

1

3,408,356

LONG CHAIN ESTERS OF 4'-FLUORO-4-[4-HYDROXY-4-(α,α,α -TRIFLUOROTOLYL)PIPERIDINO]BUTYROPHENONE AND THE LIKE

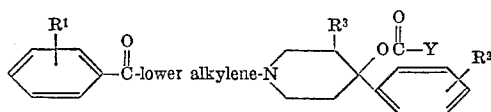
Zola P. Horovitz, East Brunswick, N.J., assignor to E. R. Squibb & Sons, Inc., New York, N.Y., a corporation of Delaware

No Drawing. Filed Aug. 31, 1965, Ser. No. 484,125

5 Claims. (Cl. 260-294.3)

ABSTRACT OF THE DISCLOSURE

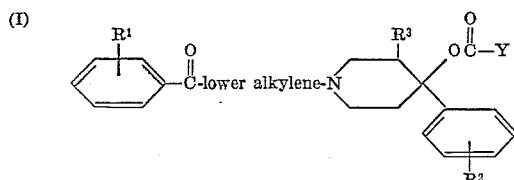
This invention relates to long chain esters of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluorotolyl)piperidino]butyrophene and related compounds having the formula



which are produced by interacting an appropriately substituted or unsubstituted [(4-hydroxy-4-phenyl)piperidino]acetophenone or the like with a long chain acyl halide and which are useful as long acting tranquilizers.

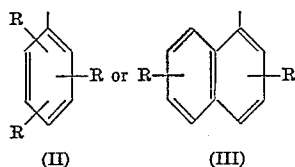
This invention relates to new derivatives of compounds having valuable therapeutic properties and pharmaceutical compositions containing the same.

The novel therapeutically active compounds of this invention include those having the general Formula I



wherein R^1 and R^2 each is hydrogen, halogen (preferably chloro or fluoro), trifluoromethyl, lower alkyl or lower alkoxy; R^3 is hydrogen or lower alkyl; and Y is higher alkyl, higher alkenyl, higher alkynyl, aryl, ω -carboxy (higher alkyl) or diphenyl-(hydroxymethyl). The terms "higher alkyl," "higher alkenyl" and "higher alkynyl" as employed herein include both straight and branched chain radicals of more than five carbon atoms up to about 17 carbon atoms.

The term "aryl" as employed herein includes substituents derived from monocyclic and bicyclic aryl carboxylic acids, and may be substituted or unsubstituted and further may be represented by the formulae



wherein each R may be hydrogen, lower alkyl, lower alkoxy or halogen (e.g. chloro or bromo) and R is preferably hydrogen, lower alkyl or lower alkoxy, and most preferably, R is hydrogen or lower alkyl. Examples of the aryl carboxylic acids which may be employed include benzoic, o-toluic, 2,6-dimethylbenzoic, 2,6-dimethylanisic, o-bromobenzoic, o-chlorobenzoic, 2,6-dichloro-

2

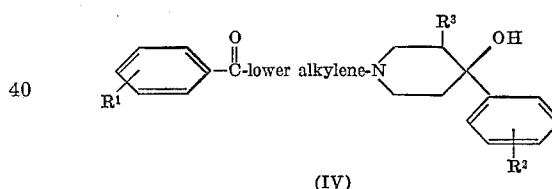
benzoic, naphthoic acid, dimethylnaphthoic acid and other like acids.

The preferred compounds of this invention are those wherein R^1 is halo, especially fluoro, R^2 is trifluoromethyl, R^3 is hydrogen, Y is a higher alkyl radical of from six to seventeen carbon atoms, especially 6 to 8 and 10 to 12 carbon atoms and R^1 is in the para position, and R^2 is in the meta position.

Since the compounds of this invention are especially adapted for parenteral administration, as more fully discussed hereinafter, they are preferably administered in the form of their free esters. The compounds, however, readily form acid-addition salts, which may be utilized in the preparation of the free esters or the purification thereof and can also be used for parenteral formulations. Acids useful for preparing the acid-addition salts include, inter alia, inorganic acids such as the hydrohalic acids (e.g., hydrochloric and hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid, and organic acids such as oxalic, tartaric, citric, pamoic, fumaric, acetic, maleic and succinic acid.

The compounds of this invention are therapeutically active substances which are utilizable as tranquilizing agents, particularly in the treatment of mental disorders such as schizophrenia. These compounds differ from the corresponding lower alkanolic acid ester derivatives or the free hydroxyl derivatives in that they are significantly longer acting when administered parenterally and thus, when injected subcutaneously, for example, in a suitable vehicle, yield a long acting tranquilizing drug which need only be administered at comparatively infrequent intervals, e.g., depending on the needs of the individual patient, twice a week to once every two or three weeks.

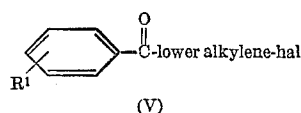
The compounds of this invention can be prepared by interacting a compound of the general Formula IV



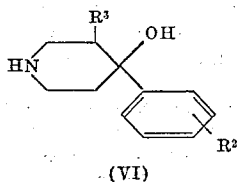
wherein the symbols have the same meaning as in Formula I, with an acyl halide (preferably acyl chloride) of the formula: YCO-halide, wherein Y is as hereinbefore defined; the reaction preferably being conducted in an organic solvent, such as chloroform, for the reactants. Among the suitable reactants may be mentioned:

- 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]butyrophene,
- 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]acetophenone,
- 2'-trifluoromethyl-4-[4-hydroxy-4-(p-chlorophenyl)piperidino]butyrophene,
- 3'-ethoxy-[4-hydroxy-(4-o-tolyl)piperidino]acetophenone, and
- 4'-bromo-[3-ethyl-4-hydroxy-4-(p-bromophenyl)piperidino]acetophenone.

The foregoing starting materials may be prepared by reacting in an inert organic solvent such as the aromatic hydrocarbons an unsubstituted or substituted benzoyl-alkyl halide of the Formula V



wherein R^1 has the same meaning as defined previously, and hal represents a halogen, preferably chlorine, with an appropriately substituted piperidine of the Formula VI



wherein R^2 and R^3 have the same meaning as in Formula I.

Among the suitable acyl halide reactants may be mentioned the acyl chlorides of higher alkanolic acids, such as heptanoic acid, octanoic acid, 2-ethylheptanoic acid, 2,2-diethylbutyric acid, capric acid, lauric acid, tridecylic acid, myristic acid, palmitic acid, and stearic acid; the acyl chlorides of higher alkenolic acids, such as 2-heptenoic acid, 2-nonenic acid, citronellic acid, undecylenic acid and oleic acid; the acyl chlorides of the alkynoic acids, such as heptynoic acid, octynoic acid, nonynoic acid, decynoic acid, dodecynoic acid, tridecynoic acid and octadecynoic acid; the acyl chlorides of the alkadienoic acids, such as heptadienoic acid, octadienoic acid, (alkyl)-octadienoic acid (e.g., 7-methyl-octadienoic acid), and nonadienoic acid; the acyl chlorides of the carboalkoxyalkanoic acids, such as carbomethoxyoctanoic acid, carbomethoxydecanoic acid and carbomethoxyundecanoic acid; the acyl chloride of aryl carboxylic acids, such as benzoic acid, o-toluic acid, dimethylbenzoic acid, dimethylanilic acid, o-bromobenzoic acid, o-chlorobenzoic acid, naphthoic acid, dimethylnaphthoic acid, diphenylacetic acid and dichlorobenzoic acid; the acyl chlorides of the carboalkoxy alkenoic acids such as ω -carbomethoxyundecylenic acid, ω -carbomethoxydodecylenic acid; and the acyl chlorides of the carboalkoxyalkynoic acids, such as ω -carbomethoxyundecylynic acid, ω -carbomethoxydodecylynic acid, and other like acids.

All of the acyl halides described hereinbefore may be prepared by heating an acid of the formula $Y-COOH$, wherein Y is as hereinbefore defined, with two parts by weight, of a thionyl halide, preferably thionyl chloride or thionyl bromide, alone, or in the presence of an anhydrous solvent, such as chloroform or benzene, under reflux for a period of about three hours, concentrating to remove the excess thionyl halide (and any solvent present), and then distilling to obtain the resultant acyl halide, $Y-CO-halide$, wherein Y is as hereinbefore defined.

The free bases, when initially formed, can be converted to acid-addition salts by treatment with the desired acid. This reaction is preferably conducted in an inert organic solvent under substantially anhydrous conditions by treating the base with the acid, whereby the acid-addition salt is formed.

To prepare the preferred compositions of this invention, the compounds of this invention, in the form of their free basic esters or acid addition salts, are dissolved or suspended, respectively, in a parenterally acceptable liquid vehicle. For prolonged action, the compounds are formulated in an oil such as peanut oil, sesame oil, cottonseed oil, corn oil, soybean oil, synthetic glycerol esters of long chain fatty acids and mixtures of these and other oils; the compound preferably being present in a concentration to give about 10 mg. to about 300 mg., preferably about 12 to about 25 mg., of the compound per ml. The preferable route of administration of these formulations is subcutaneous.

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

EXAMPLE 1

5 Heptanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]butyrophenone

(a) Preparation of the heptanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]butyrophenone hydrochloride.—To a stirred solution of 40.9 g. of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]butyrophenone in 300 ml. of dry chloroform is added, dropwise, 16.3 g. of heptanoyl chloride in 50 ml. of dry chloroform. Subsequently, the reaction mixture is stirred and heated under reflux for five hours, cooled, and shaken with 5% aqueous hydrochloric acid. The dried chloroform solution is concentrated to about 50 ml., cooled and diluted with about 450 ml. of anhydrous ether. To this cooled solution is added about 10 ml. of ethereal hydrogen chloride. The crystalline solid which separates is filtered, and the solid recrystallized from a mixture of alcohol and ether to give the product.

(b) Preparation of the heptanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]butyrophenone.—An ice-cooled mixture of the hydrochloride obtained in step (a), 500 ml. of 5% aqueous potassium carbonate solution and 1000 ml. of ether are stirred until all the solid has reacted. The ether layer is separated, dried and concentrated to give the product.

Similarly, by substituting an equivalent amount of the following acyl chlorides for the heptanoyl chloride in step (a) of Example 1, and following the procedure of steps (a) and (b), the indicated ester is obtained.

Acyl chloride:	Ester:
Octanoyl chloride	Octanoic
Lauroyl chloride	Lauric
Stearoyl chloride	Stearic
2-Heptenoyl chloride	2-Heptenoate
2-Nonenoyl chloride	2-Nonenoate
Citronelloyl chloride	Citronellic
Undecylenoyl chloride	Undecylenic
Heptadienoyl chloride	Heptadienic
Heptynoyl chloride	Heptynoic
Dodecynoyl chloride	Dodecynoic
Benzoyl chloride	Benzoic
Naphthoyl chloride	Naphthoic
Carbomethoxyundecylenoyl chloride	Carbomethoxyundecylenic
Carbomethoxyundecanoyl chloride	Carbomethoxyundecanoic
Carbomethoxyundecylynoyl chloride	Carbomethoxyundecylynic

EXAMPLE 2

2,2-diethylbutyric acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]acetophenone

To 19.3 g. of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]acetophenone in one liter of dry chloroform is added, dropwise, 8.9 g. of 2,2-diethylbutyryl chloride in 100 ml. of dry chloroform. The mixture is then refluxed for two hours and concentrated until free of chloroform. The residual oil is added to a suspension of 20 g. of sodium bicarbonate in 200 ml. of ice water and 500 ml. of ether. The mixture is shaken carefully until no further evolution of carbon dioxide occurs, the ether layer is separated, dried and concentrated to give 2,2-diethylbutyric acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)piperidino]acetophenone.

5

EXAMPLE 3

2,2-diethylbutyric acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]acetophenone, salt with maleic acid

10.2 g. of the product obtained in Example 2 is dissolved in 50 ml. of dry chloroform, the solution is cooled, and a saturated solution of 2.32 g. of maleic acid in dry acetone is added dropwise. The precipitated solid is filtered and recrystallized from dry acetone to give the 2,2-diethylbutyric acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]acetophenone, salt with maleic acid.

EXAMPLE 4

10-undecenoic acid ester of 2'-trifluoromethyl-4-[4-hydroxy-4-(p-chlorophenyl)-piperidino]butyrophenone

Following the procedure set forth in Example 2 but substituting 10.1 g. of 10-undecenoyl chloride for 2,2-diethylbutyryl chloride and 21.3 g. 2'-trifluoromethyl-4-[4-hydroxy-4-(p-chlorophenyl)-piperidino]butyrophenone for the acetophenone starting material yields the 10-undecenoic acid ester of 2'-trifluoromethyl-4-[4-hydroxy-4-(p-chlorophenyl)-piperidino]butyrophenone. 11.8 g. of this material are dissolved in 100 ml. of dry chloroform, the solution is cooled, and 20 ml. of a 1 molar solution of hydrogen chloride in anhydrous ether is added, dropwise, with stirring. The clear solution which forms is evaporated free of solvents and the residue triturated with anhydrous ether. The solid is recrystallized from anhydrous acetone-ether to yield the hydrochloride salt of the 10-undecenoic acid ester of 2'-trifluoromethyl-4-[4-hydroxy-4-(p-chlorophenyl)-piperidino]butyrophenone.

EXAMPLE 5

Decanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]acetophenone

Following the procedure set forth in Example 2, but substituting 9.5 g. of decanoyl chloride for 2,2-diethylbutyryl chloride, there is obtained the decanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]acetophenone. Treatment of 10.8 g. of this material according to the procedures set forth in Example 4 yields the hydrochloride salt of 10-decanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]acetophenone.

Similarly, following the procedure set forth in Example 2 but substituting equivalent amounts of diphenylacetyl chloride, heptynoyl chloride, 8-carbomethoxy octanoyl chloride, 2,6-dimethylbenzoyl chloride, 2,6-dichlorobenzoyl chloride, o-bromobenzoyl chloride and o-chlorobenzoyl chloride for the 2,2-diethylbutyryl chloride yields respectively, the diphenylacetic acid, heptynoic acid, 8-carbomethoxyoctanoic acid, 2,6-dimethylbenzoic acid, 2,6-dichlorobenzoic acid, o-bromobenzoic acid, and o-chlorobenzoic acid esters of the starting compounds of Examples 2 to 5.

EXAMPLE 6

8-carbomethoxyoctanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-p-tolyl)-piperidino]butyrophenone

Following the procedure set forth in Example 2, but substituting 22.0 g. of 8-carbomethoxyoctanoyl chloride for the 2,2-diethylbutyryl chloride and 41.0 g. of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-p-tolyl)-piperidino]butyrophenone for the m-tolyl starting material, there is obtained the 8-carbomethoxyoctanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-p-tolyl)-piperidino]butyrophenone. Treatment of 11.8 g. of this product in accordance with the procedure set forth in Example 3 yields the maleic acid salt.

6

Similarly, following the above procedure, but substituting equivalent amounts of 10-carbomethoxydecanoyl chloride and 11-carbomethoxyundecanoyl chloride for 8-carbomethoxyoctanoyl chloride, the respective 10-carbomethoxydecanoic acid and 11-carbomethoxyundecanoic acid esters are obtained.

EXAMPLE 7

Benzilic acid ester of 4'-fluoro-4-[4-hydroxy-3-methyl-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone

(a) To 4.23 g. of 4'-fluoro-4-[4-hydroxy-3-methyl-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone in 50 ml. of chloroform is added 2.65 g. of 2,2-bis-phenyl-2-chloroacetyl chloride in 25 ml. of chloroform. The mixture is refluxed for 24 hours and concentrated to give the ester with 2,2-bis-phenyl-2-chloroacetic acid, hydrochloride.

(b) The product from (a) in 50 ml. of ether, 250 ml. of water and 1.7 g. of sodium bicarbonate are stirred and heated at 35° for one hour. The ether layer is separated, dried and concentrated to give the free benzilic acid ester.

EXAMPLE 8

Parenteral Formulation A.—50 g. of the heptonic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone is dissolved in 1000 ml. of sesame oil, U.S.P. The solution is sterile filtered and packaged aseptically for parenteral administration.

EXAMPLE 9

Parenteral Formulation B.—A suspension of 56 g. of micronized heptanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone, hydrochloride, 0.36 g. of lectihin N.F., 0.18 g. of Tween 80 and 1.68 g. of aluminum monostearate (purified), diluted to 1000 ml. with sesame oil is prepared under sterile conditions and packaged aseptically for parenteral administration.

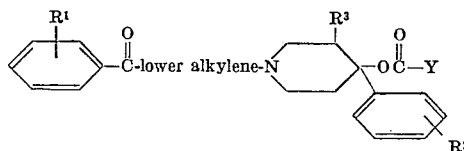
EXAMPLE 10

Parenteral Formulation C.—A solution of 50 g. of the heptanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone, 1.5 g. aluminum monostearate (purified) diluted to 1000 ml. with sesame oil, U.S.P., is sterile filtered and packaged aseptically for parenteral administration.

The esters of Examples 2 to 7 may be formulated similarly to the compositions of Examples 8 to 10.

What is claimed is:

1. A compound of the formula



wherein R¹ is selected from the group consisting of halogen, trifluoromethyl and lower alkoxy; R² is selected from the group consisting of halogen, trifluoromethyl and lower alkyl; R³ is selected from the group consisting of hydrogen and lower alkyl, and Y is selected from the group consisting of alkyl of 6 to 17 carbons, alkenyl of 6 to 17 carbons, w-carbomethoxy-alkyl wherein the alkyl has 6 to 17 carbons, phenyl, halophenyl, and diphenyl (hydroxy methyl) and the acid addition salts thereof.

2. Heptanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone.

3. Undecenoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone.

4. Decanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-m-tolyl)-piperidino]butyrophenone.

5. Heptanoic acid ester of 4'-fluoro-4-[4-hydroxy-4-(α,α,α -trifluoro-p-tolyl)-piperidino]butyrophenone.

(References on following page)

References Cited

UNITED STATES PATENTS

2,589,943	3/1952	Jensen	-----	260—294.3
2,880,211	3/1959	Elpern	-----	260—294.3

5

FOREIGN PATENTS

963,639	7/1964	Great Britain.
397,677	2/1966	Switzerland.

OTHER REFERENCES

Janssen, J. Med. Chem., vol. 2, pp. 31, 35, 41, 43, and 44 (1960).

Harper et al. J. Pharm Pharmac, 18, pp. 150—160, (1966).

HENRY R. JILES, *Primary Examiner*.

E. LEWIS, A. D. SPEVACK, *Assistant Examiners*.