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Kuhla

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[54] **IMIDAZO (2,1-b) THIAZOLE AND THIAZOLO (3,2-a) BENZIMIDAZOLE QUATERNARY SALTS HYPOGLYCEMIC AGENTS**

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[52] **U.S. Cl.** **424/270**

[51] **Int. Cl.** **A61k 27/00**

[58] **Field of Search** 424/270

[56] **References Cited**

UNITED STATES PATENTS

3,364,112	1/1968	Raeymakers	424/270
3,542,802	11/1970	Twelt	424/270 X

OTHER PUBLICATIONS

J. Am. Chem. Soc., 79, 5710 (1957).

Chem. Abstr., Vol. 50, 13911–13912, 1956.

Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Connolly and Hutz

[57] **ABSTRACT**

The use of quaternary 7-substituted imidazo[2,1-b]thiazolium and 9-substituted thiazolo[3,2-a]benzimidazolium salts as blood-sugar lowering agents.

15 Claims, No Drawings

IMIDAZO (2,1-b) THIAZOLE AND THIAZOLO (3,2-a) BENZIMIDAZOLE QUATERNARY SALTS HYPOGLYCEMIC AGENTS

BACKGROUND OF THE INVENTION

This invention relates to use of compounds as hypoglycemic agents, and more particularly to the use of quarternary 7substituted imidazo[2,1-b]-thiazolium and 9-substituted thiazolo[3,2-a]benzimidazolium salts as orally-effective blood sugar lowering agents in the treatment of diabetes.

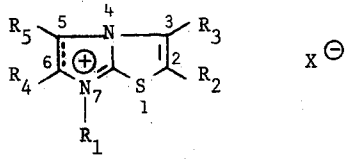
Other than insulin, which is usually administered subcutaneously, the most useful oral medication employed in the treatment of diabetes are the sulfonylureas, many of which are currently being marketed. In addition, biguanides are also employed either alone or in combination with sulfonylureas in the treatment of this disease.

More recently, 1-substituted 3-(2-pyrimidinyl)imidazolium salts have been claimed in Belgium Pat. No. 743,510 and German Pat. application No. 1,964,282, to be active as hypoglycemic agents. Japanese Pat. application No. 7,305,899 reports the synthesis of pyridimium-pyrazine and their use as lowerers of blood sugar and free fatty acid levels. Wiegand et al., *J. Med. Chem.*, 15, 1326 (1972), review and report on the hypoglycemic activity of a number of azolylpyridinium salts.

2,3,9-Trimethylbenzimidazo[2,1-b]thiazolium iodide has been prepared by de Stevens et al., *J. Am. Chem. Soc.*, 79, 5710 (1957), and imidazo[2,1-b]-thiazolium by Kondo et al., *J. Pharm. Soc., Japan*, 57, 1050 (1937) (C.A. 32 3398 (1938) and Kickhöfen et al., *Chem. Ber.*, 88, 1109 (1955) (C.A. 50, 13911 (1956).

SUMMARY OF THE INVENTION

It has now been discovered that quaternary compounds of the formula



wherein X is a pharmaceutically-acceptable anion; R_1 is propargyl, benzyl, phenethyl or substituted benzyl wherein said substituent is fluoro, chloro, methoxy, trifluoromethyl, phenyl or dichloro; R_2 is hydrogen or alkyl containing from 1 to 3 carbon atoms; R_3 is hydrogen, alkyl containing from 1 to 3 carbon atoms, adamantyl, phenyl or substituted phenyl wherein said substituent is dimethyl or dimethoxy; R_2 and R_3 when taken together is tetramethylene; R_4 is hydrogen, alkyl containing from 1 to 3 carbon atoms, phenyl, dimethylphenyl or dichlorophenyl; R_5 is hydrogen; and R_4 and R_5 when taken together with the carbon atoms to which they are attached form a 1,2-phenylene ring, are orally effective hypoglycemic agents useful in the reduction of blood sugar levels of diabetes.

The broken line shown in the above structure represents an optional bond such that the present invention is meant to embrace both the 5,6-dihydro- and dehydro- forms of the imidazo[2,1-b]thiazolium compounds.

A preferred group of hypoglycemic compounds are those wherein R_1 is benzyl, R_2, R_4 and R_5 are each hydrogen and R_3 is alkyl or adamantyl.

A second preferred group are those wherein R_1 is chlorobenzyl, R_2, R_4 and R_5 are each hydrogen and R_3 is alkyl containing from 1 to 3 carbon atoms.

A third preferred group included those compounds wherein R_2, R_3 and R_5 are each hydrogen and R_4 is phenyl or dimethylphenyl.

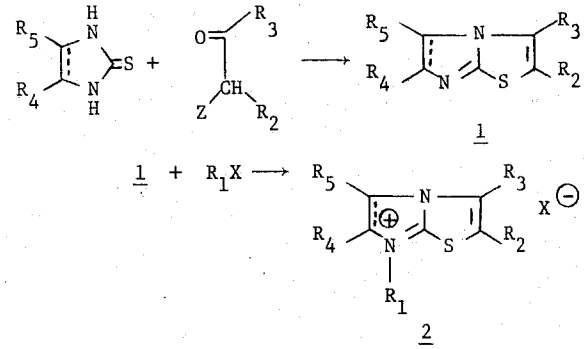
A fourth preferred group of hypoglycemic compounds are those wherein R_2 is hydrogen, R_3 is alkyl containing from 1 to 3 carbon atoms and R_4 and R_5 taken together with the carbon atoms to which they are attached form a 1,2-phenylene ring.

A fifth preferred class of compounds of the present invention are those of formula 2 wherein R_2, R_3, R_4, R_5 and X are as previously indicated and R_1 is propargyl.

In all the aforementioned preferred groups of blood sugar lowering agents, it is preferred that X is chloro or bromo.

DETAILED DESCRIPTION OF THE INVENTION

The hypoglycemic agents of the present invention are synthesized by reactions depicted in the following scheme:



wherein X and Z are chloro or bromo and R_1, R_2, R_3, R_4 and R_5 are as previously indicated.

Experimentally, equimolar amounts of the appropriate 2-mercaptoimidazole or 2-mercapto-4,5-dihydroimidazole and requisite α-halocarbonyl reagent are contacted in a reaction-inert solvent to yield the intermediate compounds one as the hydrogen halide salt.

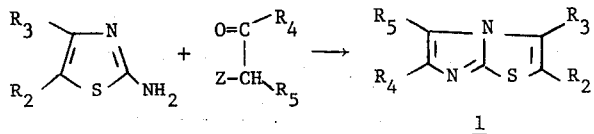
Reaction times and temperatures are not critical. In general, it is preferred that steam bath temperatures be employed in order to hasten the completion of said reaction. Under these conditions the reaction is usually complete in 1–4 hours.

Although the preparation of compounds (1) can be conducted without a solvent, i.e., neat, it is preferred that a solvent be employed. Further, it is preferred that such a solvent be a reaction-inert solvent, i.e., one which will not react with the product or starting reagents to any appreciable extent. Such a solvent should be a non-aqueous, polar solvent and include, for example, lower alkanols, lower alkylnitriles, or dialkyl ketones. The preferred solvent is ethanol.

The reaction product can be isolated from the completed reaction by removal of the solvent or, alternately, by cooling the reaction mixture to induce crystallization of the hydrogen halide salt. When the intermediates (1) have been isolated as the salt they are then converted to the free base by treating an aqueous solution or suspension of said salt with sufficient aqueous sodium hydroxide to liberate the free base, which

can be filtered or extracted with a water immiscible solvent.

An alternate method for the preparation of intermediate imidazo[2,1-b]thiazoles is as follows:



1

wherein R_2, R_3, R_4, and R_5 and Z are as previously indicated.

The condensation reaction outlined above is conducted in the same manner as that wherein the starting reagents are a mercaptoimidazole derivative and a halo carbonyl compound. Further, isolation of the product and generation of the free base is effected in the same manner.

Transformation of compounds of formula (1) to quaternary salts of formula (2) is effected by reacting (1) with a halide, R_1X, where X is chloro, bromo or iodo. Said reaction can be conducted between equimolar amounts of the two reagents either neat or in the presence of a suitable reaction-inert solvent. When conducted neat a large excess of the halide can be employed, acting under these conditions as both a reactant and solvent.

As previously indicated, by a reaction-inert solvent is meant one which does not react to any appreciable degree with the product or reactants under the conditions of said reaction. Solvents suitable for the solubilizing of the reactants leading to the quaternary compounds (2) can be of a varied nature, and can include (lower)alkanols, (lower)alkylnitriles, di(lower)alkyl ketones, cyclic- and di(lower)alkyl ethers and liquid aromatic hydrocarbons. The preferred solvent for this reaction is acetonitrile.

Reaction time is not critical, and depends on temperature, concentration and inherent reactivity of the reagents. When steam bath temperatures are employed, completion of the reaction usually requires 2 to 4 hours.

The product is isolated by cooling the reaction mixture to induce crystallization, or initial concentration of the reaction mixture followed by cooling. Further purification of the final product is facilitated by trituration or recrystallization from an appropriate solvent.

As mentioned previously, quaternary salt formation is preferably effected with RX wherein X is bromo, chloro or iodo. Following isolation of these salts the nature of the X variable can be altered by initially treating an aqueous solution of quaternary halide with an equivalent of silver oxide, followed by separation of the precipitated silver halide and treatment of the aqueous solution of the quaternary base with at least an equivalent of an appropriate acid HX.

Alternately, the quaternary base can be obtained by passing a solution of a salt through a basic ion-exchange resin column followed by treatment of the eluate with the same or a different acid.

In the utilization of the chemotherapeutic activity of those compounds of the present invention which form quaternary salts, it is preferred, of course, to use pharmaceutically acceptable salts. Although water-insolubility, toxicity, or lack of crystalline nature may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water insoluble or toxic salts can be converted to the corresponding pharmaceutically acceptable quaternary hydroxide by decomposition of the salt as described above, or alternately they can be converted to any desired pharmaceutically acceptable quaternary salt.

Examples of pharmaceutically acceptable anions other than the halides are nitrate, sulfate, phosphate, alkanoates, lactate, citrate, tartrate, succinate and maleate.

Imidazo[2,1-b]thiazole intermediates are prepared by the aforementioned procedures, said procedures being familiar to those skilled in the art and employed in the synthesis of such compounds as reported by Wilson et al., *J. Chem. Soc.*, 1955, 2943, Fefer et al., *J. Org. Chem*, 26, 828(1961), U.S. Pat. Nos. 2,969,369; 3,267,112 and 3,274,209, Iwai et al., *Chem. Pharm. Bull.* (Tokyo),12, 813 (1964), Todd et al., *Chem. Ber.*, 69, 217 (1936), Kondo et al, *J. Pharm. Soc. Japan*, 57, 1050 (1937) and Kickhöfen et al., *Chem. Ber.*, 88, 1109 (1955).

The more fundamental starting materials employed in the preparation of the imidazo[2,1-b]thiazoles, i.e., the mercaptoimidazole derivatives, α-halo carbonyl reagents and the 2-aminothiazoles are available either commercially or by synthetic procedures familiar to those skilled in the art.

As previously mentioned, the imidazo[2,1-b]thiazole and thiazolo[3,2-a]benzimidazole quaternary salts are all readily adapted to therapeutic use as oral hypoglycemic agents in view of their ability to lower blood sugar levels of diabetic subjects. Toward this end, the preferred compounds are 3-methyl-7-benzyl-5,6-dihydroimidazo[2,1-b]thiazolium chloride, 3-methyl-7-benzimidazo-[2,1-b]thiazolium chloride, 3-methyl-7-(o-chlorobenzyl)imidazo[2,1-b]thiazolium chloride, 3-methyl-7-(p-chlorobenzyl)imidazo[2,1-b]thiazolium chloride,6,-phenyl-7- benzylimidazo[2,1-b]thiazolium chloride, 3-methyl-9-benzylthiazolo[3,2-a]benzimidazolium bromide, 3-adamantyl-7-benzyl-5,6-dihydrimidazo[2,1-b]thiazolium bromide and 6-(2,4-dimethylphenyl)-7-benzylimidazo[2,1-b]thiazolium bromide.

The imidazo[2,1-b]thiazolium and thiazolo[3,2-a]benzimidazolium quaternary salts, which are useful hypoglycemic agents in mammals, can be administered either as individual therapeutic agents or as mixtures of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be combined with various pharmaceutically acceptable carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, aqueous suspensions or solutions, injectable solutions, elixirs, syrups and the like. Such carriers include solid diluents or filters, sterile aqueous media and various nontoxic organic solvents. Moreover, the oral pharmaceutical compositions of this invention may be suitably sweetened and flavored by means of various agents of the type commonly used for this purpose.

The particular carrier selected and the proportion of active ingredient to carrier are influenced by the solubility and chemical nature of the therapeutic compounds, the chosen route of administration and the

needs of the standard pharmaceutical practice. For example, where those compounds are administered orally in tablet form, excipients such as lactose, sodium citrate, calcium carbonate and dicalcium phosphate may be used. Various disintegrants such as starch, alginic acids, and certain complex silicates, together with lubricating agents such as magnesium stearate, sodium lauryl sulphate and talc, may also be used in producing tablets for the oral administration of these compounds. For oral administration in capsule form, high molecular weight polyethylene glycols are among the preferred materials for use as pharmaceutically acceptable carriers. Where aqueous suspensions are to be used for oral administration, the compounds of this invention may be combined with emulsifying or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and their combinations may be employed as well as other materials.

For purposes of parenteral administration, solutions or suspensions of the instant compounds in sesame or peanut oil or in aqueous propylene glycol solutions can be employed, as well as sterile aqueous solutions described hereinafter. These particular solutions are especially suited for intramuscular and subcutaneous injection purposes. The aqueous solutions dissolved in pure distilled water are also useful for intravenous injection purposes provided that their pH is properly adjusted beforehand. Such solutions should also be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline.

It is necessary that the active ingredient form a proportion of the composition such that a suitable dosage form will be obtained. Obviously, several dosage unit forms may be administered at about the same time. Although compositions with less than 0.005 percent by weight of active ingredient might be used in certain 0.005 it is preferred to use compositions containing not less than **0.005** percent of the active ingredient; otherwise the amount of carrier becomes excessively large. Activity increases with the concentration of the active ingredient. The composition may contain 10, 50, 75, 95, or an even higher percentage by weight of the active ingredient.

Although the use of the present invention is directed toward the treatment of mammals in general, the preferred subject is humans. In determining an efficacious dose for human therapy, results of animal testing are frequently extrapolated and a correlation is assumed between animal test behaviour and proposed human dosage. When a commercially employed standard is available, the dose level of the clinical candidate in humans is frequently determined by comparison of its performance with the standard in an animal test. For example, β-phenethylbiguanide is employed as a standard hypoglycemic agent and is administered to humans at the rate of 50 to 150 mg. daily. It is assumed, then, that if compounds of the present invention have activity comparable to β-phenethylbiguanide in the test assay, that similar doses will provide comparable responses in humans.

Obviously, the physician will ultimately determine the dosage which will be most suitable for a particular individual, and it will vary with the age, weight and response of the particular patient as well as with the nature and extent of the symptoms and the pharmacodynamic characteristics of the particular agent to be administered. Generally, small doses will be administered initially, with a gradual increase in the dosage until the optimum level is determined. It will often be found that when the composition is administered orally, larger quantities of the active ingredient will be required to produce the same level as produced by a small quantity administered parenterally.

Having full regard for the foregoing factors, it is considered that an effective daily dosage of the compounds of the present invention in humans of approximately 50 to 600 mg. per day, with a preferred range of about **50** to 400 mg. per day in single or divided doses, or at about 0.07 to 0.6 mg./kg. of body weight will effectively lower blood sugar levels in human diabetic subjects. These values are illustrative, and there may, of course, be individual cases where higher or lower dose ranges are merited.

The following examples are provided solely for the purpose of illustration and are not to be construed as limitations of this invention, many variations of which are possible without departing from the spirit or scope thereof.

EXAMPLE 1

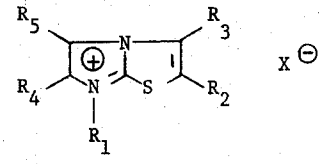
7-Propargyl-3-methyl-5,6-dihydroimidazo[2,1-b]thiazolium bromide ($R_1 = CH \equiv CCH_2$; $R_2 = H$; $R_3 = CH_3$; R_4 and $R_5 = H$; $X = Br$)

A solution of 12 g. of propargyl bromide and 14 g. of 3-methyl-5,6-dihydroimidazo[2,1-b]thiazole (prepared by basification of 3-methyl-5,6-dihydroimidazo[2,1-b]thiazole hydrochloride with 5N sodium hydroxide solution) in 160 ml. of dry acetonitrile is allowed to stir at room temperature for 16 hrs. The solution is concentrated to a small volume and the precipitated product filtered. The purified product is obtained by recrystallization from acetonitrile-ethyl acetate, 21 g., m.p. 207°–208° C.

Anal. Calc'd for $C_9H_{11}BrN_2S$: N, 10.8; Br: 30.9.
Found: N, 10.5; Br: 31.2.

EXAMPLE 2

Employing the procedure of Example 1, and starting with the requisite reagents, heating them under reflux for 16 hours, the following 5,6-dihydrocongeners are synthesized:



R_1	R_2	R_3	R_4	R_5	X	m.p., °C.
$C_6H_5CH_2$-	H-	H-	H-	H-	Br	147–149
$C_6H_5CH_2$-	H-	CH_3-	H-	H-	Br	138
$C_6H_5CH_2$-	H-	C_6H_5-	H-	H-	Br	185–186

R_1	R_2	R_3	R_4	R_5	X	m.p., °C.
$C_6H_5CH_2$-	CH_3-	CH_3-	H-	H-	Br	140
$C_6H_5CH_2$-	-$(CH_2)_4$-		H-	H-	Br	177
2-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	221-223
3-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	177-180
4-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	205-208
2,4-$Cl_2C_6H_3CH_2$-	H	CH_3-	H-	H-	Cl	272-275
2,6-$Cl_2C_6H_3CH_2$-	H-	CH_3-	H-	H-	Br	243-245
3-$FC_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	170-171
4-$FC_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	218-219
3-$CF_3C_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	168-170
4-$CH_3OC_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	191-192
4-$C_6H_5C_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	186-187
$C_6H_5CH_2CH_2$-	H-	CH_3-	H-	H-	Br	117-120
$CH{\equiv}CCH_2$-	-$(CH_2)_4$-		H-	H-	Br	196-198
$C_6H_5CH_2$-	H-	2,5-$(CH_3O)_2C_6H_3$-	H-	H-	Br	161-163
$C_6H_5CH_2$-	H-	2,4-$(CH_3)_2C_6H_3$-	H-	H-	Br	203-205
$C_6H_5CH_2$-	CH_3-	C_6H_5-	H-	H-	Br	210-213
$C_6H_5CH_2$-	H-		H-	H-	Br	182-185

EXAMPLE 3

The procedure of Example 1 is again repeated, starting with the appropriate 5,6-dihydroimidazo[2,1-b]thiazole and halide (R_1X) to provide the following compounds:

2-ethyl-3,6-dimethyl-7-(p-trifluoromethylbenzyl)-5,6-dihydroimidazo-[2,1-b]thiazolium chloride, 2-i-propyl-6-phenyl-7-(p-trifluoromethylbenzyl)-5,6-dihydromidazo[2,1-b]thiazolium chloride, 2-methyl-3-(2,4-dimethylphenyl)-7-(p-phenylbenzyl)-5,6-dihydroimidazo[2,1-b]thiazolium bromide, 3-(3,5-dimethylphenyl)-6-ethyl-7-(o-methoxybenzyl-5,6-dihydroimidazo[2,1-b]thiazolium bromide, 2,3-di-n-propyl-6-(m-chlorophenyl)-7-(p-chlorobenzyl)-5,6-dihydroimidazo[2,1-b]thiazolium chloride, 3-adamantyl-6-phenyl-7-(o-fluorobenzyl)-5,6-dihydroimadazo[2,1-b]thiazolium chloride, 3-(2,4-dimethylphenyl-6-(3,5-dimethylphenyl)-7-benzyl-5,6-dihydoimidazo[2,1-b]thiazolium chloride, 2-methycl-3-(3,5-dimethoxyphenyl)-6-(p-chlorophenyl)-7-(m-trifluoromethylbenzyl)-5,6-dihydromidazo[2,1-b]thiazolium bromide, 3-adamantyl-7-propargyl-5,6-dihydroimidazo[2,1-b]thiazolium bromide, 2,3,6-triethyl-7-(p-chlorobenzyl)-5,6-dihydroimidazo[2,1-b]-thiazolium chloride, 1-(m-trifluoromethylbenzyl)-2,3-dimethyl-2,3,5,6,7,8-hexahydroimidazo[2,1-b]benzthiazolium chloride and 1-benzyl-2-phenyl-2,3,5,6,7,8-hexahydroimidazo[2,1-b]benzthiazolium bromide.

EXAMPLE 4

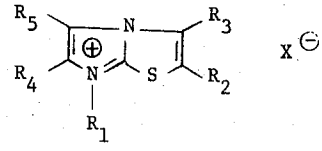
3-Methyl-7-benzylimidazo[2,1-b]thiazolium bromide ($R_1 = C_6H_5CH_2$; $R_2 = H$; $R_3 = CH_3$; R_4 and $R_5 = H$; X = Br)

Nineteen grams of 3-methylimidazo[2,1-b]thiazole, obtained by treating 23.2 g. of the hydrochloride salt in 300 ml. of water with sufficient 20% sodium hydroxide solution to render it strongly basic, is dissolved in 250 ml. of acetonitrile and subsequently treated with 27.4 g. of benzyl bromide. The reaction mixture is heated under reflux for 2 hrs., and it is then cooled and treated with 150 ml. of diethyl ether. The product is filtered and recrystallized from acetonitrile-ethyl acetate, 37.4 g., m.p. 165°–167.5° C.

Anal. Calc'd for $C_{13}H_{13}BrN_2S$: C, 50.5; H, 4.2; N, 9.1. Found: C, 50.2; H, 4.3; N, 9.2.

EXAMPLE 5

Starting with the appropriate imidazo[2,1-b]thiazole and requisite halide, and repeating the procedure of Example 4, the following quaternary salts are prepared:



R_1	R_2	R_3	R_4	R_5	X	m.p., °C.
$C_6H_5CH_2$-	H-	H-	CH_3-	H-	Br	220
$C_6H_5CH_2$-	H-	H-	C_6H_5-	H-	Br	176-178
$C_6H_5CH_2$-	H-	H-	p-ClC_6H_4-	H-	Br	195-197
o-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	174-177
m-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	156-159
2,6-$Cl_2C_6H_3CH_2$-	H-	CH_3-	H-	H-	Cl	225-229
2,4-$Cl_2C_6H_3CH_2$-	H-	CH_3-	H-	H-	Cl	269-271
p-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	206-209
p-$CH_3OC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	136-139
$C_6H_5CH_2$-	H-	CH_3-	H-	H-	Cl	152-155
$C_6H_5CH_2CH_2$-	H-	CH_3-	H-	H-	Br	206-209
$C_6H_5CH_2$-	H-	H-	2,4-$(CH_3)_2C_6H_3$-	H-	Br	170-172

EXAMPLE 6

The procedure of Example 4 is again repeated, starting with the requisite reagents, to provide the following imidazo[2,1-b]thiazolium salts:

2-methyl-3,4-diethyl-7-benzylimidazo[2,1-b]thiazolium chloride; 2-n-propyl-3,4-diethyl-7-(p-fluorobenzyl)imidazo[2,1-b]thiazolium chloride, 2-i-propyl-7-(p-fluorobenzyl)imidazo[2,1-b]thiazolium chloride, 3-phenyl-7-(o-methoxybenzyl)imidazo[2,1-b]thiazolium bromide; 3-adamantyl-6-phenyl-7-(m-trifluorobenzyl)imidazo[2,1-b]thiazolium bromide; 3-(3,5-dimethoxybenzyl)-7-benzylimidazo[2,1-b]thiazolium chloride, 3-methyl-7-(p-phenylbenzyl-)amidazo-[2,1-b]thiazolium bromide; 3-(2,4-dimethylbenzyl)-6-methyl-7-(p-chlorrobenzyl)-imidazo[2,1-b]thiazolium bromide; 3-(p-chlorophenyl)-7-proparglylimidazo[2,1-b]-thiazolium bromide; 3,6-bis(2,4-dimethylphenyl)-7-benzylimidazo[2,1-b]thiazolium chloride; 1-(p-fluorobenzyl-5,6,7,8-tetrahydroimidazo[2,1-b]benzthiazolium chloride and 1-propargyl-5,6,7,8-tetrahydroimidazo[2,1-b]benzthiazolium bromide.

EXAMPLE 7

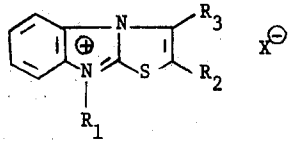
3-Methyl-9-benzylthiazolo[3,2-a]benzimidazolium bromide

(R_1 = C H CH : R_2 = H; R_3 = CH_3; R_4 and R_5 = —CH=CH—CH=CH—; X = Br)

Starting with 3-methylthiazolo[3,2-a]benzimidazole and benzyl bromide and repeating the procedure of Example 1, the desired product is obtained, m.p. 227°–229° C.

EXAMPLE 8

The procedure of Example 1 is repeated wherein the appropriate thiazolo[3,2-a]benzimidazole is condensed with the requisite halide to provide the following quaternary salts:



R_1	R_2	R_3	X
$C_6H_5CH_2$-	CH_3-	H-	Cl
m-$ClC_6H_4CH_2$-	CH_3-	CH_3-	Br
p-$ClC_6H_4CH_2$-	CH_3-	CH_3-	Cl
p-$FC_6H_4CH_2$-	H-	C_6H_5-	Cl
m-$CH_3OC_6H_4CH_2$-	H-	C_6H_5-	Cl
m-$CH_3OC_6H_4CH_2$-	CH_3-	C_6H_5-	Cl
m-$CF_3C_6H_4CH_2$-	H-	2,4-$(CH_3)_2C_6H_3$-	Cl
CH≡C-CH_2-	H-	2,4-$(CH_3)_2C_6H_5$-	Br
CH≡C-CH_2-	H-	C_6H_5-	Br
p-$C_6H_5C_6H_4CH_2$-	H-		Br
2,4-$Cl_2C_6H_3CH_2$-	H-	2,4-$(CH_3O)_2C_6H_3$-	Cl
2,6-$Cl_2C_6H_3CH_2$-	H-	2,4-$(CH_3O)_2C_6H_3$-	Cl
3,5-$Cl_2C_6H_3CH_2$-	H-	C_2H_5-	Cl
m-$CH_3OC_6H_4CH_2$-	C_2H_5-	C_2H_5-	Br

EXAMPLE 9

3-Methyl-7-benzylimidazo[2,1-b]thiazolium Chloride

A solution of 3.09 g. of 3-methyl-7-benzylimidazo[2,1-b]thiazolium bromide in 35 ml. of water is treated with 1.15 g. of silver oxide and the mixture allowed to stir at room temperature for several hours. The reaction mixture is centrifuged and the supernatant decanted from the silver bromide. Aqueous hydrochloric acid (11 ml. of a 1 M solution) is added to the clear supernatant and the water removed in vacuo. The residual quaternary salt is triturated with diethyl ether and subsequently filtered and recrystallized from acetonitrile-ethyl acetate.

In a similar manner the quaternary bromide salts in Examples 1 through 8 are converted to the quaternary chloride salts.

EXAMPLE 10

3-Methyl-7-benzylimidazo[2,1-b]thiazolium Nitrate

The procedure of Example 9 is repeated, 1.8 ml. of 6N nitric acid being substituted for the 11 ml. of 1N hydrochloric acid, to provide the desired quaternary nitrate salt.

EXAMPLE 11

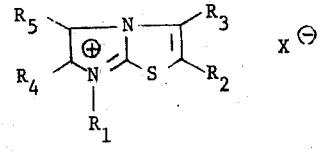
In a manner similar to that in Examples 9 and 10, the quaternary chloride and bromide salts prepared in Examples 1 through 8 are converted to other quaternary salts wherein the anion of the resulting salt, X, is a pharmaceutically acceptable anion.

EXAMPLE 12

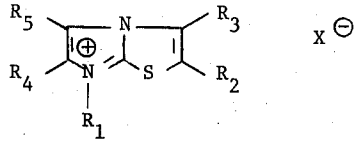
Hypoglycemic Testing

The hypoglycemic testing of the compounds of the present invention is carried out by a standard procedure, and comprises grouping eight, Hartley strain, male guinea pigs which have been fasted 18–24 hrs. in each group. Blood samples are obtained from the pentobarbital-anesthetized animals by cardiac puncture. Each of the eight animals is dosed i.p. with a given dose of the test compound. Blood samples are taken at 1, 2 and 4 hours following the dosing, and the venous blood diluted 1:10 with saline and assayed for blood sugar levels on an Auto-Analyzer, the levels being expressed as mg.%. The activity for the test compound is expressed as the percent lowering of the blood sugar at the 1, 2 and 4 hr. when compared with the blood sugar level of a group of eight control animals which have been similarly dosed with a saline solution.

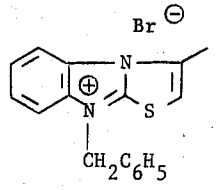
Each of the following representative imadazo[2,1-b]thiazolium salts was tested as hypoglycemic agents following the above mentioned procedure, and was found to be active at the indicated dose level.



R_1	R_2	R_3	R_4	R_5	X	Dose, mg./kg.	% Fall Blood-Sugar Level T_1	T_2	T_4
$C_6H_5CH_2$-	H-	CH_3-	H-	H-	Br	50	36	82	88
$C_6H_5CH_2CH_2$-	H-	CH_3-	H-	H-	Br	50	12	17	--
m-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Br	50	18	45	79
p-$C_6H_5C_6H_5CH_2$-	H-	CH_3-	H-	H-	Br	100	43	60	--
$C_6H_5CH_2$-	H-	C_6H_5-	H-	H-	Br	100	30	29	22
$CH{\equiv}CCH_2$-	H-	CH_3-	H-	H-	Br	50	--	18	20
$C_6H_5CH_2$-	-$(CH_2)_4$-		H-	H-	Br	50	45	87	--
p-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	50	8	18	42
2,4-$Cl_2C_6H_3CH_2$-	H-	CH_3-	H-	H-	Cl	50	20	48	--
p-$FC_6H_5CH_2$-	H-	CH_3-	H-	H-	Cl	50	16	38	77
$C_6H_5CH_2$-	CH_3	CH_3-	H-	H-	Br	50	14	45	62
$C_6H_5CH_2$-	H-	H-	H-	H-	Br	50	40	76	86
m-$CF_3C_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	50	--	10	12
$C_6H_5CH_2$-	H		H-	H-	Br	50	11	15	32



R_1	R_2	R_3	R_4	R_5	X	Dose, mg./kg.	% Fall Blood-Sugar Level T_1	T_2	T_4
$C_6H_5CH_2$-	H-	H-	CH_3-	H-	Br	50	29	68	79
$C_6H_5CH_2$-	H-	CH_3-	H-	H-	Br	25	20	62	66
p-$CH_3OC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	100	33	83	--
p-$ClC_6H_4CH_2$-	H-	CH_3-	H-	H-	Cl	25	11	16	39
2,4-$Cl_2C_6H_3CH_2$-	H-	CH_3-	H-	H-	Cl	50	8	65	--
$C_6H_5CH_2$-	H-	H-	C_6H_5-	H-	Br	25	6	26	84
$C_6H_5CH_2$-	H-	H-	p-ClC_6H_4-	H-	Br	50	5	35	78
$C_6H_5CH_2CH_2$-	H-	CH_3-	H-	H-	Br	50	26	70	85

and  50 18 32 66

EXAMPLE 13

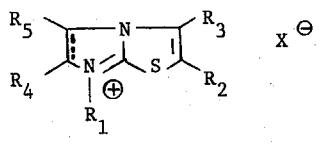
3-Methyl-7-benzylimidazo[2,3-b]thiazolium chloride

A column 1 × 20 inches is packed with Amberlite IRA-400 which has been slurried in 2N sodium hydroxide solution. After the column material is washed with deionized water, a solution of 4.0 g. of 3-methyl-7-benzylimidazo[2,1-b]-thiazolium bromide in 40 ml. of water is applied. The water eluates are collected until the pH of said eluates is neutral. The combined eluates are treated with 200 ml. of 6N hydrochloric acid and concentrated to dryness. The crystallized product is further purified by recrystallization from acetonitrileethyl acetate, 1.22 g., m.p. 152°–155° C.

In a similar manner the quaternary salts of Examples 1 through 8 are converted to other quarternary salts wherein the resulting salt anion, X, is a pharmaceutically acceptable one.

What is claimed is:

1. A method for reducing the blood-sugar levels of a diabetic mammal which comprises orally or parenterally administering to said mammal a hypoglycemic amount of a compound of the formula



wherein X is a pharmaceutically acceptable anion;

R_1 is selected from the group consisting of propargyl,

benzyl, phenethyl and substituted benzyl wherein said substituent is selected from the group consisting of fluoro, chloro, methoxy, trifluoromethyl, phenyl and dichloro;

R_2 is selected from the group consisting of hydrogen and alkyl containing from 1 to 3 carbon atoms;

R_3 is selected from the group consisting of hydrogen, alkyl containing from 1 to 3 carbon atoms, adamantyl, phenyl and substituted phenyl wherein said substituent is selected from the group consisting of dimethyl and dimethoxy;

R_2 and R_3 when taken together is tetramethylene;

R_4 is selected from the group consisting of hydrogen, alkyl containing from 1 to 3 carbon atoms, phenyl, dimethylphenyl and chlorophenyl;

R_5 is hydrogen; and

R_4 and R_5 when taken together with the carbon atoms to which they are attached form a 1,2-phenylene ring.

2. A method of claim **1** wherein X is chloro, R_1 is benzyl, R_2, R_4 and R_5 are each hydrogen and R_3 is alkyl containing from 1 to 3 carbon atoms.

3. A method of claim **2** wherein the compound is 3-methyl-7-benzyl-5,6-dihydroimidazo[2,1-b]thiazolium chloride.

4. A method of claim **2** wherein the compound is 3-methyl-7-benzyl-imidazo[2,1-b]thiazolium chloride.

5. A method of claim **1** wherein X is chloro, R_1 is chlorobenzyl, R_2, R_4 and R_5 are each hydrogen and R_3 is alkyl containing from 1 to 3 carbon atoms.

6. A method of claim **5** wherein the compound is 3-methyl-7-(o-chlorobenzyl)imidazo[2,1-b]thiazolium chloride.

7. A method of claim **5** wherein the compound is 3-methyl-7-(p-chlorobenzyl)imidazo[2,1-b]thiazolium chloride.

8. A method of claim **1** wherein X is chloro, R_2, R_3 and R_5 are each hydrogen and R_4 is phenyl.

9. A method of claim **8** wherein the compound is 6-phenyl-7-benzylimidazo[2,1-b]thiazolium chloride.

10. A method of claim **1** wherein X is bromo, R_2 is hydrogen, R_3 is alkyl containing from 1 to 3 carbon atoms and R_4 and R_5 taken together with the carbon atoms to which they are attached form a 1,2-phenylene ring.

11. A method of claim **10** wherein the compound is 3-methyl-9-benzylthiazolo[3,2-a]benzimidazolium bromide.

12. A method of claim **1** wherein X is bromo, R_1 is benzyl and R_2, R_4 and R_5 are each hydrogen.

13. A method of claim **12** wherein the compound is 3-adamantyl-7-benzyl-5,6-dihydroimidazo[2,1-b]thiazolium bromide.

14. A method of claim **1** wherein X is bromo, R_1 is benzyl and R_2, R_3 and R_5 are each hydrogen.

15. A method of claim **14** wherein the compound is 6-2,4-dimethylphenyl)-7-benzylimidazo[2,1-b]thiazolium bromide.

* * * * *