylmethylthio]-(N-methylsulphonyl)-benzimidazole was made from acetonitrile. Yield 3.7 g. Mp. 142°C.

The thio-compound was oxidized to give the corresponding sulphinyl-compound. Mp. of 2-[2-pyridylmethylsulfinyl]-(N-methylsulphonyl)-benzimidazole is 144°C.

TABLE I

Compounds of Formula I prepared



Ex.	R ³	R	R ⁴	R ⁵	Het	M.P. °C.
1	H	H	H	CH ₂	2-pyridyl	150-154
2	6-CH ₃	4-CH ₃	H	CH ₂	2-pyridyl	141
3	H	5-C ₂ H ₅	H	CH ₂	2-pyridyl	90
4	6-Cl	4-CH ₃	H	CH ₂	2-pyridyl	165
5	H	5-OCH ₃	H	CH ₂	2-pyridyl	133
6	H	5-OH	H	CH ₂	2-pyridyl	
7	H	5-COCH ₃	H	CH ₂	2-pyridyl	172
8	H	5-COOH	H	CH ₂	2-pyridyl	
9	H	5-COOC ₂ H ₅	H	CH ₂	2-pyridyl	171
10	H	H	H	CH ₂	2-(4-chloro)pyridyl	
11	H	H	H	CH ₂	2-(5-methyl)pyridyl	
12	H	H	H	CH ₂	2-piperidyl	
13	H	H	H	CH ₂	2-quinolyl	

TABLE I (Continued)

Ex.	R ³	R	R ⁴	R ⁵	Het	M.P.°C.
14	H	H	CH ₃	CH ₂	2-pyridyl	113
15	H	H	H	CH(CH ₃)	2-pyridyl	135
16	H	4-CH ₃	H	CH ₂	2-pyridyl	
17	H	H	COCH ₃	CH ₂	2-pyridyl	
18	H	H	COOCH ₃	CH ₂	2-pyridyl	135
19	H	5-CH ₃	H	CH ₂	2-pyridyl	114
20	H	5-Cl	H	CH ₂	2-pyridyl	142
21	H	5-CH(CH ₃) ₂	H	CH ₂	2-pyridyl	135
22	H	5-C(CH ₃) ₃	H	CH ₂	2-pyridyl	
23	H	5-C ₂ H ₅	H	CH ₂	2-pyridyl	110
24	H	5-CH ₃	H	CH ₂	2-(5-methyl)pyridyl	145
25	H	6-Cl	H	CH ₂	2-pyridyl	163
26	H	H	H	CH(C ₂ H ₅)	2-pyridyl	134-142
27	H	5-Cl	H	CH(C ₂ H ₅)	2-pyridyl	51-59
28	H	5-C ₂ H ₅	H	CH(CH ₃)	2-pyridyl	144
35	H	H	-CONH ₂	CH ₂	2-pyridyl	164
36	H	H	-CONH(CH ₃)	CH ₂	2-pyridyl	140

18

19

TABLE I (Continued)

Ex.	R'	R	R'	R'	Het	M.P.°C.
37	H	H	-CH ₂ COCH ₃	CH ₂	2-pyridyl	
38	H	H	-CH ₂ COOC ₂ H ₅	CH ₂	2-pyridyl	
39	H	H	-SO ₂ CH ₃	CH ₂	2-pyridyl	144
40	H	5-CH ₃	H	CH ₂	2-(4-methyl)pyridyl	
41	H	H	H	CH ₂	2-(3-methyl)pyridyl	190
42	H	5-CH ₃	H	CH ₂	2-(5-ethyl)pyridyl	138
43	H	H	H	CH ₂	2-(5-ethyl)pyridyl	152
44	H	5-C ₂ H ₅	H	CH(C ₂ H ₅)	2-pyridyl	
45	H	5-CH ₃	H	CH(CH ₃)	2-pyridyl	
46	H	5-CN	H	CH(CH ₃)	2-pyridyl	
47	H	5-CF ₃	H	CH(CH ₃)	2-pyridyl	
48	H	5-CH ₃	H	CH(C ₂ H ₅)	2-pyridyl	
49	H	5-CN	H	CH(C ₂ H ₅)	2-pyridyl	
50	H	5-CH ₃	H	CH(C ₂ H ₅)	2-pyridyl	
51	H	4-Cl	H	CH ₂	2-pyridyl	163
52	H	H	H	CH[CH(CH ₃) ₂]	2-pyridyl	80
53	6-CH ₃	5-CH ₃	H	CH(CH ₃)	2-pyridyl	
54	6-CH ₃	5-CH ₃	H	CH ₂	2-pyridyl	163

Biological effect.

The compounds of the invention possess valuable therapeutic properties such as gastric acid secretion agents as demonstrated by the following tests. To test the gastric acid secretion activity, a modified perfusion technique was performed using dogs as test animals. As anesthetized dog was fitted with one tube going through the esophagus to the stomach for instillation of fluid, and a second tube extending through the duodenum by way of the ligated pylorus for fluid drainage. Every 15 minutes, 5 ml/kg body weight of a saline solution was introduced into the test animal, and drained samples collected and titrated to pH 7.0 with 0.04N NaOH using a radiometer automatic titrator to calculate the acid output.

Gastric acid secretion was induced by pentagastrin by administering 1—2 μ g/kg per hour, giving a submaximal secretory response. Test compounds in a 0.5% Methocel (Registered Trade Mark) (methyl cellulose) suspension were introduced into the duodenum close to the ligation at least two hours following onset of stimulation, when the secretion had reached a steady level for three consecutive 15 minute periods. The gastric secretion response was noted, and it was found that 2-[2-pyridylmethylsulfinyl]-benzimidazole inhibited gastric acid secretion to 90% when administered in an amount of 1 mg per kg body weight.

The following gastric acid inhibiting effect data were obtained for a number of compounds tested according to the method described.

TABLE I

Compound	Dose mg/kg	% inhibition
Ex. 24	5	>75
19	5	95
19	1	50
2	5	94
3	5	50
21	10	80
23	5	15
20	5	35
9	5	8
4	10	41
15	5	96
15	1	37
26	5	80
26	2	65
28	5	60
40	5	>75
41	5	>75
42	5	95
43	5	90
51	5	30
53	5	30

Example 55.

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

5	2-[2-pyridylmethylsulfinyl]-4-methylbenzimidazole HCl	2.0 g	5
	Saccharin	0.6 g	
	Sugar	30.0 g	
	Glycerin	5.0 g	
	Flavoring agent	0.1 g	
10	Ethanol 96%	10.0 ml	10
	Distilled Water (sufficient to obtain a final volume of 100 ml)		

Sugar, Saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavoring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 56.

2-[2-pyridylmethylsulfinyl]-benzimidazole . HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10% solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10,000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 57.

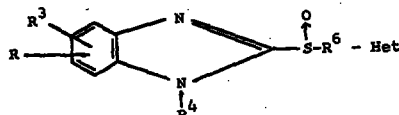
Granules were prepared from active compound of formula I (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10,000 tablets. These tablets are first coated with a 10% alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45%), gum arabic (5%), gelatin (4%), and dyestuff (0.2%). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66% sugar syrup and polished with a solution of 10% carnauba wax in carbon tetrachloride.

Example 58.

Active compound of formula I (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C. for 20 minutes.

WHAT WE CLAIM IS:—

1. A compound of formula I



(I)

or a therapeutically acceptable salt thereof in which R and R³, which are the same or different, each is hydrogen, alkyl, halogen, cyano, carboxy, carboxyalkyl, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl or acyl derived from a carboxylic acid, R⁴ is hydrogen, alkyl, acyl derived from a carboxylic acid, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkyl-carbonylmethyl, alkoxy-carbonylmethyl or alkylsulfonyl, R⁶ is a straight or branched alkylene group having 1 to 4 carbon atoms, and only one carbon atom in the chain linking S and Het and Het is 2-quinolyl, or 2-pyridyl, the Het groups being unsubstituted or substituted by a C₁—C₄ alkyl group or halogen.

2. A compound according to claim 1, wherein the Het group is substituted in at least one of the 3, 4 or 5 positions by methyl, ethyl, propyl, chloro or bromo.



Example 55.

A syrup containing 2% (weight per volume) of active substance was prepared from the following ingredients:

5	2-[2-pyridylmethylsulfinyl]-4-methylbenzimidazole HCl	2.0 g	
	Saccharin	0.6 g	5
	Sugar	30.0 g	
	Glycerin	5.0 g	
	Flavoring agent	0.1 g	
	Ethanol 96%	10.0 ml	
10	Distilled Water (sufficient to obtain a final volume of 100 ml)		10

Sugar, Saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavoring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 56.

2-[2-pyridylmethylsulfinyl]-benzimidazole . HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10% solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10,000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 57.

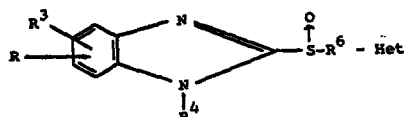
Granules were prepared from active compound of formula I (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10,000 tablets. These tablets are first coated with a 10% alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45%), gum arabic (5%), gelatin (4%), and dyestuff (0.2%). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66% sugar syrup and polished with a solution of 10% carnauba wax in carbon tetrachloride.

Example 58.

Active compound of formula I (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C. for 20 minutes.

WHAT WE CLAIM IS:—

1. A compound of formula I



(I)

or a therapeutically acceptable salt thereof in which R and R³, which are the same or different, each is hydrogen, alkyl, halogen, cyano, carboxy, carboxyalkyl, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoylalkyl, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl or acyl derived from a carboxylic acid, R⁴ is hydrogen, alkyl, acyl derived from a carboxylic acid, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkyl-carbonylmethyl, alkoxy-carbonylmethyl or alkylsulfonyl, R⁶ is a straight or branched alkylene group having 1 to 4 carbon atoms, and only one carbon atom in the chain linking S and Het and Het is 2-quinolyl, or 2-pyridyl, the Het groups being unsubstituted or substituted by a C₁—C₄ alkyl group or halogen.

2. A compound according to claim 1, wherein the Het group is substituted in at least one of the 3, 4 or 5 positions by methyl, ethyl, propyl, chloro or bromo.



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3. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R is hydrogen, hydroxy, cyano, methyl, ethyl, n-propyl, isopropyl, t-butyl, trifluoromethyl, methoxy, acetyl, carboxy or carbethoxy, R³ is hydrogen, methyl or chloro, R⁴ is hydrogen, methyl, acetyl, carbomethoxy, carbamoyl, methylcarbamoyl, methylcarbonylmethyl, ethoxycarbonylmethyl or methylsulfonyl and R⁶ is CH₂.
4. A compound according to claim 1, or a therapeutically acceptable salt thereof in which R and R³ are hydrogen, methyl, ethyl, trifluoromethyl, cyano or chloro, R⁴ is hydrogen, and Het is 2-pyridyl.
5. A compound according to claim 4 or a therapeutically acceptable salt thereof in which R⁶ is .CH(CH₃).
6. A compound according to claim 4 or a therapeutically acceptable salt thereof in which R⁶ is CH(C₂H₅).
7. A compound according to claim 4 or a therapeutically acceptable salt thereof, R⁶ is CH[CH(CH₃)₂].
8. A compound according to any one of claims 5—7 in which the 2-pyridyl group is substituted by methyl, ethyl or chloro.
9. A compound according to claim 1, which is
 - 2-[2-pyridylmethylsulfinyl]benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(4,6-dimethyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-ethyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(4-methyl, 6-chloro)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-methoxy)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-hydroxy)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-acetyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-carboxy)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-carbethoxy)benzimidazole,
 - 2-[2-(4-chloro)pyridylmethylsulfinyl]benzimidazole,
 - 2-[2-(5-methyl)pyridylmethylsulfinyl]benzimidazole,
 - 2-[2-quinolylmethylsulfinyl]benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-N-methylbenzimidazole,
 - 2-[2-pyridyl-ethylidenesulfinyl]benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(4-methyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(N-acetyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(N-methoxycarbonyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-chloro)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-isopropyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-t-butyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5-n-propyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(N-carbamoyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(N-methylcarbamoyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(N-acetylmethyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(N-ethoxycarbonylmethyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(N-methylsulfonyl)benzimidazole,
 - 2-[2-(4-methyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
 - 2-[2-(5-methyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(6-chloro)benzimidazole,
 - 2-[2-pyridyl-propylidenesulfinyl]benzimidazole,
 - 2-[2-pyridyl-propylidenesulfinyl]-(5-chloro)benzimidazole,
 - 2-[2-pyridyl-ethylidenesulfinyl]-(5-ethyl)benzimidazole,
 - 2-[2-(3-methyl)pyridylmethylsulfinyl]benzimidazole,
 - 2-[2-(5-ethyl)pyridylmethylsulfinyl]-(5-methyl)benzimidazole,
 - 2-[2-(5-ethyl)pyridylmethylsulfinyl]benzimidazole,
 - 2-[2-pyridyl-propylidenesulfinyl]-(5-ethyl)benzimidazole,
 - 2-[2-pyridyl-ethylidenesulfinyl]-(5-methyl)benzimidazole,
 - 2-[2-pyridyl-ethylidenesulfinyl]-(5-cyano)benzimidazole,
 - 2-[2-pyridyl-ethylidenesulfinyl]-(5-trifluoromethyl)benzimidazole,
 - 2-[2-pyridyl-propylidenesulfinyl]-(5-methyl)benzimidazole,
 - 2-[2-pyridyl-propylidenesulfinyl]-(5-cyano)benzimidazole,
 - 2-[2-pyridyl-propylidenesulfinyl]-(5-trifluoromethyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(4-chloro)benzimidazole,
 - 2-[2-pyridyl-isobutylidenesulfinyl]benzimidazole,
 - 2-[2-pyridyl-ethylidenesulfinyl]-(5,6-dimethyl)benzimidazole,
 - 2-[2-pyridylmethylsulfinyl]-(5,6-dimethyl)benzimidazole,or a therapeutically acceptable salt thereof.

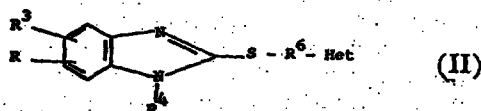


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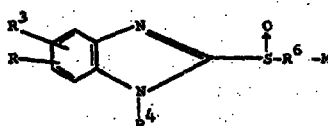
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10. A process for preparing a compound as defined in claim 1, which comprises oxidizing a compound of formula II



wherein R, R³, R⁴, R⁶ and Het are as defined in claim 1.

11. A process for preparing a compound as defined in claim 1, which comprises reacting a compound of the formula

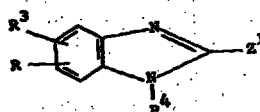


wherein R, R³, R⁴ and R⁶ are as defined in claim 1 and M is K, Na or Li with a compound of formula



wherein Het is as defined in claim 1 and Z is a reactive esterified hydroxy group.

12. A process for preparing a compound as defined in claim 1, which comprises reacting a compound of formula



with a compound of formula

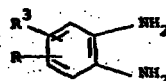


wherein R, R³, R⁴ and Het are as defined in claim 1, and one of Z¹ and Z² is SH, and the other of Z¹ and Z² is a reactive esterified hydroxy group to form an intermediate of formula II,



which then is oxidized.

13. A process for preparing a compound as defined in claim 1 which comprises reacting a compound of formula



wherein R and R³ are as defined in claim 1 with a compound of the formula



wherein Het and R⁶ are as defined in claim 1 to form an intermediate of formula II,



which then is oxidized.



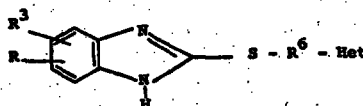
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14. A process for preparing a compound as defined in claim 1 except those in which R⁴ is hydrogen which comprises reacting a compound of the formula

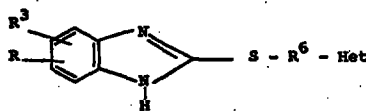


wherein R, R³, R⁶ and Het are as defined in claim 1 with a compound Z—R⁷, wherein Z is a reactive esterified hydroxy group and R⁷ is as defined for R⁴ in claim 1, but excluding hydrogen, to form an intermediate of formula II



which is then oxidized.

15. A process for preparing a compound as defined in claim 1 in which R⁴ is alkyl carbamoyl which comprises reacting a compound of the formula



wherein R, R³, R⁶ and Het are as defined in claim 1 with an alkylisocyanate to give an intermediate of formula II



where R⁴ is alkylcarbamoyl which is then oxidized.

16. A process according to any one of claims 10—15 wherein the compound is prepared in the form of a base and is then converted into a therapeutically acceptable acid addition salt.

17. A process according to any one of claims 10—15, wherein an acid addition salt of the compound is prepared and the salt is then converted into the free base.

18. A process according to any one of claims 10—15, substantially as hereinbefore described with reference to any one of the Examples.

19. A compound as defined in claim 1, or a therapeutically acceptable salt thereof obtained by a process according to any one of claims 10—18.

20. A pharmaceutical preparation containing as active ingredient a compound or salt according to any one of claims 1—9 or 19 together with a pharmaceutically acceptable carrier or diluent.

21. A preparation according to claim 20, wherein the active ingredient comprises 0.1 to 95% by weight of the preparation.

22. A preparation according to claim 20, in a form suitable for administration by injection wherein the active ingredient comprises 0.5% to 20% by weight of the preparation.

23. A preparation according to claim 20, for parenteral application which comprises an aqueous solution of a water soluble salt of said active ingredient in an amount of 0.5 to 10% by weight of the preparation.

24. A pharmaceutical preparation according to claim 20, in a form suitable for oral administration wherein the active ingredient comprises 2% to 50% by weight of the preparation.

25. A preparation according to claim 20, in a form suitable for oral administration wherein the dosage of active ingredient is in the range 100 to 400 milligrams per day.



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26. A pharmaceutical preparation according to claim 20, in a form suitable for intravenous administration wherein the dosage of active ingredient is in the range 5 to 20 milligrams per day.

5

27. A preparation according to any one of claims 20—26, substantially as hereinbefore described with reference to any one of the Examples.

5

28. A method of inhibiting gastric acid secretion in mammals excluding man which comprises administering to the mammal a compound or salt according to any one of claims 1—9, or 19, or a composition according to any one of claims 20—27.

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