

PATENT SPECIFICATION

(11) 1432378

1432378

- (21) Application No. 48595/72 (22) Filed 21 Oct. 1972
 (21) Application No. 7424/73 (22) Filed 15 Feb. 1973
 (21) Application No. 34886/73 (22) Filed 21 July 1973
 (21) Application No. 38701/73 (22) Filed 16 Aug. 1973
 (23) Complete Specification filed 17 Sept. 1973
 (44) Complete Specification published 14 April 1976
 (51) INT CL³ C07D 215/16 A61K 31/435 C07D 219/04 221/02//
 (A61K 31/435 33/00 33/06 33/08 33/12 33/14)



(52) Index at acceptance

C2C 1534 1536 1544 213 220 226 22Y 246 247 250 251
 25Y 271 280 282 292 29X 29Y 303 305 30Y 326
 342 34Y 366 367 368 375 380 488 490 491 555
 574 579 584 628 62X 62Y 638 658 65X 676 678
 68Y 69Y 73Y 752 753 755 76X 776 77Y 780 790
 79Y BE KF KG NR QZ SN ZH
 A5B 20X 20Y 272 273 274 275 27Y 285 28Y 380 38Y
 492 49X 49Y 551 55Y 576 57Y 625 626 627 62Y

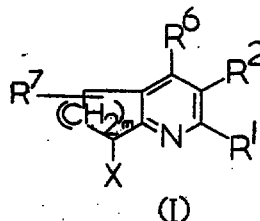
- (72) Inventors ADRIAN CHARLES WARD CURRAN
 ROGER CROSSLEY and
 DAVID GEORGE HILL

(54) FUSED CARBOCYCLIC RING DERIVATIVES OF PYRIDINE

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, England, a British Company, 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:—

The invention relates to novel fused carbocyclic ring derivatives of pyridine, to processes for preparing them and to pharmaceutical compositions containing certain of the novel derivatives.

The invention provides a compound of formula I



and acid addition salts thereof, wherein R¹, R² and R⁴ are the same or different and represent hydrogen, trifluoromethyl, or alkyl which may be substituted by alkoxy, halogen, nitro or trifluoromethyl, or an aralkyl or aryl radical, either of which radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl or R¹ and R² taken together represent an alkylene chain —CH₂(CH₂)_nCH₂— wherein n is 1, 2 or 3, R⁷ represents hydrogen or single or multiple substitution by alkyl, aralkyl or aryl radicals any of which alkyl, aralkyl or aryl radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl and when R¹ and R² taken together form an alkylene chain the resulting ring may be substituted by one or more R⁷ radicals as defined above, X is cyano, CONHR³, CSNHR³ or CO₂R³ wherein R³ is hydrogen or alkyl which may be substituted by alkoxy, bromine, chlorine, fluorine, nitro or trifluoromethyl, R⁵ is selected from hydrogen or alkyl which may be substituted as for the R³ alkyl radicals, or aralkyl or aryl radicals either of which radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl, and m is 1, 2 or 3 with the proviso that when R¹

and R² taken together represent an alkylene chain then n is equal to m, and metal, e.g. alkali-metal, salts of the compounds in which R⁵ is hydrogen.

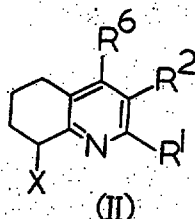
R⁷ may be in the same position as X.

When any of R¹, R², R³, R⁴, R⁶ or R⁷ is an alkyl radical it is preferred that this is a lower alkyl radical which may be a straight or branched chain, having from 1 to 6 carbon atoms, e.g. methyl, ethyl, *n*-, and *iso*-propyl and *n*-, *s*- and *t*-butyl, R⁷ may be a *gem*-dimethyl group and when a single radical may be on the same carbon atom as the group X. The term alkyl radical is also intended to embrace cyclic alkyl radicals e.g. cyclobutyl, cyclopentyl and cyclohexyl. When any of R¹, R², R³, R⁴, R⁶ or R⁷ is an aralkyl radical it is preferred that this is an aryl-lower alkyl radical where the lower alkyl portion may be as discussed above for a lower alkyl radical. The aryl portion is preferably a phenyl radical.

When any of R¹, R², R³, R⁴, R⁶ or R⁷ is an aryl radical, this is preferably phenyl or a substituted phenyl radical (substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl). However, other aryl radicals which may be used include naphthyl. Preferably when the pyridine ring carries a phenyl substituent R¹ and R² are selected from hydrogen and phenyl. Preferably R³ and R⁴ are selected from hydrogen and lower alkyl e.g. methyl or *t*-butyl.

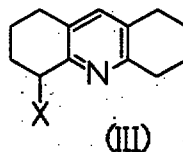
Particularly preferred compounds are those in which one of R¹, R² and R⁴ is methyl and the others are hydrogen. Also preferred are compounds wherein m is 2. Compounds wherein R⁵ is hydrogen or methyl are also preferred.

Thus the present invention provides, in one preferred aspect, compounds of formula II



and acid addition salts thereof, wherein one of R¹, R² and R⁴ are selected from hydrogen and methyl and X is CN, CONHR⁵, CSNHR⁵ or CO₂R⁵, R⁵ and R⁶ being as defined in connection with formula I, and metal e.g. alkali metal salts of those compounds wherein R⁵ is hydrogen. In formula II, it is preferred that X is CSNH₂ or CSNHCH₃.

In another preferred aspect the present invention provides compounds of formula (III)



and acid addition salts thereof, wherein X is as defined in connection with formula I. Preferably X is CSNH₂.

The compounds of formula I can form acid addition salts with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric or nitric acids, or organic acids e.g. oxalic, fumaric, maleic or tartaric acids. These acid addition salts are included in the invention.

In the compounds of formula I the carbon atom to which X is attached is asymmetric. Consequently the compounds can exist in optically active *d* and *l* forms. These optically active forms and the racemates are included in the invention. The optically active forms may be separated by standard techniques either by formation of an acid salt with an optically active acid or by use of an optically active base with a compound in which X is COOH.

Compounds of formula I, wherein X is CSNHR⁵, and compounds wherein X is CN are anti-ulcer agents which possess anti-ulcer activity as determined by the method of Brodie and Hanson, J. Applied Physiology, 15, 291, 1960 or anti-secretory activity in the test described below. In general it has been found that compounds of formula I in which X is CSNHR⁵ possess anti-ulcer activity. In the above test 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide, 2-phenyl-, 2-*t*-butyl-5,6,7,8-tetrahydroquinoline-8-

thiocarboxamide and 2- and 3-methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide have shown good activity. Compounds of formula I in which X is CONHR⁵ or CO₂R⁵ or salts of those where X is CO₂H are generally intermediates for compounds of formula I, in which X is CSNHR⁵. Compounds of formula I, wherein X is CSNHR⁵ often display antisecretory activity in the test of H. Shay, D. Sun and H. Greenstein, Gastroenterology 1954, 26, 906-13. For instance 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide, the 2 and 3-methyl analogues thereof and the 3-methyl-8-N-methyl analogue exhibited marked activity in this test. Some nitriles of formula I wherein X is CN are also active in this test. Compounds of formula I in which X is CN are also intermediates for the thioamides of formula I in which X is CSNHR⁵.

The compounds of formula I may be prepared by various methods all of which are included in the invention.

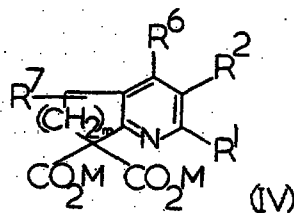
A general method of preparing the compounds of formula I comprises treating a corresponding compound in which X is hydrogen by known methods to introduce the desired group X.

A method for preparing compounds of formula I in which X is CO₂R⁵ comprises carboxylating a corresponding compound wherein X is hydrogen, to obtain a compound of formula I in which X is COOH or metal salt thereof and, if desired esterifying the product with an hydroxyl compound R⁵OH, wherein R⁵ is as defined above, except hydrogen. The carboxylation may be achieved by preparation of a metal salt of compound of formula I wherein X is COOH, by treating a corresponding compound in which X is hydrogen, with a metal alkyl, followed by treatment of the product, which has the formula I wherein X is M, *in situ* with carbon dioxide, conveniently by bubbling CO₂ gas into the reaction mixture. The compound of formula I in which X is CO₂H is obtained by treatment of the product, a metal salt of a compound of formula I in which X is COOH, with acid e.g. hydrochloric or hydrobromic acid. A convenient method is to treat a solution of the salt with gaseous hydrogen chloride. The metal alkyl may be one of a monovalent metal e.g. MR¹⁰ wherein M is sodium, potassium or lithium and R¹⁰ is alkyl, aryl or aralkyl or one of a divalent metal M(R¹⁰)₂ wherein M is calcium or magnesium. A convenient reagent MR¹⁰ is lithium phenyl or n-butyl lithium.

It has been found that when a compound of formula I in which R¹ is methyl and R², R⁶ and R⁷ are hydrogen and X is hydrogen is carboxylated, the carboxylation may occur either on the methyl group R¹ or at the desired X position. Usually a mixture of desired and undesired product is formed but the desired product can be separated during subsequent work-up.

The esterification of a compound of formula I in which X is CO₂H may be carried out using an hydroxyl compound R⁵OH, wherein R⁵ is as defined above except hydrogen according to standard procedures, e.g. in the presence of an acid catalyst e.g. some concentrated sulphuric acid or after saturation with hydrogen chloride gas or a Lewis acid e.g. boron trifluoride if desired with heat or treatment of the silver salt. (X is COOAg) with an iodide R⁵I wherein R⁵ is as defined above, except hydrogen.

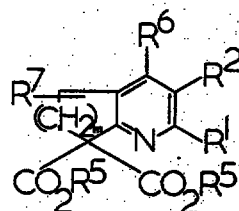
The yield of ester can be improved by introducing a further quantity of the metal alkyl after the CO₂ treatment, followed by a further amount of CO₂. It is believed that the further quantity of metal alkyl and CO₂ gives the *bis* acid-metal salt of formula IV



wherein R¹, R², R⁶ and R⁷ are as defined in connection with formula I and M is the metal of the metal alkyl e.g. sodium, potassium or lithium, and this salt spontaneously decarboxylates during the esterification.

A further method for preparing esters of formula I wherein X is CO₂R⁵ comprises treating a compound of formula I as defined above wherein X is a hydrogen atom with a metal alkyl (as defined above) and then treating the product with a haloformate of formula HalCOOR⁵ wherein Hal is a halogen atom e.g. chlorine or bromine and R⁵ is as defined above. The product is usually a mixture of the desired compound of formula I wherein X is CO₂R⁵ and the corresponding *bis*-ester of formula V

13

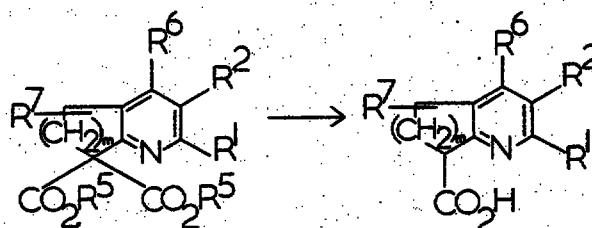


(V)

These bis-esters are useful for preparing the corresponding compounds of formula I wherein X is CO₂H. We have found that this mixture of mono and bis esters can be converted directly to the corresponding compound of formula I where X is CO₂H, by saponification with an alkali or alkaline earth metal hydroxide to give a mixture of the metal salt of the mono acid of formula I wherein X is CO₂H and the metal salt of the diacid of formula V wherein R⁵ is H. Treatment of this mixture with a mineral acid e.g. hydrochloric acid gives the desired acid of formula I wherein X is CO₂H since the diacid spontaneously decarboxylates to form the mono acid.

The product of the haloformate reaction may be treated with a further quantity of the metal alkyl followed by a further quantity of the haloformate thereby producing more of the bis ester (V).

A further method for preparing compounds of formula I in which X is CO₂H comprises decarboxylation of a compound of formula V.



wherein R¹, R², R³ and m are as previously defined. The decarboxylation can be carried out by heating and dicarboxylic acid of formula II wherein R⁵ is hydrogen. Usually the dicarboxylic acid is prepared *in situ* by hydrolysis of the corresponding di-ester, wherein R⁵ is as defined above except hydrogen. The hydrolysis and decarboxylation may be carried out by heating with a dilute mineral acid e.g. HCl or sulphuric acid or the diester may be saponified with alkali e.g. sodium or potassium hydroxide. The resulting salt is then acidified and decarboxylated by heating.

Compounds of formula I, in which X is CONHR³ may be prepared by treatment of a corresponding compound of formula I wherein X is COCl or CO₂R⁵ and R⁵ is as defined above, except hydrogen, with ammonia to give a compound of formula I in which X is CONH₂, which may be subsequently alkylated to introduce the group R³, wherein R³ is as defined above except hydrogen. Conveniently a compound of formula I wherein X is CO₂R⁵ wherein R⁵ is lower alkyl, especially methyl or ethyl, is treated with ammonia. Alternatively substituted amides of formula I wherein X is CONHR³ and R³ is other than hydrogen may be prepared by treatment of the carboxylic ester of formula I wherein X is CO₂R⁵ and R⁵ is other than hydrogen with an amine of formula R³NH₂ wherein R³ is as defined previously except hydrogen. The substituted amides may conveniently be prepared from the acid chloride of formula I wherein X is COCl by treatment with a primary amine R³NH₂ e.g. methylamine.

The acid chlorides may be prepared by treatment of the corresponding acid of formula I, wherein X is CO₂H with thionyl chloride, phosphorus oxychloride or phosphorus pentachloride.

A further process for preparing compounds of formula I as defined above wherein R¹ and R² are as defined above and X is CONHR³ wherein R³ is hydrogen or alkyl, comprises treating an ester compound of formula I, wherein X is CO₂R⁵ and R⁵ is alkyl with an amide of formula R³CONHR³ or a salt thereof wherein R³ is hydrogen or alkyl and R⁵ is hydrogen or lower alkyl in the presence of an alkali-metal alkoxide.

Preferably a molar equivalent of alkali-metal alkoxide is used for each mole of ester of formula I. The alkali-metal alkoxide may be one derived from a lower alkanol having from 1 to 6 carbon atoms e.g. methanol or ethanol. The alkali-metal is preferably sodium.

The ester of formula I is preferably a lower alkyl ester.

The amide $R^3\text{CONHR}^3$ is preferably one in which R^3 is hydrogen or methyl. R^3 is also preferably hydrogen or methyl. Thus preferred amides are formamide, N-methylformamide, acetamide and N-methylacetamide. Salts, especially alkali-metal salts of these amides may be used as starting materials.

The reaction may be carried out by heating the reactants together.

The amides of formula I, wherein X is CONH_2 , may also be prepared by partial hydrolysis of the corresponding nitriles of formula I, wherein X is CN. This hydrolysis may be accomplished in conventional manner e.g. by concentrated (e.g. 96%) sulphuric acid.

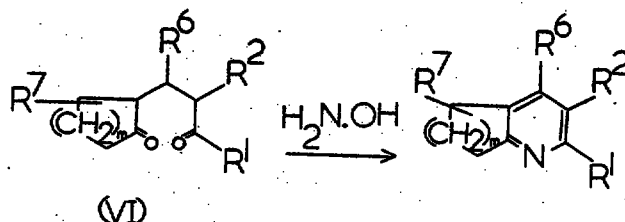
Thioamides of formula I wherein X is CSNHR^3 wherein R^3 is as already defined may be prepared by treatment of the corresponding compounds in which X is CONHR^3 with P_2S_5 , e.g. by refluxing in pyridine. As mentioned below when the starting material is one in which X is CONH_2 , decomposition to the nitrile may occur. We have found that this decomposition can be avoided by conducting the P_2S_5 reaction in the presence of H_2S . Alternatively the thioamides may be prepared by treatment of a nitrile of formula I, wherein X is CN with H_2S to give the unsubstituted thioamide wherein X is CSNH_2 . Substituted thioamides may be obtained by conducting this reaction in the presence of a primary amine R^3NH_2 wherein R^3 is as defined above except hydrogen. The H_2S reaction can be carried out in a suitable solvent in the presence of a catalyst such as a tertiary amine e.g. a trialkylamine such as triethylamine.

Substituted thioamides may also be prepared by treatment of an unsubstituted thioamide of formula I, wherein X is CSNH_2 , with an amine of formula R^3NH_2 , wherein R^3 is as previously defined except hydrogen, in the presence of H_2S . The amine may be an alkylamine e.g. methylamine.

The nitriles of formula I wherein X is CN, may be prepared by dehydration of the corresponding amides of formula I wherein X is CONH_2 . Such dehydration can be carried out with P_2O_5 , as the dehydrating agent. Other dehydrating agents are phosphorus pentachloride or thionyl chloride. It has also been found that a similar decomposition can be effected with P_2S_5 . This decomposition with P_2S_5 has been observed as a side reaction during the conversion of the amides of formula I wherein X is CONH_2 to the corresponding thioamides wherein X is CSNH_2 using P_2S_5 . The nitrile can either be separated, e.g. by chromatography or the mixture treated with H_2S for conversion of the nitrile to the corresponding thioamide. The dehydration may also be effected by heating the amide in hexamethylphosphorotriamide as solvent. When using this solvent it has been found that a compound of formula I in which X is CONMe_2 may be formed as a significant by-product. The latter is also believed to be a novel reaction *per se*.

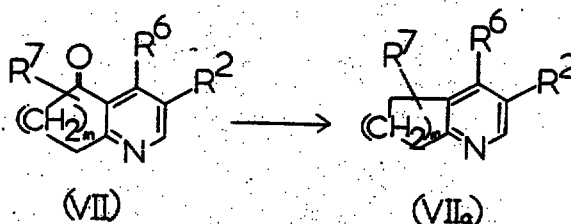
A further method for preparing the thioamides of formula I, wherein X is CSNH_2 , comprises reacting a nitrile of formula I wherein X is CN with a thioamide of formula R^3CSNH_2 , where R^3 is an alkyl group, e.g. a lower-alkyl group of 1-6 carbon atoms, preferably a methyl group, in a suitable solvent such as dimethyl formamide saturated with hydrogen chloride.

The starting compounds of formula I wherein X is hydrogen, used in the above mentioned carboxylation reaction may be prepared by cyclisation of a compound of formula VI in the presence of hydroxylamine

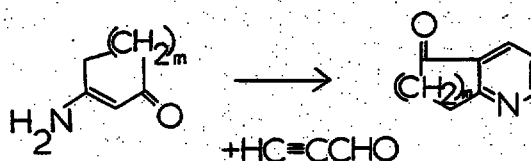


wherein R^1 and R^3 are as defined above but R^1 is preferably other than hydrogen and R^6 and R^7 are as defined above. Starting compounds of formula I, when X is hydrogen, R^1 is hydrogen and R^7 is hydrogen, or if not hydrogen is not on the 5-position may be prepared by reduction of the corresponding 5-oxo compound (VII) using a reducing agent which does not affect the unsaturation of the fused pyridine ring e.g. hydrazine i.e. a Wolff-Kishner reduction.

(15)



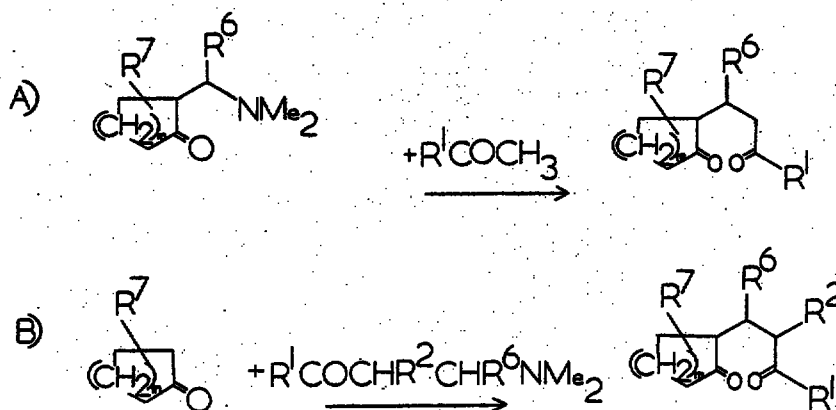
The starting material of formula (VII) wherein R^2 and R^6 are hydrogen may be prepared by the following scheme.



The reaction can be carried out in a suitable solvent e.g. dimethylformamide at room temperature followed by distillation of the products.

Compounds of formula I wherein X is hydrogen, R^1 is hydrogen and R^2 is other than hydrogen may be prepared by known methods.

The compounds of formula VI (wherein R^7 is hydrogen or is not on both positions adjacent the oxo group) may be prepared by one of the following schemes:



wherein R^1 , R^2 , R^6 , R^7 and n are as defined above, R^1 being other than hydrogen. The reactants used are known compounds or may be prepared by methods known for analogous compounds.

Other compounds for preparing starting compounds of formula I wherein X is hydrogen are described in the literature e.g. Breinmaier & Bayer Tetrahedron Letters No. 38, 1970, 3291—3294, which gives methods for preparing compounds in which X is hydrogen and R^1 and R^2 are hydrogen and X is hydrogen and R^2 is alkyl.

Another method for preparing thioamides of formula I, wherein X is CSNHR^3 wherein R^3 is as defined in connection with formula I, comprises treating a thioester of formula I wherein X is CSSR^5 and R^4 is alkyl or aralkyl with a compound of formula R^3NH_2 , wherein R^3 is as defined in connection with formula I.

The thioester starting materials may be prepared by treating a compound of formula I wherein X is hydrogen with a metal alkyl MR^{10} or $\text{M}(\text{R}^{10})_2$, as already discussed above and then treating the product with carbon disulphide to give the metal salt of the thioacid of formula I. This is then treated with an alkyl halide R^5Hal wherein R^5 is an alkyl or aralkyl group and Hal is chlorine, bromine or iodine.

The invention also includes pharmaceutical compositions comprising a compound of formula I wherein X is CSNHR^3 and R^3 is as defined in connection with formula I or X is cyano and a pharmaceutical carrier.

For the pharmaceutical carrier any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99, preferably 10-80% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, sterile organic solvent or a mixture of both. The active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil.

Preferably the pharmaceutical composition is in unit dosage form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in packaged form. The quantity of active ingredient in a unit dose of composition may be carried or adjusted from 5 mg. or less to 500 or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The anti-ulcer compositions of the invention will be administered orally in either liquid or solid composition form. These compositions may include one or more antacid ingredients e.g. aluminium hydroxide, magnesium hydroxide, bismuth carbonate, aluminium glycinate, calcium carbonate magnesium trisilicate, sodium bicarbonate or the alumina gel described in British Specification No. 1,284,394. The following Examples illustrate the invention all temperatures are in °C:

Example 1

A) 2-Phenyl-5,6,7,8-tetrahydroquinoline

2-(3'-Phenyl-3'-oxopropyl)cyclohexanone was prepared according to the method of W. Hahn and J. Epsztein (Roczniki Chem. 1963, 37, 403-12). A mixture of β -dimethylaminopropiophenone (27 gm.) and cyclohexanone (37.5 g.) were heated at reflux for 5 hours under nitrogen and the solvent removed in vacuo. The residual oil was distilled giving 2-(3'-phenyl-3'-oxopropyl)cyclohexanone (14 g.) which was cyclised to the title compound according to the method of Hahn and Epsztein by dissolving the diketone (12 g.) in ethanol (65 ml.), treating with hydroxylamine hydrochloride (9 g.) and heating under reflux for 1 hour. The cooled reaction mixture was poured onto water (300 ml.), extracted with ether (2x 50 ml.) and the extracts discarded. The aqueous solution was made basic with K_2CO_3 and extracted with ether (3x 50 ml.). The combined ether extracts were dried and the solvent removed in vacuo. The residual oil was distilled to give the title compound as a colourless oil (7 g.) b.p. 134-8°C/15 mm. Found: C, 85.40; H, 7.5; N, 6.9%, $C_{15}H_{15}N$ requires: C, 86.00; H, 7.2; N, 6.7%.

B) Methyl-2-phenyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

A solution of 2-phenyl-5,6,7,8-tetrahydroquinoline (20 g.) in ether (50 ml.) was added dropwise over 30 mins. to a preformed ethereal solution of phenyllithium (prepared from bromobenzene (40 g.) and lithium (2.78 g.) in dry ether (160 ml.). The reaction mixture was stirred for 1 hour at room temperature and the obtained 8-lithio-2-phenyl-5,6,7,8-tetrahydroquinoline treated with dry CO_2 gas until the colour was

(17)

8

5

10

discharged. The solvent was removed *in vacuo* and the residue dissolved in ethanol saturated with dry HCl gas (250 ml.) and the solid filtered and recrystallised from water giving 2-phenyl-5,6,7,8-tetrahydroquinoline-8-carboxylic acid hydrochloride (12 g.). This was dissolved in methanol (200 ml.) and the solution treated with dry HCl gas whilst heating at reflux for 4 hours. The solvent was removed *in vacuo* and the residue dissolved in water (50 ml.), made basic with 2N NaOH and extracted into chloroform (3×100 ml.). The combined extracts were dried, evaporated to dryness and the residual solid recrystallised from petroleum ether giving the title compound as colourless needles (11 g.) mpt. 75°C. Found: C, 76.8; H, 6.5; N, 5.14; C₁₇H₁₇N requires: C, 76.4; H, 6.4; N, 5.2%.

Example 2

15

2-Phenyl-5,6,7,8-Tetrahydroquinoline-8-carboxamide
Methyl-2-phenyl-5,6,7,8-tetrahydroquinoline-8-carboxylate (4 g.) was dissolved in methanol previously saturated with ammonia (90 ml.) and heated in a bomb at 100°C for 4 days. Removal of the solvent *in vacuo* gave an oily solid which on recrystallisation from ethyl acetate gave the title compound as colourless needles (1.5 g.) mpt. 145°C. Found: C, 76.4; H, 6.5; N, 11.1% C₁₈H₁₈N₂O requires: C, 76.2; H, 6.4; N, 11.1%.

Example 3

20

25

30

2-Phenyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide
2-Phenyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (8 g.) was dissolved in pyridine (20 ml.), treated with P₂S₅ (5.2 g.) and the mixture heated at reflux temperature for 30 minutes. The solvent was removed *in vacuo* and the residual oil dissolved in dilute HCl, washed with ether (2×50 ml.) and the washings discarded. The aqueous solution was made basic, extracted into chloroform (3×50 ml.) and the combined extracts dried and evaporated to dryness. The residual oil was chromatographed on silica gel by elution with chloroform giving 8-cyano-2-phenyl-5,6,7,8-tetrahydroquinoline (1.2 g.) as colourless needles from ether mpt. 100°C. Found: C, 82.0; H, 6.2; N, 11.7%; C₁₈H₁₄N₂ requires: C, 82.0; H, 6.0; N, 11.9%. Further elution with chloroform gave the title compound (1.1 g.) as colourless needles from ether mpt. 154°C. Found: C, 71.8; H, 6.1; N, 10.2%; C₁₈H₁₆N₂S requires: C, 71.6; H, 6.0; N, 10.4%.

Example 4

35

40

8-Cyano-2-phenyl-5,6,7,8-tetrahydroquinoline
2-Phenyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (6 g.) was dissolved in hexamethylphosphorictriamide (24 ml.) and the solution heated at 220°C for 2 hours. The cooled reaction mixture was poured onto water (50 ml.), extracted with chloroform (3×100 ml.) and the combined extracts washed with water (3×100 ml.), dried and evaporated to dryness. The residual oil was chromatographed on silica gel by elution with chloroform giving 2-phenyl-8-cyano-5,6,7,8-tetrahydroquinoline (2.5 g.) recrystallised from ether as colourless needles mpt. 100°C. Further elution with chloroform gave N,N-dimethyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (1.1 g.) which recrystallised from ether as colourless needles mpt. 140°C. Found: C, 77.17; H, 7.22; N, 10.24%. C₁₈H₂₀N₂O requires: C, 77.11; H, 7.19; N, 9.99%.

Example 5

45

50

55

2-Phenyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide
2-Phenyl-8-cyano-5,6,7,8-tetrahydroquinoline (2 g.) was dissolved in pyridine (5 ml.) and triethylamine (1.3 ml.) and the solution treated with H₂S gas for 6 hours and the reaction mixture allowed to stand at room temperature for 12 hours. The solvent was removed and the residual oil dissolved in dilute HCl, extracted with ether (2×50 ml.) and the extracts discarded. The aqueous solution was made basic and extracted into chloroform (3×50 ml.). The combined extracts were dried and evaporated *in vacuo* to give 2-phenyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide which was dissolved in ethanol (5 ml.), diluted with ether (25 ml.) and the solution saturated with HCl gas. The solvent was removed *in vacuo* and the residual solid recrystallised from methanol-ether giving hydrochloride of the title compound as colourless needles mpt. 211°C. Found: C, 63.41; H, 5.70; N, 8.94%; C₁₈H₁₈N₂S. HCl requires: C, 63.04; H, 5.62; N, 9.19%.

Example 6

60

A) 5,6,7,8-Tetrahydroquinoline
5-Oxo-5H-6,7,8-trihydroquinoline was prepared according to the method of F. Zymalkawski (Arch. Chem. 1961, 294, 759) by adding propionaldehyde (16 g.) to a

solution of 3-aminocyclohex-2-enone (31 g.) in DMF (150 ml.) over 5 mins. When the exothermic reaction had ceased, the flask was fitted for downward distillation and the reaction mixture heated at 100°C under a vacuum of 15 mm. and the distillate collected and discarded. The temperature was raised to 160—170° collecting the distillate which was dissolved in dilute HCl (75 ml.) and extracted with ether (2×50 ml.). The combined ethereal extracts were discarded. The aqueous solution was made basic and extracted with ether (3×150 ml.) and the combined ethereal extracts dried and evaporated *in vacuo*. The residual oil was distilled giving 5-oxo-5H-6,7,8-trihydroquinoline (21 g.) b.p. 133—4°C/15 mm. which was dissolved in diethylene glycol (190 ml.) and treated with hydrazine hydrate (14 g.) and sodium hydroxide (14 g.). The reaction mixture was heated at reflux for 30 minutes and then for 3½ hours under a Dean and Stark water separator. The cooled reaction mixture was poured onto water (100 ml.), extracted with ether (3×100 ml.) and the combined extracts dried and evaporated *in vacuo*. The residual oil was distilled giving the title compound as a colourless oil (10 g.) b.p. 100—5°C/15 mm.

B) Methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

A solution of 5,6,7,8-tetrahydroquinoline (14 g.) in dry ether (100 ml.) was added dropwise over ½ hour to an ethereal solution of phenyl lithium [prepared from bromobenzene (42 g.) and lithium (3.7 g.) in dry ether (300 ml.)] and the reaction mixture stirred at room temperature for a further one hour. The cooled reaction mixture containing 8-lithio-5,6,7,8-tetrahydroquinoline was saturated with dry CO₂ gas, evaporated *in vacuo* and the residue treated with methanol previously saturated with dry HCl (500 ml.) and the solution heated at reflux for 12 hours. The solvent was removed *in vacuo* and the residue dissolved in water (50 ml.), extracted with ether (3×150 ml.) and the extracts discarded. The aqueous solution was made basic and extracted with ether (3×100 ml.). The combined ethereal extracts were dried, evaporated *in vacuo* and the residual oil distilled giving methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate as a colourless oil (13 g.) b.p. 92°C/0.05 mm. The hydrochloride was prepared by saturating an ethereal solution with dry HCl gas and recrystallising the resultant solid from methanol-ether to give the hydrochloride of the title compound as colourless needles mpt. 183°C. Found: C, 58.2; H, 6.3; N, 6.3%. C₁₁H₁₃NO₂·HCl requires C, 58.0; H, 6.2; N, 6.2%.

Example 7

5,6,7,8-Tetrahydroquinoline-8-carboxamide

Methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate (9 g.) was dissolved in methanol previously saturated with ammonia (270 ml.) and heated in a bomb at 100°C for 5 days. The solvent was removed and the residual oil triturated with hot petroleum ether (40—60°). The resultant solid was filtered and then recrystallised from ethylacetate giving the title compound as colourless needles mpt. 132°C (5 g.). Found: C, 67.7; H, 7.1; N, 16.0%. C₁₀H₁₂N₂O requires: C, 68.1; H, 6.9; N, 15.9%.

Example 8

5,6,7,8-Tetrahydroquinoline-8-thiocarboxamide

A solution of 5,6,7,8-tetrahydroquinoline-8-carboxamide (1.2 g.) in pyridine (15 ml.) was treated with P₂S₅ (0.8 g.) and the mixture heated at reflux for 30 mins. The solvent was removed *in vacuo* and the residual oil treated with 2N NaOH (5 ml.) was saturated with solid K₂CO₃ and extracted into chloroform (3×50 ml.). The combined extracts were dried and the solvent removed *in vacuo*. The residual oil was dissolved in pyridine (4 ml.) and triethylamine (1 ml.) and the solution saturated with H₂S (6 hours) and allowed to stand overnight. Removal of the solvent gave a solid (850 mgs.) which was recrystallised from methanol giving the title compound as the quarter hydrate, colourless needles m.p. 160°C. Found: C, 59.8; H, 6.2; N, 14.0%. C₁₀H₁₂N₂S·1/4 H₂O requires: C, 59.6; H, 6.4; N, 13.9%.

The UV, IR and NMR Spectra of the title compound were determined:

1. UV Spectrum in 95% EtOH (1.07 mg. in 100 ml.) Max 272 nm, ε13,300
2. IR Spectrum

3230 cm ⁻¹	} NH ₂ stretch
3060 cm ⁻¹	
1660 cm ⁻¹	—NH ₂ deformation or/and C=CN stretch
1575 cm ⁻¹	C=C stretch
1500—900 cm ⁻¹	'fingerprint region'; numerous bands caused by complex and coupled vibrations. Two bands are particularly prominent 1280 cm ⁻¹ and 1020 cm ⁻¹

802 cm^{-1} } —CH deformation, characteristic of 2,3-disubstituted pyridine.
720 cm^{-1} }

3. NMR Spectrum—in d_6 DMSO (100 MHz)

5	δ 1.5—2.3	broad multiplet	4 protons	CH_2 —6 and 7	5
	δ 2.7	multiplet	2 protons	CH_2 —5	
	δ 4.15	triplet ($J=7\text{Hz}$)	1 proton	CH —8	
	δ 7.08	quartet	1 proton	H—3	
	δ 7.44	quartet	1 proton	H—4	
	δ 8.29	quartet	1 proton	H—2	
10	δ 9.25 and 9.45	broad doublet	2 protons	NH_2	10
Coupling constants= $J_{23}=5\text{Hz}$, $J_{34}=1.5\text{Hz}$, $J_{35}=8\text{Hz}$.					

It is indicated in the index to Chemical Abstracts that 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide is disclosed in Z. Naturforsch. 6b, 147—155 (1951), however, the actual abstract does not disclose the compound and examination of the paper reveals that the index is in error since the compound actually disclosed is 8-quinoline thio-carboxamide, the benzene ring of which has been shown without the unsaturation being marked in accordance with a custom then in use, see Organic Chemistry, Paul Karrer, 4th English Edition, Elsevier, 1950 e.g. at page 813.

Example 9

A) 2-t-Butyl-5,6,7,8-tetrahydroquinoline

5-Dimethylamino-2,2-dimethylpentan-3-one hydrochloride (100 g.), prepared from pinacolone according to the method of Casey & Ison (Tetrahedron, 1969, 25, 641—6) was dissolved in water (50 ml.) and the pH adjusted to 12.0 with 10N NaOH and extracted with ether (3×50 ml.). The combined ethereal extracts were dried (MgSO_4), evaporated *in vacuo* and the residual oil dissolved in cyclohexanone (300 ml.). The mixture was heated at reflux temperature for 8 hours and then cooled. The reaction mixture was then distilled at 15 mm. to remove excess cyclohexanone and then at 1 mm. to give 2-(3'-t-butyl-3'-oxopropyl)cyclohexanone (82 g.) which was dissolved in ethanol (275 ml.) and treated with hydroxylamine hydrochloride (70 g.). The mixture was heated at reflux temperature for 2 hours as described in the general method of W. Hahn and J. Epsztein (Roczniki Chem. 1963, 37, 403—12). The solvent was removed *in vacuo* and the residual oil dissolved in ether (100 ml.). The ethereal solution was washed with dilute HCl (3×20 ml.) and discarded. The aqueous solution was made basic with 2N NaOH and extracted with ether (3×50 ml.) and the combined extracts dried and evaporated *in vacuo*. The residual oil was distilled giving the title compound as a colourless oil b.p. $80-6^\circ\text{C}/1\text{ mm.}$ (yield 47 g., 64%).

B) 2-t-Butyl-5,6,7,8-tetrahydroquinoline-8-carboxamide

Methyl-2-t-butyl-5,6,7,8-tetrahydroquinoline-8-carboxylate was prepared from 2-t-butyl-5,6,7,8-tetrahydroquinoline (18.9 g., 0.1 m.) and phenyl lithium (0.1 m.) by the general method described in Example 1B and was isolated as a pale yellow oil (9 g.) b.p. $106^\circ\text{C}/0.4\text{ mm.}$

The title compound was prepared from methyl-2-t-butyl-5,6,7,8-tetrahydroquinoline-8-carboxylate (8 g.) by the general method described in Example 2 and was isolated as colourless needles (3 g.) after recrystallisation from n-hexane m.p. 131°C . Found: C, 72.06; H, 8.71; N, 11.62%. $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$ requires: C, 72.38; H, 8.68; N, 12.06%.

Example 10

2-t-Butyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide

The title compound was prepared from 2-t-butyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (4 g.) and P_2S_5 (3 g.) as described in Example 8 and was isolated as creamy needles after recrystallisation from n-hexane m.p. 126°C (650 mgs.). Found: C, 68.18; H, 8.25; N, 11.14%. $\text{C}_{14}\text{H}_{20}\text{N}_2\text{S}$ requires C, 67.70; H, 8.12; N, 11.23%.

Example 11

5,6,7,8-Tetrahydroquinoline

3-Methoxyacrolein was prepared from 1,1,3,3-tetramethoxypropane (Helv. Chim. Acta 1959, 42, 851) and converted to 3-aminoacrolein according to the method of Breitmaier and Gassenmann (Chem. Ber. 1971, 104, 665—7).

5,6,7,8-Tetrahydroquinoline was prepared from 3-aminoacrolein as described by Breitmaier and Bayer (Tet. Letts 1970, 38, 3291). A mixture of 3-aminoacrolein (7.3 gm, 0.1 m) and cyclohexanone (12 gm., 0.12m) was treated with triethylamine

(5 ml.) and piperidinium acetate (0.1 gr) and the mixture heated in an oil bath at 120° for 24 hours. The cooled reaction mixture was dissolved in ether (100 ml.), washed with water and 2N HCl (2×20 ml.) and the acid washings combined, made basic with sodium carbonate and extracted with ether. The combined extracts were dried, evaporated and the residue distilled to give the title compound as a pale yellow oil (4.5 gm, 35%) b.p. 100°/15 mm.

Example 12

2-Methyl-5,6,7,8-tetrahydroquinoline

4-Diethylaminopropane-2-one prepared from acetone and diethylamine (J. C. S. 1937, 53) was reacted with cyclohexanone by the general method described in C. A. 72, 132478h to give 2-(3'-methyl-3'-oxopropyl)cyclohexanone as a colourless oil b.p. 150°/20 mm.

The title compound was prepared from 2-(3'-methyl-3'-oxopropyl)cyclohexanone according to the general method described in Examples 1 and 9A and isolated as a colourless oil b.p. 116—20°/18 mm. (60% yield).

Example 13

2-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide

Reaction of 2-methyl-5,6,7,8-tetrahydroquinoline with phenyl lithium and carbon dioxide followed by esterification according to the general method described in Examples 1B and 6B gave an inseparable mixture of methyl-2-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate and methyl-5,6,7,8-tetrahydroquinoline-2-acetate which was converted without purification to a mixture of 2-methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide and 5,6,7,8-tetrahydroquinoline-2-acetamide by reaction with ammonia using the method described in Example 2. Fractional recrystallisation from diisopropyl ether gave the title compound as colourless needles m.p. 114° (overall yield 30%) (Found: C, 69.31; H, 7.45; N, 14.7. $C_{11}H_{14}N_2O$ requires: C, 69.45; H, 7.42; N, 14.72%).

Example 14

2-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide

2-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide was treated with P_2S_5 to give 2-methyl-8-cyano-5,6,7,8-tetrahydroquinoline which was treated with H_2S (both reactions being carried out by the method described in Example 8) to give the title compound as colourless needles from ethylacetate (28%) m.p. 98° (Found: C, 64.32; H, 6.93; N, 13.52%. $C_{11}H_{14}N_2S$ requires: C, 64.04; H, 6.84; N, 13.58%).

Example 15

3-Methyl-5,6,7,8-tetrahydroquinoline

The title compound was prepared from commercially available 3-amino-2-methylacrolein and cyclohexanone according to the method of Breitmaier and Bayer (Tet. Letts, 1970, 38, 3291—4) and isolated as a pale yellow oil b.p. 120°/15 mm. (30% yield).

Example 16

Methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

The title compound was prepared from 3-methyl-5,6,7,8-tetrahydroquinoline according to the general method described in Example 1B and isolated as a pale yellow oil b.p. 120°/0.25 mm. (80% yield). The hydrochloride was prepared in the usual way (cf Example 6B) and isolated as colourless needles from ethanol/ether m.p. 146° (Found: C, 59.9; H, 6.7; N, 6.0. $C_{12}H_{15}NO_2 \cdot HCl$ requires: C, 59.60; H, 6.7; N, 5.8%).

Example 17

3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide

The title compound was prepared from methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate by the method described in Example 2 and was isolated as colourless needles from hexane m.p. 118° (50% yield). (Found: C, 69.60; H, 7.5; N, 14.8; $C_{11}H_{14}N_2O$ requires: C, 69.5; H, 7.4; N, 14.7%).

Example 18

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide

3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide was treated with P_2S_5 to give 3-methyl-8-cyano-5,6,7,8-tetrahydroquinoline which was treated with H_2S as described

in Example 8 giving the title compound as colourless needles from benzene m.p. 151° (50% yield) (Found: C, 63.71; H, 6.85; N, 13.38%. $C_{11}H_{14}N_2S$ requires: C, 64.04; H, 6.84; N, 13.58%).

The hydrochloride was prepared by dissolving the title compound in the minimum amount of isopropanol and then adding a solution of ether saturated with dry HCl gas. The hydrochloride precipitated as colourless needles m.p. 219° (Found: C, 54.33; H, 6.23; N, 11.42%. $C_{11}H_{14}N_2SHCl$ requires: C, 54.42; H, 6.23; N, 11.54%).

Example 19

Methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

n-Butylbromide (285 ml.) in dry ether (500 ml.) was added to clean lithium wire (42 g., 6 m) in dry ether (1 l.) under nitrogen at such a rate to maintain an internal temperature of -15°C. Upon completion of the addition the reaction mixture was stirred until the temperature rose to 10°C (approx. 2 hours). The concentration of butyl lithium was calculated by standardising against N/10 HCl and the quantity of 3-methyl-5,6,7,8-tetrahydroquinoline required in the next stage adjusted to have a 1.2 m excess of butyl lithium.

A stirred solution of 3-methyl-5,6,7,8-tetrahydroquinoline (147 g., 1 m) in dry ether (700 ml.) was treated with a freshly prepared solution of butyl lithium (860 ml. of a 1.4 M solution i.e. 1.2 m) under nitrogen giving 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline. The reaction mixture was stirred for an additional 15 min. and a slow stream of dry CO₂ gas bubbled into the reaction mixture until colourless. The reaction mixture was diluted with water (1.2 l), filtered and the aqueous phase separated and extracted with ether (3×500 ml.). The combined ethereal extracts were processed to give recovered 3-methyl-5,6,7,8-tetrahydroquinoline (40 g.) b.p. 116—20°/15 mm.

The aqueous layer was evaporated to dryness and the residual solid treated with a solution of methanol previously saturated with dry HCl gas (1.5 l) and allowed to stand at room temperature for 12 hours. The volatiles were removed *in vacuo*. The residual oil was redissolved in water (1 l.), extracted with ether (3×250 ml.) and the extracts discarded. The aqueous solution was adjusted to pH 9.0 with Na₂CO₃ and extracted with ether (4×250 ml.). The combined extracts were dried and the solvent removed *in vacuo* to give the title compound as a pale yellow oil (85 g. 42%) GLC (10% SE30, T=200°) $R_i=3.25$ min, 93% pure.

Example 20

Methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

A solution of 3-methyl-5,6,7,8-tetrahydroquinoline (5 g., 0.034 m) in dry ether (50 ml.) was treated portionwise with a solution of butyl lithium in hexane (0.04 m) under nitrogen and the mixture allowed to stand at room temperature for 30 minutes giving 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline. A slow stream of CO₂ gas was bubbled in until the reaction mixture was colourless. A further 0.02 m. of butyl lithium in hexane solution was added. The mixture was allowed to stand for 30 minutes and then treated with dry CO₂ gas as above. The reaction mixture was diluted with water (20 ml.), the aqueous layer extracted with ether (3×50 ml.) and the combined extracts retained for recovery of unreacted 3-methyl-5,6,7,8-tetrahydroquinoline. The aqueous phase was evaporated to dryness *in vacuo*. The resultant solid was treated with methanol previously saturated with dry HCl gas (50 ml.) and allowed to stand at room temperature for 3 hours. The solvent was removed and the residual oil dissolved in water (20 ml.) and extracted with ether (3×25 ml.) and the extracts discarded. The aqueous phase was adjusted to pH 9.0 with Na₂CO₃ and extracted into ether (3=50 ml.). The combined extracts were dried and evaporated *in vacuo* to give the title compound as a colourless oil (4.3 g., 60%) GLC (10% SE30, T=200°). $R_i=3.25$ min. 98% pure.

Example 21

3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide

A mixture of methyl-3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate (25 g., 0.13 m), formamide (11.6, 0.26 m) and sodium methoxide (from 2.99 g., 0.13m sodium) was heated with stirring in an oil bath at 120° for 1 hour. The reaction mixture was further heated at 100° for 3 hours under reduced pressure (15 mm Hg). The cooled reaction mixture was diluted with 2N HCl to give an acidic solution which was extracted with ethylacetate (2×50 ml.) and the combined extracts discarded. The aqueous solution was adjusted to pH 9.0 with solid Na₂CO₃, saturated with NaCl and extracted with chloroform (3×100 ml.). The combined extracts were dried and evaporated to give a pale yellow oil which solidified on trituration with n-hexane. Recrystallisation from ethylacetate gave the title compound as colourless cubes (18.6 g., 88%)

m.p. 110°. Found: C, 69.6; H, 7.4; N, 14.4%. $C_{11}H_{14}N_2O$ requires: C, 69.5; H, 7.4; N, 14.7%.

Example 22

3-Methyl-5,6,7,8-Tetrahydroquinoline-8-carboxamide

5 A mixture of methyl-3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate (25 g. 0.13 m), formamide (11.6 g., 0.26 m) and sodium methoxide (from 2.99 g., 0.13 m sodium) was heated on a steam bath for 1 hour while bubbling nitrogen through the mixture, to blow off the methyl formate produced in the reaction. The cooled reaction mixture was diluted with 2N HCl and worked up as described in Example 21 to give the title compound in 90% yield. 10

Example 23

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide

15 A solution of 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (27.9 g. 0.14 m) in dry pyridine (300 ml.), saturated with H_2S gas, was treated with P_2S_5 (26 g., 0.14 m) and heated at reflux for 45 min. whilst maintaining a slow stream of H_2S gas. The reaction mixture was evaporated to dryness *in vacuo* and cooled to 0°C, made alkaline with 10% sodium hydroxide and the solution extracted with chloroform (3×100 ml.). The combined extracts were washed with brine, dried and evaporated *in vacuo*. The residual oil was triturated with benzene and the solid filtered and recrystallised from benzene to give the title compound as pale yellow needles, m.p. 149° (21.8 g., 87%). 20 The hydrochloride was prepared as already described in Example 18 and isolated as colourless needles m.p. 219°C.

Example 24

Methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

25 A 3-necked flask is charged with 3-methyl-5,6,7,8-tetrahydroquinoline (45 g. 0.29 moles) and ether (400 ml.). The mixture is stirred and phenyl lithium solution (330 ml. of a 1 molar solution 0.3 moles in ether) is added at a rate to give gentle reflux. Reflux is maintained for 2 hours. The resulting solution of 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline is cooled in an ice-bath and CO_2 is bubbled through the solution till no further change. Water (700 ml.) is added to dissolve the solid. The aqueous layer is separated and washed with ether (3 times). The aqueous layer is evaporated to dryness *in vacuo*. To the residue is added a saturated solution (1 litre) of methanolic HCl and the mixture allowed to stand overnight at room temperature. The solution is evaporated to dryness *in vacuo* and the residue dissolved in water. The aqueous solution is washed with ether (3 times) and the aqueous solution basified with solid sodium carbonate and extracted with ether (a heavy white solid also precipitates, but this does not interfere with the extraction). The ether layer is washed with water, then brine, dried and evaporated. Yield 25 g. (44%) of the title compound. GLC= 35 88% pure.

Example 25

Methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

40 A solution of 15% n-butyl lithium in hexane (51 ml. ca. 0.12 m) was added portionwise to a solution of 3-methyl-5,6,7,8-tetrahydroquinoline (14.7 g., 0.1 m) in ether (100 ml.) and the mixture allowed to stand at room temperature for 1 hour and then the resulting solution of 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline added dropwise to a cooled, stirred solution of methylchloroformate (9.45 g., 0.1 m) in ether (100 ml.). The mixture was stirred at 50°C for 1 hour. The reaction mixture was diluted with water (20 ml.) and then treated with 2N HCl until acidic. The ethereal solution was separated and washed with 2N HCl (2×25 ml.). The combined aqueous washings were extracted with ether and the ethereal extracts discarded. The aqueous solution was adjusted to pH 9.0 with Na_2CO_3 and extracted with chloroform (3×50 ml.) and the combined extracts dried and evaporated to give a pale yellow oil (16 g) which on GLC examination (3% SE30) showed a mixture of unreacted tetrahydroquinoline (45%), the title compound (23%) and the 8,8-dicarboxylic ester (20%). The mixture was treated with 10% sodium hydroxide (75 ml.) and heated at reflux with stirring for 4 hours, cooled and extracted with ether (3×50 ml.). The combined ethereal extracts were dried, evaporated and distilled to give unreacted 3-methyl-5,6,7,8-tetrahydroquinoline (7 g.) b.p. 116°/18 mm Hg. The basic solution was adjusted to pH 8.5—9.0 with concentrated HCl and evaporated to dryness and the residue treated with methanol previously saturated with dry HCl (50 ml.) and allowed to stand at room temperature for 5 hours. The solvent was removed and the residue 60

dissolved in water (20 ml.) and extracted with ether (2×50 ml.). The aqueous solution was adjusted to pH 9.0 with Na₂CO₃ and extracted with chloroform (3×25 ml.) and the combined extracts dried and evaporated to give the title compound (3 gm.).

Example 26

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide hydrochloride

Crystal Form A

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (1 g.) prepared as described in Example 18 was dissolved in boiling isopropylalcohol (25 ml.), filtered and allowed to cool to 40°C. An excess of an ethereal solution of hydrogen chloride was added followed by sufficient ether to cause turbidity. On cooling the title compound was isolated as fine colourless needles (0.95 g.) mpt 244°C. Found: C, 54.3; H, 6.2; N, 11.4%. C₁₁H₁₄N₂S.HCl requires: C, 54.4; H, 6.2; N, 11.5%. I.R. ν_{max} Nujol Mull 3300 (shoulder), 3230 (broad), 3060 (broad), 2540 (broad), 1650 (strong), 1605, 1555 cm⁻¹. This I.R. Spectrum was identical with that exhibited by the product of Example 18. "Nujol" is a Registered Trade Mark.

Crystal Form B

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (1 g.) prepared as described in Example 18 was dissolved in boiling isopropyl alcohol (15 ml.) and a slight excess of an ethereal solution of hydrogen chloride added without cooling. The title compound was obtained as fine colourless needles (950 mg) m.p. 244°C. Found: C, 54.58; H, 6.29; N, 11.34%. C₁₁H₁₄N₂S.HCl requires C, 54.42; H, 6.23; N, 11.54%. I.R. ν_{max} Nujol Mull 3260 (broad), 3220 (broad), 3050, 2630 (broad), 1655—1630 (3 sharp bands), 1555 cm⁻¹.

Crystal Form B—Alternative Method

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (0.5 g.) was dissolved in methanol (1 ml.) and treated with methanol saturated with hydrogen chloride (1 ml.) and the solution heated to boiling. Ethyl acetate was added, whilst the methanol evaporated, until turbid. On cooling the title compound was isolated as fine colourless needles (0.4 g.) m.p. 244°. Found: C, 54.11; H, 6.18; N, 11.31%. C₁₁H₁₄N₂S.HCl requires: C, 54.42; H, 6.23; N, 11.54%. Crystal Form A could not be converted into crystal form B by crystallising from isopropyl alcohol/ether or methanol/ethyl acetate.

Form A on standing for 2—3 days reverted to Form B. Form A could also be converted to Form B by heating at 40°C under vacuum for 6 hours.

Example 27

3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide

Crystal Form A

3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (1 g.) prepared as described in Example 17 was dissolved in boiling di-isopropyl ether (80 ml.), filtered and allowed to cool. The title compound was isolated as fine colourless cubes (0.85 g.), m.p. 118°C. Found: C, 69.6; H, 7.5; N, 14.8%. C₁₁H₁₄N₂O requires C, 69.5; H, 7.4; N, 14.7%. I.R. ν_{max} Nujol 3395, 3195, 1650 (strong), 1620, 1605 (shoulder), 1595, 1560, 1235, 875 (strong), 620 (strong) cm⁻¹. The I.R. Spectrum was identical with that of the product of Example 17.

Crystal Form B

3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (1 g.) prepared as described in Example 17 was dissolved in boiling ethyl acetate (2 ml.), filtered and allowed to cool. The title compound was isolated as colourless rhombic crystals (0.80 g.) m.p. 113°. Found: C, 68.81; H, 7.40; N, 14.45%. C₁₁H₁₄N₂O requires C, 69.50; H, 7.40; N, 14.70%. I.R. ν_{max} Nujol 3395, 3280, 3185, 1680 (strong) 1605, 1595, 1560, 900 (strong), 575 (strong) cm⁻¹.

The crystal forms A and B can be interconverted by crystallisation from the appropriate solvents. Thus crystallisation of form A from ethyl acetate will give form B and crystallisation of form B from di-isopropyl ether will give form A.

Example 28

3-Methyl-5,6,7,8-tetrahydroquinoline-8-(N-methyl)thiocarboxamide
Methyl-3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate (5 gm.) was dissolved in 33% methylamine in ethanol (50 ml.) and the solution heated at 150° for 24 hours in a stainless steel bomb. The solvent was removed in vacuo and the residual oil

crystallised on standing. Recrystallisation from 2-propanol/n-hexane gave 3-methyl-5,6,7,8-tetrahydroquinoline-8-(N-methyl)carboxamide as colourless needles (4 gm., 85%). A sample was characterised as the hydrochloride which was obtained by treating a solution of the base in ethanol with ethereal HCl and isolated as colourless needles m.p. 185°. (Found: C, 59.81; H, 7.11; N, 11.34%. $C_{12}H_{14}N_2O \cdot HCl$ requires C, 59.87; H, 7.12; N, 11.64.

A solution of 3-methyl-5,6,7,8-tetrahydroquinoline-8-(N-methyl)carboxamide (1.2 g.) in pyridine (9 ml.) was treated with phosphorus pentasulphide (1.2 g.) and the mixture heated at reflux for 3 hours. The solvent was removed *in vacuo* and the residue treated with a 10% aqueous solution of sodium hydroxide until alkaline. The solution was extracted with chloroform (3 × 50 ml.) and the combined extracts washed with water (2 × 20 ml.) brine, dried and evaporated. The residual oily solid was recrystallised from benzene to give the title compound as colourless needles (0.9 g., 65%) m.p. 159° (Found: C, 65.12; H, 7.26; N, 12.56%. $C_{12}H_{14}N_2S$ requires: C, 65.41; H, 7.32; N, 12.72%).

Example 29

Sym. Octahydroacridine-4-thiocarboxamide

Sym. octahydroacridine was prepared by converting cyclohexanone to di-(2-oxocyclohex-1-yl)-methane and further reacting with hydroxylamine according to the method of Gill *et al* (JACS 1952, 74, 4923) and was isolated as a colourless oil b.p. 110–15°/0.5 mm. in 40% overall yield.

A solution of sym. octahydroacridine (5 gm. 0.026 m.) in dry ether (50 ml.) was treated dropwise with a 15% solution of butyl lithium in hexane (11 ml.) 0.026 m and the mixture stirred at room temperature for 15 min. under an atmosphere of nitrogen to obtain 4-lithio-sym octahydroacridine. The nitrogen was replaced by CO₂ gas which was bubbled through the reaction mixture until colourless. The reaction mixture was diluted with water (50 ml.) and the organic layer separated and the aqueous phase extracted with ether (2 × 50 ml.). The combined extracts were retained for recovery of sym. octahydroacridine. The aqueous phase was evaporated to dryness, the residue treated with methanol previously saturated with dry HCl (50 ml.) and the solution allowed to stand at room temperature for 3 hours. The solvent was removed *in vacuo* the residue diluted with water (20 ml.) and extracted with ether. The aqueous phase was adjusted to pH 10. with solid Na₂CO₃ and extracted with ether (3 × 20 ml.). The combined extracts were washed with brine, dried and evaporated to give methyl-sym. octahydroacridine-4-carboxylate. (1 gm. 15%).

A solution of methyl-sym octahydroacridine-4-carboxylate (5 gm.) in methanol previously saturated with ammonia (80 ml.) was heated at 140° for 3 days in a stainless steel bomb. The solvent was removed and the residual solid recrystallised from di-isopropyl ether to give sym. octahydroacridine-4-carboxamide as colourless needles (2.6 g. 57%) m.p. 159° (Found: C, 72.98; H, 8.04; N, 12.01%. $C_{14}H_{18}N_2O$ requires: C, 73.01; H, 7.88; N, 12.17%).

A solution of sym. octahydroacridine-4-carboxamide (1.8 gm.) in pyridine (17 ml.) was treated with hydrogen sulphide for 5 mins. The reaction mixture was treated with phosphorus pentasulphide (1.4 g.) and heated at reflux for 45 mins maintaining a slow stream of hydrogen sulphide throughout. The cooled reaction mixture was evaporated and the residue treated with 10% sodium hydroxide until alkaline. The aqueous solution was extracted with chloroform (3 × 50 ml.) and the combined extracts washed with brine, dried and evaporated and the residual solid recrystallised from di-isopropyl ether giving the title compound as a pale yellow powder (0.3 g. 16%) m.p. 104–6° (solidifies and remelts at 148°). (Found: C, 68.69; H, 7.54; N, 10.98%. $C_{14}H_{18}N_2S$ requires: C, 68.26; H, 7.36; N, 11.37%).

Example 30

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide oxalate

To a solution of 3-methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (1 g.) in hot ethanol (10 ml.) was added a solution of oxalic acid dihydrate (650 mg.) in hot ethanol (6.5 ml.). The solution was filtered and allowed to cool when the oxalate crystallised. The oxalate was removed by filtration, washed with ether and dried. Yield 1 g. m.p. 186–8°C. Found: C, 52.71%; H, 5.63%; N, 9.19%. Calc. for $C_{13}H_{16}N_2O_4S$: C, 52.70%; H, 5.44%; N, 9.46%.

Example 31

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide tartrate

To a solution of 3-methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (13 g.) in hot isopropylalcohol (130 ml.) was added a solution of 9.5 g. tartaric acid in hot

isopropyl-alcohol (65 ml.). The solution was filtered and allowed to cool. The precipitated crystals of the tartrate were removed by filtration, washed with a little cold isopropyl alcohol and dried. Yield 10.2 g. m.p. 158—160°C. Found: C, 50.56%; H, 5.67%; N, 7.90%. Calc. for $C_{13}H_{10}N_2O_4S$: C, 50.55%; H, 5.65%; N, 7.86%.

Example 32

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide

3-Methyl-8-cyano-5,6,7,8-tetrahydroquinoline (1.7 g., 0.01 m.) and thioacetamide (1.5 g., 0.02 m.) were dissolved in dimethylformamide (50 ml.), the solution saturated with dry hydrogen chloride gas and then heated on a steam bath for 4 hours. The cooled reaction mixture was poured onto water (200 ml.), washed with ethyl acetate (2×200 ml.) and the extracts discarded. The aqueous solution was adjusted to pH 10.0 with 46% sodium hydroxide and extracted into methylene chloride (2×200 ml.). The combined extracts were dried (sodium sulphate), evaporated *in vacuo* and the residual oil triturated with isopropanol and filtered. Recrystallisation from benzene gave the title compound as pale yellow needles (1.3 g., 63%) m.p. 149°.

Example 33

Methyl 3-methylcyclohepteno[b]pyridine-9-carboxylate

3-Methylcyclohepteno[b]pyridine was prepared from cycloheptanone and 3-amino-2-methyl-acrolein according to the method of Breitmaier (Tet. Lett. 1970, 38, 3291) and in the manner described in the synthesis of 5,6,7,8-tetrahydroquinoline (Example 11) and was isolated as a colourless oil b.p. 140°/14 mm.

A solution of 15% n-butyl lithium in hexane (16 ml. ca. 0.04 m) was added portionwise to a solution of 3-methylcyclohepteno[b]pyridine (5 g. 0.03 m) in ether (50 ml.) under nitrogen and the mixture allowed to stand at room temperature for 30 minutes giving 9-lithio-3-methylcyclohepteno[b]pyridine. The mixture was treated with CO_2 gas until the red colour was discharged and the solvent was removed *in vacuo*. The residue was dissolved in water (25 ml.) and extracted with ether (3×50 ml.). The aqueous solution was evaporated *in vacuo* and the residue treated with methanol previously saturated with HCl gas (100 ml.) and allowed to stand at room temperature for 12 hours. The solvent was removed and the residual oil was dissolved in water (50 ml.) and extracted with ether (3×50 ml.). The aqueous solution was adjusted to pH 9.0 with sodium carbonate and extracted into ether (3×50 ml.). The combined extracts were dried, evaporated *in vacuo* to give the title compound as a pale yellow oil (0.8 g., 11%) GLC: $R_T=6.1/4$ min. (F11, 10% SE30, T=150°). I.R. Spectrum: ν_{max}^{film} 1740; 1460; 1440, 1120—1200 (broad) cm^{-1} .

Example 34

Methyl 3-methylcyclopenteno[b]pyridine-7-carboxylate

3-Methylcyclopenteno[b]pyridine was prepared from cyclopentanone and 3-amino-2-methylacrolein according to the method of Breitmaier (Tet. Lett. 1970, 38, 3291) and was isolated as a colourless oil b.p. 100—105°/15 mm.

A solution of 3-methylcyclopenteno[b]pyridine (10 g. 0.078 m.) in ether (150 ml.) was treated with a 15% solution of n-butyl lithium in hexane (30 ml. ca. 0.08 m) and the mixture containing 7-lithio-3-methylcyclopenteno[b]pyridine treated with CO_2 gas. The lithium salt of 3-methylcyclopenteno[b]pyridine-8-carboxylic acid was isolated and esterified with methanol previously saturated with HCl gas as described for methyl 3-methylcyclohepteno[b]pyridine-9-carboxylate (Example 33). The title compound was isolated as a pale yellow oil (1.1 g., 10%) GLC $R_T=1.1/2$ min. (Pye 104, 3% SE30, T=200°). I.R. Spectrum ν_{max}^{film} 1738, 1460, 1422, 1160—1220 (broad) cm^{-1} . "Pye" is a Registered Trade Mark.

Example 35

Methyl 3,7,7-trimethyl-5,6,7,8-tetrahydroquinoline-8-carboxylate

3,7,7-Trimethyl-5,6,7,8-tetrahydroquinoline (17.5 g., 0.1 m) was dissolved in dry ether (200 ml.) and treated with a solution of n-butyl lithium in hexane (15% solution 56 ml.) under nitrogen. The reaction mixture containing 8-lithio-3,7,7-trimethyl-5,6,7,8-tetrahydroquinoline was allowed to stand at room temperature for 30 minutes and then treated with CO_2 gas until the intense red colour was discharged. The solvent was removed and the residual oily solid dissolved in water (20 ml.) then extracted with ether (3×50 ml.). The ethereal extracts were retained to recover unreacted starting material. The aqueous solution was evaporated to dryness, the residue treated with methanol previously saturated with dry HCl (100 ml.) and the solution allowed to stand at room temperature for 8 hours. The solvent was removed and the residual oil

dissolved in water (50 ml.) and extracted with ether (3×50 ml.) and the extracts discarded. The aqueous solution was adjusted to pH 9.0 with sodium carbonate and extracted with ether (3×50 ml.). The combined extracts were dried and evaporated *in vacuo* to give the title compound as a pale yellow oil (1.8 g., 10%). I.R. Spectrum $\nu_{\max}^{\text{film}}$ 1748, 1570, 1460, 1160, 1030 cm^{-1} . GLC: $R_T=3.1/2$ min. (F11, 2% OV17, $T=150^\circ$).

The picrate of the title compound was formed by dissolving the free base (100 mg.) in ethanol (1 ml.) and adding a saturated solution of picric acid in ethanol (5 ml.) and allowing the picrate to crystallise. The picrate was removed by filtration, dissolved in the minimum volume of ethanol and precipitated by adding ether giving yellow needles m.p. $95-7^\circ$.

Analysis Found: C, 50.2; H, 4.7; N, 12.1%. $\text{C}_{14}\text{H}_{11}\text{NO}_2$ picrate $3/4 \text{ H}_2\text{O}$ Requires: C, 50.5; H, 5.0; N, 11.8%.

Example 36

3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide

To a solution of 3-methyl-5,6,7,8-tetrahydroquinoline (10 g; 0.068 m.) in dry hexane (50 ml.) was added 50 ml. of a 15% solution of *n*-butyl lithium in hexane (0.09 m.) dropwise with stirring under an atmosphere of nitrogen. The dark red solution of 8-lithio-3-methyl-5,6,7,8-tetrahydroquinoline was stirred for 15 minutes at room temperature and then treated with carbon disulphide (10 ml.) The resulting pale yellow suspension was poured with water (100 m.) and the aqueous solution was washed with ether (3×100 ml.).

The aqueous solution of the lithium salt of 3-methyl-5,6,7,8-tetrahydroquinoline-8-dithiocarboxylic acid was stirred vigorously and methyl iodide (40 ml.) added. The solution was stirred at room temperature for 2½ hours and extracted with ether (3×75 ml.). The ether solution was dried over anhydrous magnesium sulphate and evaporated. Methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-dithiocarboxylate was left as a red oil.

The oil was dissolved in methanol previously saturated with ammonia (200 ml.) and the solution allowed to stand for 16 hours. The solvent was evaporated and the residue dissolved in ether (100 ml.). The ethereal solution was washed with water and the aqueous layer discarded. The solution was then extracted with 2N HCl (50 ml.) and water (50 ml.). The combined extracts were washed with ether and the pH of the solution adjusted to 9 with saturated sodium carbonate solution. The solution was extracted with ether (3×50 ml.) and the ethereal solution dried over anhydrous magnesium sulphate and evaporated to give the crude 3-methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (2.5 g.) tlc. on Silica gel F254 in ethyl acetate: $R_f=0.4$ in ethanol $R_f=0.8$ identical with authentic material.

EXAMPLE 37

8-Cyano-5,6,7,8-tetrahydroquinoline

5,6,7,8-Tetrahydroquinoline-8-carboxamide (2 g.) was refluxed and stirred with P_2S_5 (1.4 g.) in pyridine 25 ml. for three hours. The mixture was evaporated to dryness *in vacuo* and then dilute sodium hydroxide was added to the residue followed by solid potassium carbonate. The product was extracted into chloroform and the chloroform extract washed with water and dried over MgSO_4 . The dried extract was evaporated to dryness and the residue purified using column chromatography on silica gel with benzene/ethyl acetate (4:1) as eluent. The nitrile was dissolved in ethanol/ether and ethereal HCl added. The solution was evaporated to dryness giving the hydrochloride of the title compound as the quarter hydrate 800 mg. m.p. 185°C dec.

Analysis Found: C, 60.8; H, 5.7; N, 14.0%; $\text{C}_{10}\text{H}_{10}\text{N}_2\text{HCl}$ $1/4 \text{ H}_2\text{O}$ requires C, 60.5; H, 5.8; N, 14.10%.

EXAMPLE 38

3-Methyl-5,6,7,8-Tetrahydroquinoline-8-carboxylic acid

Methyl 5,6,7,8-tetrahydroquinoline-8-carboxylate (5 g.) was treated with 10% NaOH (40 ml.) and heated under reflux for 1½ hours. The cooled reaction mixture was extracted with ether and the aqueous layer was acidified to pH7 with acetic acid filtered and evaporated to dryness under reduced pressure. The residue was triturated with benzene. The benzene solution was filtered and evaporated under reduced pressure and the residues were triturated with ether giving the sodium salt of the title com-

pound as a white powder 1.8 g. Found: C, 60.0; H, 5.6; N, 6.4%; $C_{11}H_{12}NO_2N$. $\frac{1}{2}$ H_2O requires C, 59.6; H, 5.8; N, 6.4%; pKa 3.42, and 6.72 were recorded.

A further 1.4 g. of the sodium salt was obtained by further extraction of the benzene insoluble material.

EXAMPLE 39

8-Cyano-3-Methyl-5,6,7,8-tetrahydroquinoline

3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide (3.6 g.) in pyridine (54 ml.) was treated with P_2S_5 (7.56 g.) and the mixture heated at reflux with stirring for 3 hours. The solvent was removed under reduced pressure and the residue cooled in ice-water then made basic with 10% NaOH. The basic solution was extracted with chloroform (3 times) and the combined extracts extracted with 2NHCl (twice). The combined acid extracts were basified with solid sodium carbonate and extracted into chloroform (3 times). The combined chloroform extracts were washed with brine dried ($MgSO_4$) and evaporated to give the title compound 1.7 g. This was converted to the hydrochloride by dissolving in ether and adding ethereal HCl. An oily residue was formed from which the supernatant liquid was decanted. The residue was triturated twice with dry ether and the remaining solid recrystallised from isopropyl alcohol giving the hydrochloride of the title compound m.p. 189°C.

Analysis Found: C, 63.08; H, 6.26; N, 13.34%; $C_{11}H_{12}N_2 \cdot HCl$ requires: C, 63.30; H, 6.28; N, 13.43%.

The following Examples illustrate pharmaceutical compositions in accordance with the invention.

Example A

Suspension	% w/v	
Aluminium hydroxide gel B.P. 5% Al_2O_3	80% = 4% Al_2O_3	25
Magnesia Magma 12% w/v MgO	10%	
5,6,7,8-tetrahydroquinoline-8-thiocarboxamide	2.0%	
Glycerin B.P.	3.0%	
Alcohol 60 O.P.*	0.08%	
Peppermint oil B.P.	0.015%	30
Saccharin sodium B.P.	0.01%	
Methyl p-hydroxybenzoate sodium salt	0.1%	
Propyl p-hydroxybenzoate sodium salt	0.02%	
Butyl p-hydroxybenzoate sodium salt	0.01%	
Water q.s. ad	100.00%	35

* O.P. denotes overproof. 60 O.P. represents 91% w/v Ethanol/Water.

The above suspension is prepared by the following procedure. Add to the Alumina gel Magnesia Magma followed by the 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide dispersed in glycerin, the peppermint oil dissolved in alcohol, the saccharin sodium dissolved in water, and the p-hydroxybenzoates dissolved in water. Make up to volume with water and stir well. Dose: 5 ml. t.d.s.

Example B

Antacid Tablet (chewable)

Saccharin	1.0 mg.	
Hydrated alumina sucrose powder	750.0 mg.	45
5,6,7,8-Tetrahydroquinoline-8-thiocarboxamide	100.0 mg.	
Mannitol B.P.	170.0 mg.	
Maize starch B.P. dried	30.0 mg.	
Talc. purified B.P.	28.0 mg.	
Magnesium stearate B.P.	20.0 mg.	50
Peppermint oil B.P.	1.0 mg.	
	1100 mg.	

Antacid tablets of the above formulation are prepared by the following procedure. Triturate peppermint oil with talc (screen 40 mesh).

Add the triturate, and other ingredients to a blender and mix thoroughly.

Slug the powder to large hard slugs.

Granulate the slugs through a 14 mesh screen.

Compress the granules on a suitable compression machine to give tablets of the required size.

Example C

Anti-ulcer tablet (without antacid)

	mg/tablet
5,6,7,8-Tetrahydroquinoline-8-thiocarboxamide	100 mg.
Celutab	147.5 mg.
Mag. Stearate	2.5 mg.
	250.0 mg.

The tablets are prepared by the following method.

Blend the ingredients in a suitable blender. Compress the blended ingredients on a suitable compression machine to form tablets of the above composition.

Celutab is a commercial product comprising 90—2% dextrose. 3—5% maltose remainder higher glucose saccharides. Spray crystallised.

Example D

A suspension is prepared as described in Example A but replacing 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide by 3 - Methyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide.

Example E

An antacid tablet is prepared as described in Example B but replacing 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide by 3 - Methyl - 5,6,7,8 - tetrahydroquinoline - 8-thiocarboxamide.

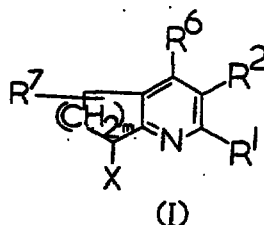
Example F

An anti-ulcer tablet is prepared as described in Example C but replacing 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide by 3 - methyl - 5,6,7,8 - tetrahydroquinoline-8-thiocarboxamide.

The tetrahydroquinoline starting materials may also be prepared by the method described in our co-pending U.K. Application 33252/73 (H—145). Serial No. 1432379.

WHAT WE CLAIM IS:—

1. A compound of formula I



and acid addition salts thereof, wherein R^1 , R^2 and R^4 are the same or different and represent hydrogen, trifluoromethyl, or alkyl which may be substituted by alkoxy, halogen, nitro or trifluoromethyl, or an aralkyl or aryl radical either of which radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl or R^1 and R^2 taken together represent an alkylene chain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$ wherein n is 1, 2 or 3, R^7 represents hydrogen or single or multiple substitution by alkyl, aralkyl or aryl radicals any of which alkyl, aralkyl or aryl radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl and when R^1 and R^2 taken together form an alkylene chain the resulting ring may be substituted by one or more R^7 radicals as defined above, X is cyano, CONHR^3 , CSNHR^3 , or CO_2R^3 wherein R^3 is hydrogen or alkyl, which may be substituted by alkoxy, bromine, chlorine, fluorine, nitro or trifluoromethyl and R^5 is selected from hydrogen, alkyl which may be substituted as for the R^3 alkyl radical, aralkyl or aryl radicals either of which radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl and m is 1, 2 or 3 with the proviso that when R^1 and R^2 taken together represent an alkylene chain then n is equal to m , and metal salts of the compounds in which R^3 is hydrogen.

2. A compound as claimed in Claim 1 wherein R^4 and R^7 are hydrogen.

3. A compound as claimed in Claim 2, wherein R^1 and R^2 are selected from hydrogen and lower alkyl.

4. A compound as claimed in Claim 3, wherein R^1 and R^2 are selected from hydrogen and methyl.



Example C

Anti-ulcer tablet (without antacid)

		mg/tablet	
5	5,6,7,8-Tetrahydroquinoline-8-thiocarboxamide	100 mg.	5
	Celutab	147.5 mg.	
	Mag. Stearate	2.5 mg.	
		250.0 mg.	

The tablets are prepared by the following method.

10 Blend the ingredients in a suitable blender. Compress the blended ingredients on a suitable compression machine to form tablets of the above composition. 10

Celutab is a commercial product comprising 90—2% dextrose. 3—5% maltose remainder higher glucose saccharides. Spray crystallised.

Example D

15 A suspension is prepared as described in Example A but replacing 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide by 3 - Methyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide. 15

Example E

20 An antacid tablet is prepared as described in Example B but replacing 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide by 3 - Methyl - 5,6,7,8 - tetrahydroquinoline - 8-thiocarboxamide. 20

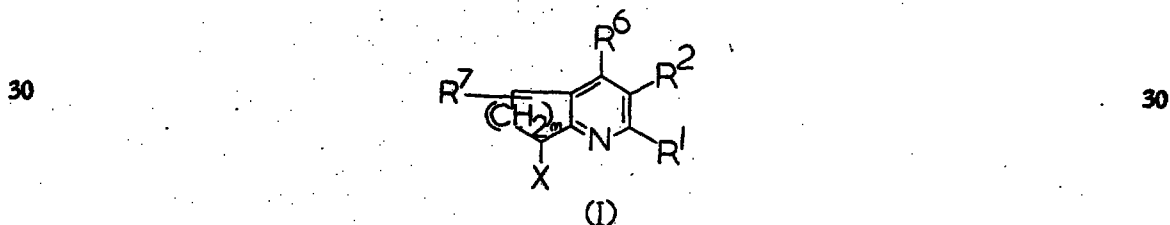
Example F

25 An anti-ulcer tablet is prepared as described in Example C but replacing 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide by 3 - methyl - 5,6,7,8 - tetrahydroquinoline-8-thiocarboxamide. 25

The tetrahydroquinoline starting materials may also be prepared by the method described in our co-pending U.K. Application 33252/73 (H—145). Serial No. 1432379.

WHAT WE CLAIM IS:—

1. A compound of formula I



35 and acid addition salts thereof, wherein R^1 , R^2 and R^6 are the same or different and represent hydrogen, trifluoromethyl, or alkyl which may be substituted by alkoxy, halogen, nitro or trifluoromethyl, or an aralkyl or aryl radical either of which radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl or R^1 and R^2 taken together represent an alkylene chain $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$ wherein n is 1, 2 or 3, R^7 represents hydrogen or single or multiple substitution by alkyl, aralkyl or aryl radicals any of which alkyl, aralkyl or aryl radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl and when R^1 and R^2 taken together form an alkylene chain the resulting ring may be substituted by one or more R^7 radicals as defined above, X is cyano, CONHR^3 , CSNHR^3 , or CO_2R^3 wherein R^3 is hydrogen or alkyl, which may be substituted by alkoxy, bromine, chlorine, fluorine, nitro or trifluoromethyl and R^3 is selected from hydrogen, alkyl which may be substituted as for the R^3 alkyl radical, aralkyl or aryl radicals either of which radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl and m is 1, 2 or 3 with the proviso that when R^1 and R^2 taken together represent an alkylene chain then n is equal to m , and metal salts of the compounds in which R^3 is hydrogen. 40

2. A compound as claimed in Claim 1 wherein R^6 and R^7 are hydrogen.3. A compound as claimed in Claim 2, wherein R^1 and R^2 are selected from hydrogen and lower alkyl. 454. A compound as claimed in Claim 3, wherein R^1 and R^2 are selected from hydrogen and methyl. 50



5. A compound as claimed in Claim 3, wherein R¹ and R² are selected from hydrogen and *t*-butyl.

6. A compound as claimed in Claim 2, wherein R¹ and R² are selected from hydrogen and phenyl.

7. A compound as claimed in any one of Claims 2 to 6 wherein n is 2.

8. A compound as claimed in Claim 2 wherein R¹ and R² are joined to form an alkylene chain —CH₂(CH₂)_n—CH₂— and n and m are each 2.

9. A compound as claimed in any one of Claims 2 to 8 wherein X is cyano.

10. A compound as claimed in any one of Claims 2 to 8, wherein X is CONHR³ wherein R³ is hydrogen or methyl.

11. A compound as claimed in any one of Claims 2 to 8, wherein X is CSNHR³ wherein R³ is hydrogen or methyl.

12. A compound as claimed in any one of Claims 2 to 8, wherein X is CO₂R⁵ wherein R⁵ is hydrogen or methyl.

13. A compound as claimed in Claim 1, wherein R⁷ is one or more lower alkyl groups.

14. A compound as claimed in Claim 13, wherein R⁷ is one or more methyl groups.

15. A compound as claimed in Claim 14 wherein R⁷ is a *gem*-dimethyl group in the 5, 6 or 7 position.

16. 2-Phenyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide.

17. 5,6,7,8-Tetrahydroquinoline-8-thiocarboxamide (having the following nmr spectrum in d₆DMSO (100 MHz).

8 1.5—2.3	broad multiplet	4 protons CH ₂ —6 and 7
8 2.7	multiplet	2 protons CH ₂ —5
8 4.15	triplet (j=7Hz)	1 proton CH—8
8 7.08	quartet	1 proton H—3
8 7.44	quartet	1 proton H—4
8 8.29	quartet	1 proton H—2
9.25 and 9.45 broad doublet 2 protons NH ₂ .		

Coupling constants = J₂₃ = 5Hz, J₂₄ = 1.5Hz, J₃₄ = 8Hz.

18. 2-*t*-Butyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide.

19. 2-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide.

20. 3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide.

21. 3-Methyl-5,6,7,8-tetrahydroquinoline-8-(N-methyl)-thiocarboxamide.

22. Sym. Octahydroacridine-4-thiocarboxamide.

23. 8-Cyano-2-phenyl-5,6,7,8-tetrahydroquinoline.

24. 2-Methyl-8-cyano-5,6,7,8-tetrahydroquinoline.

25. 3-Methyl-8-cyano-5,6,7,8-tetrahydroquinoline.

26. An acid addition salt of a compound as claimed in any one of Claims 6 to 25.

27. 2-Phenyl-5,6,7,8-tetrahydroquinoline-8-carboxylic acid.

28. Methyl 2-phenyl-5,6,7,8-tetrahydroquinoline-8-carboxylate.

29. Methyl 5,6,7,8-tetrahydroquinoline-8-carboxylate.

30. Methyl 2-*t*-butyl-5,6,7,8-tetrahydroquinoline-8-carboxylate.

31. Methyl 3-methyl-5,6,7,8-tetrahydroquinoline-8-carboxylate.

32. Methyl sym. octahydroacridine-4-carboxylate.

33. 2-Phenyl-5,6,7,8-tetrahydroquinoline-8-carboxamide.

34. 5,6,7,8-Tetrahydroquinoline-8-carboxamide.

35. 2-*t*-Butyl-5,6,7,8-tetrahydroquinoline-8-carboxamide.

36. 2-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide.

37. 3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide.

38. 3-Methyl-5,6,7,8-tetrahydroquinoline-8-(N-methyl)-carboxamide.

39. Sym. Octahydroacridine-4-carboxamide.

40. An acid addition salt of a compound as claimed in any one of Claims 27 to 39.

41. A process for preparing a compound as claimed in Claim 1 wherein X is CSNHR³ wherein R³ is as defined in Claim 1, which process comprises treating a corresponding nitrile of formula I wherein X is cyano with H₂S, if desired in the presence of an amine of formula R³NH₂ wherein R³ is alkyl, or with a compound of formula R³CSNH₂ wherein R³ is an alkyl group.

42. A process as claimed in Claim 41, wherein the starting material is one in which R⁶ and R⁷ are both hydrogen.

43. A process as claimed in Claim 42, wherein the starting material is one in which R¹ and R² are as defined in any one of Claims 3 to 8.

44. A process for preparing a thioamide of formula I as claimed in Claim 1,



* C L M S *

30

wherein X is CSNHR³ and R³ is hydrogen or alkyl, which process comprises treating a corresponding amide wherein X is CONHR³ with P₂S₅.

45. A process as claimed in Claim 44, wherein a starting materials is used in which R⁴ and R⁷ are both hydrogen.

5 46. A process as claimed in Claim 45, wherein a starting material is used in which R¹ and R² are as defined in any one of Claims 3 to 8. 5

47. A process as claimed in Claim 45 or 46 wherein an amide in which X is CONH₂ is used and the P₂S₅ reaction is conducted in the presence of H₂S.

10 48. A process for preparing a compound of formula I, as claimed in Claim 1, wherein X is CSNHR³ wherein R³ is alkyl, which process comprises treating a corresponding compound wherein X is CSNH₂ with an amine of formula R³NH₂, wherein R³ is alkyl in the presence of H₂S. 10

49. A process as claimed in Claim 48, wherein the amine is a lower alkylamine.

50. A process as claimed in Claim 49, wherein the amine is methylamine.

15 51. A process for preparing a compound of formula I as claimed in Claim 1, wherein X is cyano, which process comprises dehydrating a corresponding compound of formula I, wherein X is CONH₂. 15

52. A process as claimed in Claim 51, wherein the dehydration is carried out with phosphorus pentoxide, phosphorus pentachloride or thionyl chloride.

20 53. A process for preparing a compound of formula I as claimed in Claim 1, wherein X is cyano, which process comprises treating a corresponding compound of formula I wherein X is CONH₂ with phosphorus pentasulphide. 20

54. A process as claimed in any one of Claims 51 to 53 wherein a starting material in which R⁴ and R⁷ are both hydrogen is used.

25 55. A process as claimed in Claim 54, wherein a starting material in which R¹ and R² are as defined in any one of Claims 3 to 8 is used. 25

56. A process for preparing an amide of formula I as claimed in Claim 1, wherein X is CONHR³ and R³ is hydrogen or alkyl which process comprises treating either (a) a corresponding compound wherein X is CO₂R⁵ and R⁵ is as defined in Claim 1, except hydrogen, with ammonia, or a primary amine of formula R⁵NH₂, or (b) a compound of formula I wherein X is COCl with ammonia, a primary amine R⁵NH₂, and if desired a product in which X is CONH₂ is subsequently alkylated to introduce an alkyl group. R³.

30 57. A process as claimed in Claim 56 wherein a starting material is used in which R⁴ and R⁷ are both hydrogen. 30

58. A process as claimed in Claim 57 wherein a starting material is used in which R¹ and R² are as defined in any one of Claims 3 to 8. 35

59. A process for preparing an amide of formula I as claimed in Claim 1, wherein X is CONHR³ wherein R³ is hydrogen or alkyl which process comprises treating an ester of formula I as claimed in Claim 1, wherein X is CO₂R⁶ and R⁶ is alkyl with an amide of formula R⁶CONHR³ or a salt thereof wherein R³ is hydrogen or alkyl and R⁶ is hydrogen or lower alkyl in the presence of an alkali metal alkoxide. 40

60. A process as claimed in Claim 59 wherein a starting material in which R⁴ and R⁷ are both hydrogen is used. 45

61. A process as claimed in Claim 60, wherein a starting material in which R¹ and R² are as defined in any one of Claims 3—8 is used. 45

62. A process for preparing a compound as claimed in Claim 1, wherein X is CO₂R⁶ wherein R⁶ is as defined in Claim 1 or a metal salt of a compound wherein R⁶ is hydrogen, which process comprises treating a compound of formula I, as defined in Claim 1, wherein X is hydrogen with a metal alkyl compound MR¹⁰ wherein R¹⁰ is alkyl, aryl or aralkyl and M is sodium, potassium or lithium or M(R¹⁰)₂, wherein M is calcium or magnesium, treating the product with carbon dioxide and if desired acidifying or esterifying the product. 50

63. A process as claimed in Claim 62, wherein a starting material is used in which R⁴ and R⁷ are both hydrogen. 55

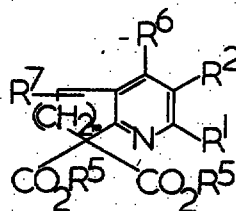
64. A process as claimed in Claim 63, wherein a starting material is used in which R¹ and R² are as defined in any one of Claims 3 to 8. 55

65. A process as claimed in Claim 63 or 64 wherein the metal alkyl is lithium phenyl.

60 66. A process as claimed in Claim 63 or 64, wherein the metal alkyl is *n*-butyl-lithium. 60

67. A process as claimed in any one of Claims 63 to 66 wherein the methyl ester is prepared.

65 68. A process for preparing a compound of formula I as claimed in Claim 1, wherein X is CO₂H, which process comprises decarboxylating a compound of formula: 65



wherein R^1 , R^2 , R^3 and R^7 and m are as defined in Claim 1.

69. A process as claimed in Claim 68, wherein R^6 and R^7 are both hydrogen.

70. A process as claimed in Claim 69, wherein R^1 and R^2 are as defined in any one of Claims 3—8.

71. A process as claimed in Claim 62, wherein after the treatment with carbon dioxide the product is treated with a further quantity of metal alkyl and then a further quantity of carbon dioxide.

72. A process as claimed in Claim 71, when carried out as defined in any one of Claims 63 to 67.

73. A process for preparing a compound as claimed in Claim 1, wherein X is CO_2R^5 wherein R^5 is as defined in Claim 1 or a metal salt of a compound wherein R^5 is hydrogen, which process comprises treating a compound of formula I as defined in Claim 1, wherein X is hydrogen, with a metal alkyl compound MR^{10} wherein R^{10} is alkyl, aryl or aralkyl and M is sodium, potassium or lithium or $M(R^{10})_2$ wherein M is calcium or magnesium, treating the product with a haloformate of formula $Hal COOR^5$, wherein Hal is a halogen atom and R^5 is defined above except hydrogen, and if desired saponifying the product with an alkali or alkaline earth metal hydroxide to give a corresponding metal salt of the acid of formula I wherein X is CO_2H and if desired acidifying this metal salt to give the corresponding acid.

74. A process as claimed in Claim 73, wherein a starting material is used in which R^6 and R^7 are both hydrogen.

75. A process as claimed in Claim 74, wherein a starting material is used in which R^1 and R^2 are as defined in any one of claims 3 to 8.

76. A process as claimed in any one of Claims 73 to 75, wherein after the treatment with the haloformate the product is treated with a further quantity of metal alkyl and then a further quantity of haloformate.

77. A process for preparing a thioamide as claimed in any one of Claims 1—8, wherein X is $CSNHR^3$ and R^3 is hydrogen or alkyl which process comprises treating a thioester of formula I wherein X is $CSSR^5$ and R^5 is alkyl or aralkyl with a compound of formula R^3NH_2 wherein R^3 is as previously defined.

78. A process as claimed in Claim 77 wherein the thioester is prepared by treating a compound of formula I wherein X is hydrogen with a metal alkyl compound MR^{10} wherein R^{10} is alkyl, aryl or aralkyl and M is sodium potassium or lithium, or $M(R^{10})_2$ wherein M is calcium or magnesium and then treating the product with carbon disulphide followed by an alkyl or aralkyl halide $R^5 Hal$ wherein R^5 is an alkyl or aralkyl group and Hal is chlorine, bromine or iodine.

79. A process as claimed in Claim 41, substantially as hereinbefore described in Example 5.

80. A process as claimed in Claim 41, substantially as hereinbefore described in Example 14 or 18.

81. A process as claimed in Claim 44, substantially as described in any one of Examples 3, 8 or 10.

82. A process as claimed in Claim 47, substantially as described in Example 23.

83. A process as claimed in Claim 44, substantially as described in Example 28.

84. A process as claimed in Claim 47, substantially as described in Example 29.

85. A thioamide whenever prepared by a process as claimed in any one of Claims 41, 44 or 48—50.

86. A thioamide whenever prepared by a process as claimed in any one of Claims 42, 43, 45, 46, 79, or 81.

87. A thioamide whenever prepared by a process as claimed in Claim 47 or Claim 82.

88. A thioamide whenever prepared by a process as claimed in Claim 80.

89. A thioamide whenever prepared by a process as claimed in Claim 83 or 84.

90. A process for preparing a nitrile as claimed in Claim 51, substantially as described in Example 3 or 4.



91. A process for preparing a nitrile as claimed in Claim 51 substantially as described in Example 14 or 18.
92. A nitrile whenever prepared by a process as claimed in any one of Claims 51, 52 or 53.
- 5 93. A nitrile whenever prepared by a process as claimed in Claim 54, 55 or 90. 5
94. A nitrile whenever prepared by a process as claimed in Claim 91.
95. A process for preparing an amide as claimed in Claim 56, substantially as hereinbefore described in any one of Examples 2, 4, 7 or 9.
- 10 96. A process for preparing an amide as claimed in Claim 56, substantially as hereinbefore described in Example 13 or 17. 10
97. A process for preparing an amide as claimed in Claim 59, substantially as hereinbefore described in Example 21 or 22.
98. A process for preparing an amide as claimed in Claim 56 substantially as described in Example 28 or 29.
- 15 99. An amide whenever prepared by a process as claimed in Claim 56 or 59. 15
100. An amide whenever prepared by a process as claimed in any one of Claims 57, 58 or 95.
101. An amide whenever prepared by a process as claimed in any one of Claims 60, 61 or 97.
- 20 102. An amide whenever prepared by a process as claimed in Claim 96. 20
103. An amide whenever prepared by a process as claimed in Claim 98.
104. A process as claimed in Claim 62, substantially as described in Example 1, 6 or 9.
- 25 105. A process as claimed in Claim 62, substantially as described in Example 13 or 16. 25
106. A process as claimed in Claim 62, substantially as described in any one of Examples 19, 20 or 24.
107. A process as claimed in Claim 62, substantially as described in Example 29.
- 30 108. A process as claimed in Claim 74, substantially as described in Example 25. 30
109. A compound whenever prepared by a process as claimed in any one of Claims 62, 68, 71, 73 or 76.
110. A compound whenever prepared by a process as claimed in any one of Claims 63—65, 69, 70 or 104.
- 35 111. A compound of formula I wherein X is CO_2R^5 wherein R^5 is as defined in Claim 1 or a metal salt of a compound wherein R^5 is hydrogen whenever prepared by a process as claimed in Claim 105. 35
112. A compound whenever prepared by a process as claimed in any one of Claims 66, 67, 72, 74, 75, 106, or 108.
- 40 113. A compound whenever prepared by a process as claimed in Claim 107. 40
114. A process as claimed in Claim 41 substantially as described in Example 32.
115. A thioamide whenever prepared by a process as claimed in Claim 114.
116. A process as claimed in Claim 62, substantially as described in Example 3, 34 or 35.
- 45 117. A compound whenever prepared by a process as claimed in Claim 116. 45
118. 3 - Methyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide oxalate or tartrate.
119. 3-Methyl-5,6,7,8-tetrahydroquinoline-8-thiocarboxamide substantially as described in Example 26.
- 50 120. 3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxamide substantially as described in Example 27. 50
121. 8-Cyano-5,6,7,8-tetrahydroquinoline.
122. 3-Methyl-5,6,7,8-tetrahydroquinoline-8-carboxylic acid or a metal salt thereof.
123. A process as claimed in Claim 77, substantially as hereinbefore described in Example 36.
- 55 124. A process as claimed in Claim 78, substantially as hereinbefore described in Example 36. 55
125. A compound whenever prepared by a process as claimed in Claim 123 or 124.
126. A pharmaceutical composition comprising a compound of formula I as claimed in Claim 1, or a salt thereof wherein X is CSNHR^3 wherein R^3 is as defined in Claim 1 and a pharmaceutically acceptable carrier.
- 60 127. A pharmaceutical composition comprising a compound of formula I, or an acid addition salt thereof, wherein X is cyano and a pharmaceutically acceptable carrier. 60
128. A pharmaceutical composition as claimed in Claim 126 or 127 in unit dosage form.



129. A pharmaceutical composition as claimed in Claim 126, 127 or 128, which includes an antacid ingredient.
130. A pharmaceutical composition as claimed in any one of Claims 126, 128 or 129 wherein the compound of formula I is as defined in any one of Claims 2—8, 11, or 16—22.
131. A pharmaceutical composition as claimed in any one of Claims 126 to 129, wherein the compound of formula I is as defined in any one of Claims 13—15.
132. A pharmaceutical composition as claimed in Claim 127, wherein the compound of formula I is a compound as claimed in any one of Claims 9 or 23—27.
133. A pharmaceutical composition substantially as described in Example A, B or C.
134. A pharmaceutical composition substantially as described in Example D, E or F.

G. R. PORTER,
Chartered Patent Agent.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1976.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.