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NO DRAWINGS

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COMPLETE SPECIFICATION

A Method for Purifying 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2)

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We, F. ~~HOFFMAN~~-LA ROCHE & Co. Aktiengesellschaft, a Swiss Company of 124–184 Grenzacherstrasse, 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:—

This invention relates to a method for purifying 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) which is useful as a sedative, muscle relaxant and anticonvulsant.

It is well known that compounds having the usefulness mentioned earlier must be manufactured in a high degree of purity. Due to impurities present in crude 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) the large scale industrial manufacture thereof has necessitated cumbersome purification procedures. The present invention provides a simple method of purification *via* salts with inorganic acids.

The method provided by the present invention comprises treating crude 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) with dilute hydrochloric acid, eliminating the insoluble material from the resulting solid/liquid mixture, treating the remaining liquid with nitric acid or sulphuric acid, separating the insoluble acid addition salt of 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2), heating this salt with a base and in the presence of a lower-alkanol at a temperature sufficient to effect complete conversion of the acid addition salt into the free base, allowing the resulting solution to cool and separating the pure 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) therefrom.

The crude 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) is obtained from the reaction mixture in which it was formed by elimination of the solvent in any convenient conventional manner (e.g. evaporation). It usually contains impurities which were already present in the starting materials as well as impurities formed during the reaction procedure. One such procedure, for example, consists in condensing 5-chloro-2-amino-benzophenone with glycine ethyl ester hydrochloride in the presence of pyridine to yield 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) which is in turn methylated to give 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2).

In the first step of the purification method of the invention, the crude 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) is treated with dilute hydrochloric acid to form the soluble salt 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) hydrochloride. It has been found that some of the impurities present in the crude 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) do not form soluble salts. Accordingly, by separating the insoluble material from the solid/liquid mixture obtained by adding the acid, these impurities can be removed. The treatment with dilute hydrochloric acid (advantageously about 3 *N*) is preferably carried out at room temperature. The separation of the resulting insoluble

[*Price 4s. 6d.*]

material from the liquid containing the soluble 7-chloro-1-methyl-5-phenyl-2,3-dihydro - 1H - 1, 4 - benzodiazepinone - (2) hydrochloride may be effected by any convenient means; for example, by filtration.

In the next step of the purification method of the invention, the liquid containing the soluble 7-chloro-1-methyl-5-phenyl - 2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2) hydrochloride and some retained impurities is treated with nitric acid or sulphuric acid. The use of nitric acid is preferred. The treatment results in the formation of insoluble acid addition salts; namely, 7-chloro-1-methyl-5-phenyl-2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2) nitrate or 7-chloro-1-methyl-5-phenyl - 2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2) sulphate. The treatment is conveniently carried out at room temperature. It has been found that certain of the remaining impurities remain in solution. Accordingly, by simply separating the insoluble material from the liquid further purification results. This separation can be effected by any convenient conventional method; e.g. filtration.

The solid 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) nitrate or sulphate obtained is then mixed with a base in the presence of a lower-alkanol and the mixture heated to a temperature sufficient to effect complete conversion. The base reacts with the nitrate or sulphate to form a corresponding salt and the free base; namely, 7-chloro-1-methyl-5-phenyl-2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2). For example, ammonium nitrate or ammonium sulphate will be formed when ammonia or a saturated aqueous solution of ammonia is used as the base.

The use of nitric acid is preferred owing to the solubility of ammonium nitrate in lower alkanols, thereby facilitating the ready separation of the insoluble base [7 - chloro - 1 - methyl - 5 - phenyl - 2, 3-dihydro-1H-1,4-benzodiazepinone-(2)] from the salt formed (i.e. ammonium nitrate) in the alkanolic reaction media.

When sulphuric acid is used as the acid and ammonia used as the base ammonium sulphate is formed and this is insoluble in lower-alkanols. Inasmuch as this salt is also insoluble in hot lower-alkanols, it has been found convenient to treat the mixture of 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) and ammonium sulphate which crystallizes out with a hot lower-alkanol and to separate the insoluble ammonium sulphate from the accompanying solution of benzodiazepine derivative. The 7-chloro-1-methyl-5-phenyl-2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2) then crystallizes out upon cooling the alkanolic solution.

When heating the mixture of the 7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro-1H-1,4-benzodiazepinone-(2) nitrate or sulphate, lower-alkanol and base to a temperature sufficient to effect complete conversion of said ingredients, the temperature should not be so high as to volatilize any substantial proportion of the lower-alkanol solvent being used. Thus, when ethanol is used as the lower-alkanol, it has been found convenient to heat to between 50°C. and 70°C. In a preferred embodiment aqueous ammonia is used to release the base from the nitric acid salt as it forms a soluble salt with the nitric acid released and the water serves to both enhance the solubility of the ammonium nitrate in the lower-alkanol and simultaneously to decrease the solubility of the desired base 7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone - (2) released.

The treatment with the base and subsequent heating to effect complete conversion yields a solution which, upon cooling, gives 7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro-1H-1,4-benzodiazepinone-(2) in a crystalline form which can be easily filtered and readily and rapidly washed. The cooling may be carried out merely by allowing the solution to stand at room temperature or it can be accelerated by any convenient cooling means (for example, refrigeration or ice-bath). The crystalline 7-chloro-1-methyl - 5 - phenyl - 2, 3 - dihydro - 1H - 1,4-benzodiazepinone-(2) thus obtained is free of substantially all impurities occurring in the crude 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2). In order to ensure substantially complete freedom from the salt formed in the final step (e.g. ammonium nitrate), the crystallized 7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro-1H-1,4-benzodiazepinone-(2) can be washed with water. In fact, the so-obtained 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) is in a crystalline form which is suitable for washing inasmuch as there is relatively little agglomeration or paste formation. Consequently the washing liquid can be passed readily and rapidly through the crystals.

7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro-1H-1,4-benzodiazepinone-(2) and its acid addition salts are claimed *per se* in the specification of our co-pending application for Letters Patent No. 42408/60 (now serial No. 972,968). Both the compound and its acid addition salts can be manufactured by the process described and claimed in the specification of our co-pending application for Letters Patent No. 42402/60 (now serial No. 972,964), namely by reacting 7-chloro-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) with a methy-

lating agent and, if desired, converting the reaction product into an acid addition salt by treatment with an acid. The compound and its acid addition salts can also be manufactured by the process described and claimed in the specification of our co-pending application for Letters Patent No. 42405/60 (now serial No. 972,967), namely by reacting 2-methylamino-5-chloro-benzophenone or a salt thereof with a strong acid with glycine or an ester thereof or a salt of glycine or a glycine ester with a strong acid and, if desired, converting the product into an acid addition salt.

It will be appreciated that the foregoing processes yield the required compound in varying degrees of purity according to the detailed techniques employed and that the present invention needs only to be applied to the impure product.

The following example illustrates the invention.

EXAMPLE

100 g of crude 7-chloro-1-methyl-5-phenyl - 2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2), assaying about 90% pure and melting at 115°–120°C. (uncorrected), were dissolved at *ca* 20°C. in 300 ml of about 3-*N* aqueous hydrochloric acid with stirring. The resulting solution was then filtered and the insoluble material remaining on the filter was washed with an additional 50 ml of about 3-*N* hydrochloric acid. The strongly coloured filtrate and wash were combined and 50 ml of 70% (by volume) nitric acid were slowly added thereto with stirring, whereupon 7-chloro-1 - methyl - 5 - phenyl - 2, 3 - dihydro - 1H-1,4-benzodiazepinone-(2) nitrate crystallized out rapidly in well defined crystals.

7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro-1H-1,4-benzodiazepinone-(2) sulphate was also prepared by the above method using sulphuric acid.

The 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1,4-benzodiazepinone-(2) nitrate obtained according to the first paragraph was suspended in 300 ml of ethanol and 20 ml of 26% (by weight) aqueous ammonia were added thereto with stirring. On warming to 65°–70°C. complete solution was obtained giving a slightly yellow to amber coloured solution which was treated with 2 g of decolourizing carbon in two equal parts and then filtered through diatomaceous earth. The resulting filtrate was permitted to cool, whereupon 7-chloro-1-methyl-5-phenyl - 2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2) crystallized out in the form of well defined crystals. The slurry was then stirred at *ca* 20°C. for 1 hour, filtered and washed with 50 ml of ethanol in two equal parts. The crystalline product was next washed with 200 ml of hot water (60°C.) to remove any co-crystallized ammonium nitrate. The product was recrystallized directly from ethanol and formed prisms melting at 129°–130·5°C. (uncorrected), and, on examination by thin-layer chromatography, showed only one spot, corresponding to the desired compound, 7-chloro-1-methyl - 5 - phenyl - 2, 3 - dihydro - 1H - 1,4-benzodiazepinone-(2). Further purification was effected by dissolving 50 g of the 7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro-1H-1,4-benzodiazepinone-(2) thus obtained in 150 ml of ethanol with stirring and heating. The resulting solution was treated with 1·0 g. of decolourizing carbon in two equal parts and then filtered through diatomaceous earth.

The filtrate was stirred for 1 hour after it had reached *ca* 20°C. The slurry of crystals obtained was then filtered with suction and washed with 20 ml of ethanol at *ca* 20°C. in two equal parts, thereby yielding 7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro-1H-1,4-benzodiazepinone-(2) as prisms melting at 130°–131°C. (uncorrected). A separate determination by the United States Pharmacopoeia method gave a melting point of 131·5°–134·5°C.

As shown herein, the heating of the base, the lower-alkanol and the mineral acid salt of 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1H-1.4-benzodiazepinone-(2) is to the point of complete conversion. In the case of the nitrate where the soluble ammonium nitrate is formed, the heating would take place until complete solution of the ingredients is effected. In the case of the sulphate where the insoluble ammonium sulphate is formed complete conversion would be indicated when excess ammonia is present.

It will be understood that by the term "lower-alkanol" used in the foregoing description and in the following claims is meant an alkanol containing from one to seven carbon atoms.

WHAT WE CLAIM IS:—

(1) A method for purifying 7-chloro-1-methyl - 5 - phenyl - 2, 3 - dihydro - 1H - 1,4-benzodiazepinone-(2), which comprises treating crude 7-chloro-1-methyl-5-phenyl-2, 3 - dihydro - 1H - 1,4 - benzodiazepinone-(2) with dilute hydrochloric acid, eliminating the insoluble material from the resulting solid/liquid mixture, treating the remaining liquid with nitric acid or sulphuric acid, separating the insoluble acid addition salt of 7-chloro-1-methyl-5-phenyl-2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone-(2), heating this salt with a base and in the presence of a lower-alkanol at a temperature sufficient to effect complete conversion of the acid addition salt into the free base, allowing the resulting solution

lating agent and, if desired, converting the reaction product into an acid addition salt by treatment with an acid. The compound and its acid addition salts can also be manufactured by the process described and claimed in the specification of our co-pending application for Letters Patent No. 42405/60 (now serial No. 972,967), namely by reacting 2-methylamino-5-chloro-benzophenone or a salt thereof with a strong acid with glycine or an ester thereof or a salt of glycine or a glycine ester with a strong acid and, if desired, converting the product into an acid addition salt.

It will be appreciated that the foregoing processes yield the required compound in varying degrees of purity according to the detailed techniques employed and that the present invention needs only to be applied to the impure product.

The following example illustrates the invention.

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It will be understood that by the term "lower-alkanol" used in the foregoing description and in the following claims is meant an alkanol containing from one to seven carbon atoms.

WHAT WE CLAIM IS:—

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to cool and separating the pure 7-chloro-1-methyl - 5 - phenyl - 2, 3 - dihydro - 1H - 1,4-benzodiazepinone-(2) therefrom.

(2) A method in accordance with claim 1 wherein the strength of the hydrochloric acid is *ca* 3-N.

(3) A method in accordance with claim 1 or claim 2, wherein the nitric acid is used in a concentration of *ca* 70% (by volume).

(4) A method in accordance with claim 1, claim 2 or claim 3, wherein ethanol is used as the lower-alkanol.

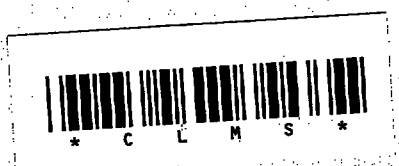
(5) A method in accordance with any one of claims 1 to 4 inclusive, wherein ammonia or a saturated aqueous solution of ammonia is used as the base.

(6) A method for purifying 7-chloro-1-methyl - 5 - phenyl - 2, 3 - dihydro - 1H - 1,4-benzodiazepinone-(2), substantially as described with reference to the Example.

(7) 7 - chloro - 1 - methyl - 5 - phenyl - 2, 3 - dihydro - 1H - 1, 4 - benzodiazepinone - (2), when purified by the method claimed in any one of claims 1 to 6 inclusive.

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