

1074102



PATENT SPECIFICATION

NO DRAWINGS

1074102

Date of filing Complete Specification (under Section 3 (3) of the Patents Act 1949) April 14, 1964.

Two Applications Dated: March 22, 1963.

Nos. 11554/63, 15359/64.

Application Date: Dec. 19, 1963.

No. 50174/63.

Complete Specification Published: June 28, 1967.

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Index at acceptance:—C2 C2B38

Int. Cl.:—C 07 c 123/00

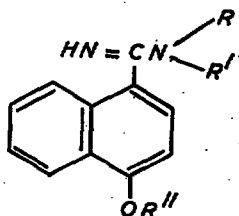
COMPLETE SPECIFICATION

Amidines and method for preparing them

We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, 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 7, 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 amidines, their preparation and compositions containing them.

In British Patent Specification No. 679,119 there are described substituted amidines having local anaesthetic properties and having the formula

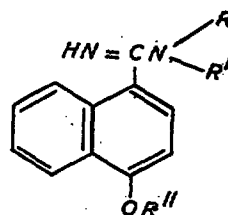


wherein R and R' are alkyl groups containing together from four to ten carbon atoms, and R'' is a lower alkyl group containing from one to four carbon atoms other than ethyl and in which, when R'' represents methyl, R and R' are other than *n*-butyl.

It has now been found that novel higher homologues (defined below in formula I) of these amidines are active against a variety of tapeworm-infections in mammals. For example, the novel amidines have been found active against infections of the tapeworms (cestodes) *Hymenolepis nana* in the mouse and *Taenia pisiformis* in the dog, and certain of the compounds active against *Dipylidium caninum* and *Echinococcus granulosus* in the dog, *Moniezia expansa* in the sheep and *Oöchoristica sym-*

[Price 4s. 6d.]

metrica in the mouse. The novel amidines are also substantially free from pharmacological and toxic effects when administered orally to the host at therapeutic doses.



The present invention therefore provides an amidine of formula (I) or an acid addition salt thereof wherein R and R' are the same and each is an alkyl group, and R'' is an alkyl group having together with R or R' a sum total of at least 9 carbon atoms, and R', R' and R'' have a sum total of not more than 19 carbon atoms. The preferred compounds of formula (I) are those in which the alkyl group R'' together with R or R' have a sum total of 9 to 12 carbon atoms, and particularly preferred compounds are those in which R and R' are butyl, hexyl or heptyl and those in which R'' is butyl, amyl or hexyl. Amidines of formula (I) in which R, R' and R'' are alkyl and have between them between 16 and 19 carbon atoms inclusive are active against the more resistant tapeworm *Oöchoristica sym-*

metrica in the mouse. Tapeworm infections which may be conveniently treated with an amidine of formula (I) or acid addition salt thereof include *Echinococcus granulosus* in dogs, *D. mansoni* or *D. erinacci* in dogs, cats or pigs, *Moniezia expansa* in sheep or cattle, *Davainea proglottina* in poultry, *Railletina tetragona*, *R. echinobothrida* in poultry, *Taenia taeniaformis* in cats or *T. hydatigena* or *T. pisiformis* in dogs.

The anthelmintic activity of the amidine acid addition salts lies in the amidine part of the molecule, and the acid may be any acid which reacts with the amidine base to give a therapeutically acceptable acid addition salt; for example embonate, hydrochloride, hydrobromide, sorbate, benzoate, cinnamate, anthranilate, *p*-toluenesulphonate, 2-hydroxy-3-naphthoate or hydrogen maleate acid addition salts.

While the amidines of formula (I) can in certain cases be isolated as the base, they are fairly strong bases having *pK_a* in the range 11–12 and hence will be positively charged (that is, present as cation components of salts) under any conditions of physiological interest. If administered as bases it would be expected that the acid gastric secretions would convert them to salts. Since, furthermore, the salts are very stable while the free bases are much less so, the amidines of formula (I) will be in practice handled, stored and administered as acid addition salts.

An amidine of formula (I) may be prepared by a method similar to the methods described in the complete specification of U.K. patent No. 619,659; namely by the reaction of a halomagnesium dialkylamine of the formula



(X being a halogen atom) with the appropriate 4-alkoxy- α -naphthonitrile and hydrolysing the product.

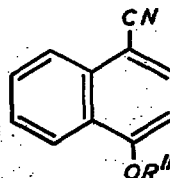
The halomagnesium radical is formed from a Grignard reagent and the appropriate secondary amine. Any Grignard reagent may be used since the Grignard hydrocarbon radical is eliminated as an inert hydrocarbon in the formation of the halomagnesium secondary amine. The halogen may be chlorine, bromine or iodine, but bromine is preferred and ethylmagnesium bromide has been found to be a convenient reagent.

The halomagnesium dialkylamine may be reacted with 4-alkoxy- α -naphthonitrile under reflux in an inert organic solvent such as ether for a period depending on the alkyl and alkoxy groups in the reactants; a period of up to 2 days is necessary in some cases to complete the reaction, though 1–4 hours is often adequate to produce sufficient product.

The initial product of the reaction mixture is the halomagnesium derivative of the amidine. This is hydrolysed, for example by an iced aqueous solution of ammonium chloride, and the halomagnesium radical is replaced by hydrogen, so liberating the required amidine. Usually the hydrolysis product is contaminated with secondary amine which is removed by distillation *in vacuo* or by other conventional means (such as crystallisation of the salts).

This invention therefore further provides a method of preparing an amidine of formula (I) or an acid addition salt thereof comprising

the reaction of a nitrile of the formula



wherein *R''* is defined above in formula (I), with a halomagnesium derivative of a secondary amine of the formula



wherein *R* and *R'* are defined above in formula (I), and subsequently hydrolysing the product to give an amidine base of formula (I) or an acid addition salt thereof and optionally converting the said amidine base or salt into an acid addition salt or another acid addition salt thereof respectively.

In practice, an amidine may be presented for the treatment of tapeworm infection in the form of an orally ingestible pharmaceutical composition comprising an amidine or a salt thereof together with a therapeutically acceptable carrier therefor. An amidine in the form produced in its chemical synthesis and its solutions and suspensions in the liquids used therein is not as such a pharmaceutical composition as defined in this specification. The amidine or a salt thereof may advantageously be presented in discrete units, such as tablets, capsules, cachets each containing a predetermined amount of the compounds. It may also be presented as a powder or granules, as a solution or suspension in a non-aqueous or emulsified liquid.

The novel amidines described herein may also be administered as a component of the feed of the hosts of a tapeworm, and the described compositions include feed supplements in which an amidine is present as an active ingredient and which are suitable for addition to the feed either directly or after dilution or blending.

The compositions may be made by any of the methods of pharmacy, which include, tableting by compression or moulding, granulating, grinding, stirring, coating, milling and tumbling. Carriers which may be included in a composition are: diluents, solutes, buffers, flavouring, binding, dispersing, surface-active, thickening, lubricating, and coating materials, preservatives, antioxidants, feedstuffs, and bacteriostats, and any other acceptable excipients. The preferred composition for the treatment of infections of tapeworms are tablets and granules comprising an amidine of the invention or a salt thereof.

In another aspect therefore, this invention provides an orally ingestible pharmaceutical composition for the treatment of a tapeworm infection comprising an amidine of formula (I) or an acid addition salt thereof, together

with a therapeutically acceptable carrier therefor. In a further aspect, this invention provides a method for making an orally ingestible pharmaceutical composition as defined in the preceding paragraph comprising the admixture of the amidine or a salt thereof with the therapeutically acceptable carrier therefor. In yet a further aspect this invention provides a method for the treatment of a tapeworm infection in a domestic animal comprising the administration to the animal of an amidine of formula (I) or an acid addition salt thereof.

The following examples illustrate the invention. All temperatures are in degrees Celsius. The mesh (#) figures of 16, 20, and 100 correspond to aperture dimensions of 1130, 965 and 100 μ respectively.

EXAMPLE 1

Preparation of *N,N*-diamyl-4-hexyloxy- α -naphthamidine hydrochloride

A Grignard solution was prepared from magnesium turnings (5 g.) and ethyl bromide (22 g., 0.2 mole) in absolute ether (200 ml.) contained in a flask equipped with a stirrer, reflux condenser and a dropping funnel. Di-*n*-amylamine (32 g.) was added to this mixture at a rate sufficient to cause gentle refluxing and after the addition was complete, the solution was refluxed for a further hour. To the refluxed solution was added an ethereal solution of 4-hexyloxy- α -naphthonitrile (38 g., 0.15 mole) over a period of 30 minutes. After the addition was complete, the reaction mixture was refluxed for 24 hours, cooled and hydrolysed with an iced hydrochloric acid solution. A considerable amount of solid separated and was filtered off. The filtrate was extracted with ether, the extract discarded, the aqueous layer was treated with a base and extracted with ether. The ethereal extract formed Extract I.

The solid originally obtained by filtration was dissolved in warm water, the solution then basified and extracted with benzene to form Extract II. Extracts I and II were then evaporated separately on a steam bath, using, if necessary, a vacuum to remove final traces of di-*n*-amylamine. The two basic residues were then dissolved in absolute ethanol and acidified with ethanolic hydrogen chloride. Absolute ether was added until the solutions were barely turbid after which crystallisation of the amidine hydrochloride was induced by scratching. The resulting salt melted at 217—218°.

EXAMPLE 2

N,N-Di-*n*-heptyl-4-butoxy- α -naphthamidine hydrochloride

To a solution of ethyl magnesium bromide prepared from magnesium turnings (3.7 g.) and ethyl bromide (16.3 g.) in anhydrous ether (200 ml.) was added di-*n*-heptylamine (32 g.) in dry ether (150 ml.). The solution was then refluxed for an hour and 4-butoxy- α -naphthonitrile (14.3 g.) dissolved in dry ether (250 ml.) was added gradually over one-half hour.

The reaction-mixture was then stirred and refluxed for 18 hours, cooled and hydrolysed with iced saturated ammonium chloride solution. The ethereal layer was separated, washed with water and dried over anhydrous potassium carbonate. This ethereal solution of the base was then evaporated and the residue was subjected to distillation at 0.03 to 0.05 mm. pressure. A portion of diheptylamine boiling at 85—93° was thus removed. The residue was dissolved in absolute ethanol, acidified with ethanolic hydrogen chloride and crystallised by addition of ether. The pure hydrochloride melted at 213—214°.

EXAMPLE 3

N,N-Diheptyl-4-amyloxy- α -naphthamidine hydrochloride

This preparation was identical with that of Example 2 except that 4-pentoxy- α -naphthonitrile (22.4 g.) was added to the solution of bromomagnesium diheptylamide, and the reflux time was 19 hours. The amidine hydrochloride, purified as described in Example 2, melted at 207°.

EXAMPLE 4

N,N-Dihexyl-4-butoxy- α -naphthamidine hydrochloride

To a solution of ethyl magnesium bromide (prepared as in Example 2) was added dihexylamine (17.6 g.) in anhydrous ether (150 ml.). After 45 minutes refluxing, a solution of 4-butoxy- α -naphthonitrile (14.3 g.) was then added and the reaction mixture was stirred and refluxed for 24 hours. After working up by the method of Example 2 the pure hydrochloride, m.p. 218—219° was isolated.

EXAMPLE 5

N,N-Dihexyl-4-hexyloxy- α -naphthamidine hydrochloride

A Grignard solution was prepared from magnesium turnings (4.85 g.) and ethyl bromide (19.7 g.) in anhydrous ether (250 ml.). To it was added a solution of di-*n*-hexylamine (40 g.) in anhydrous ether (220 ml.) and the solution was refluxed for one-half hour. To this was added over a period of 10 minutes a solution of 4-hexyloxy- α -naphthonitrile (38 g.) in warm dry benzene (100 ml.). The reaction mixture was stirred and refluxed for 42 hours and then hydrolysed with iced hydrochloric acid (containing 60 ml. of concentrated hydrochloric acid). A solid separated that appeared to contain the whole of the product together with some dihexylamine hydrochloride, the magnesium salts and any neutral impurities being in the filtrate and washings. The solid was shaken with sodium hydroxide solution and ether, and the ethereal solution of the bases was dried over potassium carbonate and subjected to distillation in high vacuum to remove dihexylamine. The residual amidine was converted to the hydrochloride which was recrystallised from alcohol-ether mixtures, and then from nitromethane, m.p. 201—202°.

EXAMPLE 6

N,N-Di-*n*-octyl-4-methoxy- α -naphthamidine hydrochloride

5 This compound was prepared by the method of Example 5 (using 27.5 g. of 4-methoxy- α -naphthonitrile). The amidine hydrochloride melted at 173°.

EXAMPLE 7

N,N-Di-hexyl-4-amyloxy- α -naphthamidine hydrochloride

10 The Grignard solution was prepared from magnesium (5.35 g.) and ethyl bromide (21.8 g.). Di-hexylamine (40.7 g.) and 4-amyloxy- α -naphthonitrile (44.8 g.) were added exactly as described in Example 5. The amidine hydrochloride melted at 213° after crystallisation from nitromethane.

EXAMPLE 8

20 The hydrochloride salts of the following amidines were prepared in the manner described in Example 1. The melting points of the salts are shown.

N,N - Di - *n* - butyl - 4 - amyloxy - α - naphthamidine; 215°

25 *N,N* - Diamyl - 4 - butoxy - α - naphthamidine; 222°.

N,N - Di - *n* - amyl - 4 - amyloxy - α - naphthamidine; 220—221°.

30 *N,N* - Di-hexyl - 4 - heptyloxy - α - naphthamidine; 197—198°.

EXAMPLE 9

N,N-Dibutyl-4-hexyloxy- α -naphthamidine

A Grignard reagent was prepared from ethyl bromide (22 g; 0.2M), magnesium turnings (5.35 g.; 0.22 g.-atom), and commercial anhydrous ether (250 ml.) under an atmosphere of nitrogen. Into this mixture was washed dry carbonate-free di-*n*-butylamine (31.3 g.; 0.243M) with anhydrous ether (about 50 ml.) over a period of about 10 seconds. A solution of 4-*n*-hexyloxy- α -naphthonitrile (47.8 g.; 0.189M) in hot dry benzene (about 250 ml.) was then added to the ethereal mixture, and the reaction mixture heated under reflux for about 19 hours. At the end of this time, aqueous hydrochloric acid (120 ml.; 6N) was added to

the reaction mixture to produce a white precipitate which was filtered off and combined with ether-benzene layer of the filtrate. The resulting suspension was largely dissolved by addition of ethanol, treated with aqueous sodium hydroxide (120 ml.; 6N), and extracted with ether. The ethereal solution was dried with magnesium sulphate and evaporated down, finally using a mechanical pump and steam heat to evaporate off the remaining di-*n*-butylamine. The residue was dissolved in a little ethanol and treated with a slight excess of a concentrated solution of hydrogen chloride in ethanol, then ethyl acetate and finally sufficient anhydrous ether to produce incipient turbidity. Two such crystallisations produced a white solid m.p. 214—214.8°.

EXAMPLE 10

Dispersible powder granules

Dispersible powder granules of *N,N*-dibutyl-4-hexyloxy- α -naphthamidine hydrochloride were made from the following:

<i>N,N</i> - dibutyl - 4 - hexyloxy - α - naphthamidine hydrochloride	90 mg.	70
Starch (Potato)	90 mg.	
Magnesium stearate	1.0 mg.	

A mixture of the hydrochloric salt and 2/3 of the starch was granulated with sufficient 2% starch mucilage made from part of the remainder of the starch. The moist mass was sifted through a 20 # sieve and dried at 50°. The dried mass was sifted 16 # and added to the remainder of the starch and the magnesium stearate sifted 100 #.

EXAMPLE 11

A tablet

A tablet of *N,N* - dibutyl - 4 - hexyloxy- α - naphthamidine hydrochloride was made from the following:

<i>N,N</i> - dibutyl - 4 - hexyloxy - α - naphthamidine hydrochloride	346 mg.	
Starch (potato)	50 mg.	
Lactose 100 #	50 mg.	
Magnesium stearate	4 mg.	90

The hydrochloride salt was mixed with the lactose and 2/3 of the starch and the mixture granulated with sufficient 2% starch mucilage made from the remainder of the starch. The moist mass was sifted through a 20 # sieve and dried at 50°. The dried mass was sifted 16 # and added to the remainder of the starch and the magnesium stearate sifted 100 #. The equivalent of 346 mg. of the hydrochloride salt was compressed on a die to form a tablet.

EXAMPLE 12

A film coated tablet

The equivalent of 250 mg. of *N,N* - dibutyl-4-hexyloxy- α -naphthamide hydrochloride (as produced in Example 11) were compressed on a die sugar coating curvature. The tablets produced were sifted on a 16 # sieve to remove as much dust as possible and the dust free tablets placed in a coating pan. The tablets were then coated with an ethanolic solution of a mixture of methyl and ethyl cellulose to produce a film coating on the tablets which were subsequently glazed in a waxed coating pan.

EXAMPLE 13

According to the procedure described in Examples 10, 11 and 12, granules, tablets and film coated tablets were made of the hydrochloride salts of the amidines described in Examples 1 to 9.

EXAMPLE 14

N,N-Di-*n*-butyl-4-hexyloxy- α -naphthamidine hydrochloride

Magnesium (4 moles) and ethyl bromide (3.6 moles) were reacted in ether (5000 ml.) to give ethyl magnesium bromide. Di-*n*-butylamine

(4.32 moles), dissolved in ether (4400 ml.) was run into the stirred reaction mixture to maintain reflux, and the whole was refluxed for a further half-hour. 4-Hexyloxy- α -naphthonitrile (3 moles) was dissolved in dry benzene (2250 ml.) and added to the mixture under reflux, and finally the stirred mixture was refluxed for a further 44 hours.

The reaction mixture was cooled, and chilled hydrochloric acid (200 ml. conc. made up to 1000 ml.) slowly run in, causing the product to precipitate. Finally chilled conc. hydrochloric acid (400 ml.) was slowly added, and the reaction mixture filtered. The precipitate was washed successively with cold hydrochloric acid (6N) and ether, then dissolved in methanol (about 2000 ml.).

The base was liberated by adding benzene (5000 ml.) then extracting with sodium hydroxide (5000 ml., 50% w/v solution), adding ether to help separation. After drying the organic layers over sodium sulphate, the solvents were removed on a steam-bath under reduced pressure. Unchanged di-*n*-butylamine was distilled off finally by heating the residue on a steam bath under reduced pressure for 1 hour.

The hydrochloride was re-precipitated by dissolving the residue in petroleum ether (60°—80°) and passing hydrogen chloride into the stirred solution. Finally, the product was recrystallised from water to give a white solid with m.p. 203°—206°.

Salts of *N,N*-di-*n*-butyl-4-*n*-hexyloxy- α -naphthamidine were prepared in the manner described above.

EXAMPLE 15

The base (20 g.) of the above-mentioned compound was dissolved in ether and the solution mixed with an ethereal solution of benzoic acid (7 g.). A white salt slowly precipitated which on recrystallisation from petroleum ether (boiling from 60 to 80° Celsius) gave *N,N*-di-*n*-butyl-4-*n*-hexyloxy- α -naphthamidine benzoate, melting point 118—120° Celsius.

EXAMPLES 16—19

In the manner described in Example 15, there were prepared the following salts of *N,N*-di-*n*-butyl-4-*n*-hexyloxy- α -naphthamidine:

Ex. 16. Cinnamate, 103—105°

Ex. 17. Sorbate, 94—97°

Ex. 18. Anthranilate, 99—102°

Ex. 19. 3-Hydroxy-2-naphthoate, 169—170°

The above figures indicate the melting point of the salts in ° Celsius.

EXAMPLE 20

A solution of *N,N*-di-*n*-butyl-4-*n*-hexyloxy- α -naphthamidine hydrochloride in acetone was mixed with stirring with a cold aqueous solution of sodium embonate. The

mixture was heated to boiling, cooled and a salt crystallised out. This salt was recrystallised from aqueous acetone to give the embonate salt, melting point 147—148° Celsius.

EXAMPLES 21 AND 22

In the manner described 20, the corresponding *p*-toluene-sulphonate and thiosalicylate salts were prepared, melting points 148—149° and 150° Celsius respectively.

EXAMPLE 23

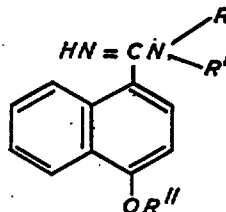
A solution of *N,N*-di-*n*-butyl-4-*n*-hexyloxy- α -naphthamidine hydrochloride in aqueous acetone was mixed with an aqueous solution of maleic acid to yield a precipitate of the hydrogen maleate salt. This was recrystallised from petroleum ether (boiling between 60 and 80° Celsius) to give the salt melting at 123—125° Celsius.

EXAMPLE 24

A solution of *N,N*-di-*n*-butyl-4-*n*-hexyloxy- α -naphthamidine hydrochloride (20 g.) in aqueous acetone was mixed with a solution of salicylic acid (12 g.) in aqueous acetone. An emulsion formed which crystallised to give a white solid. This was recrystallised from petroleum ether (boiling between 60 and 80° Celsius) to yield crystals of the salicylate salt, melting point 67—70° Celsius.

WHAT WE CLAIM IS:—

1. An amidine of the formula



or an acid addition salt thereof wherein R and R' are the same and each is an alkyl group, R'' is an alkyl group having together with R or R' a sum total of at least 9 carbon atoms, and R, R' and R'' have a sum total of not more than 19 carbon atoms.

2. An amidine as claimed in claim 1 or an acid addition salt thereof wherein R and R' are the same and R'' is an alkyl group having together with R or R' a sum total of between 9 and 12 carbon atoms inclusive.

3. An amidine as claimed in claim 1 or an acid addition salt thereof wherein R, R' and R'' are each alkyl having between them a sum total of 16 to 19 carbon atoms inclusive.

4. *N,N*-di-*n*-butyl-4-*n*-hexyloxy- α -naphthamidine.

5. *N,N*-Diheptyl-4-butoxy- α -naphthamidine.

6. *N,N*-Dihexyl-4-butoxy- α -naphthamidine.

7. *N,N*-Dihexyl-4-hexyloxy- α -naphthamidine.

8. *N,N*-Dihexyl-4-amyloxy- α -naphthamidine.

9. *N,N*-Dibutyl-4-hexyloxy- α -naphthamidine.

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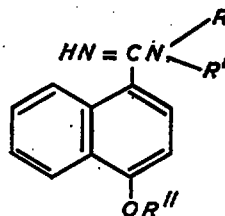
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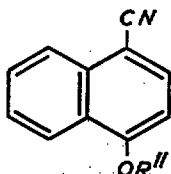
7. *N,N*-Dihexyl-4-hexyloxy- α -naphthamidine.

8. *N,N*-Dihexyl-4-amyloxy- α -naphthamidine.

9. *N,N*-Dibutyl-4-hexyloxy- α -naphthamidine.



10. *N,N* - Dibutyl - 4 - amyloxy - α - naphthamidine.
 11. *N,N* - Diamyl - 4 - hexyloxy - α - naphthamidine.
 5 12. *N,N* - Diheptyl - 4 - amyloxy - α - naphthamidine.
 13. *N,N* - Di - *n* - octyl - 4 - methoxy - α - naphthamidine.
 14. *N,N* - Diamyl - 4 - butoxy - α - naphthamidine.
 10 15. *N,N* - Di - *n* - amyl - 4 - amyloxy - α - naphthamidine.
 16. *N,N* - Dihexyl - 4 - heptyloxy - α - naphthamidine.
 15 17. An acid addition salt of an amidine base defined in any of claims 4 to 16.
 18. A hydrochloride salt of an amidine base defined in any of claims 4 to 16.
 19. *N,N* - Di - *n* - butyl - 4 - *n* - hexyloxy - α - naphthamidine hydrochloride.
 20 20. *N,N* - Di - *n* - butyl - 4 - *n* - hexyloxy - α - naphthamidine 3 - hydroxy - 2 - naphthoate.
 21. *N,N* - Di - *n* - butyl - 4 - *n* - hexyloxy - α - naphthamidine *p* - toluenesulphonate.
 25 22. *N,N* - Di - *n* - butyl - 4 - *n* - hexyloxy - α - naphthamidine hydrogen maleate.
 23. *N,N* - Di - *n* - butyl - 4 - *n* - hexyloxy - α - naphthamidine sorbate.
 24. A method of preparing an amidine or an acid addition salt thereof as defined in any of claims 1 to 23 comprising the reaction of
 30 a nitrile of the formula



35 with a halomagnesium derivative of a secondary amine of the formula



and subsequently hydrolysing the product to produce the amidine base or salt thereof.

25. A method as claimed in claim 24 wherein the halomagnesium derivative is the bromomagnesium derivative of the secondary amine.

26. A method as claimed in claim 24 wherein the hydrolysis is carried out with aqueous hydrochloric acid.

27. An orally ingestible pharmaceutical composition comprising an amidine or an acid addition salt thereof as defined in any one of claims 1 to 23 together with a therapeutically acceptable carrier therefor.

28. A composition as claimed in claim 27 which is a tablet.

29. A composition as claimed in claim 27 which is granules.

30. A composition as claimed in claim 27 which is a feed supplement.

31. A tablet containing *N,N* - di - *n* - butyl - 4 - *n* - hexyloxy - α - naphthamidine hydrochloride.

32. A method of making an orally ingestible pharmaceutical composition claimed in any of claims 27 to 31 comprising admixture of the amidine or acid addition salt thereof with a therapeutically acceptable carrier therefor.

33. A method for the treatment of a tapeworm infection in domestic animals comprising the administration to the animal of an amidine or an acid addition salt thereof as defined in any of claims 1 to 23.

34. A *N,N* - dialkyl - 4 - alkoxy - α - naphthamidine or an acid addition salt thereof substantially as hereinbefore described in Examples 1 to 9 and 14 to 24.

35. An orally ingestible pharmaceutical composition of an *N,N* - dialkyl - 4 - alkoxy - α - naphthamidine substantially as hereinbefore described in the specification and Examples 10 to 13.

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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.
 —1967. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2
 from which copies may be obtained.



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