

PATENT SPECIFICATION

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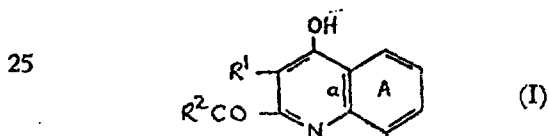
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(54) PYRIDOQUINOLINE DERIVATIVES

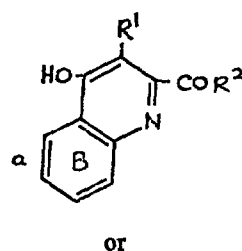
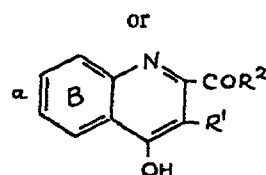
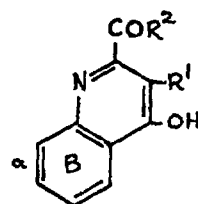
(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to heterocyclic compounds, and more particularly it relates to new pyridoquinoline derivatives which are active as inhibitors of the effects following the combination of reagin-like antibodies and their antigens. They are therefore useful for the treatment of asthma, for example allergic asthma, and they may also be useful for the treatment of other syndromes or diseases initiated by an antigen-antibody reaction, for example hay fever, urticaria and auto-immune diseases.

According to the invention there are provided pyridoquinoline derivatives of the formula:—



wherein benzene ring A stands for a group of the formula:—



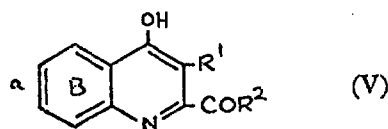
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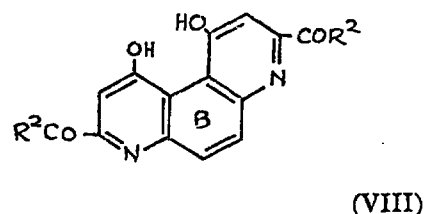
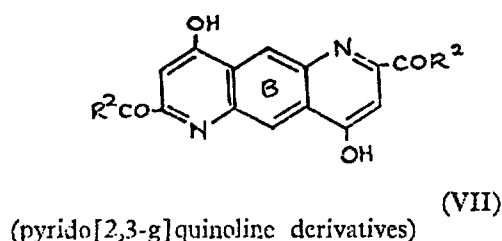
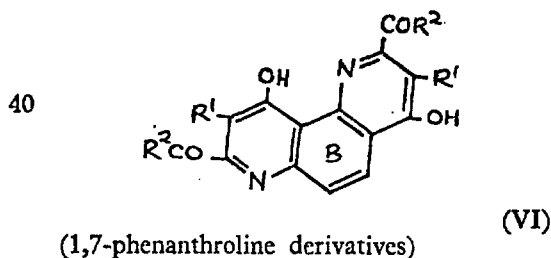
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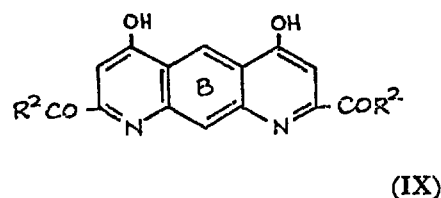


wherein a in formulae II to V indicates the common bond between the pyridine ring and the benzene ring A in formula I; R¹ stands for hydrogen or a methyl radical; R² stands for a hydroxy, C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical; and the benzene ring B may optionally bear not more than two substituents selected from C₁₋₆ alkyl, cycloalkyl of not more than 6 carbon atoms, C₁₋₆ alkoxy, trifluoromethyl, phenyl and phenoxy radicals, and halogen atoms, and NR³R⁴ radicals wherein R³ stands for a C₁₋₆ alkyl radical and R⁴ stands for a C₁₋₆ alkyl or phenyl radical or wherein —NR³R⁴ stands for a nitrogen-containing heterocyclic radical of not more than 7 ring atoms; or, in the case of formula II or IV, the said benzene ring B may optionally bear an alkylene radical of 3—5 carbon atoms; and wherein R¹ stands for a methyl radical, the compounds are 1,7-phenanthroline derivatives only, bearing either a C₁₋₃-alkyl, C₁₋₄-alkoxy, phenoxy, piperidino or morpholino substituent in the 5- or 6-position, or 5,6-dimethyl or 5-phenyl-6-methoxy substituents, or a 5,6-alkylene substituent of 3—5 carbon atoms; and non-toxic pharmaceutically-acceptable salts thereof; but excluding 2,8-dicarboxy-4,10-dihydroxy-1,7-phenanthroline and di-C₁₋₆-alkyl esters thereof, and 4,9-dihydroxy-2,7-dimethoxy-carbonylpyrido[2,3-g]quinoline, and non-toxic pharmaceutically-acceptable salts thereof.

It will be understood by those skilled in the art that the pyridoquinoline derivatives of the invention consist of compounds having the following formulae:—

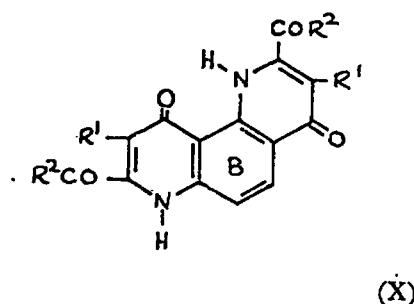


and



wherein B, R¹ and R² have the meanings stated above, and non-toxic pharmaceutically-acceptable salts thereof, but excluding the compounds specified above.

It is to be understood that the compounds of the invention can exist in a tautomeric quinoline form, for example, in the case of the compounds of formula VI, the tautomeric form having the formula:—



However, for convenience the compounds of the invention will all be referred to in this specification as 4-hydroxyquinoline derivatives.

As indicated above, those of the compounds of the invention wherein R¹ stands for a methyl radical are all 1,7-phenanthroline derivatives (i.e. formulae I, II and VI are relevant) and they all bear at least one specified substituent in the benzene ring B.

A suitable value for R² when it stands for a C₁₋₆ alkoxy radical is, for example, a methoxy, ethoxy, n-propoxy, n-butoxy or n-pentyl-oxy radical. A suitable value for R² when it stands for a C₇₋₁₀ phenylalkoxy radical is, for example, a benzyloxy radical.

Ring B may optionally bear not more than

two substituents selected from, for example, methyl, ethyl propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclohexyl, methoxy, ethoxy, propoxy, trifluoromethyl, phenyl, phenoxy, dimethylamino, diethylamino, dipropylamino, dibutylamino and *N*-methylamino radicals, and saturated heterocyclic radicals of 5,6 or 7 ring atoms, containing a nitrogen atom as hetero-atom and optionally containing a second hetero-atom which is an oxygen atom, for example a piperidino, 1-hexahydroazepinyl or morpholino radical, and fluorine, chlorine and bromine atoms. Alternatively, in the case of compounds of the formula VI or VIII, ring B may optionally bear, for example, a trimethylene, tetramethylene or pentamethylene radical.

As stated above, when R^1 stands for a methyl radical, ring B always bears one or two specified substituent(s), and suitable substituents are mentioned immediately above.

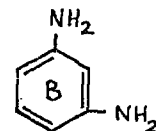
Compounds of the invention which are preferred because of their high activity are 1,7-phenanthroline derivatives (i.e. formulae I, II and VI are relevant) wherein R^1 stands for hydrogen, R^2 stands for a hydroxy radical, and the benzene ring B bears a C_{3-5} alkyl radical in the 6-position of the nucleus, for example an *n*-propyl, *n*-butyl, *t*-butyl or *n*-pentyl radical, and in particular an *n*-propyl or *n*-butyl radical, and non-toxic pharmaceutically-acceptable salts thereof.

Suitable salts of the invention in the case where the said compounds of formula I are sufficiently basic are acid-addition salts derived from inorganic or organic acids affording non-toxic pharmaceutically-acceptable anions, for example hydrochlorides, hydrobromides, tartrates or citrates. Suitable salts of the invention in the case where the said compounds of formula I are sufficiently acidic, i.e. wherein R^2 stands for a hydroxy radical and/or wherein the ring hydroxy radical(s) is or are sufficiently acidic, are salts containing a non-toxic pharmaceutically-acceptable cationic moiety; for example, ammonium, alkali metal, alkaline earth metal or aluminium salts, or salts with non-toxic pharmaceutically-acceptable organic bases, for example morpholine, *N*-methylglucamine, piperidine, triethanolamine or ethylenediamine.

Particularly preferred compounds of the invention are 6 - *n* - butyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline, 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - *n* - propyl - 1,7 - phenanthroline and 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - *n* - pentyl - 1,7 - phenanthroline, and non-toxic pharmaceutically-acceptable salts thereof.

According to a further feature of the invention there is provided a process for the manufacture of those of the compounds of the formula I wherein A and R^1 have the meanings stated above and R^2 stands for a C_{1-6}

alkoxy radical, and non-toxic pharmaceutically-acceptable salts thereof, which comprises reacting a diamino compound of the formula:—



(XI)

or



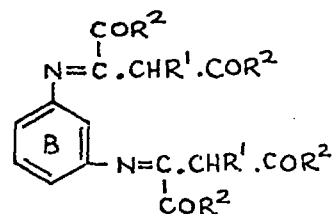
(XII)

wherein B has the meaning stated above, with a compound of the formula:—



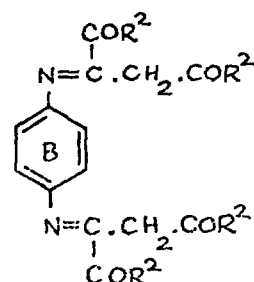
wherein R^1 and R^2 have the meanings stated immediately above (i.e. the Conrad-Limpach reaction).

The Conrad-Limpach reaction involves two stages. In the first stage a compound is produced which in one of its tautomeric forms has one of the formulae:—



(XIV)

and



(XV)

wherein B, R¹ and R² have the meanings stated immediately above, depending upon which of the said diamino compounds is used as starting material. (It will be appreciated that the reason for R' being omitted from the formula XV is that R' can only stand for hydrogen in respect of that formula.) This stage is carried out at a moderately elevated temperature, for example 80—110°C., in an aromatic hydrocarbon solvent, for example benzene, in an apparatus which facilitates the removal of water (formed during the reaction) from the reaction mixture, for example a Dean and Stark apparatus.

The second stage of the Conrad-Limpach reaction involves ring-closing the compound of formula XIV or XV so as to obtain a compound of formula VI, VII, VIII or IX, wherein B, R¹ and R² have the meanings stated immediately above. This stage may be carried out by heating the compound of formula XIV or XV at 230—250°C., for example by heating it in diphenyl ether or α -chloronaphthalene at 230—250°C., or by reacting the compound of formula XIV or XV with polyphosphoric acid at 130—180°C., for example 150°C. It is to be understood that ring-closure of the compound of formula XIV gives products of formulae VI and IX, and ring-closure of the compound of formula XV gives products of formulae VII and VIII.

According to a further feature of the invention there is provided a process for the manufacture of those of the compounds of formula I wherein A has the meaning stated above, R¹ stands for hydrogen, and R² stands for a C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical, and non-toxic pharmaceutically-acceptable salts thereof, which comprises reacting a diamino compound of the formula XI and XII with an acetylene derivative of the formula:—



wherein R² has the meaning stated immediately above, so as to give a compound which in one of its tautomeric forms has the formula XIV or XV, respectively, wherein R¹ stands for hydrogen, and then ring-closing this compound, for example by either of the methods described above, to give the desired product.

According to a further feature of the invention there is provided a process for the manufacture of those of the compounds of formula I wherein A and R¹ have the meanings stated above and R² stands for a hydroxy radical, which comprises hydrolysing the corresponding alkyl, phenylalkyl or phenyl ester or the corresponding nitrile or amide.

The hydrolysis is carried out in the presence of water, and an organic solvent may optionally be present. As a suitable hydrolytic

agent there may be mentioned, for example, an alkali metal hydroxide, for example sodium or potassium hydroxide, or an inorganic acid, for example hydrochloric acid, optionally in the presence of acetic acid.

According to a further feature of the invention there is provided a process for the manufacture of those of the compounds of the formula I wherein A and R¹ have the meanings stated above and R² stands for a C₁₋₆ alkoxy radical, which comprises esterifying the appropriate carboxylic acid, i.e. wherein R² stands for a hydroxy radical, or trans-esterifying an appropriate ester.

General methods of esterification of carboxylic acids, and of trans-esterification, are well known in the chemical art. Thus, for example, the appropriate carboxylic acid may be esterified by reacting it with the appropriate hydroxy compound of the formula R²H, wherein R² stands for a C₁₋₆ alkoxy radical, and a suitable acid, for example an inorganic acid, for example hydrochloric acid. The reaction may conveniently be carried out at a moderately elevated temperature, for example at reflux temperature. Alternatively, for example, an acid halide or anhydride of the said carboxylic acid may be reacted with the said hydroxy compound, optionally in the presence of an organic solvent.

The salts of the invention, and the compounds used as starting materials in the processes of the invention, are all obtainable by means of well known general processes, as indicated in the Examples.

The compounds of the invention, and the pharmaceutical compositions of the invention which are described hereinafter, exhibit the above-mentioned activity when administered by inhalation or intravenously. Furthermore, some of the esters of the invention, and some of the esters which are active ingredients of the pharmaceutical compositions of the invention, are orally active also. In particular, diethyl esters are orally active.

The activity of the compounds and pharmaceutical compositions of this invention is demonstrated by their ability to inhibit, in the rat, passive cutaneous anaphylaxis induced by reaginic antibodies to egg albumin, using *B. pertussis* as an adjuvant. When the said compounds are used to treat asthma in man by inhalation, a typical dose is from 0.01 mg./kg. to 1 mg./kg. at suitable intervals, for example at 6-hourly intervals during the day. When they are used intravenously to treat asthma in man, a typical total daily dose is 25 mg. per man. When the appropriate compounds which are esters are used orally to treat asthma in man, a typical dose is 50 to 200 mg. per man, three times a day. When the said compounds are used to treat other syndromes or diseases initiated by an antigen-antibody reaction, a typical total daily dose is 1 to 50 mg. per man when

given by inhalation, 25 mg. per man when given intravenously, and 300 mg. per man when given orally.

- According to a further feature of the invention there are provided pharmaceutical compositions comprising a compound of the formula I, wherein the benzene ring A stands for a group of the formula II, III, IV or V, wherein a in formulae II to V indicates the common bond between the pyridine ring and the benzene ring A in formula I; R¹ stands for hydrogen or a methyl radical; R² stands for a hydroxy, C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical; and the benzene ring B may optionally bear not more than two substituents selected from C₁₋₈ alkyl, cycloalkyl of not more than 6 carbon atoms, C₁₋₆ alkoxy, trifluoromethyl, phenyl and phenoxy radicals, and halogen atoms, and NR³R⁴ radicals wherein R³ stands for a C₁₋₆ alkyl radical and R⁴ stands for a C₁₋₆ alkyl or phenyl radical or wherein —NR³R⁴ stands for a nitrogen-containing heterocyclic radical of not more than 7 ring atoms or, in the case of formula II or IV, the said benzene ring B may optionally bear an alkylene radical of 3—5 carbon atoms; and wherein when R¹ stands for a methyl radical the compounds are 1,7-phenanthroline derivatives only, bearing either a C₁₋₅ alkyl, C₁₋₄-alkoxy, phenoxy, piperidino or morpholino substituent in the 5- or 6-position, or 5,6-dimethyl or 5-phenyl-6-methoxy substituents, or a 5,6-alkylene substituent of 3—5 carbon atoms; or a non-toxic pharmaceutically-acceptable salt thereof; and an inert non-toxic pharmaceutically-acceptable diluent or carrier.

The pharmaceutical compositions of the invention are obtainable by well known methods using conventional diluents or carriers.

Suitable compositions for administration by inhalation comprise a mixture of the active ingredient with a solid diluent or carrier, for example lactose, the said mixture being in fine particulate form suitable for administration from a powder inhalation device. Alternatively, the compositions may be administered by inhalation in the form of a suspension or solution in a suitable liquid, for example water or an aqueous or non-aqueous medium, using a conventional nebulizer or a pressurised container.

Alternatively, the said compositions may be in a form suitable for intravenous administration, for example sterile aqueous solutions.

Alternatively, the said compositions may be orally-administrable compositions, for example an orally-administrable unit dosage form, for example a tablet or capsule, or a solution, suspension, emulsion or syrup.

The pharmaceutical compositions of the invention may contain, in addition to a com-

pound of the formula I, or a non-toxic pharmaceutically-acceptable salt thereof, one or more other known active ingredients selected from β -adrenergic stimulants, for example isoprenaline, adrenaline, orciprenaline or isothachine, or a pharmaceutically acceptable acid addition salt thereof, for example a sulphate, and prostaglandins having bronchodilatory activity, for example prostaglandin E₁ or E₂, and phosphodiesterase inhibitors selected from the following compounds:—

- (a) 3 - acetamido - 6 - methyl - 8 - n - propyl - s - triazolo[4,3-a] - pyrazine;
- (b) 2 - amino - 4,6 - di - C₁₋₄ - alkyl - 5 - oxo - 4,5 - dihydro - s - triazolo [1,5-a]pyrimidines, for example 2 - amino - 6 - methyl - 5 - oxo - 4 - n - propyl - 4,5 - dihydro - s - triazolo - [1,5-a]pyrimidine;
- (c) theophylline and related 3,5 - di - C₁₋₄ - alkylxanthines; and
- (d) 6,8 - di - C₁₋₄ - alkyl - 5,6 - dihydro - 5 - oxo - s - triazolo - [4,3-c]pyrimidines, for example 5,6 - dihydro - 5 - oxo - 6,8 - di - n - propyl - s - triazolo [4,3-c]pyrimidine.

The pharmaceutical compositions of the invention may contain from 1% to 50% by weight of a compound of formula I or a non-toxic pharmaceutically acceptable salt thereof.

The invention is illustrated but not limited by the following Examples:—

Example 1

Sodio diethyl oxalacetate (15.8 g.) was added portionwise to a stirred mixture of 10N-hydrochloric acid (10 ml.), water (100 ml.) and benzene (50 ml.) at a temperature not exceeding 20°C. The mixture was stirred for 1 hour and the benzene layer was then separated and washed with water (50 ml.). The aqueous washings were back-extracted with benzene (50 ml.) and the combined benzene solutions were dried over anhydrous magnesium sulphate and filtered. 2,4-Diaminotoluene (3.2 g.) was added and the mixture was boiled in an apparatus for continuously removing water from the reaction mixture (a Dean and Stark apparatus) until no more water was collected. The benzene was removed *in vacuo* and the residue was added over 5 minutes to boiling diphenyl ether (100 ml.). The mixture was heated at 220—240°C. until no more ethanol was liberated (about 5 minutes). The solution was cooled to room temperature and diluted by the addition of petroleum ether (b.p. 40—60°C.; 500 ml.). After standing for 30 minutes, the suspension was filtered and the solid residue washed several times with acetone. There was thus obtained, as solid residue, 2,8 - diethoxycarbonyl - 4,10 -

dihydroxy - 6 - methyl - 1,7 - phenanthroline, m.p. 198—200°C.

Example 2

- 2,8 - Diethoxycarbonyl - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline (1 g.) was heated with 10% w/v aqueous sodium hydroxide (10 ml.) on a steam bath for 30 minutes. The mixture was cooled, filtered, and the solid residue of sodium salt was dissolved in water (10 ml.). The solution was acidified with concentrated hydrochloric acid. The resultant precipitate was collected by filtration, dissolved in saturated sodium hydrogen carbonate solution (15 ml.), filtered, and the filtrate acidified with concentrated hydrochloric acid. The resultant precipitate was collected by filtration, and washed successively with water and hot ethanol. There was thus obtained 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline, m.p. 316°C. (decomposition).

Example 3

- The methods described in Examples 1 and 2 were repeated using the appropriate phenylenediamine as starting material, and the following compounds were obtained:—

- 2,8 - dicarboxy - 4,10 - dihydroxy - 5,6 - dimethyl - 1,7 - phenanthroline, m.p. 310—314°C. (decomposition), from 1,3 - diamino - 4,5 - dimethylbenzene;
3,8 - dicarboxy - 1,10 - dihydroxy - 5,6 - dimethyl - 4,7 - phenanthroline, m.p. 306°C. (crystallised from dimethylsulphoxide), from 1,4 - diamino - 2,3 - dimethylbenzene;
3,8 - dicarboxy - 1,10 - dihydroxy - 4,7 - phenanthroline, m.p. 306—308°C., from *p*-phenylenediamine; and
2,7 - dicarboxy - 4,9 - dihydroxy - 5,10 - dimethylpyrido[2,3-*g*]quinoline, m.p. over 350°C., from 1,4 - diamino - 2,5 - dimethylbenzene.

- It should be noted that the structure of the next-to-last product named above, i.e. the supposed 4,7-phenanthroline derivative of m.p. 306—308°C., is not known with complete certainty. It is believed that the product was at it has been named; however, in fact it may have 2,7 - dicarboxy - 4,9 - dihydroxypyrido[2,3-*g*]quinoline.

Example 4

- The methods described in Examples 1 and 2, as appropriate, were repeated using the appropriate phenylenediamine as starting material, and the following compounds were obtained:—

2,8 - diethoxycarbonyl - 6 - ethyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 183—184°C. (crystallised from ethyl acetate), and 2,8 - dicarboxy - 6 - ethyl - 4,10 -

dihydroxy - 1,7 - phenanthroline, m.p. 316°C. (decomposition), from 2,4 - diamino - 1 - ethylbenzene;

6 - *t* - butyl - 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 253—254°C. (crystallised from ethanol), and 6 - *t* - butyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 315°C. (decomposition), from 2,4 - diamino - 1 - *t* - butylbenzene;

2,8 - dicarboxy - 4,10 - dihydroxy - 6 - isopropyl - 1,7 - phenanthroline, m.p. 306—307°C. (decomposition), from 2,4 - diamino - 1 - isopropylbenzene; and

6 - chloro - 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 155—157°C., and 6 - chloro - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. over 300°C., from 1,3 - diamino - 4 - chlorobenzene.

Example 5

3,8 - Dimethoxycarbonyl - 1,10 - dihydroxy - 5 - methyl - 4,7 - phenanthroline was hydrolysed by the process described in Example 2, and there was thus obtained 3,8 - dicarboxy - 1,10 - dihydroxy - 5 - methyl - 4,7 - phenanthroline, m.p. 295°C. (decomposition), (crystallised from 75% v/v dimethylsulphoxide/ethanol).

The 3,8 - dimethoxycarbonyl - 1,10 - dihydroxy - 5 - methyl - 4,7 - phenanthroline used as starting material was obtained as follows:—

Sodium hydride (2.4 g. of a 50% suspension in mineral oil) was added gradually to a stirred, cooled suspension of 2,5 - diamino-toluene dihydrochloride in dry methanol (100 ml.), keeping the temperature between 10 and 15°C. The solution was allowed to rise to room temperature, and then dimethyl acetylene-dicarboxylate (7.1 g.) in dry methanol (10 ml.) was added. After the resulting exothermic reaction had finished, the mixture was heated under reflux for 3 hours, and then filtered, and the filtrate was evaporated under reduced pressure. The residue solidified on trituration with ether, and was crystallised from methanol to give the bis anil, m.p. 90—92°C.

The bis anil was added to boiling diphenyl ether (100 ml.), and the mixture was maintained at 220—240°C. until no more methanol was liberated (about 5 minutes). The solution was cooled, and the resulting yellow solid filtered off, and washed with petroleum ether (b.p. 40—60°C.), and then crystallised from pyridine. There was thus obtained 3,8 - dimethoxycarbonyl - 1,10 - dihydroxy - 5 - methyl - 4,7 - phenanthroline, m.p. 302—304°C.

Example 6

2,8 - Dicarboxy - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline (0.8 g.) was

6	7	1,308,787	7
b.p. 60		stirred with a solution of sodium hydrogen carbonate (0.3 g.) in water (5 ml.) for one hour. The mixture was filtered, the filtrate was diluted with ethanol (12 ml.), and the resulting mixture was filtered. The solid residue was successively washed with hot ethanol and ether, and then dried. There was thus obtained the disodium salt of 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline, as a dihydrate; n.m.r. spectrum (in D ₂ O): —CH ₃ single peak (2.1 δ); H _a , H _b single peak for two protons (6.4 δ); H _c single peak (7.15 δ).	residue was fractionally distilled under reduced pressure and a fraction collected at b.p. 140—144°C./1 mm. There was thus obtained 1 - n - butyl - 2,4 - dinitrobenzene.
no -			65
yl -			
fine,			
ol),	5		
65			
10 -			
10°C.			
1 -			
6 -	10		
65—			
no -			
10 -			
5—	75		
cy -			
m.p.			
oro-			
80			
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pro-			
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5 -	85		
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2,8 - dicarboxy - 6 - n - hexyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 294°C. (decomposition) (crystallised from dimethylsulphoxide) from 2,4 - diamino - 1 - n - hexylbenzene;

2,8 - dicarboxy - 4,10 - dihydroxy - 6 - n - octyl - 1,7 - phenanthroline, m.p. 300°C. (decomposition) (crystallised from dimethylsulphoxide and washed with ethanol) from 2,4 - diamino - 1 - n - octylbenzene; and

2,8 - dicarboxy - 4,10 - dihydroxy - 6 - methoxy - 5 - phenyl - 1,7 - phenanthroline, m.p. 277—278°C. (decomposition) from 3,5 - diamino - 2 - methoxydiphenyl.

The 2,4 - diamino - 1 - n - pentylbenzene used in the preparation of the said 6 - n - pentyl derivative was obtained by hydrogenation of 2,4 - dinitro - 1 - n - pentylbenzene in a similar way to that described in Example 7 for the hydrogenation of 1 - n - butyl - 2,4 - dinitrobenzene. The 2,4 - diamino - 1 - n - pentylbenzene so obtained (diacetyl derivative, m.p. 200—202°C., crystallised from aqueous methanol) was used directly for the reaction with acetylene dicarboxylic acid dimethyl ester.

The said 2,4 - dinitro - 1 - n - pentylbenzene was obtained as follows:—

Fuming nitric acid (40 ml., d 1.5) was added gradually to n-pentylbenzene with stirring and cooling so that the temperature remained below 5°C. When the addition was complete, the mixture was stirred at 30°C. for 90 minutes, then poured into ice-water and the resulting oil extracted with ether. The ethereal extract was washed successively with water, sodium carbonate solution and water. The ethereal solution was dried over anhydrous magnesium sulphate, filtered, and the solvent was removed by distillation. The residue (29 g.) was stirred vigorously while fuming nitric acid (90 ml., d 1.5) was added slowly, allowing the temperature to rise to 60°C. without external cooling. When the addition was complete the mixture was stirred and heated at 45—50°C. for 2 hours. The mixture was poured into ice-water, the oil extracted with ether, and the ethereal extract washed successively with water, sodium carbonate solution, and water. The ethereal solution was dried over anhydrous magnesium sulphate, filtered, and the solvent removed by distillation. The residual oil was fractionally distilled under reduced pressure, and there was thus obtained 2,4 - dinitro - 1 - n - pentylbenzene, b.p. 150—156°C./0.7 mm.

The 2,4 - diamino - 1 - n - hexylbenzene used in the preparation of the said 6 - n - hexyl derivative was obtained by hydrogenation of 1 - n - hexyl - 2,4 - dinitrobenzene in a similar way to that described in Example 7 for the hydrogenation of 1 - n - butyl - 2,4 - dinitrobenzene. The 2,4 - diamino - 1 - n - hexylbenzene so obtained (diacetyl derivative, m.p. 198—199°C., crystallised from aqueous methanol) was used directly for the reaction with acetylene dicarboxylic acid dimethyl ester. The said 1 - n - hexyl - 2,4 - dinitrobenzene was obtained by nitration of n-hexylbenzene in a similar manner to that described above for the nitration of n-pentylbenzene.

The 2,4 - diamino - 1 - n - octylbenzene used in the preparation of the said 6 - n - octyl derivative was obtained by hydrogenation of 2,4 - dinitro - 1 - n - octylbenzene in a similar way to that described in Example 7 for the hydrogenation of 1 - n - butyl - 2,4 - dinitrobenzene. The 2,4 - diamino - 1 - n - octylbenzene so obtained (diacetyl derivative, m.p. 195—197°C., crystallised from methanol) was used directly for the reaction with acetylene dicarboxylic acid dimethyl ester.

The 2,4 - diamino - 1 - n - octylbenzene used in the preparation of the said 6 - n - octyl derivative was obtained by hydrogenation of 2,4 - dinitro - 1 - n - octylbenzene in a similar way to that described in Example 7 for the hydrogenation of 1 - n - butyl - 2,4 - dinitrobenzene. The 2,4 - diamino - 1 - n - octylbenzene so obtained (diacetyl derivative, m.p. 195—197°C., crystallised from methanol) was used directly for the reaction with acetylene dicarboxylic acid dimethyl ester.

The 3,5 - diamino - 2 - methoxydiphenyl used in the preparation of the said 6 - methoxy - 5 - phenyl derivative was obtained by hydrogenation of 2 - methoxy - 3,5 - dinitrodiphenyl (as a suspension in ethanol) in a similar way to that described in Example 7 for the hydrogenation of 1 - n - butyl - 2,4 - dinitrobenzene. The 3,5 - diamino - 2 - methoxydiphenyl so obtained (diacetyl derivative, m.p. 169—170°C., crystallised from methyl acetate) was used directly for the reaction with acetylene dicarboxylic acid dimethyl ester.

The method described in Example 1 was repeated using an equivalent amount of the appropriate phenylenediamine as starting material, and the following compounds were obtained:—

Example 10

The method described in Example 1 was repeated using an equivalent amount of the appropriate phenylenediamine as starting material, and the following compounds were obtained:—

2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 6 - n propyl - 1,7 - phenanthroline, m.p. 212—214°C. (crystallised from ethanol or 2-ethoxyethanol), from 2,4 - diamino - 1 - n - propylbenzene; and

6 - n - butyl - 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 192—193°C. (crystallised from ethanol), from 2,4 - diamino - 1 - n - butylbenzene.

The 2,4 - diamino - 1 - n - propylbenzene used as starting material was obtained as follows:—

A solution of 2,4 - dinitro - 1 - n - propylbenzene (10 g.) in ethanol (125 ml.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladium-on-charcoal (0.5 g. of 5%) as catalyst. When the theoretical amount of hydrogen (6.4 l.) had been absorbed, the mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue of 2,4 - diamino - 1 - n - propylbenzene was used directly for the reaction with diethyl oxalacetate.

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Example 11

2,8 - Diethoxycarbonyl - 4,10 - dihydroxy - 6 - n - propyl - 1,7 - phenanthroline was hydrolysed with hot aqueous sodium hydroxide by the method described in Example 8, and there was thus obtained 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - n - propyl - 1,7 - phenanthroline, m.p. 306°C. (decomposition) (crystallised from dimethylsulphoxide, and washed with ethanol).

Example 12

2,8 - Dimethoxycarbonyl - 4,6 - dihydroxy - 10 - methylpyrido - [3,2-g] quinoline was hydrolysed with hot aqueous sodium hydroxide by the method described in Example 8. There was thus obtained 2,8 - dicarboxy - 4,6 - dihydroxy - 10 - methylpyrido[3,2-g] - quinoline, m.p. above 300°C., (crystallised from dimethylsulphoxide).

The 2,8 - dimethoxycarbonyl - 4,6 - dihydroxy - 10 - methylpyrido[3,2-g]quinoline used as starting material was obtained as follows:—

A solution of acetylene dicarboxylic acid dimethyl ester (2.8 g.) in dry methanol (20 ml.) was added to a solution of 2,6 - diamino - 1 - methylbenzene (1.2 g.) in dry methanol (20 ml.), and the mixture heated under reflux for 3 hours. The mixture was then cooled and filtered, and the solid residue of bis anil (1.9 g., m.p. 194—196°C., crystallised from dimethylformamide) was added in portions to boiling diphenyl ether (50 ml.), and the mixture was kept at 240—245°C. for 10 minutes. The mixture was then cooled, and filtered, and the solid residue was washed with petroleum ether (b.p. 40—60°C.; 750 ml.), and crystallised from dimethylsulphoxide to give 2,8 - dimethoxycarbonyl - 4,6 - dihydroxy - 10 - methylpyrido[3,2-g]quinoline, m.p. 296°C.

Example 13

The methods described in Example 12 were repeated using an equivalent amount of 2,6 - diamino - 1 - chlorobenzene in place of 2,6 - diamino - 1 - methylbenzene. There was thus obtained 2,8 - dicarboxy - 10 - chloro - 4,6 - dihydroxypyrido[3,2-g]quinoline, m.p. above 300°C.

Example 14

The methods described in Examples 7 and 8 were repeated using the appropriate phenylenediamine as starting material, and the following compounds were obtained:—

2,8 - dicarboxy - 4,10 - dihydroxy - 6 - n - propoxy - 1,7 - phenanthroline, m.p. 294°C. (decomposition) (crystallising with one molecule of solvent from dimethylsulphoxide) from 2,4 - diamino - 1 - n - propoxybenzene;

2,8 - dicarboxy - 6 - ethoxy - 4,10 -

dihydroxy - 1,7 - phenanthroline, m.p. 286—287°C. (decomposition) (crystallising as a hemihydrate from dimethylsulphoxide) from 2,4 - diamino - phenetole;

2,8 - dicarboxy - 4,10 - dihydroxy - 6 - methoxy - 1,7 - phenanthroline, m.p. above 320°C. (crystallising with one molecule of solvent from dimethylsulphoxide) from 2,4 - diaminoanisole;

2,8 - dicarboxy - 6 - fluoro - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. above 320°C. (crystallised from dimethylsulphoxide) from 2,4 - diamino - 1 - fluorobenzene; and

2,8 - dicarboxy - 6 - n - heptyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 296°C. (decomposition) (crystallised from dimethylsulphoxide, and washed with boiling ethanol) from 2,4 - diamino - 1 - n - heptylbenzene.

The 2,4 - diamino - 1 - n - propoxybenzene used in the preparation of the said 6 - n - propoxy derivative was obtained by hydrogenation of 2,4 - dinitro - 1 - n - propoxybenzene, in a similar way that described in Example 7 for the preparation of 2,4 - diamino - 1 - n - butylbenzene. The 2,4 - diamino - 1 - n - propoxybenzene so obtained had m.p. 84—86°C. after crystallisation from benzene.

The 2,4 - diamino - 1 - fluorobenzene used in the preparation of the said 6-fluoro derivative was obtained in essentially the same way from 1 - fluoro - 2,4 - dinitrobenzene, and it was an oil (diacetyl derivative, m.p. 189—191°C., crystallised from water) which was used directly for the subsequent reaction with acetylene dicarboxylic acid dimethyl ester. Likewise, the 2,4 - diamino - 1 - n - heptylbenzene used in the preparation of the said 6 - n - heptyl derivative was obtained by hydrogenation of 1 - n - heptyl - 2,4 - dinitrobenzene. The 2,4 - diamino - 1 - n - heptylbenzene so obtained was used directly for the reaction with acetylene dicarboxylic acid dimethyl ester. The said 1 - n - heptyl - 2,4 - dinitrobenzene was obtained by nitration of n-heptylbenzene in a similar manner to that described for the nitration of n-pentylbenzene in Example 7.

Example 15

A solution of 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 6 - phenoxy - 1,7 - phenanthroline monohydrate (0.5 g.) in a mixture of hot glacial acetic acid (10 ml.) and hydrochloric acid (15 ml. of 3N) was heated under reflux for two hours. The mixture was cooled and then filtered, and the solid residue was washed with boiling chloroform. There was thus obtained 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - phenoxy - 1,7 - phenanthroline hemihydrate, m.p. 306—307°C. (decomposition).

The 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 6 - phenoxy - 1,7 - phenanthro-

line used in the above process was obtained as a monohydrate of m.p. 214—215°C. (crystallised from ethanol) by a similar method to that described in Example 1, using 2,4 - diaminodiphenyl ether as starting material.

Example 16

The method described in Example 7 was repeated, but using 1,3 - diamino - 4 - bromobenzene as starting material in place of 2,4 - diamino - 1 - *n* - butylbenzene, and there was thus obtained 6 - bromo - 2,8 - dimethoxycarbonyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 208—210°C.

Example 17

The method described in Example 15 was repeated, but using 6 - bromo - 4,10 - dihydroxy - 2,8 - dimethoxycarbonyl - 1,7 - phenanthroline as starting material and continuing the heating under reflux for 10 hours. There was thus obtained 6 - bromo - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 318—320°C. (decomposition).

Example 18

A mixture of 4,10 - dihydroxy - 2,8 - dimethoxycarbonyl - 6 - piperidino - 1,7 - phenanthroline (1.4 g.) and hydrochloric acid (30 ml. of 3N) was stirred and heated under the reflux for 6 hours. A clear solution was obtained, and then the product precipitated from the boiling solution. The mixture was cooled and filtered, and the solid residue was washed twice with boiling chloroform. The solid was crystallised from dimethylsulphoxide and there was thus obtained 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - piperidino - 1,7 - phenanthroline (crystallising with one molecule of solvent), m.p. 296°C. (decomposition).

The 4,10 - dihydroxy - 2,8 - dimethoxycarbonyl - 6 - piperidino - 1,7 - phenanthroline used as starting material was obtained as follows:—

A solution of acetylene dicarboxylic acid dimethyl ester (5.2 g.) in dry methanol (25 ml.) was added to a solution of 2,4 - diamino - 1 - piperidinobenzene (3.3 g.) in dry methanol (50 ml.) and, when the exothermic reaction was over, the mixture was heated under reflux for 3 hours. The solvent was removed by distillation at 60°C. *in vacuo*, and the residue of bis-anil (m.p. 122—124°C., after crystallisation from methanol) was added in portions to boiling diphenyl ether (50 ml.), and the mixture heated at 240—245°C. until no more methanol was liberated (5 minutes). The solution was cooled, and diluted with petroleum ether (b.p. 40—60°C.; 300 ml.). The solvent was decanted from the precipitated solid, and the solid was crystallised from methanol. There was thus obtained 4,10 - dihydroxy -

2,8 - dimethoxycarbonyl - 6 - piperidino - 1,7 - phenanthroline, m.p. 268—270°C.

Example 19

The appropriate methods described in Example 18 were repeated using the appropriate phenylenediamine as starting material, and the following compounds were obtained:—

2,8 - dicarboxy - 4,10 - dihydroxy - 6 - morpholino - 1,7 - phenanthroline, m.p. 317°C. (decomposition) (crystallising with one molecule of solvent from dimethylsulphoxide) from 2,4 - diamino - 1 - morpholinobenzene;

6 - di - *n* - butylamino - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 279—280°C. (decomposition) from 2,4 - diamino - 1 - di - *n* - butylaminobenzene;

4,10 - dihydroxy - 2,8 - dimethoxycarbonyl - 6 - *N* - methylanilino - 1,7 - phenanthroline, m.p. 239—240°C. (decomposition) (crystallised from dioxan), and 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - *N* - methylanilino - 1,7 - phenanthroline, m.p. 304—306°C. (decomposition) (crystallised from dimethylsulphoxide) from 2,4 - diamino - 1 - *N* - methylanilinobenzene;

6 - diethylamino - 4,10 - dihydroxy - 2,8 - dimethoxycarbonyl - 1,7 - phenanthroline, m.p. 209—210°C. (crystallised from methanol) from 2,4 - diamino - 1 - diethylaminobenzene; and

2,8 - dicarboxy - 6 - hexahydroazepin - 1 - yl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 292—293°C. (decomposition) from 2,4 - diamino - 1 - hexahydroazepinylbenzene.

The 2,4 - diamino - 1 - morpholinobenzene used in the above process was obtained as follows:—

A suspension of 4 - (2,4 - dinitrophenyl) morpholine (5 g.) in ethanol (125 ml.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of a palladium-on-charcoal catalyst (0.5 g. of 5%). When the theoretical amount of hydrogen (2.9 l.) had been absorbed, the mixture was filtered and the filtrate evaporated to dryness under the reduced pressure. The residue of 2,4 - diamino - 1 - morpholinobenzene (m.p. 126—128°C., crystallised from benzene/petroleum ether, b.p. 40—60°C.) was used directly for the subsequent reaction with acetylene dicarboxylic acid dimethyl ester.

The 2,4 - diamino - 1 - di - *n* - butylaminobenzene, 2,4 - diamino - *N* - methylanilinobenzene and 2,4 - diamino - 1 - hexahydroazepinylbenzene were obtained similarly by hydrogenation of 2,4 - dinitro - 1 - di - *n* - butylaminobenzene, 2,4 - dinitro - *N* - methylidiphenylamine and 2,4 - dinitro - 1 - hexahydroazepinylbenzene respectively. The products were oils and were used directly for

the subsequent reaction with acetylene dicarboxylic acid dimethyl ester.

Example 20

A suspension of 2,8 - dicarboxy - 6 - methyl - 4,10 - dihydroxy - 1,7 - phenanthroline (1 g.) in n-butanol (10 ml.) was saturated with hydrogen chloride gas, and then heated under reflux for 2 hours while a stream of hydrogen chloride was passed in. The clear solution was left for 12 hours at room temperature, then filtered, and the crystalline residue washed with dry ether. The solid was dissolved as much as possible in cold chloroform, the mixture filtered, and the filtrate evaporated to dryness under reduced pressure. The solid residue was crystallised from n-butanol, and there was obtained the hydrochloride of 2,8 - di - n - butoxycarbonyl - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline, m.p. 182—184°C. (decomposition), which re-solidifies above 185°C. and re-melts at 265°C. To obtain the free base, the hydrochloride was stirred and washed with water until acid-free, and the mixture was then filtered and the solid residue crystallised from n-butyl acetate. There was thus obtained 2,8 - di - n butoxycarbonyl - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline, m.p. 133—135°C.

Example 21

The method described in Example 20 was repeated, but using n-amyl alcohol in place of n-butanol, and there was obtained 4,10 - dihydroxy - 6 - methyl - 2,8 - di - n - pentyloxycarbonyl - 1,7 - phenanthroline, m.p. 127—139°C. (crystallised from diethyl ether).

Example 22

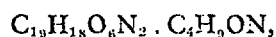
The method described in Example 8 was repeated, but using 2,8 - diethoxycarbonyl - 3,6,9 - trimethyl - 4,10 - dihydroxy - 1,7 - phenanthroline in place of 6 - n - butyl - 2,8 - dimethoxycarbonyl - 4,10 - dihydroxy - 1,7 - phenanthroline, and there was obtained 2,8 - dicarboxy - 3,6,9 - trimethyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. above 320°C. (crystallising with one molecule of solvent from dimethylsulphoxide).

The 2,8 - diethoxycarbonyl - 3,6,9 - trimethyl - 4,10 - dihydroxy - 1,7 - phenanthroline used in the above process was obtained by the method described in Example 7, but using 2,4 - diaminotoluene and ethyl ethoxalylpropionate in place of 2,4 - diamino - 1 - n - butylbenzene and acetylene dicarboxylic acid dimethyl ester respectively. There was thus obtained 2,8 - diethoxycarbonyl - 3,6,9 - trimethyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 205—206°C. (crystallised from 2-ethoxyethanol).

Example 23

A suspension of 2,8 - diethoxycarbonyl -

6 - methyl - 4,10 - dihydroxy - 1,7 - phenanthroline (0.37 g.) in ethanol (10 ml.) was mixed with a solution of morpholine (0.087 g.) in ethanol. The mixture was heated to boiling, and sufficient ethanol (40 ml.) was added to obtain almost complete dissolution. The hot mixture was filtered, the filtrate cooled and the resulting crystalline salt filtered off. There was thus obtained by morpholine salt of 2,8 - diethoxycarbonyl - 6 - methyl - 4,10 - dihydroxy - 1,7 - phenanthroline, molecular formula



m.p. 213—214°C. (decomposition) (crystallised from ethanol).

Example 24

The method described in Example 1 was repeated, but using α -chloronaphthalene in place of diphenyl ether as solvent during the cyclisation, and the mixture was heated at 220—230°C. for 10 minutes. There was thus obtained 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline, m.p. 208—209°C. (crystallised from dioxan).

Example 25

The method described in Example 1 was repeated except that the diphenyl ether was replaced by polyphosphoric acid. The residue obtained after removing the benzene was added to polyphosphoric acid (50 ml.) heated at 125°C., and the mixture was stirred and heated at 130°C. for 15 minutes. The mixture was cooled to 90°C., poured on to ice, filtered, and the filtrate basified with ammonium hydroxide (density 0.88) to pH 4. The aqueous layer was decanted from the precipitated gum, which solidified on rubbing with acetone. The mixture was filtered, and the solid residue crystallised from dioxan. There was thus obtained 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline, m.p. 208—209°C.

Example 26

The method described in Example 6 was repeated, but using an equivalent amount of 6 - n - butyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline in place of 2,8 - dicarboxy - 4,10 - dihydroxy - 6 - methyl - 1,7 - phenanthroline, and there was obtained the disodium salt of 6 - n - butyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline as a tetrahydrate after drying at room temperature in air; n.m.r. spectrum (in D₂O): H_a (or H_b) single peak (6.60 δ); H_c (or H_d) single peak (6.70 δ); H_e single peak (7.25 δ); aromatic —CH₂ of n—C₄H₉ multiplet (2.20 δ). U.V. spectrum in water: λ_{max} 231 A° (ϵ 35,000), 293 A°

(ϵ 16,400), 310 $\text{\AA}$ inflection (ϵ 13,400), 346 $\text{\AA}$ (ϵ 11,900) and 365 $\text{\AA}$ inflection (ϵ 9,160). An aqueous solution of the disodium salt had pH 4.4.

- 5 In a similar way there was obtained the disodium salt of 6 - n - propyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline as a tetrahydrate; n.m.r. spectrum (in D_2O): H_α (or H_β) single peak (6.60 δ); H_γ (or H_δ) single peak (6.70 δ); H_ϵ single peak (7.20 δ); aromatic $-\text{CH}_2-$ of $n-\text{C}_3\text{H}_7$ multiplet (2.20 δ). U.V. spectrum in water: λ_{max} 231 $\text{\AA}$ (ϵ 37,200), 293 $\text{\AA}$ (ϵ 17,500), 310 $\text{\AA}$ inflection (ϵ 14,300), 346 $\text{\AA}$ (ϵ 12,800) and 365 $\text{\AA}$ inflection (ϵ 9,530). An aqueous solution of the disodium salt had pH 4.4.

Example 27

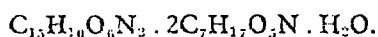
- 20 2,8 - Dicarboxycarbonyl - 6 - methyl - 4,10 - dihydroxy - 1,7 - phenanthroline (0.36 g.) was added to a hot solution of *N*-methylglucamine (0.2 g.) in ethanol (5 ml.), and the clear solution was cooled and diluted with diethyl ether. The mixture was filtered, and the solid residue was triturated with acetone, and then filtered. There was thus obtained *N*-methylglucamine salt of 2,8 - dicarboxycarbonyl - 6 - methyl - 4,10 - dihydroxy - 1,7 - phenanthroline as a hemihydrate, molecular formula



m.p. 85—90°C.

Example 28

- 35 2,8 - Dicarboxy - 6 - methyl - 4,10 - dihydroxy - 1,7 - phenanthroline (0.4 g.) was added to a solution of *N*-methylglucamine (0.39 g.) in water (3 ml.) and stirred until the solution had pH 4. The mixture was filtered, and the filtrate was diluted with ethanol (15 ml.) and decanted from the precipitated gum. The gum was stirred with acetone, and then filtered. The solid residue was the *N*-methylglucamine salt of 2,8 - dicarboxy - 6 - methyl - 4,10 - dihydroxy - 1,7 - phenanthroline, m.p. 210°C. (decomposition), and had the composition



The aqueous solution in water had pH 4.

Example 29

- 50 The method described in Example 7 was repeated, but using 1,4 - diamino - 2 - bromobenzene as starting material in place of 2,4 - diamino - 1 - n - butylbenzene, and the intermediate bis-anil (m.p. 100—101°C. after crystallisation from methanol) was cyclised in diphenyl ether by the method described in the same Example. The product (m.p. 283—284°C., crystallised from

dimethylsulphoxide) was either 5 - bromo - 2,7 - dimethoxycarbonyl - 4,9 - dihydroxypyrido[2,3-*g*]quinoline or 5 - bromo - 3,8 - dimethoxycarbonyl - 1,10 - dihydroxy - 4,7 - phenanthroline (believed more likely to be the latter). The product was hydrolysed by heating with a mixture of hydrochloric acid and acetic acid for 10 hours, according to the method described in Example 15. There was thus obtained 5 - bromo - 2,7 - dicarboxy - 4,9 - dihydroxypyrido[2,3-*g*] - quinoline or 5 - bromo - 3,8 - dicarboxy - 1,10 - dihydroxy - 4,7 - phenanthroline (believed more likely to be the latter), m.p. 290°C. (decomposition).

Example 30

The method described in Example 7 was repeated, but using 1,4 - diamino - 2 - chlorobenzene as starting material in place of 2,4 - diamino - 1 - n - butylbenzene, and the intermediate bis-anil (m.p. 100—102°C. after crystallisation from ethanol) was cyclised in diphenyl ether by the method described in the same Example.

The product [m.p. 292—294°C. (decomposition), crystallised from dimethylsulphoxide] was either 5 - chloro - 2,7 - dimethoxycarbonyl - 4,9 - dihydroxypyrido[2,3-*g*]quinoline or 5 - chloro - 3,8 - dimethoxycarbonyl - 1,10 - dihydroxy - 4,7 - phenanthroline (believed more likely to be the latter). The product was hydrolysed by heating with sodium hydroxide according to the method described in Example 8. There was thus obtained 5 - chloro - 2,7 - dicarboxy - 4,9 - dihydroxypyrido[2,3-*g*]quinoline or 5 - chloro - 3,8 - dicarboxy - 1,10 - dihydroxy - 4,7 - phenanthroline (believed more likely to be the latter) as a hemihydrate after washing with boiling ethanol, m.p. 280°C. (decomposition).

Example 31

The method described in Example 7 was repeated using 1,4 - diamino - 2 - trifluoromethylbenzene as starting material in place of 2,4 - diamino - 1 - n - butylbenzene, and the intermediate crude bis-anil was cyclised in diphenyl ether by the method described in the same example. The product [m.p. 302°C. (decomposition); crystallised from dimethylsulphoxide] was either 5 - trifluoromethyl - 2,7 - dimethoxycarbonyl - 4,9 - dihydroxypyrido[2,3-*g*]quinoline or 5 - trifluoromethyl - 3,8 - dimethoxycarbonyl - 1,10 - dihydroxy - 4,7 - phenanthroline (believed more likely to be the latter). The product was hydrolysed by heating with sodium hydroxide as described in Example 2. There was thus obtained 5 - trifluoromethyl - 2,7 - dicarboxy - 4,9 - dihydroxypyrido[2,3-*g*]quinoline or 5 - trifluoromethyl - 3,8 - dicarboxy - 1,10 - dihydroxy - 4,7 - phenanthroline (believed more likely to

be the latter) as a dihydrate, m.p. 320°C. (decomposition).

Example 32

The disodium salt of 6 - n - propyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline (20 g.; screened through mesh size 90; all mesh sizes herein are according to British Standard 410:1962) and lactose (15 g.; screened through mesh size 90) were thoroughly mixed. There was thus obtained a powder formulation suitable for inhalation for medicinal purposes.

Example 33

An aerosol formulation was prepared consisting of finely divided disodium salt of 6 - n - butyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline (2% w/w; screened through mesh size 90), isoprenaline sulphate (0.1% w/w; screened through mesh size 90), and propellant to 100% w/w (the propellant was a 60:40 v/v mixture of dichloro-difluoromethane and 1,2 - dichloro - 1,1,2,2 - tetrafluoroethane). There was thus obtained an aerosol formulation suitable for inhalation for medicinal purposes.

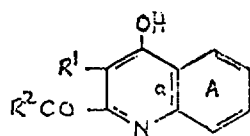
Example 34

A mixture of 6 - n - butyl - 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 1,7 - phenanthroline (50 g.) and mannitol (25 g.) was filled into hard gelatin capsules. There was thus obtained capsules containing between 25 mg. and 500 mg. of active ingredient which are suitable for oral administration for therapeutic purposes.

The active ingredient used in the above process was replaced by equivalent quantity of 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 6 - n - propyl - 1,7 - phenanthroline, and there were thus obtained capsules containing between 25 mg. and 500 mg. of active ingredient which were suitable for oral administration for therapeutic purposes.

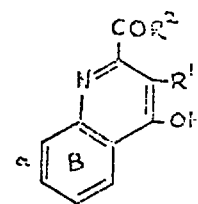
WHAT WE CLAIM IS:—

1. A pyridoquinoline derivative of the formula:



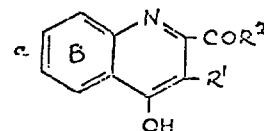
(I)

wherein the benzene ring A stands for a group of the formula:—



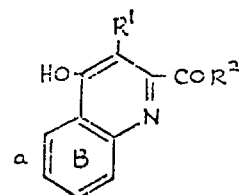
(II)

or



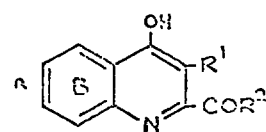
(III)

or



(IV)

or



(V)

wherein a in the formulae II to V indicates the common bond between the pyridine ring and the benzene ring A in the formula I; R¹ stands for hydrogen or a methyl radical; R² stands for a hydroxy, C₁₋₆ alkoxy, C₁₋₁₁ phenylalkoxy or phenoxy radical; and the benzene ring B may optionally bear not more than two substituents selected from C₁₋₃ alkyl, cycloalkyl of not more than 6 carbon atoms, C₁₋₆ alkoxy, trifluoromethyl, phenyl and phenoxy radicals, and halogen atoms, and NR³R⁴ radicals wherein R³ stands for a C₁₋₆ alkyl radical and R⁴ stands for a C₁₋₆ alkyl or phenyl radical or wherein —N⁺R⁴ stands for a nitrogen-containing heterocyclic radical of not more than 7 ring atoms; or, in the case of the formula II or IV, the benzene ring B may optionally bear an alkylene radical of 3—5 carbon atoms; and wherein when R¹ stands for a methyl radical, the compounds are 1,7-phenanthroline derivatives only, bearing either a C₁₋₆-alkyl, C₁₋₁₁-alkoxy, phenoxy, piperidino or morpholino substitu-



be the latter) as a dihydrate, m.p. 320°C. (decomposition).

Example 32

- 5 The disodium salt of 6 - n - propyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline (20 g.; screened through mesh size 90; all mesh sizes herein are according to British Standard 410:1962) and lactose (15 g.; screened through mesh size 90) were thoroughly mixed. There was thus obtained a powder formulation suitable for inhalation for medicinal purposes.

Example 33

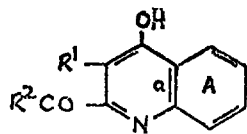
- 15 An aerosol formulation was prepared consisting of finely divided disodium salt of 6 - n - butyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline (2% w/w; screened through mesh size 90), isoprenaline sulphate (0.1% w/w; screened through mesh size 90), and propellant to 100% w/w (the propellant was a 60:40 v/v mixture of dichloro-difluoromethane and 1,2 - dichloro - 1,1,2,2 - tetrafluoroethane). There was thus obtained an aerosol formulation suitable for inhalation for medicinal purposes.

Example 34

- 25 A mixture of 6 - n - butyl - 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 1,7 - phenanthroline (50 g.) and mannitol (25 g.) was filled into hard gelatin capsules. There was thus obtained capsules containing between 25 mg. and 500 mg. of active ingredient which are suitable for oral administration for therapeutic purposes.
- 35 The active ingredient used in the above process was replaced by equivalent quantity of 2,8 - diethoxycarbonyl - 4,10 - dihydroxy - 6 - n - propyl - 1,7 - phenanthroline, and there were thus obtained capsules containing between 25 mg. and 500 mg. of active ingredient which were suitable for oral administration for therapeutic purposes.

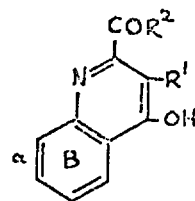
WHAT WE CLAIM IS:—

- 45 1. A pyridoquinoline derivative of the formula:



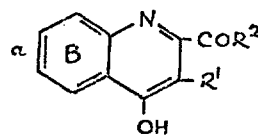
(I)

wherein the benzene ring A stands for a group of the formula:—



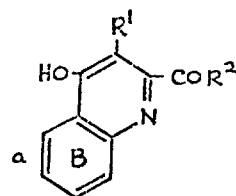
(II)

or



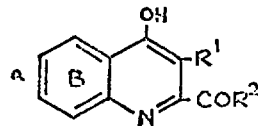
(III)

or



(IV)

or



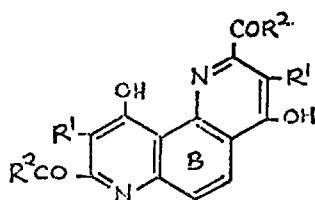
(V)

wherein a in the formulac II to V indicates the common bond between the pyridine ring and the benzene ring A in the formula I; R¹ stands for hydrogen or a methyl radical; R² stands for a hydroxy, C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical; and the benzene ring B may optionally bear not more than two substituents selected from C₁₋₈ alkyl, cycloalkyl of not more than 6 carbon atoms, C₁₋₆ alkoxy, trifluoromethyl, phenyl and phenoxy radicals, and halogen atoms, and NR³R⁴ radicals wherein R³ stands for a C₁₋₆ alkyl radical and R⁴ stands for a C₁₋₆ alkyl or phenyl radical or wherein —N³R⁴ stands for a nitrogen-containing heterocyclic radical of not more than 7 ring atoms; or, in the case of the formula II or IV, the benzene ring B may optionally bear an alkylene radical of 3—5 carbon atoms; and wherein when R¹ stands for a methyl radical, the compounds are 1,7-phenanthroline derivatives only, bearing either a C₁₋₃-alkyl, C₁₋₄-alkoxy, phenoxy, piperidino or morpholino substitu-

ent in the 5- or 6-position, or 5,6 - dimethyl or 5 - phenyl - 6 - methoxy substituents, or a 5,6-alkylene substituent of 3-5 carbon atoms; or a non-toxic pharmaceutically-acceptable salt thereof; but excluding 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline and di - C₁₋₆ - alkyl esters thereof, and 4,9 - dihydroxy - 2,7 - dimethoxycarbonylpyrido[2,3-g]quinoline, and non-toxic pharmaceutically-acceptable salts thereof.

2. A pyridoquinoline derivative of the formula I, wherein the benzene ring A stands for a group of the formula II, III, IV or V; wherein a in the formulae II to V indicates the common bond between the pyridine ring and the benzene ring A in the formula I; R¹ stands for hydrogen; R² stands for a hydroxy, C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical; and the benzene ring B may optionally bear not more than two substituents selected from C₁₋₆ alkyl, C₁₋₆ alkoxy, trifluoromethyl, phenyl and phenoxy radicals, and halogen atoms, and NR³R⁴ radicals wherein R³ and R⁴ are the same or different and either stands for a C₁₋₆ alkyl radical; or a non-toxic pharmaceutically-acceptable salt thereof; but excluding 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline and di - C₁₋₆ - alkyl esters thereof, and 4,9 - dihydroxy - 2,7 - dimethoxycarbonylpyrido[2,3-g]quinoline, and non-toxic pharmaceutically-acceptable salts thereof.

3. A 1,7 - phenanthroline derivative of the formula:—



(VI)

wherein R¹ stands for hydrogen, R² stands for a hydroxy radical, and the benzene ring B bears a C₁₋₆ alkyl radical in the 6-position of the phenanthroline nucleus, or a non-toxic pharmaceutically-acceptable salt thereof.

4. A compound as claimed in claim 3 in which the alkyl radical in the said 6-position is a C₂₋₄ alkyl radical.

5. A pyridoquinoline derivative of the formula I, wherein the benzene ring A stands for a group of the formula II, III, IV or V; wherein a in the formulae II to V indicates the common bond between the pyridine ring and the benzene ring A in the formula I; R¹ stands for hydrogen; R² stands for a hydroxy, C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical; and the benzene ring B may optionally bear not more than two substitu-

ents selected from C₁₋₆ alkyl, cycloalkyl of not more than 6 carbon atoms, C₁₋₆ alkoxy, trifluoromethyl, phenyl and phenoxy radicals, and halogen atoms, and NR³R⁴ radicals wherein R³ and R⁴ are the same or different and either stands for a C₁₋₆ alkyl radical; or, in the case of the formula II or IV, the benzene ring B may optionally bear an alkyl radical of 3 to 5 carbon atoms; or a non-toxic pharmaceutically-acceptable salt thereof; but excluding 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline and di - C₁₋₆ - alkyl esters thereof, and 4,9 - dihydroxy - 2,7 - dimethoxy - carbonylpyrido[2,3-g]quinoline, and non-toxic pharmaceutically-acceptable salts thereof.

6. A compound as claimed in claim 1 wherein R² stands for a methoxy, ethoxy, n-propoxy, n-butoxy, n-pentyloxy or benzyl-oxy radical.

7. A compound as claimed in claim 1 or 6 wherein the ring B bears not more than two substituents selected from methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclohexyl, methoxy, ethoxy, propoxy, trifluoromethyl, phenyl, phenoxy, dimethyl-amino, diethylamino, dipropylamino, dibutyl-amino and N-methylanilino radicals, and saturated heterocyclic radicals of 5,6 or 7 ring atoms, containing a nitrogen atom as hetero-atom and optionally containing a second hetero-atom which is an oxygen atom, and fluorine, chlorine and bromine atoms.

8. A compound as claimed in claim 1 or 6 which is of the formula VI or VIII, wherein the ring B bears a trimethylene, tetramethylene or pentamethylene radical.

9. A compound as claimed in claim 1 or 7 which is of the formula VI, wherein R¹ stands for hydrogen, R² stands for a hydroxy radical, and the benzene ring B bears a C₁₋₆ alkyl radical in the 6-position of the nucleus.

10. A compound as claimed in claim 9 wherein the benzene ring B bears an n-propyl, n-butyl, t-butyl or n-pentyl radical in the 6-position of the nucleus.

11. A salt as claimed in any of claims 1 to 10 which is a non-toxic pharmaceutically-acceptable acid-addition salt.

12. A salt as claimed in any of claims 1 to 10 wherein R² stands for a hydroxy radical and/or the ring hydroxy radical(s) is or are sufficiently acid, which is a salt containing a non-toxic pharmaceutically-acceptable cationic moiety.

13. 6 - n - Butyl - 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline or a non-toxic pharmaceutically-acceptable salt thereof.

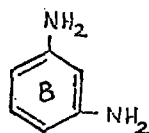
14. 2,8 - Dicarboxy - 4,10 - dihydroxy - 6 - n - propyl - 1,7 - phenanthroline or a non-toxic pharmaceutically-acceptable salt thereof.

15. 2,8 - Dicarboxy - 4,10 - dihydroxy -



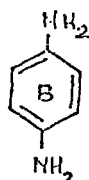
6 - n - pentyl - 1,7 - phenanthroline or a non-toxic pharmaceutically-acceptable salt thereof.

- 5 16. A process for the manufacture of a compound claimed in claim 1, wherein A and R¹ have the meanings stated in claim 1 and R² stands for a C₁₋₆ alkoxy radical, which comprises carrying out the Conrad-Limpach reaction on a diamino compound of the formula:—



(XI)

or



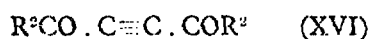
(XII)

- 15 wherein B has the meaning stated in claim 1, and a compound of the formula:—



wherein R¹ has the meaning stated in claim 1 and R² stands for a C₁₋₆ alkoxy radical.

- 20 17. A process as claimed in claim 16 in which the first stage of the Conrad-Limpach reaction is carried out at 80—110°C. in an aromatic hydrocarbon solvent and in an apparatus which facilitates the removal of water formed during the said first stage.
- 25 18. A process as claimed in claim 16 or 17 in which the second stage of the Conrad-Limpach reaction is carried out by heating the intermediate compound of the formula XIV or XV at 230—250°C. in diphenyl ether or α-chloronaphthalene, or by heating the said intermediate compound with polyphosphoric acid at 130—180°C.
- 30 19. A process for the manufacture of a compound claimed in claim 1, wherein A has the meaning stated in claim 1, R¹ stands for hydrogen, and R² stands for a C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical, which comprises reacting a diamino compound of the formula XI or XII with an
- 40 acetylene derivative of the formula:—



wherein R² has the meaning stated immediately above, so as to give an intermediate compound which in one of its tautomeric forms has the formula XIV or XV respectively, wherein R¹ stands for hydrogen, and then ring-closing this compound by heating it at 230—250°C., for example in diphenyl ether or α-chloronaphthalene, or by heating it with polyphosphoric acid at 130—180°C.

20. A process for the manufacture of a compound claimed in claim 1, wherein A and R¹ have the meanings stated in claim 1 and R² stands for a hydroxy radical, which comprises hydrolysing the corresponding alkyl, phenylalkyl or phenyl ester or the corresponding nitrile or amide.

21. A process as claimed in claim 20 wherein the hydrolytic agent is an alkali metal hydroxide or an inorganic acid.

22. A process for the manufacture of a compound claimed in claim 1, wherein A and R¹ have the meanings stated in claim 1 and R² stands for a C₁₋₆ alkoxy radical, which comprises esterifying the appropriate carboxylic acid or trans-esterifying an appropriate ester.

23. A compound of the formula I, wherein the benzene ring A stands for a group of the formula II, III, IV or V, and a, R¹, R² and B have the meanings stated in claim 1, or a non-toxic pharmaceutically-acceptable salt thereof, but excluding 2,8 - dicarboxy - 4,10 - dihydroxy - 1,7 - phenanthroline and di - C₁₋₆ - alkyl esters thereof, and 4,9 - dihydroxy - 2,7 - dimethoxycarbonylpyrido - [2,3-g]quinoline and non-toxic pharmaceutically-acceptable salts thereof, whenever prepared by a process claimed in any of claims 16 to 22.

24. A pharmaceutical composition comprising a compound of the formula I, wherein the benzene ring A stands for a group of the formula II, III, IV or V; wherein a in the formula II to V indicates the common bond between the pyridine ring and benzene ring A in the formula I; R¹ stands for hydrogen or a methyl radical; R² stands for a hydroxy, C₁₋₆ alkoxy, C₇₋₁₀ phenylalkoxy or phenoxy radical; and the benzene ring B may optionally bear not more than two substituents selected from C₁₋₈ alkyl, cycloalkyl of not more than 6 carbon atoms, C₁₋₆ alkoxy, trifluoromethyl, phenyl and phenoxy radicals, and halogen atoms, and NR³R⁴ radicals wherein R³ stands for a C₁₋₆ alkyl radical and R⁴ stands for a C₁₋₆ alkyl or phenyl radical or wherein —NR³R⁴ stands for a nitrogen-containing heterocyclic radical of not more than 7 ring atoms; or, in the case of formula II or IV, the said benzene ring B may optionally bear an alkylene radical of 3—5 carbon atoms; and wherein when R¹ stands for a methyl radical, the compounds are 1,7-phenanthroline derivatives only, bearing either a C₁₋₆-alkyl, C₁₋₄-alkoxy, phenoxy,



- 5 piperidino or morpholino substituent in the 5- or 6-position, or 5,6-dimethyl or 5-phenyl - 6 - methoxy substituents, or a 5,6-alkylene substituent of 3—5 carbon atoms; or a non-toxic pharmaceutically-acceptable salt thereof; and an inert non-toxic pharmaceutically-acceptable diluent or carrier.
- 10 25. A composition as claimed in claim 24 which is in a form suitable for administration by inhalation.
- 15 26. A composition as claimed in claim 24 which is in a form suitable for intravenous administration.
- 20 27. A composition as claimed in claim 24 which is in a form suitable for oral administration.
28. A composition as claimed in any of claims 24 to 27 which contains, in addition to a compound of the formula I, one or more other known active ingredients selected from β -adrenergic stimulants, prostaglandins having bronchodilatory activity and phosphodiesterase inhibitors selected from the following compounds:—
- 25 (a) 3 - acetamido - 6 - methyl - 8 - n - propyl - s - triazolo[4,3-a] - pyrazine; (b) 2 - amino - 4,6 - di - C₁₋₄ - alkyl - 5 -
- oxo - 4,5 - dihydro - s - triazolo[1,5-a] pyrimidines; (c) theophylline and related 3,5 - di - C₁₋₄ - alkylxanthines; and (d) 6,8 - di - C₁₋₄ - alkyl - 5,6 - dihydro - 5 - oxo - s - triazolo[4,3-c]pyrimidines.
29. A composition as claimed in any of claims 24 to 28 which contains 1% to 50% by weight of a compound of the formula I, or a non-toxic pharmaceutically-acceptable salt thereof.
30. A compound, claimed in claim 2, substantially as described in Example 1, 2 or 3.
31. A compound, claimed in claim 2, 3 or 4, substantially as described in Example 4 or 5.
32. A compound, claimed in claim 5, substantially as described in any of Examples 6 to 13.
33. A compound, claimed in claim 1, substantially as described in any of Examples 14 to 31.
34. A pharmaceutical composition, claimed in claim 24, substantially as described in Example 32, 33 or 34.
- R. ALLERTON,
Agent for the Applicants.

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ERRATA

SPECIFICATION No. 1,308,787

- Page 2, line 21, *after wherein insert when*
 Page 2, line 55, *for quinoline read quinolone*
 Page 4, lines 5 and 6, *for R' read R¹*
 Page 4, line 42, *for and read or*
 Page 6, line 47, *for at read as*
 Page 6, line 48, *after have insert been*
 Page 8, line 109, *for propylbenzene read propylbenzene*
 Page 10, line 29, *delete the*
 Page 10, line 82, *for N read N*
 Page 11, line 71, *for by read the*
 Page 13, line 69, *for —N³R⁴ read —NR³R⁴*

THE PATENT OFFICE
25th June, 1973



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