1 460 389

# PATENT SPECIFICATION (11) 1 460 389

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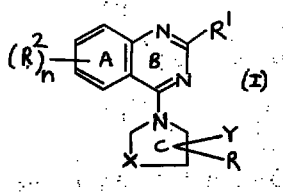
## (54) 4-SUBSTITUTED QUINAZOLINE CARDIAC STIMULANTS

(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 invention relates to therapeutic agents, which are novel derivatives of quinazoline, and is particularly concerned with such derivatives having a substituted heterocyclic group in the 4-position.

The compounds of the invention are cardiac stimulants of which a preferred class selectively increases the force of myocardial contraction without producing significant increases in the heart rate. The compounds are useful in the curative or prophylactic treatment of cardiac conditions such as congestive heart failure, angina pectoris, cardiac arrhythmias and acute heart failure.

According to the invention there is provided novel quinazoline compounds of the formula:



(I)

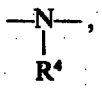
wherein (i) $R^1$ is a hydrogen atom or a lower alkyl group; $(R^2)n$ represents 1 to 3 optional substituents, each $R^2$ being a hydroxy or lower alkoxy group, and n being 0 to 3, or any two of the moieties $R^2$ constitute a methylenedioxy or ethylenedioxy group attached to adjacent positions of ring A;

(ii) X represents $-(CH_2)_p-$ wherein p is 1 to 3, —CH=CH— or $-CH_2.CH=CH-$;

(iii) Y is attached to the 3- or 4-position of ring C and represents *either:*

(a) a group of the formula $-Z^1-COR^3$

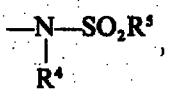
wherein $Z^1$ is $-CH_2-$ or



$R^3$ is a lower alkyl group optionally substituted by an amino (as hereinafter defined), hydroxy, lower alkoxy, aryl or heteroaryl group; a lower alkenyl- or lower alkynyl-methyl group; a lower alkoxy group optionally substituted by an amino (as hereinafter defined), aryl, heteroaryl, lower alkoxy or hydroxy group; an aryl group; an aryloxy group; or a heteroaryl group;

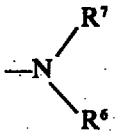
and $R^4$ is a hydrogen atom; a lower alkyl group optionally substituted by an amino (as hereinafter defined), lower alkoxy, hydroxy, carbethoxy, aryl or heteroaryl group; a lower alkenyl- or lower alkynyl-methyl group; an aryl group or a heteroaryl group;

(b) a group of the formula



wherein $R^4$ is as defined above and

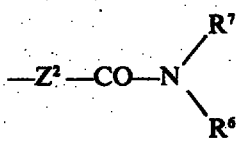
$R^5$ is a group as defined for $R^3$ above or is a group of the formula:



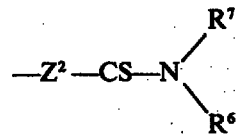
in which $R^7$ is a hydrogen atom or a lower alkyl group and $R^6$ is a group as defined for $R^4$ above, or $R^6$ and $R^7$ taken together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic ring;

*or,*

(c) a group of the formula



or



wherein $Z^2$ is $Z^1$ or $-O-$, and $R^6$ and $R^7$ are as defined above, provided that when $Z^2$ is



$R^4$ and $R^7$ taken together may represent $-(CH_2)_2-$, $-(CH_2)_3-$ or an *o*-phenylene group;

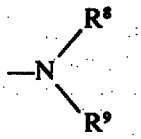
and (iv) R is a hydrogen atom or a lower alkyl group attached to the same carbon atom as Y; *provided that* when X is —CH=CH— or

—$CH_2CH$=$CH$—, R is absent and Y is —$CH_2COR^3$, —$CH_2CO\,N(R^6)(R^7)$ or —$CH_2CS\,N(R^6)(R^7)$ wherein $R^3$, $R^6$ and $R^7$ are as defined above, Y being attached to an unsaturated ring carbon atom;

and their pharmaceutically acceptable acid addition salts. The term "lower" applied to an alkyl, alkenyl, alkynyl or alkoxy group indicates that such a group contains up to 6 carbon atoms, preferably up to 4 carbon atoms, and such groups may be straight or, when appropriate, branched chain.

"Aryl" and "heteroaryl" as used herein include unsubstituted aryl and heteroaryl groups, and aryl and heteroaryl groups substituted by lower alkyl, lower alkoxy, hydroxy, halogen or acetamido groups.

By the term "amino" as used herein, is meant a group of the formula:



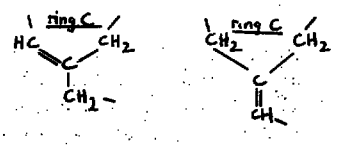
wherein $R^8$ is hydrogen or lower alkyl, and $R^9$ is hydrogen, lower alkyl, or aryl substituted lower alkyl, or $R^8$ and $R^9$ taken together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic group (e.g. piperidino).

"Halogen" means fluorine, chlorine, bromine or iodine.

The compounds of the invention containing one or more asymmetric centres will exist as one or more pairs of enantiomers, and such pairs or individual isomers may be separable by physical methods, e.g. by fractional crystallisation or chromatography of the free bases or suitable salts. The invention includes the separated pairs as well as mixtures thereof, as racemic mixtures or as separated D— and L— optically-active isomeric forms.

The pharmaceutically acceptable acid addition salts of of the compounds of the invention are those formed from acids which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate and p-toluenesulphonate salts.

It should be understood that compounds of the formula (I) in which ring C is unsaturated may exist in tautomeric forms:



The cardiac stimulant activity of the compounds of the invention is shown by their effectiveness in one or more of the following tests: (a) increasing the force of contraction in the isolated, spontaneously beating, guinea pig double atria preparation; (b) increasing myocardial contractility (left ventricular $dP/_{dt}$ max,) in the anesthetised dog with an implanted left ventricular catheter; (c) increasing myocardial contractility in the conscious dog with an implanted left ventricular transducer.

In test (a) the positive inotropic and chronotropic responses of the atria to the test compound are measured at several doses and compared with the responses elicited by isoprenaline. The comparison of the dose response curves obtained gives a measure of the force versus rate selectivity of the test compound.

In test (b) the positive inotropic action of the test compound following intravenous administration is measured in the anaesthetised dog and compared with that of isoprenaline. The potency of the inotropic action, the selectivity for increase in force versus frequency of contraction, and the duration of action of the positive inotropic effect of the test compound are obtained, as are its peripheral effects, e.g. the effect on the blood pressure.

In test (c) the positive inotropic action of the test compound following intravenous or oral administration to a conscious dog with an implanted left

ventricular transducer is measured and compared with that of isoprenaline. The potency of the inotropic action, the selectivity for increase in force versus frequency of contraction, and the duration of action of the inotropic effect of the test compound are all obtained.

By virtue of the performance of the compounds of the invention in the above tests, the preferred groups have been found to be as follows:—

$(R^2)_n$ preferably represents 6,7-di(lower alkoxy), most preferably 6,7-dimethoxy.

X preferably represents $—CH_2—$, $—(CH_2)_2—$ or $—CH=CH—$.

X is most preferably $—(CH_2)_2—$.

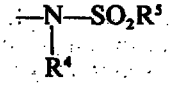
$R^1$ is preferably a hydrogen atom.

When ring C is saturated, R is preferably hydrogen.

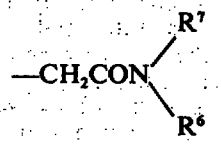
Preferred Y groups are as follows:—

$—CH_2COR^3$ wherein $R^3$ is a lower alkyl or lower alkoxy group;

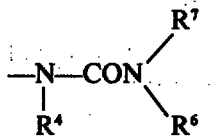
$—NR^4.COR^3$ wherein $R^3$ is a lower alkyl group; a lower alkyl group substituted by an amino (as hereinbefore defined) or alkoxy group; a lower alkoxy group; a lower alkoxy group substituted by an aryl group; an aryloxy group; or a heteroaryl group; and $R^4$ is a hydrogen atom; a lower alkyl group; or a lower alkyl group substituted by a hydroxy group;



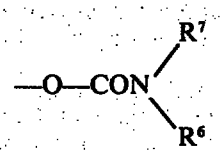
wherein $R^4$ is a hydrogen atom or a lower alkyl group; and $R^5$ is a lower alkyl, aryl or heteroaryl group, or a group of the formula $—N(R^6)(R^7)$ wherein $R^6$ is a lower alkyl group and $R^7$ is a hydrogen atom or a lower alkyl group;



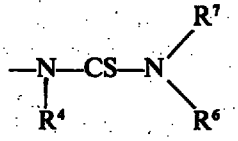
wherein $R^6$ is a lower alkyl group and $R^7$ is a hydrogen atom;



wherein $R^4$ is a hydrogen atom; a lower alkyl group; a lower alkyl group substituted by a heteroaryl, aryl, amino (as hereinbefore defined) or hydroxy group; or a heteroaryl group; $R^6$ is a hydrogen atom; a lower alkyl group; a lower alkyl group substituted by a hydroxy, carbethoxy or heteroaryl group; a lower alkenyl-methyl group; a lower alkynyl-methyl group; an aryl group or a heteroaryl group; and $R^7$ is a hydrogen atom or a lower alkyl group; or $R^4$ and $R^7$ taken together represent an o-phenylene group; or $R^6$ and $R^7$ taken together represent $—(CH_2)_5—$;

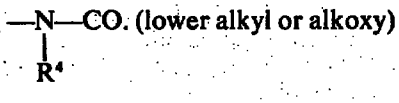


wherein $R^6$ is a hydrogen atom, a lower alkyl group or a heteroaryl group and $R^7$ is a hydrogen atom; and



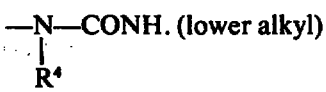
wherein $R^4$ is a hydrogen atom or a lower alkyl group; $R^6$ is a lower alkyl group; and $R^7$ is a hydrogen atom.

Y is most preferably a group selected from the following:—

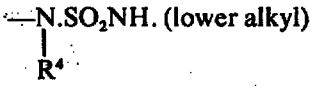


wherein $R^4$ is a hydrogen atom or a lower alkyl group;

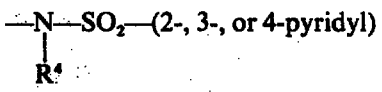
—OCONH. (lower alkyl);



wherein $R^4$ is a hydrogen atom, a lower alkyl group or a lower alkyl group substituted by a 2-, 3- or 4-pyridyl group;



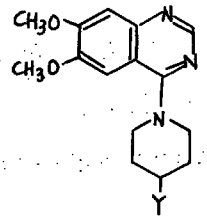
wherein $R^4$ is a hydrogen atom or a lower alkyl group; *and*



wherein $R^4$ is a hydrogen atom or a lower alkyl group.

The preferred aryl group is a phenyl group and the preferred heteroaryl group is a 2-, 3- or 4-pyridyl group. The preferred aryloxy group is a phenoxy group. The preferred alkenyl and alkynyl groups are, respectively, —$CH{=}CH_2$ and —$C{\equiv}CH$.

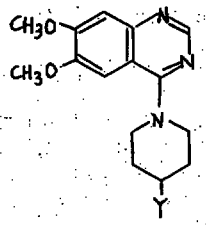
The most preferred compounds of the invention have the structure:—



(II)

wherein Y is as defined above.

The preferred individual compounds of the formula (I) have the structure:—



(IIA)

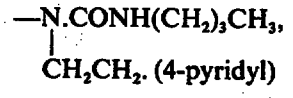
wherein Y is:—

(a) —$NHCONH(CH_2)_3CH_3$, i.e., 4-(4-[3-*n*-butyl-ureido]-piperidino)-6,7-dimethoxy-quinazoline,

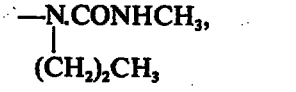
(b) —$N(CH_3)CONH(CH_2)_2CH_3$, i.e., 4-[4-[1-methyl-3-*n*-propyl-ureido]-piperidino]-6,7-dimethoxy-quinazoline

(c) —$NHCOOCH_2CH_3$, i.e., 4 - [4 - [ethoxycarbonylamino]piperidino]-6,7-dimethoxy-quinazoline

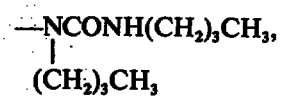
(d) —O.CONHCH$_2$CH$_3$, i.e., 4-[4-{ethylcarbamoyloxy}piperidino]-6,7-dimethoxy-quinazoline
(e) —N(CH$_3$).SO$_2$NH(CH$_2$)$_2$CH$_3$, i.e., 4-[4-{N-methyl - n - (*n* - propylsulfamoyl)-amino}piperidino]-6,7-dimethoxy-quinazoline
(f) —N(CH$_3$).COOCH$_2$CH$_3$, i.e., 4-[4-{N-methyl-N-ethoxycarbonylamino}piperidino]-6,7-dimethoxy-quinazoline
(g) —NHCOOCH$_2$.CH(CH$_3$)$_2$, i.e., 4-[4-{*iso*-butoxycarbonylamino}piperidino]-6,7-dimethoxy-quinazoline
(h) —NHCOO(CH$_2$)$_2$CH$_3$, i.e., 4-[4-{*n*-propoxycarbonylamino}piperidino]-6,7-dimethoxy-quinazoline
(i) —N(Et).COOEt, i.e., 4-[4-{N-ethyl-N-ethoxycarbonylamino}piperidino]-6,7-dimethoxy-quinazoline

(j)


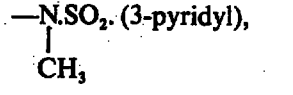
i.e., 4-[4-{3-*n*-butyl-1-(2-pyrid-4-yl-ethyl)-ureido}piperidino]-6,7-dimethoxy-quinazoline

(k)


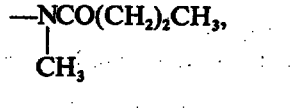
i.e., 4-[4-{3-methyl-1-*n*-propyl-ureido}piperidino]-6,7-dimethoxy-quinazoline

(l)


i.e. 4-[4-{1,3-di-*n*-butyl-ureido}piperidino]-6,7-dimethoxy-quinazoline
(m) —OCONH(CH$_2$)$_2$CH$_3$, i.e. 4-[4-{*n*-propylcarbamoyloxy}piperidino]-6,7-dimethoxy-quinazoline
(n) —NHSO$_2$NH(CH$_2$)$_2$CH$_3$, i.e. 4-[4-{N-(*n*-propylsulfamoyl) amino}piperidino]-6,7-dimethoxy-quinazoline
(o) —NHSO$_2$. (3-pyridyl), i.e. 4-[4-{3-pyridinesulfonamido}piperidino]-6,7-dimethoxy-quinazoline

(p)


i.e. 4 - [4 - {N - methyl - 3 - pyridinesulfonamido}piperidino] - 6,7 - dimethoxy-quinazoline

(q)


i.e. 4-[4-{N-methylbutyramido}piperidino]-6,7-dimethoxy-quinazoline
*and*
(r) —NHCO(CH$_2$)$_2$CH$_3$, i.e. 4-[4-{butyramido}piperidino]-6,7-dimethoxy-quinazoline.

The compounds of the invention can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They may be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough salts or glucose to make the solution isotonic.

For administration to man in the curative or prophylatic treatment of cardiac conditions such as congestive heart failure, it is expected that oral dosages of the

most active compounds of the invention will be in the range from 20 mg. to 1 g. daily, taken in 2 to 4 divided doses per day, for an average adult patient (70 kg.). Dosages for intravenous administration would be expected to be within the range 1 to 300 mg. per single dose as required, for example in the treatment of acute heart failure. Thus for a typical adult patient, individual tablets or capsules might contain from 5 to 500 mg. of active compound, in a suitable pharmaceutically-acceptable vehicle or carrier.

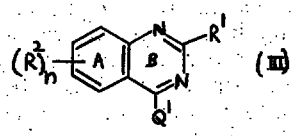
Thus the present invention provides a pharmaceutical composition comprising a compound of the formula (I) as defined above together with a pharmaceutically acceptable carrier.

The invention also provides a method of stimulating the heart of a non-human animal which comprises administering to the animal a compound of the formula (I) as defined above, or a pharmaceutical composition as defined above, in an amount sufficient to stimulate the heart of the animal.

The compounds of the invention may be prepared by a number of routes:

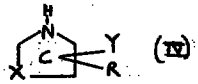
*Route A*

Compounds of the formula (I) may be prepared by reacting an appropriately substituted quinazoline of the formula:



(III)

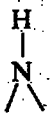
wherein $Q^1$ represents a good leaving group such as chloro-, bromo-, iodo-, lower alkoxy or (lower alkyl) thio, with an amine of the formula:



(IV)

with resultant elimination of $HQ^1$. $Q^1$ is preferably chloro or bromo. The reaction is preferably carried out in an inert organic solvent such as ethanol or dimethylformamide with heating, e.g. under reflux, in a temperature range of 75° to 150°C for one or more hours, generally 1 to 8 hours. When $Q^1$ is chloro-, bromo-, or iodo, the presence of a base such as triethylamine or of excess reagent of the formula (IV) is advantageous.

Any substituent groups in the reactants capable of displacing the leaving group $Q^1$, other than the

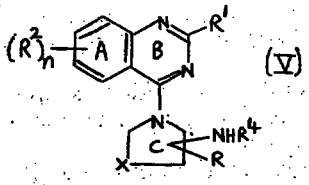


group of the compound of the formula (IV), i.e. hydroxy, primary amino and secondary amino groups, should generally be protected prior to the reaction by conventional methods, the protecting groups being removed after the reaction by standard procedures. Any hydroxy groups present may, if necessary, be protected by, for example, a benzyl group, which group may be removed after the reaction by hydrogenolysis. Any primary or secondary amino groups may, if necessary, be protected by, e.g. a benzyl or t-butoxy carbonyl group, which groups can be removed after the reaction by, respectively, hydrogenation or mild acid hydrolysis.

The product is typically isolated and purified by evaporation of the solvent *in vacuo*, followed by basification of the residue with a base such as aqueous sodium carbonate and extraction of the product into a suitable organic solvent, e.g. chloroform. After evaporation of the organic solvent, the crude product is left as a residue which is either converted to a salt and subsequently purified or recrystallised as the free base.

*Route B*

Compounds of the formula (I) in which X is —$(CH_2)p$— and Y is —$NR^4CONHR^6$ or —$NR^4CSNHR^6$ may be prepared by reacting a quinazoline of the formula:



(V)

in which X is —$(CH_2)p$—, with *either* an isocyanate $R^6NCO$ or isothiocyanate $R^6NCS$, $R^6$ being other than hydrogen, *or*, to prepare compounds wherein $R^6$ is H, sodium or potassium cyanate or thiocyanate in the presence of acid. To prepare compounds in which $R^6$ is other than hydrogen, the reaction is preferably carried out by allowing the reactants to stand together at room temperature for up to about 3 hours in an inert organic solvent such as chloroform. The product may then be isolated by evaporation of the solvent, and recrystallisation of the thus-produced residue from a suitable solvent by normal methods. Alternatively, the residue may be reacted with an acid to form a salt, and subsequently purified as such. To prepare compounds in which $R^6$ is hydrogen, the reactants are preferably heated together under reflux in a suitable solvent, e.g. aqueous ethanol, and in the presence of acid. The acid may be supplied by using and acid addition salt of the compound of the formula (V) as the starting material.

Any groups capable of reacting with isocyanate or isothiocyanate groups or, as appropriate, with the cyanate or thiocyanate, other than of course the —NH— group of —$NHR^4$ in ring C, should generally be protected by conventional protecting groups prior to the reaction, the protecting group being removed by standard procedures after the reaction. Groups which it may be necessary to protect include hydroxy, primary amino and secondary amino groups, which groups may be present in $R^2$, $R^4$ and $R^6$.

*Route C*

Compounds of the formula (I) wherein X is —$(CH_2)p$— and Y is either —$NR^4COR^3$, —$NR^4SO_2R^5$ or —$NR^4CONR^6R^7$, may be prepared by reacting a compound of the formula (V) as previously defined with, as appropriate, *either:*

(a) a haloformate or acyl halide of the formula $Q^2COR^3$ wherein $Q^2$ is chloro or bromo;

(b) a halosulfonate, sulfonyl halide or sulfamyl halide of the formula $Q^2SO_2R^5$, $Q^2$ being chloro or bromo;

(c) a carbamyl halide of the formula $R^6R^7NCOQ^2$ wherein $R^6$ and $R^7$ are both other than hydrogen, and $Q^2$ is chloro or bromo;

*or,*

(d) an anhydride or pyrocarbonate of the formula $(R^3CO)_2O$.

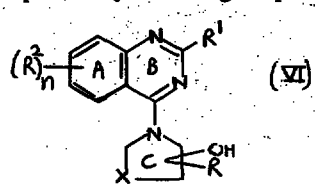
Preferably the reactants are allowed to stand together at room temperature for a period of up to a few hours in an inert organic solvent, e.g. chloroform, in the presence of a base such as triethylamine.

Any groups in $R^2$ to $R^7$ capable of reacting with, or displacing as appropriate, the anhydride, pyrocarbonate or the group $Q^2$, e.g. hydroxy, primary amino, and secondary amino groups, should, if necessary, be protected prior to the reaction by conventional protecting groups which may be removed after the reaction by standard procedures.

The product is typically isolated and purified by the method described under Route A.

*Route D*

Compounds of the formula (I) wherein X is —$(CH_2)p$— and Y is —$OCONHR^6$ or —$OCSNHR^6$ may be prepared by reacting a quinazoline of the formula:



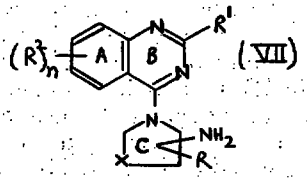
(VI)

X being —$(CH_2)p$—, with an isocyanate $R^6NCO$ or isothiocyanate $R^6NCS$, $R^6$ being other than hydrogen, or, to prepare compounds in which $R^6$ is hydrogen, sodium or potassium cyanate or thiocyanate in the presence of acid. Generally the reactants are heated together at temperatures of 100° to 200°C in e.g. a stainless steel bomb for a period of 24 to 48 hours in an inert organic solvent.

Any groups capable of reacting with isocyanate or isothiocyanate groups, or, as appropriate, with the cyanate or isocyanate, other than of course, the —OH group of ring C, should, if necessary, be protected prior to reaction e.g. in the same manner as that described under Route B. Similarly, the final product may typically be isolated by the method described under Route B.

*Route E*

Compounds of the formula (I) wherein X is —$(CH_2)p$— and Y is —$NHCONR^6R^7$ or —$NHCSNR^6R^7$ may be prepared by initially reacting a quinazoline of the formula:



(VII)

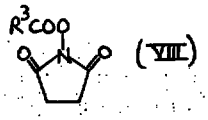
X being —$(CH_2)p$—, with phosgene $COCl_2$ or thiophosgene $CSCl_2$ in the presence of a base, e.g. triethylamine, and in the presence of an inert organic solvent such as chloroform or toluene, the —$NH_2$ group in ring C being converted to an —NCO or —NCS group. Generally strong stirring of the reaction mixture at room temperature is necessary, after which the mixture is allowed to stand for a few hours. A compound of the formula $R^6R^7NH$ is then added to the reaction mixture to react with the —NCO or —NCS group, the resulting mixture generally being allowed to stand for a few hours at room temperature to complete the reaction. If desired, the intermediate —NCO or —NCS containing quinazoline may be isolated and optionally purified before reaction with the compound $R^6R^7NH$.

Any hydroxy groups, primary amino groups (other than, of course, the —$NH_2$ group of ring C), and secondary amino groups, should, if necessary, be protected by conventional protecting groups prior to the reaction, the groups being removed by standard procedures after the reaction.

The product may typically be isolated and purified by the procedure described under Route A.

*Route F.*

Compounds of the formula (I) in which X is —$(CH_2)_p$— and Y is —$NR^4COR^3$, $R^3$ being other than lower alkoxy, substituted lower alkoxy and aryloxy, may be prepared by reacting a quinazoline of the formula (V) as previously defined with an ester of N-hydroxy succinimide of the formula:



(VIII)

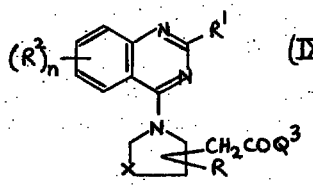
in which $R^3$ is other than lower alkoxy, substituted alkoxy and aryloxy. The reaction is generally carried out by stirring the reactants together at room temperature in an inert organic solvent, e.g. dry chloroform, for a few hours.

Any hydroxy groups or primary or secondary amino groups in $R^2$ to $R^4$ should, if necessary, be protected prior to the reaction by conventional protecting groups which may be removed after the reaction by standard procedures.

The product may generally be isolated by the method described under Route A.

*Route G*

All compounds of the formula (I) wherein Y is $—CH_2CONR^6R^7$ may be prepared by reacting a compound of the formula:



(IX)

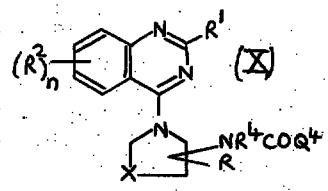
wherein $Q^3$ is a good leaving group, such as a lower alkoxy, chloro- or bromo- group, with a compound $R^6R^7NH$. The reactants are generally heated together neat, i.e. in the absence of any additional solvent, preferably in a closed stainless steel bomb at 50° to 200°C for up to 48 hours. Heating may however not be necessary when $Q^3$ is a very good leaving group such as chloro or bromo. An inert organic solvent may however be added if required, and the presence of a base such as triethylamine or excess reagent $R^6R^7NH$ is advantageous when $Q^3$ is chloro or bromo.

Any substituent groups in $R^2$, $R^6$ and $R^7$ capable of reacting with the group $—CH_2CO\,Q^3$, e.g. primary or secondary amino groups, should, if necessary, be protected prior to reaction and the protecting group removed after reaction.

The product is typically isolated and purified by the method described under Route A.

*Route H*

Compounds of the formula (I) in which X is $—(CH_2)_p—$ and Y is $—NR^4COR^3$, $R^3$ being a lower alkyl group substituted by an amino group (as hereinbefore defined), may be prepared by reacting a quinazoline of the formula:



(X)

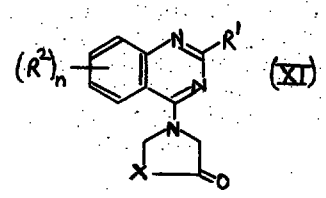
X being $—(CH_2)_p—$ and $Q^4$ being lower alkyl substituted by chloro- or bromo-, with a compound of the formula $R^8R^9NH$. Generally the reaction is carried out at room temperature in an inert organic solvent, e.g. chloroform, in the presence of a base such as triethylamine or excess compound $R^8R^9NH$, for a period of a few hours.

Any substituent groups in $R^2$ and $R^4$ capable of displacing the group $Q^4$, e.g. hydroxy and primary and secondary amino groups, should, if necessary, be protected prior to the reaction and the protecting group removed after reaction.

The product is typically isolated and purified by the method described under Route A.

*Route I*

Compounds of the formula (I) wherein ring C is unsaturated and Y is thus $—CH_2COR^3$, $—CH_2CONR^6R^7$ or $—CH_2CSNR^6R^7$ may be prepared by reacting a quinazoline of the formula:



(XI)

wherein X is $-(CH_2)_2-$ or $-(CH_2)_3-$, with a phosphonate of the formula:

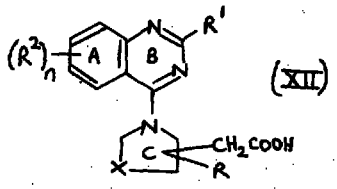
$$\text{(lower alkoxy)}_2\text{.P.Y. or (aryloxy)}_2\text{.P.Y}$$
$$\qquad\qquad\qquad\qquad\quad \| \qquad\qquad\qquad\quad \|$$
$$\qquad\qquad\qquad\qquad\quad O \qquad\qquad\qquad\quad O$$

wherein Y is $-CH_2COR^3$, $-CH_2CONR^6R^7$ or $-CH_2CSNR^6R^7$. Generally the reaction is carried out at moderate temperatures for a period of up to a few hours, and in an inert organic solvent such as dimethoxyethane in the presence of a base, e.g. sodium hydride.

The product may be purified by the purification procedure described under Route B, and may be a mixture of tautomers.

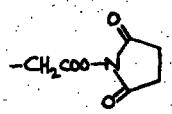
*Route J*

All the compounds of the formula (I) in which Y is $-CH_2CONR^6R^7$ may be prepared by initially reacting a quinazoline of the formula:



(XII)

with N-hydroxy succinimide in the presence of a dehydrating agent such as dicyclohexylcarbodiimide to form an "activated" ester containing the grouping:



Preferably this reaction is carried out by allowing the reactants to stand together for a few hours at room temperature in an inert organic solvent, e.g. chloroform. A compound of the formula $R^6R^7NH$ is then added to the mixture to obtain the desired product, the mixture again generally being allowed to stand at room temperature for a few hours to complete the reaction. The reaction mixture is then filtered and the product recovered from the filtrate preferably via the isolation procedure described under Route B.

Any substituent groups in $R^2$ and $R^6$ capable of reacting with the $-CH_2COOH$ or "activated" ester group, e.g. primary and secondary amino groups, should, if necessary, be protected prior to the reaction and the protecting group removed after reaction.

Acid addition salts of the compounds of formula (I) may be prepared from the crude or pure free base product by the conventional technique of reacting the free base with the acid in an inert solvent, e.g. by mixing alcoholic solutions of each and collecting the resulting precipitate by filtration. The product may then be recrystallised to purity.

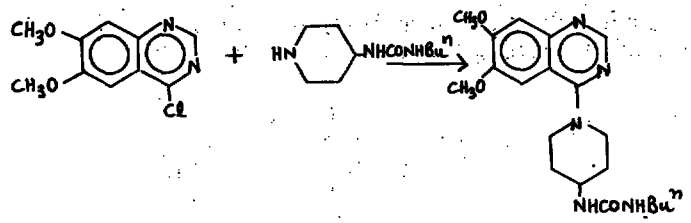
In the above methods due regard should be had to the possibility that carbethoxy-substituted lower alkyl groups may be attacked by primary and secondary amino groups, and this should be borne in mind when preparing compounds in which $R^4$ or $R^6$ contain a carbethoxy group.

The 4- substituted quinazolines used as starting materials in the previous routes are either known compounds or are obtainable by analogous procedures to those of the prior art, such as British Patent Specification No. 1,199,768, or to those described in this specification. For example, the preparation of a compound of the formula V from a ketone starting material of the formula XI is described in part A of Example 10, and many other compounds of the formula V are analogously obtainable. Furthermore, the preparation of a ketone starting material for this route is exemplified in part A of Example 91 and other such ketones are analogously obtainable. A route to the preparation of an amine of the formula VII is described in part A of Example 44, and other amines falling within this formula are analogously obtainable. An alternative route to the production of

the amines of the formula VII could be via the catalytic hydrogenation of the corresponding compounds of the formula V in which $R^4$ is a benzyl group. Also, many of the compounds of the formula IX are obtainable via Route A described herein or analogously (Example 5 describes the preparation of a compound of the formula IX wherein the "leaving group" $Q^3$ is an ethoxy group). Similarly, starting materials of the formula X can generally be obtained analogously to Route C as described herein. Starting materials of the formula XII, which materials have a $-CH_2COOH$ group, are generally obtainable by hydrolysis of the corresponding ester, e.g. $-CH_2COOEt$, the ester being obtainable via Route I described herein when ring C is unsaturated, or via Route A when ring C is saturated.

The invention is illustrated by the following Examples in which all temperatures are given in °C:—

## EXAMPLE 1.



4-Chloro-6,7-dimethoxyquinazoline (45 g), 4-(3-n-butylureido)piperidine monohydrochloride (80 g) and triethylamine (140 ml) were refluxed in ethanol (450 ml) for 1¼ hours. The mixture was then concentrated *in vacuo* and the resultant solid was stirred in water which was then basified to pH 11 with 5N NaOH solution. The suspension was shaken with chloroform and the organic layer was separated, dried ($Na_2CO_3$) and evaporated to dryness *in vacuo* to give a yellow oily solid. Trituration with ether followed by recrystallisation from ethanol gave *4-(4-[3-n-butylureido]piperidino)-6,7-dimethoxy quinazoline* (37 g). Small traces of impurities were removed by running a chloroform solution of the product down a glass column packed with "Florisil" (Registered Trade Mark) and eluting with 10% isopropanol in chloroform. After evaporation, appropriate fractions were bulked and recrystallised from ethanol to give a pure product (21 g), m.p. 204—5°C.

*Analysis*: $C_{20}H_{29}N_5O_3$ requires C, 62.0; H, 7.5; N, 18.1;
*Found*: C, 62.1; H, 7.6; N, 18.3%

The mono maleate salt was prepared by treating an alcoholic solution of the free base with an alcoholic solution of maleic acid. The precipitated salt was recrystallised (from EtOH) m.p. 195—197°C.

The following compounds were prepared, using the method of Example 1, from the appropriate 4-chloroquinazoline derivative and amine, and were isolated in the form indicated. Both the theoretical and found analyses of the compounds are given, the found analyses being in parenthesis.

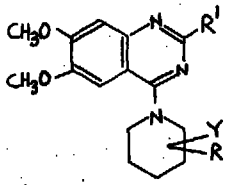
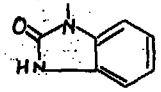


TABLE I

| Example | $R^1$ | R | Y | Position of Y and R in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % ( Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 2 | H | H | $-NHCOCH_3$ | 4- position | monohydrochloride monohydrate, 236 – 238°C | 53.05 (53.43 | 6.55 6.19 | 14.56 14.92) |
| 3 | $CH_3$ | H | $-NHCONH(CH_2)_3CH_3$ | 4- position | monomaleate, 210 – 212°C | 58.01 (57.77 | 6.82 6.72 | 13.53 13.26) |
| 4 | H | H | $-NHCOCH_3$ | 3- position | free base, 172 – 173°C | 61.80 (62.10 | 6.71 6.78 | 16.96 16.86) |
| 5 | H | H | $-CH_2COOC_2H_5$ | 4- position | monohydrochloride, 192 – 194°C | 57.64 (57.13 | 6.62 6.52 | 10.61 10.73) |
| 6 | H | H | $-NHCONH(CH_2)_3CH_3$ | 3- position | free base, 124 – 126°C | 61.99 (62.02 | 7.54 7.68 | 18.08 18.02) |
| 7 | $CH_3CH_2$ | H | $-NHCONH(CH_2)_3CH_3$ | 4- position | ½-hydrate, 154 – 156°C | 62.24 (62.14 | 8.07 7.92 | 16.49 16.34) |
| 8 | $(CH_3)_2CH$ | H | $-NHCONH(CH_2)_3CH_3$ | 4- position | monohydrochloride monohydrate, 205 – 209°C | 57.07 (56.78 | 7.91 7.45 | 14.47 14.38) |
| 9 | H | H |  | 4- position | free base, 242 – 245°C | 65.17 (64.96 | 5.72 5.89 | 17.27 16.92) |

## EXAMPLE 10.

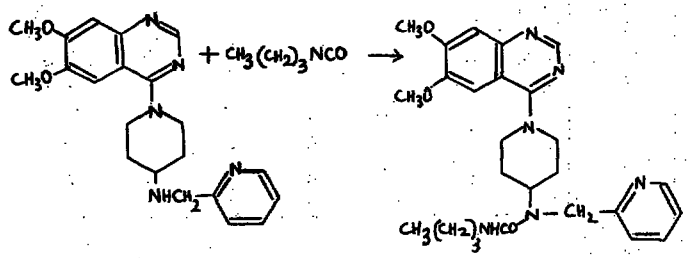
*PART A*

Preparation of 4-[4-(2-pyridylmethyl amino) piperidino]-6,7-dimethoxy quinazoline.

1-(6,7-Dimethoxyquinazoline-4-yl)piperid-4-one (2.9g) (which may be prepared as in part A of Example 91, hereinafter), and 2-amino-methylpyridine (1.19 g) were refluxed together for two hours in benzene (50 ml.) in a flask fitted with a Dean and Stark trap. Ethanol (50 ml.) was added to the cooled solution followed by the slow addition of sodium borohydride (0.76g) with stirring. On completion of the addition, stirring was continued for two hours followed by the addition of excess acetic acid. The mixture was poured into water, basified with 5*N* sodium hydroxide and extracted with chloroform. Evaporation of the chloroform layer gave a yellow oil which solidified on trituration with ether. Recrystallisation from ethyl acetate gave 4-[4-(2-pyridylmethyl-amino)piperidino]-6,7-dimethoxy quinazoline (2 g) m.p. 151—155°C.

*PART B*

Preparation of 4 - [4 - [3 - *n* - butyl - 1 - (2 - pyridylmethyl)ureido]piperidino]-6,7-dimethoxy quinazoline.



n-Butyl isocyanate (1 g) was added slowly to a stirred solution of 4-[4-(2-pyridylmethylamino)piperidino]-6,7 dimethoxy quinazoline, (1.4g) prepared as in part A above, in dry chloroform, followed by standing at room temperature for 30 minutes. The solution was evaporated to dryness *in vacuo* to give a yellow oil which crystallised on trituration with ether. Recrystallisation from ethyl acetate gave *4-[4-[3-n-butyl-1-(2-pyridylmethyl)ureido]piperidino]-6,7-dimethoxy quinazoline* (1.2 g) as pale yellow crystals, mp 162—4°C.

*Analysis*: $C_{26}H_{34}N_6O_3$ requires C, 65.25; H, 7.2; N, 17.6;
*Found*: C, 65.2; H, 7.2; N, 17.4%

## EXAMPLE 11.

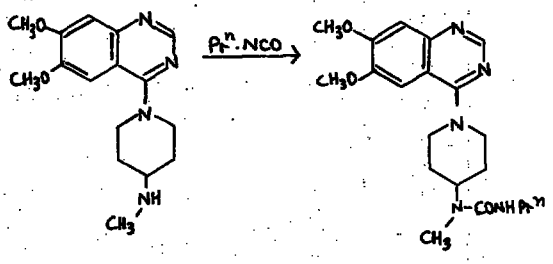
A. *Preparation of 4-4-(methylamino)piperidino-6,7-dimethoxy quinazoline acetate.*

1-(6,7-Dimethoxyquinazolin-4-yl)piperid-4-one (14.35 g — prepared as described in Example 91 Part A hereinafter) and ethanolic methylamine (33% w/w; 23.5 g) were stirred together in dry ethanol (150 ml) overnight. Sodium borohydride (2.0 g) was then added slowly under a nitrogen atmosphere with cooling. The mixture was then refluxed for 1 hour, cooled to room temperature and treated carefully with excess acetic acid. The mixture, after dilution with water and basification with 5*N* NaOH, was extracted with chloroform. After separation, the chloroform phase was dried ($MgSO_4$) and evaporated to give a crude oily product (10 g) which crystallised on trituration with a mixture of ethyl acetate and ether.

Recrystallisation from acetonitrile and then ethyl acetate gave pure *4-[4-(Methylamino)piperidino]-6,7-dimethoxy quinazoline acetate*, m.p. 169—172°C.

*Analysis*:—
Found: C, 59.2; H, 7.5; N, 15.7%
Required for $C_{16}H_{22}N_4O_2.C_2H_4O$: C, 59.7; H, 7.2; N, 15.5%

B. *Preparation of 4-[4-{1-methyl-3-n-propyl-ureido}piperidino]-6,7-dimethoxy quinazoline.*



4-[4-(Methylamino)piperidino]-6,7-dimethoxy quinazoline (1.7g) was dissolved in chloroform (10 mls.) and treated with *n*-propyl isocyanate (0.5 g). After standing overnight at room temperature the mixture was evaporated to dryness. The residue soldified on trituration with ethyl acetate. Recrystallisation from ethanol gave pure *4-[4-{1-methyl-3-n-propyl-ureido}piperidino]-6,7-dimethoxy quinazoline* (0.4 g) m.p. 209—11°.

*Analysis*:—
Found: C, 61.3; H, 7.6; N, 17.4%
Required for $C_{20}H_{29}N_5O_3.\frac{1}{4}H_2O$: C, 61.3; H, 7.6; N, 17.9%

The following compounds were prepared, using the method of Examples 10 and 11, from the appropriate 4- piperidino -quinazoline and isocyanate or isothiocyanate, and isolated in the form indicated. In Example 18, sodium cyanate was used. Both the theoretical and found analyses of the products are given, the found analyses being in parentheses.

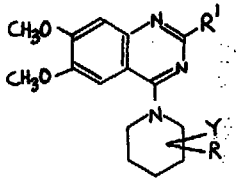


TABLE II

| Example | $R^1$ | R | Y | Position of Y and R in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C. | Analysis (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 12 | H | H | $-NHCONHCH_3$ | 4- position | monomaleate; 205–207°C | 54.66<br>(54.95 | 5.90<br>5.76 | 15.18<br>14.78) |
| 13 | H | H | $-NHCSNH(CH_2)_3CH_3$ | 4- position | monomaleate; 195–198°C | 55.47<br>(55.35 | 6.40<br>6.36 | 13.48<br>13.10) |
| 14 | H | H | $-NHCONH(CH_2)_2CH_3$ | 4- position | Free base; 212–214°C | 61.10<br>(61.25 | 7.29<br>7.33 | 18.75<br>19.22) |
| 15 | H | H | $-NHCONHCH_2CH_3$ | 4- position | Free base; 214–216°C | 60.15<br>(59.88 | 7.01<br>7.07 | 19.49<br>19.45) |
| 16 | H | H | –NHCONH.Phenyl | 4- position | Free base; 225–227°C | 64.85<br>(64.61 | 6.18<br>6.32 | 17.19<br>16.86) |
| 17 | H | H | $-N(CONH(CH_2)_3CH_3)-CH_2$(4-Pyridyl) | 4- position | Free base; 202–204°C | 65.25<br>(65.06 | 7.16<br>7.20 | 17.56<br>17.33) |
| 18 | H | H | $-NHCONH_2$ | 4- position | Free base; 237.5–240°C | 57.99<br>(57.57 | 6.39<br>5.43 | 21.13<br>20.62) |

TABLE II (Continued)

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 19 | H | H | –NHCONH(3-pyridyl) | 4- position | dimaleate ½-hydrate; 132–144°C | 53.61<br>(53.31 | 5.12<br>5.14 | 12.94<br>12.98) |
| 20 | H | H | –N(CONH$(CH_2)_3CH_3$)–$CH_2$(3-pyridyl) | 4- position | Free base; 167–169°C | 65.25<br>(64.04 | 7.16<br>7.17 | 17.56<br>17.69) |
| 21 | H | H | –N(CONH$(CH_2)_3CH_3$)–$CH_2$.Phenyl | 4- position | Free base; 196–198°C | 67.90<br>(67.55 | 7.39<br>7.47 | 14.66<br>14.72) |
| 22 | H | H | –N(CONH$(CH_2)_3CH_3$)–(3-pyridyl) | 4- position | Free base; 175–177°C | 64.63<br>(64.57 | 6.94<br>7.22 | 18.09<br>18.09) |
| 23 | H | H | –N(CONH$(CH_2)_3CH_3$)–$(CH_2)_2N(CH_3)_2$ | 4- position | Free base; 140–142°C | 62.85<br>(62.95 | 8.35<br>8.40 | 18.33<br>18.31) |
| 24 | H | H | –NHCONH$CH_2COOC_2H_5$ | 4- position | Free base; 209–211°C | 57.54<br>(57.70 | 6.52<br>6.56 | 16.78<br>16.50) |
| 25 | H | H | –N(CONH$(CH_2)_3CH_3$)–$CH_3$ | 4- position | Free base; 178–181°C | 62.82<br>(62.65 | 7.78<br>7.79 | 17.44<br>17.39) |
| 26 | H | H | –N(CONH$(CH_2)_3CH_3$)–$(CH_2)_2N(CH_2Ph)(CH_2)_3CH_3$ | 4- position | Free base; 121–124°C | 68.72<br>(68.63 | 8.39<br>8.07 | 14.57<br>14.27) |

TABLE II (Continued)

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 27 | H | H | $-NCONHCH_3$ \| $(CH_2)_3CH_3$ | 4- position | Free base; 196–198° | 62.82 (62.51 | 7.78 7.91 | 17.44 17.03) |
| 28 | H | H | $-NCONH(CH_2)_3CH_3$ \| $(CH_2)_3CH_3$ | 4- position | Free base; 151–153° | 64.98 (64.58 | 8.41 8.51 | 15.79 15.58) |
| 29 | H | H | $-NCONHCH_2CH_3$ \| $CH_2$.(4-pyridyl) | 4- position | Free base; 232–235° | 63.98 (63.87 | 6.71 6.85 | 18.65 18.46) |
| 30 | H | H | $-NCONHCH_3$ \| $CH(CH_3)_2$ | 4- position | Free base; 186–188° | 61.99 (61.25 | 7.54 7.59 | 18.08 18.19) |
| 31 | H | H | $-NCONHCH_3$ \| $(CH_2)_2CH_3$ | 4- position | Free base; 204–207° | 61.99 (61.23 | 7.54 7.63 | 18.08 17.83) |
| 32 | H | H | $-NCONHCH_2CH_3$ \| $(CH_2)_2CH_3$ | 4- position | Free base; 174–176° | 62.82 (63.01 | 7.78 7.28 | 17.44 17.49) |
| 33 | H | H | $-NCONH(CH_2)_3CH_3$ \| $CH_2CH_2$.(4-pyridyl) | 4- position | Free base; 169–172° | 65.83 (65.80 | 7.37 7.38 | 17.06 17.23) |
| 34 | H | H | $-NCONHCH_2CH_3$ \| $CH(CH_3)_2$ | 4- position | Free base; 174–175° | 62.82 (63.13 | 7.78 7.75 | 17.44 17.08) |

TABLE II (Continued)

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 35 | H | H | $-NCONH(CH_2)_2CH_3$ <br> $CH(CH_3)_2$ | 4- position | Free base; 161–162° | 63.59 <br> (63.37 | 8.00 <br> 8.13 | 16.86 <br> 16.60) |
| 36 | H | H | $-NCONH(CH_2)_3CH_3$ <br> $CH_2CH_2$.(2-pyridyl) | 4- position | Free base ½-hydrate, 130–133° | 64.64 <br> (64.48 | 7.44 <br> 7.44 | 16.76 <br> 16.80) |
| 37 | H | H | $-NCONH(CH_2)_3CH_3$ <br> $CH_2CH_3$ | 4- position | Free base; 155–159° | 63.59 <br> (63.03 | 8.00 <br> 7.89 | 16.85 <br> 16.56) |
| 38 | H | H | $-NCONHCH_2CH_3$ <br> $CH_3$ | 4- position | Free base; 192–194° | 61.11 <br> (61.46 | 7.29 <br> 7.29 | 18.75 <br> 18.62) |
| 39 | H | H | $-NCONH(CH_2)_2CH_3$ <br> $CH_2CH_3$ | 4- position | Free base; 173–175° | 62.82 <br> (63.04 | 7.78 <br> 7.95 | 17.44 <br> 17.38) |
| 40 | H | H | $-N.CONHCH_2CH_3$ <br> $CH_2CH_3$ | 4- position | Free base; 182–184° | 61.99 <br> (62.08 | 7.54 <br> 7.59 | 18.07 <br> 17.99) |
| 41 | H | H | $-NCSNHCH_3$ <br> $CH_3$ | 4- position | Free base; 212–220° | 57.58 <br> (57.18 | 6.71 <br> 6.79 | 18.65 <br> 18.70) |
| 42 | H | H | $-NCONH(CH_2)_2CH_3$ <br> $CH_2CH_2OH$ | 4- position | Free base; 161–165° | 60.41 <br> (60.10 | 7.48 <br> 7.63 | 16.77 <br> 16.81) |
| 43 | H | H | $-NCSNH(CH_2)_2CH_3$ <br> $CH_3$ | 4- position | Free base; 229–231° | 59.53 <br> (59.28 | 7.25 <br> 7.20 | 17.36 <br> 17.58) |

EXAMPLE 44.

*PART A*

Preparation of 4-[4-amino piperidino]-6,7-dimethoxy quinazoline.

4 - Chloro - 6,7 - dimethoxy quinazoline (0.9 g), 4 - (trifluor - acetylamino) piperidine hydrochloride (75% pure, 1.25g) triethylamine (2.2ml.) and ethanol (25 ml.) were refluxed together for approximately 0.75 hr. The mixture was evaporated *in vacuo* to dryness followed by basification with aqueous 5*N* sodium hydroxide solution and extraction with chloroform. The chloroform extract was dried and evaporated *in vacuo* to give, after recrystallisation from ethanol 4-(4-trifluoro-acetamido piperidino)-6,7-dimethoxy quinazoline (1.5 g) m.p. 217—220°C.

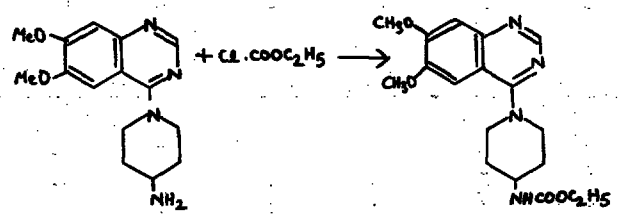
*Analysis*: $C_{17}H_{19}F_3N_4O_3$ requires C, 50.7; H, 5.3; N, 13.9%
*Found*: C, 50.8; H, 4.75; N, 13.9

4-(4-Trifluoroacetamido piperidino)-6,7-dimethoxy quinazoline (59.5 g) 5*N*-sodium hydroxide solution (250 ml.) and tetrahydrofuran (500 ml.) were refluxed together with stirring for 2½ hours. The T.H.F. layer was decanted off and concentrated to a small volume followed by treatment with water and extraction into $CHCl_3$.

Evaporation of the chloroform gave a yellow oil which on trituration with ether gave yellow crystals of 4-(4-aminopiperidino)-6,7-dimethoxy quinazoline (42 g) m.p. 133—135°C.

*PART B*

Preparation of 4 - [4 - (ethoxycarbonylamino) piperidino] - 6,7 - dimethoxy quinazoline.




4-[4-Aminopiperidino]-6,7-dimethoxy quinazoline prepared as in part A, (1.4 g), ethyl chloroformate (0.65 g) and triethylamine (1.1 ml.) were stirred together in dry chloroform (30 ml.) at room temperature for 1 hour. After concentration *in vacuo* the residue was suspended in water, basified with 5N sodium hydroxide solution and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated *in vacuo* to give the product as a pale yellow oily solid. The solid was re-dissolved in ethylacetate and converted to the tartrate salt by the addition of an ethanolic solution of tartaric acid. The tartrate was re-dissolved in hot ethanol and a small amount of impure material was allowed to crystallise out. The filtrate was taken, evaporated to dryness, rebasified in dilute aqueous sodium hydroxide solution and extracted with chloroform. Evaporation of the dried chloroform extract and recrystallisation of the residue from ethylacetate gave *4-[4-(ethoxycarbonylamino) piperidino]-6,7-dimethoxy quinazoline* (300 mg) m.p. 179—181°C.

*Analysis*: $C_{18}H_{24}N_4O_4$ requires C, 60.0; H, 6.7; N, 15.6;
*Found*: C, 60.1; H, 6.8; N, 15.1%

The following compounds were prepared, using the method of Example 44, from the appropriate 4-(4-aminopiperidino)- or 4-(4- loweralkylamino piperidino)-6,7-dimethoxy-quinazoline, and the appropriate chloroformate (Examples 55 to 59 and 63), acyl chloride (Examples 46, 50 and 52), sulfonyl chloride (Examples 48, 49, 54 and 68), sulfamyl chloride (Examples 47, 53, 62 and 64), carbamyl chloride (Examples 45 and 51), anhydride (Examples 65 and 67) and pyrocarbonate (Examples 60, 61 and 66 used $(EtO.CO)_2O$). The products were isolated in the form indicated. The theoretical and found analyses of the products are given, the found analyses being in parentheses.

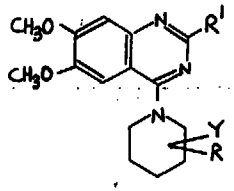


TABLE III

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 45 | H | H | $-NHCON(CH_3)_2$ | 4- position | Free base; 178–183°C | 60.15<br>(59.63 | 7.01<br>7.13 | 19.48<br>18.95) |
| 46 | H | H | –NHCO(3-pyridyl) | 4- position | Free base; 225–227°C | 64.11<br>(63.79 | 5.89<br>6.07 | 17.80<br>17.45) |
| 47 | H | H | $-NHSO_2N(CH_3)_2$ | 4- position | Free base; 182–184°C | 51.64<br>(51.97 | 6.37<br>6.43 | 17.71<br>17.61) |
| 48 | H | H | $-NHSO_2CH_3$ | 4- position | monohydrochloride monohydrate; 215–220°C | 45.66<br>(45.30 | 5.98<br>5.78 | 13.31<br>13.38) |
| 49 | H | H | $-NHSO_2$(3-pyridyl) | 4- position | Free base; 222–225°C | 55.93<br>(56.19 | 5.40<br>5.23 | 16.31<br>16.61) |
| 50 | H | H | $-NHCO(CH_2)_3CH_3$ | 4- position | monohydrochloride; 212–215°C | 58.74<br>(58.51 | 7.15<br>7.17 | 13.70<br>13.09) |
| 51 | H | H | $-NHCON(C_2H_5)_2$ | 4- position | monohydrochloride ½-hydrate; 215–218°C | 55.48<br>(55.78 | 7.22<br>7.03 | 16.18<br>15.88) |
| 52 | H | H | $-NHCOCH_2CH_2CH_3$ | 4- position | Free base; 157–159°C | 63.67<br>(63.99 | 7.31<br>7.55 | 15.63<br>15.24) |
| 53 | H | H | $-NHSO_2NH(CH_2)_2CH_3$ | 4- position | Monohydrochloride ½-hydrate; 222–224°C | 47.51<br>(47.47 | 6.42<br>6.55 | 15.39<br>15.49) |

TABLE III (Continued)

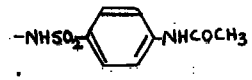
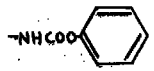
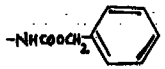
| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 54 | H | H |  | 4- position | Mono p-toluene sulphonate; 241–244°C | 54.78<br>(54.55 | 5.36<br>5.46 | 10.65<br>10.57) |
| 55 | H | H |  | 4- position | Mono-maleate; 169–173°C | 59.54<br>(59.64 | 5.38<br>5.47 | 10.68<br>10.31) |
| 56 | H | H | $-NHCOOCH_3$ | 4- position | Free base; 162–166°C | 58.95<br>(58.67 | 6.40<br>6.35 | 16.17<br>15.87) |
| 57 | H | H | $-NHCOOCH_2CH(CH_3)_2$ | 4- position | Mono-maleate; 173–175°C | 57.13<br>(56.88 | 6.39<br>6.18 | 11.10<br>10.71) |
| 58 | H | H |  | 4- position | Oxalate; 198–203°C | 58.59<br>(58.19 | 5.51<br>5.57 | 10.93<br>11.23) |

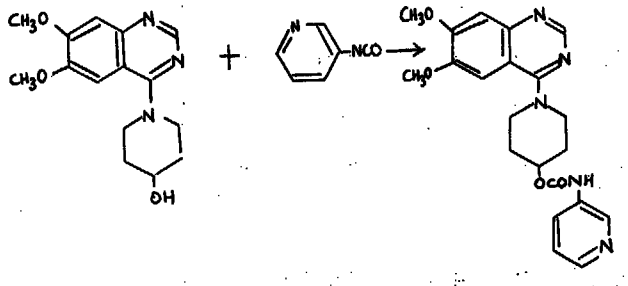
TABLE III (Continued)

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 59 | H | H | $-NHCOO(CH_2)_2CH_3$ | 4- position | Oxalate ½-hydrate, 190–196° | 53.27 (53.06 | 6.17 5.92 | 11.83 11.96) |
| 60 | H | H | $-N(CH_3)COOCH_2CH_3$ | 4- position | Free base; 145–147° | 60.95 (60.56 | 7.00 7.00 | 14.96 14.58) |
| 61 | H | H | $-N(CH_2CH_3)COOCH_2CH_3$ | 4- position | Free base; 149–152° | 61.84 (61.66 | 7.27 7.36 | 14.42 13.88) |
| 62 | H | H | $-N(CH_3)SO_2NH(CH_2)_2CH_3$ | 4- position | Free base; 174–179° | 53.88 (54.27 | 6.90 6.99 | 16.54 16.54) |
| 63 | H | H | $-N(CH_3)COOCH_2CH(CH_3)_2$ | 4- position | Free base; 159–162° | 62.67 (62.47 | 7.51 7.54 | 13.92 13.61) |
| 64 | H | H | $-N(CH_2CH_3)SO_2NH(CH_2)_2CH_3$ | 4- position | monohydrochloride monohydrate, 174–189° | 48.81 (48.90 | 6.98 6.72 | 14.23 14.02) |
| 65 | H | H | $-N(CH_3)COCH_3$ | 4- position | Free base; 177–180° | 62.77 (62.36 | 7.02 7.09 | 16.27 16.03) |
| 66 | H | H | $-N(CH_2CH_2OH)COOCH_2CH_3$ | 4- position | Free base; 185–187° | 59.39 (58.91 | 6.98 6.99 | 13.85 13.94) |

TABLE III (Continued)

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 67 | H | H | $-NCO(CH_2)_2CH_3$ <br> $CH_3$ | 4- position | Free base; 155–158° | 64.49 (64.44 | 7.58 7.65 | 15.04 14.73) |
| 68 | H | H | $-NSO_2$.(3-pyridyl) <br> $CH_3$ | 4- position | Free base; 183–187° | 56.87 (57.27 | 5.68 5.61 | 15.79 15.90) |

EXAMPLE 69.



4-[4-Hydroxy piperidino]-6,7-dimethoxy quinazoline (2.9 g) and 3-pyridyl isocyanate (1.3 g) in 40 ml. of dry dioxane were heated together at 150°C in a stainless steel bomb for 24 hours. The cooled mixture was concentrated *in vacuo* to give a brown sticky solid which was triturated with ether and filtered. The insoluble residue was crystallised from acetonitrile to give *4-[4-(3-pyridyl-carbamoyloxy)piperidino]-6,7-dimethoxy quinazoline* (1.4 g) m.p. 180—183°C.

*Analysis*: $C_{21}H_{23}N_5O_4$ requires C, 61.6; H, 5.7; N, 17.1%;
*Found*: C, 61.3; H, 5.5; N, 17.5%

The following compounds were prepared, using the method of Example 69, from the appropriate 4-(4-hydroxy-piperidino)-quinazoline [or 4-(3-hydroxy-pyrrolidin-1-yl)-6,7-dimethoxy-quinazoline in the case of Example 78] and the appropriate isocyanate (or sodium cyanate in the case of Example 76), and the products were isolated in the form indicated. The theoretical and found analyses of the products are given, the found analyses being in parentheses.

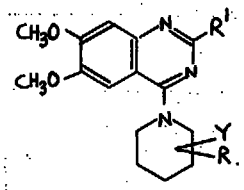


TABLE IV

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 70 | H | H | $-OCONHCH_3$ | 4- position | Free base; 195–198°C | 58.95<br>(59.05 | 6.40<br>6.47 | 16.17<br>16.19) |
| 71 | H | H | $-OCONH(CH_2)_3CH_3$ | 4- position | Free base; 127–129°C | 61.84<br>(62.09 | 7.27<br>7.30 | 14.42<br>14.08) |
| 72 | H | H | $-OCONH(CH_2)_2CH_3$ | 4- position | Free base; 164–167°C | 60.95<br>(61.00 | 7.00<br>6.98 | 14.96<br>15.29) |
| 73 | H | $CH_3$ | $-OCONH(CH_2)_2CH_3$ | 4- position | Free base; 161–165°C | 61.84<br>(61.46 | 7.27<br>7.19 | 14.42<br>14.07) |
| 74 | H | H | $-OCONHCH_2CH_3$ | 4- position | Free base; 168–170° | 59.98<br>(59.98 | 6.71<br>6.76 | 15.55<br>15.45) |
| 75 | H | $CH_3$ | $-OCONHCH_3$ | 4- position | Free base; 199–207° | 59.98<br>(59.56 | 6.71<br>6.76 | 15.55<br>15.20) |
| 76 | H | H | $-OCONH_2$ | 4- position | monohydrochloride, 232–235° | 52.11<br>(51.90 | 5.74<br>5.78 | 15.19<br>15.00) |

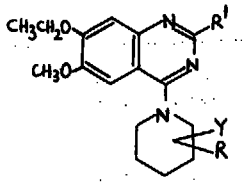


TABLE IV (Continued)

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 77 | H | H | $-OCONHCH_2CH_3$ | 4- position | Free base; 286–288° | 60.95 (60.71 | 7.00 7.12 | 14.96 14.71) |

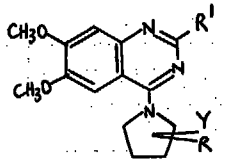
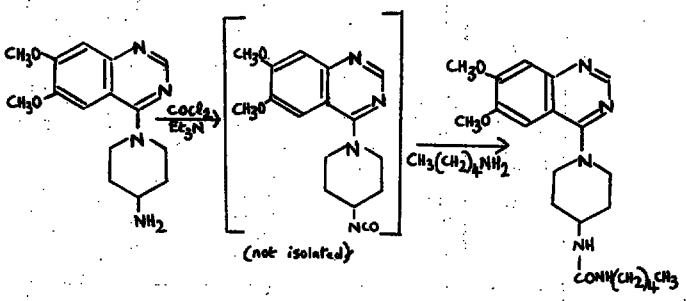


TABLE IV (Continued)

| Example | $R^1$ | R | Y | Position of Y in pyrrolidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 78 | H | H | $-OCONH(CH_2)_2CH_3$ | 3- position | Free base; 186–189° | 60.00 (59.97 | 6.71 6.94 | 15.55 15.66) |

## EXAMPLE 79.




4-[4-Amino piperidino]-6,7-dimethoxy quinazoline (which may be prepared via the route of part A of Example 44) (5.8 g), triethyl amine (14 ml.) and chloroform (100 ml.) were added slowly to a solution of phosgene in toluene (48 ml. of 12½% w/v). The mixture was stirred at room temperature during the addition and then allowed to stand overnight. 1-Amino pentane (5.23 g) was then added slowly followed by standing for a further 24 hours. 2*N* hydrochloric acid (200 ml.) was added and the organic phase was collected and evaporated to dryness *in vacuo* to give an oil. The oil was dissolved in water, basified with 5*N* NaOH and extracted with chloroform. The extract was dried and evaporated *in vacuo* to give an oil which soldified on standing under petroleum ether. Recrystallisation from acetonitrile gave *4-[4-[3-n-pentylureido]piperidino]-6,7-dimethoxy quinazoline* (1.5 g) m.p. 192—4°C.

| | | |
|---|---|---|
| *Analysis*: $C_{21}H_{31}N_5O_3$ requires | C, 62.8; | H, 7.8; N, 17.4; |
| *Found*: | C, 62.4; | H, 8.0; N, 17.8% |

The following compounds were made, using the method of Example 79, from 4-(4-amino-piperidino)-6,7-dimethoxy-quinazoline, phosgene, and the appropriate amine. The compounds were isolated in the form indicated, and the theoretical and found analyses are given, the found analyses being in brackets.

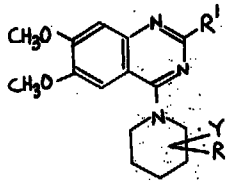
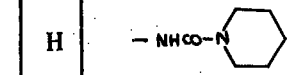
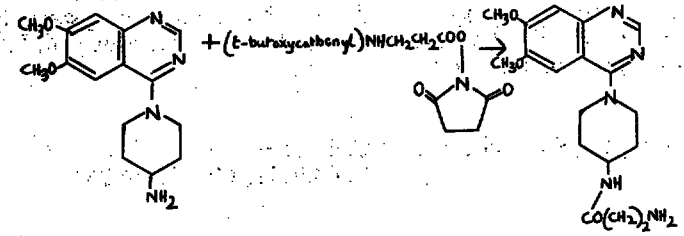


TABLE V

| Example | $R^1$ | R | Y | Position of Y in piperidine nucleus | Salt/Free Base/Hydrate m.p. °C | Analysis % (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|---|---|
| 80 | H | H | $-NHCONH.CH_2CH(CH_3)_2$ | 4- position | monotartrate; 122–135°C | 53.62 (53.39 | 6.56 6.68 | 13.03 13.31) |
| 81 | H | H |  | 4- position | Dihydrochloride; 196–201°C | 53.39 (53.87 | 6.61 6.48 | 14.82 15.54) |
| 82 | H | H | $-NHCONH(CH_2)_4OH$ | 4- position | Free base; 131–145°C | 59.54 (58.96 | 7.24 7.04 | 17.36 16.97) |
| 83 | H | H | $-NHCONH(CH_2)_2$(2-pyridyl) | 4- position | Free base; 199–201°C | 63.29 (63.26 | 6.47 6.37 | 19.25 18.96) |
| 84 | H | H | $-NHCONHCH_2CH=CH_2$ | 4- position | Free base; 211–214°C | 61.44 (61.13 | 6.78 6.81 | 18.85 18.85) |
| 85 | H | H | $-NHCONHCH_2C\equiv CH$ | 4- position | monohydrate; 187–190°C | 58.90 (59.55 | 6.50 6.30 | 18.07 17.91) |

EXAMPLE 86.



4-(4-Aminopiperidino)-6,7-dimethoxy quinazoline (which may be prepared via the route of part A of Example 44) (2.9 g) and N-[3-(-t-butoxycarbonylamino) propionyloxy]succinimide (2.9 g) were stirred for 2 hours at room temperature in dry chloroform (40 ml.). The mixture was filtered and the filtrate was treated with aqueous sodium carbonate solution (10% w/v) followed by separation of the organic phase which was dried ($Na_2CO_3$) and evaporated to dryness *in vacuo*. The t-butoxycarbonyl group was then removed by dissolving the residue in methanol (40 ml.) followed by refluxing for 4 hours with the addition of 2N aqueous NCl (12 ml.). The mixture was evaporated to dryness *in vacuo* and the residual hydrochloride was rebasified (5N NaOH) and extracted into chloroform. The concentrated chloroform solution was passed down a column packed with "Florisil" (in chloroform) followed by elution with chloroform-methanol. Appropriate fractions were bulked and evaporated *in vacuo* to give crude *4-(4-[β*-aminopropionamido]piperidino)-6,7-dimethoxy quinazoline which was dissolved in ethanol and converted to the dimaleate salt by treatment with a solution of maleic acid in isopropanol. Recrystallisation from acetonitrile gave the pure dimaleate (500 mg.) m.p. 166—170°C.

*Analysis*: $C_{18}H_{25}N_5O_3.2C_4H_4O_4$ requires C, 52.8; N, 5.6; N, 11.8%
*Found*: C, 51.9; H, 5.6; N, 11.7%

EXAMPLE 87.

Using the method of Example 86, but starting from 4 - [4 - aminopiperidino]-6,7 - dimethoxy quinazoline and N - [2 - (t - butoxycarbonylamino) iso-valeryloxy]succinimide, and using hydrochloric acid instead of maleic acid in the penultimate step, 4-(4-[α-amino-*iso*-valeramido]piperidino)-6,7-dimethoxy quinazoline dihydrochloride dihydrate was isolated, m.p. 218—222°C.

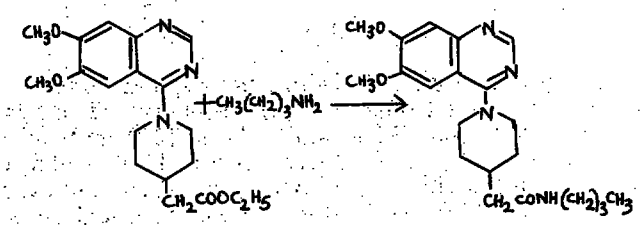
*Analysis*: $C_{20}H_{29}N_5O_3$ requires C, 48.38; H, 7.11; N, 14.11%
*Found*: C, 49.23; H, 6.86; N, 13.78%

EXAMPLE 88.

Using the method of Example 86, starting from N-(α-methoxy-acetyloxy)succinimide and 4-(4-amino-piperidino)-6,7-dimethoxy-quinazoline, 4-[4-(α-methoxyacetamido)piperidino]-6,7-dimethoxy quinazoline was prepared, m.p. 133—135°C.

*Analysis*: $C_{18}H_{24}N_4O_4$ requires C, 59.98; H, 6.71; N, 15.55%
*Found*: C, 59.77; H, 6.82; N, 15.15%

EXAMPLE 89.



4-[4-(Ethoxycarbonylmethyl)piperidino] - 6,7 - dimethoxy quinazoline (which may be prepared as in Example 5) (5 g) and *t* -butylamine (10 ml) were heated together

at about 78°C for 22 hours. The mixture was cooled, basified and extracted with chloroform. The extract was dried and evaporated to dryness *in vacuo* to give an oil which on dissolution in either crystallised as a white solid. Recrystallisation from ethyl acetate gave *4-[4-(n-butylcarbamoylmethyl)piperidino]-6,7-dimethoxy quinazoline* (710 mg) m.p. 142—4°C.

*Analysis*: $C_{21}H_{30}N_4O_3$ requires C, 65.3; H, 7.8; N, 14.5;
*Found*: C, 64.9; H, 8.01; N, 14.25%

## EXAMPLE 90.

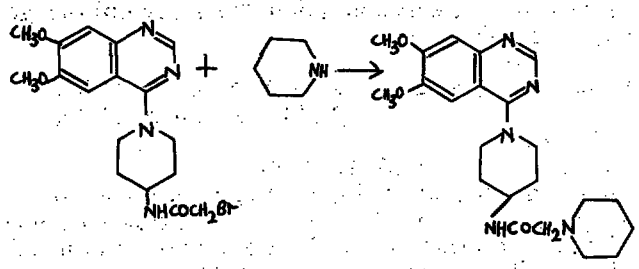
*PART A*

Preparation of 4 - (4 - [α - bromoacetamide]piperidino) - 6,7 - dimethoxy - quinazoline.

4-(4-Aminopiperidino)-6,7-dimethoxy quinazoline (2.9 g) (which may be prepared via the route of Example 44 part A), and triethylamine (1.5 g) in dry chloroform (20 ml.) were treated with α-bromoacetyl bromide (2.3 gm) to obtain a mixture containing 4 - (4 - [α - bromoacetamido]piperidino) - 6,7 - dimethoxy quinazoline.

*PART B*

Preparation of 4-[4(α-piperidinoacetamido) piperidino]-6,7-dimethoxy quinazoline ditartrate.



The mixture prepared in part A was stirred for 30 minutes at room temperature and then piperidine (1.0 gm) was added. After stirring for 3 hours at room temperature the mixture was treated with sodium carbonate solution and the chloroform layer was separated, washed, dried and evaporated to dryness *in vacuo* to give an oil. The oil was dissolved in isopropanol and converted to the ditartrate by reaction with tartaric acid. Recrystallisation from ethanol gave *4-[4-(α-piperidino acetamido) piperidino]-6,7-dimethoxy quinazoline ditartrate* (1.35 g) m.p. 138—141°C.

*Analysis*: $C_{22}H_{31}N_5O_3.2C_4H_6O_6$
requires C, 50.5; H, 6.1; N, 9.8;
*Found*: C, 50.9; H, 6.3; N, 9.9%

## EXAMPLE 91.

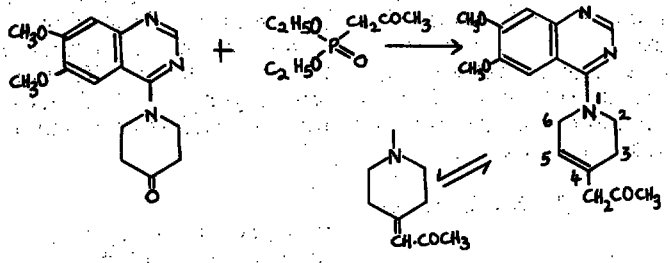
*PART A*

Preparation of 4-(4-oxopiperidino)-6, 7-dimethoxy quinazoline.

4-Chloro-6-7-dimethoxy quinazoline (30 g), 4-piperidone ethylene ketal hydrochloride (25 g), triethylamine (35 g) and ethanol (250 ml.) were refluxed together for 3 hours. Aqueous sodium carbonate was added followed by extraction with chloroform after which the chloroform extract was dried and evaporated *in vacuo* to give an oil. The oil was redissolved in aqueous hydrochloric acid (1.5*N*, 200 ml.) and refluxed for 2 hours followed by cooling, basification ($Na_2CO_3$ 10% sol$^n$) and extraction into chloroform. Evaporation of the dried chloroform extract gave 4-(4-oxo-piperidino)-6,7-dimethoxy quinazoline (37.6 g) m.p. 176—8°C.

*PART B*

Preparation of 4-[4-acetonyl-1, 2, 3,6-tetrahydro pyrid-1-yl]-6, 7-dimethoxy quinazoline monomaleate.



Diethyl acetonylphosphonate in dry 1,2-dimethoxy ethane (D.M.E.) (50 ml.) was added slowly to a stirred suspension of sodium hydride (1 g, 80% oil dispersed) in D.M.E. (50 ml.) followed by stirring at room temperature for 30 minutes. 4-(4-oxopiperidino-6, 7-dimethoxy quinazoline prepared in part A (8.8 g) in D.M.E. (100 ml.) was added rapidly followed by heating at 80°C for 1 hour. The solution was poured into ice-water and extracted with chloroform. The organic layer was separated, dried and concentrated *in vacuo* to give an oil which was dissolved in toluene and converted to the maleate by treatment with ethereal maleic acid. Recrystallisation from ethanol gave *4-[4-acetonyl-1,2,3,6 tetrahydro pyrid-1-yl]-6, 7-dimethoxy quinazoline monomaleate*, m.p. 179—181°C.

| | |
|---|---|
| *Analysis*: | C, 59.6; H, 5.7; N, 9.5; |
| *Found*: | C, 58.7; H, 5.7; N, 9.3% |

The following compound was prepared, using the method of Example 91, from 4-(4-oxo piperidino)-6, 7-dimethoxy-quinazoline and diethyl ethoxy-carbonylmethylphosphonate, the product being isolated in the form indicated. The theoretical and found analysis of the compound are given, the found analysis being in parantheses.

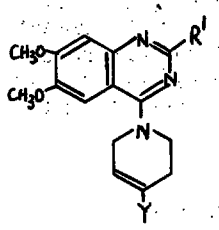
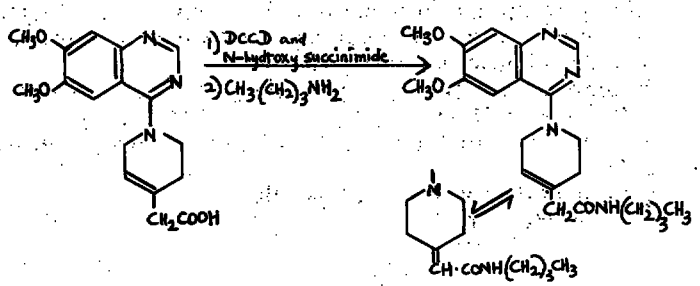


TABLE VI

| Example | $R^1$ | Y | Salt/Free Base m.p. °C | Analysis (Found in brackets) C | H | N |
|---|---|---|---|---|---|---|
| 92 | H | $-CH_2COOC_2H_5$ | Free base; 133–135°C | 63.85 (63.50 | 6.48 6.65 | 11.76 11.47) |

EXAMPLE 93.



4-(4-[Carboxymethyl]-1, 2, 3, 6-tetrahydropyrid-1-yl)-6, 7-dimethoxy quinazoline hydrochloride (0.92 g) (prepared by hydrolysis of the ester of Example 92) in dry

chloroform (20 ml.) containing triethylamine (0.3 g) was stirred until complete solution occurred. Dicyclohexylcarbodiimide (DCCD) (0.63 g) and N-hydroxy-succinimide (0.35 g) were added followed by standing overnight during which time a white solid precipitated. n-Butylamine (0.22 g) was added and the mixture again left to stand (5 hours) after which the solution was filtered, washed with water and the organic phase evaporated to dryness *in vacuo*. The residue was triturated with acetonitrile, filtered and the filtrate was treated with ethereal HCl until acid. The precipitated hydrochloride of 4-[4-(n-butylcarbamoyl methyl)-1, 2, 3, 6-tetrahydro pyrid-1-yl]-6, 7-dimethoxy quinazoline was recrystallised from ethanol (yield 340 mg) m.p. 196° (as a hemihydrate).

*Analysis*: $C_{21}H_{28}N_4O_3.HCl.\frac{1}{2}H_2O$

requires C, 58.65; H, 7.0; N, 13.0;

*Found*: C, 58.2; H, 6.6; N, 12.9%

## EXAMPLE 94.

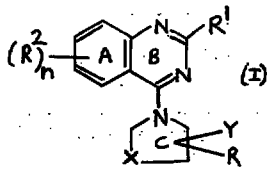
The following is an Example of a typical parenteral formulation, intended for intravenous injection, in which the active ingredient is the compound of Example 1.

| | mg/ml. |
|---|---|
| Active ingredient | 5.0 |
| Sodium chloride | 8.5 |
| Hydrochloric acid | Sufficient for pH adjustment |
| Water | Sufficient to bring correct volume |

The active ingredient and sodium chloride are dissolved in a little of the hydrochloric acid, and more of the latter is added until the pH of the solution is within the limits 3.75±0.25, and the volume as nearly approaches the desired final volume as possible. Water is then added to bring the volume to the appropriate volume for the active ingredient and the salt to be present at the desired concentrations.

WHAT WE CLAIM IS:—

1. A quinazoline of the formula:—



(I)

wherein (i) $R^1$ is a hydrogen atom or a lower alkyl group; $(R^2)n$ represents 1 to 3 optional substituents, each $R^2$ being a hydroxy or lower alkoxy group, and n being 0 to 3, or any two of the moieties $R^2$ constituting a methylenedioxy or ethylenedioxy group attached to adjacent positions of ring A;

(ii) X represents $—(CH_2)_p—$ wherein p is 1 to 3, —CH=CH— or $—CH_2.CH=CH—$;

(iii) Y is attached to the 3- or 4- position of ring C and represents *either*:

(a) a group of the formula $—Z^1—COR^3$

wherein $Z^1$ is $—CH_2—$ or



chloroform (20 ml.) containing triethylamine (0.3 g) was stirred until complete solution occurred. Dicyclohexylcarbodiimide (DCCD) (0.63 g) and N-hydroxy-succinimide (0.35 g) were added followed by standing overnight during which time a white solid precipitated. n-Butylamine (0.22 g) was added and the mixture again left to stand (5 hours) after which the solution was filtered, washed with water and the organic phase evaporated to dryness *in vacuo*. The residue was triturated with acetonitrile, filtered and the filtrate was treated with ethereal HCl until acid. The precipitated hydrochloride of 4-[4-(n-butylcarbamoyl methyl)-1, 2, 3, 6-tetrahydro pyrid-1-yl]-6, 7-dimethoxy quinazoline was recrystallised from ethanol (yield 340 mg) m.p. 196° (as a hemihydrate).

*Analysis*: $C_{21}H_{28}N_4O_3.HCl.\frac{1}{2}H_2O$

| | |
|---|---|
| requires | C, 58.65; H, 7.0; N, 13.0; |
| *Found*: | C, 58.2; H, 6.6; N, 12.9% |

EXAMPLE 94.

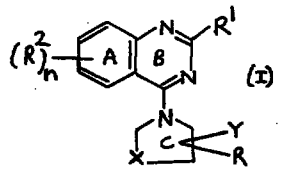
The following is an Example of a typical parenteral formulation, intended for intravenous injection, in which the active ingredient is the compound of Example 1.

| | mg/ml. |
|---|---|
| Active ingredient | 5.0 |
| Sodium chloride | 8.5 |
| Hydrochloric acid | Sufficient for pH adjustment |
| Water | Sufficient to bring correct volume |

The active ingredient and sodium chloride are dissolved in a little of the hydrochloric acid, and more of the latter is added until the pH of the solution is within the limits 3.75±0.25, and the volume as nearly approaches the desired final volume as possible. Water is then added to bring the volume to the appropriate volume for the active ingredient and the salt to be present at the desired concentrations.

WHAT WE CLAIM IS:—

1. A quinazoline of the formula:—



(I)

wherein (i) $R^1$ is a hydrogen atom or a lower alkyl group; $(R^2)n$ represents 1 to 3 optional substituents, each $R^2$ being a hydroxy or lower alkoxy group, and n being 0 to 3, or any two of the moieties $R^2$ constituting a methylenedioxy or ethylenedioxy group attached to adjacent positions of ring A;

(ii) X represents $—(CH_2)_p—$ wherein p is 1 to 3, —CH=CH— or $—CH_2.CH=CH—$;

(iii) Y is attached to the 3- or 4- position of ring C and represents *either*:

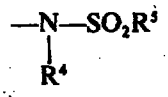
(a) a group of the formula $—Z^1—COR^3$

wherein $Z^1$ is $—CH_2—$ or

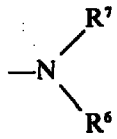


$R^3$ is a lower alkyl group optionally substituted by an amino (as hereinbefore defined), hydroxy, lower alkoxy, aryl, or heteroaryl group; a lower alkenyl- or lower alkynyl-methyl group; a lower alkoxy group optionally substituted by an amino (as hereinbefore defined), aryl, heteroaryl, lower alkoxy or hydroxy group; an aryl group; an aryloxy group; or a heteroaryl group; and $R^4$ is a hydrogen atom; a lower alkyl group optionally substituted by an amino (as hereinbefore defined), lower alkoxy, hydroxy, carbethoxy, aryl or heteroaryl group; a lower alkenyl- or lower alkynyl-methyl group; an aryl group or a heteroaryl group;

(b) a group of the formula



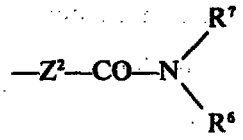
wherein $R^4$ is as defined above and
$R^5$ is a group as defined for $R^3$ above or is a group of the formula:



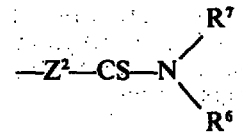
in which $R^7$ is a hydrogen atom or a lower alkyl group and $R^6$ is a group as defined for $R^4$ above, or $R^6$ and $R^7$ taken together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic ring;

*or*,

(c) a group of the formula



or



wherein $Z^2$ is $Z^1$ or —O—, and $R^6$ and $R^7$ are as defined above, provided that when $Z^2$ is



$R^4$ and $R^7$ taken together may represent $—(CH_2)_2—$, $—(CH_2)_3—$ or an *o*-phenylene group;

and (iv) R is a hydrogen atom or a lower alkyl group attached to the same carbon atom as Y; *provided that* when X is —CH=CH— or $—CH_2CH=CH—$, R is absent and Y is $—CH_2COR^3$, $—CH_2CON(R^6)(R^7)$ or $—CH_2CSN(R^6)(R^7)$ wherein $R^3$, $R^6$ and $R^7$ are as defined above, Y being attached to an unsaturated ring carbon atom;

and their pharmaceutically acceptable acid addition salts.

2. A compound as claimed in claim 1 which is in the form of a hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate or *p*-toluene sulphonate acid addition salt.

* C L M S *

3. A compound as claimed in claim 1 or 2, wherein $(R^2)n$ represents 6,7-di(lower alkoxy).

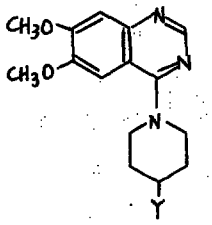
4. A compound as claimed in claim 3, wherein $(R^2)n$ represents 6,7-dimethoxy.

5. A compound as claimed in any one of claims 1 to 4 wherein X represents $-CH_2-$, $-(CH_2)_2-$ or $-CH=CH-$.

6. A compound as claimed in any one of claims 1 to 5 wherein when ring C is saturated, R is hydrogen.

7. A compound as claimed in any one of claims 1 to 6 wherein $R^1$ is a hydrogen atom.

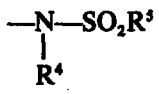
8. A compound as claimed in claim 1 having the structure:—



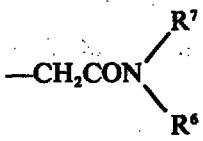
wherein Y is as defined in claim 1.

9. A compound as claimed in any one of claims 1 to 8 wherein Y is a group selected from:—

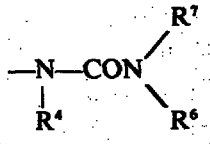
$-CH_2COR^3$ wherein $R^3$ is a lower alkyl or lower alkoxy group; $-NR^4COR^3$ wherein $R^3$ is a lower alkyl group; a lower alkyl group substituted by an amino (as hereinbefore defined) or lower alkoxy group; a lower alkoxy group; a lower alkoxy group substituted by an aryl group; an aryloxy group; or a heteroaryl group; and $R^4$ is a hydrogen atom, a lower alkyl group, or a lower alkyl group substituted by a hydroxy group;



wherein $R^4$ is a hydrogen atom or a lower alkyl group; and $R^5$ is a lower alkyl, aryl or heteroaryl group, or a group of the formula $-N(R^6)(R^7)$ wherein $R^6$ is a lower alkyl group and $R^7$ is a hydrogen atom or a lower alkyl group;

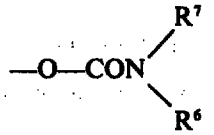


wherein $R^6$ is a lower alkyl group and $R^7$ is a hydrogen atom;



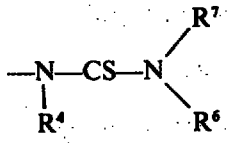
wherein $R^4$ is a hydrogen atom; a lower alkyl group; a lower alkyl group substituted by a heteroaryl, aryl, amino (as hereinbefore defined) or hydroxy group; or a heteroaryl group; $R^6$ is a hydrogen atom; a lower alkyl group; a lower alkyl group substituted by a hydroxy, carbethoxy or heteroaryl group; a lower alkenyl-methyl group; a lower alkynyl-methyl group; an aryl group or a heteroaryl group; and $R^7$ is a hydrogen atom or a lower alkyl group; or

$R^4$ and $R^7$ taken together represents an *o*-phenylene group; or $R^6$ and $R^7$ taken together represents $—(CH_2)_5—$;



wherein $R^6$ is a hydrogen atom, a lower alkyl group or a heteroaryl group and $R^7$ is a hydrogen atom;

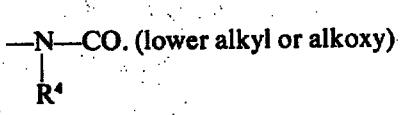
and



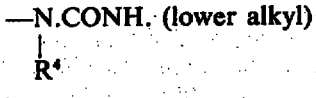
wherein $R^4$ is a hydrogen atom or a lower alkyl group, $R^6$ is a lower alkyl group and $R^7$ is a hydrogen atom.

10. A compound as claimed in claim 9, wherein when Y contains an aryl, aryloxy or heteroaryl group, said group is, respectively, a phenol, phenoxy or 2-, 3- or 4- pyridyl group.

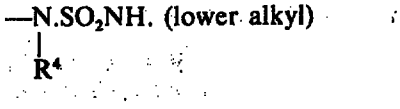
11. A compound as claimed in claim 10, wherein Y is a group selected from the following:—



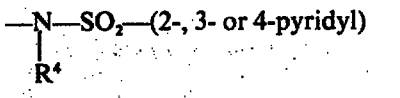
wherein $R^4$ is a hydrogen atom or a lower alkyl group;
—OCONH. (lower alkyl);



wherein $R^4$ is a hydrogen atom,
a lower alkyl group or a lower alkyl group substituted by a 2-, 3- or 4-pyridyl group;



wherein $R^4$ is a hydrogen atom or a lower alkyl group; and



wherein $R^4$ is a hydrogen atom or a lower alkyl group.

12. A compound as claimed in claim 8, wherein Y is $—NHCONH(CH_2)_3CH_3$.

13. A compound as claimed in claim 8, wherein Y is $—N(CH_3).CONH(CH_2)_2CH_3$.

14. A compound as claimed in claim 8, wherein Y is $—NHCOOCH_2CH_3$.

15. A compound as claimed in claim 8, wherein Y is $—O.CONHCH_2CH_3$.

16. A compound as claimed in claim 8, wherein Y is $—N(CH_3).SO_2NH(CH_2)_2CH_3$.

17. A compound as claimed in claim 8, wherein Y is $—N(CH_3).COOCH_2CH_3$.

18. A compound as claimed in claim 8, wherein Y is $—NHCOOCH_2CH(H_3)_2$.

19. A compound as claimed in claim 8, wherein Y is $—NHCOO(CH_2)_2CH_3$.

20. A compound as claimed in claim 8, wherein Y is —N(Et).COOEt.

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21. A compound as claimed in claim 8, wherein Y is

$$-N(CONH(CH_2)_3CH_3)-CH_2CH_2\text{-(4-pyridyl)}$$

22. A compound as claimed in claim 8, wherein Y is

$$-N(CONHCH_3)-(CH_2)_3CH_3$$

23. A compound as claimed in claim 8, wherein Y is

$$-N(CONH(CH_2)_3CH_3)-(CH_2)_3CH_3$$

24. A compound as claimed in claim 8, wherein Y is $-O.CONH(CH_2)_2CH_3$.
25. A compound as claimed in claim 8, wherein Y is $-NHSO_2NH(CH_2)_2CH_3$.
26. A compound as claimed in claim 8, wherein Y is $-NHSO_2$-(3-pyridyl).
27. A compound as claimed in claim 8, wherein Y is

$$-N(SO_2\text{-(3-pyridyl)})-CH_3$$

28. A compound as claimed in claim 8, wherein Y is

$$-N(CO(CH_2)_2CH_3)-CH_3$$

29. A compound as claimed in claim 8, wherein Y is $-NHCO(CH_2)_2CH_3$.
30. A process for preparing compounds of the formula (I) as defined in claim 1 substantially as described herein.
31. A compound of the formula (I) as defined in claim 1 which has been prepared by a process as claimed in claim 30.
32. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 29 and 31 together with a pharmaceutically acceptable carrier.
33. A method of stimulating the heart of a non-human animal which comprises administering to the animal a compound as claimed in anyone of claims 1 to 29 and 31 or a composition as claimed in claim 32 in an amount sufficient to stimulate the heart of the animal.

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