

- [54] (2-IMIDAZOLIN-2-YLAMINO)
SUBSTITUTED QUINOLINES,
-QUINOXALINES AND -QUINAZOLINES AS
ANTIHYPERTENSIVE AGENTS
- [75] Inventors: John C. Danielewicz; Michael
Snarey; Geoffrey N. Thomas, all of
Kent, England
- [73] Assignee: Pfizer Inc., New York, N.Y.
- [22] Filed: Feb. 14, 1973
- [21] Appl. No.: 332,485
- [30] Foreign Application Priority Data
Feb. 29, 1972 United Kingdom..... 9196/72
Nov. 8, 1972 United Kingdom..... 51629/72
- [52] U.S. Cl... 260/250 Q; 260/256.4 R; 260/286 R;
260/288 C; 260/289 C; 260/309.6; 424/250;

- 424/258
- [51] Int. Cl..... C07d 51/78
- [58] Field of Search..... 260/250 Q, 256.4 Q

[56] **References Cited**

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Primary Examiner—Donald G. Daus
Assistant Examiner—David E. Wheeler
Attorney, Agent, or Firm—Connolly and Hutz

- [57] **ABSTRACT**
- Novel (2-imidazolin-2-ylamino)substituted quinolines,
-quinoxalines and -quinazolines, their preparation and
use as antihypertensive agents are described.
- 9 Claims, No Drawings

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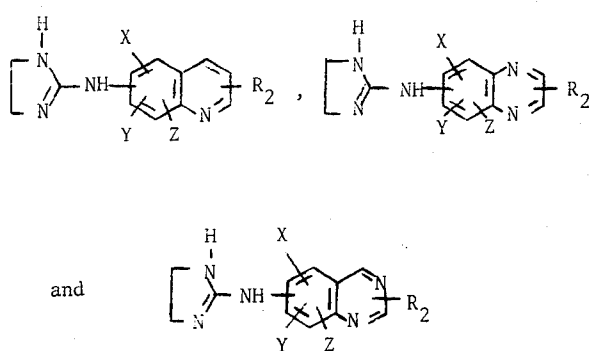
(2-IMIDAZOLIN-2-YLAMINO) SUBSTITUTED QUINOLINES, -QUINOXALINES AND -QUINAZOLINES AS ANTIHYPERTENSIVE AGENTS

BACKGROUND OF THE INVENTION

The invention relates to therapeutic agents which are novel derivatives of quinoline, quinoxaline or quinazoline, and is particularly concerned with derivatives thereof having a 2-imidazolin-2-ylamino group attached to the homocyclic ring which are useful as regulators of the cardiovascular system and, in particular, in the treatment of hypertension.

SUMMARY OF THE INVENTION

The novel compounds according to the invention are those having the general formulae:



in which the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8-positions in the quinoline, quinoxaline or quinazoline nuclei;

X, Y and Z represent up to 3 optional substituents in any of the remaining 5-, 6-, 7- or 8-positions, each of X, Y and Z being selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy or trifluoromethyl; and

R₂ represents an optional substituent in any of the 2-, 3- or 4-positions of the quinoline nucleus, or in either of the 2- or 3-, or 2- or 4-positions of the quinoxaline or quinazoline nuclei, respectively, R₂ being selected from the group consisting of hydrogen, lower alkyl or lower alkoxy;

and their pharmaceutically acceptable acid addition salts.

In this specification "lower" alkyl or alkoxy groups are those containing up to 6 carbon atoms, and "halogen" means fluorine, chlorine, bromine or iodine.

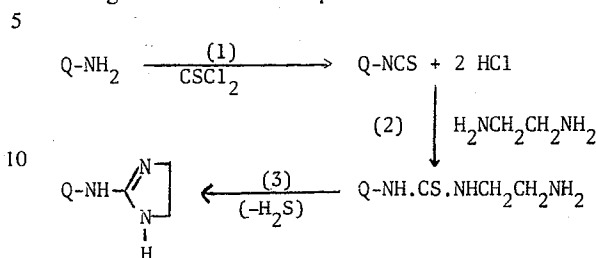
Pharmaceutically acceptable acid addition salts of the compounds of the invention are those formed from acids which form non-toxic addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulphate or bisulphate, phosphate or acid phosphate, acetate,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

DETAILED DESCRIPTION OF THE INVENTION

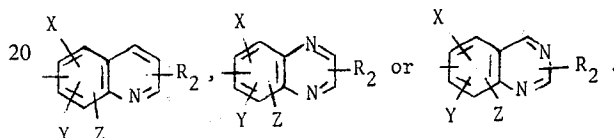
The compounds of the invention may be prepared by (1) reaction of the appropriate amino-quinoline, -quinoxaline or -quinazoline (Q—NH₂) with thiophosgene to form the corresponding isothiocyanate, (2) reacting the latter with excess ethylene diamine to form the cor-

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responding β-aminoethyl-thioureidoquinoline, -quinoxaline or -quinazoline, and (3) cyclizing to form the corresponding 2-imidazolin-2-ylamino compound, according to the reaction sequence:



where Q represents a group of the formula:



In step (1) the reaction with thiophosgene can be carried out in aqueous solution or in dilute aqueous hydrochloric acid solution at room temperature in a period of about 2 hours. Alternatively, the thiophosgene can be added to a mixture of an aqueous solution of a weak base, e.g., sodium carbonate, and a solution of the amine Q—NH₂ in a water-immiscible solvent, e.g., chloroform. In the first alternative, the isothiocyanate precipitates from the reaction mixture and precipitation can be completed by neutralization with excess alkali; the precipitate is recovered by filtration and, if necessary, basified, and may then be dissolved in a suitable solvent, e.g., chloroform. In the second alternative, the isothiocyanate is formed in solution in the water-immiscible solvent which is then separated. In either case, the solution of the isothiocyanate is dried, filtered, and evaporated to yield the isothiocyanate product as the free base.

In step (2) the isothiocyanate is reacted with an excess (e.g., 5 moles) of ethylene diamine in a suitable solvent, e.g., diethyl ether, benzene, chloroform or dioxan. The reaction is carried out at room temperature in a period of about 2 hours. The β-aminoethyl-thioureido compound precipitates and is recovered by filtration and washing with further solvent.

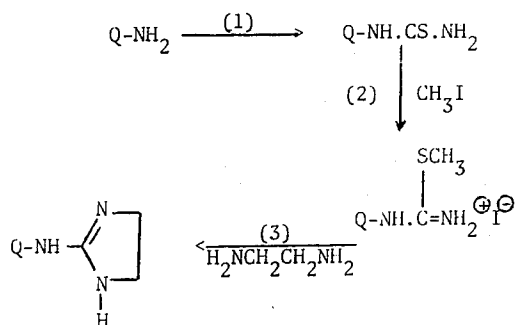
In step (3) the cyclization may be effected by heating a suspension of the thioureido compound with mercuric or cupric oxide in a suitable organic solvent medium, e.g., ethanol. The mercuric or cupric oxide can be replaced by an organic mercuric or cupric salt soluble in the medium, e.g., mercuric or cupric acetate. The reaction mixture is filtered, to remove the mercuric or cupric sulphide formed as by-product, and the filtrate is evaporated to dryness. The product may then be recrystallized as the free base or converted to an acid addition salt by reaction with a suitable acid by conventional means.

In certain cases, the cyclization may be successfully effected by simply refluxing the thioureido compound in a suitable organic solvent medium, e.g., methanol, in the absence of mercuric or cupric oxide.

The compounds of the invention can also be prepared by (1) reaction of the corresponding amino-

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quinoline, -quinoxaline or -quinazoline with benzoyl isothiocyanate to form the corresponding N-benzoyl thioureido compound, followed by hydrolysis to the thioureido compound, or reaction of the aminoquinoline, -quinoxaline or -quinazoline with ammonium thiocyanate to form the thioureido compound directly; (2) methylation to form the S-methyl derivative of the thioureido compound; and (3) reaction with ethylene diamine, according to the reaction sequence:



where Q is as previously defined.

For step (1), the benzoyl isothiocyanate starting material can be prepared in situ by reacting benzoyl chloride with ammonium thiocyanate. This may be conveniently carried out by heating under reflux a mixture of the reagents dissolved in a suitable organic solvent, e.g., acetone, for a short period, e.g., 20 minutes. To the cooled solution is then added the appropriate aminoquinoline, -quinoxaline or -quinazoline, and heating under reflux continued for a further period. Precipitation of the product, if it has not already occurred, can then be induced by adding the cooled reaction mixture to water, and the crude product is suitably collected by filtration and used directly in the subsequent hydrolysis step.

Hydrolysis is conveniently achieved by heating the (3-benzoylureido)-quinoline, -quinoxaline or -quinazoline in aqueous sodium hydroxide solution for several hours, and the product isolated by filtering the reaction mixture to remove any precipitated sodium benzoate and other solid material and collection of the precipitate formed in the cooled filtrate, if necessary, after further basification. Purification of the resulting thioureido product by recrystallization from a suitable solvent, e.g., butan-2-one, may optionally be effected.

In the alternative method the aminoquinoline, -quinoxaline or -quinazoline is reacted with ammonium thiocyanate to form the thioureido compound directly. This can be achieved by heating a solution of the reagents in water until the product has precipitated. The product, the thioureido compound, is then separated by filtration and optionally purified by crystallization before use in the next step.

In step (2), the thioureido compound is reacted with methyl iodide in a suitable solvent, e.g., methanol. The reaction is conveniently carried out by heating, e.g., in a steam bath, for a short period, e.g., 1 hour, and the product isolated by evaporation of the filtrate from filtration of the reaction mixture.

In step (3), the crude product of the previous stage, conveniently used without the necessity for purification, is dissolved in a suitable solvent, e.g., methanol, and the solution added to a boiling solution of ethylene

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diamine in the same solvent. The reaction is promoted by heating the solution for several hours, and the resulting precipitate collected by filtration and basified, e.g., using concentrated aqueous ammonium hydroxide solution, to afford the free base form of the required (2-imidazoline-2-ylamino)-quinoline, -quinoxaline or -quinazoline product.

The product may then be recrystallized to purity as the free base or converted to an acid addition salt by reaction with a suitable acid by conventional means.

The aminoquinoline, -quinoxaline or -quinazoline starting materials for these reaction sequences are either readily available materials or are readily preparable from such materials, e.g., by reduction of the corresponding nitroquinoline, -quinoxaline or -quinazoline and by halogenation of aminoquinolines, -quinoxalines or -quinazolines.

Compounds of the invention in which at least one of X, Y or Z is halogen can also be prepared from the corresponding des-halo compounds by conventional halogenation procedures.

The invention is illustrated by the following examples, in which all temperatures are given in °C.

EXAMPLE I

A.

To a vigorously stirred solution of 5-amino-8-bromo-6-methylquinoline hydrobromide (6.4g.) in distilled water (100 ml.) was added thiophosgene (1.6 ml.) in one portion. During a period of 2 hours, a brown solid precipitated. The suspension was poured into iced 4N aqueous sodium hydroxide solution (50 ml.) and the resulting brown solid was filtered off. The solid was dissolved in chloroform and the solution was dried over sodium sulphate, filtered and evaporated to yield 4.2 g. of 8-bromo-5-isothiocyanto-6-methylquinoline as free base, m.p. 145°.

B.

The isothiocyanate (3.5 g.) was dissolved in benzene (50 ml.) and added dropwise to a well-stirred solution of ethylene diamine (4.5 g.) in benzene (50 ml.). During a period of 1½ hours a light brown solid precipitated, which was filtered off and washed with fresh benzene (20 ml.) to give 4.1 g. of 1-(2-aminoethyl)-3-(8-bromo-6-methyl-quinolin-5-yl)-thiourea, m.p. 205°.

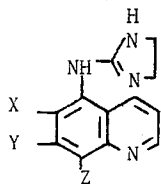
C.

A suspension of the thiourea (3.4 g.) in ethanol (100 ml.) was stirred under reflux conditions (78°) with mercuric oxide (3.25 g.) for 2½ hours and filtered while hot. Evaporation of the filtrate yielded a yellow solid which was recrystallized from an isopropanol/methanol mixture to give 2.0 g. of pure 8-bromo-5-(2-imidazolin-2-ylamino)-6-methyl-quinoline as the free base, m.p. >340°.

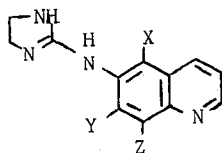
Analysis: Found: C, 51.03; H, 4.37; N, 18.44%
Required for C₁₈H₁₃BrN₄: C, 51.16; H, 4.29; N, 18.36%.

EXAMPLES II TO XVI

The following compounds were prepared by the method described in Example I from the appropriately substituted amino-quinoline, the product being isolated in each case as the free base.



Example	X	Y	Z	m.p. °C.	% C	Analysis (required) figures in brackets	
						% H	% N
II	C—CH ₃	H	8—Cl	278–280	59.67 (59.88)	5.09 5.03	21.21 21.49
III	6—CH ₃	H	H	230–232	69.08 (69.00)	6.29 6.24	24.89 24.76
IV	6—Br	H	8—CH ₃	271	51.38 (51.16)	4.52 4.29	18.61 18.36
V	6—Cl	H	8—CH ₃	251–253	59.60 (59.88)	5.20 5.03	21.41 21.49
VI	6—CH ₃ O	H	H	209–212	64.49 (64.44)	5.81 5.82	23.05 23.13
VII	H	H	H	218–220	67.94 (67.90)	5.59 5.70	26.03 26.40
VIII	6—Br	H	H	243–245	49.71 (49.49)	4.20 3.80	19.33 19.24
IX	H	H	8—CH ₃	234	68.86 (69.00)	6.25 6.24	24.52 24.76



Example	X	Y	Z	m.p. °C.	% C	Analysis (required) figures in brackets	
						% H	% N
X	H	H	H	207–210	67.97 (67.90)	5.80 5.70	26.46 26.40
XI	—Cl	H	H	213–216	58.37 (58.42)	4.53 4.49	22.56 22.73
XII	—Br	H	H	240–241	49.17 (49.50)	3.84 3.81	19.27 19.24
XIII	H	7—CF ₃	H	232–233	55.28 (55.71)	4.09 3.96	20.40 19.99
XIV	—Cl	H	8—Cl	243–245	51.51 (51.26)	3.65 3.59	20.06 19.92
XV	—Br	H	8—Cl	265–266	44.19 (44.26)	3.15 3.09	17.17 17.21
XVI	H	7—Br	H	232–234	49.38 (49.50)	3.96 3.81	19.38 19.24

EXAMPLE XVII

By a similar procedure to that described in Example I, 8-chloro-7-(2-imidazolin-2-ylamino)-4-methoxyquinazoline, m.p. 238°–239°, was prepared, starting from 7-amino-8-chloro-4-methoxyquinazoline.

Analysis:

Found: C, 51.73; H, 4.64; N, 25.06%
Required for C₁₂H₁₂ClN₃O: C, 51.90; H, 4.36; N, 25.22%.

EXAMPLE XVIII

A.

6-Amino-5-bromoquinoxaline hydrobromide (10 g.) was dissolved in water (150 ml.) and thiophosgene (3 ml.) was added. The solution was stirred for 2 hours at

room temperature, and the resultant precipitate collected by filtration, washed with water, and dried to afford 9 g. of 5-bromo-6-isothiocyanatoquinoxaline, which was used without further purification in the next stage.

B.

The product of (A) (9 g.) was dissolved in benzene (400 ml.) and the solution added to a stirred solution of ethylene diamine (15 g.) in benzene (50 ml.). Dur-

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ing a period of 2 hours with continual stirring an oil separated as a lower layer. The upper benzene layer was poured off and the oil washed with diethyl ether and then dissolved in methanol (approximately 500 ml.). After the methanolic solution had been refluxed until hydrogen sulphide evolution had ceased, it was concentrated by evaporation in vacuo to a volume of approximately 100 ml., by which stage a yellow precipitate had formed. The precipitate was collected by filtration and recrystallized from methanol to afford 3 g. of 5-bromo-6-(2-imidazolin-2-ylamino)quinoxaline, m.p. 250°-251°.

Analysis:

Found: C, 45.39; H, 3.35; N, 25.55%
Required for $C_{11}H_{10}BrN_5$: C, 45.22; H, 3.45; N, 23.97%.

EXAMPLES XIX AND XX

By similar procedures to that described in Example XVIII, the corresponding 5-chloro- and 5-iodo- compounds, 5-chloro-6-(2-imidazolin-2-ylamino)quinoxaline, m.p. 240°, and 6-(2-imidazolin-2-ylamino)-5-iodoquinoxaline, m.p. 227°, with decomposition, were prepared from 6-amino-5-chloroquinoxaline and 6-amino-5-iodoquinoxaline, respectively, in each case as the hydrochloride salt.

Analyses:

Found: C, 52.98; H, 4.09; N, 28.09%
Required for $C_{11}H_{10}ClN_5$ (5-chloro- compound): C, 53.34; H, 4.07; N, 28.28%
Found: C, 38.69; H, 3.08; N, 21.01%
Required for $C_{11}H_{10}IN_5$ (5-iodo- compound): C, 38.95; H, 2.97; N, 20.65%.

EXAMPLE XXI

A.

To a stirred solution of ammonium thiocyanate (3.9 g.) in acetone (200 ml.) at room temperature and under an atmosphere of nitrogen was added benzoyl chloride (6.95 g.). The mixture was refluxed for 20 minutes in a steam bath and then, after cooling to room temperature, added over a period of 5 minutes to a solution of 8-amino-5,7-dichloroquinoline (10.6 g.) in acetone (250 ml.). Refluxing of the mixture was carried out for 45 minutes, after which it was cooled to room temperature and poured into water (1 litre). The resulting solid was filtered off, washed with water and dissolved in approximately 2.5N aqueous sodium hydroxide solution (750 ml.) and the resulting slurry was stirred at 80° for 1½ hours. Immediately thereafter the reaction mixture was filtered through a celite pad, and the cooled (0°) filtrate was acidified with concentrated hydrochloric acid to about pH 2 and rebaseified with ammonium hydroxide, whereupon precipitation occurred. The precipitate was collected by filtration and dried in vacuo. Recrystallization from butan-2-one yielded 6.1 g. of 5,7-dichloro-8-thioureidoquinoline as a cream colored solid; m.p. 145°-150°.

B.

A mixture of the product of (A) (5.4 g.) and methyl iodide (2.9 g.) in methanol (75 ml.) was heated in a

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steam bath with stirring for 45 minutes. The solution was then filtered and the filtrate evaporated in vacuo to a gum, which was triturated in diethyl ether to afford 5.1 g. of 5,7-dichloroquinoline-8-(S-methylthiouronium)iodide as a brown solid.

C.

A solution of the product of the previous stage (4.1 g.) in methanol (45 ml.) was added dropwise to a boiling solution of ethylene diamine (1.5 g.) in methanol (5 ml.). Heating under reflux with stirring was continued for 6 hours, after which the mixture was twice allowed to stand at room temperature for 16 hours and then heated under reflux for a further 8 hours. By this stage a white precipitate had formed, and this was filtered from the cooled reaction mixture and crystallized from a mixture of dimethylacetamide and water. After drying in vacuo at 60° for 6 hours, the solid was basified by addition of concentrated aqueous ammonium hydroxide solution and the solid collected by filtration and crystallized from methanol.

The free base product so obtained was converted to the hydrochloride salt by bubbling hydrogen chloride through a suspension of the solid in methanol. The resulting solution was evaporated in vacuo to dryness and the solid residue was crystallized from isopropanol to afford 1.0 g. of 5,7-dichloro-8-(2-imidazolin-2-ylamino)quinoline hydrochloride as colorless crystals, m.p. 335° with decomposition.

Analysis:

Found: C, 45.09; H, 3.55; N, 17.45%
Required for $C_{12}H_{10}Cl_2N_4 \cdot HCl$: C, 45.38; H, 3.49; N, 17.64%.

EXAMPLE XXII

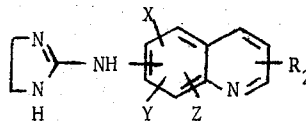
By a similar procedure to that described in Example XXI, 8-(2-imidazolin-2-ylamino)-7-methylquinoline was prepared from 8-amino-7-methylquinoline, and isolated as the hydroiodide, m.p. 289°-291°.

Analysis:

Found: C, 43.93; H, 4.29; N, 15.86%
Required for $C_{12}H_{14}N_4 \cdot HI$: C, 44.08; H, 4.27; N, 15.82%

EXAMPLE XXIII

The following compounds are prepared by the method of Example I from the appropriately substituted aminoquinoline, the product being isolated in each case as the free base.



Al	X	Y	Z	R ₂
5-	6-Br	H	8-C ₂ H ₅	H
5-	6-C ₂ H ₅	H	8-Br	H
5-	6-CH ₃	H	H	2-CH ₃

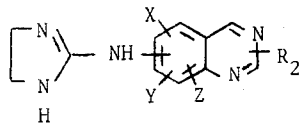
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Al	X	Y	Z	R ₂
5-	H	H	H	2-OCH ₃
5-	H	H	8-OCH ₃	H
5-	H	7-CH ₃	H	H
5-	H	H	8-O-n-C ₄ H ₉	H
5-	H	H	H	2-O-n-C ₄ H ₉
5-	H	7-CH ₃	8-CH ₃	H
5-	H	H	8-OC ₂ H ₅	H
5-	H	H	8-OC ₆ H ₁₃	H
6-	5-OC ₂ H ₅	H	8-OC ₂ H ₅	H
6-	5-OCH ₃	H	8-OCH ₃	H
6-	5-OCH ₃	H	8-OCH ₃	3-CH ₃
6-	5-OCH ₃	H	8-OCH ₃	3-C ₂ H ₅
6-	H	H	H	2-i-C ₃ H ₇
6-	H	H	8-OCH ₃	H
6-	H	H	H	2-O-n-C ₄ H ₉
6-	H	7-CH ₃	H	2-CH ₃
6-	H	H	H	3-OCH ₃
6-	H	H	H	2-O-n-C ₃ H ₇
7-	H	H	H	H
7-	5-Cl	6-OCH ₃	8-OCH ₃	H
7-	5-Cl	6-Cl	8-Cl	H
7-	5-F	6-F	8-F	H
7-	5-OCH ₃	6-OCH ₃	8-OCH ₃	H
7-	H	H	H	2-O-n-C ₄ H ₉
7-	5-CH ₃	H	8-CH ₃	H
8-	H	H	H	H
8-	H	6-Br	H	3-n-C ₄ H ₉
8-	5-CH ₃	6-CH ₃	H	3-n-C ₄ H ₉
8-	5-OCH ₃	6-OCH ₃	H	H
8-	5-CH ₃	6-CH ₃	H	3-C ₂ H ₅
8-	H	6-I	H	H
8-	H	6-OCH ₃	H	H
8-	H	H	H	3-CH ₃
8-	H	6-CH ₃	H	H
8-	H	H	H	4-n-C ₃ H ₁₁
8-	5-CH ₃	6-CH ₃	H	3-CH ₃
8-	6-Br	H	H	H
8-	5-Cl	6-Br	7-Cl	H
8-	H	H	H	2-O-n-C ₄ H ₉
8-	H	6-Cl	H	H
8-	5-Br	6-Cl	7-Br	H
8-	H	H	H	3-C ₂ H ₅
8-	H	H	H	4-C ₂ H ₅
8-	H	6-C ₂ H ₅ H	H	H
8-	5-Br	6-Br	7-Br	H
8-	5-Cl	6-Cl	7-Cl	H

Al = 2-Imidazolin-2-ylamino.

EXAMPLE XXIV

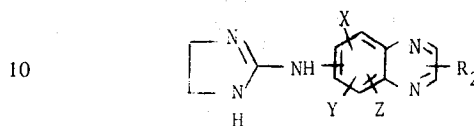
The following compounds are prepared from the appropriately substituted aminoquinazoline by the procedure of Example I, the product being isolated in each case as the free base.



Al	X	Y	Z	R ₂
5-	H	H	H	H
6-	H	H	H	H
6-	H	H	H	4-OC ₂ H ₅
6-	5-OCH ₃	H	8-OCH ₃	H
7-	H	H	H	H
8-	H	H	H	H
8-	H	H	H	4-OCH ₃
7-	H	6-OCH ₃	H	H
7-	H	6-OCH ₃	H	4-OCH ₃

EXAMPLE XXV

Repetition of the procedure of Example I, but using the appropriate aminoquinazoline hydrochloride in place of 5-amino-8-bromo-6-methylquinoline hydrobromide produces the following compounds:



Al	X	Y	Z	R ₂
5-	H	H	H	H
5-	H	H	8-OC ₂ H ₅	H
5-	6-OCH ₃	H	H	H
5-	H	H	8-OCH ₃	H
20 5-	H	7-CH ₃	H	H
5-	H	7-OCH ₃	H	H
5-	6-OCH ₃	7-OCH ₃	H	H
6-	H	H	H	H
6-	H	H	H	2-CH ₃
7-	H	H	H	2-CH ₃
7-	5-OCH ₃	H	H	H
25 7-	H	6-CH ₃	H	H
5-	H	H	H	2-CH ₃
8-	H	H	H	2-CH ₃

The quinolines, quinoxalines and quinazolines substituted in the homocyclic portion of the nuclei with both an amino group and one or two halogen atoms, which were used as starting materials in the above preparations, are either known compounds or were themselves prepared from known starting materials according to the following methods, in which all temperatures are given in °C.

EXAMPLE XXVI

Salt Formation

The free base form of the appropriate (2-imidazolin-2-ylamino) substituted quinoline, quinoxaline or quinazoline compound in a suitable solvent, e.g., methanol, ethanol, benzene, ether or water, is treated with a stoichiometric amount of the appropriate acid, warming if necessary to achieve reaction. The acid salt is recovered by filtration or evaporation of the solvent.

In this manner, the hydrochloride, hydrobromide, hydroiodide, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate, p-toluenesulfonate, sulfate, bisulfate, phosphate and acid phosphate salts of the herein described products are prepared.

In instances such as Examples XIX-XXII wherein the product is obtained as a hydrohalide salt, the free base is obtained by careful neutralization of the acid component with ammonium hydroxide, and the base recovered as in Example XXI.

Method A

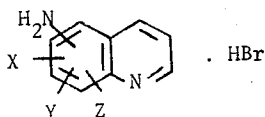
To a stirred solution of 5-amino-6-methylquinoline (6.4 g.) in glacial acetic acid (75 ml.) at room temperature was added dropwise a solution of bromine (6.4 g.) in glacial acetic acid (25 ml.). The solution was then stirred at room temperature for a further 2 hours, and the resulting precipitate filtered off, washed with isopropanol and dried at 60° in vacuo for 4 hours. Produced was 9.0 g. of 5-amino-8-bromo-6-

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methylquinoline hydrobromide, as a red-brown solid, m.p. 239°.

This compound was used directly, without further purification, in Example I.

The following amino- and bromo- substituted quinoxalines were prepared from the corresponding, previously known, des-bromo compounds by a similar bromination procedure to that described above. In each case the Example in which the compound was used is indicated.



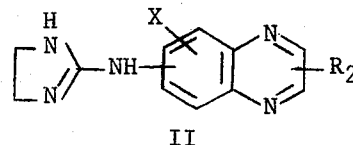
Position of amino group	X	Y	Z	m.p. °C.	Used in Example
5-	6-Br	H	8-CH ₃	262	IV
5-	6-Br	H	H	235-236	VIII
6-	5-Br	H	H	230	XII
6-	5-Br	H	8-Cl	248-251	XV

In a similar manner, 6-amino-5-bromoquinoxaline hydrobromide was prepared by bromination of 6-aminoquinoxaline, a small portion of which was characterized as the free base, with m.p. 155°-156°. The hydrobromide salt was used in Example XVIII.

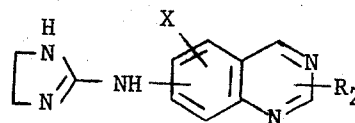
What is claimed is:

1. A compound selected from the group consisting of those having the formulae

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II



III

and the pharmaceutically acceptable acid addition salts thereof wherein X is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy and trifluoromethyl and R₂ is selected from the group consisting of hydrogen, alkyl having 1 to 6 carbon atoms and alkoxy having 1 to 6 carbon atoms.

2. A compound according to claim 1, formula II.

3. A compound according to claim 1, formula III.

4. A compound according to claim 2 wherein R₂ is hydrogen.

5. A compound according to claim 2 wherein R₂ is hydrogen, X is halogen and the 2-imidazolin-2-ylamino group is located at the 6-position.

6. A compound according to claim 5 wherein X is 5-bromo.

7. A compound according to claim 5 wherein X is 5-chloro.

8. A compound according to claim 3 wherein R₂ is hydrogen or 4-methoxy.

9. A compound according to claim 3 wherein R₂ is hydrogen or 4-methoxy, X is hydrogen and the 2-imidazolin-2-ylamino group is located at the 7-position.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,890,319

DATED : June 17, 1975

INVENTOR(S) : John C. Danielewicz et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 11, between lines 31 and 32, should read

-- METHOD B

(A) A mixture of 3-bromo-4-nitroaniline (66 g.), arsenic oxide (55 g.), glycerol (112.5 ml.) and concentrated sulphuric acid (73 ml.) was gently heated with stirring to reflux temperature. At the first sign of vigorous gas evolution, the heating source was removed from the reaction vessel for about 3 minutes. Thereafter, heating was continued for 3 hours and the reaction mixture was cooled and poured onto ice. Once the latter had melted, the brown solid was filtered off and suspended in water, which was then basified by addition of aqueous sodium hydroxide solution. The solid was collected by filtration, washed with water, and dried, yielding 35 g. of brown solid.

The latter was recrystallized from methanol and then three times from petroleum ether (b.p. 80-100°) to afford 9.2 g. of 7-bromo-6-nitroquinoline, m.p. 144-145°.

(B) The product of (A) (6.05 g.) was dissolved in concentrated hydrochloric acid (50 ml.), and to the stirred solution at room temperature was added portionwise a solution of stannous chloride (18.1 g.) in concentrated hydrochloric acid (50 ml.). After stirring the mixture for 5 minutes, the solid was filtered off, washed with concentrated hydrochloric acid and dried in air. A suspension of the solid in water was then basified by addition of 4N aqueous sodium hydroxide solution, and the solid filtered off, to be washed with distilled water, dried in air and then in vacuo at 60° for 6 hours.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,890,319 (page 2)
DATED : June 17, 1975
INVENTOR(S) : John C. Danielewicz et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

The yellow solid (3.8 g.) was finally recrystallized from petroleum ether (b.p. 100-120°) to afford 3.2 g. of 6-amino-7-bromoquinoline as straw-colored needles, m.p. 135-136°.

This compound was used in Example XVI.

METHOD C

To a stirred solution of 5-amino-8-methylquinoline (4 g.) in glacial acetic acid (90 ml.) at room temperature was added a solution of sulphuryl chloride (3.5 g.) in glacial acetic acid (10 ml.) dropwise. The solution was stirred for 2 hours at room temperature, and then poured into aqueous sodium acetate solution, resulting in the formation of a precipitate. The latter was collected by filtration and recrystallized from aqueous ethanol solution to afford 2.5 g. of 5-amino-6-chloro-8-methylquinoline as a brown solid, mp. 113-114°.

This compound was used directly, without further purification, in Example V.

The following amino- and chloro-substituted quinolines, quinoxalines and quinazolines were prepared by a similar chlorination procedure to that described above. In cases where the hydrochloride salt was isolated, the basification by sodium acetate step was omitted. The example in which the compound was used is indicated in each case.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,890,319 (page 3)
DATED : June 17, 1975
INVENTOR(S) : John C. Danielewicz et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

<u>Compound</u>	<u>m.p. °C.</u>	<u>Used in Example</u>
5-amino-8-chloro-6-methyl-quinoline	82°	II
6-amino-5-chloroquinoline hydrochloride	142-145°	XI
6-amino-5,8-dichloro-quinoline hydrochloride (from the 8-chloro compound)	236-238°	XIV
7-amino-8-chloro-4-methoxy quinazoline hydrochloride	166-167°	XVII
6-amino-5-chloroquinoxaline	139-140°	XIX
8-amino-5,7-dichloro-quinoline (from 8-amino-quinoline)	121	XXI

METHOD D

To a stirred solution of 6-aminoquinoxaline (3 g.) in glacial acetic acid at room temperature was added dropwise over a period of one minute a solution of iodine monochloride (4.5 g.) in glacial acetic acid (15 ml.). Stirring at room temperature was continued for a further 30 minutes, after which the precipitated solid was collected by filtration and washed with diethyl ether to afford 6.5 g. of 6-amino-5-iodoquinoxaline hydrochloride, as a complex with iodine, m.p. 167-169° with decomposition.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,890,319 (page 4)
DATED : June 17, 1975
INVENTOR(S) : John C. Danielewicz et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Analysis:

Found: C, 21.79; H, 1.58; N, 9.66%

Required for $C_8H_6IN_3 \cdot I \cdot HCl$: C, 22.11; H, 1.63; N, 9.67%

This compound was used in Example XX.

The starting materials for Examples III, VI, VII, IX, X, XIII and XIII-XXV are all previously known compounds.

The antihypertensive activity of the compounds of the invention is shown by their ability to lower the blood pressure of conscious hypertensive rats and dogs, when administered subcutaneously and orally, respectively, within the dosage range 0.025-10 mg./kg.

By virtue of their performance in such trials in animals, the preferred compounds of the invention are those in which at least one of X, Y or Z is a halogen atom, and those in which the 2-imidazolin-2-ylamino group is in either the 6- or the 7-position in the quinoline, quinoxaline or quinazoline nucleus. When any of X, Y or Z is a halogen atom, this is preferably a bromine atom.

Particularly preferred compounds of the invention are those of any of the three formulae given hereinbefore in which the 2-imidazolin-2-ylamino group is in the 6-position and one of X, Y or Z represents a single halogen atom in the 5-position or in which the 2-imidazolin-2-ylamino group is in the 7-position and one of X, Y or Z represents a single halogen atom in the 8-position.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 3,890,319 (page 5)
DATED : June 17, 1975
INVENTOR(S) : John C. Danielewicz et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Of particular value as antihypertensive agents have been found to be the compounds of Examples XI, XII, XVIII and XIX.

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 flavoring or coloring agents. They may be injected parenterally, for example, 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 salt or glucose to make the solution isotonic.

The compounds of the invention can be administered to humans for the treatment of hypertension by either the oral or the parenteral routes, and may be administered orally at dosage levels within the range of 20 μ g. to 1.5 mg./day for an average adult patient (70 kg.), given in a single dose or up to 3 divided doses. Intravenous dosage levels would be expected to be about one tenth of the daily oral dose, given in a single quantity. Thus, for an average adult patient, individual oral doses in tablet or capsule form will be in the range from 10 μ g. to 1.5 mg. of active compound. Variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of administration chosen.

Signed and Sealed this

twenty-eight Day of October 1975

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks