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PYRIDO-QUINAZOLINE DERIVATIVES

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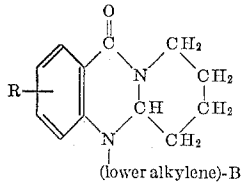
This invention relates to new chemical compounds, and more particularly, to compounds of the Formula I:



(I)

and pharmaceutically acceptable acid-addition and quaternary ammonium salts thereof, wherein R is hydrogen, lower alkyl (e.g., methyl, ethyl and isopropyl), halogen (e.g., chlorine and fluorine), halomethyl (e.g., trifluoromethyl), lower alkoxy (e.g., methoxy, ethoxy, propoxy and amyloxy), aryloxy (e.g., phenoxy), amino, or di (lower alkyl)amino (e.g., dimethylamino and diethylamino); and B is a basic nitrogen-containing radical such as amino, (lower alkyl)amino, di(lower alkyl)amino (e.g., dimethylamino and diethylamino), hydroxy(lower alkyl)amino, di[hydroxy(lower alkyl)]amino, halo(lower alkyl)amino, di[hydroxy(lower alkyl)]amino, (lower alkyl)aralkylamino (e.g., methylphenethylamino) (e.g., benzylamino), piperidyl (e.g., piperidino), (lower alkyl) piperidyl (e.g., 2, 3 and 4-methylpiperidino), di(lower alkyl)piperidyl (e.g., 2,4-, 2,6- and 3,5-dimethylpiperidino); homopiperidyl; pyrrolidyl (e.g., pyrrolidino), (lower alkyl)pyrrolidyl, di(lower alkyl)pyrrolidyl, piperazinyl (e.g., piperazino), homopiperazinyl, (lower alkyl) piperazinyl, (e.g., N^4-methylpiperazino), di(lower alkyl) piperazinyl, (lower alkoxy)piperazinyl, arylpiperazinyl (e.g., R-substituted phenylpiperazino), such as 4-phenylpiperazino, aralkylpiperazinyl (e.g., R-substituted phenyl (lower alkyl)piperazino), such as benzylpiperazino and p-chloro-phenethylpiperazino, pyridylpiperazinyl [e.g., 4-(3-pyridyl)piperazino], pyridyl(lower alkyl)piperazinyl [e.g., 4-(3-pyridylmethyl)piperazino], (alkanoyloxy-lower alkyl)piperazinyl [e.g., 4-(2-acetoxyethyl)piperazino], (hydroxy-lower alkyl)piperazinyl [e.g., 4-(2-hydroxyethyl)piperazino], morpholinyl (e.g., morpholino), (lower alkyl)morpholinyl, di(lower alkyl)-morpholinyl, thiamorpholinyl (e.g., thiamorpholino), (lower alkyl)-thiamorpholinyl and di(lower alkyl)thiamorpholinyl. The terms "lower alkyl," "lower alkoxy," and "lower alkylene" as employed herein, include both straight and branched chain radicals of less than eight carbon atoms.

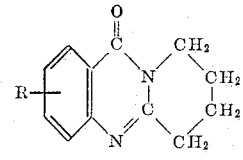
The preferred compounds of this invention are those of Formula I in which R is hydrogen, lower alkylene is ethylene, isopropylene or propylene, and B is di(lower alkyl)amino.

Examples of suitable acid-addition salts of the free bases of this invention include the mineral acid salts, such as the hydrohalides (e.g., hydrochloride, hydrobromide and hydroiodide), the sulfate and the phosphate; and organic acid salts, such as the citrate, tartrate, oxalate, ascorbate, acetate and succinate. Pharmacologically acceptable acids are, of course, employed where the salt form is prepared for therapeutic use.

Examples of suitable quaternary ammonium salts of the free bases of this invention include the lower alkyl halides (e.g., methyl chloride and methyl bromide), the lower alkyl sulfates (e.g., methosulfate), the aralkyl halides (e.g., benzyl chloride) and the aralkyl sulfates.

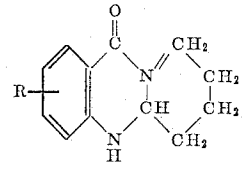
The compounds of this invention are physiologically active substances having hypotensive activity, and central nervous system depressive activity. The compounds of this invention can be administered to reduce blood pressure perorally in the usual perorally acceptable forms, such as tablets and capsules, the dosage for such treatment being adjusted for the activity of the particular compound employed.

The compounds of this invention are prepared by the process of this invention which comprises reducing a compound of the Formula II:



(II)

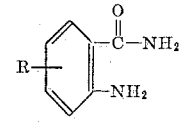
wherein R is as hereinbefore defined, with a reducing agent, such as sodium borohydride, to yield new intermediates of this invention of the Formula III:



(III)

wherein R is as hereinbefore defined; converting these intermediates into their alkali metal derivatives, as by treating with a base such as an alkali metal hydride (e.g., sodium hydride) or sodium amide or an alkali metal alkoxide such as sodium ethoxide or potassium t-butoxide, and then treating the alkali metal derivatives with an amino(lower alkylene)halide (preferably chloride) of the formula: B-(lower alkylene) halide, wherein B is as hereinbefore defined, to yield the bases of this invention of the Formula I. These bases can then be converted to either their acid-addition salts or quaternary ammonium salts in the usual manner by treating with the desired acid or quaternizing agent.

In those instances where the compounds of Formula II are new, they can be prepared by the method described by Bohme et al. in Archiv. der Pharmazie, 294/66, 556 (1961), by reacting an anthranilamide of the formula:



wherein R is as hereinbefore defined, with 2,3-dihydropyran in an aqueous acidic medium to yield the corresponding 2-(4-hydroxybutyl) - 4(3H) - quinazolinone; treating the quinazolinone with hydrogen bromide in glacial acetic acid to yield the corresponding 2-(4-bromobutyl)-4(3H)-quinazolinone hydrobromide; and heating the hydrobromide with potassium hydroxide to yield 6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one.

The following examples illustrate the invention (all temperatures being in centigrade):

EXAMPLE 1

5-(3-dimethylaminopropyl)-5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1-b]quinazolin-11-one hydrochloride

(*a*) PREPARATION OF 5,5a,6,7,8,9-HEXAHYDRO-11H-PYRIDO[2,1-b]-QUINAZOLIN-11-ONE

A solution of 30 g. (0.15 mole) of 6,7,8,9-tetrahydro-11H-pyrido[2,1-b]-quinazolin-11-one in 300 ml. of methanol is stirred at room temperature as 6.2 g. (0.16 mole) of sodium borohydride is added portionwise over a period of 20 minutes. The reaction temperature is maintained below 30° by external cooling when necessary. After remaining at room temperature overnight the methanol is removed by distillation at reduced pressure. The residue is taken up in an ether-chloroform mixture and washed with cold 3% hydrochloric acid, water, and dried over magnesium sulfate. After filtration, the solvents are removed by distillation and the residue is taken up in ether. A solid crystallizes from the ethereal solution and is collected by suction filtration. This product is recrystallized from toluene to give about 11 g. (33%) of material, M.P. about 133–134°.

Analysis.—Calcd. for $C_{12}H_{14}N_2O$: N, 13.85; C, 71.24; H, 6.97. Found: N. 13.76; C, 71.31; H, 6.99.

(*b*) PREPARATION OF 5-(3-DIMETHYLAMINOPROPYL)-5,5a,6,7,8,9- HEXAHYDRO-11H-PYRIDO[2,1-b]-QUINAZOLIN-11-ONE HYDROCHLORIDE

A solution of 7.1 g. (0.035 mole) of 5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1-b]quinazolin-11-one in 50 ml. of dry N,N-dimethylformamide is added over a period of 15 minutes to a stirred suspension of 1.68 g. (0.035 mole) of 50% sodium hydride in mineral oil dispersion in 200 ml. N,N-dimethylformamide. After stirring 2 hours at room temperature the dark red reaction mixture is warmed to 90–95° for 2½ hours, or until the effervescence of hydrogen gas has stopped. After cooling to 30°, 6 g. (50% excess) of 3-dimethylaminopropyl chloride in 25 ml. of dry N,N-dimethylformamide is added. After stirring for 30 minutes the reaction temperature is raised to 90–95° for 5 hours after which time the color has disappeared and a gray solid separates from solution on cooling. After filtration, the filtrate is concentrated by distillation under reduced pressure to remove most of the solvent. The residue is taken up in ether and the ethereal solution is extracted with 3% hydrochloric acid. The free base is released from the cooled aqueous acidic solution with solid potassium carbonate, and extracted into ether. The ethereal solution is dried over magnesium sulfate, filtered, and the ether removed by distillation leaving a residue of crude base weighing about 7 g. Solution of the base in cyclohexane results in recovery of 0.8 g. of unreacted starting material. (An additional 1.5 g. of starting material is also recovered from the above ethereal solution after the extraction with hydrochloric acid.) The cyclohexane filtrate is cooled in ice water and 10 ml. of 2.4 N ethereal hydrogen chloride is added resulting in separation of a yellow gum which readily crystallizes. The hygroscopic solid weighs about 5 g. after drying over P_2O_5 in a vacuum desiccator, and melts at about 170–175° (d.) with preliminary sintering. It is recrystallized from acetonitrile to a constant melting point of about 175–177° (d.) to give about 3.4 g. (44%) based on recovered nucleus.

Analysis.—Calcd. for $C_{17}H_{25}N_3O \cdot HCl$: N, 10.95; Cl, 12.97. Found: N, 11.11; Cl, 12.91.

Similarly, by substituting the following R-substituted-6,7,8,9-tetrahydro-11H-pyrido[2,1 - b]quinazolin-11-ones for the 6,7,8,9-tetrahydro-11H-pyrido[2,1-b]quinazolin-11-one in the procedure of step *a* of Example 1, and following the procedures in the example, the indicated 5-(3 - dimethylaminopropyl) - R - substituted-5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1 - b]quinazolin-11-one hydrochloride is formed:

Example	Reactant (R is)—	Product Formed (R is)—
2	3-Ethyl	3-Ethyl.
3	4-Isopropyl	4-Isopropyl.
4	1-Methyl	1-Methyl.
5	2-Methyl	2-Methyl.
6	3-Chloro	3-Chloro.
7	4-Trifluoromethyl	4-Trifluoromethyl.
8	4-Methoxy	4-Methoxy.
9	2-Phenoxy	2-Phenoxy.
10	3-Amino	3-Amino.
11	4-Dimethylamino	4-Dimethylamino.
12	2-Diethylamino	2-Diethylamino.
13	3-Dimethylamino	3-Dimethylamino.

EXAMPLE 14

5-(3-N-methylpiperazinopropyl)-5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1-b]quinazolin-11-one hydrochloride

Following the the procedure of Example 1, but substituting 3-(N-methylpiperazino)propyl chloride for the 3-dimethylaminopropyl chloride in step *b*, 5-(3-N-methylpiperazinopropyl) - 5,5a,6,7,8,9 - hexahydro - 11H - pyrido [2,1-b]quinazolin-11-one hydrochloride is formed.

Similarly, but substituting the following B-(lower alkylene)chlorides for the 3-dimethylaminopropyl chloride in the procedure of step *b* of Example 1, and following the procedure of the example, the indicated 5-aminoalkyl - 5,5a,6,7,8,9 - hexahydro - 11H - pyrido[2,1 - b] quinazolin-11-one hydrochloride is obtained:

Example	Reactant	Product
15	3-Diethylaminopropyl	3-Diethylaminopropyl.
16	2-Methylaminoethyl	2-Methylaminoethyl.
17	2-Diethylaminoethyl	2-Diethylaminoethyl.
18	2-Benzylaminoethyl	2-Benzylaminoethyl.
19	2-Piperidinoethyl	2-Piperidinoethyl.
20	4-Pyrrolidinobutyl	4-Pyrrolidinobutyl.
21	3-Homopiperidinopropyl	3-Homopiperidinopropyl.
22	2-(3-Piperidinyl)ethyl	2-(3-Piperidinyl)ethyl.
23	3-(N-Phenylpiperazino)-propyl.	3-(N-Phenylpiperazino)-propyl.
24	3-[N-(2-Hydroxyethyl)-piperazino]propyl.	3-[N-(2-Hydroxyethyl)-piperazino]propyl.
25	2-Homopiperazinoethyl	2-Homopiperazinoethyl.
26	6-Morpholinohexyl	6-Morpholinohexyl.
27	3-Thiamorpholinopropyl	3-Thiamorpholinopropyl.
28	2-(Methylphenethylamino) -ethyl.	2-(Methylphenethylamino) -ethyl.
29	2-(Dimethylamino)propyl	2-(Dimethylamino)propyl.

EXAMPLE 30

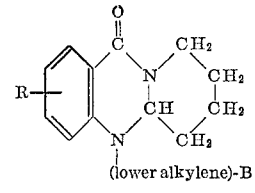
5-(3-dimethylaminopropyl)-5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1-b]quinazolin-11-one methochloride

A solution of 150.0 g. of material from Example 1 in 100 ml. of acetonitrile is cooled and treated with 25 g. of methyl chloride. After standing for several days at room temperature, the solution is diluted to 300 ml. with ether to give the methochloride.

The invention may be otherwise embodied within the scope of the appended claims.

What is claimed is:

1. A compound selected from the group consisting of bases of the formula



and the pharmaceutically acceptable acid-addition and quaternary ammonium salts thereof, wherein R is selected from the group consisting of hydrogen, lower alkyl, halogen, halomethyl, lower alkoxy, mononuclear aryloxy;

amino and di(lower alkyl)amino; and B is a basic nitrogen-containing radical selected from the group consisting of amino, (lower alkyl)amino, di(lower alkyl)amino, hydroxy(lower alkyl)amino, halo(lower alkyl)amino, di[hydroxy(lower alkyl)]amino, (lower alkyl)phenyl(lower alkyl)amino, piperidyl, (lower alkyl)piperidyl, di(lower alkyl)piperidyl, homopiperidyl, pyrrolidyl, (lower alkyl)pyrrolidyl, di(lower alkyl)pyrrolidyl, piperazinyl, homopiperazinyl, (lower alkyl)piperazinyl, di(lower alkyl)piperazinyl, (lower alkoxy)piperazinyl, R-phenylpiperazinyl, R-phenyl(lower alkyl)piperazinyl, pyridylpiperazinyl, pyridyl(lower alkyl)piperazinyl, (lower alkanoyloxy-lower alkyl)piperazinyl, (hydroxy-lower alkyl)piperazinyl, morpholinyl, (lower alkyl)morpholinyl, di(lower alkyl)morpholinyl, thiamorpholinyl, (lower alkyl)thiamorpholinyl and di(lower alkyl)thiamorpholinyl.

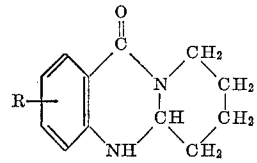
2. 5-[di(lower alkyl)amino(lower alkyl)]-5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1-b]quinazolin-11-one.

3. A pharmaceutically acceptable salt of the compound of claim **2**.

4. 5 - (3 - dimethylaminopropyl) - 5,5a,6,7,8,9 - hexahydro-11H-pyrido[2,1-b]quinazolin-11-one.

5. A pharmaceutically acceptable salt of the compound of claim **4**.

6. A compound selected from the group consisting of bases of the formula



and alkali metal derivatives thereof, wherein R is selected from the group consisting of hydrogen, lower alkyl, halogen, halomethyl, lower alkoxy, mononuclear aryloxy, amino and di(lower alkyl)amino.

7. 5,5a,6,7,8,9-hexahydro-11H-pyrido[2,1-b]quinazolin-11-one.

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