

# PATENT SPECIFICATION

NO DRAWINGS

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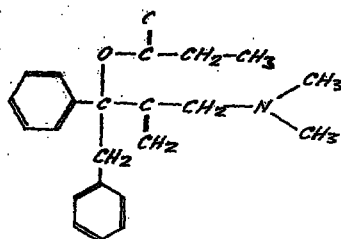
## COMPLETE SPECIFICATION

### New Tertiary Amine and Process for its Manufacture

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, 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 is concerned with a new tertiary amine and with its manufacture and use.

The present invention provides 1,2-diphenyl - 2 - propionyloxy-3-(dimethylaminoethyl) - 3 - butene of the formula



and a process for preparing it.

The new compound has valuable pharmacological properties and acts especially as an analgesic, as has been shown in animal experiments on the mouse. Moreover, it has an antagonistic action towards morphine. The compound may therefore be used as an analgesic. Moreover it has an antitussive action. It can therefore be used also as a relative medication.

The new compound may also be used as starting material or intermediate for the manufacture of other valuable compounds.

The new compound is manufactured by known methods.

Preferably, 1,2 - diphenyl - 3 - (dimethyl-

[Price 4s. 6d.]

aminomethyl) - 3 - buten - 2 - ol is propionylated.

Propionylation is achieved, for example, by reaction with a halide, such as the chloride, of propionic acid or especially with an anhydride of propionic acid, for example an inner anhydride, such as the corresponding ketene, or propionic acid anhydride.

Depending on the reaction conditions and starting materials used, the final product is obtained in the free form or in the form of its acid addition salts which are likewise included within the scope of the present invention. The acid addition salts of the final product can be converted into the free base in known manner, for example with alkalis or ion exchange resins. Acid addition salts are obtained from the free base on treating the latter with organic or inorganic acids, especially those which are capable of forming physiologically tolerable acid addition salts. As such acids there may be mentioned, for example hydrohalic, sulphuric, phosphoric acids, nitric and perchloric acids; aliphatic, alicyclic, aromatic and heterocyclic carboxylic and sulphonic acids such as formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic and laevulic acids, phenylacetic, benzoic, para-aminobenzoic, anthranilic, para - hydroxy - benzoic, salicylic and para - aminosalicylic, methanesulphonic, ethanesulphonic, hydroxyethane sulphonic and ethylenesulphonic acids; halobenzenesulphonic, toluenesulphonic, naphthalenesulphonic and sulphanilic acids, and methionine, tryptophan, lysine and arginine.

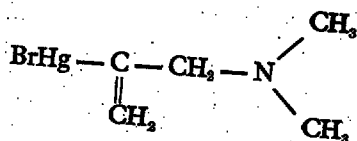
These and other acid addition salts of the new compound, for example its picrate, may also be used for purifying the resulting base by converting the latter into acid addition salts, isolating the acid addi-

tion salts and separating the free base from them again. In view of the close relationship between the new compound in the free form and in the form of its acid addition salts, what has been said above and below with reference to the free base applies also to the corresponding acid addition salts whenever this is suitable and possible.

In the process of the present invention a starting material may also be formed *in situ* or a reactant may be used in the form of a salt, if desired.

For example, 1,2 - diphenyl - 3 - (dimethylaminomethyl)-3-buten-2-ol may be used in the form of its O-salts, such as the O-metal salts, for example of the O-alkali metal salts, such as the sodium or potassium salts, or of the O-magnesium halide salts, such as the magnesium bromide salts, as formed, for example in the Grignard reaction, that is to say, the complex obtained from the Grignard reaction can be reacted as it is with the acylating agent.

The 1,2 - diphenyl - 3 - (dimethylaminomethyl) - 3 - buten - 2 - ol or its O-magnesium bromide salt used as starting material can be obtained by reacting desoxybenzoin with the compound of the formula



and if desired, decomposing the resulting complex.

The reaction of the compounds mentioned above is performed in a known manner, primarily in the presence of a solvent or diluent, for example an ether such as diethyl ether or tetrahydrofuran. The resulting complex is decomposed in the usual manner, for example by hydrolysis.

A resulting racemate can be dissolved into the optical antipodes by a known method, for example as follows: The racemic base is dissolved in a suitable inert solvent, reacted with an optically active acid, and the resulting salts are separated—for example by virtue of their different solubilities—into the diastereomers from which the antipodes of the new base can be liberated by treatment with an alkaline agent. Particularly frequently used optically active acids are the D- and L-forms of tartaric, di-ortho-toluyltartaric, malic, mandelic, camphorsulphonic and quinic acids. The separation can also be achieved, for example, by re-crystallizing the resulting pure racemate from an optically active solvent. It is advantageous to isolate the more active of the two antipodes.

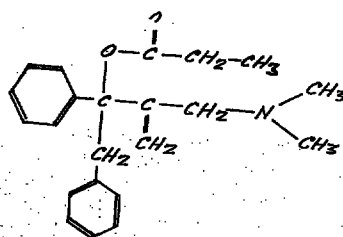
The new compound can be used, for example, in the form of pharmaceutical prepara-

tions which contain it in the free form or in the form of its physiologically tolerable acid addition salts in admixture or conjunction with an organic or inorganic, solid or liquid pharmaceutical carrier suitable for enteral, parenteral or local administration. Suitable carriers are substances that do not react with the new substances, for example water, gelatin, lactose, starches, stearyl alcohol, magnesium stearate, talcum, vegetable oils, benzyl alcohols, gums, propyleneglycols, white petroleum jelly and other known medicinal carriers. The pharmaceutical preparations may be, for example, in the form of tablets, dragees, capsules, salves and creams, or in liquid form as solutions, suspensions and emulsions. They may be sterilized and/or contain assistants such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure or buffers. They may also contain further therapeutically valuable substances. The pharmaceutical preparations are formulated by the conventional methods.

The following Examples illustrate the invention.

#### EXAMPLE 1

A mixture of 26.7 g of 1,2-diphenyl-3-(dimethylaminomethyl)-3-buten-2-ol and 100 ml of propionic acid anhydride is heated for 5 hours at 50°C. The excess propionic acid anhydride is then evaporated under vacuum; while cooling the residue thoroughly it is mixed with sodium bicarbonate solution to establish an alkaline reaction, extracted twice with ether and the ethereal solution is washed with water, dried and evaporated, to yield 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene of the formula



When this compound is reacted in ethyl acetate with ethanolic hydrochloric acid, it yields 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride melting at 188°C.

The 1,2 - diphenyl - 3 - (dimethylaminomethyl) - 3 - buten - 2 - ol can be obtained as follows:

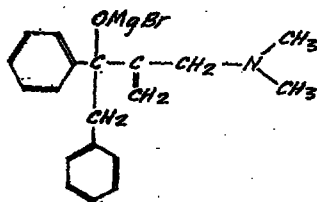
By introducing, while cooling with ice, 2 molecular equivalents of dimethylamine into a solution of 2,3-dibromopropene in benzene and subsequently heating to 50°C, N,N-di-

methyl-2-bromallylamine is obtained which boils at 63–64°C under a pressure of 76–79 mm Hg.

- 5 7.2 g of magnesium (0.3 mol) are etched with a small amount of iodine in a stirring flask and then mixed with 20 ml of absolute tetrahydrofuran and 0.8 ml of ethyl bromide. The reaction is initiated by moderate heating, and during the course of 15 to 20 minutes, 10 49.2 g (0.3 mol) of N,N-dimethyl-2-bromallylamine in 50 ml of absolute tetrahydrofuran is dropped in at such a rate that the solution keeps boiling. The batch is stirred for a further 30 minutes at the boil until practically all of the magnesium has dissolved. 15 Without cooling, 39.3 g (0.2 mol) of desoxybenzoin in 125 ml of absolute tetrahydrofuran are then dropped in at such a rate that the reaction solution keeps boiling and it is then refluxed for 6 hours, poured into a 20 solution of 60 g of ammonium chloride in 1/2 litre of water, and the precipitated oil is extracted with ether, the extract washed with water and repeatedly extracted with 2N-acetic acid (total 1/2 litre). The acetic acid 25 solution is made alkaline with 125 ml of 10N-sodium hydroxide solution and the precipitated oil dissolved in ether. The ethereal solution is dried and the ether evaporated. 30 The residue is 1,2-diphenyl-3-dimethyl-aminomethyl-3-buten-2-ol which crystallizes on storing and melts at 56 to 58°C.

#### EXAMPLE 2

- 35 In a flask equipped with a stirrer, 7.2 g of magnesium (0.3 mol) are etched with a little iodine and treated with 20 ml of absolute tetrahydrofuran and 0.8 ml of ethyl bromide. The reaction is initiated by slight heating, and in the course of 15–20 minutes, 40 49.2 g (0.3 mol) of N,N-dimethyl-2-bromallylamine in 50 ml of absolute tetrahydrofuran are added dropwise in such a manner that the solution remains constantly boiling. Heating at the boil and stirring is continued for 45 another 30 minutes to ensure that the magnesium dissolves except for small traces. After this, 39.3 g (0.2 mol) of desoxybenzoin in 125 ml of absolute tetrahydrofuran are added dropwise in such a manner that the reaction solution always remains boiling. The 50 batch is then refluxed for 6 hours. Into this solution which contains the magnesium bromide salt of the formula



there is then added dropwise at about 30°C a solution of 97.8 g (0.75 mol) of propionic anhydride in 50 ml of tetrahydrofuran. This operation is followed by heating at 50°C for 5 hours. The solution is concentrated to about 50–100 ml and then poured into 500 ml of water. The turbid aqueous solution is extracted with ether (ethereal solution A). From the aqueous phase a basic residue is obtained on treatment with 50 ml of a saturated sodium bicarbonate solution, extraction with ether and evaporation of the ether.

The ethereal solution A is extracted with 250 ml of ice-cold 2N-hydrochloric acid. Treatment of the extract with 300 ml of ice-cold 2N-ammonium hydroxide solution, extraction with ether and evaporation of the ether yields a basic residue. The latter and the aforementioned basic residue are combined, dissolved in 100 ml of ethyl acetate, and treated with 2.5 N-ethanolic hydrochloric acid until a slightly acid reaction is attained. During this operation, 1,2-diphenyl-2-propionyloxy-3-dimethylaminomethyl-3-butene hydrochloride of melting point 188°C crystallizes.

The same reaction product is obtained when the propionic acid anhydride is replaced by 60.0 g of propionyl chloride (0.75 mol) in 50 ml of tetrahydrofuran.

#### EXAMPLE 3

Tablets containing 30 mg of 1,2-diphenyl-2-propionyloxy-3-(dimethylaminomethyl)-3-butene hydrochloride can be prepared from the following ingredients:

|                                                                            | per tablet |  |
|----------------------------------------------------------------------------|------------|--|
| 1,2-diphenyl-2-propionyloxy-3-(dimethylaminomethyl)-3-butene hydrochloride | 30.0 mg    |  |
| colloidal silicic acid                                                     | 3.0 mg     |  |
| lactose                                                                    | 20.0 mg    |  |
| wheat starch                                                               | 10.0 mg    |  |
| cellulose powder                                                           | 20.0 mg    |  |
| arrowroot                                                                  | 10.0 mg    |  |
| talc                                                                       | 6.0 mg     |  |
| magnesium stearate                                                         | 1.0 mg     |  |
|                                                                            | 100.0 mg   |  |

#### Preparation

A mixture of the 1,2-diphenyl-2-propionyloxy-3-(dimethylaminomethyl)-3-butene hydrochloride, lactose, wheat starch and cellulose powder is well moistened with ethyl alcohol. The colloidal silicic acid is then added in small portions, and the whole kneaded until a plastic mass is obtained. The latter is forced through a sieve having a mesh width of 4–5 mm, and then dried at 45°C. The dry granulate is forced through a sieve having a mesh width of 0.8–1.0 mm, and then mixed homogeneously with the disintegrating

and lubricating agents. The mixture is compressed in the usual manner into tablets having a diameter of 6 mm and a gross weight of 100 mg.

#### 5 EXAMPLE 4

Hard gelatine capsules containing 30 mg of 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride can be prepared, for example, from the following ingredients:

|                                                                                          | per<br>capsule |
|------------------------------------------------------------------------------------------|----------------|
| 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride | 30.0 mg        |
| lactose                                                                                  | 74.5 mg        |
| talc                                                                                     | 5.0 mg         |
| colloidal silicic acid                                                                   | 0.5 mg         |
|                                                                                          | <hr/>          |
|                                                                                          | 110.0 mg       |

#### Preparation

The 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride is homogeneously mixed with the lactose, talc and colloidal silicic acid and the mixture filled into hard gelatine capsules No. 4 by means of a suitable filling and sealing apparatus. An average of 110 mg is filled into each capsule.

#### 30 WHAT WE CLAIM IS:—

1. 1,2 - Diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene.
2. An acid addition salt of the compound claimed in claim 1.
3. A physiologically tolerable acid addition salt of the compound claimed in claim 1.
4. The hydrochloride of the compound claimed in claim 1.
5. The pharmaceutical preparation which comprises 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene, in admixture or conjunction with a pharmaceutically suitable carrier.
6. A pharmaceutical preparation which com-

prises a physiologically tolerable acid addition salt of 1,2-diphenyl-2-propionyloxy-3-(dimethylaminomethyl)-3-butene, in admixture or conjunction with a pharmaceutically suitable carrier.

7. A pharmaceutical preparation which comprises 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride, in admixture or conjunction with a pharmaceutically suitable carrier.

8. A pharmaceutical preparation having composition substantially as described in Example 3 or 4 herein.

9. A process for the manufacture of 1,2-diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene or an acid addition salt thereof, wherein 1,2 - diphenyl - 3 - (dimethylaminomethyl) - 3 - buten - 2 - ol or a salt thereof, is propionylated and, if desired a resulting acid addition salt is converted into the free base or the resulting free base is converted into an acid addition salt.

10. A process as claimed in claim 9, wherein the propionylation is carried out with a halide or anhydride of propionic acid.

11. A process as claimed in claim 10, wherein the propionylation is carried out with the corresponding ketene.

12. A process as claimed in claim 10, wherein the propionylation is carried out with propionic acid anhydride.

13. A process for the manufacture of 1,2-diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene or an acid addition salt thereof, conducted substantially as described in Example 1 herein.

14. A process for the manufacture of 1,2-diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene or an acid addition salt thereof, substantially as described in Example 2 herein.

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and lubricating agents. The mixture is compressed in the usual manner into tablets having a diameter of 6 mm and a gross weight of 100 mg.

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#### EXAMPLE 4

Hard gelatine capsules containing 30 mg of 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride can be prepared, for example, from the following ingredients:

|                                                                                                         | per<br>capsule |
|---------------------------------------------------------------------------------------------------------|----------------|
| 1,2 - diphenyl - 2 - propionyl-<br>oxy - 3 - (dimethylamino-<br>methyl) - 3 - butene hydro-<br>chloride | 30.0 mg        |
| lactose                                                                                                 | 74.5 mg        |
| talc                                                                                                    | 5.0 mg         |
| colloidal silicic acid                                                                                  | 0.5 mg         |
|                                                                                                         | <hr/>          |
|                                                                                                         | 110.0 mg       |

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#### Preparation

The 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride is homogeneously mixed with the lactose, talc and colloidal silicic acid and the mixture filled into hard gelatine capsules No. 4 by means of a suitable filling and sealing apparatus. An average of 110 mg is filled into each capsule.

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#### WHAT WE CLAIM IS:—

1. 1,2 - Diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene.
2. An acid addition salt of the compound claimed in claim 1.
3. A physiologically tolerable acid addition salt of the compound claimed in claim 1.
4. The hydrochloride of the compound claimed in claim 1.
5. The pharmaceutical preparation which comprises 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene, in admixture or conjunction with a pharmaceutically suitable carrier.
6. A pharmaceutical preparation which com-

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prises a physiologically tolerable acid addition salt of 1,2-diphenyl-2-propionyloxy-3-(dimethylaminomethyl)-3-butene, in admixture or conjunction with a pharmaceutically suitable carrier.

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7. A pharmaceutical preparation which comprises 1,2 - diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene hydrochloride, in admixture or conjunction with a pharmaceutically suitable carrier.

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8. A pharmaceutical preparation having a composition substantially as described in Example 3 or 4 herein.

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9. A process for the manufacture of 1,2-diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene or an acid addition salt thereof, wherein 1,2 - diphenyl - 3 - (dimethylaminomethyl) - 3 - butene - 2 - ol or a salt thereof, is propionylated and, if desired a resulting acid addition salt is converted into the free base or the resulting free base is converted into an acid addition salt.

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10. A process as claimed in claim 9, wherein the propionylation is carried out with a halide or anhydride of propionic acid.

11. A process as claimed in claim 10, wherein the propionylation is carried out with the corresponding ketene.

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12. A process as claimed in claim 10, wherein the propionylation is carried out with propionic acid anhydride.

13. A process for the manufacture of 1,2-diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene or an acid addition salt thereof, conducted substantially as described in Example 1 herein.

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14. A process for the manufacture of 1,2-diphenyl - 2 - propionyloxy - 3 - (dimethylaminomethyl) - 3 - butene or an acid addition salt thereof, substantially as described in Example 2 herein.

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