Elizabeth the Second by the Grace of God of the United Kingdom of Great Britain and Northern Ireland and of Her other Realms and Territories, Queen, Head of the Commonwealth, Defender of the Faith: To all to whom these presents shall come greeting:

WHEREAS a request for the grant of a patent has been made by

Institut Toxikologii Ministerstva Zdravo-Okhranenia SSSR, a State Enterprise organised and existing under the laws of the Union of Soviet Socialist Republics, (U.S.S.R.), of 1 ulitsa Bekhtereva, Leningrad, Union of Soviet Socialist Republics,

for the sole use and advantage of an invention for

Process for producing 6-6-(3'phenyl-pyrrodidyl-1')-propionylbenzo-1, 4-dioxane, its salts, and process for producing same:

AND WHEREAS We, being willing to encourage all inventions which may be for the public good, are graciously pleased to condescend to the request:

KNOW YE, THEREFORE, that We, of our especial grace, certain knowledge, and mere motion do by these presents, for Us, our heirs and successors, give and grant unto the person(s) above named and any successor(s), executor(s), administrator(s) and assign(s) (each and any of whom are hereinafter referred to as the patentee) our especial licence, full power, sole privilege, and authority, that the patentee or any agent or licensee of the patentees and no others, may subject to the conditions and provisions prescribed by any statute or order for the time being in force at all times hereafter during the term of years herein mentioned, make, use, exercise and vend the said invention within our United Kingdom of Great Britain and Northern Ireland, and the Isle of Man, and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the term of sixteen years from the date hereunder written of these presents: AND to the end that the patentee may have and enjoy the sole use and exercise and the full benefit of the said invention, We do by these presents for Us, our heirs and successors, strictly command all our subjects whatsoever within our United Kingdom of Great Britain and Northern Ireland, and the Isle of Man, that they do not at any time during the continuance of the said term either directly or indirectly make use of or put in practice the said invention, nor in anywise imitate the same, without the written consent, licence or agreement of the patentee, on pain of incurring such penalties as may be justly inflicted on such offenders for their contempt of this our Royal Command, and of being answerable to this patentee according to law for damages thereby occasioned:

PROVIDED ALWAYS that these letters patent shall be revocable on any of the grounds from time to time by law prescribed as grounds for revoking letters patent granted by Us, and the same may be revoked and made void accordingly:

PROVIDED ALSO that nothing herein contained shall prevent the granting of licences in such manner and for such considerations as they may by law be granted: AND lastly, We do by these presents for Us, our heirs and successors, grant unto the patentee that these our letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these our letters to be made patent as of the twenty-fifth day of October one thousand nine hundred and seventy-two and to be sealed.

Comptroller-General of Patents, Designs, and Trade Marks
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The present invention relates to a process for producing 6-ω-(3' phenyl-pyrrolidyl-1')-propionylbenzo-1,4-dioxane and its salts, and to process for producing same.

6-ω-(3' phenyl-pyrrolidyl-1')-propionylbenzo-1,4-dioxane hydrochloride, referred to as pyrroxane, is useful as a medicinal compound. (Pyrroxane is a Trade Mark registered in the USSR).

A process is known in the art for producing 6-ω-(3' phenyl-pyrrolidyl-1')-propionylbenzo-1,4-dioxane, comprising the condensation of 3-phenylpyrrolidine, 6-acetylbenzo-1,4-dioxane and formaldehyde. The product yield in this prior-art process does not exceed 59% by weight.

It is an object of the present invention to provide a novel process which makes it possible to increase the product yield. It is another object of the present invention to produce novel salts of 6-ω-(3' phenyl-pyrrolidyl-1')-propionylbenzo-1,4-dioxane.

According to the present invention there is provided a novel salt of 6-ω-(3' phenyl-pyrrolidyl-1')-propionylbenzo-1,4-dioxane of the formula:

\[ \text{C}_6\text{H}_5 \text{N} \text{CH}_2\text{CH}_2\text{C} \text{O} \cdot \text{A} \]

wherein A is a chlorine-free mineral acid or an organic acid.

These salts find use in medicinal preparations.

Such acids may be exemplified by hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, benzene or p-toluenesulphonic acid, tartaric acid, nicotinic acid, maleic acid, citric acid, salicylic acid, ascorbic acid, lactic acid.
tic acid, acetic acid, formic acid, benzoic acid, succinic acid, glutaric acid and adipic acid.

Such salts may be exemplified as follows; 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane hydrobromide, 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane hydrogen sulphate; 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane tartrate; 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane succinate.

Still further according to the present invention there is provided a process for producing said salts, comprising reacting 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane with an appropriate mineral or organic acid. The reaction may be effected by adding an acid solution in a suitable solvent to a solution of the 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane in ether. Further treatment is effected by adding a current of nitrogen is introduced for a better understanding of the present invention, specific Examples are given hereinbelow by way of embodiments.

Example 1

Into a mixture of 2.94 g (0.02 g mol) of 3 - phenylpyrrolidine, 4.70 g (0.02 g mol) of 6 - ω - dimethylaminopropionylbenzo - 1,4 - dioxane, and 4.12 g (0.04 g mol) of sodium carbonate in 40 ml of dimethylformamide a current of nitrogen is introduced with stirring. After 6 hours the resulting mass is added to 200 ml of water, extracted with ether, and the extracts are dried with K₂CO₃. The desiccant is filtered off, the ether is distilled off almost until dryness (to the residue volume of 10 ml), the residue is cooled to 0 to +5°C, and kept at this temperature for 4 hours. The resulting precipitate is filtered off, washed on a filter with 3 ml of ether, and dried at a temperature of 40 to 50°C to give 4.75 g (70.5%) of 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane with a melting point of 64-65°C.

Example 2

A mixture of 2.94 g (0.02 g mol) of 3 - phenylpyrrolidine, 7.55 g (0.02 g mol) of 6 - ω - dimethylaminopropionylbenzo - 1,4 - dioxane methyl iodide and 4.12 g (0.04 g mol) of sodium carbonate in 40 ml of dimethylformamide is stirred for 6 hours, while introducing nitrogen. Further treatment is performed in accordance with the procedure described in Example 1. The yield of 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane is 5.2 g (76.5%); melting point, 64 to 65°C.

Example 3

To 14 ml of a 1.5% by weight solution of 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane in anhydrous diethyl ether a 48% by weight solution of hydrobromic acid is added to give pH of 3. The precipitate is filtered off and crystallized from acetone to yield 71% by weight of 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane hydrobromide, melting point 142 to 144°C. Found, %: N, 3.54; Br, 18.75; C₁₅H₁₃NO₃HBr. Calculated, %: N, 3.36; Br, 19.08.

Example 4

6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane hydrogen sulphate is produced by adding a 5% by weight solution of sulphuric acid in anhydrous diethyl ether to 14 ml of a 1.5% by weight solution of 6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane in anhydrous ether. Further treatment is effected in much the same manner as that described in Example 3. The desired product yield is 86% by weight; melting point, 71—75°C (isopropanol). Found, %: N, 3.36; C₁₅H₁₃(NO₃)₂. H₂SO₄. Calculated, %: N, 3.22.

Example 5

6 - ω - (3'-phenylpyrrolidyl - 1') - propionylbenzo - 1,4 - dioxane tartrate is produced in a manner similar to that described in Example 3, utilizing a saturated solution of tartaric acid in anhydrous ether. The salt is obtained having a melting point of above 50°C. Found, N, 2.70; C₁₅H₁₃NO₃. C₃H₅O₃. Calculated, %: N, 2.86.
Example 6
6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane maleate is produced in a manner similar to that described in Example 3, utilizing a saturated solution of maleic acid in anhydrous ether. The salt yield is 79% by weight; melting point, 123 to 127°C (ethanol). Found, N, 3.17. C₂₁H₂₃NO₅ . C₈H₄O₄. Calculated, %: N, 3.10.

Example 7
6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane citrate is produced in a similar manner to that described in Example 3, utilizing a saturated solution of citric acid in anhydrous ether. The salt is produced having a melting point above 60°C. Found, N, 2.86; C₂₁H₂₃NO₅ . C₆H₈O₇. Calculated, %: N, 2.66.

Example 8
6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane succinate is produced in a manner similar to that described in Example 3, utilizing a saturated solution of succinic acid in anhydrous ether. The salt yield is 82% by weight, melting point, 87 to 90°C (ethanol). Found, %: N, 3.24; C₂₁H₂₃NO₅ . C₄H₄O₄. Calculated, %: N, 3.08.

WHAT WE CLAIM IS:—
1. A process for producing 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane comprising reacting 3 - phenylpyrrolidine with 6 - ω - dimethylaminopropionylbenzo - 1,4 - dioxane in the presence of an alkaline agent in an organic solvent medium.

2. A process as claimed in claim 1, wherein the reaction of 3 - phenylpyrrolidine, 6 - ω - dimethylaminopropionylbenzo - 1,4 - dioxane, and the alkaline agent is conducted in the weight ratio of 1:1:2 respectively in an organic solvent medium at ambient temperature, with the removal of the resulting di-methylamine with an inert gas.

3. A process as claimed in claim 1 or 2, wherein the alkaline agent is sodium carbonate.

4. A process as claimed in any one of claims 1 to 3, wherein the organic solvent is dimethylformamide.

5. A salt of 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane of the formula:

wherein A is chlorine-free mineral acid or an organic acid.

6. 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane hydrobromide according to claim 5.

7. 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane hydrogen sulphate according to claim 5.

8. 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane tartrate according to claim 5.

9. 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane maleate according to claim 5.

10. 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane citrate according to claim 5.

11. 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane succinate according to claim 5.

12. A process for producing a salt as claimed in claim 5, comprising reacting 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane with an appropriate organic or mineral acid.

13. A process as claimed in claim 12, wherein the organic acid is an acid selected from tartaric acid, citric acid, lactic acid, acetic acid, formic acid, nicotinic acid, maleic acid, salicylic acid, ascorbic acid, benzoic acid, succinic acid, adipic acid and benzene or p-toluene sulphonylic acid.

14. A process as claimed in claim 12, wherein the mineral acid is an acid selected from hydrobromic acid, sulphuric acid, phosphoric acid, and nitric acid.

15. A process for producing 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane according to claim 1, substantially as hereinbefore described and with reference to Examples 1 and 2.

16. 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane whatever prepared by the process claimed in any one of claims 1 to 4 and 15.

17. A process for producing a salt of 6 - ω - (3¹ - phenylpyrrolidyl - 1¹) - propionylbenzo - 1,4 - dioxane according to claim 12.
substantially as hereinbefore described and with reference to any one of Examples 3 to 8.

18. A salt of 6-ω-(31-phenyl-
5 pyrrolidyl-11)-propionylbenzo-1,4-
dioxane whenever prepared by a process as claimed in any one of claims 12 to 14 and claim 17.

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ТОРГОВО-ПРОМЫШЛЕННАЯ ПАЛАТА СССР
Управление по патентованию изобретений

Начальнику отдела В. ГЛАДЫРЮ

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Кос. патента № 1398023
в Англии на изобретение:
"Способ получения..."
Заявка в СССР № 1788053/23

На Ваш № 0310 П. 46510 от 22.03.76

Институт токсикологии МЗ СССР подтверждает получение патентной грамоты/описания № 1398023, выданной Патентным ведомством Англии. Просим обратить внимание на ошибку в названии изобретения:
Следует писать 6-О-(3'-ферофен-1'-циклогидфил...) а не - ригидфил....

Зав. научно-организационным отделом, к.м.н.

(О. КВАСЕНКО)