991,115

PATENT SPECIFICATION

NO DRAWINGS

991,115

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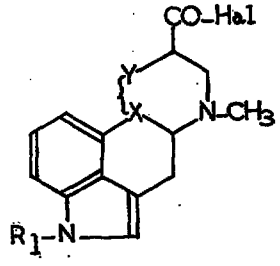
COMPLETE SPECIFICATION

Improvements in or relating to Lysergic Acid Derivatives

We, SANDOZ PATENTS LIMITED, of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, 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 provides halides of the lysergic and dihydrolysergic acid series and a process for their production.

The present invention provides compounds of the formula I,



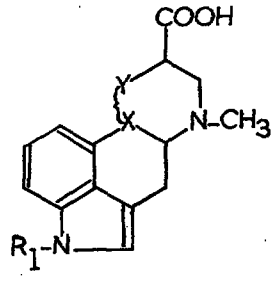
I

in which R_1 signifies a hydrogen atom or an alkyl radical containing from 1 to 4 carbon atoms inclusive,

$\overset{x}{\frown}\overset{y}{}$ signifies the radical $-CH=C<$ or $-CH_2-CH<$, and

Hal signifies a chlorine, bromine or iodine atom, in the form of their acid addition salts. The preferred compounds I are those wherein Hal signifies a chlorine atom.

The present invention also provides a process for the production of compounds I in the form of their acid addition salts, characterized in that a lysergic or dihydrolysergic acid derivative of the general formula II,



II

in which R_1 and $\overset{x}{\frown}\overset{y}{}$ have the above significance, or an alkali metal salt thereof, is converted to the corresponding acid halide with a phosphorus halide, a phosphorus oxyhalide or a thionyl halide. It should be noted that the compounds I are obtained in the form of their acid addition salts. Compounds II are described and claimed in the Specification of our Copending Application No. 287856/61 [Serial No. 988,001].

Preferred phosphorus halides for use in the process of the invention are phosphorus pentachloride and trichloride. The preferred phosphorus oxyhalide is phosphorus oxychloride. The preferred thionyl halide is thionyl chloride.

In addition to the above preferred phosphorus halides for use in the process of the invention, phosphorus pentabromide and phosphorus triiodide may also be used.

The conversion of compounds II to the corresponding acid halide is preferably effected in a solvent, e.g. acetonitrile, carbon disulphide, chloroform or dimethyl formamide; it is to be noted that the starting materials are difficultly soluble and hence they only partly dissolve in these solvents; they are mainly suspended in

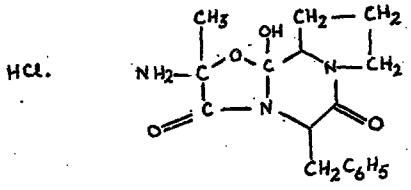
them. It is also mentioned that although phosphorus oxychloride effects the conversion of alkali metal salts of the starting materials to the end product, it acts as a solvent when the starting materials are used as free acids.

The process in accordance with the present invention may, for example, be effected as follows:— Lysergic or dihydrolysergic acid, or a dry alkali metal salt thereof, is suspended in a solvent, e.g. carbon disulphide, acetonitrile or dimethyl formamide, and an equivalent quantity or an excess of a phosphorus halide added, the reaction being effected at a temperature of from 0 to 100°C. In the case of a liquid acid halide, e.g. phosphorus trichloride or phosphorus tribromide, an excess of the acid halide may be used so that no solvent is required. Should an alkali metal salt be used instead of the free acid, then boiling in phosphorus oxychloride gives rise to the required lysergic acid chloride I.

The lysergic acid halide I in the form of an acid addition salt may be isolated by evaporating the solvent in a vacuum or by dilution of the reaction mixture with petroleum ether or hexane, the compound I precipitating as a filtrable hydrohalide which is generally a light grey crystalline powder and may be hygroscopic.

The halogen atom of compounds I is very reactive and may be replaced by many organic radicals so that compounds I are valuable intermediates for the production of pharmaceuticals.

Compounds I may be used as starting materials in the production of ergot alkaloids of the peptide type. Ergotamine or 9,10-dihydro-ergotamine may, for example, be synthesized by reacting lysergic acid chloride hydrochloride or 9,10-dihydrolysergic acid chloride hydrochloride respectively with aminocyclol hydrochloride of formula III,



III

Examples of other physiologically active amides of the lysergic and dihydrolysergic acid series, which may be obtained by conversion of the compounds I with amines, are lysergic acid diethylamide, lysergic acid butanolamide and ergonovine. The compounds I generally provide the best method of obtaining these known, useful physiologically active amides, since the method using compounds I as intermediates provides optimum yields and simplifies greatly the procedure.

Hitherto, it had been thought that classical methods of producing acid halides could not be applied to compounds II, probably because of their sensitivity (see W. L. Garbrecht "Synthesis of Amides of Lysergic Acid", J.Org. Chem. Vol. 24, pp. 368—372, at page 368, where it is stated that "The classical methods for preparing amides by acylation of amines with esters or acid chlorides fail when applied to lysergic acid."), and it is therefore highly surprising that such extremely potent acids as the phosphorus halides, oxyhalides and thionyl halides do not cause any appreciable change in the lysergic acid nucleus.

It has, however, now been surprisingly found that lysergic and dihydrolysergic acid halides, which may be substituted in the 1-position, may, under various conditions, be produced and even isolated and stored as salts.

The terms "lysergic acid" and dihydrolysergic acid", as used in this specification, include all possible stereoisomers of the lysergic acid and dihydrolysergic acid series. It should be noted, furthermore, that the notation "D" used in the nomenclature for the compounds, to which this invention relates, has the same signficance as the notation "d" in the article by Stoll *et al* in Helv.Chim.Acta, *26*, 944—965 (1943); the notation "D" was used for D-lysergic acid by H. G. Leemann and S. Fabbri in an article entitled "Über die absolute Konfiguration der Lysergsäure" in Helv.Chim.Acta, *42*, 2996—2709 (1959) at page 2700, and for D-dihydrolysergic acid by A. Stoll, J. Rutschmann and W. Schlientz in an article entitled "Synthese der optisch aktiven Dihydrolysergsäuren" in Helv.Chim.Acta, *33*, 375—388 (1950) at page 385.

In the following non-limitative Examples all temperatures are given in degrees Centigrade. The melting points are uncorrected.

EXAMPLE 1:

D-lysergic acid chloride hydrochloride.

The D-lysergic acid chloride hydrochloride is produced as follows:— 536 mg of D-lysergic acid are finely suspended in 10 cc of freshly distilled phosphorus oxychloride, and 416 mg of finely pulverised freshly sublimated phosphorus pentachloride are added whilst stirring. The reaction mixture is then shaken for 2 minutes at room temperature, heated to 90° and kept at this temperature for 2 minutes. The phosphorus oxychloride is then evaporated in a water jet vacuum and the remaining grey powder recrystallized twice from hexane. The D-lysergic acid chloride hydrochloride resulting as a light yellow crystalline powder has a melting point of 310—315° in an evacuated tube.

EXAMPLE 2:

D-lysergic acid chloride hydrochloride.

268 mg of D-lysergic acid are suspended in 3 cc of phosphorus oxychloride, 120 mg of thionyl chloride are added and the mixture

heated to 90° for 3 minutes. Evaporation of the light fractions in a vacuum results in the acid chloride hydrochloride remaining as a green-grey powder.

EXAMPLE 3:

D-lysergic acid chloride hydrochloride.

268 mg of D-lysergic acid are converted with phosphorus pentachloride in phosphorus oxychloride in a manner analogus to that described in Example 2. However, instead of evaporating the phosphorus oxychloride to dryness in a vacuum, the reaction mixture is diluted with a five-fold quantity of *n*-hexane, the D-lysergic acid chloride hydrochloride precipitating as a grey powder. The mixture is filtered and the filter cake washed well with *n*-hexane, so that the remaining residues of phosphorus oxychloride, which is easily soluble in hexane, are removed. The acid chloride hydrochloride is dried in a high vacuum and may be stored in the dark.

EXAMPLE 4:

D-dihydrolysergic acid chloride hydrochloride.

270 mg of D-dihydrolysergic acid are finely suspended in 5 cc of phosphorus oxychloride and 208 mg of phosphorus pentachloride are added while stirring. The reaction mixture is heated to 90° and kept at this temperature for 2 minutes. The phosphorus oxychloride is then evaporated in a water jet vacuum and the remaining colourless powder recrystallised twice from hexane. The hydrochloride of the D-dihydrolysergic acid chloride results, having a melting point of higher than 300°.

EXAMPLE 5:

1-methyl-D-lysergic acid chloride hydrochloride.

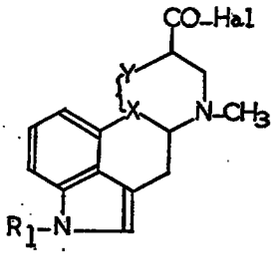
564 mg of 1-methyl-D-lysergic acid [melting point 239—240°, $[\alpha]_D^{20} = +116°$ (c=0.5 in 0.1 N methanesulphonic acid)] are suspended in 8 cc of petroleum ether containing 2 cc of ether and a mixture of 10 cc of petroleum ether containing 8 cc of phosphorus oxychloride is added at −10 to −5°. 457 mg of phosphorus pentachloride are then added at the same temperature and the mixture stirred for a further 2 hours. The reaction mixture is then diluted with 80 cc of petroleum ether and the precipitated acid chloride filtered off as a grey powder, and dried in a vacuum of 11 mm of Hg at 40°.

The 1-methyl-D-lysergic acid used as a starting material may be prepared as follows:— 5 g of 1-methyl-ergotamine [melting point 185°, $[\alpha]_D^{20} = -170°$ (c=1 in chloroform)] are boiled at reflux for three and a half hours in a suspension of 12.5 g of barium hydroxide crystals in 40 cc of water/alcohol (1:1) in an atmosphere of nitrogen. The solution is cooled to room temperature, 5 cc of concentrated ammonia solution added and the barium precipitated as barium sulphate by the addition of 40.5 cc of 2 N sulphuric acid.

The solution is then filtered, the filter cake washed 5 times each time with 40 cc of a 1 N ammonia solution in 50% alcohol and the clear solution evaporated in a vacuum. Upon evaporation the 1-methyl-D-lysergic acid crystallises from the solution in the form of fine yellowish crystals. Melting point 239—240°, $[\alpha]_D^{20} = +116°$ (c=0.5 in 0.1 N methanesulphonic acid).

WHAT WE CLAIM IS:—

1. A process for the production of compounds of the general formula I,

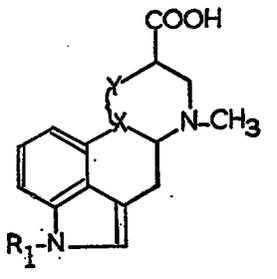


I

in which R_1 signifies a hydrogen atom or an alkyl radical containing from 1 to 4 carbon atoms inclusive,

$\overbrace{x \quad y}$ signifies the radical $-CH=C\begin{matrix}/\\\backslash\end{matrix}$ or $-CH_2-CH\begin{matrix}/\\\backslash\end{matrix}$, and

Hal signifies a chlorine, bromine or iodine atom, in the form of their acid addition salts, characterized in that a lysergic or dihydrolysergic acid derivative of general formula II,



II

in which R_1 and $\overbrace{x \quad y}$ have the above significance, or an alkali metal salt thereof, is converted to the corresponding acid halide hydrohalide with a phosphorus halide, a phosphorus oxyhalide or a thionyl halide.

2. A process for the production of compounds I stated in claim 1 in the form of their acid addition salts, characterized in that the compound II is converted to the corresponding acid chloride hydrochloride with phosphorus

heated to 90° for 3 minutes. Evaporation of the light fractions in a vacuum results in the acid chloride hydrochloride remaining as a green-grey powder.

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EXAMPLE 4:

D-dihydrolysergic acid chloride hydrochloride.

270 mg of D-dihydrolysergic acid are finely suspended in 5 cc of phosphorus oxychloride and 208 mg of phosphorus pentachloride are added while stirring. The reaction mixture is heated to 90° and kept at this temperature for 2 minutes. The phosphorus oxychloride is then evaporated in a water jet vacuum and the remaining colourless powder recrystallised twice from hexane. The hydrochloride of the D-dihydrolysergic acid chloride results, having a melting point of higher than 300°.

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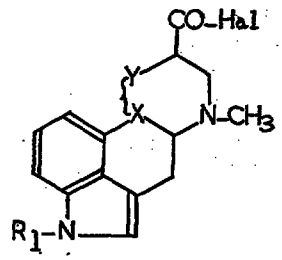
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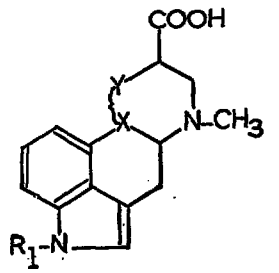


I

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$\overset{\frown}{x\ y}$ signifies the radical $-CH=C\diagup\diagdown$ or $-CH_2-CH\diagup\diagdown$, and

Hal signifies a chlorine, bromine or iodine atom, in the form of their acid addition salts, characterized in that a lysergic or dihydrolysergic acid derivative of general formula II,



II

in which R_1 and $\overset{\frown}{x\ y}$ have the above significance, or an alkali metal salt thereof, is converted to the corresponding acid halide hydrohalide with a phosphorus halide, a phosphorus oxyhalide or a thionyl halide.

2. A process for the production of compounds I stated in claim 1 in the form of their acid addition salts, characterized in that the compound II is converted to the corresponding acid chloride hydrochloride with phosphorus

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pentachloride, phosphorus trichloride or phosphorus oxychloride.

3. A process for the production of compounds I stated in claim 1 in the form of their acid addition salts, characterized in that the compound II is converted to the corresponding acid chloride hydrochloride with thionyl chloride.

4. A process for the production of compounds I stated in claim 1 in the form of their acid addition salts, substantially as herein described with reference to any one of the examples.

5. The compounds of general formula I stated in claim 1 in the form of their acid addition salts, whenever produced by the process claimed in any one of the preceding claims.

6. The compounds of the general formula I stated in claim 1 in the form of their acid addition salts.

7. The compounds according to claim 6, in which the symbol Hal in formula I signifies a chlorine atom.

8. D-lysergic acid chloride in the form of an acid addition salt.

9. D-dihydrolysergic acid chloride in the form of an acid addition salt.

10. 1-Methyl-D-lysergic acid chloride in the form of an acid addition salt.

11. Pharmaceutical compositions containing, in addition to an inert carrier, a compound claimed in any one of the claims 5 to 10.

SANDOZ PATENTS LIMITED,
by Eric Potter and Clarkson,
Chartered Patent Agents.
317, High Holborn, London, W.C.1.

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