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PHENYL-THIAZOLE-MALONIC ACID DERIVATIVES

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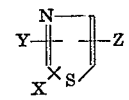
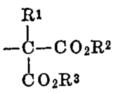
U.S. Cl. 260—302 R
6 Claims

ABSTRACT OF THE DISCLOSURE

Thiazole derivatives of the formula:



wherein Y or Z is linked to the 2-position of the thiazole nucleus, X stands for hydrogen or alkyl of up to 3 carbons, Y stands for a phenyl radical and Z stands for a group of the formula:

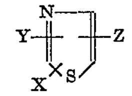


$$-\underset{CO_2R^3}{\overset{R^1}{C}}-CO_2R^2$$

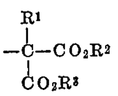
wherein R^1 stands for hydrogen, alkali metal, alkyl of not more than 3 carbons, dialkylaminomethyl of not more than 5 carbons, N-piperidinomethyl or N-morpholinomethyl, chlorine or bromine, and R^2 and R^3, stand for hydrogen or alkyl radical of not more than 3 carbons, provided that when R^2 and R^3 stand for hydrogen, R^1 stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, and non-toxic pharmaceutically-acceptable salts thereof. These phenyl-thiazole-malonic acid derivatives possess anti-inflammatory, analgesic and anti-pyretic activity. Processes for preparing these compounds, and pharmaceutical compositions containing the same are disclosed. A typical compounds is diethyl 4-(4-bromophenyl)thiazol-2-ylmalonate.

This invention relates to new heterocyclic compounds and more particularly it relates to new thiazole derivatives which have anti-inflammatory, analgesic and antipyretic activity.

According to the invention we provide compounds which in one of their tautomeric forms are thiazole derivatives of the formula:



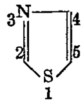
wherein Y or Z is linked to the 2-position of the thiazole nucleus, X stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, Y stands for the phenyl radical or a phenyl radical which is substituted by not more than two halogen atoms selected from fluorine, chlorine and bromine atoms, and Z stands for a group of the formula:



$$-\underset{CO_2R^3}{\overset{R^1}{C}}-CO_2R^2$$

wherein R^1 stands for hydrogen, an alkali metal atom, an alkyl radical of not more than 3 carbon atoms, a dialkylaminomethyl radical of not more than 5 carbon atoms, the N-piperidinomethyl or N-morpholinomethyl radical, or a chlorine or bromine atom, and R^2 and R^3, which may be the same or different, stand for hydrogen or an alkyl radical of not more than 3 carbon atoms, provided that when R^2 and R^3 stand for hydrogen, R^1 stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, and non-toxic, pharmaceutically-acceptable salts thereof.

The thiazole nucleus is numbered as follows:



It is to be understood that, in the thiazole derivatives of this invention, either Y is linked to position 2 and Z is linked to position 4 or 5, or Z is linked to position 2 and Y is linked to position 4 or 5. This general situation also obtains throughout this specification, thus it obtains in the case of the intermediates used in making the thiazole derivatives of the invention. It is also to be understood that, in the case where Z is in the 2-position of the thiazole nucleus and R^1 stands for hydrogen, the compounds of the invention may exist predominantly in the tautomeric Δ^4-thiazoline form. However, for convenience, in this specification all the compounds of the invention will be named as thiazole derivatives.

As a suitable value for X there may be mentioned, for example, hydrogen or the methyl radical.

As a suitable value for R^1 there may be mentioned, for example, hydrogen or the methyl radical.

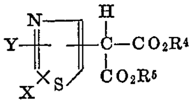
As a suitable value for R^1 there may be mentioned, for example, hydrogen, the sodium or bromine atom, or the methyl, dimethylaminomethyl, N-piperidinomethyl or N-morpholinomethyl radical.

As a suitable value for R^2 or R^3 there may be mentioned, for example, hydrogen or the methyl or ethyl radical.

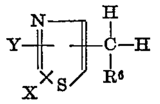
As suitable salts in the case where R^2 and/or R^3 stands for hydrogen there may be mentioned, for example, a salt formed from that carboxylic acid and a non-toxic, pharmaceutically-acceptable cation, for example an alkali metal salt, an alkaline earth metal, salt, or an aluminium or ammonium salt, or a salt with a non-toxic, pharmaceutically-acceptable organic base. In cases where the thiazole derivative of the invention is sufficiently basic, suitable salts are non-toxic pharmaceutically-acceptable acid-addition salts.

Preferred specific compounds of the invention are dimethyl α - [4 - (4 - bromophenyl)thiazol - 2 - yl] - α-methylmalonate, dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate, the α-sodium derivative of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate, and dimethyl α-[2-(4-chlorophenyl)thiazol-4-yl]-α-methylmalonate.

According to a further feature of the invention we provide a process for the manufacture of compounds which in one of their tautomeric forms have the formula:



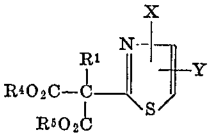
wherein Y or $—CH(CO_2R^4).CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and X stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, Y has the meaning stated above, and R^4 and R^5, which may be the same or different, stand for an alkyl radical of not more than 3 carbon atoms, and non-toxic pharmaceutically-acceptable acid-addition salts thereof, which comprises reacting a compound of the formula:



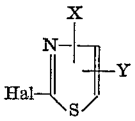
wherein Y or $-CH_2R^6$ is linked to the 2-position of the thiazole nucleus, and, when R^6 stands for hydrogen, $-CH_2R^6$ is linked to the 2-position of the thiazole nucleus, and X and Y have the meanings stated above, and R^6 stands for hydrogen or a $-CO_2R^5$ group wherein R^5 has the meaning stated above, with a carbonate of the formula $R^4O.CO.OR^4$ wherein R^4 has the meaning stated above, and sodium or potassium or a hydride, amide or C_{2-3} alkoxide thereof.

Suitable values for R^4 and R^5 are those stated above in respect of R^2 and R^3, but excluding hydrogen. The reaction may be carried out in an excess of the carbonate used as reactant and/or in an inert solvent, for example ether. The reaction may optionally be carried out under the influence of heat, for example at a temperature of 70°–150° C.

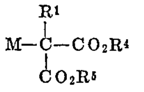
According to a further feature of the invention we provide a process for the manufacture of compounds which in one of their tautomeric forms has the formula:



wherein X, Y, R^4 and R^5 have the meanings stated above, R^1 stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, and non-toxic pharmaceutically-acceptable acid-addition salts thereof, which comprises reacting a compound of the formula:



wherein X and Y have the meanings stated above and Hal stands for a chlorine, bromine or iodine atom, with a compound of the formula:

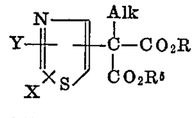


$$M-\overset{R^1}{\underset{CO_2R^5}{C}}-CO_2R^4$$

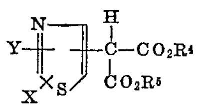
wherein R^1, R^4 and R^5 have the meanings stated above, and M stands for an alkali metal atom.

The reaction may be carried out in an excess of the appropriate malonate derivative and/or in an inert solvent, for example dimethylformamide. The reaction may optionally be accelerated or completed by the application of heat.

According to a further feature of the invention we provide a process for the manufacture of compounds of the formula:



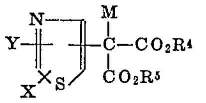
wherein Y or $-CAlk(Co_2R^4).CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and X, Y, R^4 and R^5 have the meanings stated above, and Alk stands for an alkyl radical of not more than 3 carbon atoms, an non-toxic pharmaceutically-acceptable acid-addition salts thereof, which comprises alkylating a compound which is one of its tautomeric forms has the formula:



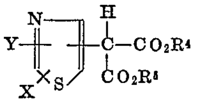
wherein Y or $-CH(CO_2R^4)\cdot CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and X, Y, R^4 and R^5 have the meanings stated above, so as to introduce an alkyl radical of not more than 3 carbon atoms into the α-position.

The alkylation may be carried out by the interaction of an alkali metal derivative of the appropriate thiazole derivative with an alkyl halide of not more than 3 carbon atoms, for example methyl iodide. An organic solvent, for example dimethylformamide, may optionally be present.

According to a further feature of the invention we provide a process for the manufacture of compounds of the formula:



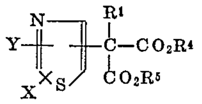
wherein Y or $-CM(CO_2R^4)\cdot CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and X, Y, R^4 and R^5 have the meanings stated above and M stands for an alkali metal atom, which comprises reacting a compound of the formula:



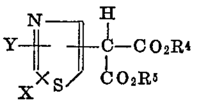
wherein Y or $-CH(CO_2R^4)\cdot CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and X, Y, R^4 and R^5 have the meanings stated above, with an alkali metal or a hydride, amide or C_{1-3} alkoxide thereof.

The reaction is conveniently carried out in an organic solvent, for example ether.

According to a further feature of the invention we provide a process for the manufacture of compounds which have the formula:



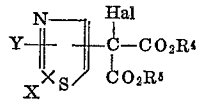
wherein Y or $-CR^1(CO_2R^4)\cdot CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and R^1 stands for a dialkylaminomethyl radical of not more than 5 carbon atoms or the N-piperidinomethyl or N-morpholinomethyl radical, and X, Y, R^4 and R^5 have the meanings stated above, and non-toxic pharmaceutically-acceptable acid-addition salts thereof, which comprises reacting a compound which in one of its tautomeric forms has the formula:



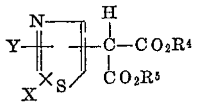
wherein Y or $-CH(CO_2R^4)\cdot CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and X, Y, R^4 and R^5 have the meanings stated above, with formaldehyde and either a dialkylamine of not more than 4 carbon atoms or piperidine or morpholine.

The formaldehyde is conveniently used in the form of an aqueous solution, and an organic solvent, for example methanol, may optionally also be present.

According to a further feature of the invention we provide a process for the manufacture of compounds of the formula:



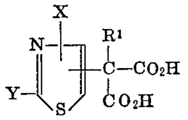
wherein Y or $-CHal(CO_2R^4)\cdot CO_2R^5$ is linked to the 2-position of the thiazole nucleus, and X, Y, R^4 and R^5 have the meanings stated above, and Hal stands for a chlorine or bromine atom, which comprises reacting a compound which in one of its tautomeric forms has the formula:



wherein Y or —CH(CO_2R^4)·CO_2R^5 is linked to the 2-position of the thiazole nucleus, and X, Y, R^4 and R^5 have the meanings stated above, with chlorine, bromine, N-bromosuccinimide or phenyltrimethylammonium perbromide.

The last named reaction may be carried out in an inert solvent, for example ether or tetrahydrofuran. The reaction involving chlorine or bromine itself may be carried out in glacial acetic acid in the presence of an alkali metal acetate.

According to a further feature of the invention we provide a process for the manufacture of compounds of the formula:



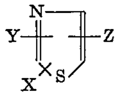
wherein X and Y have the meanings stated above, and R^1 stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, which comprises reacting a corresponding alkali metal salt, alkaline earth metal salt, aluminium salt or ammonium salt with an acid at a relatively low temperature.

As a suitable acid there may be mentioned an inorganic acid, for example hydrochloric acid, or a sufficiently strong organic acid, for example acetic acid. The reaction should be carried out at a relatively low temperature, for example at or below 0° C., in order to prevent decomposition of the product.

It is to be understood that the non-toxic, pharmaceutically-acceptable salts of the invention may be obtained by means of conventional procedures.

It is also to be understood that the starting materials used in the above process can be obtained by known general methods.

According to a further feature of the invention we provide pharmaceutical compositions comprising at least one compound which in one of its tautomeric forms is a thiazole derivative of the formula:



wherein Y or Z is linked to the 2-position of the thiazole nucleus, and X, Y and Z have the meanings stated above, or a non-toxic pharmaceutically-acceptable salt thereof, and a non-toxic pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions may, for example, be in the form of tablets, pills, capsules, suppositories, non-sterile aqueous or non-aqueous solutions or suspensions, sterile injectable aqueous or non-aqueous solutions or suspensions, creams, lotions, or ointments. These compositions may be obtained in conventional manner using conventional excipients. The compositions may optionally contain, in addition to at least one of the compounds which characterise this invention, at least one known agent having anti-inflammatory or analgesic activity, for example aspirin, paracetamol, codeine, chloroquine, phenylbutazone, oxyphenbutazone, indomethacin, mefenamic acid, flufenamic acid, ibufenac, or an anti-inflammatory steroid, for example prednisolone. Those compositions intended for oral administration may, in addition, optionally contain an anti-cholinergic agent, for example homatropine methyl bromide, and/or an antacid, for example aluminum hydroxide, or a uricosuric agent, for example probenecid. Those compositions suitable for topical application may, in addition, optionally contain a vasodilating agents, for example tolazoline, or a vasoconstricting agent, for example adrenaline; a local anaesthetic, for example amethocaine, a counter-irritant, for example capsicum; and/or at least one agent chosen from the following classes of substances: anti-bacterial agents, which includes sulphonamides and antibiotics having antibacterial action, for example neomycin; antifungal agents, for example hydroxyquinoline; anti-histamic agents, for example promethazine; and rubefacient agents, for example methyl nicotinate.

The invention is illustrated but not limited by the following examples:

EXAMPLE 1

A mixture of sodium hydride (4.8 g., weighed as a 50% dispersion in oil, and subsequently washed free from oil by decantation with light petroleum), diethyl carbonate (36 ml.), and 4-(4-bromophenyl)-2-methylthiazole (5.1 g.) was stirred under reflux for 3 hours in an oil-bath at 135–140° C. The mass, which was then of a thick consistency, was treated with sufficient ethanol to destroy the excess of sodium hydride. Water (50 ml.) was added, and the solid present was extracted with chloro (3X50 ml.), the extract being washed in turn with dilute hydrochloric acid (40 ml.), aqueous sodium carbonate (10% w./v.), and water (40 ml.). The chloroform solution was dried with anhydrous sodium sulphate, and evaporated down to give a residue which was crystallised from ethanol and yielded diethyl 4-(4-bromophenyl)thiazol-2-ylmalonate, M.P. 130–131° C.

EXAMPLE 2

A mixture of sodium hydride (7.2 g., see Example 1 for procedural details), dimethyl carbonate (52 ml.), and 4-(4-bromophenyl)-2-methylthiazole (7.6 g.) was stirred under reflux for 6 hours in an oil-bath at 105–115° C. The resulting thick suspension was cooled, and any excess of sodium hydride was destroyed by addition of methanol. Water (80 ml.), and sufficient hydrochloric acid to give a pH of 7, were added. The solid present was extracted into methylene dichloride (3×80 ml.). The extract was washed with dilute aqueous sodium carbonate (10% w./v., 50 ml.) and then with water (50 ml.). It was dried with anhydrous sodium sulphate, and evaporated down to leave a solid, which was triturated with ethyl acetate (50 ml.) to remove unchanged starting material. Crystallisation of the residue from chlorobenzene, in the presence of decolourising carbon, gave dimethyl 4-(4-bromophenyl)thiazol-2-ylmalonate, M.P. 173–174° C.

EXAMPLE 3

Dimethyl 4-(4-bromophenyl)thiazol-2-ylmalonate (1.85 g.) was added to a suspension of sodium hydride (0.24 g., see Example 1 for procedural details) in dry dimethylformamide (15 ml.), and stirred for 30 minutes at 35° C. Methyl iodide (1.25 ml.) was then added, and stirring at 35° C. was continued for a further 1 hour. The mixture was cooled to 10° C. and diluted carefully with water (30 ml.). Traces of methyl iodide were distilled off under reduced pressure, and the solid was collected by filtration, washed with water, and dried in vacuo over phosphorus pentoxide. Crystallisation from light petroleum (B.P. 60–80° C.) gave dimethyl α-[4-(4-bromophenyl)thiazol-2-yl]-α-methylmalonate, M.P. 64–65.5° C.

EXAMPLE 4

Diethyl malonate (6.1 ml.) was added to a suspension of sodium hydride (1.9 g.; see Example 1 for procedural details) in dry dimethylformamide (25 ml.) and stirred for 30 minutes. 2 - Bromo-4-(4-bromophenyl)-thiazole (5.4 g.) was then added. The mixture was stirred and heated under reflux for 4 hours in an oil-bath at 145–155° C. Water (50 ml.), and sufficient hydrochloric acid to give a pH of 7, were added to the cooled mixture, and the precipitated solid was collected by filtration, and washed successively with water (40 ml.) and ether (50 ml.) to remove coloured contaminants. The solid dissolved in methylene dichloride (100 ml.), and the solution was successively washed with aqueous sodium carbonate (10% w./v., 30 ml.) and water (30 ml.). The solution was dried over anhydrous sodium sulphate, treated with decolourising carbon, filtered and evaporated to dryness. Two crystallisations from ethanol gave diethyl 4 - (4 - bromophenyl)thiazol-2-ylmalonate, identical in physical properties with material prepared by the procedure described in Example 1.

EXAMPLE 5

Sodium hydride (0.26 g.) was suspended in dry ether (60 ml.) and a solution of methyl 2-(4-chlorophenyl) thiazol-4-ylacetate (2.6 g.) in dry ether (60 ml.) was added dropwise with stirring over 30 minutes. A solution of dimethyl carbonate (1.8 g.) in dry ether (10 ml.) was added over 15 minutes, and the resulting mixture was stirred under nitrogen for 16 hours at room temperature. A further quantity of sodium hydride (0.26 g.) was then added and the mixture was stirred for a further 3 hours. The mixture was filtered, and the residue was washed with ether and then stirred with 2 N-aqueous sodium hydroxide (30 ml.) and filtered. There was thus obtained as solid residue the α-sodium derivative of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate dihydrate, M.P. 133° C.

This sodium derivative (2 g.) was suspended in a mixture of water (50 ml.) and ether (50 ml.), and N-aqueous hydrochloric acid (50 ml.) was added with vigorous stirring. The ether layer was separated, washed well with water, dried with anhydrous magnesium sulphate, and evaporated to dryness. The residue was crystallised from n-hexane to give dimethyl 2 - (4-chlorophenyl triazol-4-ylmalonate, M.P. 46° C.

EXAMPLE 6

A solution of bromine (0.8 g.) in glacial acetic acid (10 ml.) was added over 10 minutes to a stirred mixture of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate (1.6 g.) and anhydrous sodium acetate (0.82 g.) in glacial acetic acid (20 ml.) at room temperature. After 30 minutes, the mixture was poured into water (100 ml.), and the product was extracted into ether (50 ml.). The ethereal extract was dried over anhydrous magnesium sulphate, the solvent was evaporated in vacuo, and the residue was crystallised from cyclohexane. There was thus obtained dimethyl α-bromo-α-[2-(4-chlorophenyl)thiazol-4-yl]malonate, M.P. 110–111° C.

EXAMPLE 7

An aqueous solution of 40% dimethylamine (2.8 ml.) was added to a stirred solution of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate (8 g.) in methanol (16 ml.). To the resulting suspension there was added dropwise a 36% w./v. aqueous solution of formaldehyde (2.16 ml.) over 5 minutes at room temperature. After stirring the mixture for one hour, the product was collected by filtration and washed with 50% aqueous ethanol. There was thus obtained dimethyl α-[2-(4-chlorophenyl)-thiazol-4-yl]-α-dimethylaminomethylmalonate, M.P. 95–96° C.

EXAMPLE 8

A mixture of sodium hydride (3.4 g.), 50% dispersion—see Example 1 for procedural details), dimethylcarbonate (21 ml.), and 5-(4-chlorophenyl)-2-methylthiazole (2.9 g.) was stirred under reflux in an oil-bath at 105–115° C. for 4½ hours. The mixture, which had become very thick, was cooled, diluted with ether (25 ml.), treated with sufficient methanol to destroy any remaining sodium hydride, and mixed with water (50 ml.). Sufficient acetic acid was added to give a pH of 7, and the solid present was collected by filtration, washed well with water and dried. Crystallisation from chlorobenzene in the presence of decolourising carbon gave dimethyl 5-(4 - chlorophenyl)thiazol - 2 - ylmalonate, M.P. 212.5–214° C.

In a similar fashion, but using diethyl carbonate instead of dimethyl carbonate, and a reaction time of 1½ hours at 135–140° C., there was obtained diethyl 5-(4-chlorophenyl)thiazol-2-ylmalonate, M.P. 161–161.5° C. (crystallised from n-propanol).

The 5-(4-chlorophenyl)-2-methylthiazole used as starting material was obtained as follows:

5 - (4-chlorophenyl)-2-methyloxazole (7.75 g.—M.P. 74.5–75.5° C.; prepared by the action of sodium azide and sulphuric acid on 4-chlorobenzoylacetone by an adaptation of a known procedure for the preparation of 2-methyl-5-phenyloxazole) was intimately mixed with finely-powdered phosphorus pentasulphide (8.9 g.) and heated directly over a flame to give a dark, viscous melt. After 5 minutes, the melt was allowed to cool, and the mixture was boiled with aqueous 4 N-hydrochloric acid (150 ml.) for 20 minutes. The resultant suspension was cooled and filtered, and the filtrate was clarified by addition of kieselguhr, and then filtered again. Aqueous 40% sodium hydroxide was added slowly to the filtrate, which was cooled to 10–20° C. and stirred during the addition. When the pH had reached 7, the resulting precipitate was collected by filtration, and was washed well with water. It was crystallised from a 4:1 mixture of methanol and water to give 5-(4-chlorophenyl)-2-methylthiazole, M.P. 83.5–84.5° C.

EXAMPLE 9

Dimethyl 5-(4-chlorophenyl)thiazol-2-ylmalonate (3.9 g.) was added to a suspension of sodium hydride (0.6 g., 50% dispersion, treated as in Example 1) in dry dimethylformamide (35 ml.), and the mixture was stirred at 30–35° C. for 30 minutes. Methyl iodide (7.1 g.) was added, and stirring at 30–35° C. was continued for a further hour. The liquor was then cooled to 15° C., and diluted with water (50 ml.). Extraction with ether (3×50 ml.) gave a solution which was washed with water (3×40 ml.), dried over anhydrous sodium sulphate, and evaporated to dryness. The residual solid was a mixture which was separated into its two components by passing a solution of the material in benzene down an alumina column (200 g. of alumina). One compound passed through readily, and was recovered by evaporation of the eluate and crystallised from acetonitrile to give dimethyl α-[5-(4-chlorophenyl)-thiazol-2-yl]-α-methylmalonate, M.P. 129–130° C. The second component, eluted from the column with chloroform, was 5-(4-chlorophenyl)-2-[di(methoxycarbonyl)methylene]-1-methyl-Δ^4-thiazoline.

EXAMPLE 10

The α-sodium derivative of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate (2.5 g.) was suspended in dry dimethylformamide (20 ml.), and methyl iodide (1 ml.) was added. The mixture was stood at 15–20° C. for 16 hours. Water (200 ml.) was added, and the mixture was extracted with ether (100 ml.). The ethereal layer was washed with water, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness, giving dimethyl α-[2-(4-chlorophenyl)thiazol-4-yl]-α-methylmalonate was obtained as a yellow oil, examination by N.M.R. shows a methyl signal at δ3.7 p.p.m. and methyl ester signal at δ1.65 p.p.m.

EXAMPLE 11

A mixture of methyl 2-(4-chlorophenyl)-4-methylthiazol-5-ylacetate (14.6 g.), sodium hydride (2.5 g.) and dimethylcarbonate (50 ml.) was stirred at a bath temperature of 100–110° for 3½ hours. Methanol (10 ml.) was added to destroy the excess of sodium hydride, and immediately afterwards 10% v./v. aqueous acetic acid

(200 ml.) was added. The resultant mixture was extracted with 3 separate portions of chloroform (50 ml. each). The combined chloroform extracts were washed with water (3× 100 ml.), dried over anhydrous magnesium sulphate, filtered and evaporated to dryness. The resultant solid residue was crystallised from cyclohexane to give dimethyl 2-(4-chlorophenyl)-4-methylthiazol-5-ylmalonate, M.P. 140–141° C.

EXAMPLE 12

A solution of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate (3.25 g.) and piperidine (1 ml.) in methanol (15 ml.) was stirred at 15° C., and a 36% w./v. aqeous solution of formaldehyde (1 ml.) was added over 5 minutes. After 10 hours, water (5 ml.) was added, and after a further 12 hours a solid had precipitated. This solid was collected by filtration and washed with 50% aqueous methanol (10 ml.). There was thus obtained dimethyl α-[2-(4-chlorophenyl)thiazol-4-yl]-α-(N-piperidinomethyl)malonate, M.P. 90–91° C.

In similar manner but using morpholine (1 ml.) instead of piperidine there was obtained dimethyl α-[2-(4-chlorophenyl)thiazol-4-yl] - α - (N-morpholinomethyl) malonate, M.P. 124–126° C.

EXAMPLE 13

A mixture of methyl 2-(2,4-dichlorophenyl)thiazol-4-ylacetate (1.6 g.), sodium hydride (0.7 g.) and dimethyl carbonate (10 ml.) was stirred under reflux (bath temperature 100–110° C.) for 3 hours. The mixture was cooled, and methanol (5 ml.) was added to destroy the excess of sodium hydride. An aqueous solution of 10% v./v. acetic acid (50 ml.) was added, and the resultant mixture was extracted with ether (3× 50 ml.). The combined ethereal extracts were washed with water (3× 100 ml.), dried over anhydrous magnesium sulphate, filtered, and evaporated to dryness. The residue was crystallised from petroleum ether (B.P. 60–80° C.) to give dimethyl 2-(2,4-dichlorophenyl)thiazol - 4-ylmalonate, M.P. 92–94° C.

EXAMPLE 14

Diethyl α-methylmalonate (3.5 g.) was added to a suspension of sodium hydride (0.96 g., 50% dispersion, treated as in Example 1) in dry dimethylformamide (12 ml.), and the mixture was stirred at ambient temperature until evolution of hydrogen and ceased. 2-bromo-4-(4-bromophenyl)thiazole (3.2 g.) was added, and the mixture was stirred in an oil-bath at 110° C. for 1½ hours. The solution was cooled, diluted with water (50 ml.) was extracted thoroughly with methylene dichloride (3× 50 ml.). The extract was washed with water (3× 30 ml.), dried over anhydrous sodium sulphate, and evaporated to give an oil. This was submitted to thin layer chromatography on silica, with benzene as developing solvent. Elution of the appropriate band with ether and recovery by evaporation gave diethyl α-[4-(4-bromophenyl)thiazol-2-yl]-α-methylmalonate which was crystallised from petroleum ether (B.P. 40–60° C.), and had M.P. 45–46° C.

EXAMPLE 15

A solution of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate (0.65 g.) in dimethylformamide (10 ml.) was stirred at 0–5° C. and 10 N-aqueous sodium hydroxide (0.6 ml.) was added. After stirring for 12 hours, dry ether (20 ml.) was added. The resulting precipitate was collected by filtration and washed with dry ether (20 ml.) to give disodium 2-(4-chlorophenyl)thiazol-4-ylmalonate, M.P. 296° C. (decomposition). This salt was dissolved in water (20 ml.), and glacial acetic acid was added at a temperature below 10° C. until precipitation ceased. The mixture was filtered to give 2-(4-chlorophenyl)thiazol-4-ylmalonic acid. This melted with decomposition over the range 50–70° C. (to give 2-(4-chlorophenyl)thiazol-4-ylacetic acid, M.P. 154.5° C.).

EXAMPLE 16

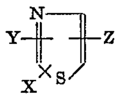
A mixture of dimethyl α-[4-(4-bromophenyl)thiazol-2-yl]-α-methylmalonate (100 g.) and maize starch (300 g.) was granulated with a sufficient quantity of 10% w./v. starch paste. The granules were passed through a 20-mesh screen, and were dried at a temperature not exceeding 50° C. The dried granules were blended with magnesium stearate (4 g.) and then compressed into tablets containing from 50 to 250 mg. of active ingredient. There were thus obtained tablets suitable for oral use for therapeutic purposes.

The thiazole derivatives of the invention are active in a test (Adjuvant induced arthritis in rats; Newbould, Brit. J. Pharmacol. Chemotherap., 1963, 21, 127–136) which is standard in the art for testing for anti-inflammatory activity. It is well known and accepted in the art that non-steroidal anti-inflammatory compounds exhibit analgesic and antipyretic activity. Accordingly, as the compounds of the invention are non-steroidal anti-inflammatory compounds, it is reasonable to conclude that they possess analgesic and antipyretic activity.

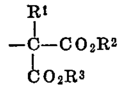
The compounds of the invention are useful in the treatment of warm-blooded animals (including mammals) and for this purpose we recommend that one of said compounds be administered orally as a suitable dosage unit form, for example a tablet or capsule, and that the daily dosage be in the range 0.75 to 15 mg. per kg. of host. In particular, when one of said compounds is used for the treatment of man we recommend that it be administered orally as a suitable dosage unit form, for example a tablet or capsule, at a total daily dose of 50 to 1000 mg. of said compound per 70 kg. man.

What we claim is:

1. A compound which in one of its tautomeric forms is a thiazole derivative of the formula:



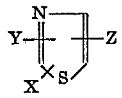
wherein Y or Z is linked to the 2-position of the thiazole nucleus, X stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, Y stands for the phenyl radical which is substituted by not more than two halogen atoms selected from fluorine, chlorine and bromine atoms, and Z stands for a group of the formula:



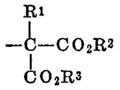
$$-\underset{\substack{|\\ CO_2R^3}}{\overset{\substack{R^1\\ |}}{C}}-CO_2R^2$$

wherein R^1 stands for hydrogen, an alkali metal atom, an alkyl radical of not more than 3 carbon atoms, a dialkylaminomethyl radical of not more than 5 carbon atoms, or the N-piperidinomethyl or N-morpholinomethyl radical, or a chlorine or bromine atom, and R^2 and R^3, which may be the same or different, stand for hydrogen or an alkyl radical of not more than 3 carbon atoms, provided that when R^2 and R^3 stand for hydrogen, R^1 stands for hydrogen or an alkyl radical of not more than 3 carbon atoms, or a non-toxic pharmaceutically-acceptable salt thereof.

2. A compound as claimed in claim 1 which in one of its tautomeric forms is a thiazole derivative of the formula:



wherein Y or Z is linked to the 2-position of the thiazole nucleus, X stands for hydrogen or the methyl radical, Y has the meaning stated in claim **1**, and Z stands for a group of the formula:



$$-\overset{R^1}{\underset{CO_2R^3}{C}}-CO_2R^2$$

wherein R^1 stands for hydrogen, the sodium or bromine atom, or the methyl, dimethylaminomethyl, N-piperidinomethyl or N-morpholinomethyl radical, and R^2 and R^3, which may be the same or different, stand for hydrogen or the methyl or ethyl radical, or an alkali metal salt, alkaline earth metal salt, aluminum or ammonium salt, or salt with a non-toxic pharmaceutically-acceptable organic base, or a non-toxic pharmaceutically-acceptable acid-addition salt.

3. Dimethyl α-[4 - (4-bromophenyl)thiazol- 2- yl]-α-methylmalonate.

4. Dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate.

5. The α-sodium derivative of dimethyl 2-(4-chlorophenyl)thiazol-4-ylmalonate.

6. Dimethyl α-[2 - (4 - chlorophenyl)thiazol-4-yl]-α-methylmalonate.

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