United States Patent

Suh et al.

[15] **3,665,006**

[45] **May 23, 1972**

[54] 2-HYDROXYBENZO[b]QUINOLIZINES

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[21] Appl. No.: **10,289**

[52] **U.S. Cl.** ..... **260/289 R**, 260/283 SA

[51] **Int. Cl.** **C07d 39/12**

[58] **Field of Search** ..... 260/289, 289 A

[56] **References Cited**

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3,408,352	10/1969	Hardtmann	260/289
3,484,443	12/1969	Watthey	260/289

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Miller, Chem. Abstr., Vol. 71, Col. 37263e, 1969

Bobbitt et al., Jour. Org. Chem., Vol. 33, 2958–9 (1968)

Primary Examiner—Donald D. Daus

Attorney—T. F. Kryshak and M. L. Youngs

[57] **ABSTRACT**

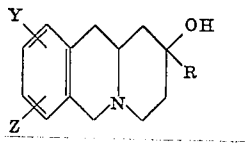
The compounds are 2-hydroxybenzo[b]quinolizines which are useful agents which affect the central nervous system and which can be used as tranquilizing agents to control aggressive antisocial behavior in animals. The compounds may also be used as intermediates in the preparation of pickling agents, mothproofing agents and wood preservatives. Representative of the compounds disclosed are 8,9-dimethoxy-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine and 8,9-dimethoxy-2-hydroxy-2-(3′-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine.

8 Claims, No Drawings

2-HYDROXYBENZO[B]QUINOLIZINES

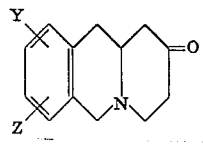
DESCRIPTION OF THE INVENTION

The compounds of the present invention may be represented by the following formula:



wherein Y and Z are the same or different members selected from hydrogen, hydroxy, a halogen such as chloro, bromo or fluoro, trifluoromethyl, a lower alkoxy of one to four carbon atoms such as methoxy, ethoxy or propoxy, sulfamoyl, a lower alkyl sulfonamide such as methyl sulfamoyl, and R is selected from hydrogen, phenyl, a halogen-substituted phenyl such as p-chlorophenyl, o-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, a trifluoromethyl-substituted phenyl such as 4-trifluoromethylphenyl, a lower alkoxy-substituted phenyl such as 4-methoxyphenyl and 3,4-dimethoxyphenyl, a hydroxy-substituted phenyl such as 4-hydroxyphenyl and 3,4-dihydroxyphenyl, a phenyl-lower alkyl containing seven to 13 carbon atoms such as benzyl, phenethyl or phenylisopropyl, a halogen-substituted phenyl-lower alkyl such as 3-chlorobenzyl, a trifluoromethyl-substituted phenyl-lower alkyl such as 3-trifluoromethylbenzyl and a lower alkoxy-substituted phenyl-lower alkyl such as o-methoxybenzyl and 3,4-dimethoxybenzyl.

The basic starting materials used for the preparation of the compounds of the present invention are 3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-ones of the following formula:

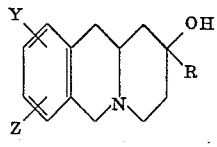


in which Y and Z are as previously defined. One method of preparing these compounds is the method described by J. M. Bobbitt and T. E. Moore, J. Org. Chem., *33*, 2958 (1968).

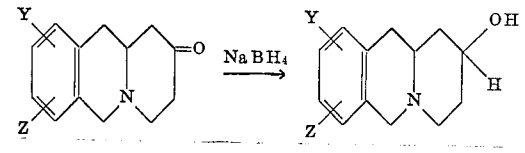
Representative of the compounds which may be employed are the following:

8,9-dimethoxy-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one,
8,9-dihydroxy-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one,
8-chloro-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one,
9-chloro-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one,
8-fluoro-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one,
9-fluoro-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one,
8-trifluoromethyl-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one,
9-trifluoromethyl-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one, and
3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one.

In the preferred practice of the present invention the compounds of the formula



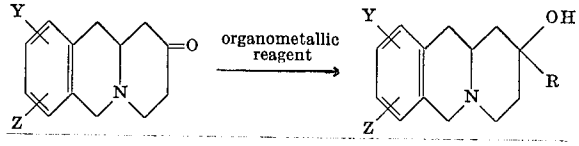
in which R is hydrogen are prepared by dissolving the desired ketone starting material in a lower alkanol such as methanol to which sodium borohydride is added. The resulting solution is then preferably refluxed for a short period of time, from 1 to about 3 hours. The solvent is removed from the reaction mixture and the resulting solids recrystallized from isopropyl alcohol. The described process may be illustrated as follows:



in which Y and Z are as defined and R is hydrogen. Representative of the compounds to be prepared by this process are the following:

8,9-dimethoxy-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8,9-dihydroxy-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-chloro-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
9-chloro-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-trifluoromethyl-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
9-trifluoromethyl-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
10-fluoro-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methylsulfamoyl-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine, and
2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine.

The compounds in which R is other than hydrogen are preferably prepared by reacting the ketone starting material with organometallic reagents such as phenyl lithium or a Grignard reagent. The reactants are advisable combined in an anhydrous solvent such as ethyl ether, tetrahydrofuran or ethyl ether with benzene, and, if desired, the reaction is conducted at reflux temperatures. When the reaction is substantially complete water is added to hydrolize the Grignard adduct to the desired tertiary alcohol. The resulting product can then be isolated from the mixture by conventional means such as by evaporation of the solvent. The described process may be illustrated as follows:



in which Y, Z and R are as previously defined and X is a reactive halogen. Among the Grignard reagents which may be employed are the following:

phenylmagnesium bromide,
phenylmagnesium iodide,
4-chlorobenzylmagnesium bromide,
3,4-dichlorobenzylmagnesium bromide,
benzylmagnesium bromide,
4-methoxybenzylmagnesium bromide,
4-chlorophenylmagnesium bromide,
3,4-dichlorophenylmagnesium bromide,
4-methoxyphenyl magnesium bromide,
4-fluorophenylmagnesium bromide,
4-trifluoromethylphenyl magnesium bromide,
3-trifluoromethylphenyl magnesium bromide, and
3-chlorobenzylmagnesium bromide.

The above described Grignard reagents may be prepared by conventional methods such as those described in U.S. Pat. No. 2,996,503 and German Pat. No. 1,109,166.

Representative of the compounds which may be prepared by the described process are the following:

8,9-dimethoxy-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2-(3',3'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2-(3'-trifluorometylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dimethoxy-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8,9-dihydroxy-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-chloro-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-chloro-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-trifluoromethyl-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

9-trifluoromethyl-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

10-fluoro-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,

8-methylsulfamoyl-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-chloro-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
i-hydroxy-9-chloro-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-chloro-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl2-hydroxy-2(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-methoxy-9-trifluoromethyl-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8-hydroxy-9-trifluoromethyl-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine, and
8-hydroxy-9-trifluoromethyl-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine.

The compounds of the present invention have demonstrated in behavioral screening tests in mice an activity upon the central nervous system. The following compounds have exhibited central nervous system depressant effect at non-lethal doses:
8,9-dimethoxy-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8,9-dimethoxy-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8,9-dimethoxy-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8,9-dimethoxy-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine,
8,9-dimethoxy-2-hydroxy-2-benzyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine, and
8,9-dimethoxy-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine.

In addition, the compounds 8,9-dimethoxy-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine; 8,9-dimethoxy-2-hydroxy-2-(4'fluorophenyl)- **2,3,4,6,11,11***a*-hexahydro-1H, Benzo[b]quinolizine; 8,9-dimethoxy-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine; and 8,9-dimethoxy-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine were found to be effective in controlling the aggressive antisocial behavior of mice which have been isolated for periods of two weeks. The effective dose was approximately 15 mg/kg intraperitoneally for each of the compounds. The central nervous system depressant effect as well as the ability to control antisocial behavior in animals is an indication that the compounds have utility as tranquilizing agents for use in animals.

The following examples are presented to illustrate this invention:

EXAMPLE 1

8,9-Dimethoxy-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine

To a cooled stirring slurry of 6.5 g. (0.025 mole) 8,9-dimethoxy-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one in 125 ml. of methanol, 0.95 g. (0.025 mole) of sodium borohydride is added. The resulting solution is refluxed for 1.5 hours. The solvent is removed in vacuo and the remaining solids triturated under water, filtered, and recrystallized in isopropyl alcohol to afford 8,9-dimethoxy-2-hydroxy-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine as a cream colored powder, m.p. 176°–178°.

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.07; N, 5.32. Found: C, 68.22; H, 7.88; N, 5.14.

EXAMPLE 2

8,9-Dimethoxy-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine

A Grignard reagent is prepared in the conventional manner using 1.2 g. (0.05 mole) of magnesium and 7.9 g. (0.05 mole) of bromobenzene in ether. The mixture is reflexed for two hours following addition of 6.5 g. (0.025 mole) of 8,9-dimethoxy-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one and 100 ml. of THF, cooled, poured into 200 ml. of ammonium chloride solution, extracted into chloroform, and dried (Na_2SO_4). Removal of the solvent leaves a brown oil which is chromatographed (500 g. silica gel, Chf:benzene: EtOH; 6:3:1) to afford two isomers. The first is recrystallized from isopropyl alcohol to afford 8,9-dimethoxy-2-hydroxy-2-phenyl-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine as a white powder, m.p. 170°–172°.

Anal. Calcd. for $C_{21}H_{25}NO_3$: C, 74.30; H, 7.42; N, 4.13.

Found: C, 74.24; H, 7.26; N, 4.12.

EXAMPLE 3

8,9-Dimethoxy-2-hydroxy-2(4'-chlorophenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

In 50 ml. of ether 0.73 g. (0.03 mole) of magnesium is suspended to which 5.7 g. (0.03 mole) of 1-bromo-4-chlorobenzene is added. When the magnesium is dissolved 4.0 g. (0.015 mole) of 8,9-dimethoxy-3,4,11,11a-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one and 100 ml. of THF are added. The mixture is refluxed for one hour, poured into 200 ml. of saturated ammonium chloride solution and extracted into chloroform, washed with brine, and dried (Na_2SO_4). Removal of the solvent affords a dark oil which is chromatographed over 400 g. of silica gel (CHf:benzene:EtOH: 3:6:1) to afford two isomers. The isomer A is recrystallized from ethanol to afford a solid, m.p. 101°–103°. The isomer B, also recrystallized from ethanol, affords a solid, m.p. 80°–82°.

Anal. Calcd. for $C_{21}H_{25}ClNO_3$: C, 67.28; H, 6.72; N, 3.74.
Found: Isomer A: C, 66.94; H, 6.36; N, 3.87.
Found: Isomer B: C, 67.60; H, 6.69; N, 3.92.

EXAMPLE 4

8,9-Dimethoxy-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

In 20 ml. ether is suspended 0.96 g. (0.04 mole) magnesium to which is slowly added 9.05 g. (0.04 mole) 1-bromo-3,4-dichlorobenzene and 2 drops 1,2-dibromoethane. When the magnesium is dissolved 5.0 g. (0.0192 mole) 8,9-dimethoxy-3,4,11,11a-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one and 50 ml. tetrahydrofuran are added. The mixture is refluxed 3 hours, poured into 10 percent ammonium chloride solution and extracted into chloroform, washed with water, and dried. Removal of solvent affords a dark oil which is chromatographed over silica gel (400 g.; Chf:Et_2O:EtOH; 3:6:1). Taking 250 ml. fractions the carbinol is obtained which is then recrystallized from ethanol:water; to yield 8,9-dimethoxy-2-hydroxy-2-(3',4'-dichlorophenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine, m.p. 201°–203°.

Anal. Calcd. for $C_{21}H_{24}NO_3Cl_2$: C, 61.61; H, 5.91; N, 3.42.
Found: C, 61.42; H, 5.74; N, 3.43.

EXAMPLE 5

8,9-Dimethoxy-2-hydroxy-2-(4'-methoxyphenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

The Grignard reagent is prepared in the usual manner from 1.2 g. (0.05 g-atom) of magnesium and 9.4 g. (0.05 mole) of p-bromoanisole in 50 ml. of ether. When the magnesium is dissolved 6.5 g. (0.025 mole) of 8,9-dimethoxy-3,4,11,11a-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one is added along with 100 ml. of THF. The solution is refluxed for 2 hours, cooled and poured into 200 ml. of saturated ammonium chloride solution, extracted with chloroform, and dried over Na_2SO_4. Removal of the solvent leaves 11.1 g. of a brown oil which is chromatographed over 300 g. of silica gel (60 percent benzene:30 percent chloroform:10 percent ethyl alcohol) to afford 0.8 g. of isomer A which is crystallized twice from isopropyl alcohol, m.p. 114°–116°.

Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.51; H, 7.37; N, 3.80.
Found: Isomer A: C, 71.69; H, 7.36; N, 3.97.
Isomer B: (EX 11—588) N, 3.46.

EXAMPLE 6

8,9-Dimethoxy-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

The Grignard reagent is prepared from 1.2 g. (0.05 mole) of magnesium and 8.8 g. (0.05 mole) of p-bromofluorobenzene in 50 ml. of dry ether. When the magnesium is dissolved, 6.5 g. (0.025 mole) of 8,9-dimethoxy-3,4,11,11a-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one and 100 ml. of THF are added and the solution is refluxed 2 hours, cooled, poured into 200 ml. of saturated ammonium chloride solution, extracted into chloroform, dried over Na_2SO_4, and the solvent removed to leave a dark oil which is chromatographed over 400 g. of silica gel (benzene:chloroform:ethanol; 6:3:1) to afford a tan solid which is crystallized from isopropyl alcohol to give 8,9-dimethoxy-2-hydroxy-2-(4'-fluorophenyl)-2,3,4,6,11,11a-hexahydro-1-benzo[b]quinolizine as a white solid, m.p. 129–130°Anal. Calcd. for $C_{21}H_{24}FNO_3$: C, 70.57; H, 6.84; N, 3.92.

Found: C, 70.36; H, 7.14; N, 3.85.

EXAMPLE 7

8,9-Dimethoxy-2-hydroxy-(4'-trifluoromethylphenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

The Grignard reagent is prepared in the conventional manner from 1.2 g. (0.05 g-atom) of magnesium and 11.3 g. (0.05 mole) of p-bromobenzotrifluoride in 50 ml. of THF. When the magnesium is dissolved 6.5 g. (0.025 mole) of 8,9-dimethoxy-3,4,11,11a-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one is added along with 100 ml. of THF. The solution is refluxed for 2 hours, cooled and poured into 200 ml. of saturated ammonium chloride solution, extracted with chloroform and dried over Na_2SO_4. Removal of the solvent leaves an oil which is chromatographed over 300 g. of silica gel (6 percent benzene:30 percent chloroform:10 percent ethyl alcohol) to afford a single isomer which is recrystallized from isopropyl alcohol, m.p. 194°–195°.

Anal. Calcd. for $C_{22}H_{24}F_3NO_3$: C, 64.86; H, 5.94; N, 3.44.
Found: C, 65.10; H, 6.16; N, 3.45.

EXAMPLE 8

8,9-Dimethoxy-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

The Grignard reagent is prepared in the conventional manner from 2.9 g. (0.12 g-atom) of magnesium and 27.0 g. (0.12 mole) of m-bromobenzotrifluoride in 100 ml. of THF. When the magnesium is dissolved, 26.1 g. (0.1 mole) of 8,9-dimethoxy-3,4,11,11a -tetrahydro-1H-benzo[b]quinolizin-2(6H)-one and 100 ml. of THF are added. The solution is stirred at room temperature for 2 hours, poured into 200 ml. of saturated ammonium chloride solution and extracted into chloroform. Removal of the solvent leaves 47.4 g. of a dark solid, of which 24.0 g. are chromatographed over 600 g. of silica gel (60 percent benzene:30 percent chloroform:10 percent ethyl alcohol) to afford isomer A, recrystallized from benzene/petroleum ether to afford 8,9-dimethoxy-2-hydroxy-2-(3'-trifluoromethylphenyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine as a beige powder, m.p. 155°–158°.

Anal. Calcd. for $C_{22}H_{24}F_3NO_3$: C, 64.86; H, 5.94; N, 3.44.
Found: C, 65.03; H, 6.17; N, 3.66.

EXAMPLE 9

8,9-Dimethoxy-2-hydroxy-2-benzyl-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

The Grignard reagent is prepared following the usual procedure using 1.2 g. (0.05 mole) of magnesium and 8.6 g. (0.05 mole) of α-bromotoluene in 50 ml. of ether. After addition of 6.5 g. (0.025 mole) of 8.9-dimethoxy-3,4,11,11a-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one and 100 ml. of THF, the solution is refluxed 2 hours, poured into ammonium chloride solution, extracted into chloroform, washed with saturated brine and dried (Na_2SO_4). Removal of the solvent leaves a dark oil which is chromatographed (400 g. silica gel, EtOAc:EtOH; 9:1) to afford a yellow glass which is recrystallized from isopropyl alcohol to afford 8,9-dimethoxy-2-hydroxy-2-benzyl-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine as a white crystalline solid, m.p. 159°–161.5°.

Anal. Calcd. for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.97.
Found: C, 74.87; H, 7.72; N, 4.10.

EXAMPLE 10

8,9-Dimethoxy-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11a-hexahydro-1H-benzo[b]quinolizine

The Grignard reagent is prepared in the usual way using 1.2 g. (0.05 mole) of magnesium and 10.2 g. (0.05 mole) of 3-chlorobenzyl bromide in 50 ml. of ether. After addition of 6.5 g. (0.025 mole) of 8,9-dimethoxy-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one and 100 ml. of THF the solution is refluxed 2 hours, cooled, poured into 200 ml. of ammonium chloride solution, extracted into chloroform, washed with brine, and dried (Na_2SO_4). Removal of the solvent leaves an amber oil which is chromatographed over 400 g. of silica gel (chloroform:benzene:ethanol; 6:3:1) to afford a brown solid which is recrystallized two times from isopropyl alcohol to afford 8,9-dimethoxy-2-hydroxy-2-(3'-chlorobenzyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine as white crystals, m.p. 93°–95°.

Anal. Calcd. for $C_{22}H_{26}NClO_3$: C, 68.12; H, 6.75.
Found: C, 67.87; H, 6.99.

EXAMPLE 11

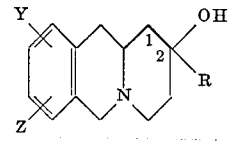
8,9-Dimethoxy-2-hydroxy-2-(2'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine

Magnesium (2.16 g., 0.089 mole) is suspended in about 25 ml. dry ether and 20 g. (0.089 mole) o-bromobenzotrifluoride slowly added with 225 ml. ether. After the magnesium has dissolved 18.3 g. (0.07 mole) 8,9-dimethoxy-3,4,11,11*a*-tetrahydro-1H-benzo[b]quinolizin-2(6H)-one is added with 80 ml. dry THF. The mixture is refluxed 15 hours, cooled and quenched with 200 ml. saturated ammonium chloride solution. The organic layer is diluted with ethyl ether, washed with water, and extracted with dilute hydrochloric acid. The acid is washed with ether, neutralized with sodium hydroxide solution, extracted with chloroform and dried. Evaporation of the chloroform gives a gum which is chromatographed over 300 g. silica gel (Chf:Et_2O:EtOH; 5:4:1) to give 8,9-dimethoxy-2-hydroxy-2-(2'-trifluoromethylphenyl)-2,3,4,6,11,11*a*-hexahydro-1H-benzo[b]quinolizine as a white solid which upon recrystallization from benzene melts at 154°–157°.

Anal. Calcd. for $C_{22}H_{24}F_3NO_3$: C, 64.86; H, 5.94; N, 3.44.
Found: C, 65.34; H, 6.24; N, 3.31.

We claim:

1. A compound of the formula



wherein Y and Z are hydroxy or lower alkoxy of one to four carbon atoms, and R is selected from phenyl, chlorophenyl, dichlorophenyl, fluorophenyl, trifluoromethyl phenyl, and lower alkoxy phenyl.

2. The compound of claim 1 in which Y and Z are methoxy and R is hydrogen.

3. The compound of claim 1 in which Y and Z are methoxy and R is phenyl.

4. The compound of claim 1 in which Y and Z are methoxy and R is chlorophenyl.

5. The compound of claim 1 in which Y and Z are methoxy and R is dichlorophenyl.

6. The compound of claim 1 in which Y and Z are methoxy and R is fluorophenyl.

7. The compound of claim 1 in which Y and Z are methoxy and R is benzyl.

8. The compound of claim 1 in which Y and Z are methoxy and R is 3'-trifluoromethylphenyl.

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