

PATENT SPECIFICATION

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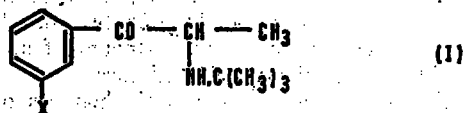
- (72) The inventor of this invention in the sense of being the actual deviser thereof within the meaning of Section 16 of the Patents Act 1949 is NARIMAN BOMANSHAW MEHTA of Springdale Estates, Route 6, Raleigh, North Carolina 27609, U.S.A., a citizen of the United States of America

(54) BIOLOGICALLY ACTIVE KETONES

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1., a company incorporated in England do hereby declare the invention which was communicated from BURROUGHS WELLCOME & CO. (U.S.A.) INC., of 1, Scarsdale Road, Tuckahoe, New York 10707, a Company incorporated in the State of New York, United States of America, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to α -alkylaminopropiophenones, the preparation thereof and pharmaceutical compositions containing them.

It has been found that the two novel compounds represented by the general formula (I)

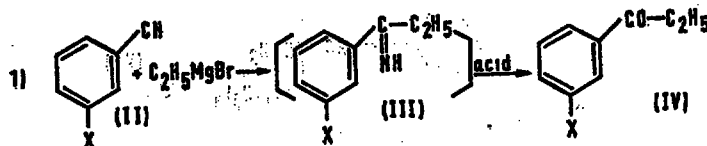


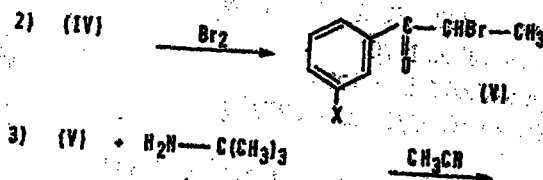
and acid addition salts thereof, in which X is chlorine or fluorine, possess valuable properties as antidepressants when tested by standard techniques used in the art for determining antidepressant activity; for example the tetrabenazine-induced sedation test in rodents. It has been found specifically that the compounds of formula (I) require much larger doses for stimulant action than for antidepressant action. The compounds are also not inhibitors of mono-amine oxidase, nor do they have a pressor effect.

Closely related alkylaminopropiophenones are already known and have been proposed for various pharmaceutical purposes; see for example British Patent Specifications 768,772; 1,011,289; and 1,069,797. The activity of the two novel compounds of the present invention appears to be outstanding and not possessed by related known compounds.

The compounds may be synthesised by the methods known in the art for this type of compound.

A particularly convenient route is that set out in the following reaction scheme:





The propiophenones, (IV), are not commercially available, and Step 1) has been found a convenient method of preparation. The bromination Step 2), is not very rapid and may require heating. It is not necessary to isolate the ketone (V) as a pure substance provided the hydrogen bromide produced in Step 2) is removed.

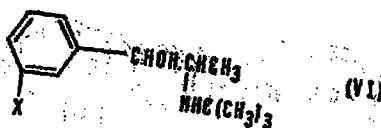
It will of course be understood that in Step 3) above, the *m*-X-α-bromopropiophenone (V) may be replaced by the corresponding α-chloro- or α-iodo compounds. *m*-X-α-Chloropropiophenones may be prepared conveniently by reaction of *m*-X-propiophenone with sulphuryl chloride. The *m*-α-dichloropropiophenone may also be conveniently prepared from α-chloropropiophenone by reaction with sulphuryl chloride in the presence of aluminium chloride. In respect of the compound *m*-α-dichloropropiophenone and the preparation thereof reference is made to application no 30404/73 (Serial No. 1340033). The reaction of Step 3) is subject to hindrance and *t*-butylamine normally reacts very slowly with α-bromopropiophenones. It is desirable to include an organic solvent in the reaction mixture, and for this purpose acetonitrile offers marked advantages. It is a "fast" solvent, is unreactive under the conditions and is relatively low boiling. Other polar solvents, protic or aprotic, may be used, for example lower aliphatic ketones (i.e. those having from 1 to 4 carbon atoms in each alkyl group) or ethers, but the reaction is slow in these solvents. Others which may be used include dimethylformamide, nitromethane, dimethylsulphoxide and hexamethylphosphoramide.

It is desirable to heat the reactants of Step 3), for example at the reflux temperature of the reaction mixture. The amine is preferably present in excess relative to the ketone; up to five times the equimolar quantity may be used. If the ketone is a *m*-X-α-chloropropiophenone, then a catalytic amount of an iodide salt, for example sodium iodide, may be included in the reaction mixture.

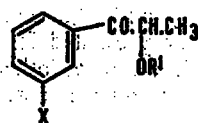
Once isolated, the *m*-X-α-*t*-butylaminopropiophenones of formula (I) are stable and can be distilled *in vacuo* although this is not normally necessary. They are moderately weak bases (pK_a around 8.5—9) and are desirably stored and administered as a pharmaceutically acceptable salt, conveniently one of a mineral acid such as the hydrochloride salt. Under physiological conditions, they would be predominantly (but not exclusively) cationic. In any case, if administered as one salt, they would be in equilibrium with the various anions corresponding to other acids present in the body and their salts with different acids can possess advantages only in convenience of isolation or solubility not in inherent physiological behaviour. Accordingly, it is considered that all salts of the bases of formula (I) with non-toxic acids are equivalent to each other and to the bases.

It will be readily understood that salts of acids which are not pharmaceutically acceptable may also have value as intermediates for the preparation of the acceptable salts by double decomposition, base exchange and other well known methods.

A further method is the oxidation of the corresponding amino-secondary alcohol of the formula (VI). Oxidation may be conveniently affected by known methods, and in particular by the Oppenauer oxidation reaction using excess of a ketone, for example acetone or cyclohexanone, in the presence of an aluminium alkoxide, for example aluminium isopropoxide.



The compounds of formula (I) and their acid addition salts may also be prepared by the reaction with *t*-butylamine of an *m*-X-α-alkoxypropiophenone of the formula (VII)



(VII)

wherein OR' is a lower alkoxy radical of 1 to 3 carbon atoms, preferably ethoxy, and X is as hereinbefore defined. This reaction is preferably carried out in a polar solvent, such as hereinbefore described, the reactants being heated at the reflux temperature of the reaction mixture. The compound of formula (VII) may be obtained by reaction of an alkali metal alkoxide with the corresponding *m*- α -dihalopropiophenone.

According to the present invention there is provided a compound of the formula (I) and a pharmaceutically acceptable salt thereof.

According to the present invention, in yet another aspect, there is provided a pharmaceutical composition (preferably in unit dosage form) comprising a compound of formula (I) (or a pharmaceutically acceptable salt thereof) together with a pharmaceutically acceptable carrier. Conveniently the compound of formula (I) or its acid addition salt comprises from 5 to 95% by weight of the composition.

According to the present invention in yet another aspect there are provided the methods described above for synthesising compounds of formula (I), analogous to those methods known in the art for the preparation of alkylaminopropiophenones.

According to a still further aspect of the present invention, there is provided a method of treating a depressed state in mammals, other than man, such as mice, rats, etc., which comprises the administration of an anti-depressant effective non-toxic amount (dose), preferably in a unit dosage form, of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The compound of formula (I) (the active ingredient) or the pharmaceutically acceptable salt thereof is preferably administered in unit dosage form to the mammal being treated.

The compounds of this invention may be administered orally, parenterally or rectally.

A pharmaceutical composition suitable for use in the treatment of the depressed state containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier therefor, may be presented in discrete units such as tablets, cachets, capsules, ampoules or suppositories, each containing an effective antidepressant non-toxic amount of the compound, and such tablets may optionally be coated.

The preferred dosage for parenteral administration of a compound of formula (I) (estimated as the base) is about 5 mg/kg to 50 mg/kg of mammal body weight, and the most preferred dosage being 15 mg/kg to 35 mg/kg of mammal body weight.

A pharmaceutical composition suitable for parenteral administration is conveniently presented as a discrete dosage unit containing from 7.5 to 250 mg. of the compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, estimated as the base.

For the oral or rectal mode of administration, the preferred dosage of a compound of formula (I) (estimated as the base) is about 10 mg/kg to 100 mg/kg of mammal body weight while the most preferred dosage (estimated as the base) is about 30 mg/kg to 70 mg/kg of mammal body weight. A compound of formula (I), or an acid addition salt thereof, is preferably administered four times daily although the number of daily administrations of the medication may vary according to the patient (mammal) being treated, and the exercise of the physician's discretion.

For the treatment of humans, the preferred unit dosage of a compound of formula (I) or an acid addition salt thereof (estimated as the base) for oral administration, or administration as a suppository, is about 15 milligrams to 500 milligrams with the more preferred unit dosage being about 100 milligrams to 300 milligrams, and the most preferred unit dosage being about 125 milligrams to 250 milligrams. All the above doses are given in terms of the weight of a compound of formula (I) in the form of its base, but as will be appreciated from the foregoing information, it is preferably administered in the form of a pharmaceutically acceptable acid addition salt thereof.

A compound of formula (I) or pharmaceutically acceptable salts thereof may be presented as an oral unit preparation (for example as a cachet, tablet or capsule) containing one or more pharmaceutically acceptable carriers which may take the form of solid diluents such as lactose, cornstarch, micronized silica gel, as well as other excipients well known in the art for this purpose.

A compound of formula (I) or a pharmaceutically acceptable salt thereof may be presented for rectal use as a suppository with the usual pharmaceutically acceptable carriers such as cocoa butter, and may be presented for parenteral use as an ampoule of a sterile solution or suspension with water or other pharmaceutically acceptable liquid as the carrier therefor, or as an ampoule of a sterile powder for dilution with a pharmaceutically acceptable liquid.

It should be understood that in addition to the aforementioned ingredients, the pharmaceutical compositions of this invention may include one or more of additional ingredients such as diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives, and the like. The formulations may be prepared by admixture of the ingredients, and, if necessary, shaping the resulting mass, and filling into suitable containers.

The compound of formula I is preferably presented for use in the treatment of depressed states as a pharmaceutically acceptable salt. Examples of some of the pharmaceutically acceptable salts which can be utilized are salts of the following acids; hydrochloric, sulfuric, phosphoric and toluenesulphonic.

The invention will now be illustrated with reference to the following examples:—

EXAMPLE 1

Preparation of *m*-Chloro- α -t-butylaminopropiophenone

a) *m*-Chloropropiophenone

To ethyl magnesium bromide (2 l.; 3M) was added over 45 minutes with stirring and cooling *m*-chlorobenzonitrile (688 gm.; 5 mole) in ether (2.5 l.). The resultant solution was heated under gentle reflux for 5 hours.

The reaction-mixture was hydrolyzed with cold dilute hydrochloric acid, the ether was distilled off, and the aqueous solution was heated at 90°C. for one hour. The flask was then cooled and seeded. The solid ketone that separated was washed with cold water and recrystallized from methanol. The recrystallized ketone, m.p. 39—40°, weighed 750 gm.

b) *m*-Chloro- α -bromopropiophenone

In methylene chloride (3 l.) was dissolved *m*-chloropropiophenone (698 gm.; 4.15 mole). The solution was stirred with charcoal ("DARCO"—Trade Mark) and magnesium sulfate for two hours and filtered. To it was added with stirring 662 grams (that is 4.15 mole less 2 g.) of bromine in methylene chloride (1 l.). When the bromine colour had faded completely, the solvent was evaporated *in vacuo*.

c) *m*-Chloro- α -t-butylaminopropiophenone hydrochloride

The oily residue obtained in the manner of paragraph (b) was dissolved in acetonitrile (1300 ml.). To this, t-butylamine (733 gm.) in acetonitrile (1300 ml.) was added while keeping the temperature below 32°C. The reaction mixture was allowed to stand over-night. It was then partitioned between water (4200 ml.) and ether (2700 ml.). The aqueous layer was extracted with a further portion of ether (1300 ml.). The combined ethereal layers were then washed with water (4200 ml.) to which hydrochloric acid was added until the pH of the aqueous layer was 9. The aqueous layer was separated and washed with ether (500 ml.) and then discarded. The combined ethereal layers were then stirred with ice (560 gm.) and concentrated hydrochloric acid (324 ml.). The ethereal layer was separated and again washed with water (200 ml.) and concentrated hydrochloric acid (50 ml.). These last two acid layers were combined and concentrated *in vacuo* until crystals appeared. The solution was then chilled to 5°C and filtered. The product was sucked dry, washed with acetone and recrystallized from a mixture of isopropanol (3 l.) and absolute ethanol (800 ml.). The DL-*m*-chloro- α -t-butylaminopropiophenone hydrochloride so obtained was analytically and spectrographically pure, m.p. 233—234°C.

EXAMPLE 2

Preparation of *m*-Floro- α -t-butylaminopropiophenone

a) *m*-Fluoropropiophenone

Ethyl magnesium bromide was reacted with *m*-fluorobenzonitrile by the procedure of Example 1(a). The ketone boils at 89°C at 8 mm pressure and melts at 29—30°C.

b) *m*-Fluro- α -t-butylaminopropiophenone hydrochloride

The bromination of the product described in paragraph 2(a) was conducted as described in Example 1(b), and reaction of the α -bromoketone with t-butylamine as

described in Example 1(c). The DL-aminoketone hydrochloride melted at 225—226°C.

While in the processes of Example 1 and 2, the hydrochlorides were obtained directly without isolation of the bases, it is also feasible to separate the bases by vacuum distillation. *m*-Chloro- α -t-butylaminopropiophenone was distilled at 52°C and 5 μ (0.005 mm.) Hg pressure. The *m*-fluoro analogue was distilled at 44—48°C and 40 μ (0.04 mm.) Hg pressure.

EXAMPLE 3

(a) α -Chloropropiophenone

Propiophenone (26 gm.; 0.2 moles) was dissolved in tetrachloroethane to give a solution (100 ml.) into which was added sulfuryl chloride (27 gm.; 0.2 mole) at room temperature. There was an immediate warming with vigorous evolution of acidic fumes for five minutes. After standing 0.5 hour, the mixture was warmed to 90°C for 20 minutes and then evaporated and the residual oil distilled to give α -chloropropiophenone in three fractions with b.p. 76°C at 0.5 mm. Hg.

(b) α -*m*-Dichloropropiophenone prepared from propiophenone via α -chloropropiophenone

Propiophenone (67.1 gm.; 0.5 mole) was dissolved in tetrachloroethane (200 ml.) and then cooled to approximately 0°C. Sulphuryl chloride (74.2 gm.; 0.55 mole) was added and the temperature maintained at less than 30°C. When the acidic fumes had ceased, the solution was heated to 90°C for 10 minutes and then cooled to 15°C while anhydrous aluminum chloride (146.7 gm.; 1.1 mole) was added. This suspension was heated at 70°C for one hour when about half the aluminum chloride had dissolved. Into this stirred suspension was added sulfuryl chloride (74.2 gm.; 0.55 mole) and the mixture heated at approximately 80°C for 7.5 hours. Further sulfuryl chloride (74 gm.; 0.5 mole) was added, and the mixture heated at 85°C for 4.75 hours. The reaction mixture was poured onto ice (1 kg.), separated, and the aqueous layer was chloroform extracted. The total organic layer (700 ml.) was washed with water ($\times 2$), 10% aqueous sodium hydroxide (3×150 ml.), water (2×400 ml.) and dried over anhydrous magnesium sulphate/charcoal. Filtration and evaporation gave a brown oil containing some tetrachloroethane and being about 80% pure by vapour phase chromatography, boiling point 98—99°C at 1 m.m. pressure of mercury.

(c) *m*-Chloro- α -t-butylaminopropiophenone

The oil (24.8 gm.; ca. 0.1 mole) from Step (b) was dissolved in acetonitrile (60 ml.) and *t*-butylamine (36.6 gm.; 0.5 mole) and sodium iodide (5 gm.; 0.033 mole) added. The solution was refluxed for 10 hours and stood at room temperature for 56 hours. Most of the excess of *t*-butylamine was removed under reduced pressure, and water (200 ml.) added. This was extracted with ether (2×110 ml.) and the ether layer washed with water containing concentrated hydrochloric acid so that the wash was pH 9. This was backwashed with ether (100 ml.). The total ether layer was treated with ice (35 gm.) and concentrated hydrochloric acid (15 ml.), separated and the ether washed with water and concentrated hydrochloric acid (2:1, 27 ml.). The total aqueous hydrochloric acid layer was washed with ether (15 ml.), charcoaled, filtered and evaporated to a thick gum to which was added acetone. The thick white crystalline precipitate was filtered, washed with acetone ($\times 2$) and dried to give *m*-chloro- α -t-butylaminopropiophenone hydrochloride.

EXAMPLE 4

Preparation of *m*-Chloro- α -t-butylaminopropiophenone

Step (a)— α -*m*-Dichloropropiophenone

m-Chloropropiophenone (8.4 gm.; 0.05 mole) was dissolved in tetrachloroethane (20 ml.) and sulfuryl chloride (7.4 gm.; 0.055 mole) added. On warming to 50°C a vigorous evolution of gasses occurred which proceeded spontaneously on standing at room temperature for one hour. Further sulfuryl chloride (3 gm.) was added and the solution heated at about 90°C for 0.5 hours. The mixture was stood over-night at room temperature and evaporated to an oil which was dissolved in a little benzene and washed twice with water, dried over anhydrous magnesium sulphate, and evaporated to a brown oil (11 gm.) containing a very small amount of tetrachlorethane and which was about 90% pure by vapour phase chromatography.

Step (b)—*m*-Chloro- α -t-butylaminopropiophenone hydrochloride
 α -*m*-Dichloropropiophenone (5.5 gm. ca. 0.025 mole) of the oil from step (a) was dissolved in acetonitrile (15 ml.) and t-butylamine (9.1 gm.; 0.125 mole) added. The reaction was refluxed 22 hours and then worked up exactly as Example 3(c) to give *m*-chloro- α -t-butylaminopropiophenone hydrochloride.

EXAMPLE 5

Tablet Formulation 300 mg Tablet Ingredients

150 mg. of a hydrochloride salt of formula (I)
 85 mg. Lactose
 50 mg. Cornstarch
 10 mg. Micronized Silica Gel
 5 mg. Polyvinyl pyrrolidone

Procedure

The lactose, cornstarch and salt were mixed together and granulated with a binder, polyvinyl pyrrolidone in alcoholic solution, to form granules. The granules were passed through a 16—20 mesh screen, then air dried, lubricated with micronized silica gel and compressed into tablets. A film coating could then have been applied if desired.

EXAMPLE 6

Capsule Formulation 400 mg. Fill Weight

150 mg. of a hydrochloride salt of a compound of formula (I) were mixed with 125 mg. of lactose and 125 mg. of cornstarch. The mixture was filled into a two piece hard gelatin capsule.

EXAMPLE 7

Parenteral Solution

150 mg. of a hydrochloride salt of formula (I) was dissolved in sterile water U.S.P. to make 1 ml. A multi-dose preparation may include bacteriostats such as 0.2 to 0.5% w/v of phenol.

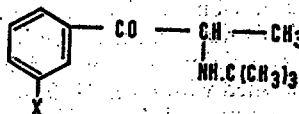
EXAMPLE 8

Suppository of 400 mg. Weight

150 mg. of a hydrochloride salt of formula (I) were mixed with 250 mg. of softened or melted cocoa butter, and suppositories were formed by chilling and shaping in moulds.

WHAT WE CLAIM IS:—

1. A compound of the formula



or an acid addition salt thereof wherein X is chlorine or fluorine.

2. A compound as claimed in claim 1 in the form of a pharmaceutically acceptable acid addition salt thereof.

3. A compound as claimed in claim 1 in the form of an acid addition salt of a mineral acid.

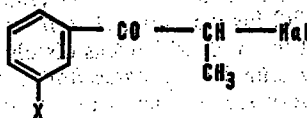
4. *m*-Chloro- α -t-butylaminopropiophenone.

5. *m*-Fluoro- α -t-butylaminopropiophenone.

6. A hydrogen halide acid addition salt of a compound as claimed in claim 4 or claim 5.

7. *m*-Chloro- α -t-butylaminopropiophenone hydrochloride.

8. A method of preparing a compound as claimed in any of claims 1 to 7 comprising the reaction of t-butylamine with a α -halopropiophenone of the formula



wherein X is as defined in any of claims 1 to 7, and Hal is chlorine, bromine or

Step (b)—*m*-Chloro- α -*t*-butylaminopropiophenone hydrochloride
 α -*m*-Dichloropropiophenone (5.5 gm. ca. 0.025 mole) of the oil from step (a) was dissolved in acetonitrile (15 ml.) and *t*-butylamine (9.1 gm.; 0.125 mole) added. The reaction was refluxed 22 hours and then worked up exactly as Example 3(c) to give *m*-chloro- α -*t*-butylaminopropiophenone hydrochloride.

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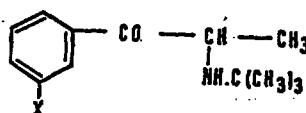
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1. A compound of the formula



or an acid addition salt thereof wherein X is chlorine or fluorine.

2. A compound as claimed in claim 1 in the form of a pharmaceutically acceptable acid addition salt thereof.

3. A compound as claimed in claim 1 in the form of an acid addition salt of a mineral acid.

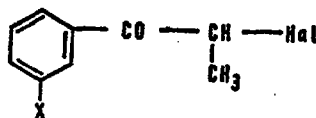
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5. *m*-Fluoro- α -*t*-butylaminopropiophenone.

6. A hydrogen halide acid addition salt of a compound as claimed in claim 4 or claim 5.

7. *m*-Chloro- α -*t*-butylaminopropiophenone hydrochloride.

8. A method of preparing a compound as claimed in any of claims 1 to 7 comprising the reaction of *t*-butylamine with a α -halopropiophenone of the formula



wherein X is as defined in any of claims 1 to 7, and Hal is chlorine, bromine or





iodine, followed by the optional conversion of the product to an acid addition salt thereof.

9. A method as claimed in claim 8 wherein the reaction is conducted in the presence of a polar organic solvent.

10. A method as claimed in claim 9 wherein the solvent is acetonitrile.

11. A method as claimed in any of claims 8 to 10 wherein the reactants are heated to the reflux temperature of the reaction mixture.

12. A method as claimed in any of claims 8 to 11 wherein the amine is present in the reaction mixture in a molar excess relative to the α -halopropiophenone.

13. A method as claimed in any of claims 8 to 12 wherein the α -halopropiophenone is the α -chloropropiophenone, and sodium iodide is included in the reaction mixture.

14. A method as claimed in claim 8 wherein *t*-butylamine is refluxed with *m*- α -dichloropropiophenone in the presence of acetonitrile and sodium iodide, and *m*-chloride- α -*t*-butylaminopropiophenone, or the hydrochloride salt thereof, is isolated from the reaction mixture.

15. A compound as defined in claim 1 or an acid addition salt thereof whenever prepared in the manner claimed in any of claims 8 to 14.

16. A pharmaceutical composition suitable for use in the treatment of the depressed state comprising a butylaminopropiophenone as defined in any of claims 1 to 7 or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutically acceptable carrier therefor.

17. A composition as claimed in claim 16 wherein the butylaminopropiophenone or its acid addition salt is present in an amount of from 5 to 95% by weight of the composition.

18. A composition as claimed in claim 16 suitable for oral or rectal administration and in the form of a discrete dosage unit containing from 15 to 500 milligrams of the butylaminopropiophenone or a pharmaceutically acceptable acid addition salt thereof, estimated as the base.

19. A composition as claimed in claim 18 wherein the butylaminopropiophenone or a pharmaceutically acceptable acid addition salt thereof is present in an amount of 100 to 300 milligrams, estimated as the base.

20. A composition as claimed in claim 19 wherein the butylaminopropiophenone or a pharmaceutically acceptable acid addition salt thereof is present in an amount of 125 to 250 milligrams, estimated as the base.

21. A composition as claimed in any of claims 18 to 20 wherein the discrete dosage unit is a tablet.

22. A composition as claimed in any of claims 18 to 20 wherein the discrete dosage unit is a coated tablet.

23. A composition as claimed in any of claims 18 to 20 wherein the discrete dosage unit is a capsule.

24. A composition as claimed in any of claims 18 to 20 wherein the discrete dosage unit is a suppository.

25. A composition as claimed in claim 16 suitable for parenteral administration in the form of a discrete dosage unit containing from 7.5 to 250 milligrams of the butylaminopropiophenone or a pharmaceutically acceptable acid addition salt thereof, estimated as the base.

26. A composition as claimed in claim 25 wherein the discrete unit comprises a sterile solution or finely divided suspension of the butylaminopropiophenone or a pharmaceutically acceptable acid addition salt thereof in a pharmaceutically acceptable liquid.

27. A tablet suitable for use in the treatment of the depressed state comprising as an active ingredient from 15 to 500 mg. of *m*-chloro- α -*t*-butylaminopropiophenone hydrochloride, estimated as the base, together with a pharmaceutically acceptable carrier therefor.

28. A method for making a pharmaceutical composition as claimed in any of claims 16 to 27 comprising the admixture of the butylaminopropiophenone or a pharmaceutically acceptable acid addition salt thereof with a pharmaceutically acceptable carrier therefor.

29. A method of preparing an acid addition salt of *m*-chloro- α -*t*-butylaminopropiophenone or *m*-fluoro- α -*t*-butylaminopropiophenone substantially as hereinbefore described with particular reference to Examples 1 to 4.

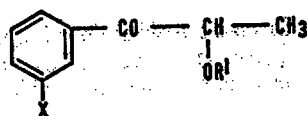
30. A method of preparing a pharmaceutical composition of a pharmaceutically acceptable acid addition salt of *m*-chloro- α -*t*-butylaminopropiophenone or *m*-fluoro-

α -butylaminopropiophenone substantially as hereinbefore described with particular reference to Examples 5 to 8.

31. A pharmaceutical composition of a pharmaceutically acceptable acid addition salt of *m*-chloro- α -t-butylaminopropiophenone or *m*-fluoro- α -t-butylaminopropiophenone substantially as hereinbefore described with particular reference to Examples 5 to 8.

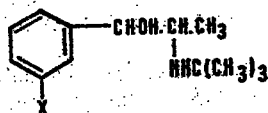
32. A method of preparing a compound as claimed in claim 1 or an acid addition salt thereof comprising

(a) the reaction of a compound of the formula



wherein OR' is a lower alkoxy group having 1 to 3 carbon atoms and X is chlorine or fluorine, with t-butylamine; followed by the optional conversion of the product to an acid addition salt thereof; or

(b) the oxidation of a secondary alcohol of the formula



wherein X is chlorine or fluorine followed by the optional conversion of the product to an acid addition salt thereof.

33. *m*-chloro- α -t-butylaminopropiophenone, *m*-fluoro- α -t-butylaminopropiophenone or an acid addition salt thereof whenever prepared by the method of claim 32.

M. P. JACKSON,
Agent for the Applicants,
Chartered Patent Agent.

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