RESERVE COPY.

PATENT SPECIFICATION

1043,489

NO DRAWINGS

1043,489

Date of Application and filing Complete Specification: May 3, 1965.
No. 18479/65.
Application made in United States of America (No. 366,638) on May 11, 1964.
Application made in United States of America (No. 387,231) on Aug. 3, 1964.
Application made in United States of America (No. 401,251) on Oct. 2, 1964.
Application made in United States of America (No. 446,408) on April 7, 1965.
Complete Specification Published: Sept. 21, 1966.
© Crown Copyright 1966.

Index at acceptance:—C2 C(1F1A2, 1F1C2, 1F1C5, 1F1C6, 1F1D3, 1F4A2, 1F4C6, 1F4D3, 1F4F5, 1G5A, 1G5B, 1G6B3, 1G6B4, 1G6B5, 1Q1A, 1Q2, 1Q6C, 1Q7A, 1Q8A, 1Q9A, 1Q9B, 1Q9F2, 1Q9L, 1Q11D, 1Q11G, 1Q11J, 2A3, 2A5, 2A13, 2B23, 2B24, 2B27, 2B54, 2R1S, 5A45E1, 5E5, B4B, B4C, B4E, B4H, B4M); A5 B2S

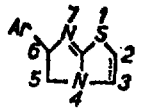
Int. Cl.:—C 07 d 99/10 // A 61 k

COMPLETE SPECIFICATION

Imidazo[2,1-b]Thiazoles and process for preparing them

We, JANSSEN PHARMACEUTICA N.V., a Belgian Body Corporate of 30 Turnhoutsebaan, Beerse, Belgium, 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:—

This invention relates to new chemical compounds and generally to new derivatives of imidazo [2,1-b] thiazole having the formula:



wherein the dotted line between the 2- and 3-positions represents an optional bond, and Ar is a thienyl, furyl, phenyl or substituted phenyl group in which said substituent is halo, preferably chloro, bromo and fluoro, nitro, amino or trifluoromethyl; naphthyl, preferably α-naphthyl; or benzyl; provided that, when said Ar is benzyl, a saturated bond exists between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus. Said substituted phenyl may bear one or more of the aforementioned substituents although, in the preferred compounds, the substituent is single and in the 3-position of the phenyl ring. The therapeutically acceptable acid addition salts of the foregoing compounds are also embraced within the scope of this invention.

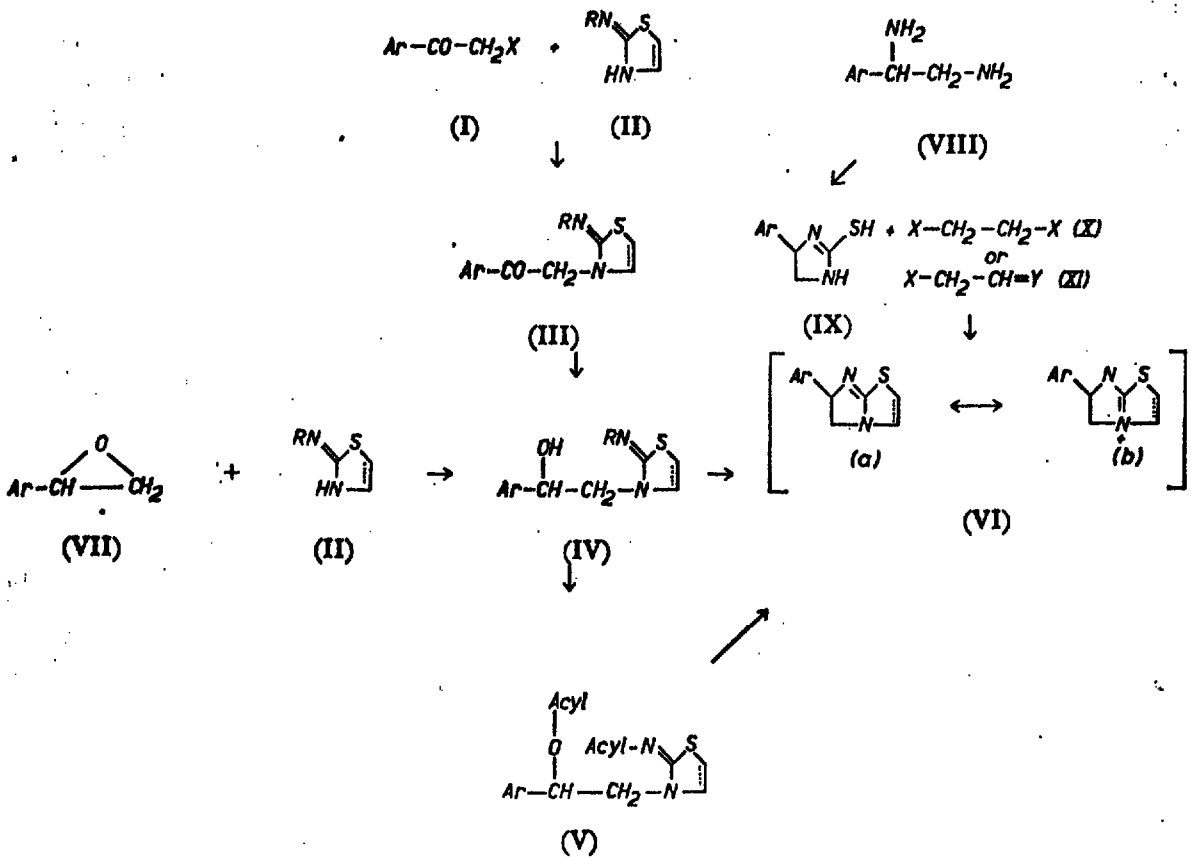
If a double bond is present between the 2- and 3-positions, the respective compounds of this invention may be denoted as 5,6-dihydro - 6 - Ar - imidazo [2,1-b] thiazoles; and, when such double bond is absent, i.e., a saturated bond exists between the 2- and 3-positions, the respective compounds may be denoted as 2,3,5,6 - tetrahydro - 6 - Ar - imidazo [2,1-b] thiazoles.

The novel compounds of this invention may be prepared by several methods as illustrated by the reactions shown in the following flow chart. Elevated temperatures may be advantageously employed during these reactions. Organic solvents of advantage in conducting the necessary reactions include 4 - methyl - 2 - pentanone, benzene, toluene, xylene, heptane, tetrahydrofuran, dioxane and ether. Where appropriate, solvents such as lower alkanols may be used, e.g., ethanol, butanol or 2-propanol.

A preferred method comprises, reacting a compound of formula (I), in which Ar is other than benzyl, with a thiazoli(di)ne of formula (II) to give a 3-substituted thiazoli(di)ne of formula (III) which may then be reduced to the corresponding carbinols of formula (IV). This reduction is carried out with suitable reducing agents, such as an alkali metal borohydride, e.g. lithium, potassium or sodium borohydride, in the presence of a suitable organic solvent, such as, an ether, e.g. diethylether, diethylene glycol or tetrahydrofuran, or an aliphatic alcohol, e.g. methanol, ethanol, 2-propanol or 2-butanol.

[*Price 4s. 6d.*]

FLOW CHART



An alternative method of preparing the compounds represented by formula (IV) comprises reacting a thiazoli(di)ne of formula (II) with a compound of formula (VII).

Acylation of these carbinols yields the corresponding compound of formula (V). The novel compounds (VI) of this invention may be obtained by ring closure of either of the compounds (IV) or (V). Ring closure can be achieved by heating compounds (IV) or (V) with a suitable condensing agent, e.g. thionyl chloride, phosphorus oxychloride, phosphorus pentachloride, zinc chloride or polyphosphoric acid, and, preferably, in the presence of a lower aliphatic acid anhydride, e.g. acetic anhydride or propionic anhydride.

Alternatively, the compounds (VI) of this invention may be prepared by ring closure of an approximately substituted ethylene diamine represented by formula (VIII), in which Ar may be benzyl, to yield a corresponding 2 - mercapto - imidazoline of formula (IX). This ring closure may be achieved with appropriate sulfur-containing reactants, e.g. carbon disulfide or thiocyanic acid. The resulting 2 - mercapto - imidazoline (IX) is then treated with a compound of formula (X) to yield the 2,3,5,6 - tetrahydro - 6 - Ar - imidazo [2,1-b] thiazoles (VI) of this invention. The 5,6 - dihydro - 6 - Ar - imidazo [2,1-b] thiazoles (VI) of this invention may be obtained by treating 2 - mercapto - imidazoline (IX) with an acetaldehyde derivative of formula (XI).

As used in the foregoing reaction schemes, the dotted line represents an optional bond; the symbol Ar is as previously indicated; the symbol X represents a reactive ester of the corresponding alcohol with a strong inorganic or organic acid, e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, *p*-toluene - sulfonic acid or methane sulfonic acid; the symbol Y represents oxygen or di-lower alkoxy and the symbol R represents hydrogen or an acyl group, which acyl group may be aliphatic or aromatic, e.g. acetyl, propionyl, butyryl, or benzoyl, although acetyl is preferred. The term "lower" when used herein refers to groups containing from 1 to 7 carbon atoms.

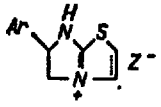
Acylation of compounds (III) wherein R is hydrogen to yield the corresponding compounds wherein R is an acyl group may be accomplished by the usual acylation technique with appropriate acylating agents such as the anhydride of a lower aliphatic acid or an acyl halide, e.g. acetyl chloride or benzoyl chloride. Similar acylation technique may be

used in the acylation of compounds (IV) to compounds (V).

An alternative method of preparing the subject compounds in which Ar is 6 - (4 - nitro - phenyl) - is by nitration of the corresponding 6 - phenyl compounds. Subsequent reduction of the 6 - (4 - nitro - phenyl) - compound with suitable reducing agents as heretofore described, or by catalytic hydrogenation, yields the corresponding 6 - (4 - amino - phenyl) compound.

The subject compounds may be isolated as the free bases by synthetic processes normally employed. These compounds, in base form, are convertible to therapeutically active non-toxic acid addition salts by treatment with an appropriate acid, for example an inorganic acid, such as hydrohalic acid, i.e. hydrochloric, hydrobromic, hydroiodic acid; sulfuric, nitric or thiocyanic acid; a phosphoric acid; or an organic acid, such as acetic, propionic, glycolic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxy-ethanesulfonic, benzene-sulfonic, *p*-toluenesulfonic, salicylic, *p*-aminosalicylic, 2-phenoxybenzoic or 2-acetoxybenzoic acid. Conversely, the salt form can be converted in the usual manner into the free base.

Without being bound to any theory thereby, it is believed that the ring nucleus of the subject bases may exist in the form exemplified by the structures (VIa) and (VIb) in the flow chart, whereas the acid addition salts may be exemplified by the following structure (XIII):



(XIII)

wherein Z^- represents the salt anion. Such forms are intended to be within the scope of this invention.

The subject novel compounds are useful as anthelmintics and have been found to be particularly effective, for example, against *Ascaridia galli, Heterakis gallinae* and *Capillaria obsignata* in chickens; against lungworms in sheep and cattle, e.g., *Dictyocaulus filaria* and *Dictyocaulus viviparus*; against gastro-intestinal worms in sheep and cattle, e.g., *Haemoncus contortos, Ostertagia* spp., *Trichostrongylus* sp., *Cooperia* sp., *Nematodirus fillicolis, Oesaphagostomum* sp., *Strongloides papillosus, Bunostomum trigonocephalum, Chabertia ovina* and *Trichuris ovis*; and against *Toxocara canis* and *Toxacaris leonina* in dogs.

Accordingly, this invention embraces methods of killing helminths which comprise treating infected subjects excluding horco sopuns with an effective anthelmintic amount of the novel compounds described herein. For this purpose, from about 1 to about 160 milligrams per kilogram of body weight may be advantageously employed. Also included within the scope of this invention are anthelmintic compositions comprising an effective anthelmintic amount of the subject compounds in combination with suitable carriers.

The subject compounds can be used, for example, in the form of pharmaceutical and veterinarian preparations containing an anthelmintic amount of said compounds or salts thereof in admixture or conjunction with a suitable organic or inorganic, solid or liquid pharmaceutical carrier, for example, water, gelatine, lactose, starch, magnesium sterate, talc, vegetable oils, gums or polyalkylene glycols. The compositions are formulated by conventional methods and may be in any one of the conventional pharmaceutical forms, for example, for oral and parental administration, such as solutions, suspensions, emulsions, injectables, powders, slugs, granules, capsules, tablets and pellets, including unit dosage forms thereof, as well as other convenient forms which might be suitable for veterinarian or pharmaceutical use. They may be sterilized, for example, for parenteral administration, and/or may contain assistants such as conventional excipients, preserving, stabilizing, wetting, dispersing, disintegrating or emulsifying agents, fillers, buffers, bacteriostats, bactericidal agents, sporicidal agents, thickening agents, preservatives and colouring agents. They may also contain further veterinary or therapeutically useful substances, including, for example, other known anthelmintics such as pyrvinium pamoate, piperazine citrate or 2 - β - methoxy - ethylpyridine. The new compounds and the anthelmintic compositions thereof may also be used as additives and pre-mixes to animal feeds, drinking water, etc.

In such compositions and formulations, the concentration of the subject compounds should be at least about 0.01% by weight, preferably at least about 0.05%. The concentration of compound may range widely above these figures, depending on the form the composition takes, and indeed, in some cases the concentration of the compound may go as high as about 50%. The amount administered may also depend on the severity of the condition being treated or on the species being treated. Generally, the compositions per dosage unit may contain at least about 0.5 mg. of the subject imidazo [2,1-b] thiazoles and in some cases the amount per dosage unit may be as high as about 500 mg.

As mentioned above, compositions of the

subject imidazo [2,1-b] thiazoles may also contain other drugs of known veterinary utility, for example, other anthelmintic agents such as the drug known as methyridine (2 - β - methoxyethylpyridine), which is described and claimed *per se* in U.K. patent specification No. 889,748. Such compositions containing 2 - β - methoxyethylpyridine are valuable for the removal of a wide range of worm infestations in sheep and cattle, are particularly effective against worm infestations containing members of the *Trichuris* sp., and may be formulated as described above so as to be suitable for either oral or parenteral administration.

For example, such compositions suitable for oral administration may be liquid or solid compositions. Suitable liquid compositions include, for example, aqueous concentrated solutions of the active ingredients, which solutions may optionally contain one or more buffers and/or stabilizing agents, for example sodium bisulfite, hydroxylamine or an acid-addition salt thereof, for example the hydrochloride. The liquid compositions also include, for example solutions in a vegetable oil, for example arachis oil, dimethylacetamide, poly-alkylene glycols. The solid compositions include tablets, slugs, pellets or capsules, which may be formulated using conventional excipients. Alternatively, the solid compositions may be in the form of dispersible compositions containing at least one absorbent solid, for example fuller's earth or kieselguhr. The solid compositions may be in the form of pre-mix compositions suitable for addition to animal foodstuffs, or in the form of medicated animal foodstuff compositions, for example compositions comprising the active ingredients and animal foodstuffs. Compositions suitable for parenteral administration include, for example, sterile injectable aqueous and non-aqueous solutions or suspensions.

As preferred compositions containing the subject imidazo [2,1-b] thiazoles and 2 - β - methoxyethylpyridine, there may be mentioned, for example, compositions containing between 50 and 200 parts by weight of 2 - β - methoxyethylpyridine or a salt thereof, for example, the hydrochloride, and 1.0—20 parts by weight of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole or a salt thereof, for example the hydrochloride. Such compositions may be formulated and administered in such a manner that there is administered a dose of 50—200 mg./kg. (of body-weight) of 2 - β - methoxyethylpyridine or a salt thereof, for example the hydrochloride, and 1.0—20 mg./kg. (of body weight) of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole or a salt thereof, for example the hydrochloride.

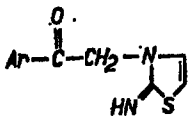
The invention is illustrated by, although not limited to, the following Examples. Examples I to VII illustrate the preparation of the starting materials.

EXAMPLE I

A mixture of 17.5 parts of 3 - chloro - phenacyl - bromide, 7.5 parts of 2 - amino - thiazole and 120 parts of acetonitrile is stirred and heated (water-bath) for one hour. After cooling the precipitated product is filtered off and dried, yielding 2 - imino - 3 - (3 - chloro - benzoyl - methyl) - thiazoline hydrobromide: m.p. 215—216°C.

Following the procedure of Example I, and replacing the 3 - chloro - phenacyl - bromide with equimolecular amounts of appropriate bromo - methylketones, and reacting these with 2 - amino - thiazoli(di)ne, the compounds listed in the following table are are obtained:

Compounds of the Formula:



Ar	tetrahydro or dihydro	base or salt	M.P. °C.
thienyl	tetrahydro	HBr	213—213.5
furyl	tetrahydro	HBr	202—203
C_6H_5	tetrahydro	HBr	200 (dec.)
3—NO_2—C_6H_4	tetrahydro	HBr	+ 300 (dec.)
3—Br—C_6H_4	tetrahydro	HBr	252—253.5
3—Cl—C_6H_4	tetrahydro	HBr	276—277 (dec.)
2—Cl—C_6H_4	tetrahydro	HBr	197—198
4—F—C_6H_4	tetrahydro	HBr	209—210
α-naphthyl	tetrahydro	HBr	192—202
2—NO_2—C_6H_4	tetrahydro	HBr	188.4—191.4
3—CF_3—C_6H_4	tetrahydro	HBr	259—263.5
2,3,4-triCl-C_6H_2	tetrahydro	HBr	282—283
thienyl	dihydro	base	117.5—118.5
furyl	dihydro	HBr	198—198.5
3—NO_2—C_6H_4	dihydro	HBr	245—309 (dec.)
4—F—C_6H_4	dihydro	HBr	235—237.5
3—Br—C_6H_4	dihydro	HBr	203—205

EXAMPLE II

A mixture of 13.5 parts 4 - nitro - phenacylbromide, 7.1 parts 2 - (acetyl - amino) - thiazole and 80 parts toluene is heated in a sealed tube for about 96 hours at a temperature between 105—115°C. The formed precipitate is filtered off, washed with boiling toluene and recrystallized from 120 parts methanol, yielding 2 - (acetyl - imino) - 3 - (4 - nitro - benzoyl - methyl) - thiazoline hydrobromide; m.p. 216—218°C.

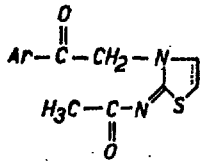
EXAMPLE III

A mixture of 21 parts of 2 - imino - 3 - (3 - bromo - benzoyl - methyl) - thiazolidine hydrobromide, 16.8 parts of acetic anhydride, 16.8 parts of dry pyridine and 275 parts of dry chloroform is stirred and refluxed for 6 hours. After cooling, the reaction mixture is washed with ammonium hydroxide solution. The organic layer is separated, dried and evaporated. The oily residue is dissolved in 2-propanol and gaseous hydrogen chloride is introduced into the solution. The precipitated salt is filtered off and dried, yielding 2 - (acetyl - imino) - 3 - (3 - bromo - benzoyl - methyl) - thiazolidine hydrochloride; m.p. 162—165°.

Following the procedure of Example III, and

replacing the 2 - imino - 3 - (3 - bromo - benzoyl - methyl) - thiazoli(di)ne with equimolecular amounts of appropriate 2 - imino - 3 - (acylmethyl) - thiazoli(di)ne, the compounds listed in the following table are obtained:

Compounds of the Formula:



Ar	tetrahydro or dihydro	M.P. °C.
thienyl	tetrahydro	145.5—147
furyl	tetrahydro	132—135
C_6H_4	tetrahydro	140—141
3—NO_2—C_6H_4	tetrahydro	116—145
3—Cl—C_6H_4	tetrahydro	90.5—91.5
2—Cl—C_6H_4	tetrahydro	116—116.5
4—F—C_6H_4	tetrahydro	126—127
α-naphthyl	tetrahydro	104—122.5
2—NO_2—C_6H_4	tetrahydro	120—123.5
3—CF_3—C_6H_4	tetrahydro	108—109
2,3,4-triCl-C_6H_2	tetrahydro	122.5—126
thienyl	dihydro	146—147.5
furyl	dihydro	142.5—143.5
3—NO_2—C_6H_4	dihydro	151—152
3—Cl—C_6H_4	dihydro	145—147
C_6H_5	dihydro	153—154

EXAMPLE IV

To a mixture of 50 parts of 2 - imino - 3 - [(4 - fluoro - benzoyl) - methyl] - thiazoline hydrobromide and 320 parts methanol are added portionwise 12 parts sodium tetrahydridoborate, while keeping a temperature of 0°C. (ice-bath). After the addition is complete (slightly exothermic reaction), the mixture is stirred for one hour at room temperature. The precipitated solid is filtered off and the filtrate is evaporated. The combined solids are stirred for 10 minutes with 175 parts hydrobromic acid 25%. The precipitated salt is filtered off, washed with 2-propanol and dried, yielding dl - 2 - imino - 3 - [2 - hydroxy - 2 - (4 - fluoro - phenyl) - ethyl] - thiazoline hydrobromide; m.p. 196—203°C.

Following the procedure in Example IV, and replacing the 2 - imino - 3 - [(4 - fluoro - benzoyl) - methyl] - thiazoline hydrobromide with an equimolecular amount of 2 - imino - 3 - [(3 - bromo - benzoyl) - methyl] - thiazoline hydrobromide, the com-

pound dl - 2 - imino - 3 - (β - hydroxy - 3 - bromo - phenethyl) - thiazoline hydrobromide is obtained; m.p. 245.5—246°C.

EXAMPLE V

A mixture of 15 parts of dl - 2 - imino - 3 - (β - hydroxy - 3 - bromo - phenethyl) - thiazoline hydrobromide, 24 parts of thionyl chloride and 115 parts acetic anhydride is stirred and refluxed for 30 minutes in an oil-bath. Then a second portion of 19 parts of thionyl chloride is added and the whole is stirred and refluxed for a further 30 minutes. The formed acetyl chloride is distilled off in an oil-bath at a temperature of 150—160°C. in the course of about 2 hours. The residue is evaporated. The oily residue is dissolved in a mixture of 300 parts of water and 30 parts of concentrated hydrochloric acid. This solution is boiled for a few minutes with activated charcoal, filtered hot and after cooling the filtrate to room temperature, a solid is precipitated. It is filtered off (filtrate is set aside) and dried, yielding dl - 2 - (acetyl - imino) - 3 - (β - acetoxy - 3 - bromo - phenethyl) - thiazoline hydrochloride; m.p. 143.5—149°C.

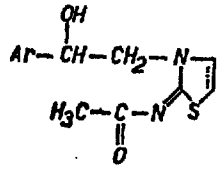
The filtrate which was set aside is alkalized with ammonium hydroxide solution and extracted with toluene. The extract is dried over sodium sulfate, filtered and evaporated. The oily residue is dissolved in acetone and this solution is evaporated again. The solid residue is recrystallized from a mixture of 64 parts benzene and 40 parts petroleum ether, to yield dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - 3 - bromo - phenethyl) - thiazoline; m.p. 151—152°C.

EXAMPLE VI

To a suspension of 9 parts of 2 - (acetyl - imino) - 3 - (3 - bromo - benzoyl - methyl) - thiazolidine hydrochloride in 80 parts of methanol are added 1.81 parts of sodium borohydride at a temperature between 0—5°C. After the addition is complete, the whole is stirred for one hour at room temperature. The reaction mixture is filtered from a solid precipitate and the filtrate is evaporated. The solid residue, together with the solid product which is filtered off, is triturated in water and the mixture is extracted with chloroform. The extract is dried and evaporated. The oily residue is crystallized in toluene, to yield dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - 3 - bromo - phenethyl) - thiazolidine; m.p. 141.5—142.5°C.

Following the procedure of Example VI, and replacing 2 - (acetyl - imino) - 3 - (3 - bromo - benzoyl - methyl) - thiazoli(di)ne with equimolecular amounts of appropriate 2 - (acetyl - imino) - 3 - (acylmethyl) - thiazoli(di)ne, the compounds listed in the following table are obtained:

Compounds of the Formula:



Ar	tetrahydro or dihydro	M.P. °C.
thienyl	tetrahydro	85.5—88
furyl	tetrahydro	110.5—112
C_6H_5	tetrahydro	100—103.5
3—NO_2—C_6H_4	tetrahydro	122—140
3—Cl—C_6H_4	tetrahydro	138—139
2—Cl—C_6H_4	tetrahydro	163—164
4—F—C_6H_4	tetrahydro	118—121
α-naphthyl	tetrahydro	176—184
2—NO—C_6H_4	tetrahydro	119—120
3—CF—C_6H_4	tetrahydro	142—143
2,3,4-triCl-C_6H_2	tetrahydro	156—156.5
thienyl	dihydro	132.5—133
furyl	dihydro	115—116.5
3—NO_2—C_6H_4	dihydro	138.5—154 (dec.)
3—Cl—C_6H_4	dihydro	140—141
C_6H_5	dihydro	158—159
4—NO_2—C_6H_4	dihydro	238—246

EXAMPLE VII

From 25.2 parts of dl - β - amino - phenethyl - amine dihydro - chloride the free base is liberated as follows: 25.2 parts dl - β - amino - phenethyl - amine dihydrochloride are dissolved in 40 parts water. This solution is alkalized with 9.6 parts of sodium hydroxide and extracted with ethanol. The precipitated sodium chloride is filtered off and to the filtrate are added 8.15 parts carbon disulfide (exothermic reaction). The mixture is stirred and refluxed for one hour in an oil-bath. Then there is added one part concentrated hydrochloric acid and the mixture is further stirred and refluxed for 10 hours. The reaction mixture is stirred overnight at room temperature. The precipitated product is filtered off, washed with water and acetone and dried, yielding dl - 2 - thio - 4 - phenyl - imidazolidine; m.p. 194—195.5°C.

Following the procedure of Example VII, and replacing the dl - β - amino - phenethyl - amine dihydrochloride with equimolecular amounts of dl - 1,2 - diamino - 3 - phenyl - propane dihydrochloride, the compound dl -

2 - mercapto - 4 - benzyl 2 - imidazoline is obtained; m.p. 152—154.5°C.

EXAMPLE VIII

To a solution of sodium ethoxide, prepared in the usual manner starting from 0.46 parts of sodium in 80 parts of ethanol, are added 3.6 parts of dl - 2 - thio - 4 - phenyl - imidazolidine. After the addition is complete, the whole is stirred and refluxed for 15 minutes. Then there are added 3.1 parts of chloroacetaldehyde-diethylacetal. The mixture is stirred and refluxed for one hour. After cooling, the ethanol is evaporated. To the residue are added 28 parts of concentrated hydrochloric acid and the unreacted starting material is filtered off. After refluxing the filtrate for one hour, the hydrochloric acid is evaporated. The residue is redissolved in 20 parts of water. The aqueous solution is alkalized with ammonium hydroxide and extracted with chloroform. The extract is dried and evaporated. The residue is dissolved in 20 parts boiling 2-propanol. To this hot solution is added a warm solution of an equivalent quantity of oxalic acid dihydrate in 20 parts of 2-propanol. After cooling to room temperature, the precipitated oxalate salt is filtered off and recrystallized from 40 parts of boiling 2-propanol. After cooling, the solid oxalate is filtered off, washed successively with 2-propanol and ether, and dried, yielding dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole oxalate; m.p. 183—184.5°C.

EXAMPLE IX

To a mixture of 75 parts of dl - 2 - imino - 3 - (β - hydroxy - phenethyl) - thiazoline hydrobromide and 184 parts of thionylchloride are added carefully 600 parts of acetic anhydride, while cooling in an ice-bath. When a homogeneous mixture is obtained, the cooling-bath is removed and the whole is stirred and refluxed for 10 minutes. Then the second part of 96 parts of thionyl chloride is added portionwise and the whole is stirred and refluxed for another 30 minutes. The formed acetylchloride is distilled off (internal temperature: 137°C). The residue is evaporated *in vacuo*. The residue is dissolved in a mixture of 800 parts of water and 80 parts of concentrated hydrochloric acid. After standing for 30 minutes, the mixture is filtered from some insoluble matter and the filtrate is alkalized with 200 parts of ammonium hydroxide and then extracted with toluene (successively: 120, 80 and 80 parts). The combined extracts are dried over magnesium sulfate, filtered, washed with 120 parts toluene and the filtrate is evaporated *in vacuo*. The residue is dissolved in a boiling mixture of 32 parts 2-propanol and 16 parts hexane. To this hot solution is added a hot solution of 31 parts oxalic acid dihydrate in 40 parts 2-propanol. After cooling to 4°C., the solid salt is filtered off, washed on the filter with 2-propanol and dried, yielding dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole oxalate; m.p. 186.8—187.5°C. (dec.).

Following the procedure of Example IX, and replacing the dl - 2 - imino - 3 - (β - hydroxy - phenethyl) - thiazoline hydrobromide with equimolecular amounts of dl - 2 - imino - 3 - [2 - hydroxy 2 - (4 - fluoro - phenyl) - ethyl] - thiazoline hydrobromide, the compound dl - 5,6 - dihydro - 6 - (4 - fluoro - phenyl) - imidazo [2,1-b] thiazole oxalate is obtained; m.p. 168—173°C.

EXAMPLE X

To 16 parts of thionyl chloride are added 4.5 parts of dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - 3 - bromo - phenethyl) - thiazolidine at a temperature below 10°C. while stirring. After the addition is complete, the whole is stirred for 2 hours at room temperature. Then there are added dropwise 50 parts of acetic anhydride at a temperated below 15°C. After the addition is complete, the formed acetyl chloride is distilled off, whereafter the mixture is stirred and refluxed for 2 hours. The reaction mixture is evaporated. The residue is dissolved in a mixture of 100 parts of water and 10 parts of hydrochloric acid. The solution is filtered. The filtrate is alkalized with ammonium hydroxide solution and extracted with toluene. The extract is dried over sodium sulfate and evaporated. The oily residue is dissolved in acetone and gaseous hydrogen chloride is introduced into the solution. The precipitated salt is filtered off and dried, yielding dl - 2,3,5,6 - tetrahydro - 6 - (3 - bromo - phenyl) - imidazo [2,1-b] thiazole hydrochloride; m.p. 194—195.5°C.

Following the procedure of Example X, and replacing the dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - 3 - bromo - phenethyl) - thiazolidine with equimolecular amounts of appropriate dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - Ar - ethyl) - thiazoli(di)ne, the compounds listed in the following table are obtained:

Compounds of the Formula:



Ar	tetrahydro or dihydro	salt	M.P. °C.
thienyl	tetrahydro	HCl	216—220
furyl	tetrahydro	$(COOH)_2$	176—176.5
C_6H_5	tetrahydro	$(COOH)_2$	195.5—196
3—NO_2—C_6H_4	tetrahydro	$(COOH)_2$	183—184
3—Cl—C_6H_4	tetrahydro	$(COOH)_2$	168—171
2—Cl—C_6H_4	tetrahydro	$(COOH)_2$	157—170 (dec.)
3—NO_2—C_6H_4	dihydro	$(COOH)_2$	192—195
4—NO_2—C_6H_4	dihydro	$(COOH)_2$	157—158
3—Br—C_6H_4	dihydro	$(COOH)_2$	153—155
3—Cl—C_6H_4	dihydro	$(COOH)_2$	155—157

EXAMPLE XI

A solution of 2 parts of dl - 2 - (acetyl - imino) - 3 - [2 - hydroxy - 2 - (2 - thienyl) - ethyl] - thiazoline in 16 parts of thionylchloride and 45 parts chloroform is stirred and refluxed for one hour. After cooling the whole is extracted with water. The acid aqueous solution is separated, washed with toluene, alkalized with ammonium hydroxide solution and extracted with chloroform. The extract is dried over magnesium sulfate and evaporated. The oily residue is dissolved in 40 parts boiling 2-propanol. To this warm solution is added a warm solution of an equivalent quantity of oxalic acid dihydrate in 2-propanol. After cooling to room temperated, the precipitated oxalate is filtered off and dried *in vacuo*, yielding dl - 5,6 - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole oxalate; m.p. 192—193°C.

Following the procedure of Example XI, and replacing dl - 2 - (acetyl - imino) - 3 - [2 - hydroxy - 2 - (2 - thienyl) - ethyl] - thiazoline with equimolecular amounts of dl - 2 - (acetyl - imino) - 3 - [(2 - furyl) - 2 - hydroxy - ethyl] - thiazoline and dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - phenethyl) - thiazoline, the compounds dl - 5,6 - dihydro - 6 - (2 - furyl) - imidazo [2,1-b] thiazole oxalate; m.p. 166—173°C (dec.) and dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole oxalate; m.p. 185.5°C. (dec.) are obtained.

EXAMPLE XII

A mixture of 6 parts dl - 2 - (acetyl - imino) - 3 - [2 - hydroxy - 2 - (2 - thienyl) - ethyl] - thiazoline and 80 parts phosphorusoxychloride is heated in a water-bath for 2 hours at a temperature of 100°C. After cooling, the reaction mixture is poured into water. The whole is alkalized with ammonium hydroxide solution and extracted with toluene. The extract is dried over magnesium sulfate and evaporated *in vacuo*. The oily residue is dissolved in 40 parts boiling 2-propanol. To this warm solution is added a warm solution of an equivalent quantity of oxalic acid dihydrate in 2-propanol. After cooling to room temperature, the precipitated salt is filtered off and dried *in vacuo*, yielding dl - 5,6 - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole oxalate; m.p. 193—194°C.

An aqueous solution of this salt is alkalized with ammonium hydroxide and extracted with toluene. The extract is dried over magnesium sulfate and evaporated. The oily residue is crystallized from 12 parts xylene. The solid is filtered off and dried *in vacuo*, yielding dl - 5,6, - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole; m.p. 58—62°C.

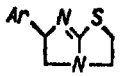
Following the procedure of Example XII, and replacing dl - 2 - (acetyl - imino) - 3 - [2 - hydroxy - 2 - (2 - thienyl) - ethyl] - thiazoline with equimolecular amounts of dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - phenethyl) - thiazoline, the compounds dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride is obtained; m.p. 175—177°C.

EXAMPLE XIII

To a stirred solution of 15 parts of dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - 4 - fluoro - phenethyl) - thiazolidine in 60 parts of dry chloroform is added dropwise 6.8 parts of thionylchloride at a temperature of 30°C. After the addition is complete, the whole is stirred for one hour at 30°C. Then there is added dropwise a solution of 21.9 parts of potassium carbonate in 40 parts of water at room temperature and after the addition is complete, the whole is further stirred for one hour at room temperature followed by stirring and refluxing for 1 hr. 30 min. After cooling there is added 100 parts of water. The chloroform layer is separated, dried over potassium carbonate, filtered and evaporated. The oily residue is dissolved in 16 parts of 2-propanol. To this solution is added 2-propanol previously saturated with gaseous hydrogen chloride. The precipitated product is filtered off and recrystallized from 2-propanol, to yield dl - 2,3,5,6 - tetrahydro - 6 - (4 - fluoro - phenyl) - imidazo [2,1-b] thiazole hydrochloride; m.p. 249—252°C.

Following the procedure of Example XIII, and replacing dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - 4 - fluoro - phenethyl) - thiazolidine with equimolecular amounts of dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - Ar - ethyl) - thiazolidine, the compounds listed in the following table are obtained:

Compounds of the formula:



Ar	salt	M.P. °C.
α-naphthyl	$(COOH)_2$	175—182
2—NO_2—C_6H_4	$(COOH)_2$	173.5—175.5
3—CF_3—C_6H_4	HCl	171—174
2,3,4-triCl-C_6H_2	HCl	261.5—264

EXAMPLE XIV

A suspension of 7.5 parts of dl - 2 - mercapto - 4 - benzyl - 2 - imidazoline, 1.15 parts of lithium amide in 160 parts of xylene is stirred and refluxed for 15 minutes. After cooling the mixture is added to a solution of 10.4 parts of 1,2 - dibromo - ethane in 40 parts of xylene. After the addition is complete, the whole is stirred and refluxed for 30 minutes. Then there is added 10 parts of pyridine and the whole is further stirred and refluxed for another 30 minutes. After cooling the reaction mixture, there is added successively 100 parts of water and 20 parts of ammonium hydroxide. The aqueous layer is separated and extracted twice with chloroform. The combined organic layers are dried over magnesium sulfate and evaporated *in vacuo*. The oily residue is dissolved in 2-propanol and to this solution is added 2-propanol previously saturated with gaseous hydrogen bromide. The precipitated product is filtered off and dried *in vacuo*, yielding dl - 2,3,5,6 - tetrahydro - 6 - benzyl - imidazo [2,1-b] thiazole hydrobromide; m.p. 200—205.5°C.

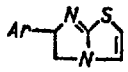
Following the procedure of Example XIV, and replacing dl - 2 - mercapto - 4 - benzyl - 2 - imidazoline with equimolecular amounts of dl - 2 - mercapto - 4(5) - phenyl - imidazoline, the compound dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride is obtained; m.p. 264-266°C.

EXAMPLE XV

From 6 parts of dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole oxalate the free base is liberated in a conventional manner and extracted with toluene. After drying, the organic solution is evaporated. The oily residue is dissolved in 80 parts of acetone and gaseous hydrogen chloride is introduced into the solution. The precipitated hydrochloride salt is filtered off and dried, yielding dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride; m.p. 261.5—264.5°C.

Following the procedure of Example XV, and replacing the hydrochloric acid with equimolecular amounts of the appropriate acid, and reacting this with the appropriate 6-substituted 5,6 - dihydro - imidazo [2,1-b] thiazole, the compounds listed in the following table are obtained:

Compounds of the Formula:



Ar	salt	M.P. °C.
furyl	HCl	206.5—209
thienyl	HCl	159—160.5
thienyl	HBr	163—164
thienyl	H_3PO_4	184—185
thienyl	malcate	109.2—110.8
thienyl	malonate	95.6—97.4
phenyl	HCl	174—176.5

EXAMPLE XVI

A mixture of 6 parts of dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole nitrate and 110 parts of sulphuric acid is stirred for 5 days at room temperature. Then the mixture is poured onto crushed ice. The whole is alkalized with ammonium hydroxide solution and then extracted with chloroform. The extract is dried over magnesium sulfate and evaporated. The oily residue is dissolved in 120 parts toluene and to this solution is added 2-propanol previously saturated with gascous hydrogen chloride. The precipitated solid is filtered off and recrystallized from 40 parts of ethanol, yielding dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole hydrochloride; m.p. 203.5—206°C. (dec.).

EXAMPLE XVII

A solution of 15 parts of dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole hydrochloride in 200 parts of methanol is filtered over activated charcoal. The filtrate is added to 10 parts of a 30% 2-propanol/ hydrochloric acid solution and the whole is hydrogenated at normal pressure and at room temperature in the presence of 3 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen is taken up (3 moles), hydrogenation is stopped. The catalyst is filtered off and the filtrate is evaporated, to yield dl - 2,3,5,6 - tetrahydro - 6 - (4 - amino - phenyl) - imidazo [2,1-b] thiazole dihydrochloride; m.p. 245—250°C. (dec.).

EXAMPLE XVIII

From an aqueous solution of 1.2 parts of dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride the free base is liberated in the usual manner. After extraction with chloroform, the extract is dried and evaporated. The oily residue is crystallized from 4 - methyl - 2 - pentanone, to yield dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole; m.p. 90—92°C.

EXAMPLE XIX

Thirteen chickens infected with Ascaridia galli and Heterakis gallinae and having an average body weight of 1.5 kilograms, are given about 40 mg/kg of body weight of dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride by the following oral routes: in gelatin capsules (7 chickens), in drinking water (3 chickens) and mixed with feed (3 chickens). The total output of faeces is collected every day for a period of four days and washed. The expelled worms in the faeces are collected by seiving, identified and counted. After the fourth day, the chickens are sacrificed and autopsied. The various internal organs of the digestive tract (e.g. stomach, duodenum, ilium, colon, etc.) are examined for the presence of worms. A total absence of worms is observed.

In accordance with the above procedure, similar results are obtained, (wherein from about 75—100 percent expulsion of worms are observed) with dl - 2,3,5,6 - tetrahydro -

6 - (2 - thienyl) imidazo [2,1-b] thiazole hydrochloride, dl - 2,3,5,6 - tetrahydro - 6 - (3 - chloro - phenyl) - imidazo [2,1-b] thiazole oxalate, dl - 2,3,5,6 - tetrahydro - 6 - (3 - bromo - phenyl) - imidazo [2,1-b] thiazole hydrochloride, dl - 2,3,5,6 - tetrahydro - 6 - (3 - nitro - phenyl) - imidazo [2,1-b] thiazole oxalate, dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride, dl - 5,6 - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole hydrochloride, and dl - 5,6 - dihydro - 6 - (3 - bromo - phenyl) - imidazo [2,1-b] thiazole oxalate.

EXAMPLE XX

Adult sheep, infected with a variety of worms, are given oral dosages of various anthelmintics in the quantities listed below. The amount of worms in the faeces and those remaining in the digestive tract of the killed sheep are determined as in Example XXI.

The results obtained are given in the following table, wherein:

A = number of worms expelled in faeces.
B = number of worms remaining in digestive tract.

$$\% = \frac{A}{A + B} \times 100$$

Compound I = dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride.

Compound II = dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride.

Compound III = dl - 5,6 - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole hydrochloride

TABLE

Compound I		Worm count												
		Trichostrongylus			*Ostertagia*			*Haemoncus*			*Nematodirus*			*St*
No. of Sheep	Dose mg/kg	A	B	%	A	B	%	A	B	%	A	B	%	A
2	40	2,165	0	100	605	0	100	—	—	—	7,538	0	100	4,625
2	20	40,888	56	100	1,376	0	100	—	—	—	918	0	100	3,252
2	10	12,928	1	100	120	0	100	—	—	—	10,204	0	100	25,356
1	2.5	4,145	4,245	50	—	—	—	—	—	—	—	—	—	—
Compound II														
2	40	4,359	0	100	—	—	—	—	—	—	11,060	0	100	184
2	10	5,581	0	100	—	—	—	—	—	—	7,364	0	100	—
1	2.5	—	6	0	—	12	0	245	1	99	—	—	—	—
Compound III														
2	40	874	1	100	—	—	—	—	—	—	7,516	0	100	91
2	10	3,866	2	100	—	—	—	—	—	—	—	—	—	496

TABLE I:

Worm		count											
		Strongyloides			*Bunostomum*			*Chabertia*			*Trichuris*		
B	%	A	B	%	A	B	%	A	B	%	A	B	%
0	100	4,625	0	100	17	11	60	182	0	100	7	0	100
0	100	3,252	88	98	28	2	93	145	1	99	105	31	80
0	100	25,356	3	100	137	34	80	245	0	100	5	5	50
—	—	—	—	—	42	1	98	23	2	91	0	4	0
0	100	184	2	99	332	0	100	176	0	100	24	0	100
0	100	—	—	—	—	—	—	12	0	100	—	2	0
—	—	—	1	0	—	—	—	4	5	45	—	2	0
0	100	91	1	99	47	0	100	87	1	98	0	2	0
—	—	496	202	70	90	3	96	65	0	100	—	34	0

EXAMPLE XXI

Adult sheep, infected with Dictyocaulus viviparus and young cattle infected with Dictyocaulus filaria are given oral dosages of various anthelmintics in the quantities listed below.

The infection rate is determined by counting the Dictyocaulus larvae found in the faeces obtained over a 24 hours-period.

The treated animals are divided in three groups:

1. In the first group the animals have been tracheotomised before treatment and a plastic bag is fixed in the tracheotubus to collect the expelled animals. After the fourth day the animals are sacrificed and autopsied. The lungs are examined for the presence of worms, which are identified and counted.
2. In the second group the effectiveness of the treatment is determined by identifying and counting the amount of larvae of Dictyocaulus, present in the faeces obtained over a 24 hours-period before treatment and in the faeces obtained over a 4 days-period after treatment.
3. In the third group the animals are treated as described for the second group. At the end of the experiment, the animals are sacrificed and autopsied. The lungs are then examined for the presence of worms.

The results obtained are given in the following table, wherein:

A = number of larvae per gram faeces before treatment (1 day).

B = number of larvae per gram faeces after treatment (4 days).

$$\%(L) = \frac{A}{A + B} \times 100$$

C = number of worms expelled in plastic bag.

D = number of worms remaining in the lungs.

$$\%(W) = \frac{C}{C + D} \times 100$$

Compound I = dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole hydrochloride.

Compound II = dl - 5,6 - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole hydrochloride.

Group 1)
Group 2) as identified above.
Group 3)

TABLE II:

COMPOUND I			Larvae count/gr faeces			Worm count			
Animal species	Number of animals	Dose mg/kg	A	B	% (L)	C	D	% (W)	Group
sheep	1	40	1,900	0	100	—	0	100	3
sheep	2	20	200	0	100	—	1	?	3
calf	2	40	12	0	100	—	—	—	2
COMPOUND II									
sheep	3	50	940	0	100	303	0	100	1
sheep	3	30	1,720	0	100	550	8	98	1

EXAMPLE XXII

5 Parts of water are added to a stirred, cooled solution of 5 Parts of dl - 6 - phenyl - 2,3,5,6 - tetrahydro imidazo [2,1-b] thiazole in 40 parts of 2 - β - methoxycthylpyridine. There is thus obtained a solution which, after suitable dilution, is suitable for oral administration to animals, and, after sterilization, is suitable for parenteral administration to animals, for the treatment of helminthiasis.

EXAMPLE XXIII

A mixture of 4 parts of hydroxylamine hydrochloride and 1 part of the sodium salt

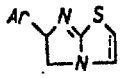
of ethylenediamine tetraacetic acid is dissolved in 400 parts of water, and the solution is cooled. The solution is stirred and 120 parts of sulphuric acid are slowly added. 360 Parts of 2 - β - methoxy - ethylpyridine and 36 parts of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole hydrochloride are then added successively to the stirred solution. The final volume of the solution is adjusted to 1000 ml. by the addition of water. There is thus obtained a drench suitable for oral administration to animals for the treatment of helminthiasis.

EXAMPLE XXIV

An aqueous solution containing 100 parts of 2 - β - methoxyethylpyridine and 15 parts of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole hydrochloride is administered orally at a dose of 100 mg/kg. (of body weight) of 2-β-methoxyethylpyridine and 15 mg./kg. (of body weight) of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole hydrochloride to sheep carrying infestations of *Haemonchus* spp., *Ostertagia* spp., *Trichostrongylus* spp., *Cooperia* spp., *Nemadodirus* spp., *Oesophagostomum* spp., *Trichuris* spp. and *Chabertia* spp. The animals are sacrificed 7 days after being dosed, and post-mortem examination shows that the percentage reduction in worm burden of each species is between 95% and 100% compared with untreated control animals.

WHAT WE CLAIM IS:—

1. An imidazo [2,1-b] thiazole having the formula:



or the therapeutically acceptable acid addition salts thereof, wherein the dotted line between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus represents an optional bond and Ar is a thienyl, furyl, phenyl, halophenyl, nitrophenyl, aminophenyl, trifluoromethylphenyl, naphthyl or benzyl group, provided that, when said Ar is benzyl, a saturated bond exists between 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus.

2. The compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitrophenyl) - imidazo [2,1-b] thiazole hydrochloride.

3. The compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - aminophenyl) - imidazo [2,1-b] thiazole hydrochloride.

4. The compound dl - 5,6 - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole hydrochloride.

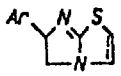
5. The compound dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole.

6. The therapeutically acceptable acid addition salts of dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole.

7. The compound dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole.

8. The therapeutically acceptable acid addition salts of dl - 2,3,5,6 - tetrahydro - 6 - phenyl imidazo [2,1-b] thiazole.

9. An anthelmintic composition comprising an effective amount of an imidazo [2,1-b] thiazole in admixture with a suitable carrier, said imidazo [2,1-b] thiazole having the formula:



or the therapeutically acceptable acid addition salts thereof, wherein the dotted line between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus represents an optional bond and Ar is a thienyl, furyl, phenyl, halophenyl, nitrophenyl, aminophenyl, trifluoromethylphenyl, naphthyl, or benzyl group, provided that, when said Ar is benzyl, a saturated bond exists between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus.

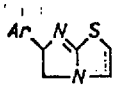
10. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole.

11. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole.

12. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole.

13. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - (4 - amino - phenyl) - imidazo [2,1-b] thiazole.

14. A method of killing helminths which comprises treating infected subjects excluding homo sapiens with an anthelmintic amount of an imidazo [2,1-b] thiazole having the formula:



or the therapeutically acceptable acid addition salts thereof, wherein the dotted line between the 2- and 3-positions of the imidazo

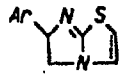
of ethylenediamine tetraacetic acid is dissolved in 400 parts of water, and the solution is cooled. The solution is stirred and 120 parts of sulphuric acid are slowly added. 360 Parts of 2 - β - methoxy - ethylpyridine and 36 parts of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole hydrochloride are then added successively to the stirred solution. The final volume of the solution is adjusted to 1000 ml. by the addition of water. There is thus obtained a drench suitable for oral administration to animals for the treatment of helminthiasis.

EXAMPLE XXIV

An aqueous solution containing 100 parts of 2 - β - methoxyethylpyridine and 15 parts of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole hydrochloride is administered orally at a dose of 100 mg/kg. (of body weight) of 2-β-methoxyethylpyridine and 15 mg./kg. (of body weight) of dl - 6 - phenyl - 2,3,5,6 - tetrahydro - imidazo [2,1-b] thiazole hydrochloride to sheep carrying infestations of *Haemonchus* spp., *Ostertagia* spp., *Trichostrongylus* spp., *Cooperia* spp., *Nemadodirus* spp., *Oesophagostomum* spp., *Trichuris* spp. and *Chabertia* spp. The animals are sacrificed 7 days after being dosed, and post-mortem examination shows that the percentage reduction in worm burden of each species is between 95% and 100% compared with untreated control animals.

WHAT WE CLAIM IS:—

1. An imidazo [2,1-b] thiazole having the formula:



or the therapeutically acceptable acid addition salts thereof, wherein the dotted line between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus represents an optional bond and Ar is a thienyl, furyl, phenyl, halophenyl, nitrophenyl, aminophenyl, trifluoromethylphenyl, naphthyl or benzyl group, provided that, when said Ar is benzyl, a saturated bond exists between 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus.

2. The compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitrophenyl) - imidazo [2,1-b] thiazole hydrochloride.

3. The compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - aminophenyl) - imidazo [2,1-b] thiazole hydrochloride.

4. The compound dl - 5,6 - dihydro - 6 - (2 - thienyl) - imidazo [2,1-b] thiazole hydrochloride.

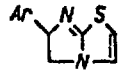
5. The compound dl - 5,6 - dihydro-6 - phenyl - imidazo [2,1-b] thiazole.

6. The therapeutically acceptable acid addition salts of dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole.

7. The compound dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole.

8. The therapeutically acceptable acid addition salts of dl - 2,3,5,6 - tetrahydro - 6 - phenyl imidazo [2,1-b] thiazole.

9. An anthelmintic composition comprising an effective amount of an imidazo [2,1-b] thiazole in admixture with a suitable carrier, said imidazo [2,1-b] thiazole having the formula:



or the therapeutically acceptable acid addition salts thereof, wherein the dotted line between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus represents an optional bond and Ar is a thienyl, furyl, phenyl, halophenyl, nitrophenyl, aminophenyl, trifluoromethylphenyl, naphthyl, or benzyl group, provided that, when said Ar is benzyl, a saturated bond exists between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus.

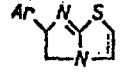
10. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole.

11. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 5,6 - dihydro - 6 - phenyl - imidazo [2,1-b] thiazole.

12. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole.

13. The anthelmintic composition of Claim 9 wherein the compound is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - (4 - amino - phenyl) - imidazo [2,1-b] thiazole.

14. A method of killing helminths which comprises treating infected subjects excluding homo sapiens with an anthelmintic amount of an imidazo [2,1-b] thiazole having the formula:



or the therapeutically acceptable acid addition salts thereof, wherein the dotted line between the 2- and 3-positions of the imidazo

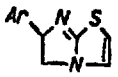
[2,1-b] thiazole nucleus represents an optional bond and Ar is a thienyl, furyl, phenyl, halophenyl, nitrophenyl, aminophenyl, trifluoromethylphenyl, naphthyl or benzyl group, provided that, when said Ar is benzyl, a saturated bond exists between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus.

15. The method of Claim 14 wherein the imidazo [2,1-b] thiazole is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole.

16. The method of Claim 14 wherein the imidazo [2,1-b] thiazole is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole.

17. The method of Claim 14 wherein the imidazo [2,1-b] thiazole is an acid addition salt of dl - 2,3,5,6 - tetrahydro - 6 - (4 - amino - phenyl) - imidazo [2,1-b] thiazole.

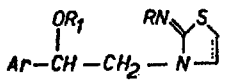
18. A process for making compounds of the general formula:



I

wherein Ar is a thienyl, furyl, phenyl, halophenyl, nitrophenyl, aminophenyl, trifluoromethylphenyl, naphthyl or benzyl group, provided that, when said Ar is benzyl, a saturated bond exists between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus, comprising

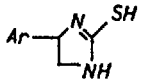
a) ring-closing a compound of the general formula



II

wherein Ar is as defined above, R_1 is an acyl radical, or a hydrogen atom, and R is a hydrogen atom or an acyl radical, provided, that when R_1 is acyl, R is also acyl, or

b) reacting a compound of the general formula

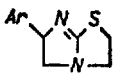


III

wherein Ar is as defined above, with a reactive di-ester of a compound of the general formula

$$HO—CH_2—CH_2—OH \qquad IV$$

to form a compound of the general formula



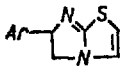
V

or,

c) reacting a compound of the general formula III with a reactive ester of a compound of the general formula

$$HO—CH_2—CH=Y \qquad VI$$

wherein Y represents oxygen or two lower alkoxy radicals, to form a compound of the general formula



VII

and, if desired, nitrating the obtained compound of formula I when Ar is a phenyl radical to form the corresponding 6 - (4 - nitro - phenyl) compound, and, if desired, reducing the obtained 6 - (4 - nitro - phenyl) compound to the corresponding 6 - (4 - amino - phenyl) compound, and, if desired, converting the obtained compounds of formula I into their therapeutically active, non-toxic acid addition salts by reaction with appropriate acids.

19. Process as claimed in Claim 18, which comprises ring-closing a compound of general formula II by contacting it with a suitable condensing agent, preferably in the presence of a lower aliphatic acid anhydride, to form a compound of the general formula I.

20. Process as claimed in Claim 19, which comprises ring-closing dl - 2 - (acetyl - imino) - 3 - (β - hydroxy - phenethyl) - thiazolidine to form dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole.

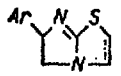
21. Process according to Claim 18, which comprises reacting the compound dl - 2 - thio - 4 - phenyl - imidazolidine with a reactive di-ester of ethylene glycol to form the compound dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole.

22. Process as claimed in any one of Claims 19 to 21, which comprises nitrating the compound dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole to form the compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole.

* C L M S *

23. Process as claimed in any one of Claims 19 to 22, which comprises reducing the compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole to form the compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - amino - phenyl) - imidazo [2,1-b] thiazole.

24. Compounds of the general formula



and the therapeutically acceptable acid addition salts thereof wherein Ar is a thienyl, furyl, phenyl, halophenyl, nitrophenyl, aminophenyl, trifluoromethylphenyl, naphthyl or benzyl group, provided that, when said Ar is benzyl, a saturated bond exists between the 2- and 3-positions of the imidazo [2,1-b] thiazole nucleus, whenever prepared by the process of Claim 18 or by any obvious chemical equivalent thereof.

25. The compound dl - 2,3,5,6 - tetrahydro - 6 - phenyl - imidazo [2,1-b] thiazole, whenever prepared by the process of Claim 21 or by any obvious equivalent thereof.

26. The compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - nitro - phenyl) - imidazo [2,1-b] thiazole, whenever prepared by the process of Claim 22 or by any obvious chemical equivalent thereof.

27. The compound dl - 2,3,5,6 - tetrahydro - 6 - (4 - amino - phenyl) - imidazo [2,1-b] thiazole, whenever prepared by the process of Claim 23 or by any obvious chemical equivalent thereof.

28. A process for preparing an imidazo [2,1-b] thiazole of general formula VI or its addition salts substantially as described herein with reference to the foregoing Examples I to XVIII.

29. Imidazo [2,1-b] thiazoles of general formula VI and their addition salts, when prepared by the process of Claim 28.

JANSSEN PHARMACEUTICA N.V.
Per: Boult, Wade & Tennant,
112, Hatton Garden,
London, E.C.1.
Chartered Patent Agents.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1966. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

ERRATA

SPECIFICATION No. 1,043,489
Amendment No. 1

Page 2, line 20, *for* "approximately" *read* "appropriately"
Page 3, lines 52 and 53, *for* "strongloides" *read* "strongyloides"
Page 6, Formula Table, Column 1, *for* "C_6H_4" *read* "C_6H_5"
Page 8, Formula Table, Column 1, *for* "CF" *read* "CF_3"
Page 9, line 1, *after* "benzl" *insert* "hyphen"
Page 9, line 74, *after* "hydroxy" *insert* "hyphen"
Page 10, lines 17 and 18, *for* "temperated" *read* "temperature"
Page 11, line 6, *for* "compounds" *read* "compound"

THE PATENT OFFICE
7th November 1966

* C L M S *