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SPECIFICATION

8 - substituted - 4 - amino - 3 - quinolinecarboxlic acids and esters - antisecretory, anti-ulcer compounds

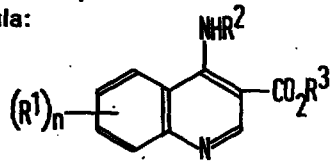
The present invention relates to certain novel 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acids and esters and pharmaceutical compositions incorporating such compounds and novel pharmaceutical uses and compositions therefor for 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acids and esters and pharmaceutical compositions incorporating such compounds. More particularly, the invention relates to certain 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acids and esters which reduce gastric secretion stimulated by secretagogues such as histamine, tetragastrin, and food and as such are useful in preventing or treating peptic ulcers in mammals.

Diuretic and antidepressant activity in certain 4 - anilino - 3 - quinolinecarboxylic acid esters and 6 - chloro derivatives thereof have been disclosed by Hanifin, J. W. in U.S. Patent 3,470,186, and *J. Med. Chem.* 1969, 12(6), 1096-7.

Kermack et al., *J. Chem. Soc.*, 1951, 1389-92 appears to disclose the preparation of 6 - substituted 4 - anilino - 3 - quinolinecarboxylic acids and esters therefrom. Sen et al., *J. Indian Chem. Soc.*, 34, 906-8 (1975) appears to disclose the preparation of 7-substituted 4 - amino - 4 - quinoline - carboxylic amides. Elslager et al., *J. Med. Pharm. Chem* 5, 546-58 (1962) discloses the preparation of 4 - anilino - 7 - chloro - 3 - quinolinecarboxylic acid and its ethyl ester.

Antisecretory or anti-ulcer activities for 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acids and ester have not been disclosed prior to this invention.

The present invention in one of its aspects extends to compounds for use in a novel method of inhibiting secretion of gastric acid e.g. hydrochloric acid and/or treating peptic ulcers in mammals which compounds are 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acids and esters thereof having the formula:



(I)

wherein;

R^1 represents a halogen atom or a loweralkyl, phenyl, O-loweralkyl, S-loweralkyl, trifluoromethyl, cyano or dialkylamino group;

R^2 represents a loweralkyl, phenyl, or phenyl-loweralkyl group or a phenyl group substituted by one to three radicals taken from among loweralkyl, O-loweralkyl, S-loweralkyl, cyano, hydroxy, carbamoyl, carboxy, acetyl, trifluoromethyl, and nitro groups or halogen atoms;

R^3 represents a hydrogen atom or a loweralkyl, dimethylamino - loweralkyl, loweralkoxy - loweralkyl or allyl group.

R^4 represents a halogen atom or a loweralkyl, phenyl, O-loweralkyl, S-loweralkyl, trifluoromethyl, cyano or dialkylamino group, and

n is 0 or 1; and

the pharmaceutically acceptable addition salts thereof.

The antisecretory effect of reduced flow of gastric juice and hydrochloric acid in pyloric-ligated rats was demonstrated when the esters of 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acid of this invention were adminstered orally, subcutaneously, intraperitoneally, intraduodenally or intravenously. Effective ulceration reduction was also demonstrated in pylorictligated rats. The compounds of Formula I as stated hereinabove also were shown to reduce gastric secretion induced, for example, by histamine, tetragastrin and methacholine. Gastric acid output in Heidenhain pouch dogs stimulated with food was also reduced.

Accordingly, it is an object of the present invention to provide a compound of Formula I wherein R^1, R^2, R^3, R^4 and n are as hereinabove defined, for use in controlling excess gastric acid output in mammals by administering an acid-reducing amount of the said compound.

Another object is to provide an 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acid or ester compound of Formula I wherein R^1, R^2, R^3, R^4 and n are as defined herein for use in treating mammals for peptic ulceration by administering to the mammal a peptic ulcer inhibiting amount of the said compound.

Another object is to provide novel 8 - substituted - 4 - amino - 3 - quinolinecarboxylic acids and esters particularly effective for their control of gastric ulcers.

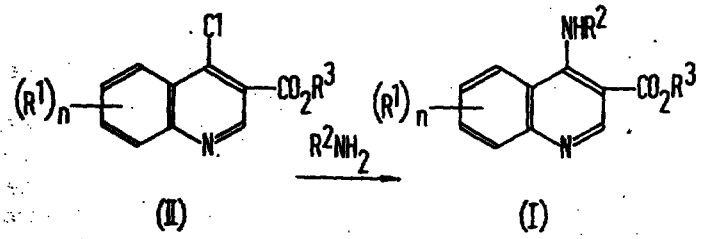
Still another object is to provide pharmaceutical compositions for accomplishing the foregoing objects comprised of suitable pharmaceutical carriers, for various routes of administration, of certain of the compounds of this invention.

The term "loweralkyl" as used herein means straight and branched chain radicals of up to eight carbon atoms inclusive and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, amyl, isoamyl, hexyl, heptyl, and octyl.

Representative of "phenylloweralkyl" radicals are benzyl (phenylmethyl), α-methylbenzyl, phenylethyl, phenylpropyl, and phenylbutyl.

The compounds of the present invention may be prepared from appropriate 4 - chloro - 3 - quinolinecarboxylic acid esters as represented by the following equation:

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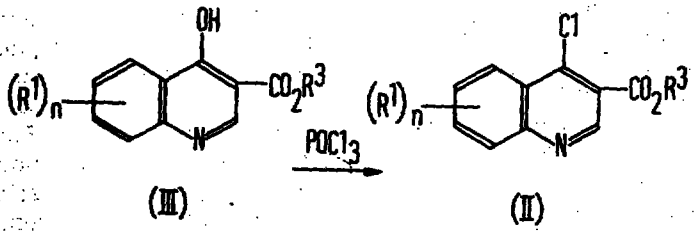
(II) (I)

wherein:

R^1, R^2, R^4 and n are as hereinabove defined; and

R^3 represents a loweralkyl group.

The Formula II compounds may be prepared by chlorinating appropriate 8 - substituted - 4 - hydroxy - 3 - quinolinecarboxylic acid esters with phosphorus oxychloride generally by the method described by Kermack & Storey, *J. Chem. Soc.* 1951, pp 1389-92. The reaction may be represented by the following equation:



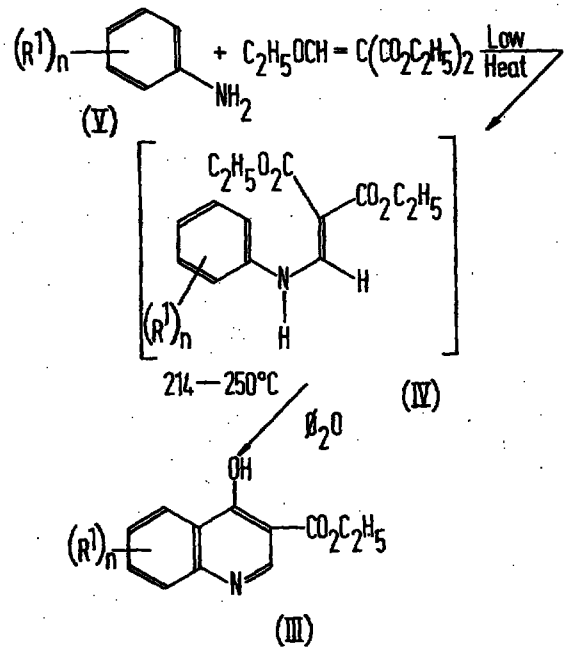
(III) (II)

wherein:

R^1, R^4 and n are as defined hereinabove; and

R^3 represents a loweralkyl group.

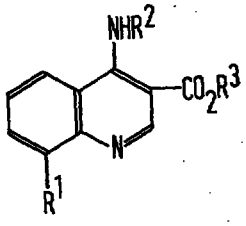
The Formula III compounds wherein R^3 represents an ethyl group may be prepared by heating a mixture of appropriately substituted anilines and diethyl ethoxymethylenemalonate to form an intermediate anilino-acrylate and thereafter cyclizing in a high boiling solvent such a diphenyloxide as described by Price and Roberts in *J. Amer. Chem. Soc. 68*, 1204-8. The reaction may be represented by the following equation:



(V) (IV) (III)

Acids (in which R^3 represents a hydrogen atom) of the present invention may be prepared from esters (in which R^3 represents a loweralkyl group) by usual methods of hydrolysis and other esters of this invention may be prepared by usual methods of re-esterification.

Compounds preferred for their effectiveness in control of gastric secretion and/or treatment or prevention of peptic ulcers in mammals have the formula:



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wherein:

R^1 represents a loweralkyl, phenyl, O-loweralkyl, S-loweralkyl, trifluoromethyl, cyano or dialkylamino group or a halogen atom;

R^2 represents a loweralkyl, phenyl, or phenyl - loweralkyl group or a phenyl group substituted by one to three radicals taken from among loweralkyl, O-loweralkyl, S-loweralkyl, cyano, carbamoyl, carboxy, acetyl, trifluoromethyl, or nitro groups or halogen atoms;

R^3 represents a hydrogen atom or a loweralkyl, dimethylamino - loweralkyl, loweralkoxy - loweralkyl, or allyl group; and

the pharmaceutically acceptable addition salts thereof, and the invention extends to such compounds per se.

The invention also extends to pharmaceutical compositions for inhibiting secretion of gastric acid and/or treating peptic ulcers in mammals which comprise a pharmaceutical carrier and an effective amount of a compound in accordance with the invention.

The invention may be put into practice in various ways and a number of specific embodiments will be described by way of example to illustrate the invention.

Preparation of starting materials

Utilizing the foregoing method described by Price and Roberts, the following ethyl - 4 - hydroxy - 3 - quinolinecarboxylates were prepared from diethylethoxymethoxymalonate and aniline or known aniline derivatives as follows:

Ethyl 4 - hydroxy - 8 - methoxy - 3 - quinolinecarboxylate from 2 - methoxyaniline; m.p. 243-246°C.

Ethyl 4 - hydroxy - 8 - ethoxy - 3 - quinolinecarboxylate from 2 - ethoxyaniline; m.p. 198-200°C.

Ethyl 4 - hydroxy - 5,8 - dimethoxy - 3 - quinolinecarboxylate from 2,5 - dimethoxyaniline; m.p. 197-199.5°C.

Ethyl 4 - hydroxy - 8 - methoxy - 5 - methyl - 3 - quinolinecarboxylate from 2 - methoxy - 5 - methylaniline; m.p. 180-182°C.

Ethyl 4 - hydroxy - 8 - phenyl - 3 - quinolinecarboxylate from 2 - aminobiphenyl; m.p. 250-252.2°C.

Ethyl 4 - hydroxy - 8 - methyl - 3 - quinolinecarboxylate from 2 - methylaniline; m.p. 271-274°C.

Ethyl 4 - hydroxy - 8 - trifluoromethyl - 3 - quinolinecarboxylate from 2 - trifluoromethylaniline; m.p. 211-213.5°C.

Ethyl 4 - hydroxy - 8 - methylthio - 3 - quinolinecarboxylate from 2 - methylthioaniline; m.p. 201-204°C.

Ethyl 4 - hydroxy - 8 - chloro - 3 - quinolinecarboxylate from 2 - chloroaniline; m.p. 255-259°C.

Ethyl 4 - hydroxy - 6, 8 - dimethyl - 3 - quinolinecarboxylate from 2, 4 - dimethylaniline;

Ethyl 4 - hydroxy - 6 - methoxy - 3 - quinolinecarboxylate from 4 - methoxyaniline; m.p. 283-287°C.

Ethyl 4 - hydroxy - 8 - cyano - 3 - quinolinecarboxylate from 2 - cyanoaniline; m.p. 234-236°C.

Ethyl 4 - hydroxy - 7 - methoxy - 3 - quinolinecarboxylate from 3 - methoxyaniline; m.p. 280-282.5°C.

Ethyl 4 - hydroxy - 8 - dimethylamino - 3 - quinoline - carboxylate from 2 - dimethylaminoaniline; m.p. 176-180°C.

Preparation 1 illustrates the synthesis procedure used to make, from the hydroxy compounds listed above, the 4 - chloro compounds of Formula II which are the starting materials used in making compounds of Formula I.

Preparation 1

Ethyl 4 - chloro - 8 - methoxy - 3 - quinolinecarboxylate.

A stirred mixture of ethyl 4 - hydroxy - 8 - methoxy - quinoline - 3 - carboxylate, 66.63 g (0.269 mole) and phosphorous oxychloride (350 ml) was warmed until all the solid has dissolved and then heated at reflux temperature for two hours. After cooling to below 100°C the mixture was concentrated in a rotary evaporator. The residual oil was dissolved in 100 ml acetone and the solution poured onto an ice-water mixture (800 ml). The mixture was neutralized with 6N sodium hydroxide solution and the solid product extracted successively with 450 ml, 250 ml and 100 ml portions of methylene chloride. The extracts were combined, washed with water, dried over anhydrous magnesium sulphate and concentrated to yield 68.16 g crude product. This crude product was dissolved in 500 ml hot toluene and filtered to remove a small quantity of insoluble material. The toluene solution was filtered through a bed of 250 g Fluorisil followed by two litres of toluene and four litres of chloroform. The purified solution was concentrated to give 64.17 g of oil (89%) which crystallized to an off-white solid on cooling. The solid melted at 75-77°C.

Analysis: Cakculated for $C_{13}H_{12}NO_3Cl$: C,58,77; H,4.55; N,5.27

Found: C,58.58; H,4.61; N,5.33

Preparations 2 to 15

Utilizing the procedure of Preparation 1, and substituting appropriate ethyl 4 - hydroxy - 3 - quinolinecarboxylates listed above as Formula III compounds, the following ethyl 4 - chloro - quinoline - 3 - carboxylates were prepared and used directly.

(2) Ethyl - 4 - chloro - 8 - ethoxy - 3 - quinolinecarboxylate

(3) Ethyl 4 - chloro - 5,8 - dimethyl - 3 - quinolinecarboxylate

(4) Ethyl 4 - chloro - 8 - methoxy - 5 - methyl - 3 - quinolinecarboxylate

(5) Ethyl 4 - chloro - 8 - phenyl - 3 - quinolinecarboxylate

(6) Ethyl 4 - chloro - 8 - methyl - 3 - quinolinecarboxylate

(7) Ethyl 4 - chloro - 8 - trifluoromethyl - 3 - quinolinecarboxylate

(8) Ethyl 4 - chloro - 8 - methylthio - 3 - quinolinecarboxylate

(9) Ethyl 4,8 - dichloro - 3 - quinolinecarboxylate

(10) Ethyl 4 - chloro - 6,8 - dimethyl - 3 - quinolinecarboxylate

(11) Ethyl 4 - chloro - 6 - methoxy - 3 - quinolinecarboxylate

(12) Ethyl 4 - chloro - 8 - cyano - 3 - quinolinecarboxylate

(13) Ethyl 4 - chloro - 7 - methoxy - 3 - quinolinecarboxylate

(14) Ethyl 4 - chloro - 8 - (dimethylamino) - 3 - quinolinecarboxylate.

A general procedure for preparing esters of For-

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mula I (in which R^3 represents a loweralkyl group) of the present invention is to react an appropriate 8 - substituted - 4 - chloro - 3 - quinolinecarboxylic acid ester with an appropriate amine in a polar aprotic solvent such as tetrahydrofuran or dioxane, following the reaction by thin-layer chromatography and modifying temperature and time to complete the reaction. In some instances the reacting amine may be used as the reaction solvent.

Various solvents are used for recrystallizing. To prepare the free base from a salt the salt is dissolved and a base such as sodium hydroxide is added and the free base is extracted into a suitable organic solvent. To prepare additional salts the free base is mixed with an alcoholic solution of an acid, for example, phosphoric acid or sulphuric acid.

The foregoing is a general description of how to prepare the esters of the invention. The following Examples 1 and 2 generally illustrate the preparation of the ester compounds. The esters of Examples 3 to 62 and 65 to 71 were also prepared by reacting the appropriate amine with the appropriate ethyl 4 - chloro - 3 - quinolinecarboxylate selected from Preparations 1 to 14. Examples 72 to 75 and 79 illustrate the preparation of esters wherein R^3 represents a loweralkyl, dimethylamino - loweralkyl, loweralkoxy - loweralkyl or allyl group by the re-esterification of esters wherein R^3 represents a loweralkyl group. Preparation of the acids and acid salts thereof of Formula I (in which R^3 represents a hydrogen atom) is illustrated in Examples 62 and 64, wherein the ester is hydrolyzed to the acid. Metal salts of the acids such as alkali metal salts may also be prepared by usual methods of reacting with an alkali metal base and isolating the salts. Examples 76 to 79 further illustrate the conversion of free bases of esters of this invention to their acid addition salts. Physical data and analyses obtained are in Tables 1 and 2.

Example 1

Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride

To a solution of 5.31 g (19.98 mmoles) of ethyl 4 - chloro - 8 - methoxy - 3 - quinolinecarboxylate (see Preparation 1) dissolved in 40 ml of tetrahydrofuran was added 2.15 g (20.06 mmoles) of *o*-toluidine dissolved in 40 ml of tetrahydrofuran. The solution was stirred with exclusion of moisture at 60°C for 18 hours. The yellow solid precipitate was filtered and washed with isopropyl ether; yield 7.13 g (95.7%). The product was recrystallized three times from methylene chloride: ethyl acetate, m.p. 191-193.5°C.
Analysis: Calculated for $C_{20}H_{21}ClN_2O_3$: C,64.43; H,5.68; N,7.51
Found: C,64.36; H,5.65; N,7.62

Example 2

Ethyl 8 - methoxy - 4 - (phenylamino) - 3 - quinoline - carboxylate.

To a solution of 6.0 g (22.5 mmoles) of ethyl 4 - chloro - 8 - methoxy - 3 - quinolinecarboxylate (see Preparation 1) in 80 ml of tetrahydrofuran was added 2.3 g (24.8 mmoles) of aniline in 60 ml of tetrahydrofuran. The solution was briefly warmed and after standing for 10 minutes, a yellow solid began to precipitate. The mixture was kept at room temperature for 18 hours. The solvent was rotary evaporated. The residue dissolved in 200 ml of methanol and the pH was made slightly basic (pH 8) with sodium bicarbonate. Water (700 ml) was added and an oil formed which solidified and after standing, additional solid crystallized. The solid was filtered and air-dried to give 6.9 g (95%) of crude material. The solid was dissolved in 300 ml of hot isooctane and the solution was treated with charcoal and filtered. The volume of the filtrate was reduced to 150 ml. Upon cooling, pale yellow needles separated; 6.5 g (89%); m.p. 120-121°C.
Analysis: Calculated for $C_{19}H_{18}N_2O_3$: C,70.79; H,5.63; N,8.69
Found: C,70.91; H,5.65; N,8.77

Examples 3 to 71

3. Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate by neutralization of Example 1.

4. Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate sulphate (1:1) from Example 3 and sulphuric acid.

5. Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate phosphate (1:1) from Example 3 and phosphoric acid.

6. Ethyl 8 - methoxy - 4 - (phenylamino) - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and aniline.

7. Ethyl 8 - methoxy - 4 - [(2 - methoxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and *o* - anisidine.

8. Ethyl 8 - methoxy - 4 - [(2 - methylthiophenyl) - amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and 2 - methylthioaniline.

9. Ethyl 8 - methoxy - 4 - [(2 - chlorophenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and 2 - chloroaniline.

10. Ethyl 8 - methoxy - 4 - [(2 - cyanophenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and 2 - aminobenzonitrile.

11. Ethyl 8 - methoxy - 4 - [(2 - trifluoromethyl-phenyl) - amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and 2 - trifluoromethylaniline.

12. Ethyl 8 - methoxy - 4 - {[2 - (aminocarbonyl) phenyl] - amino} - 3 - quinolinecarboxylate monohydrochloride ethanol (5:2) from Preparation 1 and anthranilamide.

13. Ethyl 8 - methoxy - 4 - [(2 - fluorophenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and 2 - fluoroaniline.

14. Ethyl 8 - methoxy - 4 - [(2 - acetylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and 2' - aminoacetophenone.

15. Ethyl 8 - methoxy - 4 - (butylamino) - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and n - butylamine.

16. Ethyl 8 - methoxy - 4 - [(3 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride monohydrate from Preparation 1 and *m* - toluidine.

17. Ethyl 8 - methoxy - 4 - [(4 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride monohydrate from Preparation 1 and *p* - toluidine.

18. Ethyl 8 - methoxy - 4 - {[(2 - methoxyphenyl) - methyl] amino} - 3 - quinolinecarboxylate from Prep-

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aration 1 and 2 - methoxybenzylamine.

19. Ethyl 8 - methoxy - 4 - [(2 - 6 - dimethylphenyl) amino] - 3 - quinolinecarboxylate from Preparation 1 and 2, 6 - dimethylaniline.

20. Ethyl 8 - methoxy - 4 - [(2, 6 - dimethylphenyl) - amino] - 3 - quinolinecarboxylate hydrobromide from Example 18 and hydrogen bromide (HBr).

21. Ethyl 8 - methoxy - 4 - [(1 - phenylethyl) amino] - 3 - quinolinecarboxylate monohydrate from Preparation 1 and *α* - methylbenzylamine.

22. Ethyl 8 - methoxy - 4 - [(2 - chloro - 5 - methoxy - phenyl)amino] - 3 - quinolinecarboxylate hydrobromide from Preparation 1 and 2 - chloro - 5 - methoxyaniline.

23. Ethyl 8 - methoxy - 4 - [(3 - methylthiophenyl) - amino] - 3 - quinolinecarboxylate from Preparation 1 and 3 - methylmercaptoaniline.

24. Ethyl 8 - methoxy - 4 - benzylamino - 3 - quinoline - carboxylate phosphate (1:1) methanolate (1:1) from Preparation 1 and benzylamine.

25. Ethyl 8 - methoxy - 4 - [(2, 4 - dimethoxyphenyl) - amino] - 3 - quinolinecarboxylate from Preparation 1 and 2, 4 - dimethoxyaniline.

26. Ethyl 8 - methoxy - 4 - [(2 - ethoxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 1 and 2 - ethoxyaniline.

27. Ethyl 8 - methoxy - 4 - [(4 - methoxy - 2 - methyl - phenyl) amino] - 3 - quinolinecarboxylate from Preparation 1 and 2 - methyl - 4 - methoxyaniline.

28. Ethyl 8 - methoxy - 4 - [(2 - ethylphenyl) amino] - 3 - quinolinecarboxylate from Preparation 1 and 2 - ethylaniline.

29. Ethyl 8 - methoxy - 4 - [(2 - ethylphenyl) amino] - quinolinecarboxylate phosphate (1:2) from Example 28 and anhydrous phosphoric acid (H_3PO_4).

30. Ethyl 8 - methoxy - 4 - [(2 - ethylphenyl) amino] - 3 - quinolinecarboxylate sulphate (1:1) from Example 28 and alcoholic sulphuric acid (H_2SO_4).

31. Ethyl 8 - methoxy - 4 - [(2, 6 - dichlorophenyl) - amino] - 3 - quinolinecarboxylate from Preparation 1 and 2, 6 - dichloroaniline.

32. Ethyl 8 - methoxy - 4 - [(2 - methyl - 5 - nitrophenyl) amino] - 3 - quinolinecarboxylate from Preparation 1 and 2 - methyl - 5 - nitroaniline.

33. Ethyl 8 - methoxy - 4 - {[(2 - methylphenyl) - methyl]amino} - 3 - quinolinecarboxylate hydrochloride ethanol (2:1) from Preparation 1 and *o* - methylbenzylamine, ethanol and hydrochloric acid.

34. Ethyl 8 - ethoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 3 and *o* - toluidine.

35. Ethyl 8 - ethoxy - 4 - [2 - (trifluoromethylphenyl) amino] - 3 - quinolinecarboxylate hydrobromide from Preparation 2 and *o* - trifluoromethylaniline.

36. Ethyl 8 - ethoxy - 4 - [(2 - methoxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 3 and *o* - anisidine.

37. Ethyl 8 - ethoxy - 4 - [2 - (methylthiophenyl) - amino] - 3 - quinolinecarboxylate phosphate (1:1) from Preparation 3 and methylthioaniline and alcoholic phosphoric acid (H_3PO_4).

38. Ethyl 5, 8 - dimethoxy - 4 - (phenylamino) - 3 - quinolinecarboxylate hydrochloride hemihydrate from Preparation 3 and aniline.

39. Ethyl 5, 8 - dimethoxy - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylate from Preparation 3 and *o* - toluidine.

40. Ethyl 7 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 13 and *o* - toluidine.

41. Ethyl 6 - methoxy - 4 - (phenylamino) - 3 - quinolinecarboxylate from Preparation 11 and aniline.

42. Ethyl 6 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate from Preparation 11 and *o* - toluidine.

Examples 40 to 42 are comparison examples.

43. Ethyl 8 - methoxy - 4 - [(2 - methoxyphenyl) amino] - 5 - methyl - 3 - quinolinecarboxylate dihydrochloride from Preparation 4 and *o* - anisidine.

44. Ethyl 8 - methoxy - 5 - methyl - 4 - [2 - (methylthiophenyl) amino] - 3 - quinolinecarboxylate phosphate (2:3) from Preparation 4 and 2 - methylthioaniline.

45. Ethyl 8 - methoxy - 5 - methyl - 4 - [(2 - methyl - phenyl)amino] - 3 - quinolinecarboxylate from Preparation 4 and *o* - toluidine.

46. Ethyl 8 - trifluoromethyl - 4 - [2 - (methylphenyl) - amino] - 3 - quinolinecarboxylate from Preparation 7 and *o* - toluidine.

47. Ethyl 8 - methylthio - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate from Preparation 8 and *o* - toluidine.

48. Ethyl 8 - methylthio - 4 - [(2 - methoxyphenyl) - amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 8 and *o* - toluidine.

49. Ethyl 8 - methylthio - 4 - [(2 - methylthiophenyl) - amino] - 3 - quinolinecarboxylate from Preparation 8 and 2 - methylthioaniline.

50. Ethyl 8 - methyl - 4 - [2 - (methylthiophenyl) - amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 6 and 2 - methylthioaniline.

51. Ethyl 8 - methyl - 4 - [(2 - methoxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 6 and *o* - anisidine.

52. Ethyl 8 - methyl - 4 - [(2 - methylphenyl) methyl] - amino - 3 - quinolinecarboxylate hydrobromide from Preparation 6 and 2 - methylbenzylamine.

53. Ethyl 8 - chloro - 4 - [(2 - methoxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 9 and *o* - anisidine.

54. Ethyl 8 - cyano - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride from Preparation 12 and aniline.

55. Ethyl 8 - phenyl - 4 - (phenylamino) - 3 - quinolinecarboxylate from Preparation 5 and aniline.

56. Ethyl 8 - phenyl - 4 - [(2 - carboxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride hemihydrate from Preparation 5 and 2 - aminobenzoic acid.

57. Ethyl 8 - phenyl - 4 - benzylamino - 3 - quinolinecarboxylate from Preparation 5 and benzylamine.

58. Ethyl 6, 8 - dimethyl - 4 - (phenylamino) - 3 - quinolinecarboxylate from Preparation 10 and aniline.

59. Ethyl 8 - (dimethylamino) - 4 - (phenylamino)

- 3 - quinolinecarboxylate hydrochloride from Preparation 14 and aniline.

60. Ethyl 8 - (dimethylamino) - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylate from Preparation 14 and *o* - toluidine.

61. Ethyl 8 - cyano - 4 - (phenylamino) - 3 - quinolinecarboxylate from Preparation 12 and aniline.

62. Ethyl 8 - methoxy - [(2 - hydroxyphenyl) amino] - 3 - quinolinecarboxylate from Preparation 1 and *o* - hydroxyaniline.

Example 63

8 - Methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylic acid.

A mixture of ethyl 8 - methoxy - 4 - [(2 - methyl - phenyl) amino] - 3 - quinolinecarboxylate (see Example 3), 15.00 g (0.0445 mole), 100 ml of 3N sodium hydroxide solution and 100 ml of ethanol was stirred at room temperature for 16 hours. The mixture was diluted with 300 ml of water and acidified to pH 6.8 with 6N hydrochloric acid solution. The precipitate was collected by filtration, washed in succession with water and acetone and air dried for about 1.5 hr. Weight of solid was 13.41 g (98%), m.p. 272°C (d) (with decomposition).

Analysis: Calculated for $C_{18}H_{16}N_2O_3$: C,70.12; H,5.23; N,9.09

Found: C,70.10; H,5.27; N,9.09

Example 64

8 - Methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylic acid hydrochloride.

A portion of the 8 - methoxy - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylic acid, 4.35 g from Example 63 was triturated with 100 ml hot absolute ethanol. After cooling, the solid was collected by filtration and air dried to give 3.87 g. The solid was suspended in 25 ml of absolute ethanol and excess ethereal hydrogen chloride solution added. A clear solution was obtained. Addition of isopropyl ether produced a yellow precipitate which was collected and recrystallized from absolute ethanol-isopropyl ether to yield 3.14 g solid, m.p. 257°C (d).

Analysis: Calculated for $C_{18}H_{17}N_2O_3Cl$: C,62.70; H,4.97; N,8.12

Found: C,62.53; H,4.93; N,8.18

Examples 65 to 71

65. Ethyl 8 - methyl - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate monohydrochloride from Preparation 6 and *o* - toluidine.

66. Ethyl 8 - methoxy - 4 - [[2 - (1 - methylethyl) - phenyl] amino] - 3 - quinolinecarboxylate from Preparation 1 and *o* - isopropylaniline.

67. Ethyl 8 - chloro - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate from Preparation 9 and *o* - toluidine.

68. Ethyl 8 - methoxy - 4 - [(2 - chloro - 6 - methylphenyl) amino] - 3 - quinolinecarboxylate monohydrochloride from Preparation 1 and 2 - chloro - 6 - methylaniline.

69. Ethyl 8 - methoxy - 4 - [(2, 3 - dimethylphenyl) - amino] - 3 - quinolinecarboxylate monosulphate from Preparation 1 and 2, 3 - dimethylaniline.

70. Ethyl 8 - methoxy - 4 - [(2 - nitrophenyl) amino] - 3 - quinolinecarboxylate from Preparation 1 and 2 - nitroaniline.

71. Ethyl 8 - methoxy - 4 - [(2 - nitrophenyl) amino] - 3 - quinolinecarboxylate, ethylsulphate (1:1), ethanol (1:1) from Example 70 and concentrated sulphuric acid in absolute ethanol.

Example 72

1 - Methylethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate, monohydrochloride, monohydrate.

To 150 ml of dry 2 - propanol was added 2 sodium pellets followed by 5.38 g (15.99 mmoles) of ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate (see Example 3) dissolved in 50 ml of dry 2 - propanol. The solution was stirred and refluxed with exclusion of moisture for 6 hours during which time 120 ml of distillate was collected in a Dean - Starke trap and discarded. The solvent was evaporated and the residue was dissolved in 50 ml of 2.9 M hydrochloric acid and 100 ml of water added thereto. The solution was adjusted to a pH of 8 with 1 M aqueous sodium bicarbonate and the oil which separated was extracted three times with 100 ml of methylene chloride. The combined extracts were dried over magnesium sulphate. The solvent was evaporated to give 4.60 g (82%) of the free base of the titled compound having a m.p. of 120-122°C after recrystallization from acetone-hexane.

The free base was dissolved in isopropyl ether and ethereal hydrogen chloride added thereto. The solvent was evaporated and the residue recrystallized from methylene chloride-acetone to obtain the titled compound as yellow crystalline solid having a m.p. of 140-143°C.

Example 73

2 - (Methoxyethyl) 8 - methoxy - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylate.

Following the procedure of Example 72, the compound of Example 2 was re-esterified with 2 - methoxy - ethanol to give the titled compound.

Example 74

2 - (Dimethylamino) ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate.

Following a procedure similar to that given in Example 72, the compound of Example 3 was re-esterified with 2-dimethylaminoethanol substituting sodium ethoxide catalyst and toluene solvent to give the titled compound.

Example 75

3 - (Dimethylamino)propyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate.

Following a procedure similar to that given in Example 72, the compound of Example 3 was re-esterified with 3 - dimethylamino - 1 - propanol substituting toluene solvent to give the titled compound.

Example 76

2 - (Dimethylamino) ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate, Fumarate (1:1.5).

The titled compound was prepared from the compound of Example 74 and fumaric acid.

Example 77

3 - (Dimethylamino) propyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxlate, dihydrochloride, monohydrate.

The titled compound was prepared from the com-

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pound of Example 75 and ethereal hydrogen chloride.

Example 78

Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate, ethanesulphonate (1:1) (salt).

The titled compound was prepared from the compound of Example 3 and ethanesulphonic acid in absolute ethanol.

Example 79

Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate, 2 - hydroxyethanesulphonate (1:1) (salt).

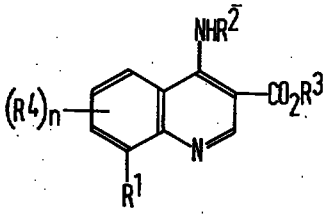
The titled compound was prepared from the compound of Example 3 and 2 - hydroxyethylsulphonic acid in absolute ethanol.

Allyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate.

Following a procedure similar to Example 72, substituting allyl alcohol for 2 - propanol, the titled compound was prepared.

TABLE 1

(Examples 1 to 79)



Ex.	R^1	n	R^2	R^3	Salt	M.P. °C.
1	CH_3O-	o	2-CH_3-C_6H_4-	C_2H_5-	HCl	191-193.5
2	CH_3O-	0	C_6H_5-	C_2H_5-	-	120-121
3	CH_3O-	0	2-CH_3-C_6H_4-	C_2H_5-	-	138.5-140
4	CH_3O-	o	2-CH_3-C_6H_4-	C_2H_5-	H_2SO_4	192-194
5	CH_3O-	o	2-CH_3-C_6H_4-	C_2H_5-	H_3PO_4	99-102
6	CH_3O-	o	C_6H_5-	C_2H_5-	HCl	165.5-168
7	CH_3O-	o	2-CH_3O-C_6H_4-	C_2H_5-	HCl	204-207
8	CH_3O-	o	2-CH_3S-C_6H_4-	C_2H_5-	HCl	275-278
9	CH_3O-	o	2-Cl-C_6H_4-	C_2H_5-	HCl	193-194.5
10	CH_3O-	o	2-CN-C_6H_4-	C_2H_5-	HCl	204-206.5
11	CH_3O-	o	2-CF_3-C_6H_4-	C_2H_5-	HCl	199-201d
12	CH_3O-	o	2-NH_2OC-C_6H_4-	C_2H_5-	1 HCl. 0.4 C_2H_5OH	251-154
13	CH_3O-	o	2-F-C_6H_4-	C_2H_5-	HCl	204-206
14	CH_3O-	o	2-CH_3CO-C_6H_4-	C_2H_5-	HCl	203-204d
15	CH_3O-	o	$CH_3(-CH_2)_3$-	C_2H_5-	HCl	171-172d
16	CH_3O-	o	3-$CH_3C_6H_4$-	C_2H_5-	HCl-H_2O	156-158d
17	CH_3O-	o	4-$CH_3C_6H_4$-	C_2H_5-	HCl-H_2O	155-156d
18	CH_3O-	o	2-CH_3O-$C_6H_4CH_2$-	C_2H_5-	-	132-137
19	CH_3O-	o	2,6$(CH_3)_2C_6H_3$-	C_2H_5-	-	160-163
20	CH_3O-	o	2,6$(CH_3)_2C_6H_3$-	C_2H_5-	HBr	182-184
21	CH_3O-	o	$C_6H_5(CH_3)CH$-	C_2H_5-	H_2O	97-99
22	CH_3O-	o	2-Cl-5-CH_3O-C_6H_3-	C_2H_5-	HBr	160-162
23	CH_3O-	o	3-CH_3S-C_6H_4-	C_2H_5-	-	123-124.5
24	CH_3O-	o	$C_6H_5CH_2$-	C_2H_5-	H_3PO_4. CH_3OH	221-223
25	CH_3O-	o	2,4$(CH_3O)_2$-C_6H_3-	C_2H_5-	-	128-131
26	CH_3O-	o	2-C_2H_5O-C_6H_4-	C_2H_5-	HCl	208d
27	CH_3O-	o	2-CH_3-4-CH_3O-C_6H_3-	C_2H_5-	-	175-176
28	CH_3O-	o	2-C_2H_5-C_6H_4-	C_2H_5-	-	152-153
29	CH_3O-	o	2-C_2H_5-C_6H_4-	C_2H_5-	$2H_3PO_4$	140-142
30	CH_3O-	o	2-C_2H_5-C_6H_4-	C_2H_5-	H_2SO_4	177-178.5
31	CH_3O-	o	2,6-Cl-C_6H_5-	C_2H_5-	-	178-180
32	CH_3O-	o	2-CH_3-5-NO_2-C_6H_3-	C_2H_5-	-	251.5-253
33	CH_3O-	o	2-CH_3-$C_6H_4CH_2$-	C_2H_5-	HCl. ½C_2H_5OH	197.5-198
34	C_2H_5O-	o	2-CH_3-C_6H_4-	C_2H_5-	HCl	208-209
35	C_2H_5O-	o	2-CF_3-C_6H_4-	C_2H_5-	HBr	185-191d

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TABLE 1 (cont.)

Ex.	R^1	n	R^2	R^3	Salt	M.P. °C.
36	C_2H_5O-	o	2-CH_3O-C_6H_4-	C_2H_5-	HCl	205-206.5
37	C_2H_5O-	o	2-CH_3S-C_6H_4-	C_2H_5-	H_3PO_4	185-190
46	CF_3 -	o	2-CH_3-C_6H_4-	C_2H_5-	-	147-148
47	CH_3S-	o	2-CH_3-C_6H_4-	C_2H_5-	-	168-170
48	CH_3S-	o	2-CH_3O-C_6H_4-	C_2H_5-	HCl	169-172
49	CH_3S-	o	2-CH_3S-C_6H_4-	C_2H_5-	-	140.5-142
50	CH_3 -	o	2-CH_3S-C_6H_4-	C_2H_5-	HCl	172-174d
51	CH_3 -	o	2-CH_3O-C_6H_4-	C_2H_5-	HCl	186-188
52	CH_3 -	o	2-CH_3-$C_6H_4CH_2$-	C_2H_5-	HBr	182-183
53	Cl-	o	2-CH_3O-C_6H_4-	C_2H_5-	HCl	203-205d
54	CN-	o	2-CH_3-C_6H_4-	C_2H_5-	HCl	215-219
55	C_6H_5-	o	C_6H_5-	C_2H_5-	-	123-125
56	C_6H_5-	o	2-COOH-C_6H_4-	C_2H_5-	HCl.$\frac{1}{2}H_2O$	213-214
57	C_6H_5-	o	$C_6H_5CH_2$-	C_2H_5-	-	130-131
59	$(CH_3)_2N$-	o	C_6H_5-	C_2H_5-	HCl	179-181
60	$(CH_3)_2N$-	o	2-CH_3-C_6H_4-	C_2H_5-	-	110-114
61	CN	o	C_6H_5-	C_2H_5-	-	194-196
62	CH_3O-	o	2-OH-C_6H_4-	C_2H_5-	-	229-231
63	CH_3O-	o	2-CH_3-C_6H_4-	H-	-	272(d)
64	CH_3O-	o	2-CH_3-C_6H_4-	H-	HCl	257
65	CH_3-	o	2-CH_3-C_6H_4-	C_2H_5-	HCl	162-164
66	CH_3O-	o	2-$(CH_3)_2CH$-C_6H_4-	C_2H_5-	-	136-138
67	Cl	o	2-CH_3-C_6H_4-	C_2H_5-	-	189-191
68	CH_3O-	o	2-CH_3-C_6H_4-	C_2H_5-	HCl	207-209
69	CH_3O-	o	2,3-$(CH_3)_2$-C_6H_3-	C_2H_5-	H_2SO_4	177-181
70	CH_3O-	o	2-NO_2-C_6H_4	C_2H_5-	-	180-182
71	CH_3O-	o	2-NO_2-C_6H_4-	C_2H_5-	C_2H_5OH	85-90
72	CH_3O-	o	2-CH_3-C_6H_4-	$(CH_3)_2$HC-	HCl.H_2O	140-143
73	CH_3O-	o	2-CH_3-C_6H_4-	$CH_3O(CH_2)_2$-	HCl	184-187
74	CH_3O-	o				
75	CH_3O-	o	2-CH_3-C_6H_4-	$(CH_3)_2N(CH_2)_2$-	-	100-103
76	CH_3O-	o	2-CH_3-C_6H_4-	$(CH_3)_2N(CH_2)_3$-	-	95-97.5
77	CH_3O-	o	2-CH_3-C_6H_4-	$(CH_3)_2N(CH_2)_2$-	fumarate	186-189
			2-CH_3-C_6H_4-	$(CH_3)_2N(CH_2)_3$-	.H_2O .HCl	177-180
78	CH_3O-	o	2-CH_3-C_6H_4-	C_2H_5-	$CH_3CH_2SO_2OH$	113-116
79	CH_3O-	o	2-CH_3-C_6H_4-	C_2H_5-	$HO\text{-}CH_2CH_2SO_2OH$	142-145

TABLE 1 (cont..)

EX.	R^1	n	R^4	R^2	R^3	Salt	M.P. °C
38	CH_3O-	1	5-CH_3O-	C_6H_5-	C_2H_5-	HCl.$\frac{1}{2}H_2O$	166-167
39	CH_3O-	1	5-CH_3O-	2-CH_3-C_6H_4	C_2H_5-	-	156-158d
43	CH_3O-	1	5-CH_3O-	2-CH_3O-C_6H_4-	C_2H_5-	2HCl	183-185d
44	CH_3O-	1	5-CH_3O-	2-CH_3S-C_6H_4-	C_2H_5-	$1.5H_3PO_4$	204-205
45	CH_3O-	1	5-CH_3O-	2-CH_3-C_6H_4-	C_2H_4-	-	167.5-169
58	CH_3-	1	6-CH_3-	C_6H_5-	C_2H_5-	-	164.5-165
40	-	1	7-CH_3O-	2-CH_3-C_6H_4	C_2H_5-	HCl	147-159d
41	-	1	6-CH_3O-	C_6H_5-	C_2H_5-	-	99.5-102.5
42	-	1	6-CH_3O-	2-CH_3-C_6H_4-	C_2H_5-	HCl	193d.

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TABLE 2

Analytical Data of Examples 1 to 79

Ex.	Empirical Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
1	$C_{20}H_{21}ClN_2O_3$	64.63	5.68	7.51	64.36	5.65	7.62
2	$C_{19}H_{18}N_2O_3$	70.79	5.63	8.69	70.91	5.65	8.77
3	$C_{20}N_{20}N_2O_3$	71.41	5.99	8.33	71.52	5.94	8.35
4	$C_{20}H_{22}N_2O_7S$	55.29	5.10	6.45	55.68	5.02	6.42
5	$C_{20}H_{23}N_2O_7P$	55.30	5.34	6.45	54.92	5.37	6.53
6	$C_{19}H_{19}ClN_2O_3$	63.60	5.34	7.81	63.25	5.33	7.69
7	$C_{20}H_{21}ClN_2O_4$	61.78	5.44	7.20	61.55	5.57	7.07
8	$C_{20}H_{21}ClN_2O_3S$	59.33	5.23	6.92	59.04	5.38	6.87
9	$C_{19}H_{18}Cl_2N_2O_3$	58.03	4.61	7.12	57.89	4.69	7.13
10	$C_{20}H_{18}ClN_3O_3$	62.59	4.73	10.95	62.23	4.95	10.73
11	$C_{20}H_{18}N_2O_3F_3Cl$	56.28	4.25	6.56	56.33	4.34	6.60
12	$C_{104}H_{112}Cl_5N_{15}O_{22}$	59.44	5.37	10.00	59.25	5.21	10.03
13	$C_{19}H_{18}N_2O_3FCl$	60.56	4.81	7.43	60.28	4.87	7.32
14	$C_{21}H_{21}N_2O_4Cl$	62.92	5.28	6.99	62.56	5.48	6.76
15	$C_{17}H_{23}N_2O_3Cl$	60.26	6.84	8.26	59.39	6.80	8.20
16	$C_{20}H_{23}N_2O_4Cl$	61.46	5.93	7.17	61.40	5.92	7.21
17	$C_{20}H_{23}N_2O_4Cl$	61.46	5.93	7.17	61.73	5.76	7.33
18	$C_{21}H_{22}N_2O_4$	68.84	6.05	7.65	68.61	6.04	7.51
19	$C_{21}H_{22}N_2O_3$	71.98	6.33	7.99	72.16	6.33	8.01
20	$C_{21}H_{23}BrN_2O_3$	58.48	5.37	6.49	58.48	5.41	6.52
21	$C_{21}H_{24}N_2O_4$	68.46	6.57	7.60	68.47	6.51	7.59
22	$C_{20}H_{20}N_2O_4ClBr$	51.35	4.31	5.99	51.27	4.30	6.04
23	$C_{20}H_{20}N_2O_3S$	65.20	5.47	7.60	65.18	5.48	7.66
24	$C_{21}H_{27}N_2O_8P$	54.08	5.84	6.01	54.32	5.58	6.23
25	$C_{21}H_{22}N_2O_5$	65.96	5.80	7.33	66.06	5.75	7.28
26	$C_{21}H_{23}N_2O_4Cl$	62.61	5.75	6.95	62.61	5.84	6.94
27	$C_{21}H_{22}N_2O_4$	68.84	6.05	7.65	68.94	6.06	7.68
28	$C_{21}H_{22}N_2O_3$	71.98	6.33	7.99	72.02	6.29	8.03
29	$C_{21}H_{28}N_2O_{11}P_2$	46.16	5.17	5.13	46.07	5.22	5.12
30	$C_{21}H_{24}N_2O_7S$	56.24	5.39	6.25	56.09	5.43	6.24
31	$C_{19}H_{16}N_2O_3Cl_2$	58.33	4.12	7.16	58.52	4.13	7.21
32	$C_{20}H_{19}N_3O_5$	62.99	5.02	11.02	63.02	5.08	11.03
33	$C_{44}H_{52}N_4O_7Cl_2$	64.46	6.39	6.83	64.09	6.22	6.96
34	$C_{21}H_{23}N_2O_3Cl$	65.20	5.99	7.24	65.25	6.01	7.26
35	$C_{21}H_{20}N_2O_3F_3Br$	51.97	4.15	5.77	52.22	4.14	5.89
36	$C_{21}H_{23}N_2O_4Cl$	62.61	5.75	6.95	62.67	5.76	7.05
37	$C_{21}H_{25}N_2O_7SP$	52.50	5.75	5.83	52.08	5.35	5.77
38	$C_{20}H_{21}ClN_2O_4$	60.37	5.57	7.04	60.22	5.55	7.05
39	$C_{21}H_{22}N_2O_4$	68.84	6.05	7.67	69.19	6.09	7.70
40	$C_{20}H_{21}N_2O_3Cl$	64.43	5.68	7.51	64.71	5.76	7.54
41	$C_{19}H_{18}N_2O_3$	70.79	5.63	8.69	70.96	5.66	8.62
42	$C_{20}H_{21}N_2O_3Cl$	64.43	5.68	7.51	64.40	9.67	7.62
43	$C_{21}H_{24}N_2O_4Cl_2$	57.41	5.50	6.38	57.02	5.79	6.25
44	$C_{42}H_{53}N_4O_{18}S_2P_3$	47.64	5.04	5.29	48.06	5.08	5.43
45	$C_{21}H_{22}N_2O_3$	71.98	6.33	7.99	72.32	6.35	8.02
46	$C_{20}H_{17}F_3N_2O_2$	64.17	4.58	7.48	64.16	4.62	7.49
47	$C_{20}H_{20}N_2O_2S$	68.16	5.72	7.95	68.19	5.76	8.14
48	$C_{20}H_{21}ClN_2O_3S$	59.33	5.23	6.92	59.55	5.32	6.86
49	$C_{20}H_{20}N_2O_2S_2$	62.47	5.24	7.29	62.16	5.16	7.12
50	$C_{20}H_{21}N_2O_2SCl$	61.77	5.44	7.20	61.84	5.41	7.31
51	$C_{20}H_{21}ClN_2O_3$	64.73	5.68	7.51	64.47	5.61	7.50
52	$C_{21}H_{23}BrN_2O_2$	60.73	5.58	6.93	60.76	5.60	6.82
53	$C_{19}H_{18}N_2O_3Cl_2$	58.03	4.61	7.12	57.97	4.65	7.11
54	$C_{20}H_{17}N_3O_2$	72.49	5.17	12.68	72.16	5.26	12.54
55	$C_{24}H_{20}N_2O_2$	78.24	5.47	7.60	78.22	5.47	7.50
56	$C_{50}H_{44}Cl_2N_4O_9$	65.57	4.84	6.11	66.04	5.00	6.09
57	$C_{25}H_{23}N_2O_2$	78.32	6.05	7.31	78.52	5.90	7.30
58	$C_{20}H_{20}N_2O_2$	74.98	6.71	8.74	75.22	6.37	8.77

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TABLE 2 (cont.)

Ex.	Empirical Formula	Calculated C	H	N	Found C	H	N
59	$C_{20}H_{22}N_3O_2Cl$	64.60	5.96	11.30	64.60	5.96	11.39
60	$C_{21}H_{23}N_3O_2$	72.18	6.63	12.03	72.24	6.57	12.09
61	$C_{19}H_{15}N_3O_2$	71.91	4.76	13.24	71.95	4.86	13.26
62	$C_{19}H_{18}N_2O_4$	67.45	5.36	8.78	67.49	5.38	8.50
63	$C_{18}H_{16}N_2O_3$	70.12	5.23	9.09	70.10	5.27	9.09
64	$C_{18}H_{17}N_2O_3Cl$	62.70	4.97	8.12	62.53	4.93	8.18
65	$C_{20}H_{21}ClN_2O_2$	67.32	5.93	7.85	67.22	5.92	7.83
66	$C_{22}H_{24}N_2O_3$	72.51	6.64	7.69	72.56	6.55	7.67
67	$C_{19}H_{17}N_2O_2Cl$	66.90	5.03	8.22	66.60	5.14	8.20
68	$C_{20}H_{20}N_2O_3Cl_2$	58.98	4.95	6.88	58.90	4.94	6.90
69	$C_{21}H_{24}N_2O_7S$	56.24	5.39	6.25	56.37	5.42	6.28
70	$C_{19}H_{17}N_3O_5$	62.12	4.66	11.44	62.05	4.66	11.54
71	$C_{23}H_{29}N_3O_{10}S$	51.20	5.42	7.79	51.20	5.36	8.01
72	$C_{21}H_{25}ClN_2O_4$	62.30	6.22	6.92	62.49	6.23	6.94
73	$C_{21}H_{23}ClN_2O_4$	62.61	5.75	6.95	62.72	5.76	7.04
74	$C_{22}H_{25}N_3O_3$	69.64	6.64	11.07	69.73	6.64	11.07
75	$C_{23}H_{27}N_3O_3$	70.21	6.92	10.68	70.42	6.95	10.67
76	$C_{28}H_{31}N_3O_9$	60.75	5.64	7.59	60.89	5.69	7.53
77	$C_{23}H_{31}Cl_2N_3O_4$	57.03	6.45	8.67	57.05	6.31	8.79
78	$C_{22}H_{26}N_2O_6S$	59.18	5.87	6.27	59.16	5.93	6.25
79	$C_{22}H_{26}N_2O_7S$	57.13	5.67	6.06	57.08	5.71	6.10

Pharmacology

The action of 4 - amino - 3 - quinolinecarboxylic acids and esters of this invention on gastric secretion was studied in rats and dogs. Inhibition of secretion was measured and expressed in terms of percent of gastric acid output. Anti-ulcer studies were also done in rats. The results of studies with a preferred compound of this invention are described below. Other compounds of this invention show qualitatively similar effects in one or more of these tests.

TABLE 3
Effect of compound of Example 1 on Stimulated Gastric Secretion

Species	Dose (μmoles/kg)	Route	Stimulating Agent	Inhibition[1] (%)
Rat[2]	0.3 - 8.1	IV	Histamine	43 - 96
Rat[2]	0.3 - 10.7	ID	Histamine	40 - 70
Rat[2]	0.3 - 8.1	IV	Tetragastrin	27 - 85
Rat[2]	0.9 - 8.1	IV	Tetragastrin	25 - 76
Dog[3]	2.7 and 8.1	IV	Food	50 and 83
Dog[3]	32.4	PO	Food	56

[1] Inhibition was measured as output of gastric acid.

[2] Rats were studied according to modification of the method of Ghosh and Shield, 1958, *Brit. J. Pharmacol. 13:*54-61.

[3] Dogs were Heidenhain pouch dogs.

The compound of Example 1 was administered to pyloric-ligated rats having no artifical stimulation of gastric secretion. The doses used were 33 to 134 μmoles/kg; acid output was inhibited by 38-55%.

The gastric anti-ulcer effects of the compound of Example 1 were examined in rats studied according to the method of Shay et al., 1945, *Gastroenterology 5:*43-61. Protection against ulceration of 4-90% was provided by doses of 12-198 μmoles/kg.

The effect of ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride (see Example 1) on histamine-induced gastric secretion was found to be over 43% more effective than ethyl 6 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate (see Example 42) at one half the dosage level.

Effective quantities of the foregoing compounds represented by Formula I may be administered to a living animal body for therpeutic purposes relating to the control of acid release due to histamine stimulation and peptic ulcer control or combatting peptic ulcers in mammals according to usual modes of administration for pharmaceuticals in usual forms such as orally in solution, emulsions, suspensions, pills, tablets, troches, lozenges, pellets, or capsules in pharmaceutically acceptable carriers; parenterally in the form of sterile solutions or mixtures.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Exemplary of liquid carriers are syrup, peanut oil,

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olive oil, arachis oil, water or any parenterally acceptable liquid.

Although very small quantities of the active materials of the present invention are effective when minor therapy for gastric irritation is involved or in cases of administration to subjects having a low body weight, unit dosages will usually contain the active ingredient in an amount to supply 2 to 6 mg/kg to the host. Unit dosages may vary from 100 to 500 mg active agent, preferably for an adult human from 200 to 500 mg. The active ingredient will preferably be administered in equal doses one to four times per day. The daily dosage regimen will vary from about 100 to 1200 mg, most preferably from about 300 to 900 mg/day. It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of the physical or veterinarian.

The following formulations are representative:

Example 80

Capsules

Ingredients	*Amount, mg.*
Active ingredient, e.g. Example 1 = Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride	200
Sucrose	100
Starch	30
Talc	5
Stearic Acid	3
	338

Blend and fill into gelatin capsules.

Example 81

Tablets

Ingredients	*Amount mg. per tablet*
Active ingredient, e.g. Example 1 = Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride	350.0
Alginic acid	20.0
Calcium and ammonium alginate	40.0
Starch	54.0
Lactose	75.0
Magnesium stearate	2.2
	721.2

All the ingredients of the mixture, except the magnesium stearate and one half of the calcium ammonium alginate, are blended and granulated with ethanol and passed through a number eight mesh screen and the mixture dried for 16 hours at 140°F. The dried granulated material is then blended thoroughly with the remainder of the calcium ammonium alginate and magnesium stearate and tableted.

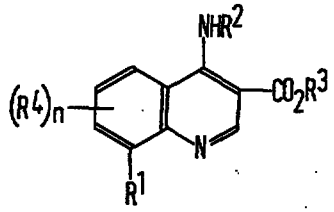
Example 82

Intravenous Injection

Ingredients	*Amount, mg.*
Active ingredient, e.g. Example 1 = Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylate hydrochloride	200
Water	2,000
Preservative, e.g. chlorobutanol	20
	2,200

CLAIMS

1. A compound having the formula:



wherein:

R^1 represents a halogen atom or a loweralkyl, phenyl, O-loweralkyl, S-loweralkyl, trifluoromethyl, cyano or dialkylamino group,

R^2 represents a loweralkyl, phenyl, or phenyl - loweralkyl group or a phenyl group substituted by one to three radicals taken from among loweralkyl, O-loweralkyl, S-loweralkyl, cyano, hydroxy, carbamoyl, carboxy, acetyl, trifluoromethyl and nitro groups or halogen atoms,

R^3 represents a hydrogen atom or a loweralkyl, dimethylamino - loweralkyl, loweralkoxy - loweralkyl, or allyl group,

R^4 represents a halogen atom or a loweralkyl, phenyl, O-loweralkyl, S-loweralkyl, trifluoromethyl, cyano or dialkylamino group, and

n is 0 or 1, and

the pharmaceutically acceptable addition salts, alcoholates and hydrates thereof.

2. A compound as claimed in Claim 1, in which R^1 represents a methoxy group.

3. A compound as claimed in Claim 1, in which R^1 represents an ethoxy group.

4. A compound as claimed in Claim 1, in which R^1 represents a trifluoromethyl, methylthio, methyl, chloro, cyano, phenyl or dimethylamino group.

5. A compound as claimed in Claim 2, 3 or 4, in which n is 0.

6. A compound as claimed in any one of Claims 1 to 4, in which n is 1 and R^4 is a methoxy group, or a methyl group in the 5 or 6 position.

7. A compound as claimed in any one of Claims 1 to 6, in which R^3 represents an ethyl group.

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olive oil, arachis oil, water or any parenterally acceptable liquid.

Although very small quantities of the active materials of the present invention are effective when minor therapy for gastric irritation is involved or in cases of administration to subjects having a low body weight, unit dosages will usually contain the active ingredient in an amount to supply 2 to 6 mg/kg to the host. Unit dosages may vary from 100 to 500 mg active agent, preferably for an adult human from 200 to 500 mg. The active ingredient will preferably be administered in equal doses one to four times per day. The daily dosage regimen will vary from about 100 to 1200 mg, most preferably from about 300 to 900 mg/day. It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of the physical or veterinarian.

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	721.2

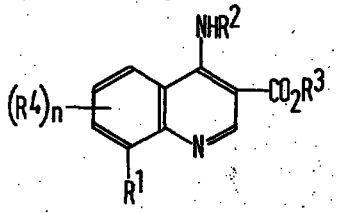
All the ingredients of the mixture, except the magnesium stearate and one half of the calcium ammonium alginate, are blended and granulated with ethanol and passed through a number eight mesh screen and the mixture dried for 16 hours at 140°F. The dried granulated material is then blended thoroughly with the remainder of the calcium ammonium alginate and magnesium stearate and tableted.

Example 82
Intravenous Injection

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Water	2,000
Preservative, e.g. chlorobutanol	20
	2,200

CLAIMS

1. A compound having the formula:



wherein:

R^1 represents a halogen atom or a loweralkyl, phenyl, O-loweralkyl, S-loweralkyl, trifluoromethyl, cyano or dialkylamino group,

R^2 represents a loweralkyl, phenyl, or phenyl - loweralkyl group or a phenyl group substituted by one to three radicals taken from among loweralkyl, O-loweralkyl, S-loweralkyl, cyano, hydroxy, carbamoyl, carboxy, acetyl, trifluoromethyl and nitro groups or halogen atoms,

R^3 represents a hydrogen atom or a loweralkyl, dimethylamino - loweralkyl, loweralkoxy - loweralkyl, or allyl group,

R^4 represents a halogen atom or a loweralkyl, phenyl, O-loweralkyl, S-loweralkyl, trifluoromethyl, cyano or dialkylamino group, and

n is 0 or 1, and

the pharmaceutically acceptable addition salts, alcoholates and hydrates thereof.

2. A compound as claimed in Claim 1, in which R^1 represents a methoxy group.

3. A compound as claimed in Claim 1, in which R^1 represents an ethoxy group.

4. A compound as claimed in Claim 1, in which R^1 represents a trifluoromethyl, methylthio, methyl, chloro, cyano, phenyl or dimethylamino group.

5. A compound as claimed in Claim 2, 3 or 4, in which n is 0.

6. A compound as claimed in any one of Claims 1 to 4, in which n is 1 and R^4 is a methoxy group, or a methyl group in the 5 or 6 position.

7. A compound as claimed in any one of Claims 1 to 6, in which R^3 represents an ethyl group.

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8. A compound as claimed in any one of Claims 1 to 6, in which R^3 represents a dimethylamino ethyl or dimethyl amino propyl group.

9. A compound as claimed in any one of Claims 1 to 6, in which R^3 represents a methylethyl, methoxyethyl or allyl group.

10. A compound as claimed in any one of Claims 1 to 9, in which R^2 represents a 2 - methylphenyl group.

11. A compound as claimed in any one of Claims 1 to 9, in which R^2 represents a phenyl group.

12. A compound as claimed in any one of Claims 1 to 9, in which R^2 represents a phenyl group substituted in the 2 position by a methyl, methoxy, methylthio, chloro, cyano, trifluoromethyl, aminocarbonyl, fluoro, acetyl, ethoxy, ethyl, carboxy, hydroxy, 1 - methylethyl, or nitro group.

13. A compound as claimed in any one of Claims 1 to 9, in which R^2 represents a methylphenyl methyl group, a benzyl group, or a 2,3 - dimethylphenyl group.

14. Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate.

15. Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride.

16. Ethyl 8 - methoxy - 4 - [(2 - methoxyphenyl) amino] - 3 - quinolinecarboxylate.

17. Ethyl 8 - methoxy - 4 - [(2 - methoxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride.

18. Ethyl 8 - methoxy - 4 - [(2 - methylthiophenyl) - amino] - 3 - quinolinecarboxylate.

19. Ethyl 8 - methoxy - 4 - [(2 - methylthiophenyl) - amino] - 3 - quinolinecarboxylate hydrochloride.

20. Ethyl 8 - methoxy - 4 - [(2 - trifluoromethylphenyl) amino] - 3 - quinolinecarboxylate.

21. Ethyl 8 - methoxy - 4 - [(2 - trifluoromethylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride.

22. Ethyl 8 - methoxy - 4 - [(2 - ethoxyphenyl) amino] - 3 - quinolinecarboxylate.

23. Ethyl 8 - methoxy - 4 - [(2 - ethoxyphenyl) amino] - 3 - quinolinecarboxylate hydrochloride.

24. Ethyl 8 - methoxy - 4 - [(2 - ethylphenyl) amino] - 3 - quinolinecarboxylate.

25. Ethyl 8 - methoxy - 4 - [(2 - ethylphenyl) amino] - 3 - quinolinecarboxylate phosphate (1:2).

26. Ethyl 8 - methoxy - 4 - [(2, 6 - dichlorophenyl) - amino] - 3 - quinolinecarboxylate.

27. Ethyl 8 - ethoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate.

28. Ethyl 8 - ethoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate hydrochloride.

29. Ethyl 8 - ethoxy - 4 - [(2 - methoxyphenyl) - amino] - 3 - quinolinecarboxylate.

30. Ethyl 8 - ethoxy - 4 - [(2 - methoxyphenyl) - amino] - 3 - quinolinecarboxylate hydrochloride.

31. Ethyl 8 - methoxy - 4 - [(2 - methoxyphenyl) - amino] - 5 - methyl - 3 - quinolinecarboxylate.

32. Ethyl 8 - methoxy - 4 - [(2 - methoxyphenyl) - amino] - 5 - methyl - 3 - quinolinecarboxylate dihydrochloride.

33. Ethyl 8 - methyl - 4 - [(2 - methoxyphenyl) - amino] - 3 - quinolinecarboxylate.

34. Ethyl 8 - methyl - 4 - [(2 - methoxyphenyl) - amino] - 3 - quinolinecarboxylate hydrochloride.

35. Ethyl 8 - methyl - 4 - [(2 methylphenyl) - amino] - 3 - quoinlinecarboxylate, monohydrochloride.

36. Ethyl 8 - methoxy - 4 - {[2 - (1 - methylethyl) - phenyl] amino} - 3 - quinolinecarboxylate.

37. Ethyl 8 - chloro - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylate.

38. Ethyl 8 - methoxy - 4 - [(2 - chloro - 6 - methylphenyl) amino] - 3 - quinolinecarboxylate, monohydrochloride.

39. Ethyl 8 - methoxy - 4 - [(2, 3 - dimethylphenyl) - amino] - 3 - quinolinecarboxylate, monosulphate.

40. 1 - Methylethyl 8 - methoxy - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate, monohydrochloride, monohydrate.

41. Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylate, ethanesulphonate (1:1) (salt).

42. Ethyl 8 - methoxy - 4 - [(2 - methylphenyl) - amino] - 3 - quinolinecarboxylate, 2 - hydroxyethane sulphonate (1:1) (salt).

43. Ethyl 8 - methoxy - 4 - [(2, 6 - dimethylphenyl) - amino] - 3 - quinolinecarboxylate.

44. Ethyl 8 - methoxy - 4 - [(2, 6 - dimethylphenyl) - amino] - 3 - quinolinecarboxylate hydrobromide.

45. Ethyl 8 - dimethylamino - 4 - [(2 - methylphenyl) amino] - 3 - quinolinecarboxylate.

46. A pharmaceutical composition for inhibiting secretion of gastric acid and/or treating peptic ulcers in mammals comprising a pharmaceutical carrier and an effective amount of a compound as claimed in any one of Claims 1 to 45.

47. A pharmaceutical composition as claimed in Claim 46, substantially as specficially described herein with reference to Example 80, 81 or 82.

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