

PATENT SPECIFICATION

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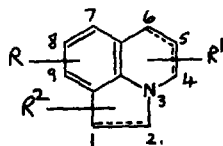


(54) PYRROLO-QUINOLINE AND PYRIDO-QUINOLINE DERIVATIVES

(71) We, PFIZER LIMITED, a British Company of Ramsgate Road, Sandwich, Kent, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This application relates to novel pyrrolo-quinolines and pyrido-quinolines which are useful in the treatment or control of plant diseases, particularly the treatment or control of fungal and/or bacterial diseases of the rice plant. It is a divisional of our copending patent application No. 23158/72 (Serial No. 1,394,373) which describes and claims methods and compositions for the treatment or control of plant diseases using a class of compounds which includes the novel compounds of this invention.

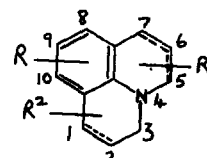
According to the invention, there are provided novel pyrrolo-[3, 2, 1-i, j]-quinolines of the formula:



where R is a lower alkyl, lower alkoxy, lower alkanoyl, benzoyl, hydroxy, lower alkanoyloxy, or cyano group or represents one or two halogen atoms, R¹ and R² each independently represent hydrogen or one or more halogen, lower alkyl, phenyl, oxo or thioxo substituents in the pyrido and pyrrolo rings respectively, and the dotted lines represent an optional bond in each such ring.

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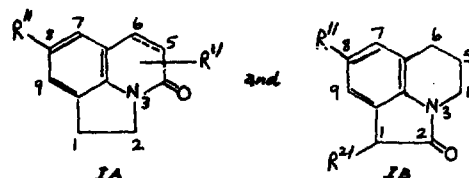
Also according to the invention, there are provided novel pyrido-[3, 2, 1-i, j]-quinolines of the formula:



where R is as previously defined other than 9-chloro, R¹ and R² each represent hydrogen or substituents (as previously defined) in the respective pyrido rings and the dotted lines represent an optional bond in each such ring.

Also included in the invention are the non-phytotoxic acid addition salts of those compounds which form acid addition salts.

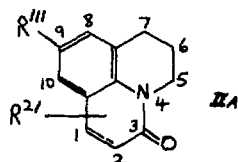
One class of preferred novel compounds of the invention are those of the formula I, in which either R¹ or R² includes a single oxo [=O] or thioxo [=S] group in a position adjacent to the ring nitrogen atom, and R is halogen or a lower alkyl, lower alkoxy or lower alkanoyl group in the 8- position. Particularly preferred compounds of this class are those of the formulae:



where R'' is halogen or a lower alkyl, lower alkoxy or lower alkanoyl group, and R¹ and

R^{2'} are each hydrogen or one or more lower alkyl groups.

Another class of preferred novel compounds of the invention are those of the formula II in which R is a lower alkyl, lower alkoxy or lower alkanoyl in the 9- position. Particularly preferred compounds of this class are those of the formula:



where R''' is a lower alkyl, lower alkoxy or lower alkanoyl group, and R^{2'} is hydrogen or represents one or more lower alkyl groups or a 1-oxo group and an optional 2-phenyl or 2-lower alkyl group.

In this specification, "lower" when applied to an alkyl, alkoxy, alkanoyl or alkanoyloxy group means that such a group contains up to four carbon atoms. Thus, when R, R'' or R''' in formulae I to IIA, or R¹, R^{1'}, R² or R^{2'} in formulae I to IIA, is or includes a lower alkyl group, that group may be a methyl, ethyl, *n*-propyl, *isopropyl*, *n*-butyl, *iso*-butyl, *sec*-butyl or *tert*-butyl group, and when R, R'' or R''' in formulae I to IIA is a lower alkoxy group it may be a methoxy group or any other alkoxy group containing up to four carbon atoms. When R, R'' or R''' in formulae I to IIA is a lower alkanoyl or alkanoyloxy group it may be a formyl, acetyl, propionyl, butyryl, or isobutyryl group or a corresponding acyloxy group.

Compounds of the formulae I to IIA which form acid addition salts include those in which there is no oxo or thioxo group adjacent to the ring nitrogen atom, but are not limited to such compounds. Non-phytotoxic acid addition salts are those which are formed with acids having non-phytotoxic anions, for example, the hydrochloride, hydrobromide, phosphate, nitrate, sulfate, acetate, β,β -dimethylbutyrate, citrate, gluconate, benzoate, propionate, butyrate, sulfo-salicylate, maleate, laurate, malate, fumarate, succinate, oxalate, tartrate, amsonate (4,4'-diamino-stilbene-2,2'-disulfonate), pamoate, (1,1'-methylene-bis-2-hydroxy-3-naphthoate), stearate, 2-hydroxy-3-naphthoate and *p*-toluene-sulfonate salts.

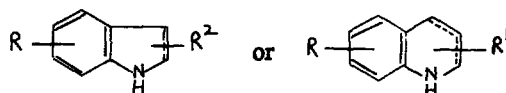
Also provided by the invention are the novel compounds lilolidine-2-thione, lilolidine-4-thione, julolidine-3-thione, 8-acetyl-4-lilolidone, and 8-benzoyl-2-lilolidone.

The compounds of the invention may be used as described in the parent application No. 23158/72 (Serial No. 1,394,373) to treat or control fungal and/or bacterial diseases of plants, particularly diseases of the rice plant, including the fungal diseases known as rice blast (caused by *Piricularia oryzae*) and leaf

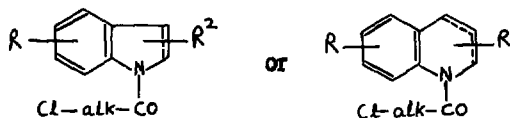
blight (caused by *Xanthomonas oryzae*), and the bacterial disease known as sheath blight (caused by *Corticium sasakii*). Other plants, for which the compounds of the invention may be used to treat or control fungal or bacterial disease, include tomato and cucumber plants.

The novel compounds of the invention may be prepared by a number of methods, including the following:—

(1) An indole or quinoline compound of the formula:

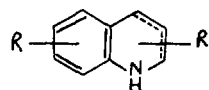


where R, R¹ and R² are as previously defined, with the provisos that R cannot be a substituent in the 7- position of the indole ring or the 8- position of the quinoline ring and cannot be a substituent of such a nature as to de-activate that position or be an acylatable group, and R¹ or R² does not include an oxo or thioxo substituent, may be reacted with a chloro-substituted acid chloride of the formula Cl-alk-COCl, in which "alk" is a methylene, ethylene or vinylene group which may be substituted with one or more lower alkyl or phenyl groups, in the presence of a base, e.g. trimethylamine, to form a compound of the formula:

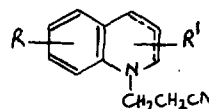


which is then cyclised in the presence of aluminium chloride to form a compound of the formula I or II, in which, respectively, R² and R¹ do not include an oxo or thioxo substituent, but the ring formed by cyclisation includes an oxo substituent adjacent to the ring nitrogen atom and may also include one or more lower alkyl or phenyl substituents. If in this method R includes an alkoxy group, such group is converted under the conditions of cyclisation to a hydroxyl group.

(2) A quinoline compound of the formula:

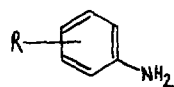


where R and R¹ are as defined for method (1), may be reacted with acrylonitrile or a β -halopropionitrile of the formula XCH₂CH₂CN (in which X is halogen) to form a compound of the formula:

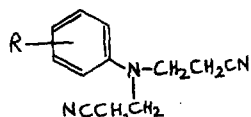


which is hydrolysed to convert the nitrile group to a carboxy group and then cyclised in the presence of a dehydrating agent, e.g. phosphoric anhydride, to form a compound of formula II in which R^2 is 1-oxo and R^1 does not include an oxo or thioxo substituent.

(3) An aniline derivative of the formula:

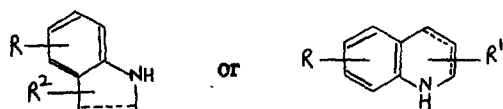


where R is as previously defined, with the provisos that it cannot be a substituent in the 2- or 6- position of the benzene ring and cannot be a substituent of such a nature as to deactivate either of these positions or be an acylatable group, may be reacted with 2 moles of acrylonitrile or a β -halo-propionitrile as defined in method (2) to form a compound of the formula:

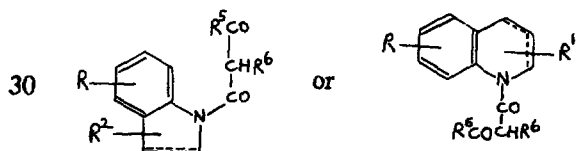


which is then hydrolysed and cyclised as in method (2) to form a compound of formula II in which R^1 is 7-oxo and R^2 is 1-oxo.

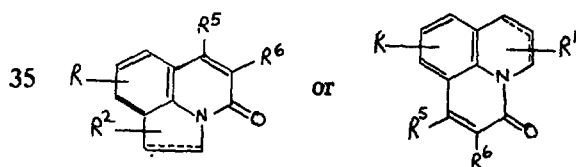
(4) A compound of the formula:



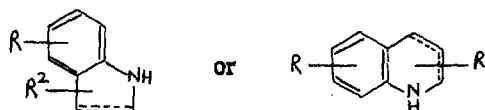
where R , R^1 and R^2 are as defined for method (1) may be reacted with an ester of the formula $R^5\text{COCHR}^6\text{COOC}_2\text{H}_5$, in which R^5 is a lower alkyl or phenyl group and R^6 is hydrogen or a lower alkyl group, to form a compound of the formula:



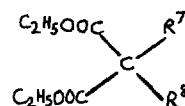
which is then cyclised in the presence of a dehydrating agent, e.g. concentrated sulphuric acid or polyphosphoric acid, to form a compound of the formula:



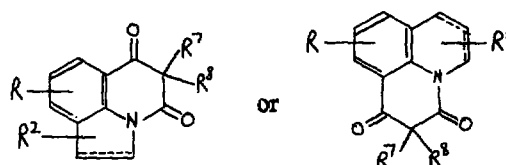
(5) A compound of the formula:



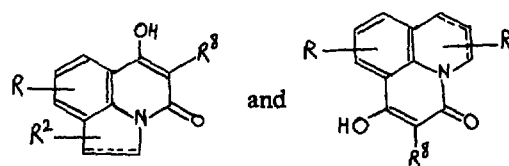
where R , R^1 and R^2 are as defined for methods (1), (2) or (3), is reacted with a malonic acid ester of the formula:



in which R^7 and R^8 are each hydrogen or a lower alkyl or phenyl group, to form a compound of the formula:



which, in the case where R^7 is hydrogen, are tautomeric with the formulae:



respectively

(6) A compound of the formula I or II, in which R^1 and/or R^2 includes one or more oxo substituents, may be reduced with lithium aluminium hydride to replace the oxo substituent(s) with hydrogen.

(7) A compound of the formula I or II, in which R^1 and/or R^2 includes one or more oxo substituents, may be treated with diphosphorus pentasulphide to replace the oxo substituent (2) with sulphur.

(8) A compound of formula I or II, in which the pyrido and/or pyrrolo rings include an unsaturated group, may be converted to the corresponding saturated compounds by catalytic hydrogenation, which may also result in replacement of halogen substituents by hydrogen.

(9) A compound of the formula I or II, but in which R is hydrogen, may be converted to a compound of the same formula in which R is halogen, alkyl, alkanoyl or benzoyl, by well known techniques of nuclear aromatic halogenation, alkylation or acylation, respectively, and R may then be converted to other groups by well-known reaction sequences, including (for example) replacement of halogen by cyano.

Aromatic halogenation, e.g. chlorination with gaseous chloride or with dichlorourethane, may also result in the introduction of halogen into R^1 and R^2 , especially at positions adjacent to any oxo group(s). Such halogen may subsequently be removed, if not required, by selective reduction to replace it by hydrogen, converted to other groups, e.g. to an oxo group by hydrolysis of a gem-dihalo group, or replaced by phenyl by Friedel-Crafts reaction with benzene.

(10) A compound of the formula I or II in which R includes one or more hydroxyl groups, may be converted to lower aliphatic acyl esters thereof by conventional esterification techniques.

(11) Compounds of the formula I or II, in which R^1 or R^2 includes one or more halogen substituents, may also be formed from the corresponding hydroxy compounds by conventional methods for the conversion of alcohols to halides, e.g. treatment with phosphorus or thionyl halides. The hydroxy compound starting materials may, for example, be the enolic forms of β -diketones, i.e. compounds in which R^1 or R^2 includes two oxo substituents separated by a methylene group, which may be substituted by an alkyl or phenyl group.

(12) Non-phytotoxic acid addition salts of any compound of the formula I or II, which is sufficiently basic to form such salts, may be formed by conventional methods, e.g. by dissolving the compound in a suitable solvent and adding the appropriate acid, either in a solvent also, or as the acid itself if liquid or gaseous, to precipitate the required salt.

The invention is illustrated by the following Examples, in which temperatures are given in $^{\circ}\text{C}$.

Example 1.

(A) To a stirred solution of 6-methyl-1,2,3,4-tetrahydroquinoline (7.4 g) in dry benzene (120 ml.) containing triethylamine (8.4 ml.) was added over a period of $\frac{1}{2}$ hour chloroacetyl chloride (6.0 g, 4.3 ml.). Stirring was continued for a further 2 hours, after which the precipitate of triethylamine hydrochloride was filtered off and the benzene filtrate was washed in turn with 2N hydrochloric acid (100 ml.) and water (2×100 ml.). The benzene solution was then dried over anhydrous magnesium sulphate and evapo-

rated *in vacuo* to afford a gum (9.5 g), most of which was used directly in the next stage (B).

A portion (3.5 g) of the aforementioned gum was purified by passage through a silica column using chloroform as the eluent, and the chloroform solution was evaporated *in vacuo* to an oil which eventually solidified. A sample was recrystallised from petroleum ether (b.p. $40-60^{\circ}$) to yield a solid, m.p. $58-60^{\circ}$, shown by standard analytical techniques to be 1-chloroacetyl-6-methyl-1,2,3,4-tetrahydroquinoline.

Analysis:

Found:

C, 64.09; H, 6.26; N, 6.22%

Calculated for $\text{C}_{12}\text{H}_{14}\text{NOCl}$:

C, 64.46; H, 6.27; N, 6.27%

(B) The gummy product of the previous stage (6.0 g) and finely powdered anhydrous aluminium chloride (5.0 g) were mixed at room temperature, whereupon the temperature of the mixture rose to about 130° . The mixture was then warmed in an oil bath at 140° for 30 minutes (during which time the temperature within the mixture rose to 170°) and thereafter poured while still hot onto a mixture of ice and hydrochloric acid. Extraction of the aqueous solution with chloroform (2×50 ml.) was followed by washing the organic solution with water and drying over anhydrous magnesium sulphate. Evaporation of the chloroform layer *in vacuo* afforded an oil (3.7 g) which solidified. The crude solid product was recrystallised from petroleum ether (b.p. $60-80^{\circ}$) to yield 1.6 g of 8-methyl-1,2,5,6-tetrahydro-4H-pyrrolo-(3,2,1-*i,j*)-quinoline-2-one, m.p. $115-7^{\circ}$.

Analysis:

Found:

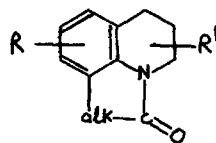
C, 77.01; H, 6.93; N, 7.47%

Calculated for $\text{C}_{12}\text{H}_{13}\text{NO}$:

C, 77.01; H, 6.95; N, 7.49%

Examples 2 and 3

By procedures similar to that described in Examples 1, the following novel compounds were prepared starting from the appropriate substituted 1,2,3,4-tetrahydroquinoline and chloroacetyl chloride.



Example	R	R¹	alk	m.p. °C	Analysis (theoretical in brackets)		
					C%	H%	N%
2	9-CH ₃	H	-CH ₂ -CH ₂ -	63-5°	77.32 (77.58)	7.46 7.57	6.62 6.96
3	8-CH ₃	1-H	-CH- Ph	80-81°	82.22 (82.20)	6.52 6.47	5.66 5.33

Example 4.

Chlorine was passed into a solution of 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (5.0 g) in chloroform (50 ml.) for a period of 20 minutes, and the resultant pale orange solution was then concentrated by evaporation *in vacuo* to an oil. A small sample was crystallised by trituration in petroleum ether, and the crystals were used as seeds to bring about total crystallisation of the oil. The crystalline solid was recrystallised from a mixture of benzene and petroleum ether, yielding 1,1,8 - trichloro - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinoline - 2 - one, m.p. 148-9°.

Analysis:

Found:

C, 47.30; H, 2.76; N 5.03%

Calculated for C₁₁H₈Cl₃NO:

C, 47.70; H, 2.90; N, 5.07%

Example 5.

1,2,5,6 - Tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (5 g) was dissolved in 80% acetic acid and dichloroethane (4.5 g, 5.5 ml.) was added whereupon the temperature of the solution was observed to rise to about 60°. The solution was stirred for 4 hours after which water (10 ml.) was added, resulting after a few minutes in the precipitation of a white powder. The latter was collected by filtration and recrystallised in turn from glacial acetic acid and a mixture of benzene and petroleum ether, yielding what was believed from infra-red and nuclear magnetic resonance spectroscopic evidence to be 1,1,7,8 - tetrachloro - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one, m.p. 167-170°.

Analysis:

Found:

C, 43.29; H, 2.61; N, 4.66%

Calculated for C₁₁H₇Cl₄NO:

C, 42.50; H, 2.27; N, 4.51%

Example 6.

To a solution of 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 4 - one (1.0 g) in carbon tetrachloride (20 ml.) was added a solution of bromine (0.35 ml.) in the same solvent (5 ml.). After a few minutes a solid separated, and this was filtered off and recrystallised from a mixture of water and methanol to afford 0.75 g of 8 - bromo - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 4 - one, m.p. 107-9°.

Analysis:

Found:

C, 52.36; H, 4.00; N, 5.66%

Calculated for C₁₁H₁₀BrNO:

C, 52.40; H, 4.00; N, 5.56%

Example 7.

A solution of 1,2,5,6 - tetrahydro - 4H - pyrrolo [3,2,1 - i, j] - quinolin - 2 - one (50 g) and bromine (1.5 ml.) in chloroform (15 ml.) was warmed to 45° and maintained at that temperature. Within 5 minutes a precipitate had formed and this was collected by filtration and recrystallised from 75% aqueous acetic acid solution, yielding 8 - bromo - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one, m.p. 125-6°.

Analysis:

Found:

C, 53.09; H, 4.02; N, 5.59%

Calculated for C₁₁H₁₀BrNO:

C, 52.30; H, 3.99; N, 5.56%

Example 8.

A solution of bromine in chloroform (1 ml. taken from 5.52 ml. in 10 ml.) was slowly added to a solution of 1 - phenyl - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (2.49 g) in chloroform (50 ml.) whereupon an exothermic reaction ensued with evolution of hydrogen bromide. The mixture was warmed for ½ hour on a steam bath after which the solution was evapo-

- rated to dryness *in vacuo* and a portion of the solid was submitted to nuclear magnetic resonance spectroscopy. The evidence suggested incomplete reaction, and so more bromine in chloroform solution was added to a solution of the residue in chloroform with warming and the reaction allowed to continue for a further short period of time.
- The solution was evaporated *in vacuo* and the solid residue recrystallised from a mixture of cyclohexane and petroleum ether, affording 1,8 - dibromo - 1 - phenyl - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one, m.p. 119.5—120.5°.
- Analysis:
Found:
C, 51.04; H, 3.50; N, 3.41%
Calculated for $C_{12}H_{11}NOBr_2$:
C, 50.15; H, 3.22; N, 3.44%
- Example 9.
By a procedure similar to that described in Example 8, 1, 8 - dibromo - 1 - methyl - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one, m.p. 138—9°, was prepared by bromination of 1 - methyl 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one.
- Analysis:
Found:
C, 42.14; H, 3.58; N, 4.00%
Calculated for $C_{12}H_{11}NOBr_2$:
C, 41.77; H, 3.21; N, 4.06%
- Example 10
To a solution of 1,2,5,6 - tetrahydro 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (10 g) in chloroform (30 ml.) was added bromine (3.1 ml.), after which the solution was allowed to stand at room temperature. Within a few minutes a precipitate had formed, and this was filtered off, washed with chloroform and dried, the yield of 8 - bromo - compound being 10 g.
- The 8 - bromo - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (10 g) was suspended in chloroform and chlorine was bubbled into the suspension, whereupon dissolution rapidly occurred. Chlorine passage was continued for about 20 minutes after which the solution was evaporated *in vacuo* and the resulting gummy solid was triturated in petroleum ether. Recrystallisation of the resultant solid afforded 8 - bromo - 1,1 - dichloro - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one, buff coloured crystals, m.p. 149—150°.
- Analysis:
Found:
C, 40.96; H, 2.57; N, 4.32%
Calculated for $C_{11}H_8BrCl_2NO$:
C, 41.10; H, 2.51; N, 4.36%
- Example 11.
A mixture of 1,2,5,6 - tetrahydro - 4H - pyrrolo[3,2,1 - i, j] - quinolin - 4 - one (1.0g), propionic acid (1.0 ml.) and polyphosphoric acid (phosphorus pentoxide content 82—5%. 80 g) was heated on a steam bath for 3 hours and then poured while still hot into water. The mixture was then stirred until appearing homogeneous and extracted with diethyl ether (2 x 100 ml.), the ethereal layer then being separated, washed with water, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to dryness.
- Crystallisation of the resultant solid from ethanol afforded 0.45 g of 8 - propionyl - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 4 - one, m.p. 144—7°.
- Analysis:
Found:
C, 73.34; H, 6.59; N, 6.11%
Calculated for $C_{14}H_{13}NO_2$:
C, 73.67; H, 6.47; N, 5.89%
- Examples 12 to 18
By procedures similar to that described in Example 11, the compounds of Examples 12 to 17 were prepared by acylations with appropriate carboxylic acids of appropriately substituted or unsubstituted 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolinones in the presence of polyphosphoric acid. The compound of Example 18 was prepared by the benzylation of 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one under similar dehydrating conditions.



Example	Formula	alk	R'	m.p. °C	Analysis (theoretical in brackets) C% H% N%		
12	IV	-CH- CH ₃	C ₂ H ₅ CO-	115-6°	73.00 (72.73)	7.06 7.12	5.56 5.65 (based on C ₁₅ H ₁₇ NO ₂ ·½H ₂ O)
13	IV	-CH- CH ₃	CH ₃ (CH ₂) ₂ CO-	102-4°	74.52 (74.68)	7.40 7.44	5.69 5.44
14	IV	-CH ₂ -	CH ₃ CO-	154-6°	72.33 (72.50)	6.14 6.05	6.46 6.52
15	IV	-CH ₂ -	C ₂ H ₅ CO-	169-170°	73.99 (73.34)	6.26 6.59	5.86 6.11
16	III	-CH ₂ -CH ₂ -	CH ₃ CO-	97-100°	71.77 (72.50)	6.07 6.05	5.87 6.52
17	IV	-CH- CH ₃	CH ₃ CO-	113-5°	73.46 (73.34)	6.68 6.59	6.10 6.11
18	IV	-CH ₂ -	C ₆ H ₅ CO-	127-130°	77.17 (76.96)	5.31 5.70	5.24 5.28

Example 19

To a suspension of 1,1,8 - trichloro - 1,2,5,6-tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (prepared as in Example 4) (2.0 g) in 50% aqueous methanol (100 ml.) contained in a bomb was added anhydrous sodium acetate (0.5 g). The suspension was heated for 24 hours at 100°. The resulting dark red solution containing a little undissolved material was freed of the latter by filtration and concentrated by evaporation *in vacuo*. A solid precipitate was collected by filtration and recrystallised from a mixture of benzene and petroleum ether, affording deep red crystals of 8 - chloro - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 1,2 - dione, m.p. 185°.

Analysis:

Found:

C, 59.7; H, 3.66; N, 6.17%
Calculated for $C_{11}H_8ClNO_2$:
C, 59.45; H, 3.64; N, 6.32%

Example 20.

By a procedure similar to that described in the previous Example, 8 - bromo - 1,1 - dichloro - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (prepared as in Example 10) was hydrolysed and yielded 8 - bromo 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 1,2 - dione, as dark red crystals, m.p. 185—7°.

Analysis:

Found:

C, 49.90; H, 3.10; N, 5.42%
Calculated for $C_{11}H_8BrNO_2$:
C, 49.60; H, 3.30; N, 5.27%

Example 21.

To a stirred suspension of 1,1,8 trichloro-1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (prepared as in Example 4) (5 g) in acetic acid (100 ml.) was added zinc dust (5 g) at such a rate as to keep the temperature of the mixture below 50°.

After complete addition of zinc, the mixture was refluxed with stirring for 5 hours. The supernatant liquid was decanted into water whereupon a solid precipitated. The precipitate was collected by filtration, recrystallised from cyclohexane and dried *in vacuo*, yielding 2g of 8 - chloro - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] quinolin - 2 - one, m.p. 120—2°.

Analysis:

Found:

C, 63.60; H, 5.13; N, 6.74%
Calculated for $C_{11}H_{10}ClNO$:
C, 63.70; H, 4.88; N, 6.75%

Example 22.

To a solution of 1,1,8 - trichloro - 1,2,5,6-tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (prepared as in Example 4) (4.5 g) in dry benzene (100 ml.) was added aluminium chloride (4.3 g) and the mixture was then heated, gently at first, to reflux whereafter refluxing was continued for 2 hours. Throughout this period hydrogen chloride was evolved.

The mixture was then allowed to cool to room temperature, poured into water and resultant solid filtered, washed with diethyl ether and crystallised from benzene, affording crystals, m.p. 265—7°. A second crop of crystals was produced on addition of petroleum ether to the benzene filtrate, and this was collected by filtration. Both crops were seen to be pure from thin layer chromatography evidence and so were combined, and constituted the total yield of 8 - chloro - 1,1 - diphenyl-1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one.

Analysis:

Found:

C, 76.53; H, 5.39; N, 3.45%
Calculated for $C_{23}H_{18}ClNO$:
C, 76.80; H, 5.04; N, 3.89%

Example 23.

A mixture of 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one (1.73 g), tert-butyl chloride (5 ml.) and aluminium chloride (5 g) was heated at about 60° for 2 hours, at the end of which period the whole had virtually solidified. It was then added to water and the suspension was extracted with chloroform, the chloroform solution then being separated, dried over anhydrous magnesium sulphate and evaporated *in vacuo* to dryness. The solid was recrystallised from 60—80° petroleum ether and submitted to gas liquid chromatography, the evidence suggesting that there was present a mixture of 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one and its 8 - tert - butyl derivative.

Dissolution of the solid in hot petroleum mixture and subsequent cooling resulted in precipitation of a solid, believed to be an impurity, the precipitate was removed by filtration and the filtrate evaporated *in vacuo* to dryness, the resultant solid then being submitted to gas liquid chromatography, the evidence from which suggesting a 96% pure product. Standard analytical techniques confirmed that this product was 8 - tert - butyl - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2 - one, m.p. 122—4°.

Analysis:

Found:

C, 80.09; H, 8.10; N, 5.86%
Calculated for $C_{15}H_{18}NO$:
C, 78.90; H, 8.30; N, 6.12%

Example 24.

- (A) To a stirred solution of 6 - methoxy - 1,2,3,4 - tetrahydro - quinoline (4.02 g) and triethylamine (3.0 g) in dry benzene (80 ml.) was added dropwise over 30 minutes chloroacetyl chloride (2.82 g). Stirring was continued for a further 3 hours at room temperature, after which the triethylamine hydrochloride in suspension was removed by filtration and the benzene solution filtrate was washed in turn with 2N hydrochloric acid and water, and then dried over anhydrous magnesium sulphate.
- (B) The product of (A) (9.0 g) was mixed with powdered anhydrous aluminium chloride (18.0 g) and the mixture was gradually heated to 100°, fumes of hydrogen chloride being evolved, and heating was continued until an oil-bath temperature of 200° had been attained, at which point the mixture was a molten mass. The reaction mixture was heated for a further

1 hour at an oil bath temperature of 200°, and then cooled to room temperature, the mixture by then having solidified. The ground mixture was added to an ice-water mixture, and the aqueous solution then extracted with chloroform, the chloroform solution then being extracted with sodium hydroxide solution. On standing the latter afforded a precipitate, and the suspension was extracted with fresh chloroform. The chloroform solution was dried over anhydrous magnesium sulphate and evaporated to dryness *in vacuo*, the resultant acid (3.5 g) then being recrystallised from absolute ethanol to afford 8 - hydroxy - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 2-one, m.p. 200—202°.

Analysis:

Found:

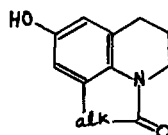
C, 69.09; H, 5.96; N, 7.44%.

Calculated for $C_{11}H_{11}NO_2$:

C, 69.82; H, 5.86; N, 7.40%.

Examples 25 and 26

By procedures similar to that described in Example 24, the following compounds were prepared starting from 6 - methoxy - 1,2,3,4-tetrahydroquinoline and the appropriate chloroacetyl chloride.



Example	alk	m.p. °C	Analysis (theoretical in brackets)		
			C%	H%	N%
25	$\begin{array}{c} -CH- \\ \\ CH_3 \end{array}$	197—200°	70.23 (70.91)	6.50 6.45	6.82 (6.89)
26	$-CH_2CH_2-$	230—5°	70.52 (70.91)	6.56 6.45	6.53 (6.89)

Example 27.

- 9 - Hydroxy - 2,3,6,7 - tetrahydro - 1H,5H-pyrrolo - [3,2,1 - i, j] - quinolin - 3 - one (the compound of Example 26) (0.5 g) was added to benzene (20 ml.) containing sodium acetate (0.1 g) and acetic anhydride (0.3 ml.) and the mixture was refluxed for 3 hours. After cooling, the sodium acetate was removed by filtration and the solution was evaporated *in vacuo* to dryness. The resultant solid was washed with 60—80° petroleum ether and

crystallised from a mixture of benzene and 60—80° petroleum ether to yield 0.33 g of 9 - acetoxy - 2,3,6,7 - tetrahydro - 1H, 5H-pyrrolo - [3,2,1 - i, j] - quinolin - 3 - one as pale yellow crystals, m.p. 124—6°.

Analysis:

Found:

C, 68.56; H, 6.17; N, 5.68%.

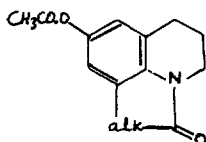
Calculated for $C_{11}H_{11}NO_3$:

C, 68.10; H, 6.24; N, 5.28%.

Examples 28 and 29
By procedures similar to that described in
Example 27, the following two compounds

were prepared starting from the compounds of
Examples 24 and 25, respectively.

5



Example	alk	m.p. °C	Analysis (theoretical in brackets)		
			C%	H%	N%
28	-CH ₂ -	140-2°	67.71 (67.52)	5.71 5.67	6.33 6.06
29	-CH- CH ₃	130-1°	68.55 (68.10)	6.16 6.24	5.71 5.28

Example 30.

A solution of 8 - bromo - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 4 - one (prepared as in Example 6) (1.5 g) and cuprous cyanide (0.63 g) in N - methyl - 2 - pyrrolidone (13 ml) was refluxed for 6 hours, and then allowed to cool to room temperature, whereupon a precipitate had formed. The precipitate (700 mg) was collected by filtration and 400 mg thereof recrystallised from ethanol, yielding 250 mg of 8 - cyano - 1,2,5,6 - tetrahydro - 4H - pyrrolo - [3,2,1 - i, j] - quinolin - 4 - one. m.p. 204-5°.

Analysis: —

Found:

C, 72.96; H, 5.02; N, 14.20%

Calculated for C₁₂H₁₀N₂O:

C, 72.71; H, 5.09; N, 14.13%

Example 31.

(A) A solution of 6 - methyl - 1,2,3,4 - tetrahydroquinoline (3.0 g) and ethyl acetoacetate (2.8 g) in xylene (7.0 ml) containing 2 drops of dry pyridine was refluxed for 12 hours. The solution was then allowed to cool to room temperature, washed in turn with 2N hydrochloric acid (2 x 20 ml) and water (2 x 20 ml), dried over anhydrous magnesium sulphate and evaporated under reduced pressure at 100° to dryness, yielding 1 - acetoacetyl - 6 - methyl - 1,2,3,4 - tetrahydroquinoline (1.7 g) as a crude solid, to be used directly in the next stage.

(B) The product of (A) (1.6 g) was slowly added to concentrated sulphuric acid (2 ml) with stirring, keeping the temperature below 100°. The mixture was then heated on a steam bath for 15 minutes and poured onto ice, the aqueous solution

then being basified by addition of dilute sodium hydroxide solution and extracted with chloroform. Evaporation of the previously dried chloroform solution *in vacuo* yielded a solid, which was crystallised from a mixture of benzene and 60-80° petroleum ether to afford crystals (0.7 g) of 1,9 dimethyl - 6,7 - dihydro - 5H - pyrido - [3,2,1 - i, j] - quinolin - 3 - one, m.p. 136-7°.

Analysis:

Found:

C, 79.34; H, 6.90; N, 6.61%

Calculated for C₁₄H₁₃NO:

C, 78.84; H, 7.09; N, 6.57%

Example 32.

By a procedure similar to that described in Example 31, 1 - methyl - 9 - methoxy - 6,7 - dihydro - 5H - pyrido - [3,2,1 - i, j] - quinolin - 3 - one, m.p. 115-7°, was prepared

starting from 6 - methoxy - 1,2,3,4 - tetrahydro - quinoline and ethyl acetoacetate.

Analysis:

Found:

C, 73.34; H, 6.60; N, 6.03%

Calculated for C₁₄H₁₃NO₂:

C, 72.76; H, 6.59; N, 6.11%

Example 33.

Phosphorus pentasulphide (1.1 g) was added in small portions over a 15 minute period to a solution of 1,2,5,6-tetrahydro-4H-pyrrolo-[3,2,1-i, j] - quinoline - 4 - one (1.73 g) in dry pyridine (12.5 ml) with shaking. The solution was then refluxed for 10 minutes, cooled, and poured into water, the resultant precipitate then being collected by filtration

and dried. Produced was 1.3 g of crude product, m.p. 115—7°.

- 5 Soxhlet extraction with 60—80° petroleum ether afforded, after evaporation of the solution to dryness, 1.0 g of pale yellow crystals. Recrystallisation of the latter from *n*-hexane afforded 0.6 g of 1,2,5,6 - tetrahydro - 4*H*-pyrrolo - [3,2,1 - *i*, *j*] - quinolin - 4 - thione, m.p. 126—126.5°.

- 10 Analysis:

Found:

C, 69.60; H, 5.89; N, 7.30%

Calculated for C₁₁H₁₁NS:

C, 69.80; H, 5.86; N, 7.41%

- 15 Examples 34 and 35

By procedures similar to that described in Example 33, the following thiones were prepared starting from the corresponding oxo compounds and phosphorus pentasulphide. The oxo compound starting materials were the known compounds 2 - lilolidone and 3 - julolidone respectively.

- 20 Example 36.
By a similar procedure to that described in Examples 6 and 7, 9 - bromo - 2,3,6,7 - tetrahydro - 1*H*, 5*H* - pyrido - [3,2,1 - *i*, *j*] - quinolin - 3 - one, m.p. 101—102°, was prepared from 3 - julolidone.

Analysis:—

- 30 found:
C, 54.21; H, 4.45; N, 5.41%

calculated for C₁₂H₁₂BrNO:

C, 54.0; H, 4.51; N, 5.21%

- 35 Example 37.
Phosphorus oxychloride (52 g) was mixed with *N* - methyl formanilide (8.6 g) at room temperature and then a solution of 2 - liloli-

done (17.2 g) in ether (600 ml) was added. A homogeneous solution was formed on shaking and allowed to stand overnight, when an oily layer separated. The mixture was poured onto ice, washed with dilute acid and then with water, extracted with chloroform and the organic layer separated, dried and evaporated to yield 3.5 g of crude 8 - formyl - 1,2,5,6 - tetrahydro - 4*H* - pyrrolo - [3,2,1 - *i*, *j*] - quinolin - 2 - one as a yellow solid. Recrystallisation from acetic acid yielded 2.2 g of product, m.p. 210—213°.

Analysis:—

found:

C, 71.63; H, 5.73; N, 7.27%

calculated for C₁₂H₁₁NO₂:

C, 71.7; H, 5.5; N, 6.96%

Example 38.

The following compound was prepared by the method of Example 34 of the parent application No. 23158/72, (Serial No. 1,394,373) from 6 - methoxy - 1,2,3,4 - tetrahydroquinoline and ethyl α - methyl - acetoacetate: 9 - methoxy - 1,2 - dimethyl - 6,7 - dihydro-3*H*, 5*H* - pyrido - [3,2,1 - *i*, *j*] - quinolin-3 - one. m.p. 115—117°

Analysis:

Found:

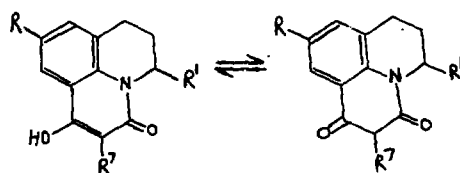
C, 73.77; H, 7.08; N, 5.87%

Calculated for C₁₅H₁₃NO₂:

C, 74.05; H, 7.04; N, 5.76%

Examples 39 to 45.

By a similar procedure to that described in Example 36 of the parent application, the compounds shown in the following Table were prepared from the appropriately substituted tetrahydro - quinoline and α -substituted diethyl melonate:

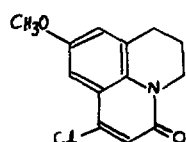


Example	Structure	m.p. °C	Analysis (theoretical in brackets)		
			C%	H%	N%
34		121—3°	69.31 (69.80)	5.83 5.85	7.02 7.41)
35		73—5°	71.06 (70.93)	6.57 6.40	6.97 6.90)

Example	R	R ¹	R ²	m.p. °C	Analysis (calculated in brackets)		
					C	H	N
39	CH ₃ O	H	CH ₃	234–237°	68.57 (68.55)	6.16 6.16	6.01 5.71)
40	CH ₃ O	H	H	295–300°	67.40 (67.52)	5.62 5.67	6.02 6.06)
41	CH ₃ O	H	C ₆ H ₅	214–215°	74.29 (74.25)	5.61 5.58	4.56 4.56)
42	CH ₃	H	C ₂ H ₅	286–288°	74.12 (74.05)	7.09 7.04	6.01 5.76)
43	CH ₃	H	<i>iso</i> -C ₃ H ₇	269–271°	74.95 (74.68)	7.58 7.44	5.16 5.44)
44	CH ₃	H	<i>iso</i> -C ₃ H ₇	198–200°	74.13 (74.05)	7.03 7.04	5.47 5.76)
45	CH ₃ O	H	<i>iso</i> -C ₃ H ₇	178–180°	71.25 (71.05)	7.31 7.30	4.53 4.87)

Example 46.

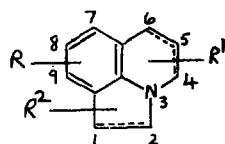
- 5 By a similar procedure to that described in Example 38, of the parent application, the following compound was prepared from the product of Example 40 herein:



m.p. °C	Analysis (calculated in brackets)		
	C	H	N
138–9°	62.70 (62.51)	4.85 4.95	5.30 5.62)

WHAT WE CLAIM IS:—

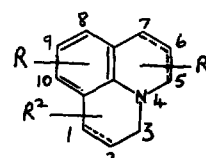
- 10 1. Pyrrolo - [3,2,1-*i,j*] - quinolines of the formula:



15 where R is a lower alkyl, lower alkoxy, lower alkanoyl, benzoyl, hydroxy, lower alkanoyloxy or cyano group or represents one or two halogen atoms;
R¹ and R² each independently represent hydrogen or one or more halogen, lower

alkyl, phenyl, oxo or thioxo substituents in the pyrido and pyrrolo rings, respectively;
and the dotted lines represent an optional bond in each such ring;
and the non-phytotoxic acid addition salts of those compounds which form acid addition salts.

- 20 2. Compounds according to claim 1, in which either R¹ or R² includes a single oxo or thioxo group adjacent to the ring nitrogen atom, and R is a halogen atom or a lower alkyl, lower alkoxy or lower alkanoyl group in the 8- position.
3. 8-Methyl-2-lilolidone.
4. 8-Bromo-4-lilolidone.
5. 8-*tert*-butyl-2-lilolidone.
- 35 6. Pyrido - [3,2,1 - *i,j*] - quinolines of the formula:

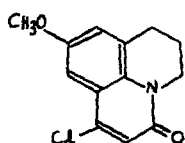


40 where R is a lower alkyl, lower alkoxy, lower alkanoyl, benzoyl, hydroxy, lower alkanoyloxy or cyano group or represents one or two halogen atoms, but is not a single chlorine atom in the 9 - position;
R¹ and R² each independently represent hydrogen or one or more halogen, lower alkyl, phenyl, oxo or thioxo substituents in the respective pyrido rings;

Example	R	R ¹	R ²	m.p. °C	Analysis (calculated in brackets)		
					C	H	N
39	CH ₃ O	H	CH ₃	234–237°	68.57 (68.55)	6.16 6.16	6.01 5.71
40	CH ₃ O	H	H	295–300°	67.40 (67.52)	5.62 5.67	6.02 6.06
41	CH ₃ O	H	C ₆ H ₅	214–215°	74.29 (74.25)	5.61 5.58	4.56 4.56
42	CH ₃	H	C ₂ H ₅	286–288°	74.12 (74.05)	7.09 7.04	6.01 5.76
43	CH ₃	H	<i>iso</i> -C ₃ H ₇	269–271°	74.95 (74.68)	7.58 7.44	5.16 5.44
44	CH ₃	H	<i>iso</i> -C ₃ H ₇	198–200°	74.13 (74.05)	7.03 7.04	5.47 5.76
45	CH ₃ O	H	<i>iso</i> -C ₃ H ₇	178–180°	71.25 (71.05)	7.31 7.30	4.53 4.87

Example 46.

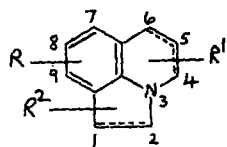
- 5 By a similar procedure to that described in Example 38, of the parent application, the following compound was prepared from the product of Example 40 herein:



m.p. °C	Analysis (calculated in brackets)		
	C	H	N
138–9°	62.70 (62.51)	4.85 4.95	5.30 5.62

WHAT WE CLAIM IS:—

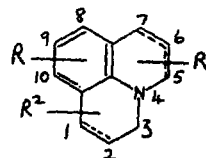
- 10 1. Pyrrolo - [3,2,1-i,j] - quinolines of the formula:



- 15 where R is a lower alkyl, lower alkoxy, lower alkanoyl, benzoyl, hydroxy, lower alkanoyloxy or cyano group or represents one or two halogen atoms;
R¹ and R² each independently represent hydrogen or one or more halogen, lower

alkyl, phenyl, oxo or thioxo substituents in the pyrido and pyrrolo rings, respectively;
and the dotted lines represent an optional bond in each such ring;
and the non-phytotoxic acid addition salts of those compounds which form acid addition salts.

- 20 2. Compounds according to claim 1, in which either R¹ or R² includes a single oxo or thioxo group adjacent to the ring nitrogen atom, and R is a halogen atom or a lower alkyl, lower alkoxy or lower alkanoyl group in the 8- position.
25 3. 8-Methyl-2-lilolidone.
4. 8-Bromo-4-lilolidone.
30 5. 8-*tert*-butyl-2-lilolidone.
35 6. Pyrido - [3,2,1 - i, j] - quinolines of the formula:



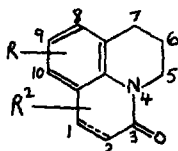
- where R is a lower alkyl, lower alkoxy, lower alkanoyl, benzoyl, hydroxy, lower alkanoyloxy or cyano group or represents one or two halogen atoms, but is not a single chlorine atom in the 9 - position;
R¹ and R² each independently represent hydrogen or one or more halogen, lower alkyl, phenyl, oxo or thioxo substituents in the respective pyrido rings;



and the dotted lines represent an optional bond in each such ring;
and the non-phytotoxic acid addition salts or those compounds which form acid addition salts.

5

7. Pyrido - [3,2,1 - i, j] - quinolines of the formula:



in which R is a lower alkyl, lower alkoxy

or lower alkanoyl group in the 9- position, R² is hydrogen or represents (a) one or more lower alkyl groups or (b) an oxo group in the 1- position and an optional phenyl or lower alkyl group in the 2- position.

10

8. Lilolidine - 2 - thione
9. Lilolidine - 4 - thione.
10. Julolidine - 3 - thione.
11. 8 - Acetyl - 4 - lilolidone.
12. 8-Benzoyl-2-lilolidone.

15

20

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Agent for the Applicants.

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