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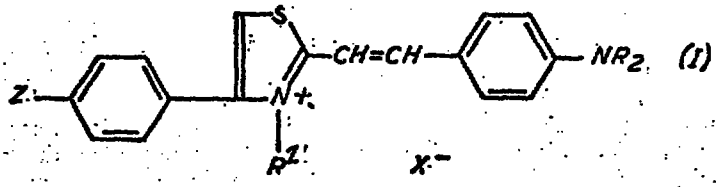


(54) THIAZOLE DERIVATIVES

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1, a company incorporated in England do hereby declare the invention which was communicated from BURROUGHS WELLCOME & Co. (U.S.A.) INC., of 1, Scarsdale Road, Tuckahoe, New York 10707, a Company incorporated in the State of New York, United States of America, 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:—

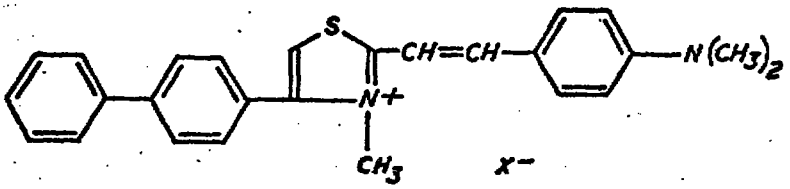
This invention relates to quaternary ammonium salts, their synthesis, pharmaceutical compositions containing them, and their use as therapeutic agents.

The present invention provides compounds of formula (I)



wherein NR_2 is dimethylamino, diethylamino or pyrrolidino, R^1 is methyl or ethyl, Z is phenyl, and X^- is a pharmaceutically acceptable anion of an acid; or NR_2 is pyrrolidino, R^1 and X^- are as defined above, and Z is hydrogen, halogen, phenoxy or *p*-methoxyphenyl wherein, when Z is halogen, the halogen is chlorine, bromine, iodine or fluorine.

The compounds of formula (I) have been found active against parasitic nematodes, specially hookworms, infecting the gastro-intestinal tract of warm-blooded animals. Thus the compounds have been found active against infections of *Syphacia obvelata* in the mouse, *Strongyloides ratti* in the rat, *Nematospiroides dubius* in the mouse, and *Ancylostoma caninum* and *Uncinaria stenocephala* in the dog. An important compound of formula (I) has the formula



and the iodide salt is active against hookworm in dogs and cats at doses of 5 mg./kg., and has an oral LD_{50} in mice of 1650 mg./kg.

Examples of other compounds of formula (I) are

2-(*p*-pyrrolidinostyryl)-4-phenylthiazole methiodide

2-(*p*-pyrrolidinostyryl)-4-(*p*-chlorophenyl)thiazole methiodide

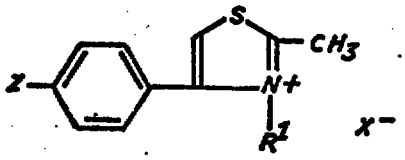
2-(*p*-dimethylaminostyryl)-4-(*p*-biphenylyl)thiazole ethiodide

2-(*p*-diethylaminostyryl)-4-(*p*-biphenylyl)thiazole methiodide

2-(*p*-pyrrolidinostyryl)-4-(*p*-biphenylyl)thiazole methiodide
2-(*p*-pyrrolidinostyryl)-4-(*p*-biphenylyl)thiazole ethiodide
2-(*p*-pyrrolidinostyryl)-4-(*p*-bromophenyl)thiazole methiodide
2-(*p*-pyrrolidinostyryl)-4-phenylthiazole ethiodide
2-(*p*-pyrrolidinostyryl)-4-(*p*-chlorophenyl)thiazole ethiodide
2-(*p*-pyrrolidinostyryl)-4-(*p*-bromophenyl)thiazole ethiodide
2-(*p*-pyrrolidinostyryl)-4-(*p*-fluorophenyl)thiazole methiodide
2-(*p*-pyrrolidinostyryl)-4-(*p*-phenoxyphenyl)thiazole methiodide
2-(*p*-pyrrolidinostyryl)-4-(*p*-methoxybiphenylyl)thiazole methiodide

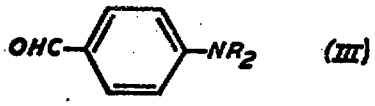
Unless otherwise indicated, references in the specification and claims to styrylthiazolium salts of formula (I) mean salts of a pharmaceutically acceptable anion.

The compounds of formula (I) may be made by any method known for preparing compounds of an analogous chemical structure. Thus, they may be prepared by the reaction of a thiazolium compound of the formula (II)



(II)

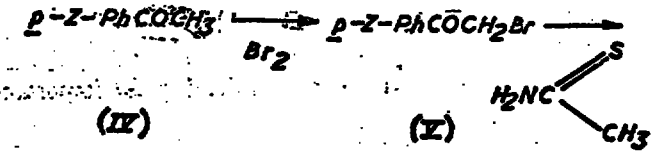
with an aldehyde of the formula (III)



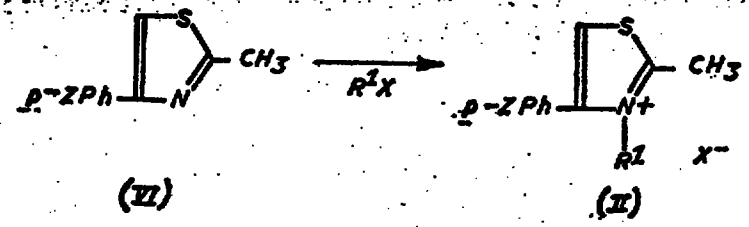
(III)

wherein Z, R^1, NR_2 and X^- are defined above. The reaction is preferably carried out in the presence of a basic catalyst such as piperidine, but other bases of comparable or greater basic strength may be used, for examples amines (pyrrolidine, *N*-methylpyrrolidine) or an alkali metal hydroxide or an alkoxide. The reaction is conveniently carried out in the presence of a liquid medium which is, or contains, a polar liquid, in which the reactants may be dissolved or suspended in a finely divided form. The liquid medium for the reaction is preferably a lower alcohol (optionally containing water) such as methanol, ethanol or industrial methylated spirits, or may be some other polar medium not reactive to the reactants such as dimethyl sulphoxide or sulfolane. The reaction is preferably conducted at a temperature from 20° to the boiling point of the reaction mixture.

The intermediate 2 - methyl - 3 - R^1 - 4 - Z - phenylthiazolium salts of formula (II) may be prepared by the following sequence of reactions, the last step providing for the quaternisation of the 2 - methyl - 4 - Z - phenylthiazole of formula (VI) by a methyl or ethyl halide,



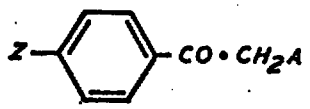
(IV) (V)



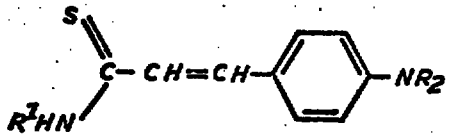
(VI) (II)

where the symbols Z, R^1 and X^- have the meanings given above.

The compounds of formula (I) may also be prepared by the reaction of a phenacyl derivative of formula (VII) with a thiocinnamamide of formula (VIII)

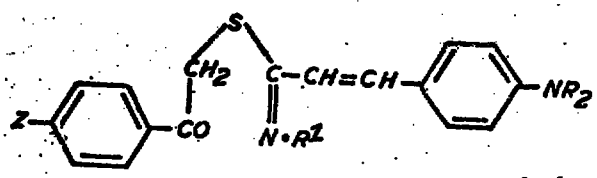


(VII)



(VIII)

wherein Z, R^1 and NR_2 are as defined above, and A is a nucleophilic group or atom for example chlorine, bromine and iodine. This reaction proceeds via an intermediate thioimidate of formula (IX)

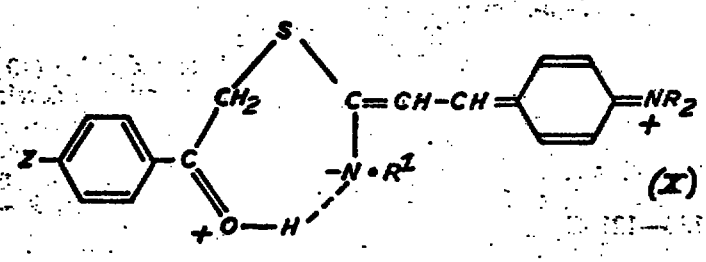


(IX)

wherein Z, R^1 and NR_2 are as defined above, and this thioimidate itself, if desired, may be isolated and then converted to a compound of formula (I) as described below. The compounds of formula (I) are formed by the reaction of the phenacyl derivative of formula (VII) and the thiocinnamamide of formula (VIII) under conditions which convert the thioimidate intermediate (IX) to a compound of formula (I). In general, heating the reactants, or reacting them in the presence of an acid, will tend to form the compounds of formula (I). A temperature of 80 to 150°C is conveniently employed to effect a rapid conversion to the compounds of formula (I). The acid may be a mineral acid such as hydrochloric or hydrobromic acid and preferably corresponds to the nucleophilic group or atom A which provides the anion X^- of formula (I). The reaction is preferably performed in the presence of a polar liquid medium for example a lower alkanol such as ethanol or butanol, or a water/butanol mixture. The optimum reaction conditions for forming the compounds of formula (I) vary according to the nature of the thioimidate intermediate, the group A and the liquid medium employed.

Further salts of compounds of formula (I) may of course be prepared by double decomposition, if desired, before or after the isolation of the end product of the reaction.

The infra-red spectra of the acid addition salts of the thioimidates of formula (IX) show no absorption typical of the keto-group or its enol form, and nuclear magnetic resonance measurement suggests that a resonance structure of formula (X) makes a substantial contribution to the molecule.



(X)

The thioimidates of formula (IX) and their acid addition salts may themselves be converted to the compounds of formula (I) by treatment with an acid, preferably a mineral acid for example hydrochloric or hydrobromic acid, which should preferably

correspond to the thioimidate salt, if used, and to the desired thiazolium salt of formula (I). The acid addition salts of the thioimidates of formula (IX) may also be converted to the compounds of formula (I) by heating the salts, preferably in a polar liquid medium, for example a lower alkanol such as butanol, conveniently at a temperature of 80 to 150°C. If desired, the thiazolium salt product may then be converted by double decomposition into further salts; for example the chloride and bromide salts of compounds of formula (I) may be converted to the iodide salts by reaction with potassium iodide, either before or after isolation of the end-product of the reaction. In respect of the thioimidates of formula (IX), reference is made to Divisional Application No. 7183/71 (Serial No. 1244962).

The activity against nematodes in the compounds of formula (I) resides in the cation, and the nature of the anion X^- is unimportant providing that the salt is pharmaceutically acceptable. Examples of suitable salts are chloride, bromide, iodide, sulphate and methosulphate. The iodide and methosulphate salts are preferred since they can be conveniently introduced in the quaternisation step by the use of the appropriate ethyl or methyl iodide or sulphate. The bromide salt may be prepared by use of methyl or ethyl bromide. Other salts may be prepared by conventional procedures, for example by replacing the anion in one of the above-mentioned salts by double decomposition, of either the 2 - methyl - 3 - R^1 - 4 - Z - phenylthiazolium salt or the 2 - (*p* - R_2 - aminostyryl) - 3 - R^1 - 4 - Z - phenylthiazolium salt. For example the chloride salts may be prepared from the iodide salts by shaking the latter with silver chloride in alkanolic solution.

For the treatment of nematode infections in warm-blooded animals, a compound of formula (I) is administered in an orally ingestible pharmaceutical composition comprising a compound of formula (I) and an acceptable carrier therefor. For administration of the compounds of formula (I) in dry solid form, they may be presented as capsules, granules, pills, powders, tablets, boluses, or in a gelatin cube, containing the desired amount of the compound distributed in such carriers as are usually employed. The compositions are prepared by intimately and uniformly mixing the active ingredient with the carrier which may comprise one or more diluents, filiers, disintegrating agents and binders. Boluses and tablets may of course be compounded by techniques well known in the art, for example by compression on a tabletting machine. The tablets may be formed so as to disintegrate rapidly, or to provide a prolonged or delayed action or to provide a predetermined release of the active ingredient at successive intervals. The tablets also may be coated. Capsules are readily prepared by mixing the active ingredient with the carrier and filling into the capsule.

The compounds of formula (I) may also be administered in a liquid preparation or as a component of the feed of the animal. Liquid preparations may comprise a suspension or solution of the active ingredient in water or in a vegetable or mineral oil or an emulsion thereof. The liquid carrier itself may consist of one or more ingredients for example liquid diluents, buffers, bacteriostats, sweeteners, colouring matter, dispersing agents, suspending agents and emulsifiers.

The invention therefore further provides a method for the treatment of a nematode infection in warm-blooded animals excluding man comprising the oral administration of a compound of formula (I) to the host of the infection. It also provides an orally ingestible pharmaceutical composition comprising a compound of formula (I) together with an acceptable carrier therefor, and a method of preparing such a composition by admixture of the components.

The following examples illustrate the invention. All temperatures are in degrees Celsius.

EXAMPLE 1

2-(*p*-Dimethylaminostyryl)-4-(*p*-biphenylyl)-thiazole methiodide

p-Phenyl phenacyl bromide (27.5 g., 0.1M) and thioacetamide (10 g., 0.133M) were mixed and heated in methanol (150 ml.). The reaction mixture developed a strong acidic reaction almost at once. After heating at 100° for 1—2 hours, a part of the methanol was evaporated, and water and ammonia were added thus precipitating the thiazole base. This was collected and purified by recrystallisation from methanol and gave colourless crystals of 2-methyl-4-*p*-biphenylyl thiazole (23 g., 90—95% yield) melting at 120—121°C.

A solution of 2-methyl-4-*p*-biphenylyl thiazole (25 g., 0.1M) and methyl iodide (22 g.) in dimethylformamide and (70 ml.) was heated for 6—8 hours at 100°C. Upon addition of excess ether and cooling, there was obtained 2-methyl-4-(*p*-biphenylyl)-

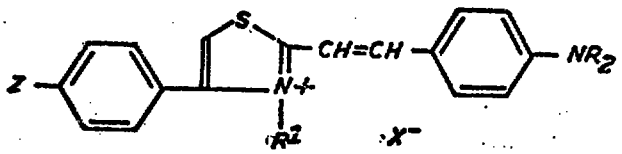
thiazole methiodide (30—32 g., 75—80%). After purification by digesting with hot methanol, this compound had a melting point of 272—273°C.

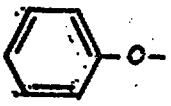
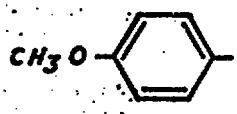
A suspension of 2-methyl-4-(*p*-biphenylyl)thiazole methiodide (79 g., 0.02M) and *p*-dimethylaminobenzaldehyde (4.5 g.) in hot methanol (90 ml.) containing piperidine (2 ml.) was heated on a steam bath for 2 hours. An insoluble red precipitate was formed in less than 5 minutes — but because the starting compound (thiazole methiodide) was rather insoluble in methanol, the reaction mixture was digested hot for about 2 hours to ensure nearly complete transformation of this insoluble reactant into the insoluble product.

The product was collected from the cooled methanol and the solid was washed well with methanol and with ether. After purification by digestions with hot methanol and washings with methanol and ether there was obtained red crystals of 2-(*p*-dimethylaminostyryl)-4-(*p*-biphenylyl)thiazole methiodide, melting at 253—256°C.

EXAMPLES 2 TO 12

By the method described in Example 1 the following were prepared, all salts being characterised as iodides.



Example No.	Z	R^1	NR_2	M.P., °C.
2	H	CH_3	$N(CH_2)_4$	234—235
3	Cl	CH_3	$N(CH_2)_4$	219—220
4	C_6H_5	C_2H_5	$N(CH_3)_2$	233—235
5	C_6H_5	CH_3	$N(C_2H_5)_2$	208—209
6	C_6H_5	CH_3	$N(CH_2)_4$	262—263
7	C_6H_5	C_2H_5	$N(CH_2)_4$	264—265
8	Br	CH_3	$N(CH_2)_4$ (hemihydrate)	211—213
9	Br	C_2H_5	$N(CH_2)_4$	223—225
10		CH_3	$N(CH_2)_4$ (hemihydrate)	214—215
11		CH_3	$N(CH_2)_4$ (hemihydrate)	279—280
12	F	CH_3	$N(CH_2)_4$	238—239

Thiazolium intermediates used in the preparation of Examples 2 to 12 had the following melting points:—

3-Ethyl-2-methyl-4-(*p*-bromophenyl)thiazolium iodide, 209—210°
3-Ethyl-2-methyl-4-(*p*-biphenylyl)thiazolium iodide, 236—237°
2,3-Dimethyl-4-(*p*-phenoxyphenyl)thiazolium iodide monohydrate, 185—186°
2,3-Dimethyl-4-(*p*-phenoxyphenyl)thiazolium iodide, 261—262°

EXAMPLE 13

A tablet was made of the following composition:—

2-(*p*-Dimethylaminostyryl)-4-(*p*-biphenylyl)thiazole methiodide (calculated as base)	50 mg.
Lactose B.P.	75 mg.
Microcrystalline Cellulose	80 mg.
Starch B.P.	25 mg.
Magnesium Stearate B.P.	3 mg.
Gelatin B.P.	4 mg.

The 2-(*p*-dimethylaminostyryl)-4-(*p*-biphenyl)thiazole methiodide, the lactose and the cellulose were granulated with a 10% solution of starch in 50% aqueous alcohol. The magnesium stearate and the gelatin were added to the dried granules and compressed to form tablets.

EXAMPLE 14

A paediatric suspension, containing 2-(*p*-pyrrolidinostyryl)-4-(*p*-biphenylyl)thiazole ethiodide equivalent to 200 mg. base in each 5 ml., was prepared from the following ingredients:—

2-(*p*-Pyrrolidinostyryl)-4-(*p*-biphenylyl)thiazole ethiodide equivalent to	200 mg. base/5 ml.
Sucrose B.P.	500.0 g.
Glycerin B.P.	100.0 g.
Microcrystalline cellulose mixture	25.0 g.
Sodium carboxymethylcellulose	1.0 g.
Methyl hydroxybenzoate B.P.	1.0 g.
Sodium Benzoate B.P.	1.0 g.
Purified water B.P.	to 1000.0 ml.

The microcrystalline cellulose mixture used was a blend of microcrystalline cellulose and carboxymethyl cellulose.

Two solutions were made up, one containing the 2-(*p*-pyrrolidinostyryl)-4-(*p*-biphenylyl)thiazole ethiodide, the methyl hydroxybenzoate and the glycerin, and the other containing the remaining ingredients. The two solutions were mixed using a high-speed stirrer.

EXAMPLE 15

A tablet was made from the following ingredients by the technique of moist granulation and compression:—

2-(*p*-Dimethylaminostyryl)-4-(*p*-biphenyl)thiazole methiodide	300 mg.
Microcrystalline Cellulose	150 mg.
Starch B.P.	60 mg.
Magnesium stearate B.P.	3 mg.

EXAMPLE 16

A dispersible powder was made from the following ingredients:—

(1)	2-(*p*-Dimethylaminostyryl)-4-(*p*-biphenylyl)thiazole methiodide	0.30 g.
(2)	Starch, B.P.	0.32 g.
(3)	Cetrimide, B.P.	0.10 g.
(4)	Sodium Saccharin, B.P.	0.02 g.
(5)	Polyvinylpyrrolidone	0.09 g.
(6)	Methylcellulose	0.15 g.
(7)	Calcium Silicate	0.02 g.

in each gramme.

Ingredients 1, 2 and 4 were granulated with a solution of 3, 5 and 6 in 50% aqueous ethanol, and the granules dried. Ingredient 7 was added to the dried granules.

EXAMPLE 17

2-(*p*-Dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl) thiazolium *p*-toluenesulphonate

2-Methyl-4-biphenylylthiazole (25.1 g.; 0.100 mole), dimethylformamide (100 ml.) and methyl-*p*-toluenesulphonate (37.2 g.; 0.200 mole) were mixed and heated on the steam bath at 80—90°C for a period of 43 hours. The solid which crystallised on cooling was filtered, washed with ether and recrystallised from isopropanol to give a product melting at about 180—182°C.

2,3-Dimethyl-4-*p*-biphenylylthiazolium *p*-toluenesulphonate (26.0 g.; 0.0594 mole), *p*-dimethylaminobenzaldehyde (13.4 g.; 0.0893 mole), methanol (275 ml.) and piperidine (6.3 ml.) were mixed and heated at reflux for 19 hours. The red solid which crystallised on cooling was filtered, washed with ether and recrystallised from methanol to give a product melting at about 248—254°C.

EXAMPLE 18

2-(*p*-Dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl) thiazolium methosulphate

2-Methyl-4-biphenylylthiazole (9.0 g.; 0.036 mole), dimethylformamide (40 ml.) and dimethyl sulphate (5.0 g.; 0.040 mole) were mixed and heated on a steam bath at 80—90°C for a period of 18 hours. The solid which crystallised upon cooling was recrystallised from ethanol to give a product melting at about 235—240° (decomp.).

2,3-Dimethyl-4-*p*-phenylylthiazolium methosulphate (4.0 g.; 0.0106 mole), *p*-dimethylaminobenzaldehyde (2.4 g.; 0.0160 mole), methanol (50 ml.) and piperidine (1.0 ml.) were mixed in the cold and then heated at reflux for 18 hours. On cooling and the addition of an excess of ether a red solid was precipitated which was filtered, washed with ether and dried at 80°C to give a red-coloured solid; the product melted at about 210—225°.

In a further experimental preparation, the product melted at 240—245°.

EXAMPLE 19

2-(*p*-Dimethylaminostyryl)-4-(*p*-biphenylyl)- thiazole methiodide

2-Methyl-4-biphenylylthiazole methiodide (5.0 g.; 0.0127 gm. moles) and *p*-dimethylaminobenzaldehyde (2.3 g.; 0.0154 gm. moles) were mixed in chloroform (32 ml.); piperidine (1.3 ml.) was added and the mixture stirred and heated to reflux. After about 1 hour the mixture was dark red and apparently homogeneous. The mixture was stirred at reflux for 20 hours and then cooled to 15—20°C. The product was precipitated by the addition of cold methanol (60 ml.), filtered and washed with methanol (10 ml.). After drying at 80—90°C, the product was identified as 2-(*p*-dimethylaminostyryl)-4-(*p*-biphenylyl)thiazole methiodide.

EXAMPLE 20

2-(*p*-Pyrrolidinostyryl)-4-phenylthiazole ethiodide

A mixture of phenacyl bromide (140 g.; 0.7M), methanol (500 ml.) and thioacetamide (65 g.) was warmed gradually then heated for 1—2 hours on a steam bath. About 1/2 of the methanol was allowed to evaporate during this heating and then water (300 ml.) and excess concentrated ammonium hydroxide were added to a pH of 10—11. The insoluble product was filtered off by suction and washed with much cold water. After two recrystallisations from methanol there was obtained 92 g. (75—80%) of pure 2-methyl-4-phenylthiazole, melting at 68—69°C.

A mixture of the above thiazole (35 g.; 0.2M) in dimethylformamide (75 ml.) containing ethyl iodide (25 ml.; 48 g.) was heated for 96 hours at 100°C. After cooling the product was precipitated with ether. Two further crystallisations from methanol-ether mixtures yielded 45 g. (67—70%), m.p. 175—176°C, of 2-methyl-4-phenylthiazole ethiodide.

A mixture of the ethiodide (5 g.; 0.015M) described above, *p*-pyrrolidinobenzaldehyde (3 g.), methanol (40 ml.), and piperidine (2 ml.) was heated for 1—2 hours at 100°C. The product was precipitated with ether, and had a m.p. 230—233°C. After an additional crystallisation from methanol the product melted at 228—230°C.

EXAMPLE 21

2-(*p*-Pyrrolidinostyryl)-4-(*p*-chlorophenyl)- thiazole ethiodide

In similar fashion to Example 19, the reaction of *p*-chlorophenacyl bromide with

thioacetamide gave 2-methyl-4-*p*-chlorophenyl thiazole, m.p. 122—123°C, crystallised from methanol or hexane.

This thiazole, when heated for 48 hours with excess of ethyl iodide in dimethylformamide, gave the ethiodide in about 35% yield, m.p. 201—202°C, crystals from methanol-ether.

Condensation of this ethiodide with *p*-pyrrolidinobenzaldehyde in methanol with piperidine catalyst gave the product, m.p. 217—218°C, from methanol.

EXAMPLE 22

2-(*p*-Dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl)thiazolium salts

To a stirred suspension of *p*-dimethylaminocinnamic acid (Shoppee, *J. Chem. Soc.* 1930, 982) (47.75 g.) in chloroform (500 ml.) was added thionyl chloride (31.25 g.) with the mixture maintained at 10°C by cooling. After 30 minutes' stirring, the clear solution was added gradually to stirred aqueous methylamine (400 ml. of 25% solution) with the internal temperature kept at 0—5° by cooling, and the mixture stirred for another 30 minutes. The chloroform layer was separated and washed with water, dried, and evaporated. The residual solid, after washing with a little acetone to remove coloured impurities, was recrystallised from benzene to give almost colourless needles, m.p. 165—166°, of *p*-dimethylaminocinnamomethylamide.

A mixture of the foregoing methylamide (20.4 g.) and phosphorus pentasulphide (11.1 g.) in pyridine (70 ml.) was refluxed for 15 minutes, and then poured into water (200 ml.). A precipitated solid was collected, washed well with water and then with acetone. Recrystallisation from ethanol gave the pure *p*-dimethylaminocinnamothiomethylamide as yellow needles, m.p. 214—216°.

A solution of this thioamide (8.8 g.) and *p*-phenylphenacyl bromide (11.0 g.) in acetone (400 ml.) was boiled under reflux. Red solid soon began to precipitate and was collected and washed with acetone. The pure *p*-phenylphenacyl *N*-methyl-(*p*-dimethylaminocinnamo)thioimidate hydrobromide had m.p. 167—169°.

The thioimidate hydrobromide (5 g.) was suspended in water (50 ml.) and hydrobromic acid (80 ml. of 48%) and warmed for 5 minutes on a steambath during which time the red colour disappeared and the suspended solid became cream-coloured and crystalline. After cooling, the mixture was neutralised with sodium hydroxide solution, and a deep red solid was collected and washed well with water. This 2-(*p*-dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl) thiazolium bromide crystallised from methanol in deep red plates with a green reflex, m.p. 253—255°. The corresponding iodide, m.p. 253—255°, was obtained by treating a solution of the bromide in aqueous methanol with potassium iodide solution.

The thiazolium bromide was also obtained by warming a mixture of the above thioimidate hydrobromide with about 10 parts by weight of *N*-hydrobromic acid on the steam-bath for 1 hour, diluting with water, and collecting the thiazolium salt, m.p. 250—252°.

EXAMPLE 23

A solution of *p*-phenylphenacyl chloride (1.15 g.) and *p*-dimethylaminocinnamothiomethylamide (1.1 g.) in ethanol (50 ml.) was refluxed for 2 hours and then evaporated to dryness. The residue was crystallised from a mixture of ethanol and ethyl acetate to give hydrated red plates of *p*-phenylphenacyl *N*-methyl-(*p*-dimethylaminocinnamo)thioimidate hydrochloride, melting point 145—150°C.

This hydrochloride (2 g.) was warmed on the steam-bath with 0.5*N*-hydrochloric acid (20 ml.) for 30 minutes. Water (20 ml.) was added and the solution was cooled. Crystalline 2-(*p*-dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl)thiazolium chloride was collected and recrystallised from a mixture of ethanol and ethyl acetate to give red needles, m.p. 251—253°.

EXAMPLE 24

p-Phenylphenacyl *N*-methyl-(*p*-dimethylaminocinnamo)thioimidate hydrochloride was prepared as in Example 23. This salt (100 mg.) was heated in butanol (2 ml.) at 120° for 45 minutes. Ether was added to the cooled solution and the precipitated 2-(*p*-dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl)thiazolium chloride was collected, m.p. 251—253°, after crystallisation from a mixture of ethanol and ethyl acetate. This was dissolved in aqueous methanol and potassium iodide solution added to give the corresponding iodide, m.p. 253—255°C.

EXAMPLE 25

A solution of *p*-phenylphenacyl iodide (330 mg.) (Rheinboldt and Perrier, *J. Amer. Chem. Soc.* 1947, *69*, 3148) and *p*-dimethylaminocinnamothiomethylamide (220 mg.)

in butanol (10 ml.) was heated at 120° for 2 hours. The solid crystallising on cooling was recrystallised from methanol to give 2-(*p*-dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl) thiazolium iodide.

EXAMPLE 26

p-Phenylphenacyl *N*-methyl-(*p*-dimethylaminocinnamo)thioimidate hydrochloride (100 mg.) was warmed on the steam-bath with water (1 ml.). After 30 minutes, methanol was added and the solution was clarified by filtration. Addition of potassium iodide solution precipitated 2-(*p*-dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl)thiazolium iodide, m.p. 250—252°, after recrystallisation from methanol.

EXAMPLE 27

p-Pyrrolidinocinnamic acid, obtained as yellow plates, m.p. 248° (efferv.), was prepared from *p*-pyrrolidinobenzaldehyde (U.S. Patent 3,075,975 (1963)) by the method of *J. Chem. Soc.*, 1930, 982. To a stirred suspension of this acid (21.7 g.) in chloroform (150 ml.) was added thionyl chloride (12.5 g.) with the mixture maintained between 0° and 10°C by cooling. After 30 minutes' stirring, the clear solution was added gradually to stirred aqueous methylamine (125 ml. of 25% solution) with the internal temperature kept at 10—15° by cooling, and stirred for another 30 minutes. The solid which had come out of solution was collected and recrystallised from ethanol to give *p*-pyrrolidinocinnamomethylamide as pale yellow needles, m.p. 237—239°.

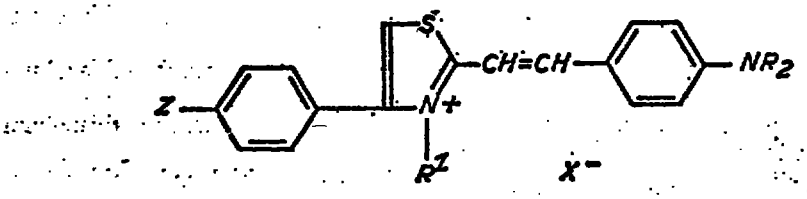
A mixture of the foregoing methylamide (2.3 g.) and phosphorus pentasulphide (1.2 g.) in pyridine (10 ml.) was refluxed for 15 minutes, and poured into water (100 ml.). The precipitated solid was collected and washed with water. Recrystallisation from pyridine gave the pure *p*-pyrrolidinocinnamothiomethylamide m.p. 262—264°.

A solution of the foregoing thioamide (1.23 g.), phenacyl bromide (0.98 g.) and hydrobromic acid (0.5 ml. of 47%) in alcohol (25 ml.) was refluxed for 2 hours. The crystals of 2-(*p*-pyrrolidinostyryl)-3-methyl-4-phenylthiazolium bromide which separated on cooling had m.p. 236—237° (efferv.). It was converted to the corresponding iodide, m.p. 233—234° (efferv.) by means of potassium iodide solution.

Similarly, from the reaction of *p*-dimethylaminocinnamothiomethylamide with *p*-phenylphenacyl bromide in the presence of hydrobromic acid, was obtained 2-(*p*-dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl)thiazolium bromide, m.p. 253—255°.

WHAT WE CLAIM IS:—

1. A styrylthiazolium salt of the formula



wherein NR_2 is dimethylamino, diethylamino or pyrrolidino, R^1 is methyl or ethyl, Z is phenyl, and X^- is a pharmaceutically acceptable anion of an acid; or NR_2 is pyrrolidino, R^1 and X^- are as defined above, and Z is hydrogen, halogen, phenoxy or *p*-methoxyphenyl wherein, when Z is halogen, the halogen is chlorine, bromine, iodine or fluorine.

2. A compound as claimed in claim 1 wherein NR_2 is pyrrolidino, R^1 is methyl or ethyl, Z is hydrogen, halogen or phenyl, and X^- is a pharmaceutically acceptable anion of an acid.

3. A compound as claimed in claim 1 wherein NR_2 is dimethylamino, diethylamino or pyrrolidino, R^1 is methyl or ethyl, Z is phenyl, and X^- is a pharmaceutically acceptable anion of an acid.

4. A compound as claimed in claim 1 wherein NR_2 is pyrrolidino, R^1 is methyl or ethyl, Z is phenoxy or *p*-methoxyphenyl, and X^- is a pharmaceutically acceptable anion of an acid.

5. A compound as claimed in claim 1 or 2 wherein halogen is chlorine.

6. A compound as claimed in claim 1 or 2 wherein halogen is bromine.

7. A compound as claimed in claim 1 or 2 wherein halogen is iodine.

8. A compound as claimed in claim 1 or 2 wherein halogen is fluorine.

9. A compound as claimed in any preceding claim wherein X^- is the anion of a hydrogen halide acid.

10. A compound as claimed in claim 9 wherein the anion is chloride.

11. A compound as claimed in claim 9 wherein the anion is iodide.

in butanol (10 ml.) was heated at 120° for 2 hours. The solid crystallising on cooling was recrystallised from methanol to give 2-(*p*-dimethylaminostyryl)-3-methyl-4-(*p*-biphenylyl) thiazolium iodide.

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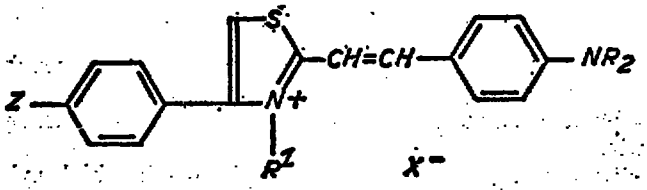
A mixture of the foregoing methylamide (2.3 g.) and phosphorus pentasulphide (1.2 g.) in pyridine (10 ml.) was refluxed for 15 minutes, and poured into water (100 ml.). The precipitated solid was collected and washed with water. Recrystallisation from pyridine gave the pure *p*-pyrrolidinocinnamothiomethylamide m.p. 262—264°.

A solution of the foregoing thioamide (1.23 g.), phenacyl bromide (0.98 g.) and hydrobromic acid (0.5 ml. of 47%) in alcohol (25 ml.) was refluxed for 2 hours. The crystals of 2-(*p*-pyrrolidinostyryl)-3-methyl-4-phenylthiazolium bromide which separated on cooling had m.p. 236—237° (efferv.). It was converted to the corresponding iodide, m.p. 233—234° (efferv.) by means of potassium iodide solution.

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WHAT WE CLAIM IS:—

1. A styrylthiazolium salt of the formula



wherein NR_2 is dimethylamino, diethylamino or pyrrolidino, R^1 is methyl or ethyl, Z is phenyl, and X^- is a pharmaceutically acceptable anion of an acid; or NR_2 is pyrrolidino, R^1 and X^- are as defined above, and Z is hydrogen, halogen, phenoxy or *p*-methoxyphenyl wherein, when Z is halogen, the halogen is chlorine, bromine, iodine or fluorine.

2. A compound as claimed in claim 1 wherein NR_2 is pyrrolidino, R^1 is methyl or ethyl, Z is hydrogen, halogen or phenyl, and X^- is a pharmaceutically acceptable anion of an acid.

3. A compound as claimed in claim 1 wherein NR_2 is dimethylamino, diethylamino or pyrrolidino, R^1 is methyl or ethyl, Z is phenyl, and X^- is a pharmaceutically acceptable anion of an acid.

4. A compound as claimed in claim 1 wherein NR_2 is pyrrolidino, R^1 is methyl or ethyl, Z is phenoxy or *p*-methoxyphenyl, and X^- is a pharmaceutically acceptable anion of an acid.

5. A compound as claimed in claim 1 or 2 wherein halogen is chlorine.

6. A compound as claimed in claim 1 or 2 wherein halogen is bromine.

7. A compound as claimed in claim 1 or 2 wherein halogen is iodine.

8. A compound as claimed in claim 1 or 2 wherein halogen is fluorine.

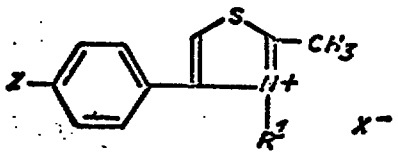
9. A compound as claimed in any preceding claim wherein X^- is the anion of a hydrogen halide acid.

10. A compound as claimed in claim 9 wherein the anion is chloride.

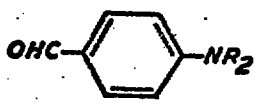
11. A compound as claimed in claim 9 wherein the anion is iodide.

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12. A compound as claimed in claim 9 wherein the anion is bromide.
13. A salt of the 2 - (*p* - dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium cation.
14. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - methyl - 4 - phenyl thiazolium cation.
15. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - methyl - 4 - (*p* - chlorophenyl) thiazolium cation.
16. A salt of the 2 - (*p* - dimethylaminostyryl) - 3 - ethyl - 4 - (*p* - biphenylyl) thiazolium cation.
17. A salt of the 2 - (*p* - diethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium cation.
18. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium cation.
19. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - ethyl - 4 - (*p* - biphenylyl) thiazolium cation.
20. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - methyl - 4 - (*p* - bromophenyl) thiazolium cation.
21. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - ethyl - 4 - phenylthiazolium cation.
22. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - ethyl - 4 - (*p* - chlorophenyl) thiazolium cation.
23. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - ethyl - 4 - (*p* - bromophenyl) thiazolium cation.
24. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - methyl - 4 - (*p* - fluorophenyl) thiazolium cation.
25. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - methyl - 4 - (*p* - phenoxyphenyl) thiazolium cation.
26. A salt of the 2 - (*p* - pyrrolidinostyryl) - 3 - methyl - 4 - (*p*-methoxybiphenyl) thiazolium cation.
27. The chloride salt of a thiazolium cation claimed in any of claims 13 to 26.
28. The iodide salt of a thiazolium cation claimed in any of claims 13 to 26.
29. The bromide salt of a thiazolium cation claimed in any of claims 13 to 26.
30. 2 - (*p* - Dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium iodide.
31. 2 - (*p* - Dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium chloride.
32. 2 - (*p* - Dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium bromide.
33. 2 - (*p* - Dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium *p*-toluenesulphonate.
34. 2 - (*p* - Dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium methosulphate.
35. 2 - (*p* - Pyrrolidinostyryl) - 3 - ethyl - 4 - (*p* - biphenylyl) thiazolium iodide.
36. A method for preparing a styrylthiazolium salt as defined in any of claims 1 to 35 comprising the reaction of a thiazolium salt of the formula



wherein Z, X^- and R^1 are defined in any of claims 1 to 35 with an aldehyde of the formula



wherein NR_2 is defined in any of claims 1 to 35.
37. A method as claimed in claim 36 wherein the reaction is performed in the presence of a basic catalyst, such as, for example, piperidine.

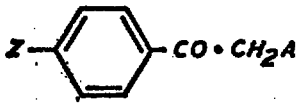


38. A method as claimed in either claim 36 or 37 wherein the reaction is performed in the presence of a polar liquid medium.

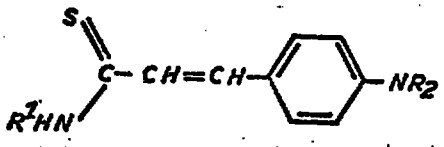
39. A method as claimed in claim 38 wherein the polar liquid medium is a lower alkanol.

40. A method as claimed in any of claims 36 to 39 wherein the thiazolium salt is the iodide salt.

41. A method for preparing a styrylthiazolium salt as defined in any of claims 1 to 35 comprising the reaction of a phenacyl derivative of the formula



with a thiocinnamamide of the formula



wherein Z, R^1 and NR_2 are as defined in any of claims 1 to 35 and A is a nucleophilic group or atom corresponding to the desired anion of the styrylthiazolium salt.

42. A method as claimed in claim 41 wherein the reactants are heated together to form the styrylthiazolium end-product.

43. A method as claimed in claim 42 wherein the reactants are heated to from 80 to 150° Celsius.

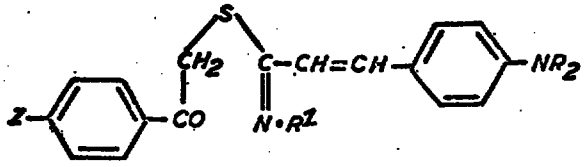
44. A method as claimed in claim 41 wherein the reactants are reacted together in the presence of an acid.

45. A method as claimed in claim 44 wherein the acid is a hydrogen halide acid.

46. A method as claimed in claim 45 wherein the hydrogen halide acid is hydrochloric or hydrobromic acid.

47. A method as claimed in claim 44 wherein the anion of the acid corresponds to the group or atom A.

48. A method for preparing a styrylthiazolium salt as claimed in any of claims 1 to 35 which comprises the conversion of a thioimidate of the formula



or an acid addition salt thereof, wherein Z, R^1 and NR^2 are as defined in any of claims 1 to 35.

49. A method as claimed in claim 48 wherein the conversion is effected by heating an acid addition salt of the thioimidate.

50. A method as claimed in claim 49 wherein the salt is heated to from 80 to 150° Celsius.

51. A method as claimed in either claim 49 or 50 wherein the acid addition salt is the hydrogen chloride or hydrogen bromide acid addition salt.

52. A method as claimed in claim 48 wherein the conversion is effected by treating the thioimidate, or an acid addition salt thereof, with an acid.

53. A method as claimed in claim 52 wherein the acid is a mineral acid.

54. A method as claimed in claim 53 wherein the mineral acid is hydrochloric or hydrobromic acid.

55. A styrylthiazolium salt as defined in any of claims 1 to 35 when prepared by a method claimed in any of claims 36 to 54.

56. An orally ingestible pharmaceutical composition comprising a styrylthiazolium salt as defined in any of claims 1 to 35 in association with an acceptable carrier therefor.

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57. A composition as claimed in claim 56 wherein the carrier is a solid.

58. A composition as claimed in claim 56 wherein the carrier is a liquid.

59. A tablet suitable for oral administration comprising as an active ingredient a styrylthiazolium salt as defined in any of claims 1 to 35 together with an acceptable carrier therefor.

60. A capsule suitable for oral administration comprising as an active ingredient a styrylthiazolium salt as defined in any of claims 1 to 35 together with an acceptable carrier therefor.

61. A suspension in a liquid carrier of a styrylthiazolium salt as defined in any of claims 1 to 35, suitable for oral administration.

62. A suspension as claimed in claim 61 wherein the styrylthiazolium salt is a 2 - (*p* - pyrrolidinostyryl) - 3 - ethyl - 4 - (*p* - biphenylyl) thiazolium salt.

63. A suspension as claimed in claim 61 wherein the salt is the iodide salt.

64. A composition as claimed in any of claims 56 to 61 wherein the styrylthiazolium salt is a 2 - (*p* - dimethylaminostyryl) - 3 - methyl - 4 - (*p* - biphenylyl) thiazolium salt.

65. A composition as claimed in claim 64 wherein the styrylthiazolium salt is the iodide salt.

66. A tablet suitable for oral administration comprising 2 - (*p* - dimethylaminostyryl) - 4 - (*p* - biphenylyl) thiazole methiodide together with an acceptable carrier therefor.

67. A method of preparing an orally ingestible pharmaceutical composition as defined in any of claims 56 to 66 comprising the admixture of the styrylthiazolium salt with an acceptable carrier therefor.

68. A method for preparing a styrylthiazolium salt as defined in any of claims 1 to 35 substantially as hereinbefore described with reference to Examples 1 to 12 and 21 to 27.

69. An orally ingestible pharmaceutical composition comprising a styrylthiazolium salt as defined in any of claims 1 to 35 in association with an acceptable carrier therefor, substantially as hereinbefore described with reference to Examples 13 to 16.

70. A method for the treatment of a nematode infection in a warm-blooded animal other than man comprising the oral administration to the animal of a compound claimed in any of claims 1 to 35.

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