

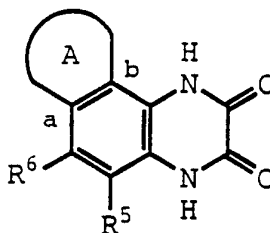


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(54) Title: QUINOXALINEDIONE DERIVATIVES AS EAA ANTAGONISTS



(I)

(57) Abstract

A compound having formula (I) or a pharmaceutically acceptable salt thereof, wherein R is hydrogen or hydroxy; R¹ is hydrogen, alkyl, arylalkyl, (CH₂)_nOH or (CH₂)_nNR⁷R⁸; R⁵ and R⁶ are each independently hydrogen, halogen, NO₂, CN, CF₃, SO₂NR⁷R⁸, PO₃R⁹R¹⁰, alkyl, alkenyl, alkylnyl, (CH₂)_nCONR⁷R⁸, (CH₂)_nCO₂R¹⁰, NHCOR¹¹, wherein R⁷ and R⁸ are each independently hydrogen or alkyl or together R⁷ and R⁸ form a ring of from three to seven atoms, R⁹ is hydrogen or alkyl, R¹⁰ is hydrogen or alkyl, R¹¹ is hydrogen or alkyl, and n is an integer of from zero to four; A is a ring of five to seven atoms fused with the benzo ring at the positions marked a and b, and formed by the following bivalent radicals: a-NR¹²-CHR¹³-CHR¹⁴-b, a-CHR¹³-CHR¹⁴-NR¹²-b, a-CHR¹³-NR¹²-CHR¹⁴-b, a-CHR¹⁴-CH₂-NR¹²-CHR¹³-b, a-CHR¹³-NR¹²-CH₂-CHR¹⁴-b, a-CH₂-CH₂-CHR¹³-NR¹²-b, a-NR¹²-CHR¹³-CH₂-CH₂-b, a-CH₂-CH₂-NR¹²-CH₂-CH₂-b, a-CH₂-CH₂-CH₂-NR¹²-CH₂-b, a-CH₂-NR¹²-CH₂-CH₂-CH₂-b, a-CH₂-CH₂-CH₂-CH₂-NR¹²-b, a-NR¹²-CH₂-CH₂-CH₂-CH₂-b, wherein R¹² is hydrogen, CH₂CH₂OH, or alkyl, and R¹³ and R¹⁴ are each independently hydrogen, CN, CONH₂, CH₂NH₂, CH₂OH, alkyl, arylalkyl, alkenyl or CO₂R¹⁵, wherein R¹⁵ is hydrogen or alkyl. The compounds are useful in the treatment of disorders of mammals, responsive to the blockade of glutamic and aspartic acid receptors. Processes for preparing the compounds and novel intermediate useful in the processes are also included.

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QUINOXALINEDIONE DERIVATIVES AS EAA ANTAGONISTS

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CROSS REFERENCE

This application is a continuation-in-part of U.S. Serial Number 07/960,157, filed October 13, 1992. The present invention relates to novel ring fused
10 quinoxaline-2,3-dione derivatives, a method of treatment therewith, pharmaceutical compositions comprising the compounds and to a method of preparing the novel compounds of the invention.

15

OBJECT OF THE INVENTION

It is an object of the present invention to provide novel quinoxaline dione compounds which are
20 useful in the treatment of diseases in mammals, including a human, and especially in the treatment of diseases which can be treated by antagonizing an excitatory amino acid of such mammals.

Another object of the present invention is to provide a method of treating diseases in mammals,
25 including a human, responsive to the blockade of glutamic and aspartic acid receptors which comprises administering to a mammal in need thereof a compound of the invention.

30 A third object of the present invention is to provide novel pharmaceutical compositions for the treatment of diseases in mammals, including a human, responsive to the blockade of glutamic and aspartic acid receptors.

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BACKGROUND OF THE INVENTION

Excessive excitation by neurotransmitters can cause the degeneration and death of neurons. It is believed that this degeneration is in part mediated by the excitotoxic actions of the excitatory amino acids (EAA) glutamate and aspartate at the N-methyl-D-aspartate (NMDA), the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor, and the kainate receptor. This excitotoxic action is responsible for the loss of neurons in cerebrovascular disorders such as cerebral ischemia or cerebral infarction resulting from a range of conditions, such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery, and cerebral trauma, as well as lathyrism, Alzheimer's, and Huntington's diseases.

The compounds of the present invention may also be useful in the treatment of schizophrenia, Parkinsonism, epilepsy, anxiety, pain, and drug addiction.

25

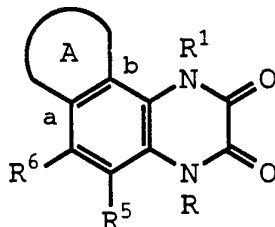
SUMMARY OF THE INVENTION

The invention then, inter alia, comprises the following, alone or in combination:

30

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A compound having the formula



or a pharmaceutically acceptable salt thereof
 10 wherein

R is hydrogen or hydroxy;

R¹ is hydrogen,

alkyl,

arylalkyl,

15 (CH₂)_nOH, or

(CH₂)_nNR⁷R⁸;

R⁵ and R⁶ are each independently

hydrogen,

halogen,

20 NO₂,

CN,

CF₃,

SO₂NR⁷R⁸,

PO₃R⁹R¹⁰,

25 alkyl,

alkenyl,

alkynyl,

(CH₂)_nCONR⁷R⁸,

(CH₂)_nCO₂R¹⁰,

30 NHCOR¹¹,

wherein R⁷ and R⁸ are each independently hydrogen or
 alkyl or together R⁷ and R⁸ form a ring of from three
 to seven atoms,

R⁹ is hydrogen or alkyl,

35 R¹⁰ is hydrogen or alkyl,

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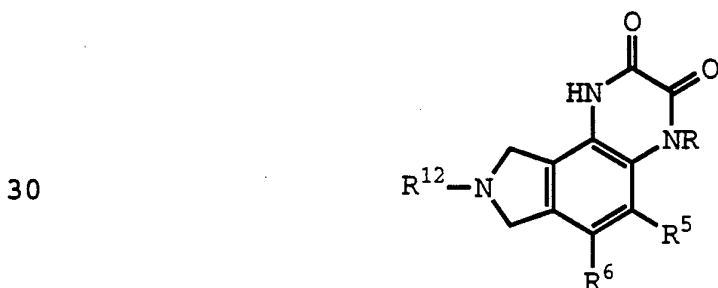
R^{11} is hydrogen or alkyl, and
 n is an integer of from zero to four;

A is a ring of five to seven atoms fused with the benzo
 5 ring at the positions marked a and b, and formed by
 the following bivalent radicals:

10 a-NR¹²-CHR¹³-CHR¹⁴-b,
 a-CHR¹³-CHR¹⁴-NR¹²-b,
 a-CHR¹³-NR¹²-CHR¹⁴-b,
 a-CHR¹⁴-CH₂-NR¹²-CHR¹³-b,
 a-CHR¹³-NR¹²-CH₂-CHR¹⁴-b,
 a-CH₂-CH₂-CHR¹³-NR¹²-b,
 a-NR¹²-CHR¹³-CH₂-CH₂-b,
 15 a-CH₂-CH₂-NR¹²-CH₂-CH₂-b,
 a-CH₂-CH₂-CH₂-NR¹²-CH₂-b,
 a-CH₂-NR¹²-CH₂-CH₂-CH₂-b,
 a-CH₂-CH₂-CH₂-CH₂-NR¹²-b,
 a-NR¹²-CH₂-CH₂-CH₂-CH₂-b,

20 wherein

R^{12} is hydrogen, CH₂CH₂OH, or alkyl, and R^{13} and
 R^{14} are each independently hydrogen, CN, CONH₂,
 CH₂NH₂, CH₂OH, alkyl, arylalkyl, alkenyl, or
 CO₂R¹⁵, wherein R^{15} is hydrogen or alkyl;
 25 and a compound as above having the formula

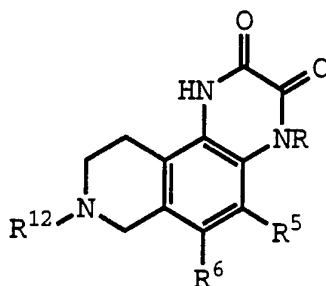


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wherein R, R¹², R⁵, and R⁶ have the meanings set forth above;

and a compound as above having the formula

5

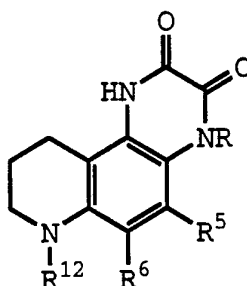


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wherein R, R¹², R⁵, and R⁶ have the meanings set forth above;

and a compound as above having the formula

15

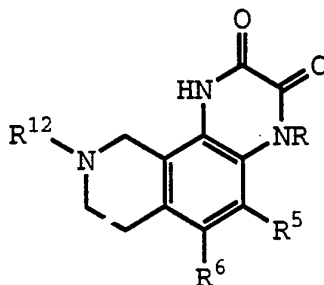


20

wherein R, R¹², R⁵, and R⁶ have the meanings set forth above;

and a compound as above having the formula

25



30

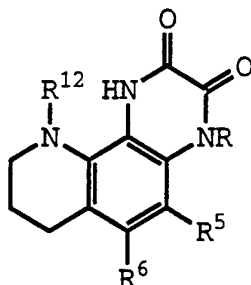
wherein R, R¹², R⁵, and R⁶ have the meanings set forth above;

35

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and a compound as above having the formula

5



10

wherein R, R¹², R⁵, and R⁶ have the meanings set forth above;

and further a compound as any above wherein R⁵ and R⁶ independently are

15

hydrogen,

halogen,

NO₂,

CN,

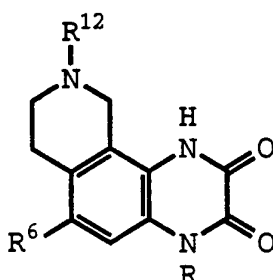
SO₂NR⁷R⁸

20

wherein R⁷ and R⁸ independently are hydrogen or C₁₋₃-alkyl which may be straight or branched or cyclic, and wherein R¹² is C₁₋₃-alkyl which may be straight or branched or cyclic;

and a compound having the formula

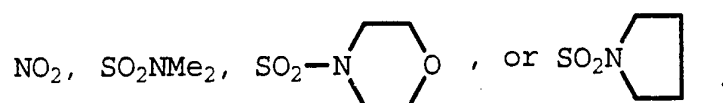
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wherein R¹² is hydrogen, methyl, or ethyl and R⁶ is

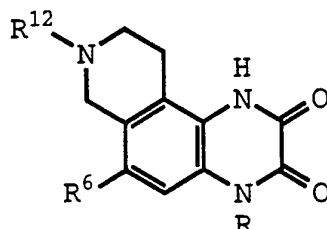
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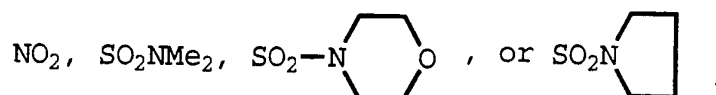
and a compound having the formula

5



10

wherein R^{12} is hydrogen, methyl, or ethyl and R^6 is



15

and further method of treating disorders of a mammal, including a human, responsive to the blockade of glutamic and aspartic acid receptors, which comprises administering to a patient in need thereof an effective amount of a compound as any above in unit dosage form;

20

and a method as above wherein cerebrovascular disorders are treated;

25

and further a pharmaceutical composition comprising a therapeutically effective amount of a compound as any above together with a pharmaceutically acceptable carrier.

30

Examples of pharmaceutically acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, oxalate, and the acetate.

35

Halogen is fluorine, chlorine, bromine, or iodine; fluorine, chlorine, and bromine are preferred groups.

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Alkyl means a straight chained or branched chain of from one to six carbon atoms or cyclic alkyl of from three to seven carbon atoms including, but not limited to methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

Alkenyl means a straight chained or branched chain alkenyl group of two to six carbon atoms or a cyclic alkenyl group of three to seven carbon atoms, for example, but not limited to ethylene, 1,2- or 2,3-propylene, 1,2-, 2,3-, or 3,4-butylene, cyclopentene, or cyclohexene.

Alkynyl means a straight chained or branched chain alkynyl group of two to six carbon atoms, for example, but not limited to ethynyl, 2,3-propynyl, 2,3- or 3,4-butynyl.

Aryl means a monocyclic or bicyclic carbocyclic aromatic ring system, for example, but not limited to phenyl, 2-naphthyl, or 1-naphthyl.

Arylalkyl means aryl as defined above and alkyl as defined above, for example, but not limited to benzyl, 2-phenylethyl, 3-phenylpropyl; a preferred group is benzyl.

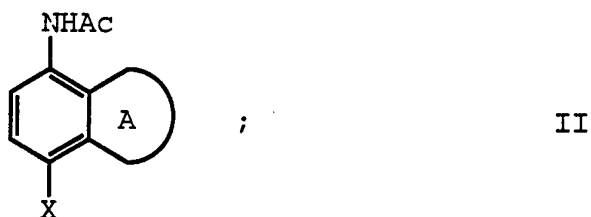
Also included in the instant invention is a process for preparing a compound of formula (see Scheme I).

The process comprises

(1) reacting a compound of Formula I (Scheme I) with a brominating agent, for example, bromine in trifluoroacetic acid, bromine in acetic acid or mixtures thereof, or reacting a compound of Formula I with a chlorinating agent, for example, sodium hypochlorite in hydrochloric acid to give a compound of Formula II

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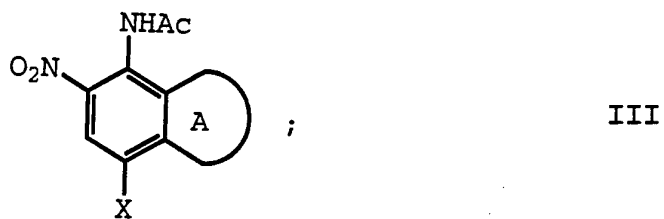
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wherein X is bromine or chlorine;

(2) treating a compound of Formula II above with
fuming nitric acid in a solvent such as trifluoroacetic
acid, acetic acid, or with mixtures thereof to give a
compound of Formula III

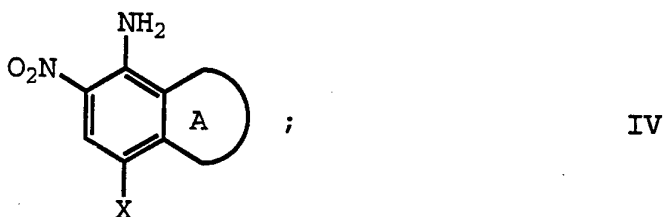
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(3) deprotecting a compound of Formula III with
under acidic or basic conditions to provide a compound
of Formula IV

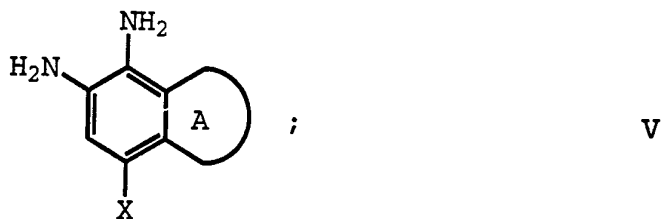
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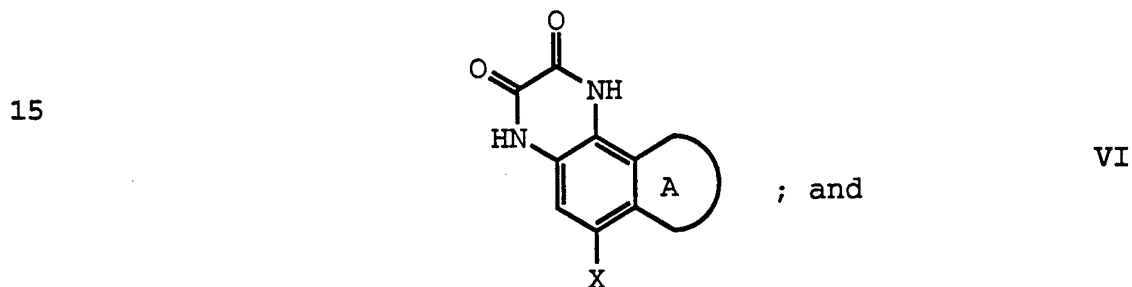
(4) hydrogenating a compound of Formula IV in a
solvent to give a compound of Formula V

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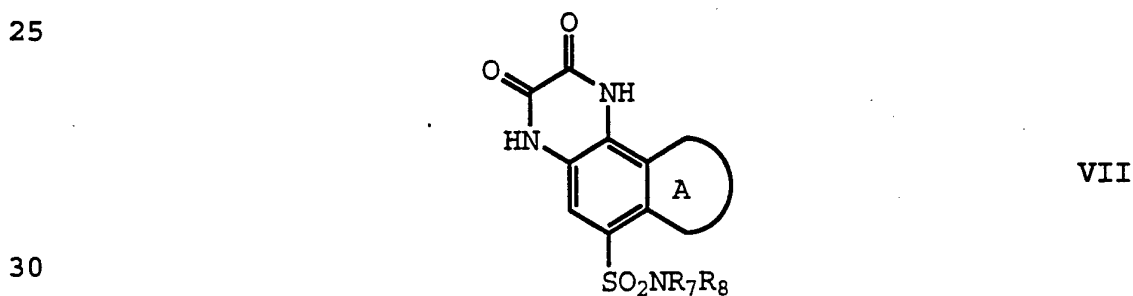


wherein X may be hydrogen, bromine, or chlorine;

10 (5) reacting a compound of Formula V with oxalic acid in a solvent such as aqueous HCl or aqueous methanesulfonic acid or with diethyl oxylate to give a compound of Formula VI



20 (6) reacting a compound of Formula VI wherein X is hydrogen sequentially with chlorosulfonic acid neat or in a solvent followed by treatment with a primary or secondary amine to give a compound of Formula VII

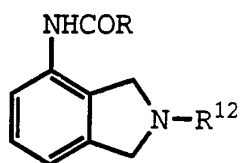


wherein R₇ and R₈ are as previously defined.

Also included in the invention is a process for the preparation of formula

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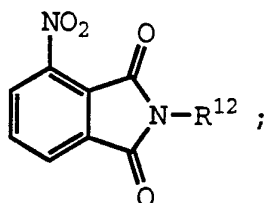
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which comprises;

10 (1) reacting 3-nitrophthalic acid with a
1,3-dialkyl urea, neat or in a solvent to provide a
compound of the formula

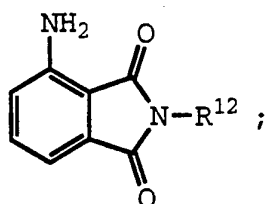
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(2) hydrogenating a compound of the above formula
in a solvent to give a compound of the formula

25

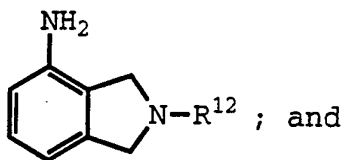


(3) reacting a compound of the above formula
with a hydride reducing agent, for example, lithium

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aluminum hydride or the like in a solvent to give the compound of the formula

5



10

(4) reacting a compound of the above formula with an acid chloride or acid anhydride, for example, acetyl chloride, ethyloxalyl chloride, acetic anhydride, or the like in a solvent to give a compound of the formula

15



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BIOLOGICAL ACTIVITY

The compounds of the invention exhibit valuable biological properties because of their strong
5 excitatory amino acid (EAA) antagonizing properties at the AMPA ((RS)- α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) binding site.

The compounds of the present invention exhibit binding affinity for the AMPA receptor as described by
10 Honoré T, et al, Neuroscience Letters 1985;54:27-32 with IC₅₀ values of <100 μ M in this assay. Values for selected compounds are found in Table I.

To functionally measure AMPA antagonist activity, the effects of the excitatory amino acid antagonists on
15 AMPA-induced neuronal degeneration in primary cortical neuronal cultures were examined using techniques similar to those outlined by Koh, et al. (J. Neurosci. 1990;10:693-705). When using a 100 μ M AMPA challenge, the claimed compounds generally had IC₅₀ values <30 μ M.

20 Also, compounds of the present invention when administered IV or IP in the in vivo AMPA seizure test, as described below, inhibit the clonic seizures induced by AMPA.

25 AMPA-Induced Clonic Seizures

AMPA given ICV (intracerebroventricular) (15 μ g/kg) to NMRI mice induces clonic seizures which should be inhibited by non-NMDA receptor antagonists.

30 Method

Test compound was given IV 5 minutes (or PO 30 minutes) before a 0.3 μ g ICV administration of AMPA to ten female NMRI mice (weighing 24-26 g) per dose. The number of mice experiencing clonic seizures within
35 the next 5 minutes was noted. An ED₅₀ value was

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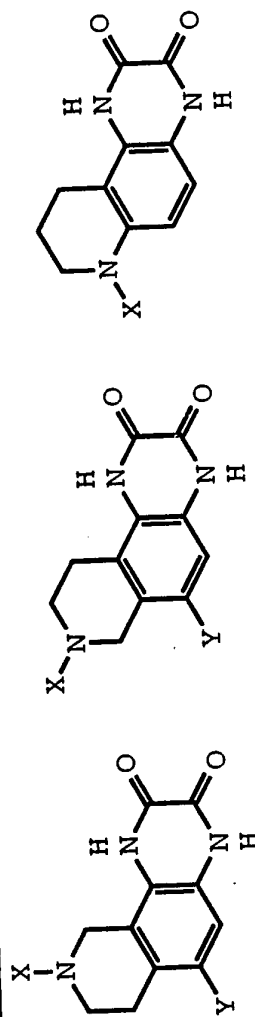
calculated as the dose inhibiting 50% of the mice from having clonic seizures.

As a preliminary indicator of in vivo CNS activity, a maximal electroshock assay in CF-1 strain mice (20-25 g) is performed with corneal electrodes by conventional methods as described previously (Krall, et al., Epilepsia 1988;19:409-428). The claimed compounds generally demonstrated ED₅₀ values of <50 mg/kg.

10

TABLE I. Inhibition of [³H]Ligand Binding to Cortical Membranes From Rat Brain

Compound	Substituent (X,Y)	IC ₅₀ (μM)	
		[³ H]AMPA	[³ H]GLY
AMPA		0.036	>100
Kainic acid		8.2	>100
Glutamate		0.2	--
Glycine		58	0.16
NEQX		0.1	>100
<u>Type A</u> Example			
	CH ₃ , H	18 μM	
	CH ₃ , Br	0.57 μM	
	C ₂ H ₅ , H	41 μM	
	C ₂ H ₅ , Br	0.74 μM	
<u>Type B</u>			
	CH ₃ , H	8	>30
	CH ₃ , Br	2.4	41
	C ₂ H ₅ , H	21	>30
	C ₂ H ₅ , Br	1.3	14
	C ₃ H ₇ , H	18.5	>30
<u>Type C</u>			
	H	24	47
	CH ₃	24	*150
	COCOCOC ₂ H ₅		



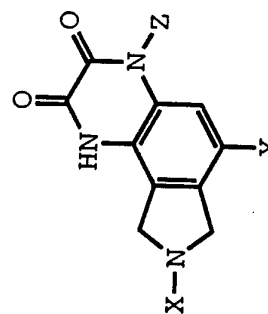
A
B
C

25

TABLE I. Inhibition of [³H]Ligand Binding to Cortical Membranes From Rat Brain (Cont'd)

Compound	Substituent (X, Y)	IC ₅₀ (μM)	
		[³ H]AMPA	[³ H]KA
5	AMPA	0.036	30
	Kainic acid	8.2	0.013
	Glutamate	0.2	0.2
	Glycine	58	>300
	NBQX	0.1	8
10	<u>Quinoxalinediones</u>		
	Example		
	CH ₃ , Br, H	1.1	12
	CH ₃ , Br, OH	0.94	13
	CH ₃ , H, H	3	56
	CH ₃ , H, OH	0.38	17
	CH ₃ , Cl, H	1.3	13
	C(CH ₃) ₃ , Br, H	1.6	30
	CH ₃ , SO ₂ N(CH ₃) ₂ , H	2.6	NT
	CH ₃ , SO ₂ N(CH ₂) ₂ O, H	3.0	NT
20	CH ₃ , SO ₂ N(CH ₂) ₂ , H	3.4	NT

NT = not tested



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PHARMACEUTICAL COMPOSITIONS

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing 10 mg of active ingredients or, more broadly, 0.1 to 100 mg per tablet, are accordingly suitable representative unit dosage forms.

Solid forms of pharmaceutical compositions for PO administration and injectable solutions are preferred.

METHOD OF TREATING

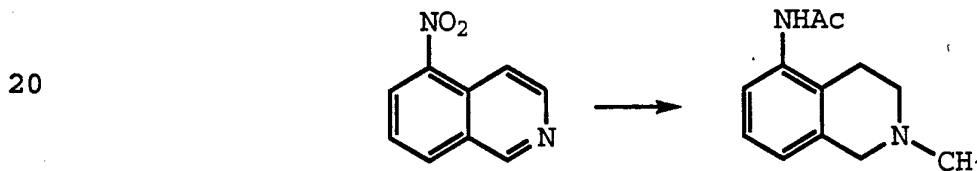
The compounds of this invention are extremely useful in the treatment of central nervous system disorders related to their biological activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of an indication associated with the biological activity of the compounds. This includes especially excitatory

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amino-acid-dependent psychosis, excitatory amino-acid-dependent anoxia, excitatory amino-acid-dependent ischemia, excitatory amino-acid-dependent Parkinsonism, excitatory amino-acid-dependent convulsions, and
5 excitatory amino-acid-dependent migraine. Suitable dosage ranges are 0.1 to 1000 mg daily, 10 to 500 mg daily, and especially 30 to 100 mg daily, dependent as usual upon the exact mode of administration, form in
10 which administered, the indication toward which the administration is directed, the subject involved, and the body weight of the subject involved, and further, the preference and experience of the physician or veterinarian in charge.

The following nonlimiting examples illustrate the
15 present invention.

EXAMPLE 1



25 N-(1,2,3,4-tetrahydro-2-methyl-5-isoquinolinyl)-acetamide

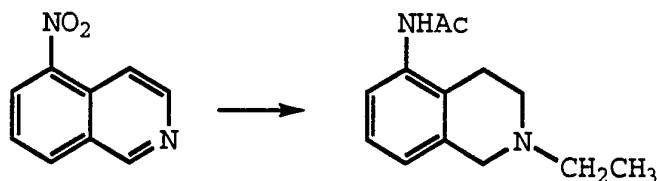
A solution of 5-nitroisoquinoline (200 g, 1.15 mol) in 1000 mL of dimethylformamide was treated with dimethylsulfate (160 g, 1.27 mol), and the resulting solution was heated to 90°C until no starting
30 material remained. The reaction mixture was cooled and concentrated. The residue was dissolved in 1500 mL of methanol and hydrogenated over PtO₂ (1.0 g) at 52 psi for 15.5 hours. The reaction mixture was then concentrated and the residue dissolved in CHCl₃
35 (1000 mL) and washed with aqueous 1N NaOH solution (500 mL). The aqueous phase was extracted with an

-20-

additional 3000 mL of chloroform, and the combined organic extracts were dried (Na_2SO_4) and concentrated to give an oil. The oil was treated with acetic anhydride (700 mL) and the resulting solution stirred at room temperature overnight. The reaction mixture was concentrated and the residue was dissolved in chloroform and washed with aqueous 1N NaOH solution. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (10:2 EtOAc:EtOH). The purified residue was recrystallized from EtOAc to give the product (60.6 g, 26%) as a white solid, mp = 138-139°C.

EXAMPLE 2

15



20

N-(2-ethyl-1,2,3,4-tetrahydro-5-isoquinolinyl)acetamide

A solution of 5-nitroisoquinoline (25 g, 0.144 mol) in 250 mL of EtOH was treated with iodoethane (26.9 g, 0.172 mol) and the resulting solution heated at reflux for 24 hours. The reaction mixture was cooled and the material which formed was collected and dried. The material obtained was converted to the title compound by the procedures described in Example 1. A white solid was obtained (4.42 g, 17%).

30

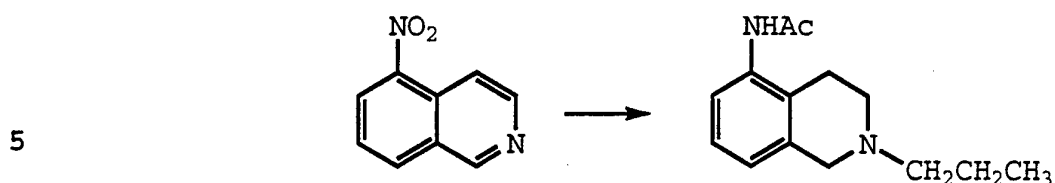
Analysis for ($\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$):

Calc.: C, 71.53; H, 8.31; N, 12.83.

Found: C, 71.43; H, 8.31; N, 12.91.

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EXAMPLE 3



N-(1,2,3,4-tetrahydro-2-propyl-5-isoquinolinyl)-
acetamide

10 A solution of 5-nitroisoquinoline (25 g, 0.144 mol) and iodopropane (36.7 g, 0.216 mol) in 500 mL of EtOH was converted to the title compound by the procedures described in Example 1. The crude title compound was purified by chromatography (silica gel, 95:5 EtOAc:EtOH). The purified product was recrystallized from *i*Pr₂O/THF to give the title compound as a

15 white solid (3.33 g, 18%), mp = 123°C.

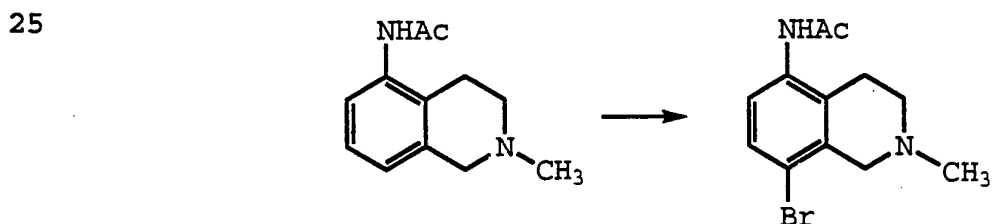
Analysis for (C₁₄H₂₀N₂O):

Calc.: C, 72.38; H, 8.68; N, 12.06.

Found: C, 72.38; H, 8.67; N, 12.14.

20 The filtrate was concentrated and the residue suspended in *i*Pr₂O and filtered to give a second crop of product (3.38 g, 19%).

EXAMPLE 4



30 N-(8-bromo-1,2,3,4-tetrahydro-2-methyl-5-isoquinolinyl)acetamide

A solution of the product from Example 1 (22.6 g, 0.111 mol) in 500 mL of trifluoroacetic acid was treated dropwise with a 1 M solution of bromine in acetic acid (122 mL). The resulting solution was

35 stirred at room temperature overnight during which time

-22-

an orange suspension formed. The reaction was concentrated to an oil which was dissolved by the addition of EtOAc (200 mL) and saturated aqueous NaHCO₃ solution (100 mL). The aqueous phase was separated and
5 extracted with additional EtOAc. The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was recrystallized from hot EtOAc to give the title compound as a white solid, mp = 188-189°C.

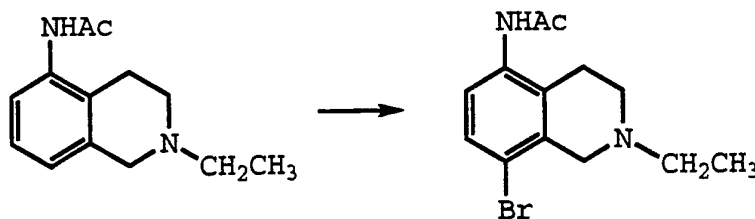
Analysis for (C₁₂H₁₅BrN₂O):

10 Calc.: C, 50.90; H, 5.34; N, 9.89.

Found: C, 50.93; H, 5.01; N, 9.78.

EXAMPLE 5

15



20

N-(8-bromo-2-ethyl-1,2,3,4-tetrahydro-5-isoquinolinyl)-acetamide

The product from Example 2 (3.65 g, 16.7 mmol) was converted to the title compound by the procedure described in Example 4. A white solid was obtained
25 (2.64 g, 53%), mp = 168-169°C.

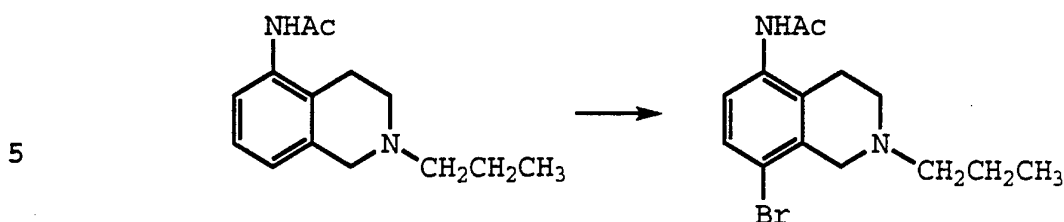
Analysis for (C₁₃H₁₇BrN₂O):

Calc.: C, 52.54; H, 5.77; N, 9.43.

Found: C, 52.81; H, 5.23; N, 9.09.

-23-

EXAMPLE 6



N-(8-bromo-1,2,3,4-tetrahydro-2-propyl-5-isoquinolinyl)acetamide

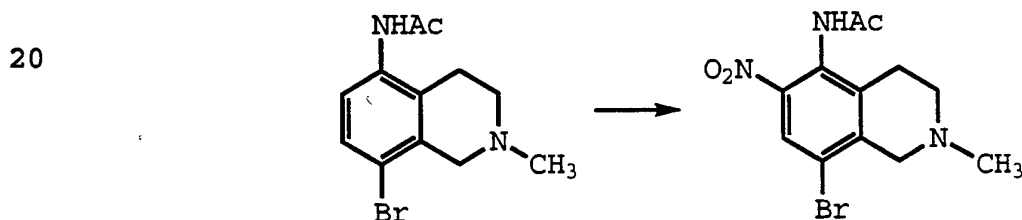
10 The product from Example 3 (6.33 g, 27.2 mmol) was converted to the title compound by the procedure described in Example 4. A white solid was obtained (6.17 g, 73%), mp = 144-145°C.

Analysis for (C₁₄H₁₉BrN₂O):

15 Calc.: C, 54.01; H, 6.15; N, 9.00.

Found: C, 54.19; H, 6.06; N, 8.97.

EXAMPLE 7



25 N-(8-bromo-1,2,3,4-tetrahydro-2-methyl-6-nitro-5-isoquinolinyl)acetamide

A solution of the product from Example 4 (19.8 g, 69.9 mmol) in 400 mL of trifluoroacetic acid was treated dropwise with fuming nitric acid (87 mL). The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was concentrated and the residue dissolved by treatment with 3:1 EtOAc:THF and saturated aqueous NaHCO₃ solution. The organic phase was collected and the aqueous phase was extracted with additional 3:1 EtOAc:THF. The combined organic extracts were dried (Na₂SO₄) and concentrated. The

30

35

-24-

residue was suspended in a THF/*i*Pr₂O solution and the solid collected. Recrystallization from hot THF/*i*Pr₂O provided the title compound as a beige solid (18.4 g, 80%), mp = 190-192°C.

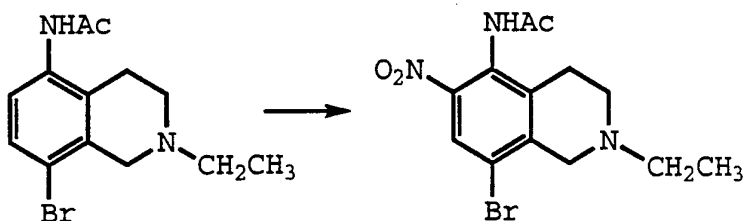
5 Analysis for (C₁₂H₁₄BrN₃O₃):

Calc.: C, 43.79; H, 4.59; N, 12.77.

Found: C, 43.98; H, 4.21; N, 12.84.

EXAMPLE 8

10



15

N-(8-bromo-2-ethyl-1,2,3,4-tetrahydro-6-nitro-5-isoquinolinyl)acetamide

The product from Example 5 (3.50 g, 11.8 mmol) was converted to the title compound by the procedure described in Example 7. A white solid was obtained (2.88 g, 71%), mp = 168°C.

20

Analysis for (C₁₃H₁₆BrN₃O₃):

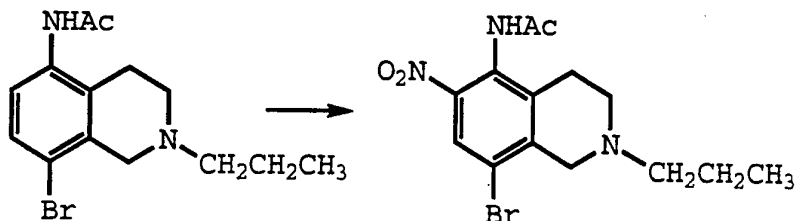
Calc.: C, 45.63; H, 4.71; N, 12.28.

Found: C, 45.84; H, 6.65; N, 12.06.

25

EXAMPLE 9

30



N-(8-bromo-1,2,3,4-tetrahydro-6-nitro-2-propyl-5-isoquinolinyl)acetamide

35

The product from Example 6 (5.50 g, 17.7 mmol) was converted to the title compound by the procedure

-25-

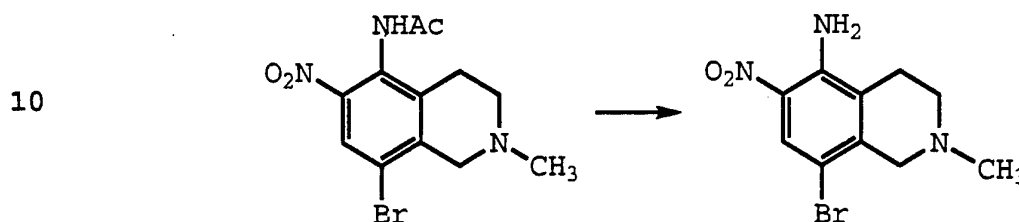
described in Example 7. A white solid was obtained (4.41 g, 70%), mp = 166-167°C.

Analysis for (C₁₄H₁₈BrN₃O₃):

Calc.: C, 47.20; H, 5.09; N, 11.80.

5 Found: C, 47.39; H, 5.00; N, 11.52.

EXAMPLE 10

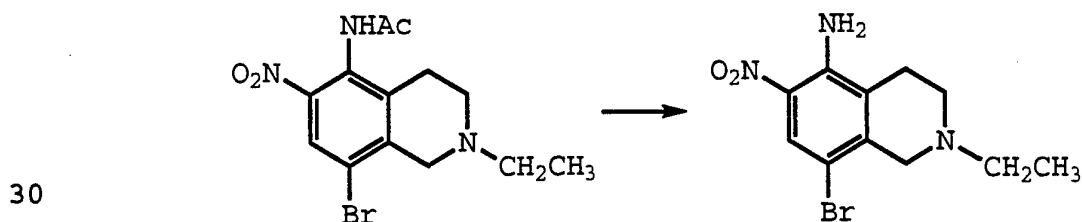


15 8-Bromo-1,2,3,4-tetrahydro-2-methyl-6-nitro-5-isoquinolinamine

A solution of the product from Example 7 (3.68 g, 11.2 mmol) and 80 mL of 3:2 H₂SO₄:H₂O was heated at 90°C for 1 hour. The reaction mixture was cooled and poured onto ice, and the resulting solution was made basic with concentrated aqueous NH₄OH solution. The solid that formed was collected by suction filtration and dried under vacuum to give the title compound as a yellow solid (3.17 g, 99%).

25

EXAMPLE 11



8-Bromo-2-ethyl-1,2,3,4-tetrahydro-6-nitro-5-isoquinolinamine

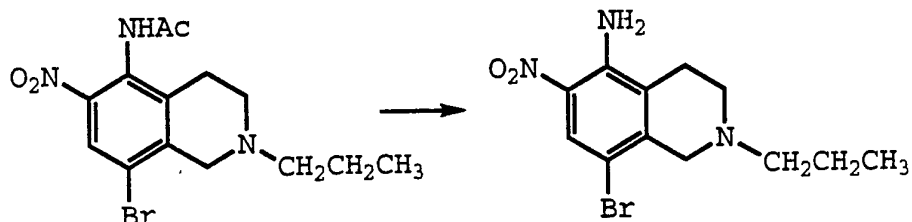
35 The product from Example 8 (2.50 g, 7.30 mmol) was converted to the title compound by the procedure

-26-

described in Example 10. A yellow solid was obtained (2.05 g, 82%).

EXAMPLE 12

5



10

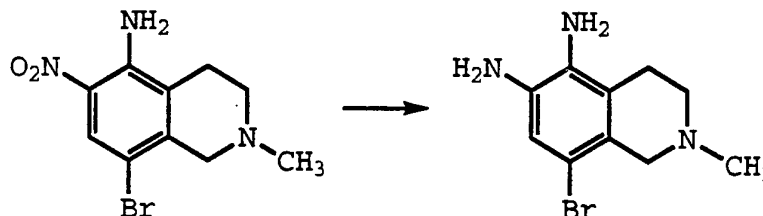
8-Bromo-1,2,3,4-tetrahydro-6-nitro-2-propyl-5-isoquinolinamine

The product from Example 9 (4.24 g, 11.9 mmol) was converted to the title compound by the procedure described in Example 10. A yellow solid was obtained (3.68 g, 98%).

15

EXAMPLE 13

20



25

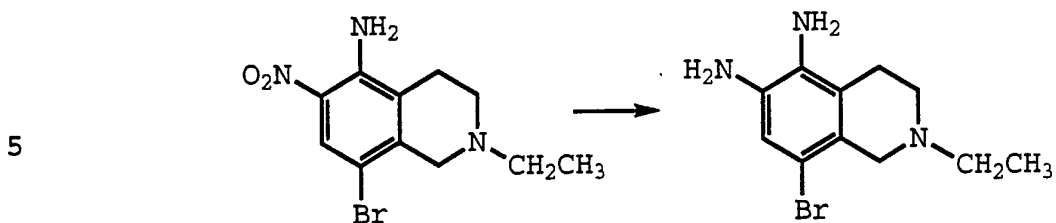
8-Bromo-1,2,3,4-tetrahydro-2-methyl-5,6-isoquinolinediamine

A solution of the product from Example 10 (0.78 g, 2.73 mmol) in 100 mL of THF was treated with Raney nickel (1.0 g) and hydrogenated for 1.5 hours at room temperature. The reaction mixture was filtered and concentrated to give the title compound as a tan solid (0.63 g, 90%).

30

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EXAMPLE 14

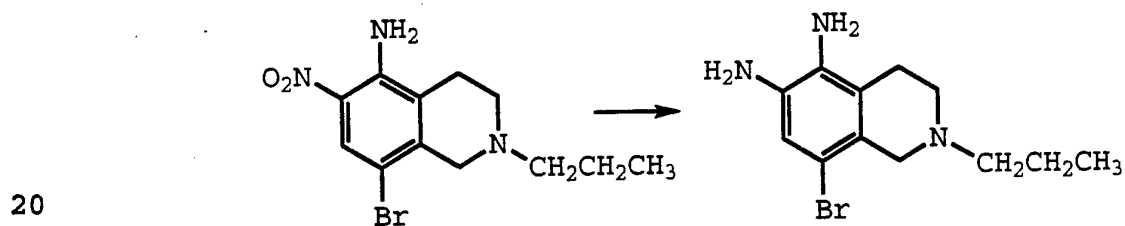


8-Bromo-2-ethyl-1,2,3,4-tetrahydro-5,6-isouquinoline-diamine

10 The product from Example 11 (1.00 g, 3.33 mmol) was converted to the title compound by the procedure described in Example 13. An oil was obtained (0.88 g, 98%).

15

EXAMPLE 15

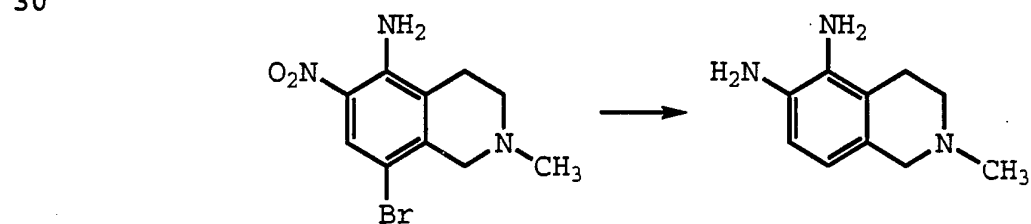


8-Bromo-1,2,3,4-tetrahydro-2-propyl-5,6-isouquinoline-diamine

25 The product from Example 12 (0.98 g, 3.12 mmol) was converted to the title compound by the procedure described in Example 13. An oil was obtained (0.77 g, 87%).

30

EXAMPLE 16

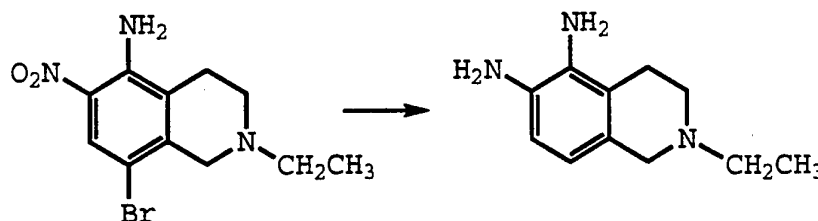


-28-

1,2,3,4-Tetrahydro-2-methyl-5,6-isoquinolinediamine

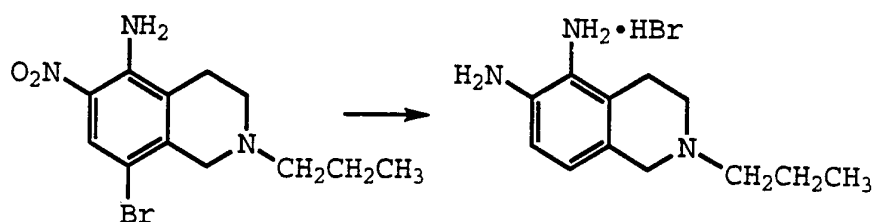
A solution of the product from Example 10 (1.50 g, 5.24 mmol) and 20% Pd on carbon (0.30 g) in 100 mL of MeOH was hydrogenated at room temperature and pressure for 24 hours. The reaction mixture was filtered and the filtrate concentrated. The residue was partitioned between CHCl₃ and saturated aqueous NaHCO₃ solution. The organic phase was separated and the aqueous phase was extracted with additional CHCl₃ and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. The residue was filtered through a plug of silica gel eluting with 25% EtOH/EtOAc. The eluant was concentrated to give the title compound as an oil (0.45 g, 48%).

EXAMPLE 17

2-Ethyl-1,2,3,4-tetrahydro-5,6-isoquinolinediamine

The product from Example 11 (1.00 g, 3.33 mmol) was converted to the title compound by the procedure described in Example 16. An oil was obtained (0.70 g). This material was used without further purification.

EXAMPLE 18



-29-

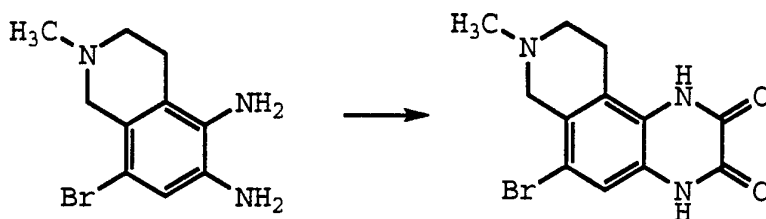
1,2,3,4-Tetrahydro-2-propyl-5,6-isoquinolinediamine

A solution of the product from Example 12 (1.50 g, 4.77 mmol) and 20% Pd on carbon (0.30 g) in 75 mL of MeOH was hydrogenated at room temperature and pressure for 24 hours. The reaction mixture was concentrated and the residue was suspended in $i\text{Pr}_2\text{O}$ and collected by filtration to give the title compound as a yellow solid (1.27 g, 93%).

10

EXAMPLE 19

15

6-Bromo-1,4,7,8,9,10-hexahydro-8-methylpyrido[4,3-f]quinoxaline-2,3-dione

20

A solution of the product from Example 13 (0.62 g, 2.56 mmol) and oxalic acid (0.23 g, 2.56 mmol) in 25 mL of 3N aqueous HCl solution were heated at reflux for 18 hours. The reaction mixture was cooled to room temperature and the solid which formed was collected by filtration and washed with cold water. The solid was recrystallized from hot water and dried under vacuum (100°C, P_2O_5) to give the title compound as a tan solid (0.191 g, 20 %), mp = 315-320°C (dec.).

25

30

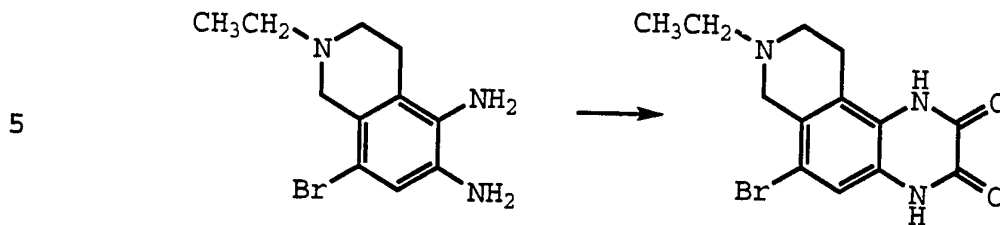
Analysis for $(\text{C}_{12}\text{H}_{12}\text{BrN}_3\text{O}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O})$:

Calc.: C, 39.53; H, 4.15; N, 11.53.

Found: C, 39.19; H, 4.09; N, 11.21.

-30-

EXAMPLE 20



10 6-Bromo-8-ethyl-1,4,7,8,9,10-hexahydropyrido[4,3-f]-
quinoxaline-2,3-dione

The product from Example 14 (0.88 g, 3.26 mmol) was converted to the title compound by the procedure described in Example 19. A white solid was obtained (0.71 g, 59%), mp = 325-350°C (dec.).

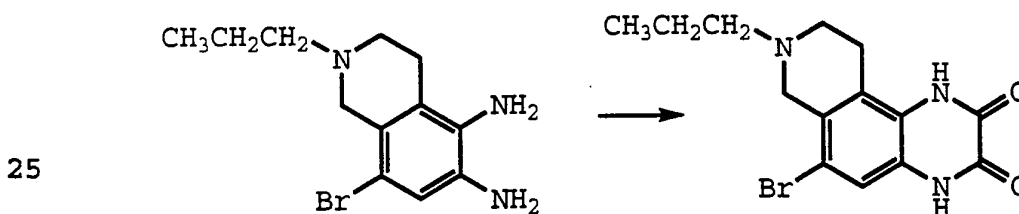
15 Analysis for (C₁₃H₁₄BrN₃O₂·HCl·0.6H₂O):

Calc.: C, 42.03; H, 4.40; N, 11.31; Cl, 9.55.

Found: C, 42.15; H, 4.39; N, 11.21; Cl, 9.57.

20

EXAMPLE 21



30 6-Bromo-1,4,7,8,9,10-hexahydro-8-propylpyrido[4,3-f]-
quinoxaline-2,3-dione

The product from Example 15 (0.77 g, 2.71 mmol) was converted to the title compound by the procedure described in Example 19. A white solid was obtained.

Analysis for (C₁₄H₁₆BrN₃O₂·1.35HCl·0.4H₂O):

Calc.: C, 42.61; H, 4.64; N, 10.65; Br, 20.25;

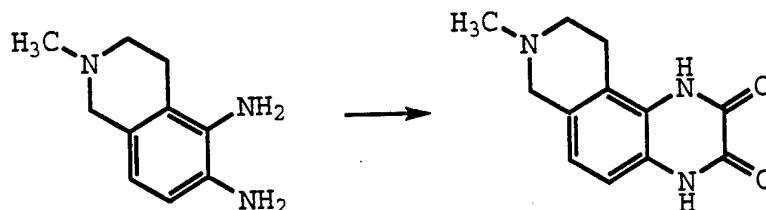
35 Cl, 12.13.

-31-

Found: C, 42.74; H, 4.93; N, 10.42; Br, 19.68;
Cl, 12.05.

EXAMPLE 22

5



1,4,7,8,9,10-Hexahydro-8-methylpyrido[4,3-f]-
quinoxaline-2,3-dione

15 The product from Example 16 (0.45 g, 2.54 mmol) was converted to the title compound by the procedure described in Example 19. A white solid was obtained (0.46 g, 68%), mp = 310-335°C.

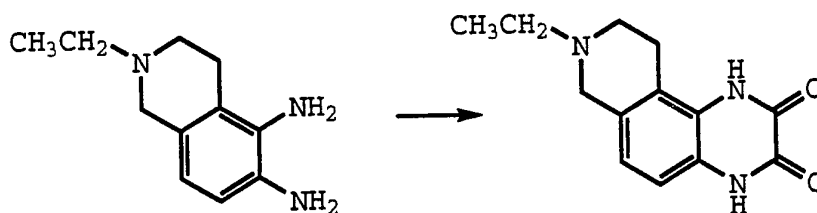
Analysis for (C₁₂H₁₃BrN₃O₂·0.95HCl·0.10H₂O):

Calc.: C, 53.84; H, 5.32; N, 15.70; Cl, 12.58.

20 Found: C, 53.88; H, 5.30; N, 16.04; Cl, 12.46.

EXAMPLE 23

25



8-Ethyl-1,4,7,8,9,10-tetrahydropyrido[4,3-f]-
quinoxaline-2,3-dione

35 The product from Example 17 (0.70 g, 3.66 mmol) was converted to the title compound by the procedure described in Example 19. A white solid was obtained (0.40 g, 38%), mp = 325-330°C.

- 32 -

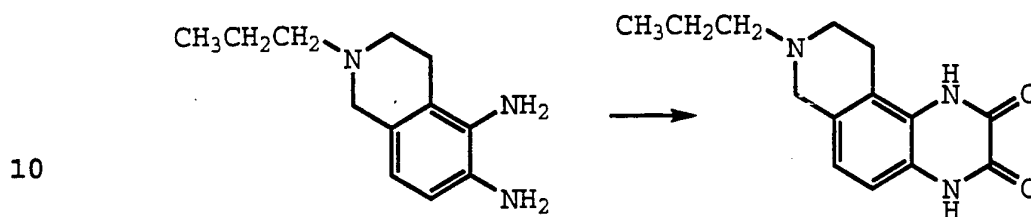
Analysis for (C₁₃H₁₅BrN₃O₂·HCl·0.3H₂O):

Calc.: C, 54.38; H, 5.83; N, 14.63.

Found: C, 54.50; H, 5.97; N, 14.72.

5

EXAMPLE 24



1,4,7,8,9,10-Hexahydro-8-propylpyrido[4,3-f]-
quinoxaline-2,3-dione

15

The product from Example 18 (1.24 g, 4.33 mmol) was converted to the title compound by the procedure described in Example 19. A white solid was obtained (0.833 g, 65%), mp = 340-350°C.

Analysis for (C₁₄H₁₇N₃O₂·HCl·0.1H₂O):

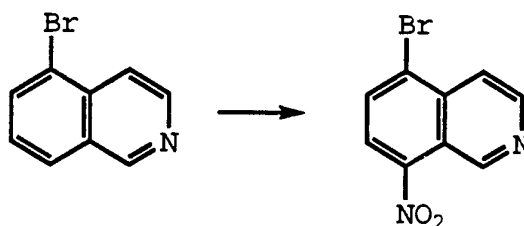
20

Calc.: C, 56.51; H, 6.17; N, 14.12.

Found: C, 56.62; H, 6.19; N, 14.19.

EXAMPLE 25

25



30

5-Bromo-8-nitroisoquinoline

The procedure described by Osborn AR, et al, J Chem Soc 1956:4191 was used. 5-Bromoisoquinoline (101 g, 0.485 mol) was dissolved in 300 mL concentrated H₂SO₄. KNO₃ (58.85 g, 0.582 mol) was dissolved in 200 mL of concentrated H₂SO₄ and added dropwise to the

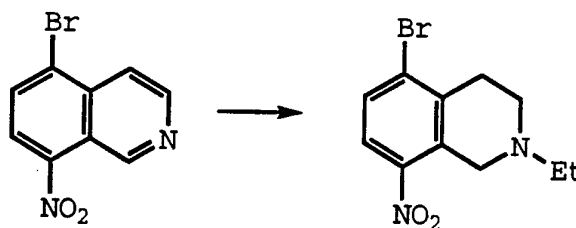
35

-33-

isoquinoline/acid solution. After addition, the reaction was stirred at room temperature for 2 hours. The reaction mixture was poured onto ice and the acid quenched carefully with the addition of NH_4OH until the solution was strongly basic. The solids were dissolved in chloroform and filtered through a silica gel plug and eluted with chloroform. Evaporation, followed by trituration of the yellow solid with 5% ethyl acetate in hexane, gave the product (114.2 g, 93%).

$^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 10.01 (s, 1H), 8.84 (d, 1H, $J = 5.9$ Hz), 8.2 (d, 1H, $J = 8.1$ Hz), 8.15 (d, 1H, $J = 5.6$ Hz), 8.1 (d, 1H, $J = 8.2$ Hz).

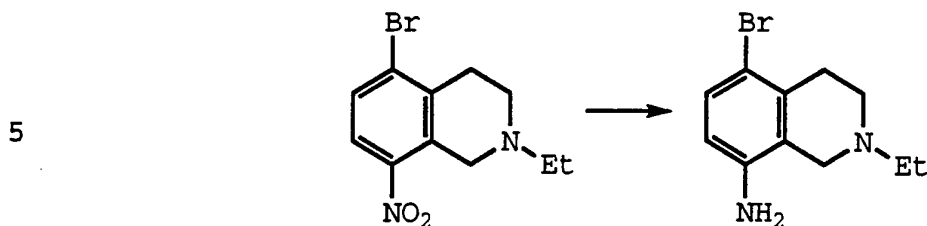
EXAMPLE 26

5-Bromo-2-ethyl-1,2,3,4-tetrahydro-8-nitroisoquinoline

A solution of 5-bromo-8-nitroisoquinoline (1 g, 3.95 mmol) in 20 mL THF was cooled to 0°C and treated sequentially with sodium borohydride (0.75 g, 19.83 mmol) followed by the slow addition of acetic acid (20 mL). The reaction mixture was allowed to warm to room temperature, and an additional 2 equiv. of sodium borohydride was added. After quenching with water and treatment with sodium hydroxide solution to make basic, the reaction mixture was extracted with ethyl acetate. The organic residue was chromatographed on silica gel (25% ethyl acetate in hexane) to give the N-ethyl-5-bromo-8-nitrotetrahydroisoquinoline (0.8 g, 70% yield).

-34-

EXAMPLE 27

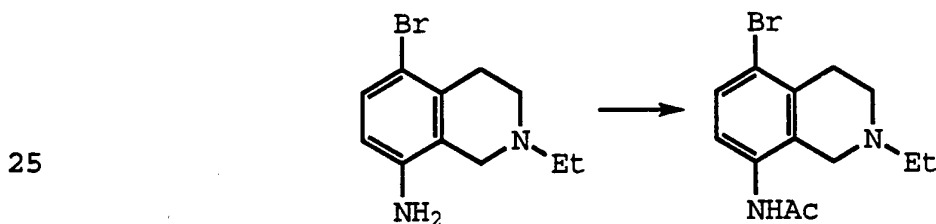


10 5-Bromo-2-ethyl-1,2,3,4-tetrahydro-8-isoquinolinamine

Raney nickel was refluxed in acetone for 2 hours prior to use to deactivate the metal. The product from Example 26 (0.1 g, 0.35 mmol) was dissolved in THF (10 mL), the Raney nickel added, and the reaction vessel charged with hydrogen gas. After stirring for 15 1 hour, the Raney nickel was removed by filtration and the solvent removed by filtration to give N-ethyl-5-bromo-8-aminotetrahydroisoquinoline (used without further purification).

20

EXAMPLE 28



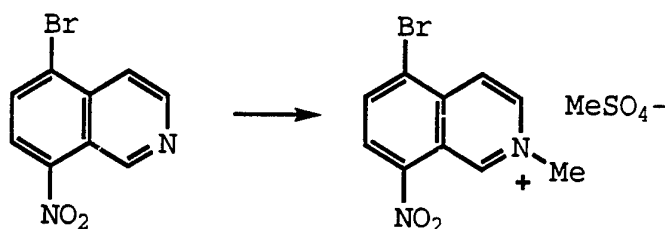
30 N-(5-bromo-2-ethyl-1,2,3,4-tetrahydro-8-isoquinolinyl)-acetamide

The product from Example 27 (0.35 mmol) was cooled in an ice bath, treated with acetic anhydride (10 mL), and stirred at room temperature under nitrogen overnight. Excess acetic anhydride was evaporated, the residue washed with ether, and evaporated. The white solid was triturated with ether and collected by

-35-

filtration. The solid was washed with a mixture of ethyl acetate and saturated sodium bicarbonate. The organic layer was washed with sodium bicarbonate and sodium chloride solutions, dried over MgSO_4 , filtered, and evaporated. The acetamide was obtained as a white solid (crystallized from ethyl acetate, 0.07 g, 67% yield).

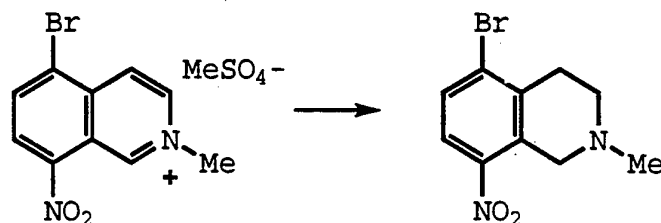
EXAMPLE 29



5-Bromo-2-methyl-8-nitro-2-isouquinolinium
methanesulfonate

A mixture of 5-bromo-8-nitroisoquinoline (0.99 g, 3.91 mmol) and dimethylsulfate (0.41 mL) in anhydrous DMF (20 mL) was heated at 80°C for 24 hours. After removing the DMF in vacuo, the isoquinoline methylammonium salt was obtained (used without further purification).

EXAMPLE 30



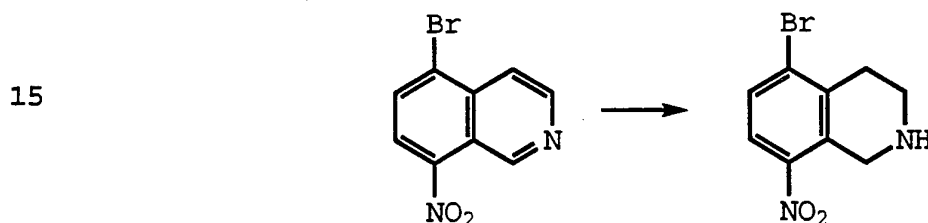
5-Bromo-1,2,3,4-tetrahydro-2-methyl-8-nitroisoquinoline

The product from Example 29 (3.9 mmol) was dissolved in acetic acid (10 mL) and sodium borohydride

-36-

(0.15 g, 3.97 mmol) was added. After stirring for 24 hours, the reaction mixture was diluted with a mixture of ethyl acetate and water, and potassium carbonate was added portionwise to neutralize the acetic acid. The aqueous layer was extracted with ethyl acetate (2x), washed with saturated NaCl, dried over MgSO₄, filtered, and evaporated. The residue was chromatographed on silica gel (30% ethyl acetate in hexane) to give the light sensitive N-methyl-5-bromo-8-nitrotetrahydroisoquinoline (0.47 g, 45% yield).

EXAMPLE 31

5-Bromo-1,2,3,4-tetrahydro-8-nitroisoquinoline

20 A mixture of 5-bromo-8-nitroisoquinoline (1.0 g, 3.95 mmol) and sodium borohydride (1.02 g, 26.96 mmol) in anhydrous THF (25 mL) at 0°C was treated dropwise with formic acid (reaction turns from deep red to bright yellow). The reaction mixture was warmed to room temperature and stirred overnight in the dark. The reaction was quenched with water and basified with sodium hydroxide solution and then extracted with ethyl acetate (3x). The combined organic layers were washed with saturated NaCl, dried over MgSO₄, filtered, and evaporated. The residue was chromatographed on silica gel (65% ethyl acetate in hexane) to give the substituted tetrahydroisoquinoline (0.54 g, 53% yield).

30 Alternatively, a solution of 5-bromo-8-nitroisoquinoline (1.0 g) in glacial acetic acid (30 mL) was cooled to 0°C and, before freezing, was treated with sodium cyanoborohydride (1.10 g). The reaction mixture

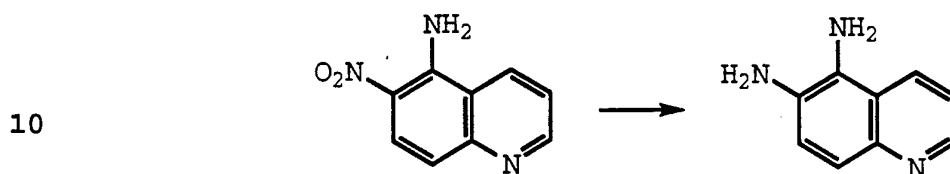
35

-37-

was warmed slowly to room temperature under nitrogen. The reaction mixture was diluted with water and basified. Organic layer extracts were chromatographed on silica gel as before.

5

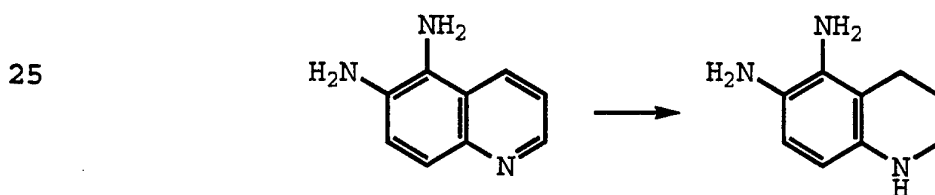
EXAMPLE 32

5,6-Quinolinediamine

15 A solution of 5-amino-6-nitroquinoline (25 g, 0.13 mol) in THF (500 mL) and methanol (500 mL) was treated with Raney nickel (7 g) under a hydrogen atmosphere (50.4 psi) on a Parr apparatus for 3.4 hours. Standard work-up gave the 5,6-diamino-

20 quinoline.

EXAMPLE 33

1,2,3,4-Tetrahydro-5,6-quinolinediamine

30 A solution of 5,6-quinolinediamine (12.5 g, 0.065 mol) and sulfuric acid (8 mL) in methanol (250 mL) was treated with platinum oxide (1 g) in a Parr apparatus under hydrogen for 16 hours. An

35 additional 1 g portion of platinum oxide was added and hydrogenation continued for 44 hours additional.

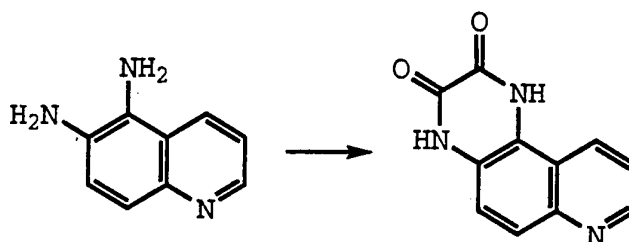
-38-

Standard work-up gave the 5,6-diaminotetrahydroquinoline.

EXAMPLE 34

5

10

1,4-Dihydropyrido[3,2-f]quinoxaline-2,3-dione

A mixture of 5,6-quinolinediamine (11.3 g, 0.071 mol) and oxalic acid hydrate (17.9 g, 0.142 mol) in 200 mL 2N HCl was heated at reflux for 2 hours. The solid (12.3 g, 83% yield) was collected by filtration and washed consecutively with water and ether.

Analysis for (C₁₁H₇N₃O₂·2H₂O):

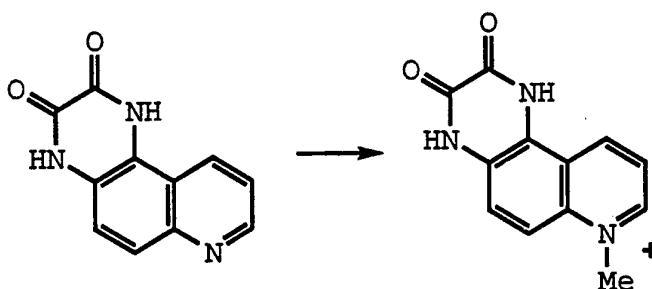
20 Calc.: C, 53.07; H, 4.43; N, 16.88.

Found: C, 52.99; H, 3.27; N, 16.88.

EXAMPLE 35

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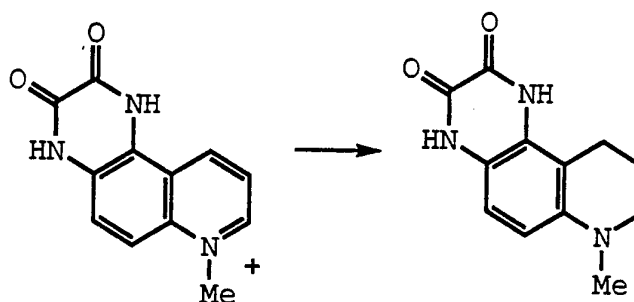
1,2,3,4-Tetrahydro-7-methyl-2,3-dioxopyrido[3,2-f]-quinoxalin-7-ium methanesulfonate

A mixture of the product from Example 34 (5 g, 23 mmol) and dimethylsulfate (3.7 g, 29 mmol) in DMF (40 mL) was heated at 100°C for 20 hours. An

-39-

additional portion of dimethylsulfate (3.5 g) was added, and the mixture was heated at 120°C for 3 hours. After concentration, methanol was added and the solid collected by filtration to give the methylammonium derivative (6 g).

EXAMPLE 36



1,4,7,8,9,10-Hexahydro-7-methylpyrido[3,2-f]quinoxaline-2,3-dione

A mixture of the product from Example 35 (6 g, 18 mmol) and platinum oxide (0.5 g) in methanol (100 mL) was shaken on a Parr apparatus under a hydrogen atmosphere (52 psi) for 7.2 hours. After filtration, the solvent was evaporated to give a syrupy residue. The residue was triturated with water and the resulting solid collected by filtration and recrystallized from DMF/water to give the N-methyl derivative (1.7 g).

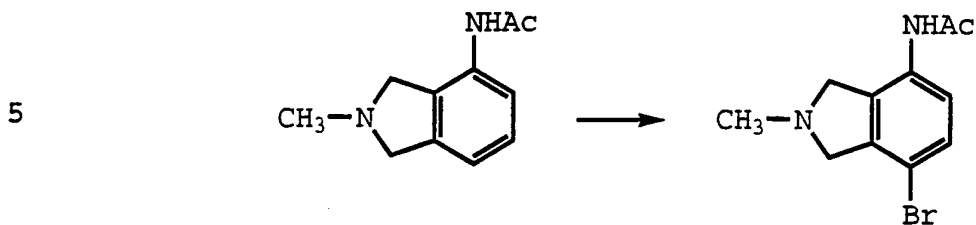
Analysis for (C₁₂H₁₃N₃O₂·0.18H₂O):

Calc.: C, 61.44; H, 5.74; N, 17.91.

Found: C, 61.44; H, 5.50; N, 17.75.

-40-

EXAMPLE 37



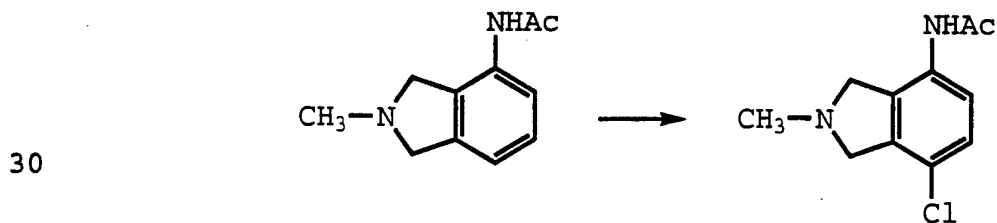
10 N-(7-bromo-2,3-dihydro-2-methyl-1H-isoindol-4-yl)acetamide

A solution of N-(2,3-dihydro-2-methyl-1H-isoindol-4-yl)acetamide (10 g) and bromine (3.0 g) in trifluoroacetic acid (150 mL) was stirred at 50°C for 40 hours. The solution was evaporated in vacuo. The residue was dissolved in water (300 mL), and pH was adjusted to neutral with saturated Na₂CO₃. This treatment afforded a crystalline precipitate of the product, which was collected by filtration. Yield 9 g, mp 145-148°C.

In a similar manner was prepared:

N-[7-bromo-2-(1,1-dimethylethyl)-2,3-dihydro-1H-isoindol-4-yl]acetamide, mp 140-144°C.

25 EXAMPLE 38

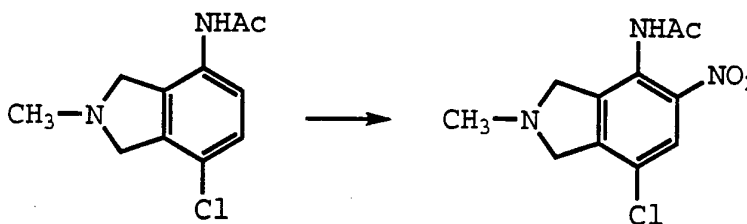


-41-

N-(7-chloro-2,3-dihydro-2-methyl-1H-isoindol-4-yl)acetamide

A mixture of N-(2,3-dihydro-2-methyl-1H-isoindol-4-yl)acetamide (20 g), hydrochloric acid (37%, 2.5 mL), and sodium chlorite (15%, 10 mL) in 96% ethanol (20 mL) was stirred at room temperature for 4 hours. The solvent was removed by evaporation, whereafter the residue was treated with saturated Na₂CO₃ in water to pH = 7. The precipitated product was filtered off and washed with water and ether. Yield 1.1 g, mp 147-150°C.

EXAMPLE 39



N-(7-chloro-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-yl)acetamide

To a stirred 10°C warm solution of KNO₃ (0.5 g) in sulphuric acid (10 mL) was added portionwise 4-acetamido-7-chloro-2-methyl-2H-1,2-dihydro-pyrrolo[3,4]benzene. In total 1 g. After additional stirring for 30 minutes at 10°C, the reaction mixture was poured on ice, and the resulting solution was neutralized with saturated Na₂CO₃. The precipitated product was then collected by filtration and washed with water. Yield 0.8 g, mp 165-166°C.

In a similar manner were prepared:

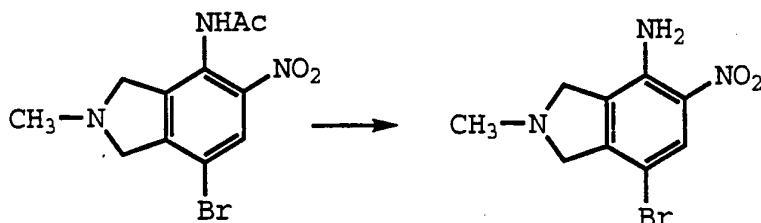
N-(7-bromo-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-yl)acetamide, mp 161-163°C and

-42-

N-(7-bromo-2,3-dihydro-2-(1,1-dimethylethyl)-5-nitro-1H-isoindol-4-yl)acetamide, mp 203-206°C.

EXAMPLE 40

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7-Chloro-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-amine

15

A solution of N-(7-chloro-2,3-dihydro-2-methyl-1H-isoindol-4-yl)acetamide (1.5 g) in sulphuric acid (25 mL, 65%) was heated to 90°C for 15 minutes, whereafter it was cooled to ambient temperature and neutralized with ammonia. This treatment left the product as a pale solid, which was isolated by filtration. Yield 1.1 g, mp 171-173°C.

20

In a similar manner were prepared:

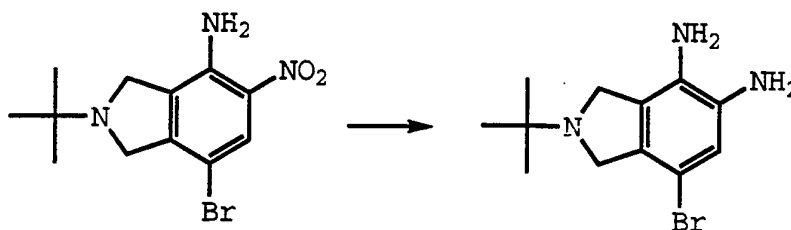
7-Bromo-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-amine, mp 174-176°C and

25

7-Bromo-2,3-dihydro-2-(1,1-dimethylethyl)-5-nitro-1H-isoindol-4-amine, mp 220-221°C.

EXAMPLE 41

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-43-

7-Bromo-2,3-dihydro-2-(1,1-dimethylethyl)-1H-isoindole-4,5-diamine

Hydrogenation of the nitro groups in the compounds of Example 40 were performed under standard conditions using RaNi as catalyst and ethanol as solvent.

H₂ pressure 1 atm.

This afforded:

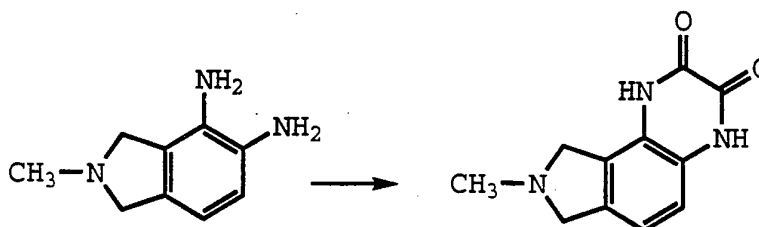
7-Bromo-2,3-dihydro-2-(1,1-dimethylethyl)-1H-isoindole-4,5-diamine hydrochloride, mp >300°C;

7-chloro-2,3-dihydro-2-methyl-1H-isoindole-4,5-diamine, hydrochloride, mp 235-238°C;

7-bromo-2,3-dihydro-2-methyl-1H-isoindole-4,5-diamine, hydrochloride, mp 90-95°C; and

2,3-dihydro-2-methyl-1H-isoindole-4,5-diamine, hydrobromide, mp 198-200°C. Palladium on carbon (Pd/C) was used as catalyst.

EXAMPLE 42



1,7,8,9-Tetrahydro-8-methyl-2H-pyrrolo[3,4-f]-quinoxaline-2,3(4H)-dione

A solution of oxalic acid (1.3 g) and 4,5-diamino-1,3-dihydro-2-methyl-2H-pyrrolo[3,4]benzene, hydrobromide (1.5 g) in hydrochloric acid (4N, 20 mL) was refluxed for 4 hours. The reaction mixture was then reduced in vacuo to a volume of 10 mL, whereafter it was cooled on ice. The formed crystalline precipitate was collected by filtration and washed with water. Yield 1.25 g.

-44-

In a similar manner were prepared:

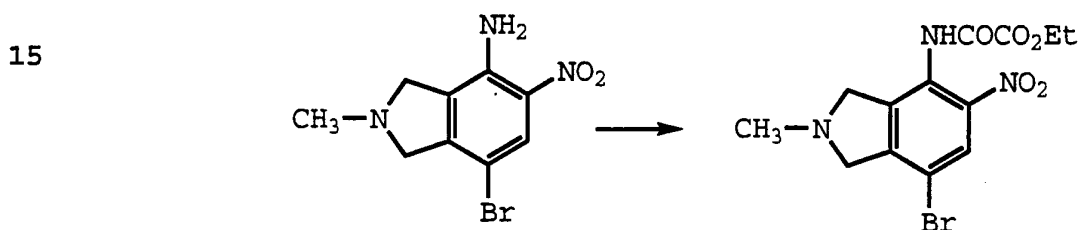
6-bromo-1,7,8,9-tetrahydro-8-methyl-
2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione, mp >300°C;

6-chloro-1,7,8,9-tetrahydro-8-methyl-
5 2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione, mp >300°C;

6-bromo-8-(1,1-dimethylethyl)-1,7,8,9-tetrahydro-
2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione, mp >300°C;
and

2,3,4,7,8,9-hexahydro-8-methyl-2,3-dioxo-
10 1H-pyrrolo[3,4-f]quinoxaline-6-sulfonamide, mp >300°C.

EXAMPLE 43

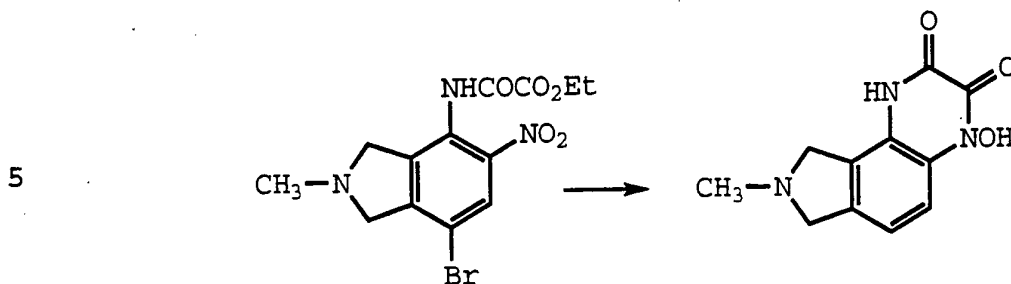


Ethyl [(7-bromo-2,3-dihydro-2-methyl-5-nitro-
1H-isoindol-4-yl)aminoloxoacetate]

To a stirred solution of triethylamine (0.83 mL)
and 7-chloro-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-
25 4-amine (1.1 g) in THF (15 mL) was dropwise added a
solution of ethyloxalylchloride (0.7 mL) in THF (5 mL).
After the addition was completed, the reaction mixture
was brought to reflux for 1 hour, then cooled to room
temperature, whereafter the precipitate was removed by
30 filtration. The filtrate was evaporated in vacuo. The
residue was treated with 5 mL of ethanol which left the
product as pale crystals. The crystals were collected
by filtration. Yield 1.0 g, mp 153-154°C.

-45-

EXAMPLE 44



10 6-Bromo-1,7,8,9-tetrahydro-4-hydroxy-8-methyl-2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione

The product of Example 43 was hydrogenated under standard conditions to give the above listed products.

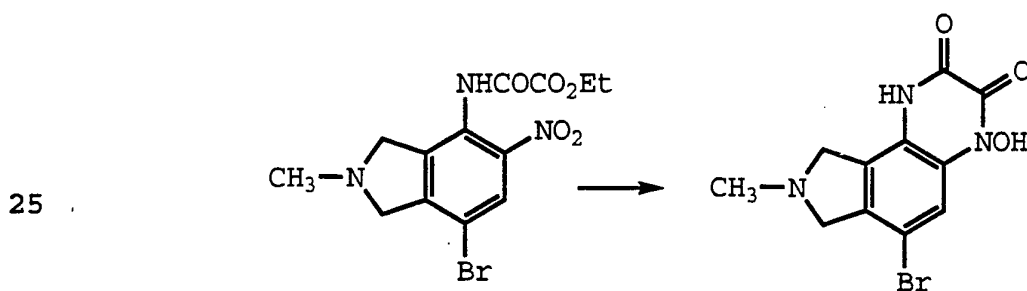
The following compounds are prepared in a similar manner:

15 1,4,7,8,9,10-hexahydro-4-hydroxy-8-methylpyrido[4,3-f]quinoxaline-2,3-dione and

1,4,7,8,9,10-hexahydro-4-hydroxy-9-methylpyrido[3,4-f]quinoxaline-2,3-dione.

20

EXAMPLE 44a



-46-

The following compounds are prepared in a similar manner:

6-Bromo-1,4,7,8,9,10-hexahydro-4-hydroxy-8-methylpyrido[4,3-f]quinoxaline-2,3-dione and

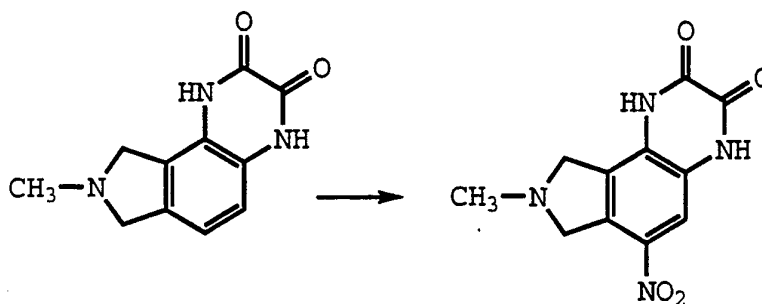
5 6-Bromo-1,4,7,8,9,10-hexahydro-4-hydroxy-9-methylpyrido[3,4-f]quinoxaline-2,3-dione.

1,7,8,9-Tetrahydro-4-hydroxy-8-methyl-2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione

10 The product of Example 43 was hydrogenated under standard conditions to give the above listed products.

EXAMPLE 45

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25

1,7,8,9-Tetrahydro-8-methyl-6-nitro-2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione

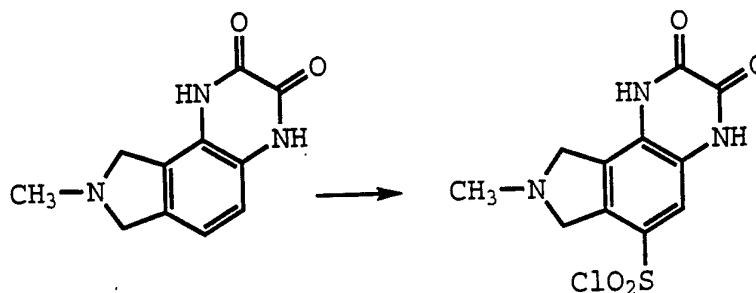
30

To a stirred 5°C cold solution of potassium nitrate (0.2 g) in sulphuric acid (5 mL) was added 1,7,8,9-tetrahydro-8-methyl-2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione (0.4 g). Stirring was continued for 15 minutes, whereafter the reaction mixture was poured on ice. The solution was now neutralized, whereby the product precipitated as a pale solid which was filtered off, mp >300°C.

-47-

EXAMPLE 46

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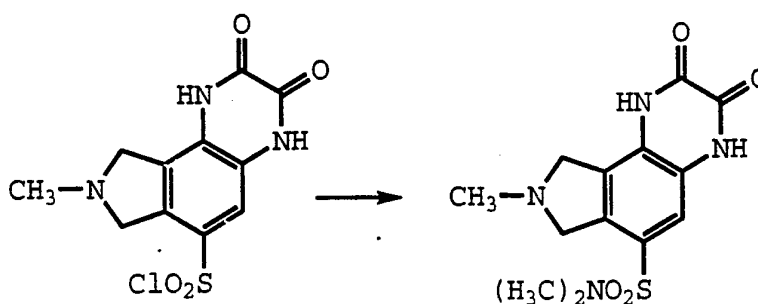
6-(Chlorosulfonyl)-1,7,8,9-tetrahydro-8-methyl-2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione

A solution of 1,7,8,9-tetrahydro-8-methyl-2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione in chlorosulfonic acid was stirred at 120°C for 3 hours, whereafter it was cooled and poured on ice. This afforded a crystalline precipitate of the product, which was filtered off and washed with water, mp >300°C.

20

EXAMPLE 47

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30

2,3,4,7,8,9-Hexahydro-N,N,8-trimethyl-2,3-dioxo-1H-pyrrolo[3,4-f]quinoxaline-6-sulfonamide

-48-

The product of Example 46 (0.5 g) was slurred in tetrahydrofuran (10 mL) at room temperature while exposed to gaseous dimethylamine.

When the reaction had come to completion (monitored by TLC), the solvent was decanted from the oily precipitate. The precipitate was now treated with water which left the product as a white solid. The solid was filtered off and washed with water, mp 290-293°C.

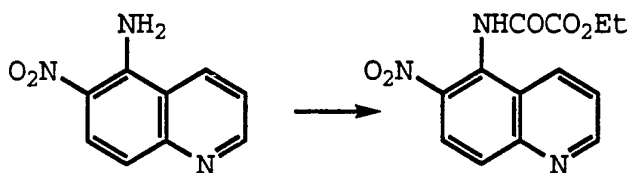
In a similar manner were prepared the following sulfonamides:

4-[(2,3,4,7,8,9-hexahydro-8-methyl-2,3-dioxo-1H-pyrrolo[3,4-f]quinoxalin-6-yl)sulfonyl]morpholine, mp >300°C;

1-[(2,3,4,7,8,9-hexahydro-8-methyl-2,3-dioxo-1H-pyrrolo[3,4-f]quinoxalin-6-yl)sulfonyl]pyrrolidine, mp >300°C; and

2,3,4,7,8,9-hexahydro-8-methyl-2,3-dioxo-1H-pyrrolo[3,4-f]quinoxaline-6-sulfonamide, mp >300°C.

EXAMPLE 48

Ethyl [(6-nitro-5-quinolinyl)aminooxalacetate]

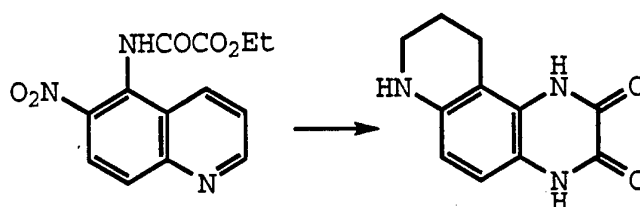
A solution of 5-amino-6-nitroquinoline (3 g, 16 mmol) in 50 mL DMF was treated with triethylamine (3.2 g, 32 mmol) and ethyl oxalylchloride (24 mmol) and then heated at 50°C for 1 hour. A solid was removed by filtration, and the filtrate was concentrated in vacuo and treated with diethyl ether to precipitate a solid.

-49-

A solid was collected by filtration and washed with ether (3.7 g, 80% yield).

EXAMPLE 49

5



1,4,7,8,9,10-Hexahydropyrido[3,2-f]quinoxaline-
2,3-dione

15

The reaction product, Example 48, was dissolved in 100 mL acetic acid, treated with PtO₂ (0.01 g), and then placed on a Parr apparatus under 51.1 psi hydrogen gas for 15.5 hours. Additional PtO₂ (0.15 g) was added and the apparatus recharged with hydrogen (52.7 psi).

20

After a total of 47 hours, the catalyst was removed by filtration and washed with additional hot acetic acid. The filtrate was evaporated to a syrupy solid and then heated on a steam bath in methanol/ether. A solid

25

(1 g, 38%) was collected by filtration and crystallized from methanol, DMF, and water and then washed with ether to give a light yellow solid, mp >285°C.

Analysis for C₁₁H₁₁NO₂·0.5H₂O:

Calc.: C, 58.40; H, 5.35; N, 18.57.

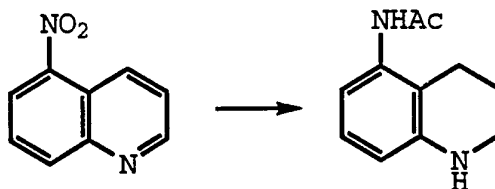
Found: C, 58.70; H, 5.22; N, 18.63.

30

- 50 -

EXAMPLE 50

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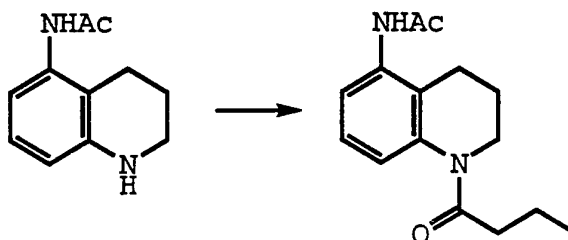
10 N-(1,2,3,4-tetrahydro-5-quinolinyl)acetamide

A solution of 5-nitroquinoline (50 g, 0.29 mol) in 1 L acetic acid and 30 mL acetic anhydride was treated with 5% Pd/C (3 g) and shaken on a Parr apparatus under a H₂ atmosphere (50.8 psi) for 10.4 hours. The reaction was then treated with PtO₂ (1 g) and recharged with H₂ (50.8 psi) and shaken an additional 2 hours. After removing the catalyst by filtration, the filtrate was evaporated and the residue was separated between methylene chloride and water. The aqueous layer was basified with 50% NaOH and washed with methylene chloride. The combined organic layer was dried over sodium sulfate, filtered, and evaporated. The resulting solid was crystallized from ethyl acetate (23 g, 42%).

25

EXAMPLE 51

30



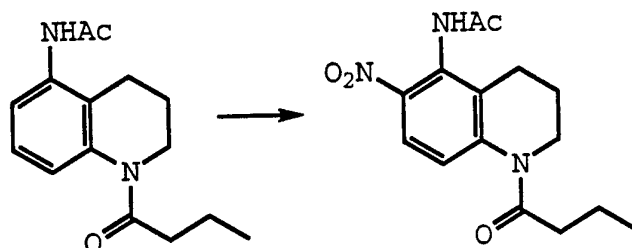
35

N-[1,2,3,4-tetrahydro-1-(1-oxobutyl)-5-quinolinyl]-acetamide

-51-

A mixture of the product from Example 50 (10 g, 53 mmol), butyric anhydride (12.5 g, 79 mmol), and triethylamine (10 g, 0.1 mol) in 50 mL methylene chloride was heated at reflux for 4 hours. The mixture was washed with water, and the organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (40-60% ethyl acetate in heptane as eluant) to give the product (9.5 g, 69%).

EXAMPLE 52

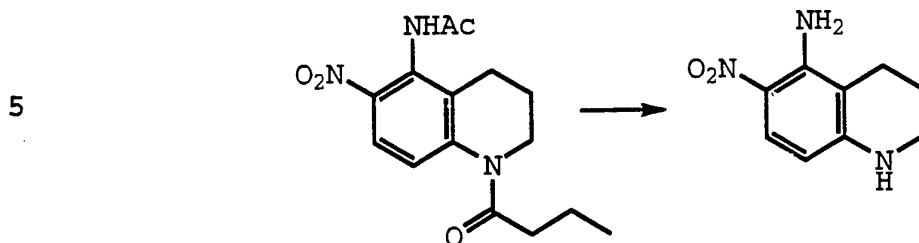


N-[1,2,3,4-tetrahydro-6-nitro-1-(1-oxobutyl)-5-quinolinyl]acetamide

A solution of the product from Example 51 (7.3 g, 28 mmol) in 50 mL acetic acid was treated with fuming nitric acid (10 mL) and stirred at room temperature for 1 hour. The reaction mixture was concentrated by rotoevaporation and added to a solution of potassium carbonate in water. After extraction with methylene chloride, the organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (40% ethyl acetate in heptane to 100% ethyl acetate as eluant). Obtained from the chromatography 4.5 g of the 6-nitro adduct, 2.2 g of mixture of the 6-nitro and 8-nitro products, and 1 g of the pure 8-nitro adduct.

- 52 -

EXAMPLE 53



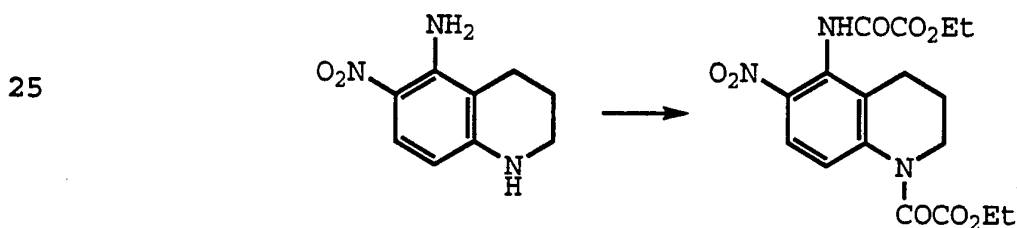
15

1,2,3,4-Tetrahydro-6-nitro-5-quinolinamine

The product from Example 52 (2.1 g, 6.9 mmol) was refluxed in 50 mL 2N HCl for 4 hours. The mixture was cooled and basified with 12.5% NaOH and then extracted with methylene chloride. Sodium chloride was added to the aqueous solution and then extracted again. The combined organic extracts were dried over sodium sulfate, filtered, and evaporated to an orange solid (1.29 g, 97%).

20

EXAMPLE 54



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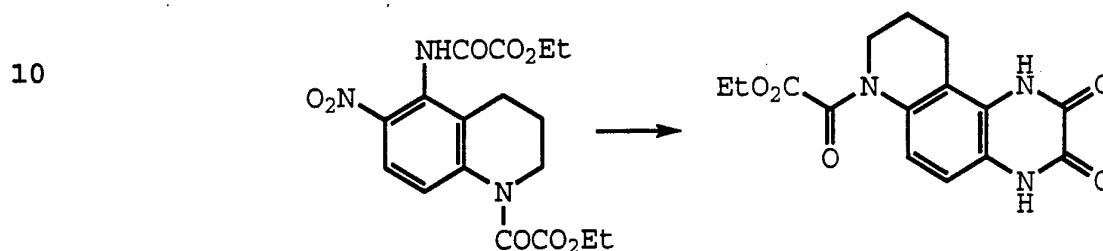
Ethyl [6-[(ethoxyoxoacetyl)amino]-3,4-dihydro-6-nitro- α -oxo-1(2H)-quinolineacetate

A mixture of the product from Example 53 (1.29 g, 6.7 mmol), ethyl oxalylchloride (2.7 g, 20 mmol), and triethylamine (2.7 g, 27 mmol) in 40 mL THF was stirred at room temperature for 18 hours. The solvent was

-53-

evaporated and the residue was extracted with methylene chloride/water. The organic layer was dried over sodium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel (50% ethyl acetate in heptane as eluant) to give a syrup (2.8 g, 85%).

EXAMPLE 55



Ethyl 1,2,3,4,9,10-hexahydro- α ,2,3-trioxopyrido[3,2-f]-quinoxaline-7(8H)-acetate

A solution of the product from Example 54 (2.9 g) in 100 mL EtOH was treated with 5% Pd/C (1 g) and shaken on a Parr apparatus under a H₂ atmosphere (50.2 psi) for 40 minutes. After removing the catalyst by filtration, the filtrate was evaporated and the residue chromatographed on silica gel (10-50% ethyl acetate in heptane as eluant). Partially purified material from the column was triturated in hot toluene/MeOH. A solid (0.3 g, 14%) was collected by filtration, mp >285°C.

Analysis for C₁₅H₁₅N₃O₅:

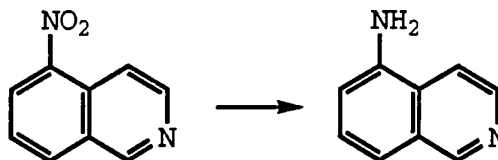
30 Calc.: C, 56.78; H, 4.77; N, 13.24.

Found: C, 54.23; H, 4.82; N, 13.16.

- 54 -

EXAMPLE 56

5

5-Isoquinolinamine

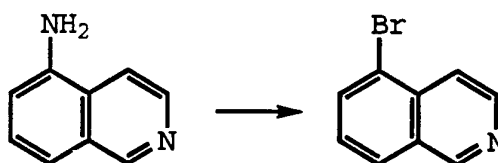
10

5-Nitroisoquinoline (100.3 g, 0.576 mol) was dissolved in MeOH and shaken with Raney nickel (10 g) on a Parr apparatus under a H₂ atmosphere (50 psi) for 21 hours. The MeOH was removed in vacuo, the residue dissolved in chloroform (150 mL), and filtered into 600 mL petroleum ether. The solid was collected by filtration. This trituration procedure was repeated several times to give 81.24 g (98%) of the desired product.

20

EXAMPLE 57

25

5-Bromoisoquinoline

30

The procedure described by Osborn AR, et al, J Chem Soc 1956:4191 was used. 5-Aminoisoquinoline (43.6 g, 0.302 mol) was dissolved in 300 mL 48% HBr and 200 mL water and cooled in an ice bath. NaNO₂ (21.21 g, 0.307 mol) in 130 mL of water was added dropwise to the HBr solution and the reaction stirred for 1 hour. CuBr (52 g, 0.363 mol) in 500 mL of 48% HBr was heated to 85°C, the diazonium solution

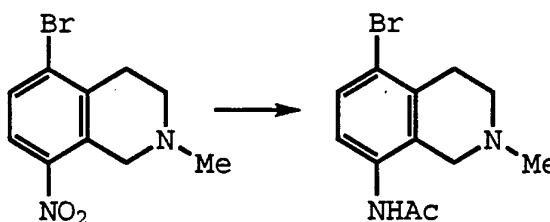
35

-55-

added dropwise from an ice-cooled jacketed-addition funnel, and the reaction stirred overnight at 50°C. The reaction mixture was cooled in an ice bath and the acid neutralized by dropwise addition of concentrated
5 NH₄OH solution. The solid precipitates were filtered off, washed with concentrated NH₄OH until colorless, and then water. The solid was dissolved in ethyl acetate, washed with brine (2x), and dried over magnesium sulfate, filtered, and evaporated. The
10 residue was chromatographed on silica gel (30% ethyl acetate in hexane as eluant) to give 53.7 g (86%) of the product as an off-white solid.

EXAMPLE 58

15



20

N-(5-bromo-1,2,3,4-tetrahydro-2-methyl-8-isoquinolinyl)acetamide

A solution of the product of Example 30 (6 g, 22.1 mmol) was dissolved in 100 mL THF. Raney nickel washed with acetone (2 x 5 mL) and THF (3 x 5 mL) was added and the reaction vessel purged with hydrogen. The reaction was stirred for 3 hours and freshly rinsed catalyst added. After 90 minutes, the reaction was
25 complete. The catalyst was removed by filtration, washed with THF, and the filtrate evaporated. The residue was dissolved in 100 mL acetic anhydride and stirred for 72 hours. Excess acetic anhydride was removed in vacuo and the solid residue washed with
30 ether. The solid was dissolved in chloroform and washed with saturated sodium bicarbonate. The organic
35

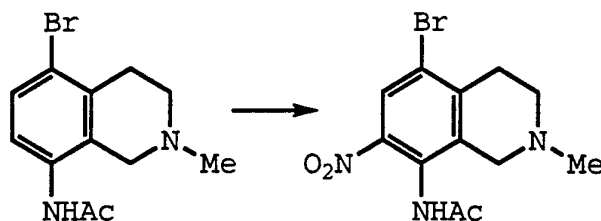
-56-

layer was dried over magnesium sulfate, filtered, and evaporated. The solid was washed with ether and dried to give 5.03 g (80%) of the desired product, mp 192-194°C (dec).

5 In a similar manner, N-5-bromo-2-ethyl-1,2,3,4-tetrahydro-8-isoquinolinyl)acetamide was prepared.

EXAMPLE 59

10



15

N-(5-bromo-1,2,3,4-tetrahydro-2-methyl-7-nitro-8-isoquinolinyl)acetamide

20 The product of Example 58 (4.93 g, 17.4 mmol) was dissolved in 85 mL trifluoroacetic acid, and then 20 mL fuming nitric acid was added over 2 hours. After stirring for 16 hours, the TFA/HONO₂ was removed in vacuo, and the residue was washed with chloroform and saturated sodium bicarbonate solution. The organic

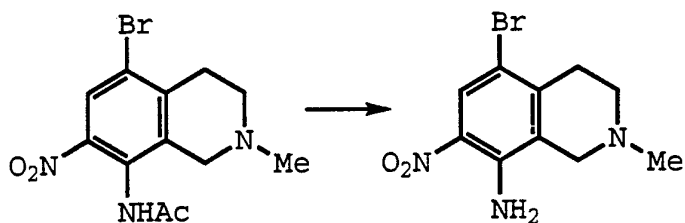
25 layer was dried over magnesium sulfate, filtered, and evaporated to give a light brown solid. This was washed with ether and dried to give 5.16 g (90%) of the desired product.

30 In a similar manner, N-(5-bromo-2-ethyl-1,2,3,4-tetrahydro-8-isoquinolinyl)acetamide was prepared.

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EXAMPLE 60

5



10

5-Bromo-1,2,3,4-tetrahydro-2-methyl-7-nitro-8-isouquinolinamine

15

The product from Example 59 (3.01 g, 9.17 mmol) was added to a cooled solution of sulfuric acid:water (50 mL:25 mL) and heated to 90°C for 15 minutes. The reaction was cooled in an ice bath and poured onto ice. After the reaction mixture was neutralized with ammonium hydroxide, the solid was collected by filtration, washed with water and redissolved in ethyl acetate/THF, then dried over magnesium sulfate, filtered, and evaporated to give 2.48 g (95%) product.

20

Analysis for C₁₀H₁₂BrN₃O₂·0.35H₂O:

Calc.: C, 41.06; H, 4.37; N, 14.36.

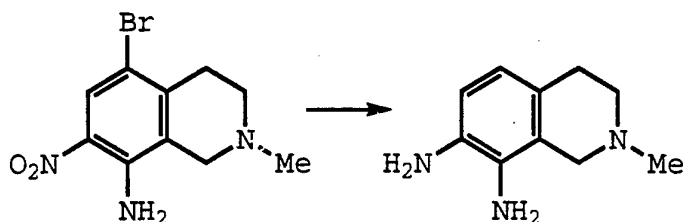
Found: C, 41.06; H, 4.16; N, 13.96.

25

In a similar manner, 5-bromo-2-ethyl-1,2,3,4-tetrahydro-7-nitro-8-isouquinolinamine was prepared.

EXAMPLE 61

30



35

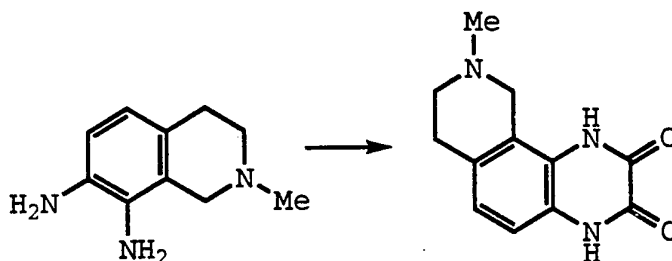
1,2,3,4-Tetrahydro-2-methyl-7,8-isouquinediamine

-58-

The product from Example 60 (1.0 g, 3.49 mmol) was suspended in 100 mL MeOH and treated with 20% Pd/C (0.2 g). The reaction mixture was purged with H₂ and stirred for 4 hours. The catalyst was removed by filtration and the filtrate was concentrated to give a brown solid (0.81 g, 90%).

In a similar manner, 2-ethyl-1,2,3,4-tetrahydro-7,8-isoquinolinediamine hydrobromide was prepared.

EXAMPLE 62



20 1,4,7,8,9,10-Hexahydro-9-methylpyrido[3,4-f]-
quinoxaline-2,3-dione

The product from Example 61 (0.7 g, 2.71 mmol) and oxalic acid dihydrate (0.66 g, 5.24 mmol) in 25 mL 3N HCl were heated at reflux for 5 hours. After cooling to room temperature, the solids were collected by filtration, washed with cold water, and dried (0.5 g). Recrystallized from hot water, washed with ethyl acetate, and dried in vacuo over P₂O₅ to give 0.36 g (49%), mp >327°C, (>99.8% pure by C-18 reverse phase HPLC).

30 Analysis for C₁₂H₁₃N₃O₂·HCl·0.4H₂O:

Calc.: C, 52.46; H, 5.42; N, 15.30; Cl, 12.89.

Found: C, 42.47; H, 5.20; N, 15.16; Cl, 11.09.

In a similar manner, the 9-ethyl-1,4,7,8,9,10-hexahydropyrido[3,4-f]quinoxaline-2,3-dione was prepared.

-59-

Analysis for $C_{13}H_{15}N_3O_2 \cdot HCl$:

Calc.: C, 55.42; H, 5.72; N, 14.91; Cl, 12.58.

Found: C, 54.73; H, 5.81; N, 14.84; Cl, 11.95. (>99.9% pure by C-18 reverse phase HPLC).

5

In a similar manner, 6-bromo-9-ethyl-1,4,7,8,9,10-hexahydropyrido[3,4-f]quinoxaline-2,3-dione was prepared.

Analysis for $C_{12}H_{12}BrN_3O_2 \cdot HCl$:

10 Calc.: C, 41.58; H, 3.78; N, 12.12.

Found: C, 41.20; H, 3.80; N, 11.97.

In a similar manner, 6-bromo-1,4,7,8,9,10-hexahydro-9-methylpyrido[3,4-f]-quinoxaline-2,3-dione was prepared.

15

Analysis for $C_{13}H_{14}BrN_3O_2 \cdot CH_3SO_3H$:

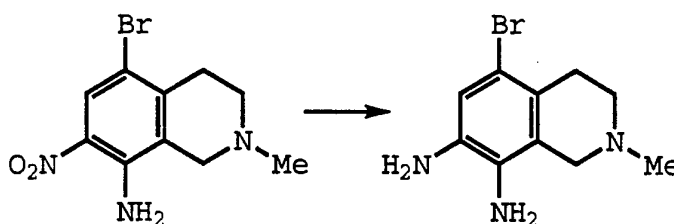
Calc.: C, 40.01; H, 4.32; N, 10.00; S, 7.63.

Found: C, 39.70; H, 4.26; N, 9.89; S, 7.13.

20

EXAMPLE 63

25



30

5-Bromo-1,2,3,4-tetrahydro-2-methyl-7,8-isouquinoline-diamine

35

A solution of the product from Example 60 (1.02 g, 3.49 mmol) in 50 mL THF was treated with Raney nickel (prewashed with acetone followed by THF), and the reaction vessel was purged with H_2 . After stirring for 2.5 hours, the catalyst was removed by filtration and

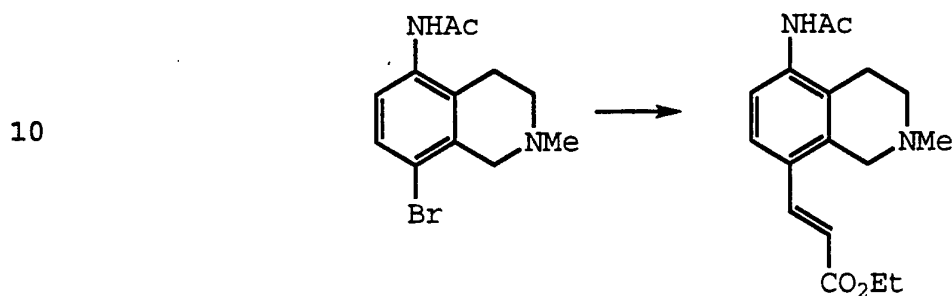
-60-

the filtrate evaporated to give a tan oil. The product was used without further purification.

In a similar manner, 5-bromo-2-ethyl-1,2,3,4-tetrahydro-8-isoquinolinediamine was prepared.

5

EXAMPLE 64



Ethyl 3-[5-(5-acetylamino)-1,2,3,4-tetrahydro-2-methyl-8-isoquinolinyl]-2-propenoate

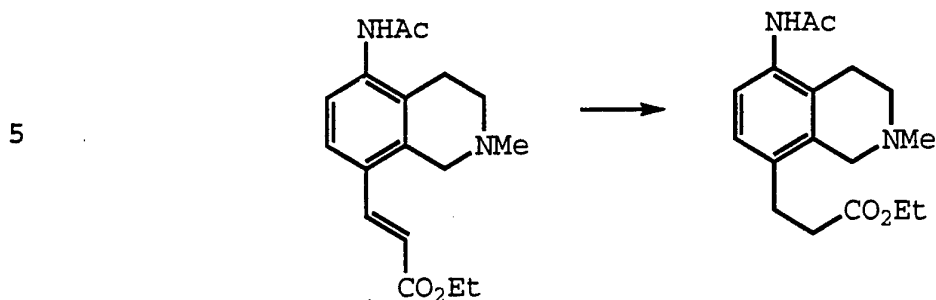
A solution of the product from Example 5 (2.00 g, 7.06 mmol) in 25 mL of acetonitrile and 5 mL of triethylamine was treated with ethylacrylate (2.0 mL) and bis(triphenylphosphine)palladium(II) chloride (0.30 g). The resulting solution was heated at reflux for 72 hours. The reaction mixture was cooled and dissolved in chloroform. The organic phase was washed with saturated aqueous sodium bicarbonate, dried (Na₂SO₄), and concentrated. The residue was crystallized from acetonitrile to give 0.94 g (44%) of the desired product.

20

25

- 61 -

EXAMPLE 65

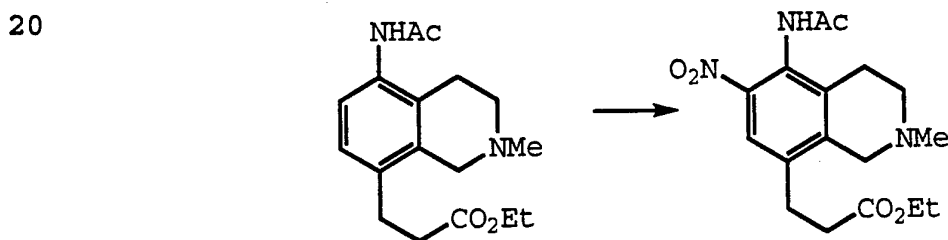


10 Ethyl 5-(acetylamino)-1,2,3,4-tetrahydro-2-methyl-
8-isoquinolinepropanoate

A solution of the product from Example 64 (0.90 g, 2.98 mmol) was dissolved in tetrahydrofuran and hydrogenated at 52 psi over 5% Pd/C for 16.4 hours.

15 The reaction mixture was filtered and concentrated to give 0.65 g (72%) of the desired product.

EXAMPLE 66



Ethyl 5-(acetylamino)-1,2,3,4-tetrahydro-2-methyl-
7-nitro-8-isoquinolinepropanoate

A solution of the product from Example 65 (0.50 g, 1.65 mmol) in 5 mL of trifluoroacetic acid was treated with 0.5 mL of fuming nitric acid dropwise. The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was concentrated and the residue dissolved using chloroform/saturated aqueous NaHCO₃ solution. The organic phase was separated, and the aqueous phase was extracted with

30

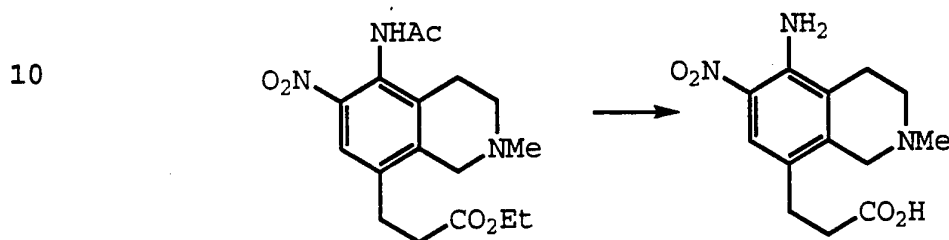
35

- 62 -

additional chloroform. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography (SiO_2 , 20:1:1 CHCl_3 : EtOH : Et_3N) to give 0.52 g (90%) of the desired product.

5

EXAMPLE 67

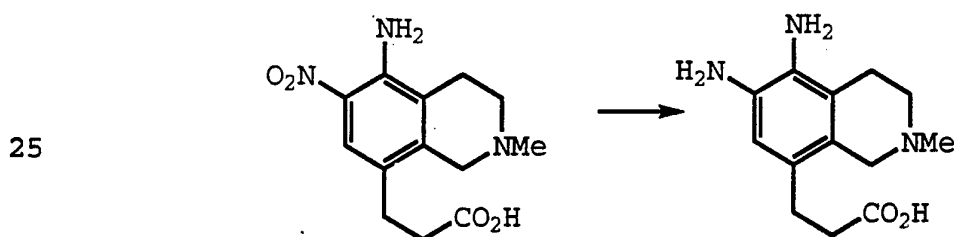


5-Amino-1,2,3,4-tetrahydro-2-methyl-7-nitro-8-isoquinolinepropanoic acid

The product from Example 66 is converted to the desired product by the method described in Example 66.

20

EXAMPLE 68

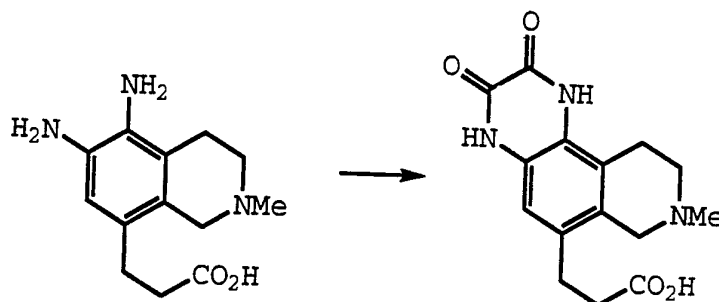


5,6-Diamino-1,2,3,4-tetrahydro-2-methyl-8-isoquinolinepropanoic acid

The product from Example 67 is converted to the desired compound by the method described in Example 67.

- 63 -

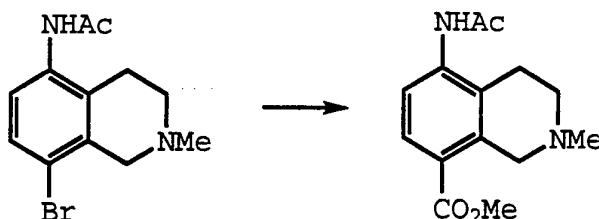
EXAMPLE 69



1,2,3,4,7,8,9,10-octahydro-8-methyl-2,3-dioxo-
pyrido[4,3-f]quinoxaline-6-propanoic acid

The product from Example 68 is converted to the
 15 desired compound by the method described in Example 62.

EXAMPLE 70



Methyl [8-(2-methyl-5-acetamido-1,2,3,4-tetrahydroiso-
quinolinyl)]carboxylic acid

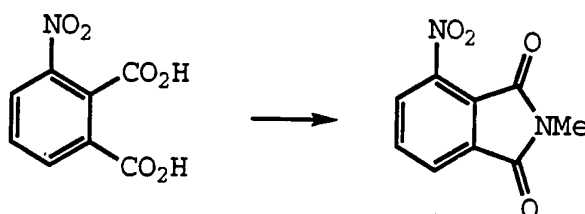
A solution of the product from Example 5 (0.76 g,
 2.70 mmol) in 50 mL of acetonitrile, 0.75 mL MeOH, and
 1.3 mL of triethylamine was treated with
 bis(triphenylphosphine)palladium(II) chloride (0.30 g).
 30 The resulting solution was placed in a high pressure
 reactor, charged to 800 psi with carbon monoxide, and
 heated at 120°C for 8 days. The reaction mixture was
 cooled and dissolved in chloroform. The organic phase
 was washed with saturated aqueous sodium bicarbonate,
 35 dried (Na₂SO₄), and concentrated. The residue was
 purified by chromatography (SiO₂, 10:1:1

-64-

CHCl₃:EtOH:Et₃N) to give 0.26 g (37%) of the desired product.

EXAMPLE 71

5



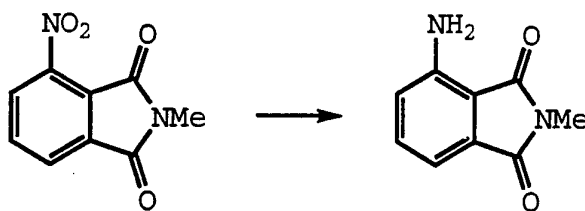
10,

Ethyl 5-(acetylamino)-1,2,3,4-tetrahydro-2-methyl-7-nitro-8-isoquinolinepropanoate

A 3 L 3-neck flask was charged with 3-nitro-
 15 phthalic acid (502 g, 2.38 mol) and 1,3-dimethyl urea
 (230 g, 2.62 mol). This was heated slowly to 170°C
 then allowed to cool. One liter ethanol was added to
 the reaction product before it solidified. The product
 which crystallized was filtered, washed with ethanol
 20 and ether, and air dried to a yellow powder, 420.7 g.
 A second crop was 50.4 g for a yield of 96%.

EXAMPLE 72

25



30

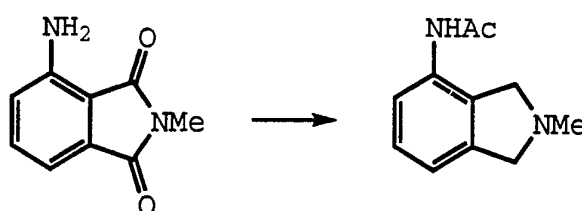
4-Amino-2-methyl-1H-isoindole-1,3(2H)-dione

A pressure reactor was charged with 2-methyl-
 4-nitro-1H-isoindole-1,3(2H)-dione (59.0 g, 0.286 mol),
 1 L acetic acid, and 2 g 5% Pd/C. The reactor was
 35 pressurized to 48 psi hydrogen, and the exothermic
 reaction was complete in 2 hours. The catalyst was
 removed with hot filtration, and the filtrate combined

-65-

with the contents of another reactor which contained 53.2 g of 3-nitrophthalimide under the same conditions. The acetic acid was removed at the rotovap, then the salt was cracked by adding 2 M ammonium hydroxide. The slurry was stirred 30 minutes; then filtered; washed with water, ethanol, and ether; and dried at the pump to give 91.4 g, 95% of the product.

EXAMPLE 73

2,3-Dihydro-2-methyl-1H-isoindol-4-amine

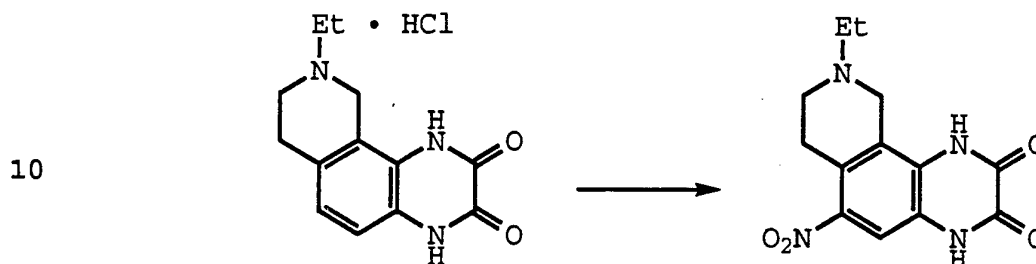
A 5-L flask was set up with an overhead stirrer, temperature probe, and 500-mL addition funnel. The flask was charged with lithium aluminum hydride (100 g) and anhydrous tetrahydrofuran (1.5 L). The resulting suspension was treated with 4-amino-2-methyl-1H-isoindole-1,3(2H)-dione (100 g, 0.56 mol) at a rate such that the reaction did not become too vigorous. The resulting suspension was heated at reflux for 18 hours. The reaction vessel was cooled, placed in an ice bath, and cautiously quenched with 100 mL water, 100 mL 1N NaOH, and 300 mL water. The resulting suspension was treated with chloroform (1.5 L) and the pH of the suspension adjusted to 12 with 50% aqueous sodium hydroxide solution. The resulting suspension was treated with acetic anhydride (300 mL) while maintaining the pH at approximately 12. The reaction mixture was treated with sodium sulfate (800 g) and potassium carbonate (200 g), and the reaction mixture was filtered. The filter cake was washed with additional chloroform, and the combined filtrates were

-66-

concentrated. The residue was crystallized from ethyl acetate to give 71 g (66%) of the desired product, mp 157°C.

5

EXAMPLE 74



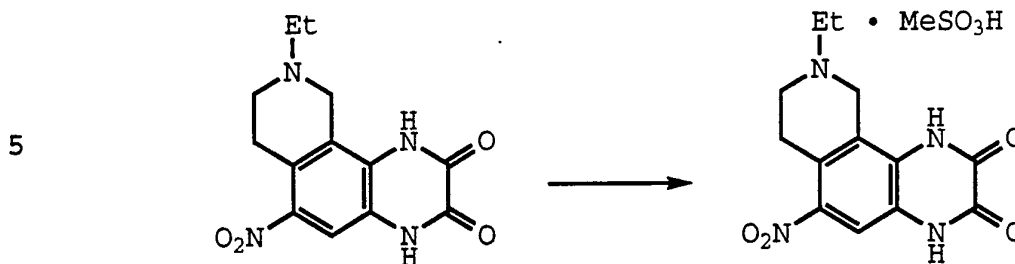
15 9-Ethyl-1,4,7,8,9,10-hexahydro-6-nitro-pyrido[3,4-f]quinoxaline-2,3-dione

A solution of 9-ethyl-1,4,7,8,9,10-hexahydro-pyrido[3,4-f]quinoxaline-2,3-dione (0.61 g, 2.16 mmol) in 20 mL of concentrated sulfuric acid was treated with a solution of potassium nitrate (0.25 g, 2.47 mmol) in 20 mL concentrated sulfuric acid. After stirring for 3 hours at room temperature, the reaction mixture was poured onto ice and cooled in an isopropyl alcohol/dry ice bath. Ammonium hydroxide was added to adjust the pH to 8.9, and the yellow solid was collected by filtration (0.59 g, 94% yield).

25

- 67 -

EXAMPLE 75



10 9-Ethyl-1,4,7,8,9,10-hexahydro-6-nitro-pyrido-
[3,4-f]quinoxaline-2,3-dione methanesulfonate

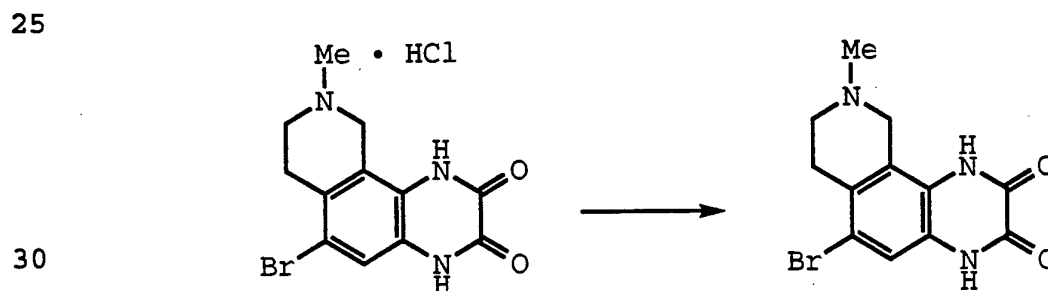
The product from Example 74 was suspended in
 300 mL dimethylformamide and 1 mL of 3 N
 methanesulfonic acid added. The suspension was warmed
 15 to 100°C. The colour changed from orange to yellow and
 all of the solid dissolved. Solvent was evaporated in
 vacuo, the yellow residue washed with acetone and then
 dried under vacuum over P₂O₅ to give the title compound
 (0.73 g, 92% yield) mp = 302-304°C.

20 Analysis for C₁₃H₁₄N₄O₄ · 1.07 CH₃SO₃H · 0.25 H₂O:

Calc: C, 42.54; H, 4.76; N, 14.11; S, 8.60.

Found: C, 42.54; H, 4.72; N, 14.27; S, 8.60.

EXAMPLE 76



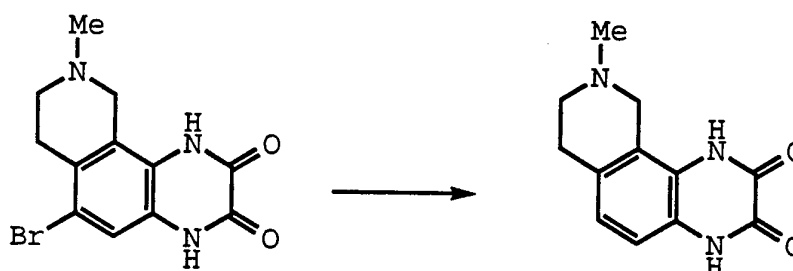
35 6-Bromo-1,4,7,8,9,10-hexahydro-9-methyl-pyrido-
[3,4-f]quinoxaline-2,3-dione methansulfonate

6-Bromo-1,4,7,8,9,10-hexahydro-9-methylpyrido-
 [3,4-f]-quinoxaline-2,3-dione hydrochloride (3.16 g,

-68-

9.12 mmol) was dissolved in 1.8 L boiling water and treated with sodium bicarbonate (0.8 g, 9.2 mmol). The mixture was cooled and placed in a 5°C freezer. The precipitate was collected, washed with acetone and ether and dried to give the title compound (2.17 g, 77% yield).

EXAMPLE 77



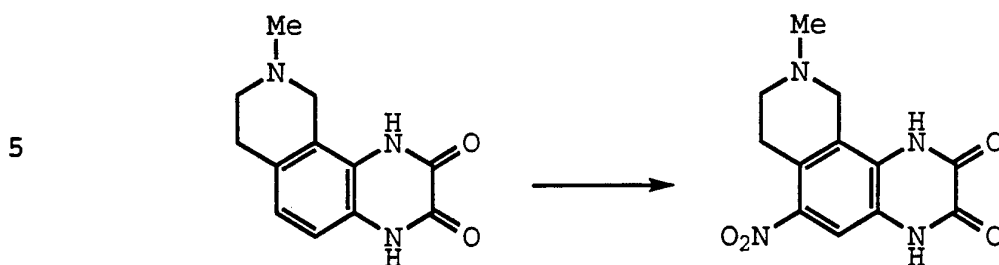
1,4,7,8,9,10-Hexahydro-9-methyl-pyrido-
[3,4-f]quinoxaline-2,3-dione monohydrochloride

The product from Example 76 (1.25 g) and 20% Pd/C (0.5 g) in 100 mL dimethylformamide was shaken on a Parr apparatus under 52 psi H₂ (g) for 15.5 hours. After filtration of the catalyst, the solvent was removed and the residue washed with ether and ether/acetone. The tan solid was dissolved in a minimum of water and neutralized with 5 drops of ammonium hydroxide which induce slow precipitation. The solid was again collected and washed with water/acetone to give of the title compound (0.65 g, 70% yield).

30

- 69 -

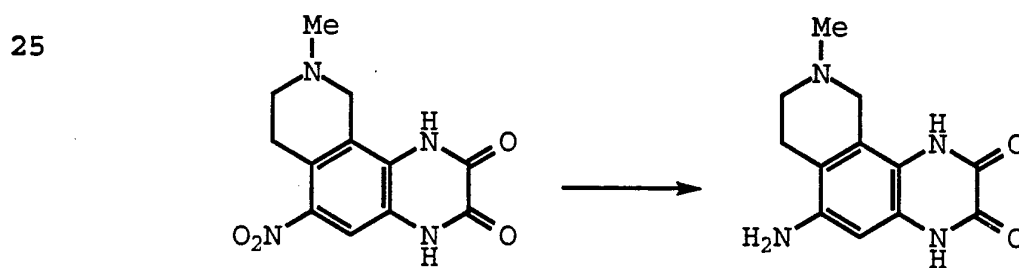
EXAMPLE 78



10 1,4,7,8,9,10-Hexahydro-9-methyl-6-nitro-pyrido-
[3,4-f]quinoxaline-2,3-dione methansulfonate

A solution of the product from Example 77
(0.64 g, 2.77 mmol) in 20 mL concentrated sulfuric acid
was treated with potassium nitrate (0.29 g, 2.87 mmol)
15 in 2 mL concentrated sulfuric acid. After stirring
overnight at room temperature the reaction mixture was
poured onto ice, cooled in a dry ice bath, and then
basified with ammonium hydroxide to pH 8.9. The
orange/yellow solid was collected by filtration and
20 washed consecutively with water, acetone and ether and
dried to give the title compound (0.78 g, 100% yield).

EXAMPLE 79



35 6-Amino-1,4,7,8,9,10-hexahydro-9-methyl-pyrido-
[3,4-f]quinoxaline-2,3-dione

A solution of the product from Example 78 (0.77 g,
2.79 mmol) in 100 mL acetic acid was treated with 5%
Pd/C (0.1 g) and shaken on a Parr apparatus at 52 psi

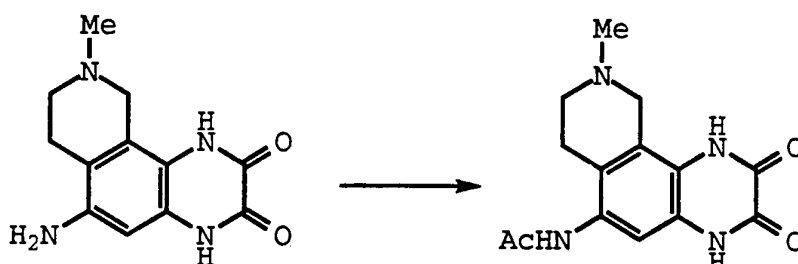
-70-

for 9.5 hours. After removing the catalyst by filtration, the solvent was removed and the residue recrystallized from water to give the mono acetic acid salt (0.14 g). The filtrate was basified to pH 9 with ammonium hydroxide to precipitate the free base, which was further washed with water and then ether to give the title compound as a brown solid (0.46 g).

EXAMPLE 80

10

15



N-(1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxo-pyrido[3,4-f]quinoxalin-6-yl) acetamide

20

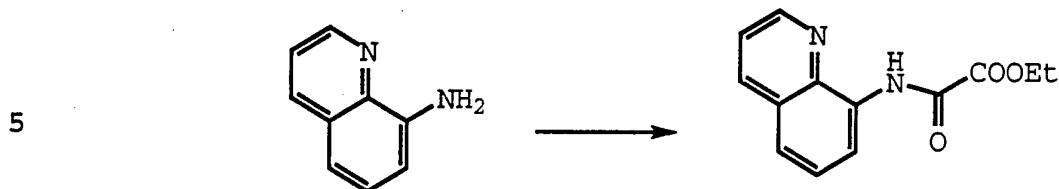
25

30

A mixture of the product from Example 79 (0.27 g, 1.1 mmol) in 25 mL acetic acid and 10 mL acetic anhydride was stirred at room temperature for 18 hours. After removing the solvent, the residue was washed with ether, dissolved in water and then basified with saturated sodium bicarbonate. The flask was cooled in the freezer for 2 hours and the precipitate collected by filtration, washed consecutively with water and ether, and dried over P₂O₅ in vacuo to give the title compound (0.2 g).

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EXAMPLE 81



10 Oxo[(8-quinolinyl)aminolacetic acid ethyl ester

A mixture of 8-aminoquinoline (14.4 g, 0.1 mol), ethyloxalyl chloride (16.4 g, 0.12 mol) and triethylamine (15 g, 0.15 mol) in 150 mL chloroform was stirred at room temperature for 18 hours. The mixture was washed with water and extracted with methylene chloride. The combined organic layers were washed with saturated NaCl solution, dried over sodium sulfate, filtered and evaporated. The residue was then crystallized from toluene/heptane to give the title compound (20.6 g, 86% yield).

15

20

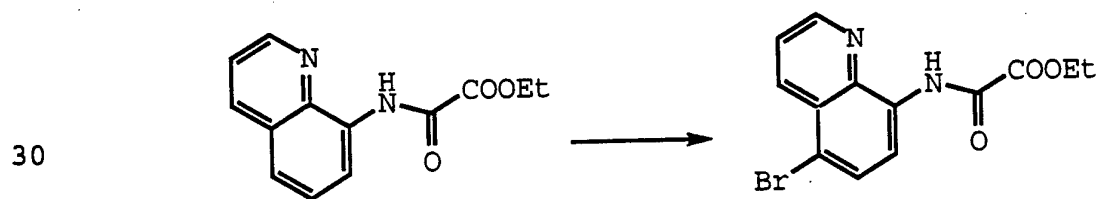
Analysis for $C_{13}H_{12}N_2O_3$:

Calc: C, 63.93; H, 4.95; N, 11.47.

Found: C, 63.20; H, 5.12; N, 11.35.

25

EXAMPLE 82



35

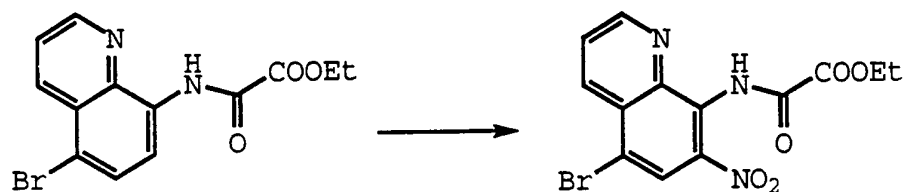
[(5-Bromo-8-quinolinyl)amino]oxo-acetic acid ethyl ester

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A solution of the product from Example 81 (20 g, 82 mmol) in 200 mL acetic acid was treated with a solution of bromine (15.7 g, 0.198 mol) in 50 mL of acetic acid and stirred at room temperature for 1 hour. The solid was collected by filtration and washed with ether to give the title compound (23.5 g, 89% yield).

EXAMPLE 83

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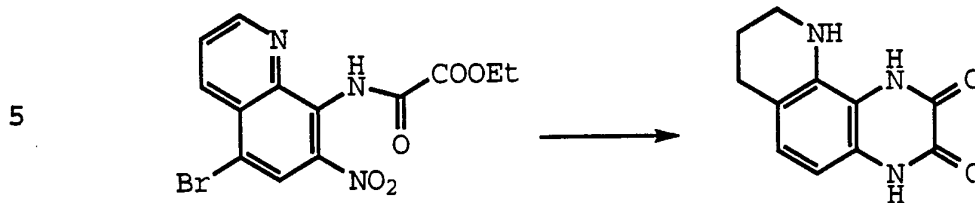
[(5-Bromo-7-nitro-8-quinolinyl)amino]oxo-acetic acid ethyl ester

A solution of the product from Example 82 (23.5 g, 58 mmol) in 30 mL fuming nitric acid and 150 mL trifluoroacetic acid was heated at 80°C for 18 hours. The solvent was removed and the residue was treated with water to give a solid. The solid was collected by filtration and washed with ether and dried to give the title compound (9.5 g, 45% yield).

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-73-

EXAMPLE 84



10 1,4,7,8,9,10-Hexahydro-pyrido[2,3-f]quinoxaline-
2,3-dione

A solution of the product from Example 83 (1 g, 2.7 mmol) in 250 mL acetic acid was treated with 20% Pd/C (0.1 g) and shaken on a Parr apparatus under 52
15 psi hydrogen gas for 21 hours. After removal of the catalyst, the solvent was evaporated but gave negligible material. The catalyst/celite was washed two times with 1 N HCl, and the aqueous solution was
20 basified with sodium bicarbonate. The precipitate was collected by filtration, dried and then recrystallized from methanol/dimethylformamide to give the title
compound (0.26 g, 44% yield) mp >300°C.

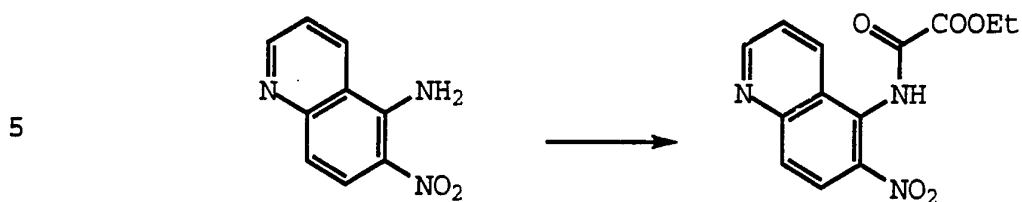
Analysis for $C_{11}H_{11}N_3O_2 \cdot 1.5H_2O$:

Calc: C, 54.09; H, 5.78; N, 17.20.

25 Found: C, 54.20; H, 5.82; N, 17.17.

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EXAMPLE 85

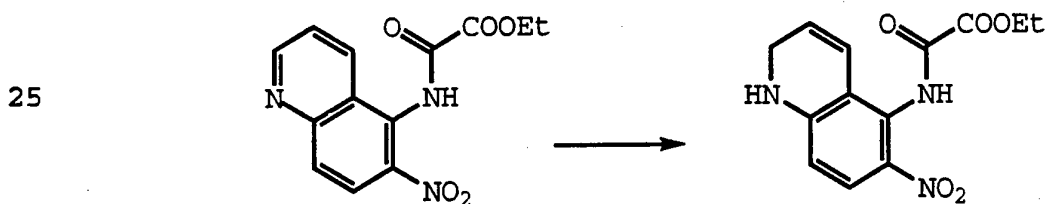


10 [(6-Nitro-5-quinolinyl)aminoloxo-acetic acid ethyl ester

A solution of 5-amino-6-nitroquinoline (3 g, 16 mmol) in 50 mL dimethylformamide was treated with triethylamine (3.2 g, 32 mmol) and ethyloxalyl chloride (3.2 g, 24 mmol) and heated at 50°C for 1 hour. After removing the triethylamine hydrochloride by filtration, the filtrate was concentrated and diethyl ether added. The filtrate was concentrated and diethyl ether added. The title compound (3.7 g, 80% yield) was collected by filtration.

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EXAMPLE 86



30 [(1,2-Dihydro-6-nitro-5-quinolinyl)aminoloxo-acetic acid ethyl ester

A solution of the product from Example 85 (5 g, 17.5 mmol) in 80 mL acetic acid was treated with sodium cyanoborohydride (2.2 g, 35 mmol) portionwise under an argon atmosphere and stirred for 4 hours. Water (100 mL) was added to the reaction mixture, and the

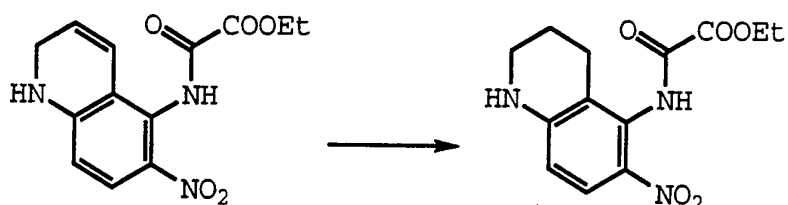
35

-75-

resulting solid was collected by filtration and dried (3.9 g, 78% yield).

EXAMPLE 87

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[(1,2,3,4-Tetrahydro-6-nitro-5-quinolinyl)aminoloxoacetic acid ethyl ester

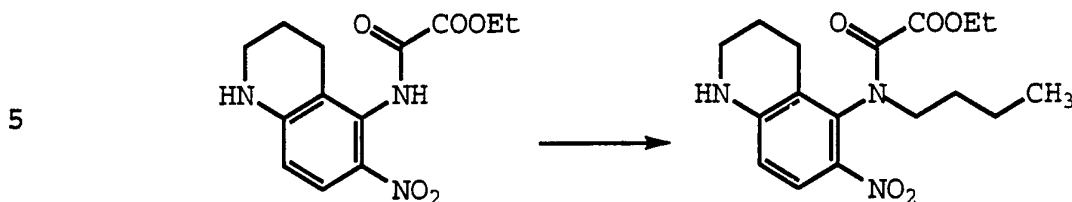
15

A solution of the product from Example 86 (4.8 g, 16.5 mmol) in 250 mL tetrahydrofuran was treated with triphenylphosphine (5 g) and rhodium trichloride (0.83 g) and shaken in a Parr apparatus under a hydrogen atmosphere (54 psi) for 40 minutes. The solvent was evaporated and the residue was purified by silica gel chromatography (4:1 to 1:1 heptane:ethyl acetate as eluant) to give the title compound as a red solid (4.22 g, 87% yield).

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-76-

EXAMPLE 88



10 [Butyl(1,2,3,4-tetrahydro-6-nitro-5-quinolinyl)-
amino]oxo-acetic acid ethyl ester

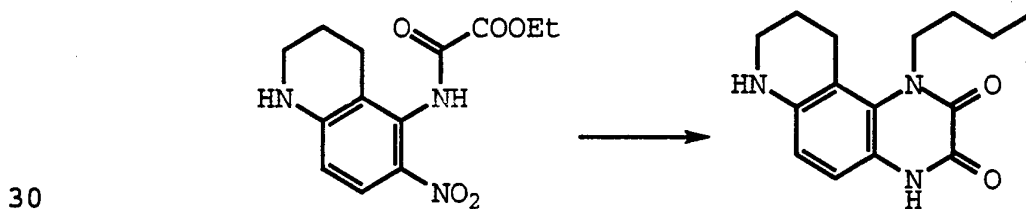
A mixture of the product from Example 87 (0.87 g, 3 mmol), bromobutane (0.49 g, 3.6 mmol) and cesium carbonate (1.17 g, 3.6 mmol) in 10 mL acetonitrile was stirred at room temperature for 4 hours. An additional equivalent of bromobutane and cesium carbonate was added and the reaction heated at 50°C for 5 hours. Solids were removed by filtration and the filtrate concentrated. The residue was purified by silica gel chromatography (4:1 to 3:2 heptane:ethyl acetate as eluant) to give the title compound as a yellow syrup (0.63 g, 61% yield).

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EXAMPLE 89

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1-Butyl-1,4,7,8,9,10-hexahydropyrido[3,2-f]quinoxaline-
2,3-dione

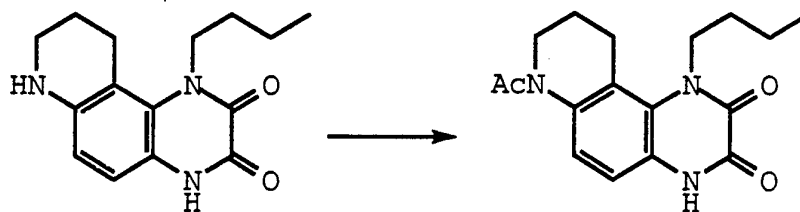
35

A solution of the product from Example 88 (0.63 g) in 75 mL of acetic acid was treated with 5% Pd/C

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(0.2 g) and shaken on a Parr apparatus under a hydrogen atmosphere (52 psi) for 12 hours. The catalyst was removed by filtration and the filtrate evaporated. The residue was washed with ether to give the title compound (0.35 g, 71% yield).

EXAMPLE 90

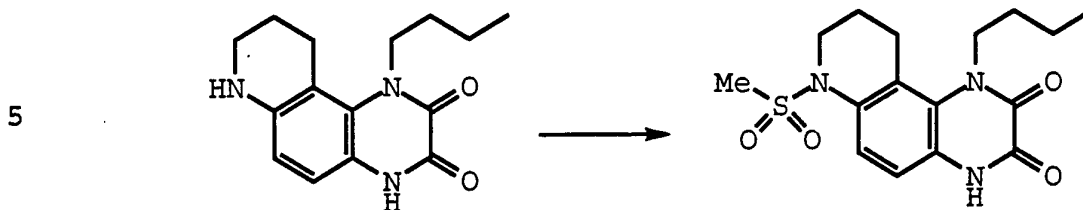


7-Acetyl-1-butyl-1,4,7,8,9,10-hexahydro-pyrido-
[3,2-f]quinoxaline-2,3-dione

The product from Example 89 (0.14 g, 0.5 mmol) was solubilized in a minimal amount of dimethylformamide and then treated with 2 mL dichloromethane, acetic anhydride (0.15 g) and triethylamine (0.15 g). After the mixture stirred at room temperature for 18 h, it was poured onto dichloromethane/water. The aqueous layer was washed with dichloromethane and the combined organic layers over sodium sulfate, filtered and evaporated to give a dark syrup. The syrup was purified by silica gel chromatography (ethyl acetate as eluant) to give the title compound (30 mg, 19% yield).

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EXAMPLE 91

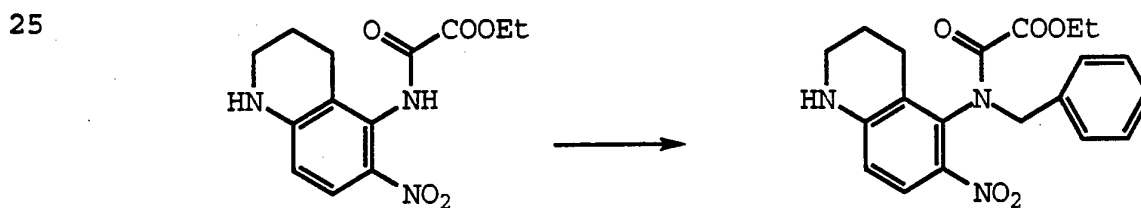


10 1-Butyl-1,4,7,8,9,10-hexahydro-7-methanesulfonyl-
pyrido[3,2-f]quinoxaline-2,3-dione

The product from Example 89 (0.12 g, 0.45 mmol) was solubilized in a minimal amount of dimethylformamide and then treated with 2 mL dichloromethane, methanesulfonyl chloride (0.17 g) and triethylamine (0.15 g). After stirring at room temperature for 4 h, the mixture was washed with water, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (4:1 heptane:ethyl acetate as eluant) to give the title compound (30 mg, 17% yield).

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EXAMPLE 92



Oxo[(phenylmethyl)(1,2,3,4-tetrahydro-6-nitro-
5-quinolinyl)aminolacetic acid ethyl ester

A mixture of the product from Example 87 (0.58 g, 2 mmol), benzylbromide (0.41 g, 2.4 mmol) and cesium carbonate (0.78 g, 2.4 mmol) in 10 mL of acetonitrile

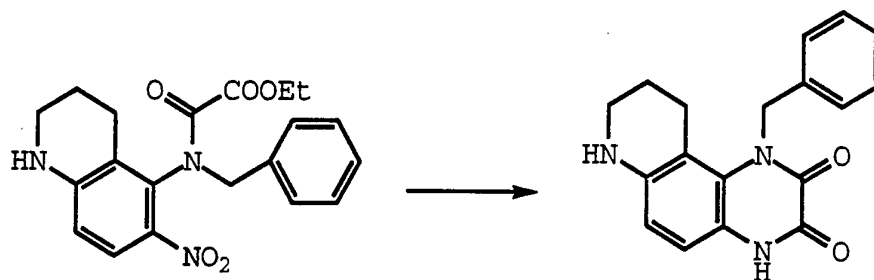
35

- 79 -

was stirred at room temperature for 2 hours. The triethylamine hydrobromide was removed by filtration and the filtrate evaporated. The residue was purified by silica gel chromatography (2:1 heptane:ethyl acetate as eluant) to give the title compound as a yellow solid (0.7 g, 91% yield).

EXAMPLE 93

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1,4,7,8,9,10-Hexahydro-(1-phenylmethyl)-pyrido-
[3,2-f]quinoxaline-2,3-dione

A solution of the product from Example 92 (0.67 g, 1.7 mmol) in 20 mL tetrahydrofuran was treated with Raney nickel (0.1 g) and stirred under a hydrogen atmosphere (1 atm) for 48 hours. The Raney nickel was removed with a magnet and washed with methanol. The remaining solid was collected by filtration, washed with methanol and then dissolved in 2 N HCl and filtered. The filtrate was neutralized with saturated sodium bicarbonate and the precipitate collected by filtration and dried to give the title compound (0.30 g, 57% yield) mp >300°C.

30

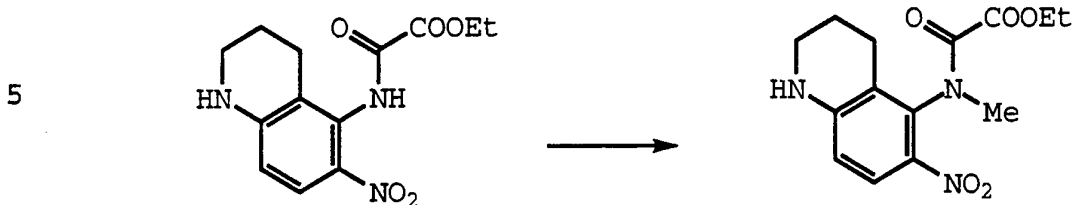
Analysis for $C_{18}H_{16}N_3O_2 \cdot 0.6 H_2O$:

Calc: C, 67.95; H, 5.77; N, 13.21.

Found: C, 67.68; H, 5.57; N, 13.11.

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EXAMPLE 94



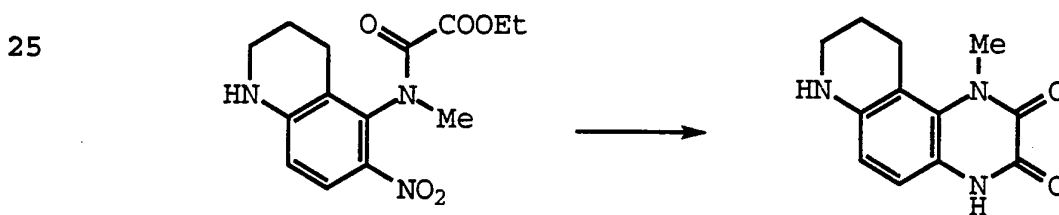
10 [Methyl(1,2,3,4-tetrahydro-6-nitro-5-quinolinyl)-
amino]oxo-acetic acid ethyl ester

A mixture of the product from Example 87 (0.87 g, 3 mmol), methyl iodide (0.51 g, 3.6 mmol) and cesium carbonate (1.17 g, 3.6 mmol) in 15 mL of acetonitrile was stirred at room temperature for 2 hours. The inorganic salts were removed by filtration and the filtrate evaporated. The residue was dissolved in methylene chloride, filtered and evaporated. The product was then used without further purification (0.86 g, 93% yield).

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EXAMPLE 95



30 1,4,7,8,9,10-Hexahydro-1-methyl-pyrido-
[3,2-f]-quinoxaline-2,3-dione

A solution of the product from Example 94 (1.1g) in 100 mL of acetic acid was treated with 20% Pd/C (0.3 g) and shaken on a Parr apparatus under a hydrogen atmosphere (50 psi) for 15.5 hours. After removing the

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catalyst by filtration through a celite pad, the filtrate was evaporated and the yellow solid was washed with diethyl ether and dried to give the title compound (0.55 g, 69% yield) mp >285°C.

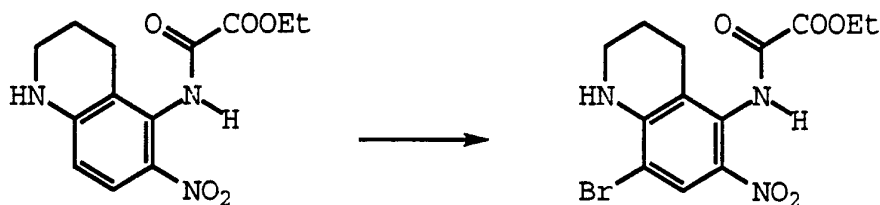
5 Analysis for $C_{12}H_{13}N_3O_2 \cdot 0.1 H_2O$:

Calc: C, 61.83; H, 5.71; N, 18.03.

Found: C, 61.44; H, 5.71; N, 18.01.

EXAMPLE 96

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[(8-Bromo-1,2,3,4-tetrahydro-6-nitro-5-quinolinyl)-amino]oxo-acetic acid ethyl ester

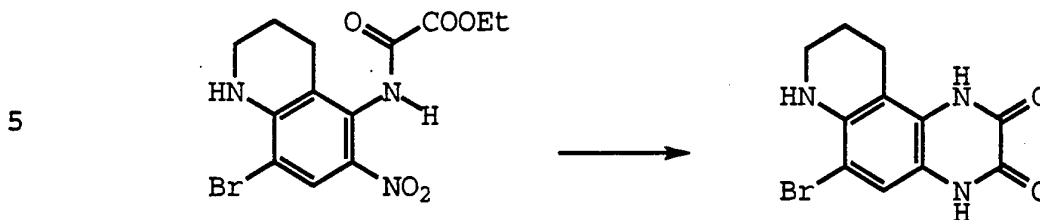
20

A mixture of the product from Example 87 (0.15 g, 0.5 mmol) and N-bromosuccinimide (0.23 g, 1 mmol) in 2 mL dimethylformamide was stirred at room temperature for 18 hours. The solution was poured onto methylene chloride/water and separated and the water layer back extracted with methylene chloride. The combined organic layers were washed with water, dried over sodium sulfate, filtered and evaporated. The residue was purified by silica gel chromatography (4:1 to 1:1 heptane:ethyl acetate as eluant) to give the title compound (0.15 g, 81% yield).

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EXAMPLE 97



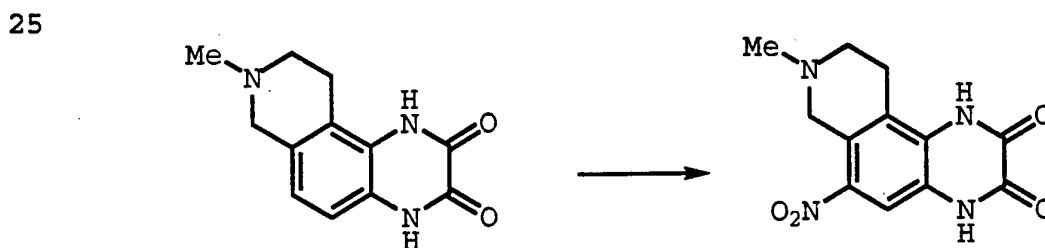
10 6-Bromo-1,4,7,8,9,10-hexahydro-pyrido[3,2-f]quinoxaline-2,3-dione

Raney nickel was washed with acetone (2 x) and then with tetrahydrofuran (2 x). A solution of the product from Example 96 (0.3 g, 0.8 mmol) in 30 mL tetrahydrofuran was added to the Raney nickel and was stirred at room temperature under a hydrogen atmosphere (1 atm) for 2 hours. The solution was decanted and filtered. The Raney nickel was washed with methanol and filtered and the combine filtrates were evaporated to give a yellow solid (0.1 g, 42% yield). HPLC analysis showed that 7% of the product was the debrominated quinoxalinedione.

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EXAMPLE 98



35 1,4,7,8,9,10-Hexahydro-8-methyl-6-nitro-pyrido[4,3-f]quinoxaline-2,3-dione methansulfonate

A solution of the product from Example 22 (1.07 g, 4.7 mmol) was dissolved in 20 ml sulfuric acid.

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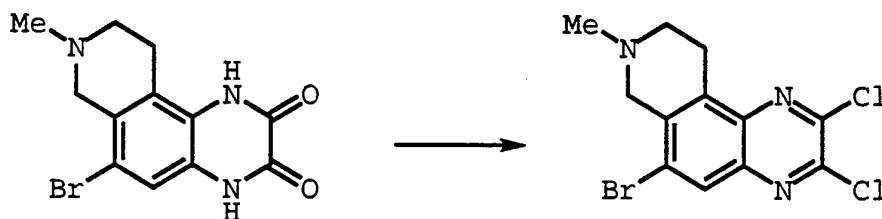
Potassium nitrate (0.51 g, 5.0 mmol) was added in one portion, and the solution stirred for 1 hour. The solution was poured onto ice and made basic with ammonium hydroxide. The yellow solid which formed was filtered and washed with water and ether. The solid was purified by crystallization from water. The solid was suspended in water/DMF and 0.5 g methane sulphonic acid was added. The solution was concentrated, and the solid suspended in acetone, filtered and dried under vacuum (100°C) to give the title compound (0.60 g, 35% yield), mp = 292-294°C.

Analysis for (C₁₃H₁₅N₃O₂·1.07 CH₃SO₃H·0.9 H₂O):

Calc: C, 41.04; H, 4.39; N, 14.65; Cl, 8.97.

Found: C, 41.02; H, 4.12; N, 14.25; Cl, 8.72.

EXAMPLE 99



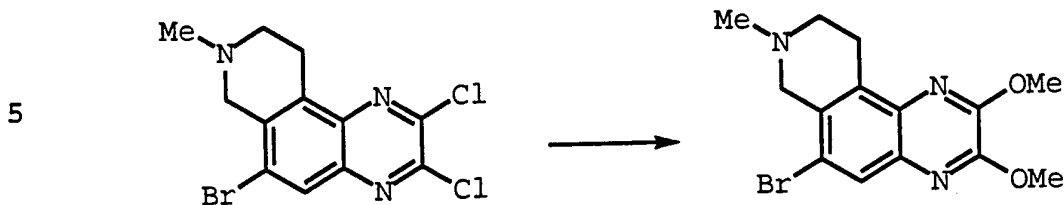
25 6-Bromo-2,3-dichloro-7,8,9,10-tetrahydro-8-methyl-
pyrido[4,3-f]quinoxaline

A solution of the product from Example 19 (5.00 g, 14.4 mmol) was suspended in 200 mL thionyl chloride and dimethyl formamide (10.0 mL) was added. The resulting suspension was heated at reflux for 48 hours. The reaction mixture was cooled and concentrated. The residue was broken up in ether and collected by filtration to give the title compound as a yellow solid (5.44 g, 98% yield).

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EXAMPLE 100



6-Bromo-7,8,9,10-tetrahydro-2,3-dimethoxy-8-methyl-
pyrido[4,3-f]quinoxaline

Sodium (2.85 g, 124 mmol) was dissolved in 200 mL of MeOH. The resulting solution was treated with the product from Example 99 (4.44 g, 11.6 mmol) and the resulting solution was stirred at room temperature for 18 hours. The reaction mixture was concentrated to approximately 1/2 volume and diluted with CHCl₃ (200 mL) and water (200 mL). The organic phase was collected and the aqueous phase was extracted with additional CHCl₃. The combined organic extracts were dried and concentrated. The residue was dissolved in hot acetonitrile, treated with activated charcoal and filtered. The solid which formed on cooling was collected and dried under vacuum to give the title compound as a white solid (2.12 g, 54% yield), mp = 162°C.

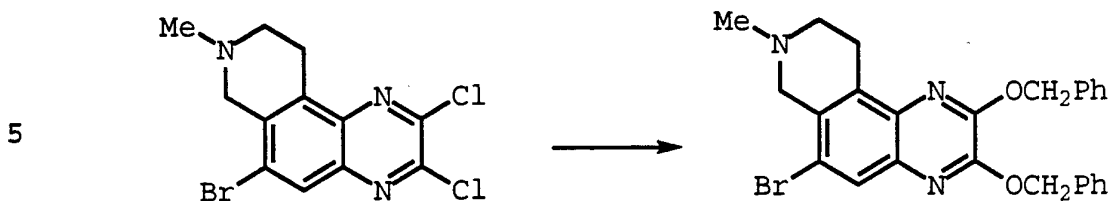
Analysis for C₁₄H₁₆BrN₃O₂:

Calc: C, 49.72; H, 4.77; N, 12.42.

Found: C, 49.54; H, 4.73; N, 12.38.

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EXAMPLE 101



10 6-Bromo-7,8,9,10-tetrahydro-8-methyl-
2,3-bis(phenylmethoxy)-pyrido[4,3-f]quinoxaline

Sodium hydride (15.0 g, 375 mmol) was suspended in
 500 mL of tetrahydrofuran and treated dropwise with
 benzyl alcohol (50 mL). When no further hydrogen
 15 evolution was observed the product from Example 99
 (14.97 g, 39.0 mmol) was added in portions and the
 resulting solution stirred at room temperature for
 48 hours. The reaction mixture was concentrated to
 approximately 100 mL volume and treated with CH_2Cl_2
 20 (250 mL) and water (250 mL). The organic phase was
 collected and the aqueous phase was extracted with
 additional CH_2Cl_2 (4x 200 mL). The combined organic
 extracts were dried and concentrated. The residue was
 placed under vacuum to remove the excess benzyl
 25 alcohol. The residue was purified by chromatography
 (SiO_2 , 1:1 ethyl acetate, CHCl_3) to give a yellow
 solid. The solid was dissolved in hot acetonitrile,
 treated with charcoal and filtered. The solid which
 formed on cooling was collected by suction filtration
 and dried under vacuum to give the title compound as a
 30 yellow solid (7.16 g, 37% yield), mp = 147°C.

Analysis for $\text{C}_{26}\text{H}_{24}\text{BrN}_3\text{O}_2$:

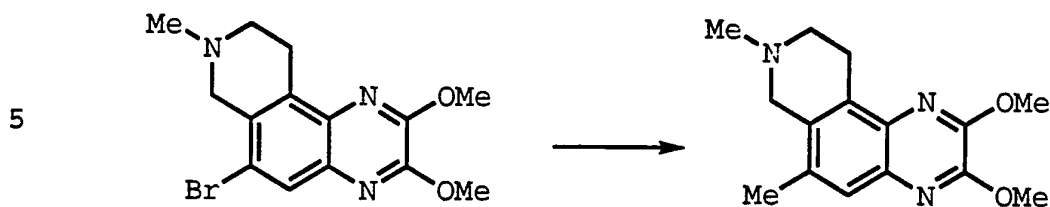
Calc: C, 63.68; H, 4.93; N, 8.57.

Found: C, 63.65; H, 4.92; N, 8.60.

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EXAMPLE 102

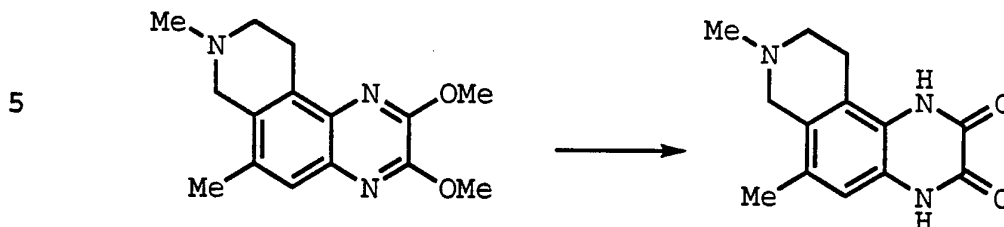


7,8,9,10-tetrahydro-2,3-dimethoxy-6,8-dimethyl-
pyrido[4,3-f]quinoxaline

A solution of the product from Example 100 (0.50 g, 1.48 mmol) in 20 mL of tetrahydrofuran was cooled to -78°C and treated dropwise with *sec*-BuLi (1.7 mL, 1.17 M in cyclohexane). The resulting green-black solution was stirred at -78°C for 30 minutes. The reaction mixture was treated with MeI (123 μL , 2.00 mmol) and the resulting solution stirred at -78°C for 30 minutes. The reaction mixture was warmed to room temperature and quenched with saturated aqueous NH_4Cl solution (2.0 mL). The reaction mixture was extracted with CHCl_3 (4x 20 mL) and the combined organic extracts were dried and concentrated. The residue was broken up in heptane and collected by suction filtration to give the title compound as a orange solid (0.196 g, 48% yield).

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EXAMPLE 103



10 1,4,7,8,9,10-Hexahydro-6,8-dimethyl-pyrido-
[4,3-f]quinoxaline-2,3-dione hydrochloride

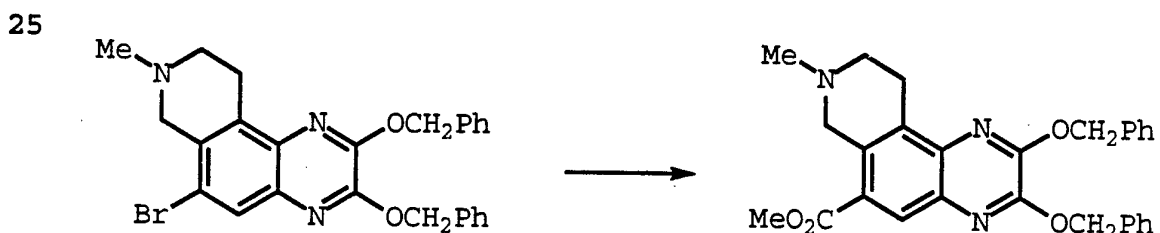
A solution of the product from Example 102
 (0.172 g, 0.63 mmol) in 4 mL of aqueous 3N HCl solution
 was heated at reflux for 2 hours. The hot solution was
 15 treated with charcoal and filtered. The filtrate was
 cooled to 5°C and the solid which formed was collected
 by filtration and dried at 90°C under vacuum to give
 the title compound as a white solid (83 mg, 43%
 yield), mp = 323-330°C.

20 Analysis for (C₁₃H₁₅N₃O₂·HCl·1.25 H₂O):

Calc: C, 51.32; H, 6.13; N, 13.81; Cl, 11.65.

Found: C, 51.41; H, 5.88; N, 13.58; Cl, 11.62.

EXAMPLE 104



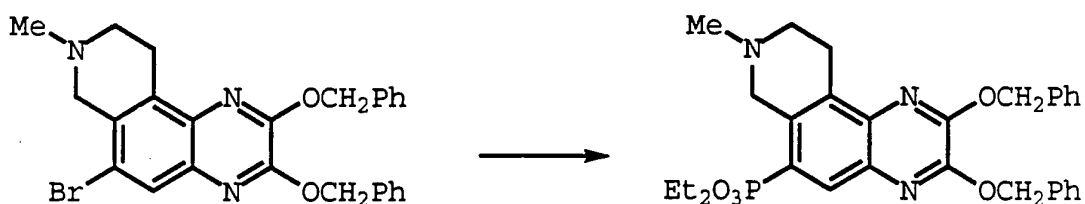
35 7,8,9,10-Tetrahydro-8-methyl-2,3-bis(phenylmethoxy)-
pyrido[4,3-f]quinoxaline carboxylic acid methyl ester

A suspension of the product from Example 100
 (2.40 g, 5.19 mmol) was placed in a pressure reactor

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and acetonitrile (75 mL), methanol (5.0 g), triethylamine (1.5 g), and bis(triphenylphosphine)-palladium dichloride (0.5 g) was added. The reactor was sealed and charged to 820 psi with carbon monoxide and heated to 100°C for 63 hours. The reaction vessel was cooled to room temperature and the contents dissolved in CHCl₃ and washed with saturated aqueous NaHCO₃ solution. The organic phase was separated and the aqueous phase washed with additional CHCl₃. The combined organic extracts were dried and concentrated. The residue was suspended in acetonitrile and collected by filtration. The solid was dried under vacuum to give the title compound as a yellow solid (1.17 g, 48% yield) mp = 167-168°C.

EXAMPLE 105



7,8,9,10-Tetrahydro-8-methyl-2,3-bis(phenylmethoxy)-pyrido[4,3-f]quinoxalin-6-yl phosphonic acid diethyl ester

A solution of the product from Example 100 (1.83 g, 3.73 mmol) was dissolved in dry toluene and treated with diethylphosphite (0.72 mL, 5.59 mmol), triethylamine (1.56 mL, 11.2 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.44 g, 0.37 mmol). The resulting solution was heated to reflux under a nitrogen atmosphere for 48 hours. The reaction mixture was concentrated and the residue was dissolved in CHCl₃ and washed with saturated aqueous NaHCO₃ solution.

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The organic phase was dried, filtered and concentrated. The residue was purified by chromatography (SiO₂, gradient elution EtOAc then 5:1 EtOAc/EtOH). The material obtained was dissolved in hot iPr₂O, filtered and concentrated. The residue was then broken up in a small amount of iPr₂O and the solid collected by filtration and dried under vacuum to give the title compound as a yellow solid (0.74 g, 36% yield), mp = 104°C. The filtrates were concentrated to give an additional 0.77 g of the title compound.

Analysis for C₃₀H₃₄N₃O₅P:

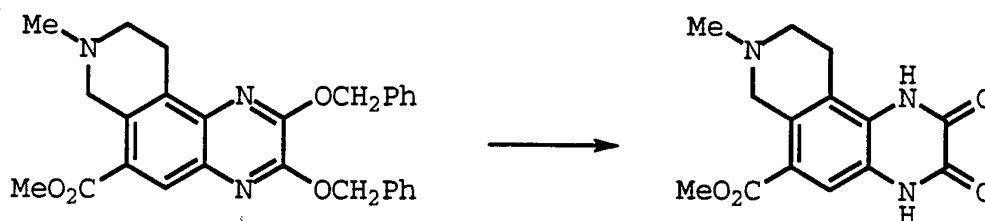
Calc: C, 65.80; H, 6.26; N, 7.27.

Found: C, 65.38; H, 6.33; N, 7.62.

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EXAMPLE 106

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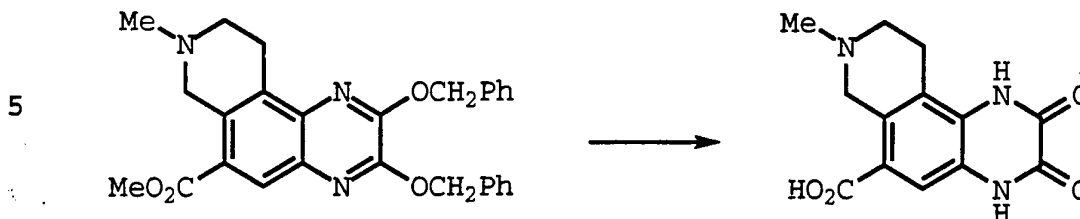
1,2,3,4,8,9,10-Octahydro-8-methyl-2,3-dioxo-
pyrido[4,3-f]quinoxaline-6-carboxylic acid methyl ester

30

A solution of the product from Example 104 (0.10 g, 0.21 mmol) in 75 mL acetic acid was hydrogenated at 52 psi over 20% Pd/C (0.1 g). The reaction mixture was filtered and concentrated. The residue was broken up in ether and collected by filtration to give the title compound as a white solid (42 mg, 69% yield), mp = 290-300°C (dec.).

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EXAMPLE 107



10 1,2,3,4,8,9,10-Octahydro-8-methyl-2,3-dioxo-pyrido-
[4,3-f]quinoxaline-6-carboxylic acid hydrochloride

A suspension of the product from Example 104
 (0.20 g, 0.73 mmol) in 5 mL of aqueous 3N HCl solution
 was heated at reflux for 24 hours. The reaction
 15 mixture was cooled and the solid collected by
 filtration. The solid obtained was crystallized from
 hot water and collected. The solid was dissolved in
 aqueous 1N NaOH (1.0 mL) and stirred for 24 hours at
 room temperature. The reaction was treated with 0.5 mL
 20 aqueous 3N HCl and the solid which formed was collected
 by filtration, washed with cold water and dried under
 vacuum to give the title compound as a white solid
 (51 mg) mp >325°C.

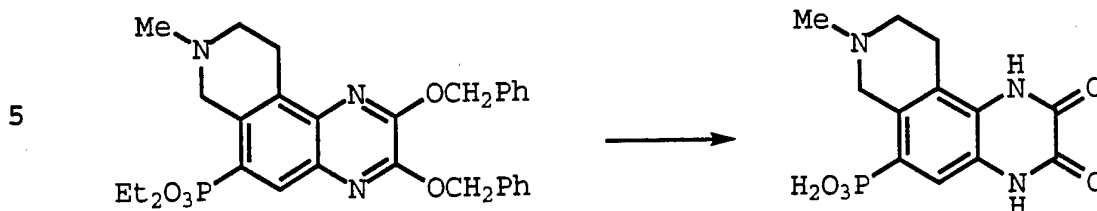
Analysis for $C_{13}H_{13}N_3O_4 \cdot HCl$:

25 Calc: C, 50.09; H, 4.53; N, 13.48.

Found: C, 49.50; H, 4.72; N, 13.31.

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EXAMPLE 108

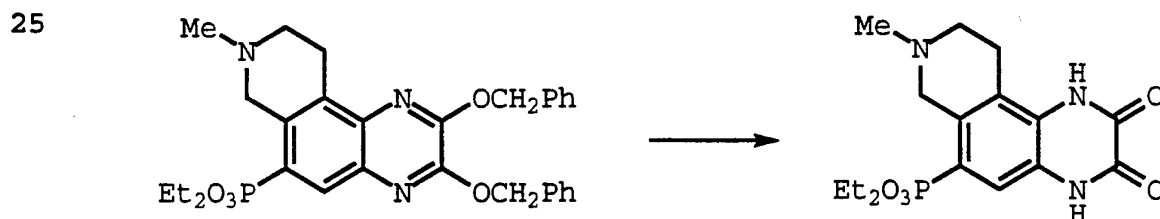


10 1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxo-
pyrido[4,3-f]quinoxalin-6-yl phosphonic acid

A solution of the product from Example 105 (0.70 g, 1.28 mmol) in 30 mL of aqueous 6N HCl was heated at reflux for 24 hours. The reaction mixture was cooled to room temperature and washed with ether. The aqueous phase was heated to 50°C and treated with charcoal, filtered and concentrated. The residue was crystallized from hot water. The solid which formed was collected by filtration and dried under vacuum to give the title compound as a tan solid (56 mg) mp >325°C.

15
20

EXAMPLE 109



1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxo-
pyrido[4,3-f]quinoxalin-6-yl phosphonic acid diethyl
ester

35 A solution of the compound from Example 105 (0.34 g, 0.65 mmol) was dissolved in 60 mL of acetic

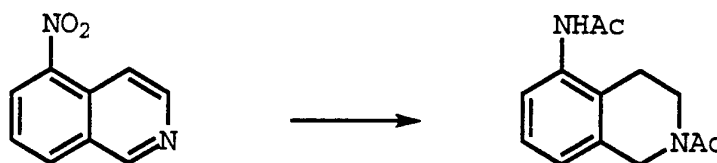
-92-

acid and hydrogenated at 52 psi over 20% Pd/C. The reaction mixture was filtered and concentrated. The residue was dissolved in EtOH (3 mL) and concentrated. This procedure was repeated several times. The residue
5 was then dissolved in EtOH and triturated with ethyl acetate. The solid which formed was collected by suction filtration and dried under vacuum to give the title compound as a yellow solid (0.20 g, 83% yield) mp = 310-330°C (dec).

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EXAMPLE 110

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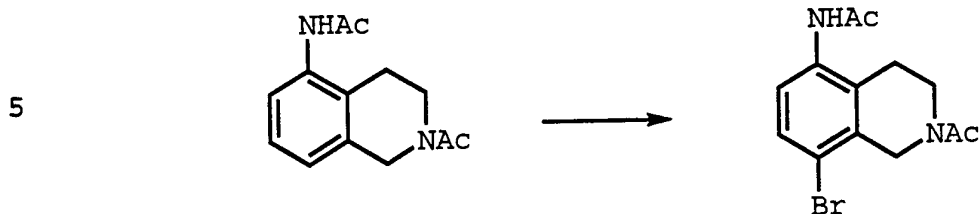
N-(2-acetyl-1,2,3,4-tetrahydro-5-isoquinolinyl)-acetamide

A solution of 5-nitroisoquinoline (44.8 g, 0.257 mol) in 600 mL of acetic acid and 50 mL acetic anhydride was hydrogenated at 62 psi over PtO₂ (0.5 g).
25 The reaction mixture was filtered and concentrated. The residue was purified by chromatography (SiO₂, 10:1 EtOAc/EtOH) to give the title compound as a white solid (11.25 g, 19% yield). An analytical was obtained by crystallization from THF/iPr₂O, mp = 154-156°C.

30

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EXAMPLE 111



10 N-(2-acetyl-8-bromo-1,2,3,4-tetrahydro-5-isoquinolinyl)acetamide

A solution of the product from Example 110 (6.67 g, 28.7 mmol) in trifluoroacetic acid (200 mL) was treated with 30 mL of a 1M solution of bromine in acetic acid and the resulting solution was stirred at room temperature for 24 hours. The reaction mixture was concentrated and the residue was partitioned between CHCl_3 and saturated aqueous NaHCO_3 . The organic phase was collected, dried over K_2CO_3 , filtered and concentrated. The residue was flushed through a plug of silica gel eluting with 4.5:4.5:1 EtOAc/EtOH/ NH_4OH and concentrated to give the title compound as a pale pink solid (3.00 g, 34% yield). An analytical was obtained by crystallization from THF/ $i\text{Pr}_2\text{O}$, mp = 192-193°C.

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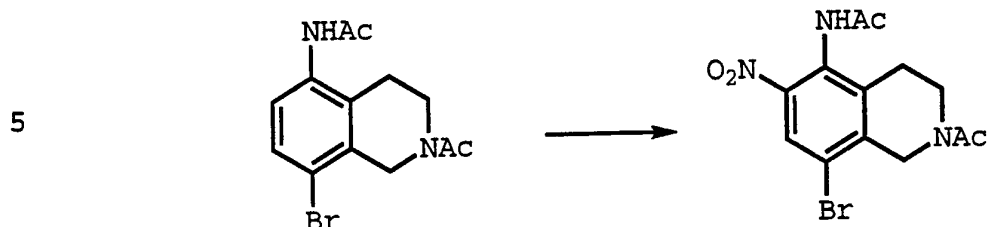
Analysis for $\text{C}_{13}\text{H}_{15}\text{BrN}_2\text{O}_2$:

Calc: C, 50.18; H, 4.86; N, 9.00.

Found: C, 50.29; H, 4.99; N, 8.83.

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EXAMPLE 112



10 N-(2-acetyl-8-bromo-1,2,3,4-tetrahydro-6-nitro-
5-isoquinolinyl)acetamide

A solution of the product from Example 111 (1.00 g, 3.21 mmol) in 20 mL of trifluoroacetic acid was treated with 4 mL of fuming nitric acid dropwise with stirring. The resulting solution was stirred at room temperature for 24 hours. The reaction mixture was concentrated and the residue was dissolved in CHCl₃ and washed with saturated aqueous NaHCO₃ solution. The organic phase was dried and concentrated to give the title compound as a tan solid (0.774g, 68% yield). An analytical was obtained by crystallization from ethyl acetate, mp = 171°C.

15

20

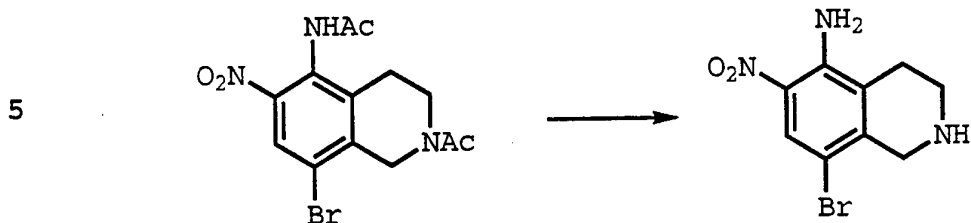
Analysis for C₁₃H₁₄BrN₃O₄:

Calc: C, 43.83; H, 3.96; N, 11.79.

25 Found: C, 43.96; H, 3.96; N, 11.91.

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EXAMPLE 113

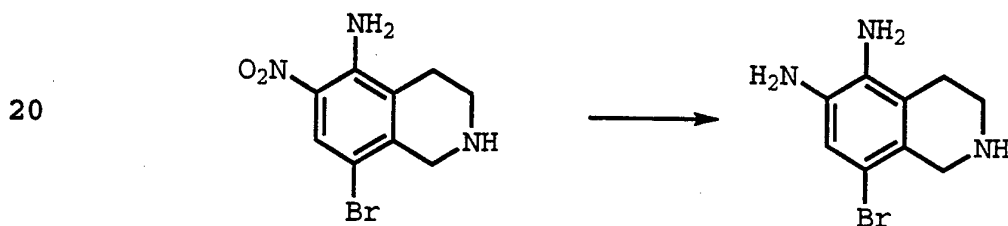


10 8-Bromo-1,2,3,4-tetrahydro-6-nitro-5-isoquinolinamine

A solution of the product from Example 112 is heated in aqueous 3N HCl until no starting material remains. The reaction mixture is concentrated to give the title compound.

15

EXAMPLE 114

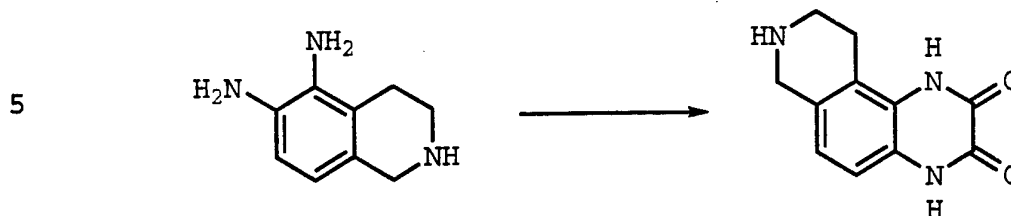


25 8-Bromo-1,2,3,4-tetrahydro-5,6-isoquinolindiamine

The product from Example 113 is converted to the title compound by the procedure described in Example 13.

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EXAMPLE 117

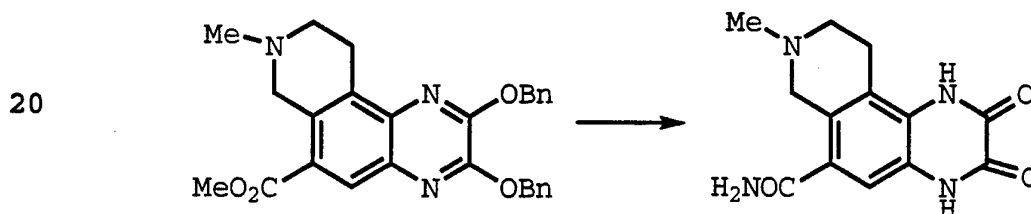


10 1,4,7,8,9,10-Hexahydropyrido[4,3-f]quinoxaline-2,3-dione

The product from Example 115 is converted to the title compound by the procedure described in Example 19.

15

EXAMPLE 118



25 1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxopyrido[4,3-f]quinoxalin-6-carboxamide

The product from Example 104 is dissolved in toluene and treated dropwise with a solution of trimethylaluminum and ammonium hydrochloride in toluene. The product obtained is hydrolyzed in 3N HCl solution to give the title compound.

30

In a similar manner are prepared:

1,2,3,4,7,8,9,10-Octahydro-N,N,8-trimethyl-2,3-dioxopyrido[4,3-f]quinoxalin-6-carboxamide;

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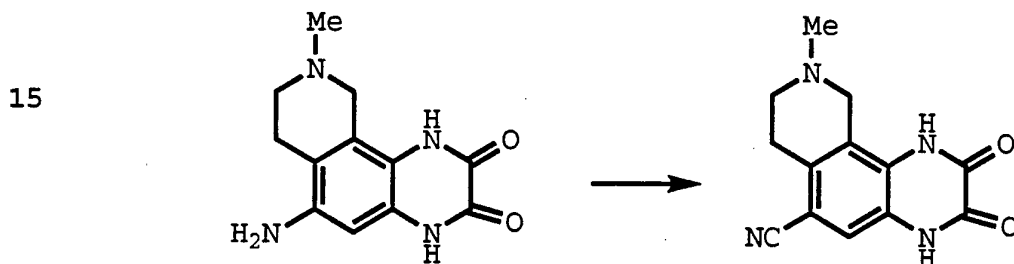
1-[(1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxalin-6-yl) carbonyl pyrrolidine;

1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxo-
5 pyrido[3,4-f]quinoxalin-6-carboxamide;

1,2,3,4,7,8,9,10-Octahydro-N,N,9-trimethyl-2,3-dioxypyrido[3,4-f]quinoxalin-6-carboxamide; and

1-[(1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxypyrido[3,4-f]quinoxalin-6-yl) carbonyl
10 pyrrolidine.

EXAMPLE 119



20

1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxo-
pyrido[3,4-f]quinoxaline-6-carbonitrile

The product from Example 79 is treated with sodium nitrite in 37% HCl solution at 0°C. The reaction
25 mixture is poured into a solution of CuCN and the title compound is isolated by filtration.

In a similar manner is prepared:

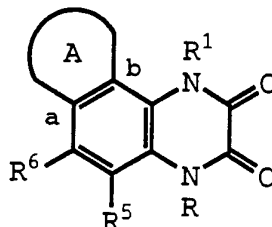
1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxo-
pyrido[4,3-f]quinoxaline-6-carbonitrile.

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CLAIMS

1. A compound having the formula

5



10

or a pharmaceutically acceptable salt thereof
wherein

R is hydrogen or hydroxy;

R¹ is hydrogen,

alkyl,

arylalkyl,

15

(CH₂)_nOH, or

(CH₂)_nNR⁷R⁸;

R⁵ and R⁶ are each independently

hydrogen,

halogen,

20

NO₂,

CN,

CF₃

SO₂NR⁷R⁸,

PO₃R⁹R¹⁰,

25

alkyl,

alkenyl,

alkynyl,

(CH₂)_nCONR⁷R⁸,

(CH₂)_nCO₂R¹⁰,

30

NHCOR¹¹,

wherein R⁷ and R⁸ are each independently hydrogen
or alkyl or together R⁷ and R⁸ form a ring of from
three to seven atoms,

R⁹ is hydrogen or alkyl,

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35 R^{10} is hydrogen or alkyl,
 R^{11} is hydrogen or alkyl, and
 n is an integer of from zero to four;

40 A is a ring of five to seven atoms fused with the
benzo ring at the positions marked a and b, and
formed by the following bivalent radicals:

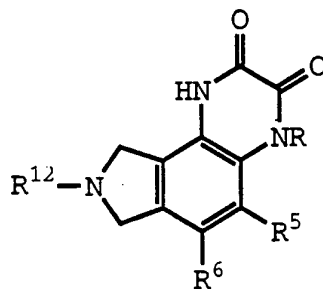
a- NR^{12} - CHR^{13} - CHR^{14} -b,
a- CHR^{13} - CHR^{14} - NR^{12} -b,
a- CHR^{13} - NR^{12} - CHR^{14} -b,
45 a- CHR^{14} - CH_2 - NR^{12} - CHR^{13} -b,
a- CHR^{13} - NR^{12} - CH_2 - CHR^{14} -b,
a- CH_2 - CH_2 - CHR^{13} - NR^{12} -b,
a- NR^{12} - CHR^{13} - CH_2 - CH_2 -b,
a- CH_2 - CH_2 - NR^{12} - CH_2 - CH_2 -b,
50 a- CH_2 - CH_2 - CH_2 - NR^{12} - CH_2 -b,
a- CH_2 - NR^{12} - CH_2 - CH_2 - CH_2 -b,
a- CH_2 - CH_2 - CH_2 - CH_2 - NR^{12} -b,
a- NR^{12} - CH_2 - CH_2 - CH_2 - CH_2 -b,

wherein

55 R^{12} is hydrogen, CH_2CH_2OH , or alkyl, and R^{13}
and R^{14} are each independently hydrogen, CN,
 $CONH_2$, CH_2NH_2 , CH_2OH , alkyl, arylalkyl,
alkenyl, or CO_2R^{15} , wherein R^{15} is hydrogen or
alkyl;

2. A compound of Claim 1 having the formula

5



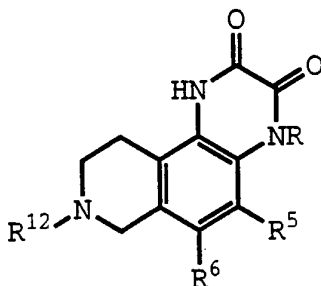
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wherein R, R¹², R⁵, and R⁶ have the meanings set forth in Claim 1.

3. A compound of Claim 1 having the formula

5

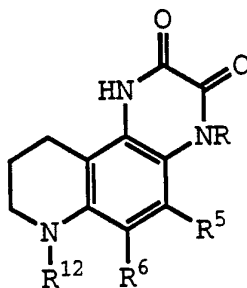


10

wherein R, R¹², R⁵, and R⁶ have the meanings set forth in Claim 1.

4. A compound of Claim 1 having the formula

5

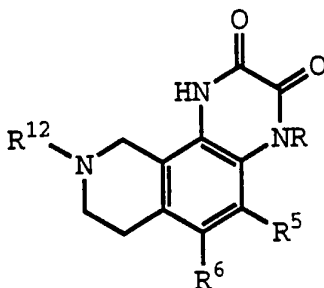


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wherein R, R¹², R⁵, and R⁶ have the meanings set forth in Claim 1.

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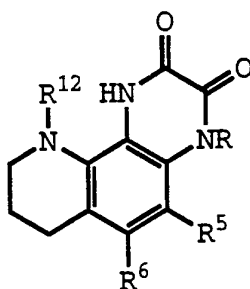
5. A compound of Claim 1 having the formula



10

wherein R, R¹², R⁵, and R⁶ have the meanings set forth in Claim 1.

6. A compound of Claim 1 having the formula



10

wherein R, R¹², R⁵, and R⁶ have the meanings set forth in Claim 1.

7. A compound of Claim 1 wherein R⁵ and R⁶ independently are hydrogen, halogen, SO₂NR⁷R⁸ wherein R⁷ and R⁸ independently are hydrogen or C₁₋₃-alkyl which may be straight or branched or cyclic, NO₂, or CN and wherein R¹² is C₁₋₃-alkyl which may be straight or branched or cyclic.

5

8. A compound of Claim 2 wherein R⁵ and R⁶ independently are hydrogen, halogen, SO₂NR⁷R⁸ wherein R⁷ and R⁸ independently are hydrogen or

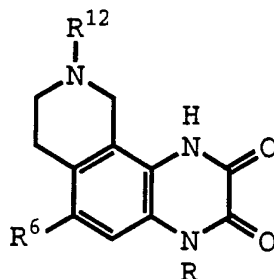
-103-

- 5 C₁₋₃-alkyl which may be straight or branched or cyclic, NO₂, or CN and wherein R¹² is C₁₋₃-alkyl which may be straight or branched or cyclic.
9. A compound of Claim 3 wherein R⁵ and R⁶ independently are hydrogen, halogen, SO₂NR⁷R⁸ wherein R⁷ and R⁸ independently are hydrogen or C₁₋₃-alkyl which may be straight or branched or cyclic, NO₂, or CN and wherein R¹² is C₁₋₃-alkyl which may be straight or branched or cyclic.
- 5 10. A compound of Claim 4 wherein R⁵ and R⁶ independently are hydrogen, halogen, SO₂NR⁷R⁸ wherein R⁷ and R⁸ independently are hydrogen or C₁₋₃-alkyl which may be straight or branched or cyclic, NO₂, or CN and wherein R¹² is C₁₋₃-alkyl which may be straight or branched or cyclic.
- 5 11. A compound of Claim 4 wherein R⁵ and R⁶ independently are hydrogen, halogen, SO₂NR⁷R⁸ wherein R⁷ and R⁸ independently are hydrogen or C₁₋₃-alkyl which may be straight or branched or cyclic, NO₂, or CN and wherein R¹² is C₁₋₃-alkyl which may be straight or branched or cyclic.
- 5 12. A compound of Claim 6 wherein R⁵ and R⁶ independently are hydrogen, halogen, SO₂NR⁷R⁸ wherein R⁷ and R⁸ independently are hydrogen or C₁₋₃-alkyl which may be straight or branched or cyclic, NO₂, or CN and wherein R¹² is C₁₋₃-alkyl which may be straight or branched or cyclic.

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

13. A compound according to Claim 1 of formula

5



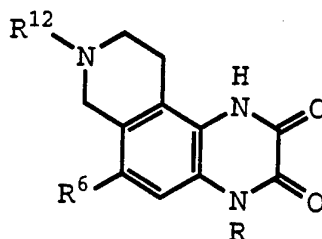
10

wherein R^{12} is hydrogen, methyl, or ethyl and R^6

is NO_2 , SO_2NMe_2 , $\text{SO}_2\text{-N}$  , or SO_2N  .



14. A compound according to Claim 1 of formula

5



10

wherein R^{12} is hydrogen, methyl, or ethyl and R^6

is NO_2 , SO_2NMe_2 , $\text{SO}_2\text{-N}$  , or SO_2N  .

15

15. A method of treating disorders of a mammal, including a human, responsive to the blockade of glutamic and aspartic acid receptors, which comprises administering to a patient in need

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- 5 thereof an effective amount of a compound of
Claim 1 in unit dosage form.
16. A method of Claim 15 wherein cerebrovascular
disorders are treated.
17. A pharmaceutical composition comprising a thera-
peutically effective amount of a compound of
Claim 1 together with a pharmaceutically
acceptable carrier.
18. A method of treating Parkinsonism in a mammal
suffering therefrom which comprises administering
a composition according to Claim 15.
19. A compound according to Claim 1 selected from:
 8-ethyl-1,4,7,8,9,10-hexahydropyrido[4,3-f]-
 quinoxaline-2,3-dione, monohydrochloride;
 1,4,7,8,9,10-hexahydro-8-propylpyrido[4,3-f]-
5 quinoxaline-2,3-dione, monohydrochloride;
 1,4,7,8,9,10-hexahydro-7-methylpyrido[3,2-f]-
 quinoxaline-2,3-dione;
 6-bromo-1,4,7,8,9,10-hexahydro-8-methyl-
 pyrido[4,3-f]quinoxaline-2,3-dione, monohydro-
10 chloride;
 6-bromo-1,4,7,8,9,10-hexahydro-8-propyl-
 pyrido[4,3-f]quinoxaline-2,3-dione, monohydro-
 chloride;
 1,4,7,8,9,10-hexahydro-8-methylpyrido[4,3-f]-
15 quinoxaline-2,3-dione, monohydrochloride; and
 6-bromo-8-ethyl-1,4,7,8,9,10-hexahydro-
 pyrido[4,3-f]quinoxaline-2,3-dione, monohydro-
 chloride.

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20. A compound according to Claim 1 named
- 6-bromo-1,7,8,9-tetrahydro-8-methyl-
2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione;
- 6-chloro-1,7,8,9-tetrahydro-8-methyl-
5 2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione;
- 6-bromo-8-(1,1-dimethylethyl)-
1,7,8,9-tetrahydro-2H-pyrrolo[3,4-f]quinoxaline-
2,3(4H)-dione;
- 2,3,4,7,8,9-hexahydro-8-methyl-2,3-dioxo-1H-
10 pyrrolo[3,4-f]quinoxaline-6-sulfonamide;
- 6-bromo-1,7,8,9-tetrahydro-4-hydroxy-
8-methyl-2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-
dione;
- 1,7,8,9-tetrahydro-4-hydroxy-8-methyl-
15 2H-pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione;
- 1,7,8,9-tetrahydro-8-methyl-6-nitro-2H-
pyrrolo[3,4-f]quinoxaline-2,3(4H)-dione;
- 2,3,4,7,8,9-hexahydro-N,N,8-trimethyl-
2,3-dioxo-1H-pyrrolo[3,4-f]quinoxaline-
20 6-sulfonamide;
- 4-[(2,3,4,7,8,9-hexahydro-8-methyl-2,3-dioxo-
1H-pyrrolo[3,4-f]quinoxalin-6-yl)sulfonyl]-
morpholine;
- 1-[(2,3,4,7,8,9-hexahydro-8-methyl-2,3-dioxo-
25 1H-pyrrolo[3,4-f]quinoxalin-6-yl)sulfonyl]-
pyrrolidine;
- 1,4,7,8,9,10-hexahydropyrido[3,2-f]-
quinoxaline-2,3-dione;
- 1,4,7,8,9,10-hexahydro-7-methyl-
30 pyrido[3,2-f]quinoxaline-2,3-dione;
- Ethyl 1,2,3,4,9,10-hexahydro- α ,2,3-trioxo-
pyrido[3,2-f]quinoxaline-7(8H)-acetate;
- 1,4,7,8,9,10-hexahydro-9-methylpyrido[3,4-f]-
quinoxaline-2,3-dione;
- 35 9-ethyl-1,4,7,8,9,10-hexahydropyrido[3,4-f]-
quinoxaline-2,3-dione;

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- 6-bromo-9-ethyl-1,4,7,8,9,10-hexahydro-pyrido[3,4-f]quinoxaline-2,3-dione;
- 40 6-bromo-1,4,7,8,9,10-hexahydro-9-methyl-pyrido[3,4-f]quinoxaline-2,3-dione;
- 1,2,3,4,7,8,9,10-octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxaline-6-propanoic acid;
- 45 1,2,3,4,7,8,9,10-octahydro-N,N,8-trimethyl-2,3-dioxypyrido[4,3-f]quinoxaline-6-sulfonamide;
- 1-[(1,2,3,4,7,8,9,10-octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxalin-6-yl)sulfonyl]-pyrrolidine;
- 50 1,2,3,4,7,8,9,10-octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxaline-6-sulfonamide;
- 8-ethyl-1,2,3,4,7,8,9,10-octahydro-N,N-dimethyl-2,3-dioxypyrido[4,3-f]quinoxaline-6-sulfonamide;
- 55 1-[(8-ethyl-1,2,3,4,7,8,9,10-octahydro-2,3-dioxypyrido[4,3-f]quinoxalin-6-yl)sulfonyl]-pyrrolidine;
- 1,2,3,4,7,8,9,10-octahydro-N,N,9-trimethyl-2,3-dioxypyrido[3,4-f]quinoxaline-6-sulfonamide;
- 60 1-[(1,2,3,4,7,8,9,10-octahydro-9-methyl-2,3-dioxypyrido[3,4-f]quinoxalin-6-yl)sulfonyl]-pyrrolidine;
- 1,2,3,4,7,8,9,10-octahydro-9-methyl-2,3-dioxypyrido[3,4-f]quinoxaline-6-sulfonamide;
- 65 9-ethyl-1,2,3,4,7,8,9,10-octahydro-N,N-dimethyl-2,3-dioxypyrido[3,4-f]quinoxaline-6-sulfonamide;
- 9-Ethyl-1,4,7,8,9,10-hexahydro-6-nitropyrido[3,4-f]quinoxaline-2,3-dione;
- 70 9-Ethyl-1,4,7,8,9,10-hexahydro-6-nitropyrido[3,4-f]quinoxaline-2,3-dione methanesulfonate;

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- 6-Bromo-1,4,7,8,9,10-hexahydro-9-methyl-pyrido[3,4-f]quinoxaline-2,3-dione methansulfonate;
- 75 1,4,7,8,9,10-Hexahydro-9-methyl-pyrido[3,4-f]quinoxaline-2,3-dione monohydrochloride;
- 1,4,7,8,9,10-Hexahydro-9-methyl-6-nitro-pyrido[3,4-f]quinoxaline-2,3-dione methansulfonate;
- 80 6-Amino-1,4,7,8,9,10-hexahydro-9-methyl-pyrido[3,4-f]quinoxaline-2,3-dione;
- N-(1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxypyrido[3,4-f]quinoxalin-6-yl) acetamide;
- 85 1,4,7,8,9,10-Hexahydro-pyrido[2,3-f]quinoxaline-2,3-dione;
- 1-Butyl-1,4,7,8,9,10-hexahydro-pyrido[3,2-f]quinoxaline-2,3-dione;
- 7-Acetyl-1-butyl-1,4,7,8,9,10-hexahydro-pyrido[3,2-f]quinoxaline-2,3-dione;
- 90 1-Butyl-1,4,7,8,9,10-hexahydro-7-methanesulfonyl-pyrido[3,2-f]quinoxaline-2,3-dione;
- 1,4,7,8,9,10-Hexahydro-(1phenylmethyl)-pyrido[3,2-f]quinoxaline-2,3-dione;
- 1,2,4,7,8,9,10-Hexahydro-1-methyl-pyrido[3,2-f]quinoxaline-2,3-dione;
- 95 6-Bromo-1,4,7,8,9,10-hexahydro-pyrido[3,2-f]quinoxaline-2,3-dione;
- 1,4,7,8,9,10-Hexahydro-8-methyl-6-nitro-pyrido[4,3-f]quinoxaline-2,3-dione methansulfonate;
- 100 1,4,7,8,9,10-Hexahydro-6,8-dimethyl-pyrido[4,3-f]quinoxaline-2,3-dione hydrochloride;
- 1,2,3,4,8,9,10-Octahydro-8-methyl-2,3-dioxo-pyrido[4,3-f]quinoxaline-6-carboxylic acid methyl ester;
- 105 1,2,3,4,8,9,10-Octahydro-8-methyl-2,3-dioxo-pyrido[4,3-f]quinoxaline-6-carboxylic acid;

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- 110 7,8,9,10-Tetrahydro-8-methyl-2,3-bis(phenyl-methoxy)pyrido[4,3-f]quinoxalin-6-yl phosphonic acid;
- 1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxalin-6-yl phosphonic acid;
- 115 1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxalin-6-yl phosphonic acid diethyl ester;
- 6-Bromo-1,4,7,8,9,10-Hexahydropyrido-[4,3-f]quinoxaline-2,3-dione;
- 1,4,7,8,9,10-Hexahydropyrido-
- 120 [4,3-f]quinoxaline-2,3-dione;
- 1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxalin-6-carboxamide;
- 1,2,3,4,7,8,9,10-Octahydro-N,N,8-trimethyl-2,3-dioxypyrido[4,3-f]quinoxalin-6-carboxamide;
- 125 1-[(1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxalin-6-yl carbonyl pyrrolidine;
- 1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxypyrido[3,4-f]quinoxalin-6-carboxamide;
- 130 1,2,3,4,7,8,9,10-Octahydro-N,N,9-trimethyl-2,3-dioxypyrido[3,4-f]quinoxalin-6-carboxamide;
- 1-[(1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxypyrido[3,4-f]quinoxalin-6-yl carbonyl pyrrolidine;
- 135 1,2,3,4,7,8,9,10-Octahydro-9-methyl-2,3-dioxypyrido[3,4-f]quinoxaline-6-carbonitrile;
- 1,2,3,4,7,8,9,10-Octahydro-8-methyl-2,3-dioxypyrido[4,3-f]quinoxaline-6-carbonitrile;
- 6-Bromo-1,4,7,8,9,10-hexahydro-4-hydroxy-
- 140 8-methylpyrido[4,3-f]quinoxaline-2,3-dione;
- 6-Bromo-1,4,7,8,9,10-hexahydro-4-hydroxy-9-methylpyrido[3,4-f]quinoxaline-2,3-dione;

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1,4,7,8,9,10-hexahydro-4-hydroxy-8-methyl-
pyrido[4,3-f]quinoxaline-2,3-dione; and

145 1,4,7,8,9,10-hexahydro-4-hydroxy-9-methyl-
pyrido[3,4-f]quinoxaline-2,3-dione.

21. A compound selected from

N-(8-bromo-1,2,3,4-tetrahydro-2-methyl-
6-nitro-5-isoquinolinyl)acetamide;

5 N-(8-bromo-2-ethyl-1,2,3,4-tetrahydro-
6-nitro-5-isoquinolinyl)acetamide;

N-(8-bromo-1,2,3,4-tetrahydro-6-nitro-
2-propyl-5-isoquinolinyl)acetamide;

8-Bromo-1,2,3,4-tetrahydro-2-methyl-6-nitro-
5-isoquinolinamine;

10 8-Bromo-2-ethyl-1,2,3,4-tetrahydro-6-nitro-
5-isoquinolinamine;

8-Bromo-1,2,3,4-tetrahydro-6-nitro-2-propyl-
5-isoquinolinamine;

15 8-Bromo-1,2,3,4-tetrahydro-2-methyl-
5,6-isoquinolinediamine;

8-Bromo-2-ethyl-1,2,3,4-tetrahydro-
5,6-isoquinolinediamine;

8-Bromo-1,2,3,4-tetrahydro-2-propyl-
5,6-isoquinolinediamine;

20 1,2,3,4-Tetrahydro-2-methyl-5,6-isoquinoline-
diamine;

2-Ethyl-1,2,3,4-tetrahydro-5,6-isoquinoline-
diamine;

25 1,2,3,4-Tetrahydro-2-propyl-5,6-isoquinoline-
diamine;

5-Bromo-1,2,3,4-tetrahydro-2-methyl-
8-nitroisoquinoline;

5-Bromo-1,2,3,4-tetrahydro-2-methyl-
8-nitroisoquinoline;

30 5-Bromo-1,2,3,4-tetrahydro-
8-nitroisoquinoline;

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- N- (7-bromo-2,3-dihydro-2-methyl-1H-isoindol-4-yl) acetamide;
- 35 N- [7-bromo-2- (1,1-dimethylethyl) -2,3-dihydro-1H-isoindol-4-yl] acetamide;
- N- (7-chloro-2,3-dihydro-2-methyl-1H-isoindol-4-yl) acetamide;
- N- (7-chloro-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-yl) acetamide;
- 40 N- (7-bromo-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-yl) acetamide;
- N- (7-bromo-2,3-dihydro-2- (1,1-dimethylethyl) -5-nitro-1H-isoindol-4-yl) acetamide;
- 45 7-Chloro-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-amine;
- 7-Bromo-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-amine;
- 7-Bromo-2,3-dihydro-2- (1,1-dimethylethyl) -5-nitro-1H-isoindol-4-amine;
- 50 7-Bromo-2,3-dihydro-2- (1,1-dimethylethyl) -1H-isoindole-4,5-diamine;
- 7-chloro-2,3-dihydro-2-methyl-1H-isoindole-4,5-diamine;
- 7-bromo-2,3-dihydro-2-methyl-1H-isoindole-4,5-diamine;
- 55 2,3-dihydro-2-methyl-1H-isoindole-4,5-diamine;
- Ethyl [(7-bromo-2,3-dihydro-2-methyl-5-nitro-1H-isoindol-4-yl) amino] oxoacetate;
- 60 Ethyl 5- (acetylamino) -1,2,3,4-tetrahydro-2-methyl-8-isoquinolinepropanoate;
- N- (5-bromo-2-ethyl-1,2,3,4-tetrahydro-8-isoquinolinyl) acetamide;
- 5-Bromo-1,2,3,4-tetrahydro-2-methyl-7-nitro-8-isoquinolinamine;
- 65 5-bromo-2-ethyl-1,2,3,4-tetrahydro-7-nitro-8-isoquinolinamine;

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- 1,2,3,4-Tetrahydro-2-methyl-7,8-isoquinoline-diamine;
- 70 2-ethyl-1,2,3,4-tetrahydro-7,8-isoquinoline-diamine;
- 5-Bromo-1,2,3,4-tetrahydro-2-methyl-7,8-isoquinolinediamine;
- Ethyl 3-[5-acetylamino)-1,2,3,4-tetrahydro-2-methyl-8-isoquinolinyl]-2-propenoate;
- 75 Ethyl 5-(acetylamino)-1,2,3,4-tetrahydro-2-methyl-8-isoquinolinepropanoate;
- Ethyl 5-(acetylamino-1,2,3,4-tetrahydro-2-methyl-7-nitro-8-isoquinolinepropanoate;
- 80 5-Amino-1,2,3,4-tetrahydro-2-methyl-7-nitro-8-isoquinolinepropanoic acid;
- 5,6-Diamino-1,2,3,4-tetrahydro-2-methyl-8-isoquinolinepropanoic acid;
- [(5-Bromo-7-nitro-8-quinolinyl)amino]oxo-acetic acid ethyl ester;
- 85 [(1,2-Dihydro-6-nitro-5-quinolinyl)amino]oxo-acetic acid ethyl ester;
- [(1,2,3,4-Tetrahydro-6-nitro-5-quinolinyl)-amino]oxo-acetic acid ethyl ester;
- 90 [Butyl (1,2,3,4-tetrahydro-6-nitro-5-quinolinyl)amino]oxo-acetic acid ethyl ester;
- Oxo[(phenylmethyl)(1,2,3,4-tetrahydro-6-nitro-5-quinolinyl)amino]acetic acid ethyl ester;
- 95 [(8-Bromo-1,2,3,4-tetrahydro-6-nitro-5-quinolinyl)amino]oxo-acetic acid ethyl ester;
- 6-Bromo-2,3-dichloro-7,8,9,10-tetrahydro-8-methyl-pyrido[4,3-f]quinoxaline;
- 6-Bromo-7,8,9,10-tetrahydro-2,3-dimethoxy-8-methyl-pyrido[4,3-f]quinoxaline;
- 100 6-Bromo-7,8,9,10-tetrahydro-8-methyl-2,3-bis(phenylmethoxy)-pyrido[4,3-f]quinoxaline;

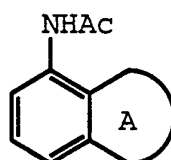
-113-

- 7,8,9,10-tetrahydro-2,3-dimethoxy-
6,8-dimethyl-pyrido[4,3-f]quinoxaline;
- 105 1,4,7,8,9,10-Hexahydro-6,8-dimethyl-
pyrido[4,3-f]quinoxaline-2,3-dione hydrochloride;
- 7,8,9,10-Tetrahydro-8-methyl-2,3-bis(phenyl-
methoxy)-pyrido[4,3-f]quinoxaline carboxylic acid
methyl ester;
- 110 7,8,9,10-Tetrahydro-8-methyl-2,3-bis(phenyl-
methoxy)pyrido[4,3-f]quinoxalin-6-yl phosphonic
acid diethyl ester;
- N-(2-acetyl-8-bromo-1,2,3,4-tetrahydro-
6-nitro-5-isoquinolinyl)acetamide;
- 115 8-Bromo-1,2,3,4-tetrahydro-6-nitro-
5-isoquinolinamine;
- 8-Bromo-1,2,3,4-tetrahydro-5,6-isoquino-
lindiamine; and
- 1,2,3,4-Tetrahydro-5,6-isoquinolindiamine.

22. A process for preparing a compound according to
Claim 1 which comprises:

- (1) reacting a compound of formula

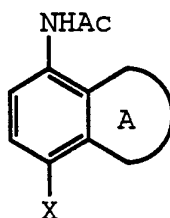
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with a halogenating agent to produce a compound of
formula

15



wherein X is bromine or chlorine;

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20 (2) treating the compound from Step (1) with
fuming nitric acid in a solvent to produce a
compound of formula



wherein X is bromine or chlorine;

30 (3) deprotecting the compound from Step (2)
with under acidic or basic conditions to produce a
compound of formula



40 (4) hydrogenating the compound from Step (3)
in a solvent to give a compound of formula



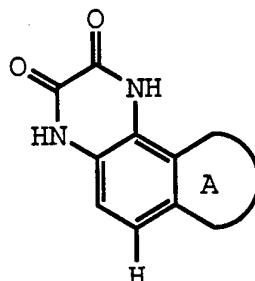
wherein X may be hydrogen, bromine, or chlorine;

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(5) reacting the compound from Step (4) with oxalic acid in a solvent to produce a compound of formula

50

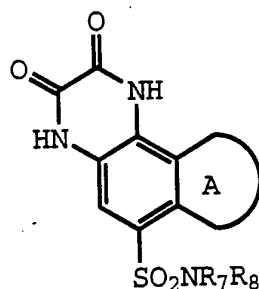
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(6) reacting the compound from Step (5) sequentially with chlorosulfonic acid, neat or in a solvent followed by treatment with a primary or secondary amine to produce a compound of formula

60

65

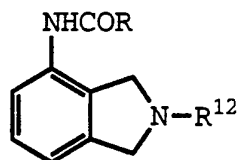


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wherein A, R₇, and R₈ are as defined in Claim 1.

23. A process for preparing a compound of formula

5



wherein R is alkyl and R¹² is as previously defined, which comprises;

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10 (1) reacting 3-nitrophthalic acid with
1,3-dialkyl urea to produce a compound of the
formula



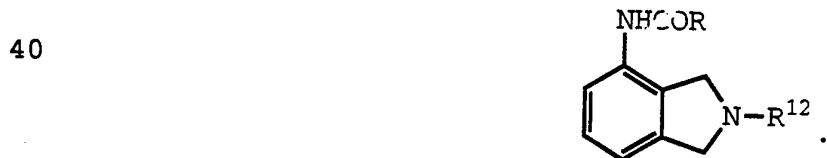
20 (2) hydrogenating a compound from Step (1)
above in a solvent to produce a compound of
formula



30 (3) reacting a compound from Step (2) above
with a hydride reducing agent in a solvent to
produce a compound of the formula



40 (4) reacting a compound from Step (3) above
with an acid chloride or acid anhydride in a
solvent to produce a compound of formula



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/09667

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D471/04 C07D487/04 A61K31/495 A61K31/55 C07F9/6561
 A61K31/675 C07D215/40 C07D215/38 C07D217/02 C07D217/04
 C07D209/48 //(C07D471/04,241:00,221:00),(C07D487/04,241:00,

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 374 534 (FERROSAN) 27 June 1990 see claims 1,8	1,17
X	see example 7b	21
A	EP,A,0 283 959 (FERROSAN) 28 September 1988 see claims 1,8	1,17
X	CHEMICAL ABSTRACTS, vol. 105, no. 19, 1986, Columbus, Ohio, US; abstract no. 172255q, M. REAY ET AL. 'Synthesis of 8-substituted 2-methyl-1,2,3,4-tetrahydroisoquinolines' page 727 ; see formula II & HELV. CHIM. ACTA 1985, 68(7),1828-34	21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search

21 January 1994

Date of mailing of the international search report

- 3. 02. 94

Name and mailing address of the ISA

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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/09667

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 209:00), (C07D487/04, 241:00, 223:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

21 January 1994

Date of mailing of the international search report

03 FEB 1994

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Authorized officer

Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

international application No.

PCT/US 93/09667

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 15, 16 and 18 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/US 93/09667

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0374534	27-06-90	AU-B- 624885	25-06-92
		AU-A- 4687489	28-06-90
		CA-A- 2004077	22-06-90
		JP-A- 2221264	04-09-90
		US-A- 5081123	14-01-92
		US-A- 5153195	06-10-92

EP-A-0283959	28-09-88	AU-B- 596737	10-05-90
		AU-A- 1326088	22-09-88
		CA-A- 1315789	06-04-93
		DE-A- 3867268	13-02-92
		US-A- 4889855	26-12-89
		US-A- 4912108	27-03-90
ZA-A- 8801139	15-08-88		
