United States Patent Office

2,995,492

Patented Aug. 8, 1961

2,995,492

PIPERIDINE DERIVATIVES WITH PSYCHOTOGENIC ACTIVITY

John H. Biel, Milwaukee, Wis., assignor, by mesne assignments, to Lakeside Laboratories, Inc., Milwaukee, Wis., a corporation of Delaware

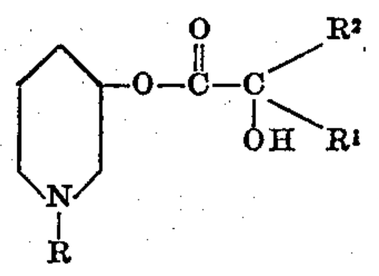
No Drawing. Filed Dec. 23, 1957, Ser. No. 704,247

18 Claims. (Cl. 167—65)

This invention relates to piperidine derivatives. More particularly, this invention is concerned with novel N-alkyl-3-piperidyl glycolates, methods of preparing such compounds, and uses of such compounds.

This application is a continuation-in-part of my copending application Serial No. 217,413, filed March 24, 1951, which is in turn a continuation-in-part of my copending application Serial No. 180,295, filed August 18, 1950; and is also a continuation-in-part of my copending application Serial No. 321,745, filed November 20, 1952, all now abandoned.

According to one aspect of the present invention there are provided novel compounds of the formula



and nontoxic acid addition salts thereof, wherein R is a lower alkyl group, aralkyl groups such as benzyl, phenethyl, chlorobenzyl, methoxyphenethyl, trimethoxyphenylpropyl and p-aminophenylethyl, and aralkenyl groups such as cinnamyl, and R^1 and R^2 are phenyl, cycloalkyls such as cyclohexyl and cyclopentyl or thienyl groups. Some of the specific compounds within the scope of this invention are N-methyl-3-piperidyl benzilate, N-ethyl-3-piperidyl benzilate, N-propyl-3-piperidyl benzilate, N-methyl-3-piperidyl phenylcyclohexyl glycolate, N-ethyl-3-piperidyl phenylcyclohexyl glycolate, N-methyl-3-piperidyl dicyclohexyl glycolate, N-ethyl-3-piperidyl dicyclohexyl glycolate, N-methyl-3-piperidyl phenyl-2-thienyl glycolate, N-methyl-3-piperidyl phenylcyclopentyl glycolate, N-ethyl-3-piperidyl phenylcyclopentyl glycolate, N-ethyl-3-piperidyl phenyl-2-thienyl glycolate, and nontoxic acid addition salts thereof including the hydrochloride, sulfate, maleate, fumarate, succinate, phosphate, benzoate and tartrate.

These compounds, as nontoxic acid addition salts, are powerful psychotogens.

In humans, N-methyl-3-piperidyl benzilate hydrochloride, N-ethyl-3-piperidyl benzilate hydrochloride, N-ethyl-3-piperidyl phenylcyclohexyl glycolate hydrochloride, N-methyl-3-piperidyl phenylcyclopentyl glycolate hydrochoride, and N-methyl-3-piperidyl phenyl 2-thienyl glycolate hydrochloride have been found to be extremely powerful hallucinogens. When administered in 10–15 mg. doses orally to human volunteers N-methyl-3-piperidyl benzilate hydrochloride and N-ethyl-3-piperidyl benzilate hydrochloride induced distinct auditory and visual hallucinations within one hour in each individual and these recurred periodically for periods up to 10 hours after the administration of the compound. The hallucinations were accompanied by gross distortions of visual images and severe alterations in feeling state. Some of the subjects exhibited paranoid and megalomanic delusions, while the affective states ranged from a feeling of unpleasantness to extreme terror.

Humans to whom 20 mgm. of N-methyl-3-piperidyl benzilate hydrochloride and N-ethyl-3-piperidyl benzilate hydrochloride were given orally were in complete loss of contact with the environment for many hours while experiencing dramatic visual and auditory hallucinations. Animals such as cats and rodents which received these agents showed marked behavioral changes such as initial excitement and marked hyperactivity, spontaneous squealing, lack of responsiveness to stimuli, muscular weakness and lethargy.

Surprisingly, similar compounds without the hydroxyl group, such as N-ethyl-3-piperidyl diphenylacetate hydrochloride, are lacking in hallucinogenic properties. Furthermore, quaternary salts such as N-methyl-3-piperidyl benzilate methobromide orally administered do not induce hallucinations.

The compounds of this invention produce a state in humans closely approaching schizophrenia. Ceruloplasmin determinations were made on humans given N-methyl or N-ethyl-3-piperidyl benzilate hydrochloride since this enzyme was known to be increased in the serum of acute schizophrenics. Observations indicated that as much as a 50–75% elevation in the blood ceruloplasmin accompanies the hallucinatory episode produced by these agents. Ceruloplasmin increased only when marked psychogenic disturbances were apparent and returned to normal shortly after the psychogenic effects disappeared.

The artificial production of hallucinations and the schizophrenia-like syndrome by the compounds provided by this invention can be, and is, being used by the psychiatrist in his study of these conditions. By being able to quickly induce these conditions in an animal or human it is possible to screen agents to discover those which are antidotes and block the conditions and can be used in psychotherapeutic treatment. For example, it has been found that the hallucinations produced in humans by N-methyl or N-ethyl-3-piperidyl benzilate hydrochloride and N-ethyl-3-piperidyl phenylcyclohexyl glycolate hydrochloride can be blocked by 4-hydroxyethyl-piperazinoethyl benzilate hydrochloride and that this compound possesses psychotherapeutic properties. The 4-hydroxyethyl piperazinoethyl benzilate hydrochloride produced a marked beneficial effect in all disturbed schizophrenic patients to whom it was given. Psychomotor epileptics who were actively hallucinating when treated with this compound partly or almost completely lost evidence of hallucinations. Humans with ulcers, spastic colitis and hypertension that exhibited psychogenic disturbances have also responded effectively to 4-hydroxyethyl piperazinoethyl benzilate hydrochloride. Four or five 20 mgm. doses daily are entirely adequate for these purposes.

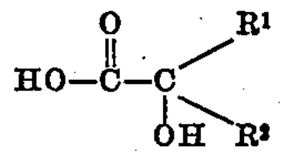
The compounds of this invention, such as N-methyl and N-ethyl-3-piperidyl benzilate hydrochloride, N-ethyl-3-piperidyl phenylcyclohexyl glycolate hydrochloride, N-methyl-3-piperidyl phenylcyclopentyl glycolate hydrochloride, N-methyl-3-piperidyl phenyl-2-thienyl glycolate hydrochloride and the like, are also useful in the shock-like treatment of mental diseases or psychocatharsis produced by the psychoanalyst. Patients in whom an intense hallucinatory state is induced by these substances have shown a considerable improvement over their previous condition. Depressed and anxious patients who complained of psychogenic disorders such as hypertension, colitis and ulcers showed distinct psychogenic improvement after one or two episodes induced by the agents of this invention. In addition to the disappearance of colitis and pains due to ulcer, there was a distinct improvement in the psychological or feeling state of the individuals which persisted for a period of months in some cases.

The described effects may be achieved in humans with compounds having the hydroxy group replaced in the above formula by groups such as halogen, acyloxy (acetoxy) phenylacyloxy (benzoxy) and related groups

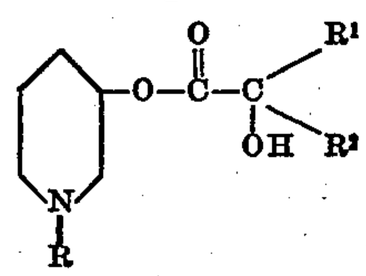
which readily split or are cleaved by hydrolysis in the body to form the hydroxy group.

The compounds of this invention, advisably in the form of nontoxic quaternary ammonium salts such as the alkyl halides like methobromide, are antispasmodics and relieve musculotropic and neurotropic spasm in animals including humans. The compounds have long duration of action and few undesirable side reactions.

The compounds of this invention are conveniently prepared by reacting an N-lower alkyl-3-halopiperidine with a compound of the formula



to produce the desired compound of the formula



wherein R, R^1 and R^2 have the significance previously assigned.

Some 3-halopiperidines which may be used in this process are N-methyl-3-chloropiperidine, N-ethyl-3-chloropiperidine, N-propyl-3-bromopiperidine and N-methyl-3-bromopiperidine, N-phenethyl-3-chloropiperidine, N-p-aminophenethyl-3-chloropiperidine and the like.

Some of the other reactants which may be employed in the process are benzilic acid, phenylcyclohexyl glycolic acid, dicyclohexyl glycolic acid, phenylcyclopentyl glycolic acid and phenyl 2-thienyl glycolic acid.

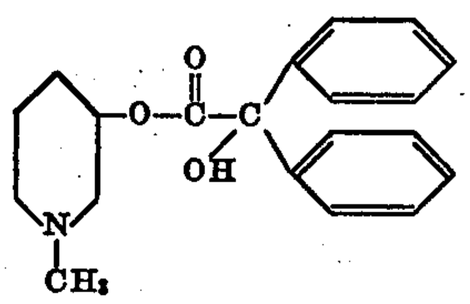
The reaction is conveniently effected by combining the reactants in a suitable inert liquid reaction medium, such as isopropanol, and refluxing the mixture. After filtering and concentrating the reaction mixture in vacuo it is added to water, acidified and the unreacted acid removed with ether. After neutralizing the aqueous layer, the product is extracted with ether and the solution dried. After removing the ether the free base is obtained by vacuum distillation.

Acid addition salts of the tertiary bases provided by this invention are readily produced by contacting the free base with a suitable acid in the presence of a solvent such as acetone, benzene, ethanol, isopropanol and ether. Typical acids which may be used are hydrochloric acid, sulfuric acid, citric acid, tartaric acid, succinic acid and benzoic acid.

The following examples illustrate the preparation of specific compounds within the scope of this invention.

EXAMPLE 1

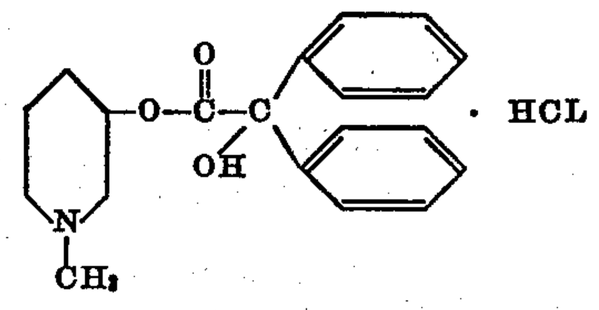
N-methyl-3-piperidyl benzilate



A mixture containing 8 g. (0.06 mole) of N-methyl-3-chloropiperidine and 13.6 g. (0.06 mole) of benzilic acid in 50 cc. of anhydrous isopropyl alcohol was refluxed for 3 days; the isopropyl alcohol was removed by distillation in vacuo, the residue treated with dilute aqueous hydrochloric acid and the aqueous acid mixture extracted repeatedly with ether. The aqueous phase was separated, made strongly alkaline with 20% aqueous sodium hydroxide and extracted with ether. The ether extracts were dried with potassium carbonate and distilled; the product was collected at 175–176° C. (0.03 mm.); yield 11.5 g. (59%).

EXAMPLE 2

N-methyl-3-piperidyl benzilate hydrochloride

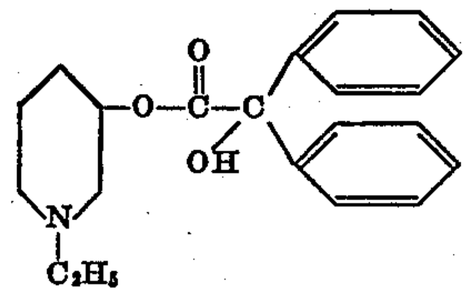


The free base of Example 1 was dissolved in isopropyl alcohol and the solution acidified to pH 3 with ethereal hydrochloric acid. The hydrochloride salt precipitated out on cooling, yield 25 g. (84%), M.P. 212–213° C.

Analysis.—Calcd. for $C_{20}H_{24}ClNO_3$: Cl, 9.78; N, 3.87. Found: Cl, 9.73; N, 3.76.

EXAMPLE 3

N-ethyl-3-piperidyl benzilate



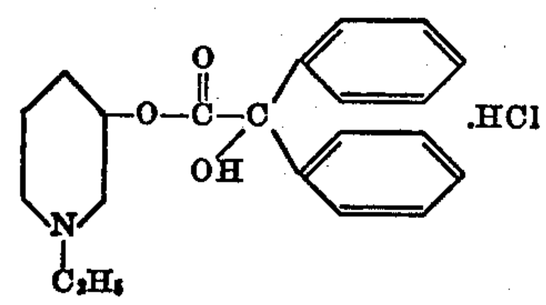
N-ethyl-3-chloropiperidine was prepared according to the method of Fuson and Zirkle described in volume 70, J. Am. Chem. Soc., page 2760.

12.0 grams (0.081 mole) of N-ethyl-3-chloropiperidine was mixed with 18.6 g. (0.081 mole) of benzilic acid and 80 cc. of anhydrous isopropyl alcohol as a solvent. The mixture was refluxed for seventy-two hours. The solution was then filtered and concentrated at 30 mm. of mercury. The concentrate was dissolved in water, acidified with hydrochloric acid and extracted with ether to remove the unreacted benzilic acid.

The aqueous layer was neutralized with sodium bicarbonate and the product was extracted with ether. The ethereal solution of the product was dried with potassium carbonate, the ether was removed by distillation and the residue was distilled at 0.12–0.18 mm. of mercury, the boiling point being 194–198° C. A yield of 16.5 g. (60%) of the compound was obtained.

EXAMPLE 4

N-ethyl-3-piperidyl benzilate hydrochloride

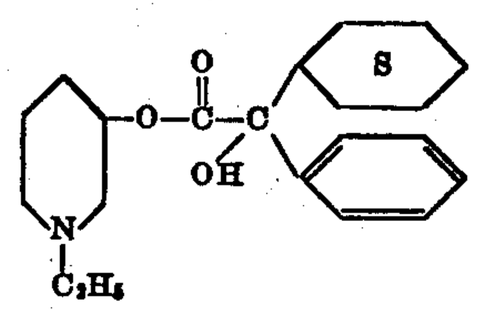


6.4 grams of the free base from Example 3 was dissolved in acetone and ethereal hydrochloric acid added. A yield of 6.2 g. of white crystals melting at 186–187° C. was obtained.

Analysis.—Calcd. for $C_{21}H_{25}ClNO_3$: Cl, 9.45%; N, 3.72. Found: Cl, 9.29%; N, 3.62.

EXAMPLE 5

N-ethyl-3-piperidyl phenylcyclohexyl glycolate and its hydrochloride



A mixture containing 31 g. (0.13 mole) of phenylcyclohexyl glycolic acid, 25 g. (0.17 mole) of N-ethyl-3-chloropiperidine and 70 cc. of dry isopropyl alcohol was refluxed

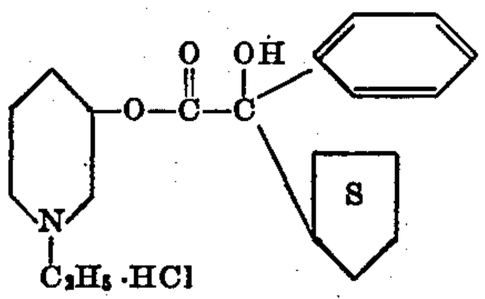
for 3 days; the solvent was removed by vacuum distillation and the residue suspended in water. The aqueous suspension was acidified with hydrochloric acid, extracted with ether and the aqueous phase made alkaline with 12 g. of sodium hydroxide. The alkaline mixture was extracted with ether, the ether extracts dried with K_2CO_3 and the ether removed by distillation. The base was distilled at 166–167° C. (0.05 mm.); yield 24 g. (53%).

The hydrochloride salt was prepared by the addition of ethereal hydrochloric acid solution to an acetone solution of the base. The white, crystalline precipitate was removed by filtration, yield 25 g. (94%); M.P. 213–215° C.

Analysis.—Calcd. for $C_{21}H_{32}ClNO_3$: Cl, 9.30; N, 3.67. Found: Cl, 9.11; N, 3.66.

EXAMPLE 6

N-ethyl-3-piperidyl-phenyl-cyclopentyl-glycolate hydrochloride

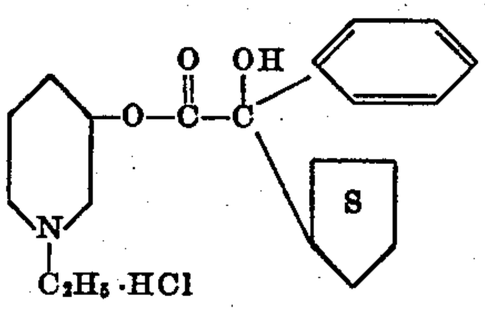


A mixture of 12.4 g. (0.056 mole) of phenyl-cyclopentyl glycolic acid, 8.3 g. (0.056 mole) N-ethyl-3-chloropiperidine and 50 cc. of dry isopropyl alcohol, as a solvent, was refluxed for 48 hours. The solvent was then removed by distillation in vacuum of the order of 15 mm. Hg. The residue was partially dissolved in aqueous hydrochloric acid and was repeatedly extracted with ether. The aqueous layer was separated, made alkaline with 20% sodium hydroxide and again extracted with ether. The ether extract was dried over anhydrous potassium carbonate at room temperature, filtered, and the ether removed by distillation at 35° C. Any low boiling materials were removed by distillation at a pressure reduced to 0.3 mm. Hg and at an oil bath temperature of 170° C. The residue was dissolved in acetone and acidified with 9.6 cc. of 3.77 M ethereal hydrochloric acid. A white precipitate formed which was filtered, washed with acetone and dried at 80° C. A yield of 11.0 g. (82% of theoretical) was obtained; M.P. of the product was 205–207° C. After recrystallization from isopropyl alcohol, the compound melted at 206–208° C.

Analysis.—Calcd. for $C_{20}H_{30}ClNO_3$: Cl, 9.66; N, 3.81. Found: Cl, 9.61; N, 3.70.

EXAMPLE 7

N-ethyl-3-piperidyl-phenyl-2-thienyl-glycolate hydrochloride



Equimolar amounts of N-ethyl-3-chloropiperidine and phenyl-2-thienyl glycolate were reacted in anhydrous isopropyl alcohol at reflux for 48 hours. The mixture was concentrated in vacuum of 15 mm. Hg. The residue was dissolved in an excess of aqueous hydrochloric acid and extracted with ether. The aqueous acid solution was neutralized with 20% aqueous sodium hydroxide solution and extracted with ether. The ether extract was dried over anhydrous potassium carbonate at room temperature, filtered and distilled to remove the ether. The basic ester was distilled, dissolved in 100 cc. of acetone and acidified with ethereal hydrochloric acid to yield a precipitate. The precipitate was filtered, washed with acetone and dried at 80° C.

The compound was obtained in 18% yield and had a melting point of 181–182° C.

Analysis.—Calcd. for $C_{19}H_{24}ClNO_3S$: Cl, 9.30%; N, 3.67%. Found: Cl, 9.19; N, 3.67%.

The psychotogens of this invention may be administered to animals and humans as pure compounds. It is advisable, however, to first combine one or more of the compounds with a suitable pharmaceutical carrier to attain a more satisfactory size to dosage relationship.

Pharmaceutical carriers which are liquid or solid may be used. The preferred liquid carrier is water. Flavoring materials may be included in the solutions as desired.

Solid pharmaceutical carriers such as starch, sugar, talc, and the like, may be used to form powders. The powders may be used as such or be tableted, or be used to fill gelatin capsules. Suitable lubricants like magnesium stearate, binders such as gelatin and disintegrating agents like sodium carbonate in combination with citric acid may be used to form the tablets.

Unit dosage forms such as tablets and capsules may contain any suitable predetermined amount of one or more of the psychotogens and may be administered one or more at a time at regular intervals. Such forms should, however, generally contain a minimum concentration of 0.1% to 10% by weight of the psychotogen.

A typical tablet may have the composition:

	Mg.
(1) N-methyl-3-piperidyl benzilate hydrochloride	10
(2) Starch, U.S.P	57
(3) Lactose, U.S.P	73
(4) Talc, U.S.P	9
(5) Stearic acid	6

Powders 1, 2 and 3 are slugged, then granulated, mixed with 4 and 5, and tableted.

Tablets may also be made of the following ingredients from the stated quantities:

	Grams
(1) N-ethyl-3-piperidyl benzilate hydrochloride	2000
(2) Lactose, U.S.P	800
(3) Dibasic calcium phosphate, U.S.P	1527.2
(4) Starch, U.S.P	799.3
(5) Calcium stearate	56.7
(6) Gelatin solution—1.5 lb./gal. of H_2O	

Powders 1, 2 and 4 are granulated using enough gelatin solution to wet the mixture. The granules are then combined with the other ingredients, gelatin solution is added to wet the mixture, and it is tableted. The size of the tablets may be varied at will although tablets of 0.25 to 0.50 gm. are satisfactory for many uses.

Capsules are prepared by filling No. 3 hard gelatin capsules with the following ingredients, thoroughly mixed:

	Mg.
N-ethyl-3-piperidyl-phenylcyclohexyl glycolate hydrochloride	5
Lactose, U.S.P	200
Starch, U.S.P	16
Talc, U.S.P	8

The most active compound appears to be N-ethyl-3-piperidyl phenylcyclohexyl glycolate hydrochloride and it is effective at a total dose of 2 to 5 mgm. orally. The other psychotogens produce the stated effects in doses ranging from 5 to 20 mgm. orally The duration of such effects vary from a minimum of a few hours for N-methyl-3-piperidyl phenyl-2-thienyl glycolate hydrochloride to over 24 hours in the case of N-ethyl-3-piperidyl phenylcyclohexyl glycolate hydrochloride.

As used herein "psychotogens" means compounds or compositions which induce, supplement, or amplify in humans and animals a state comparable or similar to the manifestations observed in a diseased mind. "Psychotogenic" is the adjective form of "psychotogens."

Various changes and modifications of the invention can be made and, to the extent that such variations incorpo-

rate the spirit of this invention, they are intended to be included within the scope of the appended claims.

What is claimed is:

1. N-methyl-3-piperidyl phenylcyclohexyl glycolate.

2. N-ethyl-3-piperidyl phenylcyclohexyl glycolate.

3. N-ethyl-3-piperidyl phenylcyclohexyl glycolate hydrochloride.

4. N-methyl-3-piperidyl phenylcyclohexyl glycolate hydrochloride.

5. The nontoxic acid addition salts of N-lower alkyl-3-piperidyl phenylcyclohexyl glycolates.

6. N-lower alkyl-3-piperidyl phenylcycloalkyl glycolate.

7. N-lower alkyl-3-piperidyl phenylcyclopentyl glycolate.

8. N-methyl-3-piperidyl phenylcyclopentyl glycolate hydrochloride.

9. A pharmaceutical tablet containing a nontoxic acid addition salt of N-methyl-3-piperidyl phenylcyclopentyl glycolate.

10. A pharmaceutical tablet containing a nontoxic acid addition salt of N-ethyl-3-piperidyl phenylcyclohexyl glycolate.

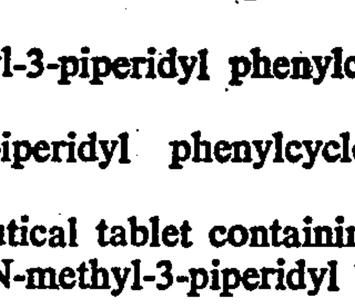
11. The method of inducing a psychotogenic state in humans and animals which comprises administering to them an effective amount of a nontoxic acid addition salt of N-ethyl-3-piperidyl phenylcyclohexyl glycolate.

12. The method of inducing a psychotogenic state in humans and animals which comprises administering to them an effective amount of a nontoxic acid addition salt of N-methyl-3-piperidyl phenylcyclopentyl glycolate.

13. N-ethyl-3-piperidyl phenylcyclopentyl glycolate.

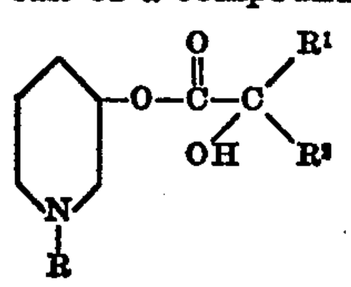
14. N-ethyl-3-piperidyl phenylcyclopentyl glycolate hydrochloride.

15. A compound of the group consisting of compounds of the formula



and nontoxic acid addition salts thereof, wherein R is a member of the group consisting of lower alkyl, phenyl-lower alkyl and phenyl-lower alkenyl, R^1 is a member of the group consisting of phenyl, cycloalkyl and thienyl and R^2 is a member of the group consisting of cycloalkyl and thienyl but is not thienyl when R^1 is phenyl.

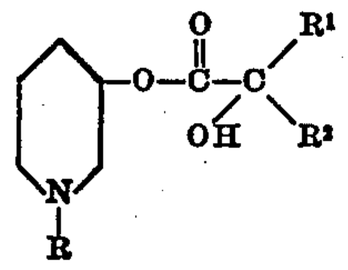
16. A pharmaceutical composition comprising a nontoxic acid addition salt of a compound of the formula



wherein R is a member of the group consisting of lower alkyl, phenyl-lower alkyl and phenyl-lower alkenyl, R^1 is a member of the group consisting of phenyl, cycloalkyl and thienyl and R^2 is a member of the group consisting of cycloalkyl and thienyl but is not thienyl when R^1 is phenyl, and in inert pharmaceutical carrier.

17. A composition according to claim 16 in which the carrier is a solid.

18. The method of inducing a psychotogenic state in humans and animals which comprises administering to them an effective amount of a compound of the formula



and nontoxic acid addition salts thereof, wherein R is a member of the group consisting of lower alkyl, phenyl-lower alkyl and phenyl-lower alkenyl, R^1 is a member of the group consisting of phenyl, cycloalkyl and thienyl and R^2 is a member of the group consisting of cycloalkyl and thienyl but is not thienyl when R^1 is phenyl.

References Cited in the file of this patent

UNITED STATES PATENTS

2,167,351	Eisleb	July 25, 1939
2,265,185	Miescher	Dec. 9, 1941
2,477,937	Paul	Aug. 2, 1949
2,486,794	Miescher	Nov. 1, 1949
2,553,002	Feldkamp	Dec. 5, 1950
2,648,667	Steinbach	Aug. 11, 1953
2,792,399	Ekenstam et al.	May 14, 1957
2,816,895	Ehrhart	Dec. 17, 1957
2,844,591	Feldkamp et al.	July 22, 1958
2,918,406	Biel	Dec. 22, 1959
2,918,408	Biel	Dec. 22, 1959

FOREIGN PATENTS

448,181	Great Britain	May 25, 1936
483,258	Great Britain	Apr. 14, 1938

OTHER REFERENCES

McElvain et al.: J.A.C.S., vol. 70, pp. 1826–1828, 1948.

Biel et al.: J.A.C.S., vol. 74, pp. 1485–1488, 1952.

Richter's Organic Chemistry, vol. 13, Blakiston's Son and Co., 1923, pp. 3–4.

Blicke et al.: J.A.C.S., vol. 64, February 1942, pp. 431–433.

Ford-Moore et al.: J. Chem'l Soc. (London), Part I, (1947), pp. 55–60.

UNITED STATES PATENT OFFICE

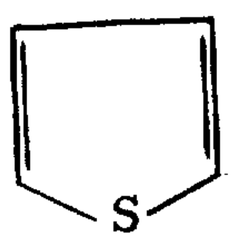
CERTIFICATE OF CORRECTION

Patent No. 2,995,492 August 8, 1961

John H. Biel

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 4, line 6, right-hand portion of the formula, for ". HCL" read -- .HCl --; column 5, lines 58 to 60, the lower right-hand portion of the formula should appear as shown below instead of as in the patent:



column 6, line 34, for "nixed" read -- mixed --; line 64, after "orally" insert a period; column 8, line 6, for "in" read -- an --; line 34, for "2,553,002" read -- 2,533,002 --; same column 8, line 35, for "Steinbach" read -- Sternbach --.

Signed and sealed this 2nd day of January 1962.

(SEAL)
Attest:
ERNEST W. SWIDER
Attesting Officer

DAVID L. LADD
Commissioner of Patents