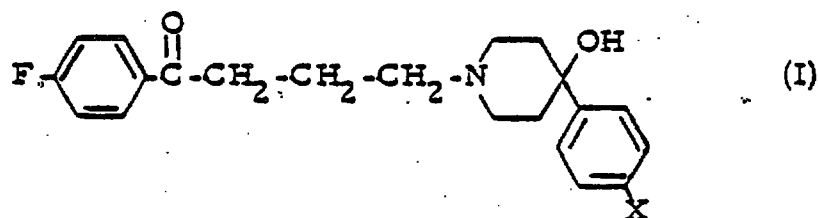


LONG-ACTING PARENTERAL COMPOSITIONS OF HALOPERIDOL
AND BROMPERIDOL DERIVATIVES.

Haloperidol, being chemically designated as 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidiny]l-1-(4-fluorophenyl)-1-butanone, and bromperidol, being chemically designated as 4-[4-(4-bromophenyl)-4-hydroxy-1-piperidiny]l-1-(4-fluorophenyl)-1-butanone, are both well-known psychotropic agents belonging to the class of 4-piperidinols which are described in Japanese Pat. No. 300,049.

Structurally, haloperidol and bromperidol are represented by the formula



wherein X is respectively chloro (haloperidol) or bromo (bromperidol).

The compounds are powerful psychotropic drugs which can be used in psychotropic therapy permitting the return to normal pursuits of patients who otherwise might require prolonged or repeated hospitalization.

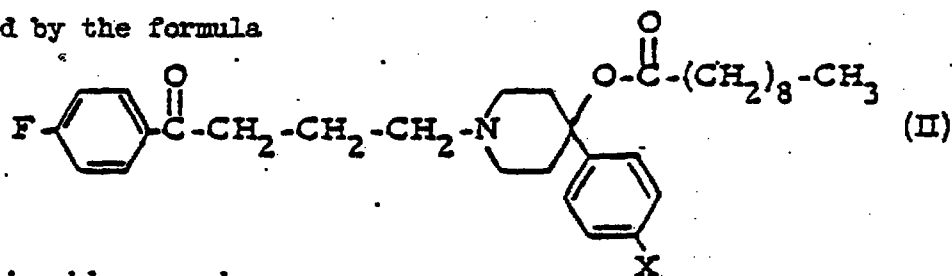
After initial recovery or discharge of the patients it is advisable and mostly indispensable to continue the therapy with a maintenance dose to prevent the frequent relapses which are recorded at varying lengths of time after the suspension of treatment. Although parenteral administration is replaced by oral administration,

as soon as possible, many times it is not practicable and then the frequency of injection gets burdensome. This frequency of injection, which is oftentimes accompanied by tissue irritation, makes it desirable to find a composition for intramuscular administration which preserves the psychotropic properties of haloperidol or bromperidol while the frequency of administration can be reduced.

In U.S. Pat. No. 3,408,356 there are described a series of long-chain esters of piperidinols and in particular, long-chain esters of 1-(4-fluorophenyl)-4-[3-(trifluoromethyl)phenyl]-4-hydroxy-1-piperidinyl-1-butanone, which is generally known as trifluoperidol or triperidol. Also disclosed are pharmaceutical compositions comprising said long-chain esters in suitable vehicles. According to U.S. Pat. No. 3,408,356 the concerned compounds exhibit prolonged tranquilizing activity, particularly in the treatment of mental disorders.

The present invention is specifically concerned with pharmaceutical compositions comprising a decanoic acid ester of haloperidol or bromperidol in sesame oil as a solvent.

The decanoic acid esters, which are used as active ingredients in the compositions according to the present invention, are represented by the formula



wherein X is chloro or bromo.

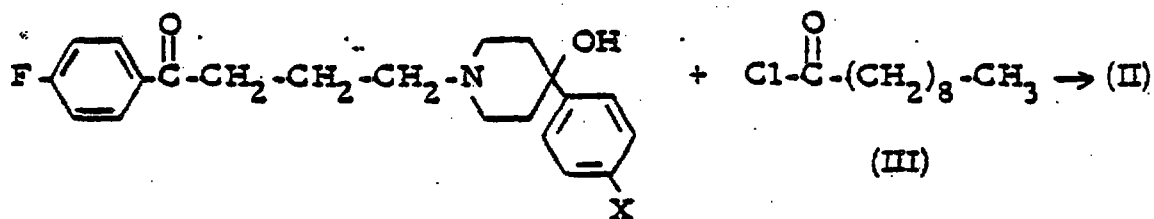
The subject compositions of the present invention are highly efficacious and at the same time remarkably safe and almost completely free of any undesired side-effects. More especially, when administered to warm-blooded animals, the said compositions provoke a long-lasting and nevertheless uniform psychotropic effect, which can be varied in duration to up to several weeks depending upon the concentration and the amount of decanoic acid ester which is present in the composition.

The compositions of the present invention have been found remarkably free of excitatory and extrapyramidal side-effects which are rather frequently encountered during trifluoperidol therapy.

It is evident that a reduction or even complete absence of such side-effects are a prerequisite to a therapy with long-acting psychotropic agents since such effects, if existing, will continue during a long period of time, even after interruption of the treatment. The reduction of these side-effects or even the complete disappearance thereof renders the compositions of the present invention particularly attractive for long-term parenteral therapy. In this respect the subject compositions show a marked superiority over any long-acting psychotropic composition presently in use.

It has been found that the intramuscular or subcutaneous administration of piperidinols such as haloperidol and bromperidol is often associated with tissue irritation. Quite unexpectedly, the compositions of the present invention are found to be substantially free of any tissue irritation.

The compounds of formula (II) may easily be prepared by acylating haloperidol (I-a) or bromperidol (I-b) with decanoyl chloride (III).



(I-a) X = Cl

(I-b) X = Br

Said acylating reaction is preferably carried out following art-known acylating procedures, such as by stirring the reactants together, if desired, in the presence of a suitable solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile, 2-propanone, and the like. Somewhat elevated temperatures are appropriate to enhance the rate of the reaction. Most preferably the reaction is carried out in the presence of an appropriate base, e.g., sodium

carbonate, pyridine and the like, to captivate the hydrochloric acid which is liberated during the course of the reaction.

The preparations of the piperidinols of formula (I) are generally known. They may be prepared following one of the procedures described in the literature, e.g., following one of the procedures described in Japanese Pat. No. 300,049.

The effectiveness and the extended duration of action of the compositions comprising a decanoate ester of haloperidol or bromperidol can be demonstrated by apomorphine emesis studies.

- 10 Apomorphine hydrochloride is a central emetic which induces vomiting within a few minutes after subcutaneous injection, except when the test-animals are pretreated with effective neuroleptics. The duration of effectiveness may be determined by chronic induction of apomorphine emesis.
- 15 Appropriately selected dogs are injected intramuscularly in the biceps femoris with a test dose. Four hours after dosing and 90 minutes following feeding, apomorphine hydrochloride (0.31 mg/kg) is injected subcutaneously. The animals are observed during 30 minutes following the injection. Thereafter, the apomorphine hydrochloride is administered daily, 90 minutes following feeding, and observations of the response made during 30 minutes. The duration of action is the period between the first absence of emetic response and the first of three consecutive positive emetic responses.

Table I illustrates the median duration of action, the test being carried out on 5 dogs.

Table I

Compound	Dose mg/kg	Median duration of action (days)
haloperidol	2.5	5
haloperidol decanoate	2.5	21
bromperidol	1.5	4
bromperidol decanoate	1.5	19

The compositions according to the present invention may contain a suitable antimicrobial preservative but other additives normally are not necessary. An example of such a preservative is benzyl alcohol.

5 The compositions may be prepared in a conventional manner, e.g., by admixing the ester with the preservative, if present, and then with the sesame oil. The concentration of the decanoic acid ester may be from about 30 to about 150 mg per milliliter.

10 By the present invention there is also provided a method of effecting psychotropic therapy which comprises administering to a subject needing such therapy, a psychotropically effective amount of a compound of formula (II) in a composition according to the invention. Psychotropic therapy may generally be effected by administering such compositions in an amount sufficient to supply from 0.4 to 20 mg
15 of active ingredient per kg of body weight.

The preferred route of administration is intramuscular although subcutaneous administration may also be employed.

The following Examples I and II illustrate the preparation of compounds for use in the composition of the invention.

20 Example III is an illustration of the invention.

Example I

To a warmed suspension of 37.6 parts of 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone in 320 parts of propanone are added successively 15.3 parts of N, N-diethylethanamine and 28.9 parts of decanoyl chloride. The resulting mixture is heated and refluxed for 18 hours. After cooling the mixture is filtered and the filtrate is evaporated under reduced pressure, yielding a residue which is triturated with 1,1'-oxybisethane to separate the triethylamine hydrochloride by-product. The filtrate is concentrated and purified by column-chromatography using 1,1'-oxybisethane as eluent, yielding 33 parts (66.3%) of 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl decanoate, as a viscous oil.

Example II

To a stirred and warm (60°C) solution of 10 parts of 4-[4-(4-bromophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone in 90 parts of N,N-dimethylformamide are added dropwise 5.76 parts of decanoyl chloride. Upon completion, stirring at 60°C is continued overnight. The reaction mixture is cooled and poured onto water. The mixture is alkalized with a sodium hydroxide solution 2N. The aqueous phase is decanted and the sticky oil is dissolved in 1,1'-oxybisethane at room temperature whereupon the unreacted starting material is filtered off. The 1,1'-oxybisethane-phase is washed twice with water, dried, filtered and evaporated. The oily residue is purified by column-chromatography over silica gel using 1,1'-oxybisethane as eluent, yielding 8.4 parts of 4-(4-bromophenyl)-1-[4-(4-fluorophenyl)-4-oxobutyl]-4-piperidinyl decanoate as an oil.

Example III

Injectable compositions are prepared by intermixing the components:

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composition A:

Haloperidol decanoate	70.5 grams
Benzyl alcohol	12 grams
Sesame oil, q. s. ad	1 liter

composition B:

Haloperidol decanoate	141 grams
Benzyl alcohol	12 grams
Sesame oil, q. s. ad	1 liter

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composition C:

Bromperidol decanoate	34 grams
Benzyl alcohol	12 gram
Sesame oil, q. s. ad	1 liter

composition D:

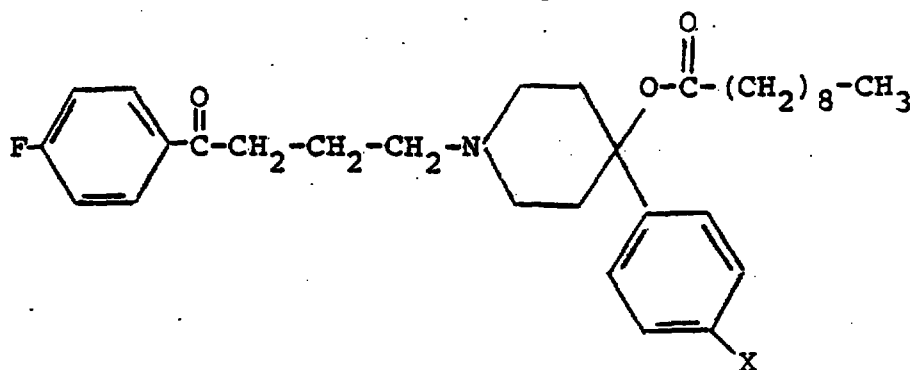
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Bromperidol decanoate	136 grams
Benzyl alcohol	12 grams
Sesame oil, q. s. ad	1 liter.



CLAIMS

1. A psychotropic composition, suitable for parenteral administration, comprising sesame oil as a solvent and as an active ingredient an effective psychotropic amount of a decanoic acid ester having the formula:



wherein X is a chlorine or bromine atom.

2. A composition as claimed in claim 1 comprising from 30 mg to 150 mg of 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxo-butyl]-4-piperidiny decanoate per ml.

3. A composition as claimed in claim 1 comprising from 30 mg to 150 mg of 4-(4-bromophenyl)-1-[4-(4-fluorophenyl)-4-oxo-butyl]-4-piperidiny decanoate per ml.

4. A composition as claimed in claim 2 which is suitable for intramuscular and subcutaneous administration.



5. A composition as claimed in claim 3 which is suitable for intramuscular and subcutaneous administration.

6. A composition as claimed in any one of the preceding claims which contains an antimicrobial preservative.

7. A composition as claimed in claim 6 wherein the preservative is benzyl alcohol.

8. A composition as claimed in claim 1 substantially as hereinbefore described.

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