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3,654,275

QUINOXALINECARBOXAMIDE ANTIINFLAMMATORY AGENTS

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8 Claims

ABSTRACT OF THE DISCLOSURE

1,2,3,4-tetrahydro-1-acyl-3-oxo-2-quinoxalinecarboxamides, a novel class of heterocyclic compounds possessing antiinflammatory activity.

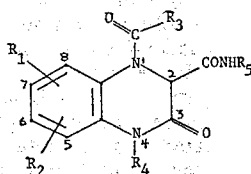
BACKGROUND OF THE INVENTION

The invention relates to 1,2,3,4-tetrahydro-1-acyl-3-oxo-2-quinoxalinecarboxamides, a novel class of heterocyclic compounds possessing chemotherapeutic activity.

Compounds of the present invention are synthesized via aminolysis of the corresponding 2-carboalkoxyquinoxalines.

SUMMARY OF THE INVENTION

The novel antiinflammatory compounds of this invention are quinoxalinecarboxamides; in particular, they are 1,2,3,4-tetrahydro-1-acyl-3-oxo-2-quinoxalinecarboxamides of the formula:



and the basic metal salts thereof, wherein R_1 and R_2 are each selected from the group consisting of hydrogen, alkyl containing up to 3 carbon atoms, fluorine, chlorine, bromine, alkoxy and alkylthio each of up to 2 carbon atoms and hydroxy; R_3 and R_4 are each selected from the group consisting of hydrogen, alkyl containing up to 3 carbon atoms; alkenyl containing up to 4 carbon atoms; cycloalkyl of from 3 to 6 carbon atoms; and phenyl and substituted phenyl having a substituent selected from the group consisting of fluorine, chlorine, bromine, alkoxy containing up to 2 carbon atoms and alkyl containing up to 3 carbon atoms; R_5 is selected from the group consisting of alkyl and alkenyl each of up to 6 carbon atoms; cycloalkyl of from 3 to 6 carbon atoms; pyridyl and substituted pyridyl with 1 or 2 methyl substituents; thiazolyl; and phenyl, benzyl and mono- and disubstituted phenyl and benzyl, said substituents being selected from the group consisting of fluorine, chlorine, bromine, alkyl containing up to 3 carbon atoms, alkoxy and alkylthio each having up to 2 carbon atoms, hydroxy, amino, acylamino containing up to 3 carbon atoms, trifluoromethyl and trifluoromethoxy.

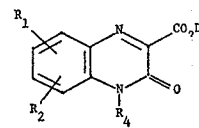
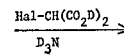
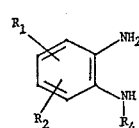
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Of particular interest are compounds wherein R_1 and R_2 are each hydrogen, R_3 is methyl, R_4 is either hydrogen or alkyl containing up to 3 carbon atoms and R_5 is substituted phenyl with 0 to 2 substituents, said substituents being selected from the group consisting of fluorine, chlorine, bromine, alkyl containing up to 3 carbon atoms, alkoxy and alkylthio each having up to 2 carbon atoms, hydroxy, amino, acylamino containing up to 3 carbon atoms, trifluoromethyl and trifluoromethoxy.

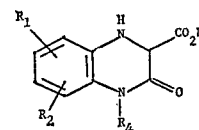
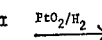
DETAILED DESCRIPTION OF THE INVENTION

The quinoxalinecarboxamides of the instant invention are prepared by several alternate procedures. In the procedure illustrated in Scheme I an appropriately substituted o-phenylenediamine is reacted with a halomalonate ester to yield the quinoxaline ester, I.

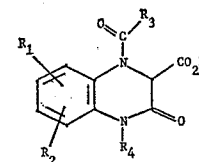
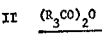
SCHEME I



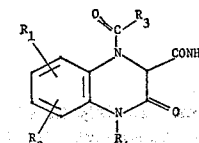
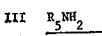
I



II



III



IV

R_1 , R_2 , R_3 , R_4 , and R_5 are as previously defined; Hal— represents a halogen, preferably, chlorine or bromine, and D may be lower alkyl containing up to three carbon atoms.

A solution of the requisite halomalonate dissolved in a reaction-inert solvent such as ethanol, tetrahydrofuran, dimethylformamide or dimethylsulfoxide is added, preferably dropwise, to a solution or suspension of the appropriately substituted o-phenylenediamine and a tertiary organic amine, the tertiary amine acting as a receptor for the hydrogen halide formed during the reaction. It is

preferable to use at least a molar equivalent amount of said reactants and tertiary amine. The reaction is carried out at ambient temperatures, although it may be heated from about 50–80° C. to hasten product formation. Reaction time is not critical, but conversion is usually complete within 2–5 hours, after which the product is isolated. A convenient means of isolation is to cool the reaction mixture, filter the product and remove any co-precipitated tertiary amine hydrogen halide through a water wash. Alternately, the reaction mixture is added to water, which causes the product to precipitate.

The requisite o-phenylenediamines and halomalonate esters are available commercially or may be synthesized by one skilled in the art. For example, C. H. Roeder et al., *J. Org. Chem.*, 6, 25 (1941), teaches the preparation of N-substituted-o-phenylenediamines and Palmer et al., *Org. Syn. Coll.*, vol. I, 245 (1941), teaches the synthesis of a halomalonate.

Surprisingly, the condensation of the aforesaid o-phenylenediamines with halomalonate esters gives a product resulting from cyclization and an in situ oxidation of 1,2,3,4-tetrahydroquinoxaline to a 3,4-dihydroquinoxaline structure.

Products from the reaction of a o-phenylenediamine unsymmetrically substituted ($R_3=H$) in the aromatic moiety and a halomalonate ester give rise to two positional isomers, the separation of which is achieved using thick layer or column chromatography. Structural assignments to the separated isomers are readily carried out through the interpretation of their respective nuclear magnetic resonance spectra.

Reaction product from N-substituted-o-phenylenediamine ($R \neq H$) and a halomalonate ester, regardless of the substitution in the aromatic portion of the structure, are, almost exclusively, those resulting from alkylation, followed by cyclization and oxidation, on the less hindered, primary amino group.

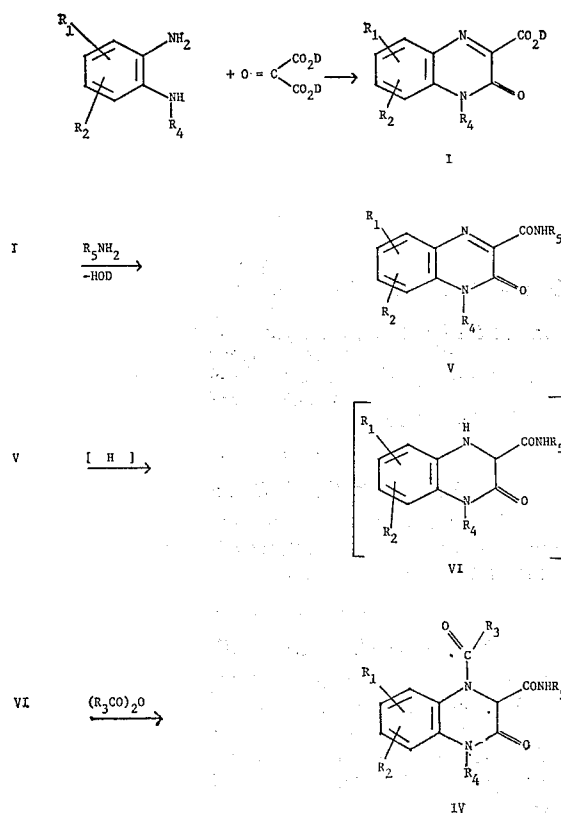
Reduction of the aforesaid 3,4-dihydroester, I, to II is carried out in a reaction-inert solvent such as ethanol or tetrahydrofuran, using hydrogen gas and a catalytic amount of platinum oxide. Pressures of from 2–50 p.s.i. and temperatures of from 25–50° C. may be employed. These pressure and temperature parameters are not critical, and influence only rate of product formation. The reaction product is best isolated by filtration of the spent catalyst, and concentration of the filtrate to dryness.

Acylation of the 1,2,3,4-tetrahydroquinoxaline ester, II, to provide III may be effected by adding an equimolar amount, plus as much as a 10% excess, of the corresponding acrylanhydride to II in a reaction-inert solvent such as tetrahydrofuran or benzene. Reflux temperatures are preferred, although lower temperatures may be used with correspondingly longer reaction times. Removal of the solvent in vacuo leads to the isolation of the crude product, which is further purified by recrystallization from appropriate solvents.

Aminolysis of III to the products of the instant invention, IV, is carried out by heating III with a primary amine, R_5NH_2 , in a suitable solvent such as benzene, toluene, mestitylene or tetraline for such periods of time as to allow for the formation of the desired product, in general 5–10 hours. In instances when R_5NH_2 is a high boiling amine, the formation of the product, IV, is facilitated by co-distilling the alcohol formed in the reaction with the solvent. Fresh solvent is periodically added to maintain a relatively constant volume. When R_5NH_2 is low boiling the reaction is carried out using the same solvents in a sealed bomb or autoclave. Temperatures used in these reactions may vary from 80–200° C. They are not critical, and reflect only on the rate of product formation. A convenient means of isolation for the reaction product is to cool the reaction mixture to precipitate the product.

An alternate method for the preparation of quinoxalinecarboxamides of the instant invention is outlined in Scheme II.

SCHEME II



The first step of Scheme II is a condensation and cyclization of an appropriately substituted o-phenylenediamine and an oxomalonate ester, the products of which are water, an alcohol and I. The reaction is most conveniently carried out by adding an equimolar amount of the oxomalonate to a solution or suspension of the suitable diamine in a reaction-inert solvent such as ethanol. It is preferred that the reaction be heated from about 50–100° C. for a period of 1–5 hours. The reaction product, which is identical in every respect to I prepared via Scheme I, is isolated as a precipitated solid after the reaction mixture is concentrated in volume and cooled.

As in Scheme I, positional isomers are formed. They are separated and identified by aforesaid procedures. Again, as in Scheme I, the condensation of N-substituted-o-phenylenediamines with an oxomalonate ester takes place preferentially on the unsubstituted $-NH_2$ group.

Conversion of the ester, I, to the carboxamide, V, is achieved by heating I with as much as a three fold excess of the aforesaid amine, R_5NH_2 , in a reaction-inert solvent such as dimethylformamide. When R_5NH_2 is a low boiling amine, a sealed bomb or autoclave is employed as the reaction vessel. Aminolysis of I to V is carried out at temperatures of from 100–200° C., with a preferred temperature of about 150° C. The completion time for the reaction is not critical, longer reaction periods being required when lower temperatures are used. Isolation of the product, as a precipitate, is achieved by concentration of the reaction mixture in volume, preferably in vacuo, and cooling.

Transformation of the 3,4-dihydroquinoxalinecarboxamide, V, to the product of the instant invention, IV, is carried out without isolation of the 1,2,3,4-tetrahydroquinoxalinecarboxamide intermediate, VI. Reduction of the aforesaid 3,4-dihydro compound to the 1,2,3,4-tetrahydro analog is most conveniently carried out in a reac-

tion-inert solvent such as tetrahydrofuran, using hydrogen gas and a catalytic amount of platinum oxide. Pressures of from 2–50 p.s.i. and temperatures of from 25–50° C. are preferred. When the theoretical amount of hydrogen has been absorbed, the spent catalyst is filtered, and the filtrate containing VI is treated with at least an equimolar amount, and preferably a 10–20% excess, of an acylanhydride, $(R_3CO)_2O$. It is preferred that the reaction be heated from between 50° C. to the reflux temperature. The product precipitates after the reaction mixture is concentrated in vacuo, and cooled.

The final products from Schemes I and II are identical in every respect.

It is noted that a common characteristic of many anti-inflammatory agents is that they contain an acidic hydrogen atom. Each of the 3-carboxamides of the instant invention shares this property and is an effective proton source, with the active hydrogen being located at the 3-position.

Pharmaceutically acceptable, basic metal salts of the compounds of the present invention are also therapeutic agents, wherein the cations of said salts include the ammonium, sodium, potassium, calcium, and magnesium ions. The pharmaceutically acceptable salts of the compounds described herein are prepared by conventional procedures, as for example, by adding the acid to an aqueous solution containing an equivalent amount of a pharmaceutically acceptable base, i.e., a base containing one of the above cations, followed by concentration of the resultant mixtures to obtain the desired product. The bases may be selected from the hydroxides, oxides and carbonates. Pharmaceutically unacceptable, basic metal salts of the compounds of the present invention, wherein the cations of said salts include barium, strontium, cesium and rubidium are also prepared by the aforementioned procedure. While said salts are not useful therapeutic agents per se, they are valuable in the purification of the compounds of the present invention and in the preparation of pharmaceutically acceptable salts.

As indicated hereinbefore, the 1,2,3,4-tetrahydro-1-acyl-3-oxo-2-quinoxalinecarboxamides and the pharmaceutically acceptable salts thereof are useful anti-inflammatory agents. These compounds are of value in alleviating swelling and inflammation which are symptomatic of rheumatoid arthritis and related disorders which are responsive to treatment with anti-inflammatory agents. Either as individual therapeutic agents or as mixtures of therapeutic agents, they may be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk, sugar or certain types of clay, etc. They may be administered orally in the form of elixirs or oral suspensions with the active ingredients combined with emulsifying and/or suspending agents. They may be injected parenterally, and for this use they, or appropriate derivatives, may be prepared in the form of sterile aqueous solutions. Such aqueous solutions should be suitably buffered, if necessary, and should contain other solutes such as saline or glucose to render them isotonic.

The dosage required to reduce inflammation or swelling in arthritic subjects would be determined by the nature and extent of the symptoms. Generally, small doses will be administered initially, with a gradual increase in the dosage until the optimum level is determined. It will generally be found that when the composition is administered orally, larger quantities of the active ingredient will be required to produce the same level as produced by a small quantity administered parenterally. In general, from about 0.10 to about 200 mg. of active ingredient per kilogram of body weight, administered in single or multiple dose units, will effectively reduce inflammation and swelling.

Particularly effective as anti-inflammatory agents are those carboxamides of Formula IV wherein R_1 and R_2 are hydrogen, R_3 is methyl, R_4 is either hydrogen or alkyl containing up to 3 carbon atoms and R_5 is phenyl with up to 2 substituents selected from the group consisting of fluorine, chlorine, bromine, alkyl containing up to 3 carbon atoms, alkoxy and alkylthio each having up to 2 carbon atoms, hydroxy, amino, acylamino containing up to 3 carbon atoms, trifluoromethyl and trifluoromethoxy. Among these compounds, 1,2,3,4-tetrahydro-1-acetyl-2',4'-difluoro-3-oxo-2-quinoxalinecarboxanilide, 1,2,3,4-tetrahydro-1-acetyl-3-oxo-4-methyl-4'-bromo-2-quinoxalinecarboxanilide and 1,2,3,4-tetrahydro-1-acetyl-3-oxo-4-ethyl-2-quinoxalinecarboxanilide are preferred.

A standard procedure for detecting and comparing anti-inflammatory activity of compounds is the carrageenin rat foot edema test, whereby unanesthetized adult male albino rats of 150–190 g. body weight are each numbered, weighed and marked with ink on the right lateral malleolus. One hour after administration of the drug by gavage, edema is induced by injection of 0.05 ml. of 1% solution of carrageenin into the plantar tissue of the marked paws. Immediately thereafter, the volume of the injected paw is measured. The increase in volume three hours after the injection of carrageenin constitutes the individual response. Compounds are considered active if the difference in response between a control and the drug being tested is significant. Standard compounds are phenylbutazone at 33 mg./kg. and acetylsalicylic acid at 100 mg./kg., both with oral administration.

The following examples are given to more fully illustrate the instant invention. They are not the only possible embodiments of the invention and are not to be considered as a limitation on the scope thereof. Roman numerals in Examples I and II refer to structures in Schemes I and II, respectively.

EXAMPLE I

3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid, ethyl ester (I; $R_1, R_2, R_4=H$)

To a suspension of 108 g. (1.0 mole) of o-phenylenediamine in 400 ml. of ethanol is added 101 g. (1.0 mole) of triethylamine followed by the dropwise addition of 429 g. (1.37 moles) of ethyl bromomalonate dissolved in 350 ml. of ethanol. The resulting solution is allowed to stir for five hours. The precipitate which forms is filtered, washed with water, and dried, 74.2 g. Recrystallization of a portion from ethanol gives the pure product, M.P. 245–246° C.

Analysis.—Calcd. for $C_{11}H_{10}N_2O_3$ (percent): C, 60.54; H, 4.62; N, 12.84. Found (percent): C, 60.31; H, 4.44; N, 12.82.

1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylic acid, ethyl ester (II; $R_1, R_2, R_4=H$)

A suspension of 2.18 g. (0.01 mole) of I and 500 mg. of platinum oxide in 40 ml. of tetrahydrofuran is shaken in a hydrogen atmosphere at a pressure of 30 p.s.i. for a period of two hours. The resulting reaction mixture is filtered, concentrated to dryness in vacuo, and the residue slurried in water. The solid is filtered, dried and recrystallized from benzene, M.P. 148–149° C.

Analysis.—Calcd. for $C_{11}H_{12}N_2O_3$ (percent): C, 59.99; H, 5.49; N, 12.72. Found (percent): C, 59.77; H, 5.43; N, 12.75.

1,2,3,4-tetrahydro-1-acetyl-3-oxo-2-quinoxalinecarboxylic acid, ethyl ester (III; $R_1, R_2, R_4=H; R_3=CH_3$)

To a solution of 14.4 g. (0.065 mole) of II in 80 ml. of tetrahydrofuran is added 7.14 g. (0.07 mole) of acetic anhydride. The reaction mixture is heated to reflux 40

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hours followed by removal of the solvent in vacuo. The residue is recrystallized from ethyl acetate-ether, M.P. 172–174° C.

Analysis.—Calcd. for $C_{13}H_{14}N_2O_4$ (percent): C, 59.53; H, 5.38; N, 10.68. Found (percent): C, 59.28; H, 5.29; N, 10.73.

1,2,3,4 - tetrahydro-1-acetyl-2',5'-difluoro-3-oxo-2-quinoxalinecarboxanilide (IV; $R_1, R_2, R_4=H$; $R_3=CH_3$; $R_5=2,5-F_2C_6H_3$)

A mesitylene (65 ml.) solution containing 2.62 g. (0.01 mole) of III and 1.42 g. (0.011 mole) of 2,5-difluoroaniline is heated to the boiling point. The mesitylene which distills off is gradually replaced by fresh solvent. When 110 ml. of mesitylene has been distilled the reaction mixture is cooled, and the solid which precipitates is filtered. The product is dried, and recrystallized from ethyl acetate, M.P. 209–210° C.

Analysis.—Calcd. for $C_{17}H_{13}F_2N_3O_3$ (percent): C, 59.13; H, 3.79; N, 12.71. Found (percent): C, 59.21; H, 3.94; N, 11.91.

EXAMPLE II

3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid, ethyl ester (I; $R_1, R_2, R_4=H$)

To a suspension of o-phenylenediamine in ethanol is added an equimolar amount of diethyl oxomalonate, and the resulting solution is heated at steam bath temperatures for 1–2 hours. The resulting solution is concentrated in vacuo and cooled. The desired product is filtered, dried and recrystallized from benzene. The product is identical to that synthesized by the procedures outlined in Example I.

3,4-dihydro-2',5'-difluoro-3-oxo-2-quinoxalinecarboxanilide (V; $R_1, R_2, R_4=H$; $R_3=2,5-F_2C_6H_3$)

To a suspension of I in dimethylformamide is added two molar equivalents of 2,5-difluoroaniline, and the mixture is heated to the reflux temperature for 6 hours. The reaction mixture is concentrated in vacuo, followed by cooling. The resulting product precipitates from solution, and is filtered. Further purification is carried out by recrystallization from ethanol-water.

1,2,3,4-tetrahydro - 1-acetyl-2',5'-difluoro-3-oxo-2-quinoxalinecarboxanilide (IV; $R_1, R_2, R_4=H$; $R_3=CH_3$; $R_5=2,5-F_2C_6H_3$)

To a solution of V in tetrahydrofuran is added platinum oxide, and the resulting mixture shaken in a hydrogen atmosphere at an initial pressure of 50 p.s.i. for a period of 3 hours. The catalyst is filtered, and an equimolar amount of acetic anhydride is added to the filtrate. The resulting solution is heated to the reflux temperature for 1 hour, after which the reaction mixture is concentrated under reduced pressure. On cooling, the desired product precipitates from solution. Further purification is carried out by recrystallization from benzene. The product is identical to that synthesized by the conditions outlined in Example I.

EXAMPLE III

1,2,3,4-tetrahydro-1-acetyl-4'-bromo-3-oxo-2-quinoxalinecarboxanilide

A suspension of 2.62 g. (0.01 mole) of 1,2,3,4-tetrahydro-2-oxo-3-carbethoxy-4-acetylquinoxaline and 1.89 g. (0.011 mole) of 4-bromoaniline in 65 ml. of mesitylene is heated to the boiling point, and the mesitylene allowed to distill. After 23 ml. of the solvent is removed (2 hr.) a precipitate starts to form. The reaction mixture is cooled, and the solid is filtered, 3.35 g., M.P. 232–243°

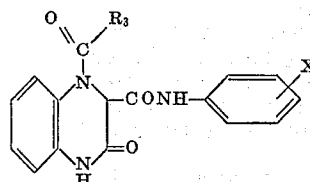
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C. The product is further purified by recrystallization from acetonitrile, M.P. 258–259° C.

Analysis.—Calcd. for $C_{17}H_{14}BrN_3O_3$ (percent): C, 52.59; H, 3.63; N, 10.82. Found (percent): C, 52.91; H, 3.59; N, 10.85.

EXAMPLE IV

The procedure of Example I is repeated, using equivalent amounts of appropriately substituted substrates, to produce the following compounds:



R ₃	X	M.P., ° C.	Analysis					
			Calculated			Found		
			C	H	N	C	H	N
25	CH ₃ ...	260-262	59.40	4.10	12.22	59.38	4.04	12.24
	{4'-Cl	203-204	53.98	3.46	11.11	54.22	3.48	11.05
	{2',4'-Cl ₂	240-241	62.38	4.31	12.84	62.29	4.29	12.72
	{4'-F	237-238.5	59.13	3.79	12.17	59.22	3.74	12.19
	{2',4'-F ₂							

EXAMPLE V

1,2,3,4-tetrahydro-1-acetyl-3-oxo-4'-bromo-4-methyl-2-quinoxalinecarboxanilide

A mixture of 1.89 g. (0.011 mole) of p-bromoaniline and 2.76 g. (0.01 mole) of 1,2,3,4-tetrahydro-1-acetyl-3-oxo-4-methyl-2-quinoxalinecarboxylic acid, ethyl ester in 75 ml. of mesitylene is heated to the boiling point, and the solvent is allowed to distill. Fresh solvent is continually added such that the volume of the reaction mixture remains constant. This process is continued until 250 ml. of solvent has been distilled. The reaction mixture is cooled, and the precipitated solid collected by filtration, dried and recrystallized from benzene.

EXAMPLE VI

The procedure of Example V is repeated, using equivalent amounts of appropriately substituted substrates, to produce the following compounds:

- 1,2,3,4-tetrahydro-1-propionyl-3-oxo-4-ethyl-6-methoxy-2-quinoxalinecarboxanilide
- 1,2,3,4-tetrahydro-1-acetyl-3-oxo-4-ethyl-7-methoxy-2-quinoxalinecarboxanilide
- 1,2,3,4-tetrahydro-1-isobutyryl-3-oxo-4-ethyl-8-methoxy-quinoxalinecarboxanilide
- 1,2,3,4-tetrahydro-1-formyl-3-oxo-4-ethyl-5-methoxy-2-quinoxalinecarboxanilide
- 1,2,3,4-tetrahydro-1-acetyl-3-oxo-4-ethyl-6-methoxy-2-quinoxalinecarboxanilide
- 1,2,3,4-tetrahydro-1-acetyl-3-oxo-4-ethyl-8-methoxy-2-quinoxalinecarboxanilide

EXAMPLE VII

The following products are prepared by the procedure of Example VI, by substituting the appropriate starting materials:

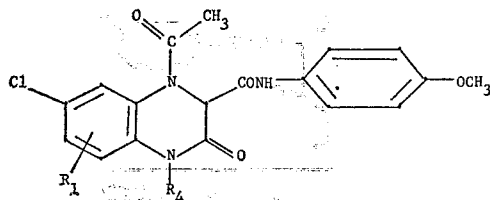
- 1,2,3,4-tetrahydro-1-propionyl-3-oxo-4',7'-dichloro-6-methyl-2-quinoxalinecarboxanilide
- 1,2,3,4-tetrahydro-1-propionyl-3-oxo-4'-chloro-7-methyl-2-quinoxalinecarboxanilide
- 1,2,3,4-tetrahydro-1-propionyl-3-oxo-4'-chloro-5-ethyl-2-quinoxalinecarboxanilide

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- 1,2,3,4-tetrahydro-1-propionyl-3-oxo-4'-chloro-6-ethyl-
2-quinoxalinecarboxanilide
1,2,3,4-tetrahydro-1-propionyl-3-oxo-4'-chloro-8-methyl-
2-quinoxalinecarboxanilide
1,2,3,4-tetrahydro-1-propionyl-3-oxo-4'-chloro-7-n-
propyl-2-quinoxalinecarboxanilide

EXAMPLE VIII

The procedure of Example VI is repeated, using equivalent amounts of appropriately substituted starting materials, to produce the following compounds:

R₁:

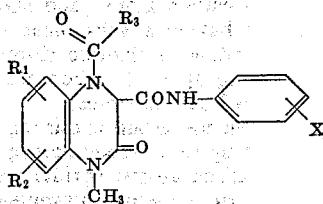
- 6-Cl
5-Cl
8-Cl
5-F
6-F
5-Br
5-OCH₃
5-OCH₃
5-OC₂H₅
H
H
H
H

R₄:

- CH₃
CH₃
CH₃
C₂H₅
C₂H₅
n-C₃H₇
n-C₃H₇
CH₃
CH₃
CH₃
C₂H₅
i-C₃H₇
n-C₃H₇

EXAMPLE IX

The procedure of Example V is repeated, using equivalent amounts of appropriately substituted substrates, to produce the following compounds:



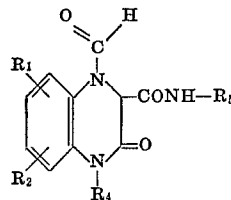
R ₁	R ₂	R ₃	X
5-Cl	H	CH ₃	2'-OCH ₃
6-Cl	H	CH ₃	3'-OCH ₃
7-Cl	H	CH ₃	4'-OCH ₃
8-Cl	H	C ₂ H ₅	3'-OC ₂ H ₅
5-Br	H	C ₂ H ₅	4'-OC ₂ H ₅
6-Br	H	C ₂ H ₅	3',4'-(OCH ₃) ₂
7-Br	H	n-C ₃ H ₇	3'-OCH ₃ ,4'-OC ₂ H ₅
6-F	H	n-C ₃ H ₇	3'-SCH ₃
7-F	H	n-C ₃ H ₇	4'-SCH ₃
6-Cl	7-Cl	i-C ₃ H ₇	4'-SC ₂ H ₅
5-F	6-F	i-C ₃ H ₇	3'-OCH ₃ ,4'-SCH ₃
6-F	7-Br	i-C ₃ H ₇	2',4'-(SCH ₃) ₂

EXAMPLE X

The procedure of Example II is repeated, using equivalent

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amounts of appropriately substituted substrates, to produce the following compounds:



R ₁	R ₂	R ₄	R ₅
6-methyl	Hydrogen	Methyl	Ethyl
7-methyl	do	n-Propyl	n-Hexyl
6-ethyl	7-methyl	i-Propyl	Cyclohexyl
6-n-propyl	Hydrogen	Ethyl	Cyclopropyl
5-methyl	7-methyl	Methyl	Methyl
8-methyl	Hydrogen	n-Propyl	2,2-dimethyl-3-butenyl

EXAMPLE XI

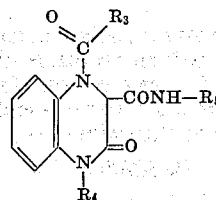
1,2,3,4-tetrahydro-1-acetyl-3-oxo-quinoline-2-[N-(6-methyl-2-pyridyl)]carboxamide

A mixture of 1.19 g. (0.011 mole) of 2-amino-6-methyl-pyridine and 2.62 g. (0.01 mole) of 1,2,3,4-tetrahydro-1-acetyl-3-oxo-2-quinolinecarboxylic acid, ethyl ester in 65 ml. of mesitylene is heated to the boiling point. Fifty milliliters of the solvent is allowed to slowly distill from the reaction mixture and is replaced by 50 ml. of fresh solvent. This process is repeated until 265 ml. of mesitylene has been distilled. The resulting solution is cooled, and the solid which precipitates is filtered and dried, 2.0 g., M.P. 212.5° C. dec. The purified product is obtained by recrystallization from ethanol, M.P. 230° C. dec.

Analysis.—Calcd. for C₁₇H₁₆N₄O₃ (percent): C, 62.95; H, 4.97; N, 17.28. Found (percent): C, 62.92; H, 5.02; N, 16.17.

EXAMPLE XII

The procedure of Example V is repeated, using equivalent amounts of the appropriately substituted substrates, to provide the following compounds:

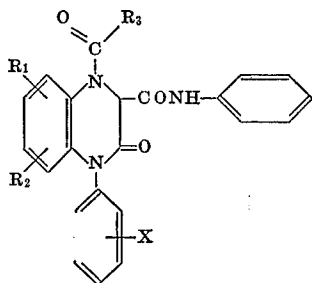


R ₃	R ₄	R ₅
Cyclopropyl	Allyl	4'-pyridyl
Cyclopentyl	Methyl	2',4'-dimethyl-6'-pyridyl
Cyclohexyl	Allyl	2'-thiazolyl
Cyclobutyl	Crotyl	3'-pyridyl

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EXAMPLE XIII

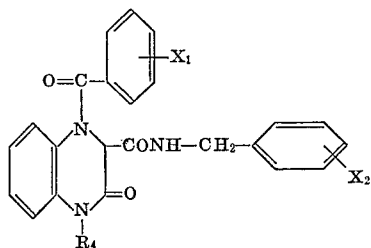
The procedure of Example XII is repeated, using equivalent amounts of aniline in place of said heterocyclic amine, to produce the following compounds:



R ₁	R ₂	R ₃	X
6-OCH ₃	H	CH ₂ CH=CH ₂	H
7-OCH ₃	H	CH ₂ CH=CH ₂	4''-Cl
5-OCH ₃	7-OCH ₃	CH ₂ C=CH ₂ CH ₃	3''-OCH ₃
6-OC ₂ H ₅	H	CH ₂ -CH=CH-CH ₃	4''-C ₂ H ₅
8-OC ₂ H ₅	H	CH ₂ CH=CH ₂	4''-F
6-OH	H	CH ₂ CH=CH ₂	H
7-OH	H	CH ₂ C=CH ₂ CH ₃	4''-OC ₂ H ₅
5-SCH ₃	H	CH ₂ CH=CH ₂	3''-CH ₃
6-SCH ₃	H	CH ₂ CH=CH ₂	3''-C ₂ H ₅
7-SC ₂ H ₅	H	CH ₂ CH=CHCH ₃	4''-Br

EXAMPLE XIV

The procedure of Example I is repeated, using equivalent amounts of the appropriately substituted substrates, to produce the following compounds:



R ₄	X ₁	X ₂
Cyclopropyl...	p-Chloro...	4'-fluoro.
Do	m-Methoxy...	4'-chloro.
Cyclopentyl...	p-Ethoxy...	3'-trifluoromethyl.
Do	p-Methyl...	3', 4'-difluoro.
Cyclohexyl...	Hydrogen...	4'-methoxy.
Do	do	3'-chloro-4'-ethoxy.
Do	o-Fluoro...	Hydrogen.
Cyclobutyl...	p-Bromo...	3'-amino.
Do	Hydrogen...	4'-hydroxy.

EXAMPLE XV

Sodium salt of 1,2,3,4-tetrahydro-1-propionyl-3-oxo-2-quinoxalinecarboxanilide

To a methanol solution of 1,2,3,4-tetrahydro-1-propionyl-3-oxo-2-quinoxalinecarboxanilide is slowly added one equivalent of sodium hydroxide dissolved in a minimum amount of the same solvent. The resulting turbid solution is concentrated in vacuo, and the residue induced to solidifying by trituration with ether.

EXAMPLE XVI

Purification of 1,2,3,4-tetrahydro-1-acetyl-3-oxo-2-carboxanilide via barium salt

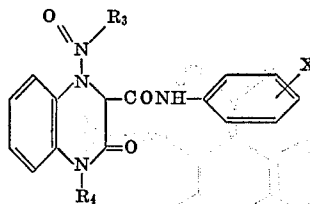
To a methanol-water solution containing .01 mole of barium hydroxide is added dropwise a solution of .02 mole of crude 1,2,3,4-tetrahydro-1-acetyl-3-oxo-2-carboxanilide dissolved in a minimum amount of methanol. The mixture

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is cooled overnight at 0° C., and the resulting barium salt filtered. The wet cake is suspended in 100 ml. of water and sufficient 6 N hydrochloric acid solution added to bring the suspension to pH 3. After stirring in the cold for 30 minutes the purified product is filtered, washed several times with water and dried.

EXAMPLE XVII

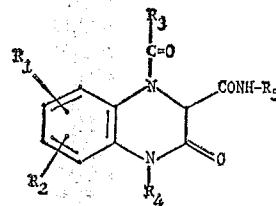
Using the aforementioned rat foot edema test, each of the following 1,2,3,4-tetrahydro-1-acetyl-3-oxo-2-quinoxalinecarboxanilides were tested for anti-inflammatory activity and were found to be active at the indicated dose level:



X	R ₃	R ₄	Dose, mg./kg.
4'-F	CH ₃	H	33
2'-F	CH ₃	H	33
2',4'-F ₂	CH ₃	H	33
2',5'-F ₂	CH ₃	H	100
4'-Cl	CH ₃	H	100
2',4'-Cl ₂	CH ₃	H	33
4'-Br	CH ₃	H	33

What is claimed is:

1. A compound selected from those of the formula:



and the basic metal salts thereof, wherein:

R₁ and R₂ are each selected from the group consisting of hydrogen, alkyl containing up to 3 carbon atoms, fluorine, chlorine, bromine, alkoxy and alkylthio each of up to 2 carbon atoms and hydroxy;

R₃ and R₄ are each selected from the group consisting of hydrogen; alkyl containing up to 3 carbon atoms; alkenyl containing up to 4 carbon atoms; cycloalkyl of from 3 to 6 carbon atoms; and phenyl and substituted phenyl having a substituent selected from the group consisting of fluorine chlorine, bromine, alkoxy containing up to 2 carbon atoms and alkyl containing up to 3 carbon atoms;

R₅ is selected from the group consisting of alkyl and alkenyl each of up to 6 carbon atoms; cycloalkyl of from 3 to 6 carbon atoms; pyridyl and substituted pyridyl with 1 or 2 methyl substituents; thiazolyl; and phenyl, benzyl, and mono- and disubstituted phenyl and benzyl, said substituents being selected from the group consisting of fluorine, chlorine, bromine, alkyl containing up to 3 carbon atoms, alkoxy and alkylthio each having up to 2 carbon atoms, hydroxy, amino, acylamino containing up to 3 carbon atoms, trifluoromethyl and trifluoromethoxy.

2. The compound of claim 1 wherein R₁ and R₂ are hydrogen, R₃ is alkyl containing up to 4 carbon atoms and R₄ is hydrogen.

3. The compound of claim 1 wherein R₁ and R₂ are hydrogen R₃ is methyl and R₄ is alkyl containing up to 4 carbon atoms.

4. The compound of claim 1 wherein R₁ is hydrogen, R₂ is alkoxy of up to 2 carbon atoms, R₄ is ethyl and R₅ is phenyl.

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5. The compound of claim 1 wherein R₁ is alkyl containing up to 4 carbon atoms, R₃ is ethyl, R₄ is hydrogen and R₅ is 4'-chlorophenyl.

6. The compound of claim 1 wherein R₂ is 7-chloro, R₃ is methyl, R₄ is alkyl containing up to 3 carbon atoms and R₅ is 4'-methoxyphenyl.

7. 1,2,3,4-tetrahydro-1-acetyl-2',4'-difluoro - 3 - oxo-2-quinoxalinecarboxanilide.

8. 1,2,3,4-tetrahydro-1-acetyl-4' - bromo - 3 - oxo - 4-methyl-2-quinoxalinecarboxanilide.

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NICHOLAS S. RIZZO, Primary Examiner

U.S. Cl. X.R.

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