

1.120.587



PATENT SPECIFICATION

NO DRAWINGS

Inventors: WILLIAM CHARLES AUSTIN, LLOYD HILLYARD CONOVER and JAMES WILLIAM McFARLAND

1.120.587

Date of filing Complete Specification: 7 Dec., 1966.

Application Date: 22 Dec., 1965.

No. 54269/65.

Complete Specification Published: 17 July, 1968.

© Crown Copyright 1968.

Index at acceptance: —C2 C(2A3, 2B22, 2T16, B4A1, B4C, B4H, B4M)

Int. Cl.: —C 07 d 99/06

COMPLETE SPECIFICATION

Thiophen Derivatives

We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, 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 provides certain thiophen derivatives and their non-toxic acid addition salts. These compounds have anthelmintic properties.

The compounds of the invention are 2,3- where

X represents —CH₂—CH₂—, —CH₂—CH₂—CH₂—, or —CH=CH—;

Y represents —CH₂—CH₂—, or —CH₂—CH₂—CH₂—; and

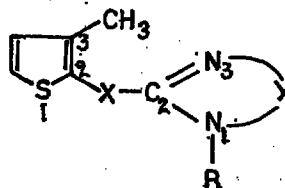
R represents —H or —CH₃;

and the non-toxic acid addition salts thereof.

The 2,3-disubstituted thiophen derivatives of the invention are bases, and can be converted by treatment with appropriate acids into non-toxic acid addition salts, such as the hydrochloride, hydrobromide, nitrate, sulphate, phosphate, hexafluorophosphate, acetate, propionate, butyrate, laurate, stearate, oxalate, succinate, maleate, fumarate, malate, tartrate, citrate, gluconate, benzoate, toluene p-sulphonate, amsonate (4,4'-diaminostilbene-2,2' - disulphonate), sulphosalicylate, 2-hydroxy - 3 - naphthoate, 3 - hydroxy - 2 - naphthoate, pamoate (1,1' - methylene - bis - 2-hydroxy-3-naphthoate), suramin salt and absorbates with cation exchange materials.

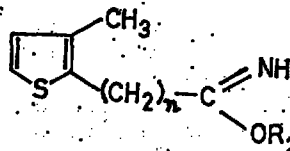
Those compounds of the invention in which X in the general formula given earlier is —CH₂—CH₂— or —CH₂—CH₂—CH₂— can be prepared by the reaction of an acid

disubstituted thiophen derivatives of the general formula:



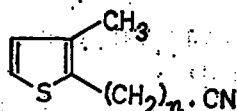
15

addition salt of an imidate ester (iminoether) of the formula



in which n is 2 or 3 and R₂ is a lower alkyl (C₁₋₃) radical, with an alkylene diamine H₂N—Y—NH.R, where Y and R are as defined earlier. Such a method is illustrated in Example 3 later in this specification.

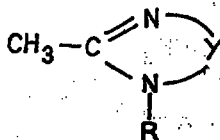
Another method of preparing such compounds entails the reaction of a nitrile



with the alkylene diamine $H_2N-Y-NH.R$ in the presence of an organic sulphonic acid, for example, *p*-toluene sulphonic acid, following the procedure described in the specification of our Patent 1,045,838.

In a further method of preparing such compounds, a nitrile as defined above is reacted with the alkylene diamine $H_2N-Y-NH.R$ in the presence of hydrogen sulphide or phosphorus pentasulphide (see Patent Specification 1,045,838).

Those compounds of the invention in which X in the general formula is $-CH=CH-$ can be prepared by the reaction of 3-methyl-2-thiophencarboxaldehyde with a 2-methyl Δ^2 -imidazoline or tetrahydro pyrimidine of the formula



where Y and R are as defined earlier. Such a method is illustrated in Example 4.

Another method of preparing such compounds consists in the reaction of 3-(1'-imino-3'-(3''-methyl-2''-thienyl)allyloxy)-propane sulphonic acid with an alkylene diamine $H_2N-Y-NH.R$ as defined earlier. (See Patent Specification 1,045,838. The sulphonic acid referred to is prepared from 3-methyl-2-thienyl acrylamide and 1,3-propanesultone).

The compounds of the invention are specially effective against certain types (e.g. *Thichostrongylus* species) of the helminth order *Strongyloidea* found in the stomachs and intestines of sheep and cattle.

The compounds are preferably administered to animals orally. For therapeutic use, a dose equivalent to 10-50 mg. (calculated as free base) per kg. of body weight can be given. This can if necessary be repeated on two or three successive days. In prophylaxis, a daily dose of 1-50 mg. per kg. of body weight can be given. The compounds can be administered *via* the drinking water, as throat drench solutions, in admixture with feed or mineral supplements such as salt, or in the form of dosage units such as tablets, boluses and capsules.

Of the following examples, Nos. 1 and 2 illustrate the preparation of starting materials, Nos. 3 and 4 illustrate the preparation of compounds according to the invention, and No. 5 illustrates various forms in which the

compounds of the invention can be administered to animals.

EXAMPLE 1

3-(3-Methyl-2-thienyl)acrylonitrile
3-Methyl-2-thiophencarboxaldehyde (1.10 moles), cyanoacetic acid (1.00 mole), ammonium acetate (3 g.), pyridine (100 ml.), and toluene (200 ml.) were heated under reflux for 48 hours in an apparatus having a moisture trap. The reaction mixture was allowed to cool, and the more volatile ingredients were distilled off under reduced pressure. The residue was fractionally distilled to obtain the product as an oil: b.p. $75^\circ C.$ at 0.1 mm.; n_D^{24} 1.6330.

EXAMPLE 2

3-(3-Methyl-2-thienyl)propionitrile
3-(3-Methyl-2-thienyl)acrylonitrile (0.5 mole), 1N sodium hydroxide (50 cc.), methanol (300 cc.), and 5% palladium-on-carbon catalyst (10 g.), were mixed, and the mixture was treated with hydrogen under pressure until the theoretical amount (0.5 mole) of hydrogen had been absorbed. The catalyst was removed by filtration and methanol was distilled off from the filtrate obtained. Water was added to the residue; the mixture was extracted with ether; and the ether extract was dried, filtered and evaporated under reduced pressure to give a pale yellow oil. Fractional distillation of the oil gave 3-(3-methyl-2-thienyl)propionitrile b.p. $66^\circ C.$ at 0.1 mm.

EXAMPLE 3

1-Methyl-2-(2-(3-methyl-2-thienyl)ethyl- Δ^2 -tetrahydropyrimidine)
Methyl β -(3-methyl-2-thienyl)propionimide hydrochloride (31.8 g.; prepared from the nitrile of Example 2; methanol and hydrogen chloride by conventional procedure) was added to a solution of N-methyltrimethylenediamine (18.5 g.) in methanol (250 ml.) at $0^\circ C.$ The mixture was heated under reflux for 16 hours and then evaporated to dryness under reduced pressure.

The residue was treated with ice-cold 40% aqueous sodium hydroxide solution (100 ml.), and the mixture was shaken for several minutes and then extracted with ether. The ethereal extract was separated and dried (anhydrous sodium sulphate), and ether was then evaporated from it to leave a residue of the desired tetrahydropyrimidine free base in crude form. (Extraction with chloroform of the separated aqueous layer gave a further amount of the desired base). The base was purified by vacuum distillation.

The base was converted to its hexafluorophosphate salt by adding it to an ice-water mixture containing an equivalent proportion of hexafluorophosphoric acid. The salt precipitated, and was filtered off and recrystallized.



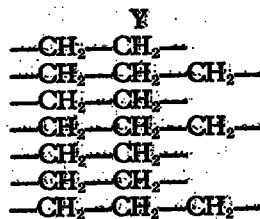
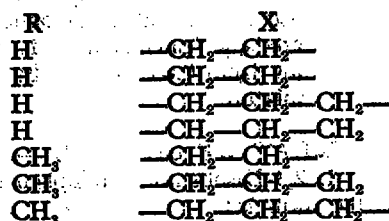
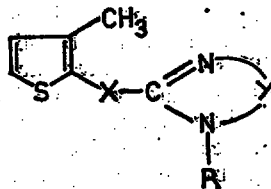
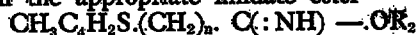
cyanoacetic acid

lised from isopropanol; m.p. 116–117.5°C. (Found: C, 39.30; H, 5.32; N, 7.61%. $C_{12}H_{10}F_2N_2PS$ requires C, 39.12; H, 5.19; N, 7.61%).

and alkylene diamine $H_2N-Y-NH.R$

10

- 5 Following generally the procedure of Example 3, the following imidazoline and tetrahydropyrimidine compounds can be prepared from the appropriate imidate ester



EXAMPLE 4

1-Methyl-2-(2-(3-methyl-2-thienyl)vinyl)- Δ^2 -tetrahydropyrimidine

a) A mixture of 3-methyl-2-thiophencarboxaldehyde (12.6g.), 1,2-dimethyl- Δ^2 -tetrahydropyrimidine (11.2g.), piperidine (1ml.) and dry benzene (30 ml.) was heated under reflux for 20 hours in an apparatus having a moisture trap. Benzene and piperidine were then distilled off *in vacuo*, and the residue was fractionally distilled. The fraction (12.5g.) of boiling point 160–165°/2mm. was the desired thienylvinyltetrahydropyrimidine free base.

b) A mixture of 3-methyl-2-thiophencarboxaldehyde (12.6g.), 1,2-dimethyl- Δ^2 -tetrahydropyrimidine (11.2g.), piperidine (1.5 ml.) and benzene (25 ml.) was heated under reflux for 4 hours under an atmosphere of nitrogen in an apparatus having a moisture trap. Benzene and piperidine were then distilled off *in vacuo*, and the residue of the desired tetrahydropyrimidine free base in crude form was taken up in N-hydrochloric acid (150 ml.). The resulting aqueous solution of hydrochloride salt of the base was washed with ether, and then extracted with chloroform. The chloroform extract was decolorised, dried (anhydrous sodium sulphate) and evaporated to give the solid yellow hydrochloride. On recrystallisation from chloroform/benzene, this had m.p. 239–241°C. (Found: C, 55.58; H, 6.80; N, 11.01%. $C_{12}H_{11}ClN_2S$ requires C, 56.12; H, 6.67; N, 10.91%).

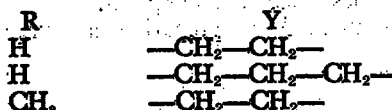
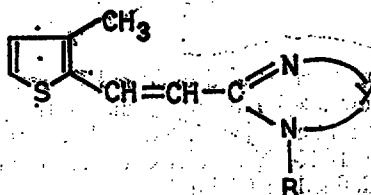
The above procedure yields the vinyl compound in the *trans* form; this form is converted to the *cis* form by irradiation.

c) A solution of fumaric acid (6.6g.) in methanol (35 ml.) was added to a solution of the product of a, (12.5g.) in

methanol (25 ml.). Addition of dry ether precipitated the fumarate salt. (8.4g.) of the *trans* form of the thienylvinyltetrahydropyrimidine; and this salt was then recrystallised from absolute ethanol. It had m.p. 192–3°C. (Found: C, 56.92; H, 6.14; N, 8.08; S, 9.31. $C_{16}H_{18}N_2O_4S$ requires C, 57.14; H, 5.99; N, 8.33; S, 9.53%).

d) An aqueous solution of the hydrochloride of b (7g.) was added slowly to an aqueous solution obtained by treating a suspension of pantoic acid (10.4g.) in water (75 ml.) with 5N sodium hydroxide solution. The pantoate salt of the thienylvinyltetrahydropyrimidine separated as a pale yellow solid. The solid was dissolved in hot dimethyl formamide, and was precipitated from the cooled solution by addition of water. It had m.p. 267–269°C (dec.). (Found: C, 69.52; H, 5.57; N, 4.28; S, 5.00; $C_{22}H_{24}N_2O_6S$ requires C, 69.06; H, 5.30; N, 4.61; S, 5.27%).

Following generally the procedure of Example 4b, the following tetrahydropyrimidine and imidazoline compounds can be prepared from 3-methyl-2-thiophencarboxaldehyde and the appropriate 2-methyl- Δ^2 -tetrahydropyrimidine or imidazoline.



pyrimidine

95

EXAMPLE 5

This Example illustrates various forms in which the compounds of the invention can, in admixture with a carrier, be administered to animals. These forms are: dosage units such as tablets; mixtures with a mineral supplement; and mixtures with nutrient material.

a) 250 g. of free imidazoline or tetrahydropyrimidine base or the equivalent weight of a salt thereof are mixed with 50 g. of starch, and this mixture is mixed with ethanol to form a paste. The paste is extruded through a 10-mesh (U.S.) screen, and the extruded material is dried *in vacuo* to form granules.

The granules are coated with magnesium stearate (die lubricant) and pressed into the form of tablets containing 250 mg. of free base or its equivalent.

Bohuses of various sizes can be prepared similarly.

A suitable daily dose of active ingredient (calculated as free base) carries from $\frac{1}{2}$ gm. to 25 gm. per day, depending on the weight of the animal to be dosed.

b) The active ingredient is mixed with a solid diluent, for instance from 15 to 50% by weight of tricalcium phosphate

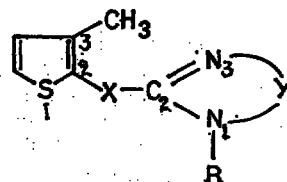
and the mixture is loaded into capsules of hard gelatin in an amount such that each capsule contains 250 mg.—1 g. of active ingredient.

c) 1 Part by weight of active ingredient (calculated as free base) is mixed with 19 parts by weight of a mineral supplement of the usual kind, such as common salt.

d) In prophylaxis, the animal is fed with a mixture of a feed supplement of the usual kind and an amount of active ingredient (calculated as free base) forming from 0.05 to 10% by weight of the mixture.

WHAT WE CLAIM IS:—

1. 2,3-Disubstituted thiophen derivatives of the formula:



where

X represents $-\text{CH}_2-\text{CH}_2-$, $\text{CH}_2-\text{CH}_2-\text{CH}_2-$, or $-\text{CH}=\text{CH}-$;

Y represents $-\text{CH}_2-\text{CH}_2-$, or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; and

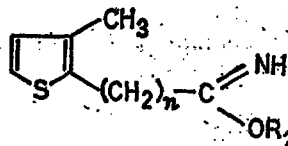
R represents $-\text{H}$ or $-\text{CH}_3$;

and the non-toxic acid addition salts thereof.

2. 1 - Methyl - 2 - (2 - (3 - methyl - 2 - thienyl)ethyl) - Δ^2 - tetrahydropyrimidine and its non-toxic acid addition salts.

3. 1 - Methyl - 2 - (2 - (3 - methyl - 2 - thienyl)vinyl) - Δ^2 - tetrahydropyrimidine and its non-toxic acid addition salts.

4. A method of preparing a compound according to Claim 1 in which X represents $-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, in which method an acid addition salt of an imidate ester of the formula:

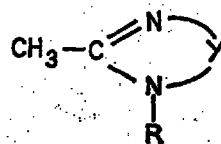


n having a value of 2 or 3 and R_2 representing a low alkyl radical containing from 1 to 6 carbon atoms, is reacted with an alkylene diamine $\text{H}_2\text{N}-\text{Y}-\text{NHR}$ where Y and R are as defined in Claim 1.

5. A method according to Claim 4, substantially as described in Example 3.

6. A method of preparing a compound

according to Claim 1 in which X represents $-\text{CH}=\text{CH}-$, in which method 3-methyl-2-thiophen carboxaldehyde is reacted with a 2-methyl- Δ^2 -imidazoline or -tetrahydropyrimidine of the formula



where Y and R are as defined in Claim 1.

7. A method according to Claim 6, substantially as described in Example 4.

8. A compound according to Claim 1 whenever obtained by a method according to any one of Claims 4 to 7.

9. A composition comprising a compound as claimed in any one of Claims 1 to 3 and 8 in admixture with a carrier.

10. A composition according to Claim 9, in the form of dosage units such as tablets.

11. A composition according to Claim 9, in which the carrier is a mineral supplement.



1,120,587

EXAMPLE 5

This Example illustrates various forms in which the compounds of the invention can, in admixture with a carrier, be administered to animals. These forms are: dosage units such as tablets; mixtures with a mineral supplement; and mixtures with nutrient material.

a) 250 g. of free imidazoline or tetrahydropyrimidine base or the equivalent weight of a salt thereof are mixed with 50 g. of starch, and this mixture is mixed with ethanol to form a paste. The paste is extruded through a 10-mesh (U.S.) screen, and the extruded material is dried *in vacuo* to form granules.

The granules are coated with magnesium stearate (die lubricant) and pressed into the form of tablets containing 250 mg. of free base or its equivalent.

Boluses of various sizes can be prepared similarly.

A suitable daily dose of active ingredient (calculated as free base) varies from $\frac{1}{2}$ gm. to 25 gm. per day, depending on the weight of the animal to be dosed.

b) The active ingredient is mixed with a solid diluent, for instance from 15 to 50% by weight of tricalcium phosphate

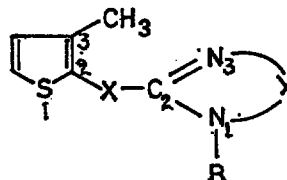
and the mixture is loaded into capsules of hard gelatin in an amount such that each capsule contains 250 mg.—1 g. of active ingredient.

c) 1 Part by weight of active ingredient (calculated as free base) is mixed with 19 parts by weight of a mineral supplement of the usual kind, such as common salt.

d) In prophylaxis, the animal is fed with a mixture of a feed supplement of the usual kind and an amount of active ingredient (calculated as free base) forming from 0.05 to 10% by weight of the mixture.

WHAT WE CLAIM IS:—

1. 2,3-Disubstituted thiophen derivatives of the formula:



where

X represents $-\text{CH}_2-\text{CH}_2-$, $\text{CH}_2-\text{CH}_2-\text{CH}_2-$, or $-\text{CH}=\text{CH}-$;

Y represents $-\text{CH}_2-\text{CH}_2-$, or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; and

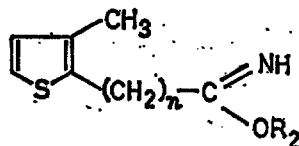
R represents $-\text{H}$ or $-\text{CH}_3$;

and the non-toxic acid addition salts thereof.

2. 1 - Methyl - 2 - (2 - (3 - methyl - 2 - thienyl)ethyl) - Δ^2 - tetrahydropyrimidine and its non-toxic acid addition salts.

3. 1 - Methyl - 2 - (2 - (3 - methyl - 2 - thienyl)vinyl) - Δ^2 - tetrahydropyrimidine and its non-toxic acid addition salts.

4. A method of preparing a compound according to Claim 1 in which X represents $-\text{CH}_2-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$, in which method an acid addition salt of an imide ester of the formula:

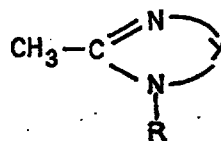


n having a value of 2 or 3 and R_2 representing a low alkyl radical containing from 1 to 6 carbon atoms, is reacted with an alkylene diamine $\text{H}_2\text{N}-\text{Y}-\text{NHR}$ where Y and R are as defined in Claim 1.

5. A method according to Claim 4, substantially as described in Example 3.

6. A method of preparing a compound

according to Claim 1 in which X represents $-\text{CH}=\text{CH}-$, in which method 3-methyl-2-thiophen carboxaldehyde is reacted with a 2-methyl- Δ^2 -imidazoline or -tetrahydropyrimidine of the formula



where Y and R are as defined in Claim 1.

7. A method according to Claim 6, substantially as described in Example 4.

8. A compound according to Claim 1 whenever obtained by a method according to any one of Claims 4 to 7.

9. A composition comprising a compound as claimed in any one of Claims 1 to 3 and 8 in admixture with a carrier.

10. A composition according to Claim 9, in the form of dosage units such as tablets.

11. A composition according to Claim 9, in which the carrier is a mineral supplement.

12. A composition according to Claim 9,
in which the carrier is nutrient material.

D. D. E. NEWMAN
Chartered Patent Agent
Agent for the Applicants. *DN*

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.



* C L M S *