

PATENT SPECIFICATION

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

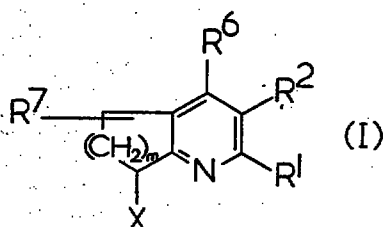


(54) TETRAHYDROQUINOLINE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, 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 tetrahydroquinoline derivatives, to processes for preparing them and to pharmaceutical compositions containing the derivatives.

In our U.K. Specification 1,432,378 we have described and claimed compounds of formula I



and acid addition salts thereof, wherein R¹, R² and R⁶ 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



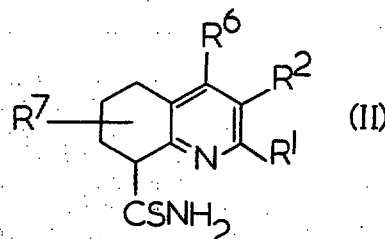
wherein n is 1, 2 or 3, R⁷ represents hydrogen or single or multiple substitution by alkyl, aralkyl or aryl radicals any of which alkyl, aralkyl or aryl radicals may be substituted by alkyl, alkoxy, halogen, nitro or trifluoromethyl

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 CO₂R⁵ wherein R⁵ is hydrogen or alkyl which may be substituted by alkoxy, bromine, chlorine, fluorine, nitro or trifluoromethyl, R³ 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.

The compounds of formula I wherein X is CN or CSNHR³ are anti-ulcer agents since they possess either anti-ulcer activity or anti-secretory activity or both these activities.

We have now discovered that certain compounds of formula I which are not exemplified in Specification 1,432,378 are particularly useful anti-ulcer agents, possessing good anti-ulcer activity or good anti-secretory activity or both.

Accordingly, the present invention provides a compound of formula II,



or a pharmaceutically acceptable acid addition salt thereof wherein R¹, R², R⁶ and R⁷ are selected from hydrogen and methyl, at least one of R⁶ and R⁷ being methyl.

In a preferred aspect at least two of R^2 , R^6 and R^7 are methyl and R^1 is hydrogen. Specific compounds of the invention are 4-methyl-, 3,4-dimethyl-, 3,5-dimethyl- and 3,6-dimethyl - 5,6,7,8 - tetrahydroquinoline - 8-thiocarboxamide and their pharmaceutically acceptable acid addition salts. The compounds of this invention may be prepared by any of the methods disclosed in our aforesaid complete specification such methods are included in the present invention. The compounds may also be prepared by any of the methods disclosed in our copending cognate applications 58307/73; 13514/74 and 30934/74 (Serial No. 1,463,666).

The acid addition salts of the present invention include salts with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric and nitric acids and with organic acids e.g. citric acid, fumaric, maleic or tartaric acids.

In the compounds of formula II the carbon atom at the 8-position 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 e.g. by formation of an acid salt with an optically active acid. Alternatively optical resolution can be carried out using a precursor in which the thioamide group has not yet been formed e.g. an 8-carboxylic acid may be resolved with an optically active base and then converted to the desired thioamide. When R^7 is methyl there is a further asymmetric centre and further optical isomers are possible. These are also included in the invention.

The present invention also includes pharmaceutical compositions containing the compounds of formula II and a pharmaceutically acceptable carrier. Suitable carriers are discussed in Specification 1,432,378.

The invention is illustrated by the following examples.

EXAMPLE 1

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

Following the general procedures of Examples 20, 21 and 23 of the complete specification of Specification 1,432,378 4 - methyl - 5,6,7,8 - tetrahydroquinoline is converted to the title compound.

Thus 4 - methyl - 5,6,7,8 - tetrahydroquinoline is treated with butyl lithium in hexane to give 8 - lithio - 4 - methyl - 5,6,7,8 - tetrahydroquinoline which is treated with carbon dioxide gas to give 4 - methyl - 5,6,7,8 - tetrahydroquinoline - 8 - carboxylic acid, which is esterified with methanol. The methyl ester is reacted with formamide in the presence of sodium methoxide to give 4 - methyl - 5,6,7,8 - tetrahydroquinoline - 8 - carboxamide which is treated with P_2S_5 in pyridine saturated with H_2S gas to give the title com-

pound. This is converted to the hydrochloride by treatment of an isopropanol solution of the thioamide with ether saturated with dry HCl gas. 4 - Methyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide hydrochloride forms colourless needles m.p. 213°C.

EXAMPLE 2

3,4 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide

By the method described in Example 1 above, 3,4 - dimethyl - 5,6,7,8 - tetrahydroquinoline may be converted to 8 - lithio - 3,4 - dimethyl - 5,6,7,8 - tetrahydroquinoline, 3,4 - dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - carboxylic acid methyl ester, the corresponding 8-carboxamide and then 3,4-dimethyl - 5,6,7,8 - tetrahydroquinoline - 8-thiocarboxamide m.p. 163-5°C. (Found: C, 65.1; H, 7.8; N, 12.2. $C_{12}H_{14}N_2S$ requires C, 65.4; H, 7.3; N, 12.2%).

EXAMPLE 3

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

A solution of 3,5 - dimethyl - 5,6,7,8-tetrahydroquinoline (4.5 g; 0.028 mole) in benzene (30 ml) was cooled in an ice bath and treated with *n* - butyl - lithium solution (14 ml, 9%, w/v, 0.025 mole) with stirring. After 1 hour trimethylsilyl isothiocyanate (4 ml, 0.028 mole) was added and the mixture was stirred at 0°C for 1 hour. The resulting solution was acidified with 2N HCl and the aqueous layer was separated, washed with ethyl acetate and basified with 0.880 N NH_4OH solution. The resulting emulsion was extracted with chloroform (3 x 75 ml) and the chloroform solution was dried ($MgSO_4$) and evaporated. The residue was triturated twice with hot hexane and the residue was dissolved in hot isopropyl alcohol. Excess ethereal HCl was added followed by di-isopropyl ether until slightly turbid and the solution was allowed to crystallise to give 3,5 - dimethyl - 5,6,7,8-tetrahydroquinoline - 8 - thiocarboxamide hydrochloride (0.5 g) m.p. 226°C. Found: C, 56.2; H, 6.7; N, 10.6. $C_{12}H_{14}N_2S \cdot HCl$ requires: C, 56.1; H, 6.7; N, 10.9%.

EXAMPLE 4

a) 3,6 - Dimethyl - 5,6,7,8 - tetrahydroquinoline

A solution of 3,6 - dimethylquinoline hydrochloride (56 g) in acetic acid (200 ml) and water (10 ml) was hydrogenated at 50 psi and room temperature using platinum oxide (1 g) as catalyst. On completion the catalyst was removed by filtration on a bed of kieselguhr. The filtrate was evaporated to dryness in vacuo and the residue dissolved in water. The resulting solution was basified with sodium carbonate and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated to dryness and the residual oil

was distilled to give 3,6 - dimethyl - 5,6,7,8-tetrahydroquinoline (18 g) b.p., 120—124°C.

The hydrochloride was prepared in dry ether by the addition of ethereal HCl. m.p. 189°C. Found: C, 66.2; H, 8.2; N, 6.9. $C_{11}H_{14}N.HCl$ requires: C, 66.8; H, 8.2; N, 7.1%.

b) 3,6 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide

To an ice-cooled stirred solution of 3,6-dimethyl - 5,6,7,8 - tetrahydroquinoline (10 g) in dry benzene (63 ml) under nitrogen was added 9% w/v butyl lithium solution (28 ml). The solution was stirred for 1 hour at 0°C and trimethylsilyl isothiocyanate (8.7 ml) was added dropwise over 10 mins and the stirring continued for 1 hour. Water was added to the solution and the mixture acidified with 2N aqueous hydrochloric acid. The aqueous layer was separated and washed with ethyl acetate. It was then basified with 0.880 ammonia solution and extracted with chloroform (3×). The combined chloroform extracts were washed with water and dried ($MgSO_4$). The solvent was removed in vacuo and the residue triturated with hexane till crystalline. The mixture was refrigerated and the solid removed by filtration, and recrystallised from benzene/hexane to give 3,6 - dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide (1.6 g) m.p. 149°C.

The free base was dissolved in hot isopropyl alcohol and excess ethereal HCl added to give 3,6 - dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide hydrochloride (1.7 g) m.p. 237°C. Found: C, 55.7; H, 6.7; N, 10.6. $C_{12}H_{14}N_2S.HCl$ requires: C, 56.1; H, 6.7; N, 10.9%.

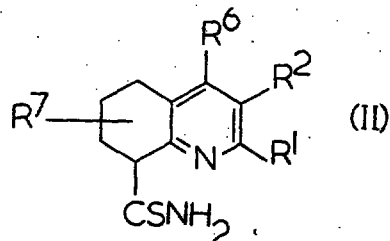
EXAMPLE 5

2,4 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide

Following the procedure of Example 4(b) 2,4 - dimethyl - 5,6,7,8 - tetrahydroquinoline is treated with n-butyl lithium and the product is treated with trimethylsilyl - isothiocyanate to give 2,4 - dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide which is recrystallised from hexane m.p. 84°C. Found: C, 65.8; H, 7.3; N, 12.6. Calc. for $C_{12}H_{14}N_2S$ C, 65.4; H, 7.3; N, 12.7.

WHAT WE CLAIM IS:—

1. A compound of formula II,



or a pharmaceutically acceptable acid addition salt thereof wherein R^1 , R^2 , R^6 and R^7 are selected from hydrogen and methyl, at least one of R^6 and R^7 being methyl.

2. A compound as claimed in Claim 1, wherein at least two of R^2 , R^6 and R^7 are methyl and R^1 is hydrogen.

3. 4 - Methyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

4. 3,4 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

5. 3,5 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

6. 3,6 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

7. 2,4 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

8. A pharmaceutical composition comprising a compound as claimed in Claim 1 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition as claimed in Claim 8, wherein the active ingredient comprises a compound as claimed in Claim 2.

10. A pharmaceutical composition as claimed in Claim 8, wherein the active ingredient comprises a compound as claimed in Claim 3.

11. A pharmaceutical composition as claimed in Claim 8, wherein the active ingredient comprises a compound as claimed in Claim 4.

12. A pharmaceutical composition as claimed in Claim 8, wherein the active ingredient comprises a compound as claimed in Claim 5, Claim 6, or Claim 7.

G. R. PORTER,
Chartered Patent Agent.

was distilled to give 3,6 - dimethyl - 5,6,7,8-tetrahydroquinoline (18 g) b.p., 120—124°C.

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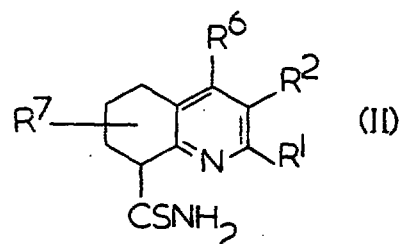
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2. A compound as claimed in Claim 1, wherein at least two of R^2 , R^6 and R^7 are methyl and R^1 is hydrogen.

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4. 3,4 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

5. 3,5 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

6. 3,6 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

7. 2,4 - Dimethyl - 5,6,7,8 - tetrahydroquinoline - 8 - thiocarboxamide or a pharmaceutically acceptable acid addition salt thereof.

8. A pharmaceutical composition comprising a compound as claimed in Claim 1 and a pharmaceutically acceptable carrier.

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12. A pharmaceutical composition as claimed in Claim 8, wherein the active ingredient comprises a compound as claimed in Claim 5, Claim 6, or Claim 7.

WHAT WE CLAIM IS:—

1. A compound of formula II,

G. R. PORTER,
Chartered Patent Agent.

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