1,017,277

PATENT SPECIFICATION

NO DRAWINGS

1,017,277

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Application made in United States of America (No. 156,988) on Dec. 4, 1961.
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Int. Cl.:—C 07 c, d

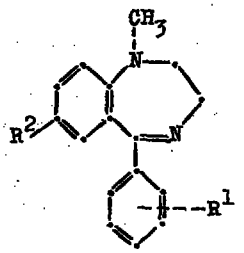
COMPLETE SPECIFICATION

Process for the Manufacture of Benzodiazepine Derivatives

We, F. HOFFMANN—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:—

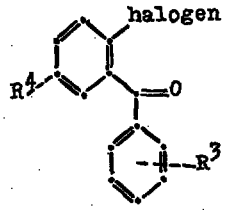
The present invention is concerned with a process for the manufacture of benzodiazepine derivatives.

The derivatives produced in accordance with the process are claimed *per se* in the specification of our copending application for Letters Patent No. 28946/62 (now serial no: 1017276) and are compounds of the general formula



wherein each of the symbols R^1 and R^2 represents a halogen atom or a trifluoromethyl group and the broken lines indicate that the substituents (i.e. CH_3 and R^1) attached thereby are optional, and acid addition salts thereof. The preferred derivatives are those in which R^1 is either absent or is present in the 2'-position. The compounds and their medicinally acceptable acid addition salts are valuable therapeutic agents as they are useful as muscle relaxants, sedatives and anticonvulsants. They may be administered internally (for example, parenterally or orally) and can be compounded into conventional pharmaceutical dosage forms containing amounts adjusted to individual requirements; for example, tablets, capsules, lozenges, suppositories, suspensions and solutions.

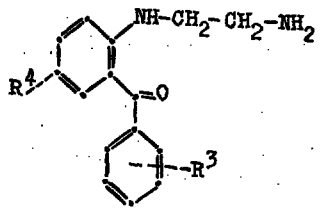
According to the process of the invention, the foregoing compounds and salts are manufactured by reacting a benzophenone of the formula



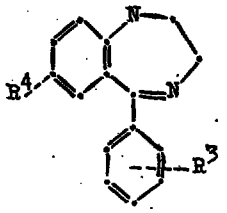
wherein each of the symbols R^3 and R^4 represents a halogen atom or a trifluoro-methyl or nitro group and the broken lines denote that R^3 and R^4 are optional substituent atoms or groups, with ethylene-diamine, introducing a nitro group into the reaction product where R^4 is absent, replacing said nitro group and/or any nitro group or groups already present in the reaction product by halogen in a manner known *per se* and, if desired, converting the product into an acid addition salt; said process also including, if desired, a methylation step at any suitable stage for the purpose of introducing a methyl group in the 1-position in the product.

Those benzophenone starting materials in which the 2-halogen substituent is chloro and R^4 is trifluoro-methyl and in which R^3 is either absent or is a 2-trifluoromethyl substituent are claimed *per se* in the specification of our copending application for Letters Patent No. 20071/63 (now serial no: 972,976).

The reaction with ethylene-diamine passes through intermediates of the formula



(wherein R_3, R_4 and the broken lines have the meanings given earlier) which, in certain cases, can be isolated. On prolonged standing or with the application of heat, these cyclise to form compounds of the formula



wherein R^3 and R^4 and the broken lines have the meanings given earlier.

The ethylene-diamine can be used in excess and thus serve as the reaction medium. Alternatively, a conventional inert organic solvent (e.g. an alcohol or a tertiary base such as pyridine, picoline or quinoline) can be used as the reaction medium. In a preferred embodiment, the reaction is carried out at elevated temperature; for example, above 75°C. The maximum temperature will, of course, be the boiling point of the reaction medium. The halogen atom in the 2-position is capable of reaction since the carbonyl substituent adjacent thereto and also any of the above mentioned substituents in *para*-position thereto exert an activating influence on the 2-halo atom. Preferred activating substituents are the trifluoro-methyl and nitro groups.

Compounds of the formula last written wherein R^4 is absent can be nitrated; preferably by treatment with nitric acid. As indicated earlier the nitro compound obtained, as well as those compounds wherein one or both of the symbols R^3 and R^4 represent nitro groups, can be converted to the corresponding halo compounds in a manner known *per se*, that is to say by methods which are in actual use for, or described in the literature on, the replacement of nitro groups by halogen atoms; for example, by reduction of the nitro group or groups to an amino group or groups (e.g. catalytically in the presence of RANEY-nickel), diazotisation of the amino group or groups and treatment of the resulting mono- or di-diazonium salt with a hydrohalic acid.

Compounds of the formula last written can, if desired, be converted into the corresponding compounds carrying a methyl group on the nitrogen atom in the 1-position. The methylation can be carried out by treatment with a methyl ester of an inorganic acid (for example, with a methyl halide or dimethyl sulphate). It is also possible to use diazomethane. The methylation is preferably carried out in a medium such as ether, benzene, alcohol, dioxan or N,N-dimethyl-formamide. Furthermore, it is advantageous to carry out the methylation in the presence of an acid binding agent (such as a sodium alcoholate) except when diazo-methane is used. The methylation may also be carried out in two steps, by first forming a sodium derivative by reaction with a sodium alcoholate and then reacting the sodium derivative with a methyl ester of an inorganic acid. The methylation is preferably carried out at *ca* 20°C or up to the boiling point of the reaction mixture.

The compounds of the formula first written hereinbefore form acid addition salts with both inorganic acids (such as nitric acid, sulphuric acid, hydrochloric acid, hydrobromic acid and phosphoric acid) and with organic acids (such as acetic acid, citric acid, succinic acid, benzoic acid, formic acid and *para*-toluenesulphonic acid).

The following Examples illustrate the invention.

Example 1

82.1 g of 2-chloro-5-trifluoromethyl-benzophenone [prepared as described in the specification of our copending application no 20071/63 (now serial no: 972,976)] were dissolved in 300 ml of anhydrous pyridine and the solution was treated with 100 ml (89.9 g) of ethylene-diamine. The mixture was stirred and heated under reflux for 5 hours under dry conditions and then allowed to cool for *ca* 16 hours. The solution was evaporated *in vacuo* and the residue dissolved in 500 ml of 0.6-*N* hydrochloric acid and extracted with ether. The aqueous layer was cooled in an ice-bath and made basic with 3-*N* sodium hydroxide solution. The resulting suspension was extracted with ether, the extract washed with water, dried over anhydrous magnesium sulphate, and evaporated to give the product as a pale yellow gum which rapidly crystallized. This material was recrystallized from hexane, giving yellow needles of 5-phenyl-7-trifluoromethyl - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine. Two further recrystallizations from hexane yielded pale yellow needles melting at 110°—111°C.

29.4 g of 5-phenyl-7-trifluoromethyl-1,2-dihydro-3H-1,4-benzodiazepine were dissolved in 56 ml of methanol and the solution was treated with 56 ml of 2-*N* hydrochloric acid in methanol while cooling the stirred mixture in an ice-bath during the addition of the acid solution. The mixture was then evaporated at 25°C under reduced pressure and the residue was dried by azeotropic distillation with anhydrous benzene. The residue was then triturated with benzene and the crystalline

product filtered off, washed with ether and dried at 60°C *in vacuo* to give crude 5-phenyl - 7 - trifluoromethyl - 1, 2 - dihydro - 3H-1,4-benzodiazepine hydrochloride as yellow crystals. Recrystallization from methanol/ether yielded bright yellow prisms melting at 283°—285°C.

EXAMPLE 2

A solution of 208 g of 2-chloro-5-nitrobenzophenone in a mixture of 500 ml of pyridine and 200 ml of ethylene-diamine was heated under reflux for 5 hours. Some solvent was distilled off at atmospheric pressure and the reaction mixture was then concentrated to dryness *in vacuo*. Methanol was added to the residue and the crude reaction product filtered off. The filtrate was concentrated to dryness and the residue dissolved in a mixture of methylene chloride and water. The organic layer was separated, dried and concentrated to a small volume yielding the second crop. The reaction product was recrystallized from acetone and formed yellow needles of 5-phenyl - 7 - nitro - 1, 2 - dihydro - 3H - 1, 4-benzodiazepine melting at 211°—212°C.

35.6 g of sodium methoxide were added to a solution of 160 g of 5-phenyl-7-nitro-1, 2-dihydro-3H-1,4-benzodiazepine in 1.6 litres of N,N-dimethyl-formamide and the resulting mixture was stirred at *ca* 20°C for 1 hour. Then 62.5 ml of dimethyl sulphate were added and the stirring was continued for a further 2 hours. Water was then added to the reaction mixture and the crude product was filtered off. Upon recrystallization from a mixture of methylene chloride and ether, 1 - methyl - 5 - phenyl - 7 - nitro - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine was obtained as yellow prisms melting at 187°—188°C.

A suspension of 126.5 g of 1-methyl-5-phenyl - 7 - nitro - 1, 2 - dihydro - 3H - 1, 4-benzodiazepine in 2.2 litres of methanol was hydrogenated at *ca* 20°C and at atmospheric pressure in the presence of 40 g of RANEY-nickel. After absorption of 1.35 mol of hydrogen (taking 3 hours), the RANEY-nickel was filtered off, the filtrate acidified with an excess of methanolic hydrogen chloride and the solution concentrated *in vacuo* to a smaller volume with stirring. Ether was added and the precipitated crystals were filtered off giving orange prisms of 1-methyl-5-phenyl-7-amino - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine dihydrochloride which melted at 267°—268°C after recrystallization from a mixture of methanol and ether.

An ice-cold solution of 20 g of 1-methyl-5 - phenyl - 7 - amino - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine dihydrochloride in water was made alkaline with 50% potassium hydroxide and extracted with methylene chloride. The organic layer was separated, dried, concentrated to a small volume and treated with petroleum ether. The crystalline base, 1 - methyl - 5 - phenyl - 7 - amino - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine, was separated by filtration and recrystallized from ether to form yellow prisms melting at 158°—159°C.

40 ml of 1-*N* aqueous sodium nitrite were added, within 10 minutes, to a cooled (0°C to +5°C) stirred solution of 12.4 g of 1-methyl-5 - phenyl - 7 - amino - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine dihydrochloride in 40 ml of 1-*N* hydrochloric acid. The resulting diazonium chloride solution was added within 10 minutes to a hot (80°—90°C), stirred solution of 3.8 g of cuprous chloride in 70 ml of concentrated hydrochloric acid which had been diluted with 35 ml of water. The mixture was kept for a further 10 minutes at 80°—90°C and was then cooled. Ice, water and an excess of ammonium hydroxide were added and the reaction product then extracted with methylene chloride. The organic layer was dried, concentrated to dryness *in vacuo* and the residue dissolved in methanol. An excess of methanolic hydrogen chloride was added and the solution was concentrated to dryness *in vacuo*. *Iso*propanol was added to the residue and the crude reaction product was separated by filtration. This product was repeatedly crystallized from *iso*propanol, yielding 1 - methyl - 5 - phenyl - 7 - chloro - 1,2 - dihydro - 3H - 1,4 - benzodiazepine hydrochloride melting at 250°—251°C (decomposition).

EXAMPLE 3

A solution of 4 g of 2,5-dichloro-benzophenone in 50 ml of ethylene-diamine was heated under reflux for 17 hours. The cooled mixture was poured into 500 ml of ice-water and extracted with ether. The ether was evaporated and the residue heated under reflux for 5 hours in a mixture of 25 ml of ethanol and 50 ml of 20% hydrochloric acid. The majority of the ethanol was removed *in vacuo* and the aqueous phase was extracted with ether. The aqueous phase was made alkaline with sodium hydroxide and extracted with ether. After washing with water and drying with sodium sulphate, the ether was evaporated and the residue consisting mainly of 2-(2 - amino - ethylamino) - 5 - chloro - benzophenone was cyclised by heating under reflux for 17 hours in 30 ml of pyridine containing 0.5 g of pyridine hydrochloride. The pyridine was removed *in vacuo* and the residue partitioned between ether and 2-*N* sodium hydroxide. The ether layer was washed with water, dried with sodium sulphate and concentrated. Yellow prisms of 7-chloro-1,2-dihydro - 5 - phenyl - 3H - 1, 4 - benzodiazepine were obtained which melted at 170°—171°C after recrystallization from ether. 7-Chloro - 5 - (2 - chloro - phenyl) - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine, in the

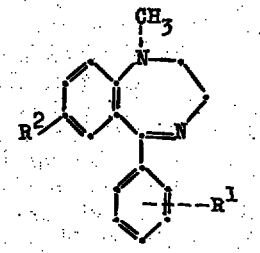
form of yellow crystals of melting point 175°—177°C, can be obtained in a similar manner to that described in this Example.

EXAMPLE 4

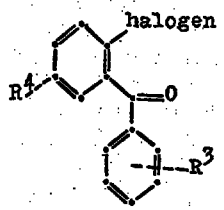
200 g of 2 - chloro - 5 - trifluoromethyl - benzophenone were dissolved in 250 ml of anhydrous pyridine and treated with 210 g of ethylene-diamine. The solution was stirred and heated under reflux for 5 hours, with protection from atmospheric moisture. The dark coloured mixture was then evaporated *in vacuo* and the oily residue was dissolved in 1 litre of methylene chloride. This solution was washed with 0.5 litre of water containing sufficient sodium carbonate to make the aqueous layer strongly basic. The methylene chloride extract was further washed with water until the washings were neutral, then dried over anhydrous sodium sulphate and evaporated *in vacuo*. This gave the crude product as a light brown oil which was dissolved in 200 ml of methanol and the resulting solution slowly poured into 4 litres of stirred ice-cold 1-*N* hydrochloric acid, resulting in precipitation of a yellow hydrochloride. The mixture was stirred for *ca* 16 hours at *ca* 20°C and then the yellow precipitate was filtered off and washed with ether. The aqueous and ether filtrates were shaken together and separated, and the ether layer was washed with water until neutral. The aqueous acid layer, together with the yellow-coloured washings, were combined with the precipitated hydrochloride, and the mixture was carefully made basic by dropwise addition of 5-*N* sodium hydroxide solution, with cooling and stirring of the mixture. The resulting precipitate was extracted with methylene chloride, the extract was washed with water, dried over sodium sulphate and evaporated to give a yellow-brown gum which consisted mostly of the desired base, 5-phenyl-7 - trifluoromethyl - 1, 2 - dihydro - 3H - 1, 4-benzodiazepine, and another compound, 2-(2 - amino - ethylamino) - 5 - trifluoro - methyl-benzophenone. This mixture was dissolved in 600 ml of pyridine and the solution was heated under reflux for 3 hours in order to effect cyclisation of the amino-ketone. Evaporation of the pyridine solution yielded a brown gum which was purified by dissolving it in methylene chloride, washing the solution three times with 250 ml of water each time, drying over sodium sulphate, followed by filtration of the solution through a short, wide, chromatography column containing 125 g of "WOELM" neutral alumina (activity III). Evaporation of the eluates and recrystallization of the residue from a mixture of 150 ml of benzene and 1 litre of hexane yielded 5-phenyl - 7 - trifluoromethyl - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine as yellow prisms which, upon recrystallization from hexane, formed pale yellow prisms of melting point 116°—118°C. This material appeared to be a dimorphic crystalline form of the compound described in Example 1. The two compounds had identical infrared spectra in chloroform solution, identical R_f values in thin-layer chromatography and were interconvertible by recrystallization from hexane. The said interconversion was surprising in view of the fact that hexane had already been used in their purification, but appears to be a peculiarity of the compound in question. Both forms of the compound formed the same monohydrochloride described in Example 1.

WHAT WE CLAIM IS:—

1) A process for the manufacture of benzodiazepine derivatives of the general formula



wherein each of the symbols R^1 and R^2 represents a halogen atom or a trifluoro-methyl group and the broken lines indicate that the substituents attached thereby are optional, and acid addition salts thereof, which process comprises reacting a benzophenone of the formula



wherein each of the symbols R^3 and R^4 represents a halogen atom or a trifluoro-methyl or nitro group and the broken lines denote that R^3 and R^4 are optional substituent atoms or groups, with ethylene-diamine, introducing a nitro group into the reaction product where R^4 is absent, replacing said nitro group and/or any nitro group or groups already present in the reaction product by halogen in a manner known *per se* and, if desired, converting the product into an acid addition salt; said process also including, if desired, a methylation step at any suitable stage for the purpose of introducing a methyl group in the 1-position in the product.

2) A process in accordance with claim 1, wherein 2 - chloro - 5 - trifluoromethyl - benzophenone, 2, 5 - dichloro - benzophenone or 2 - chloro - 5 - nitro - benzophenone is used as the starting material.

3) A process in accordance with claim 1 or claim 2, wherein 2 - chloro - 5 - nitro - benzophenone is reacted with ethylene-diamine, the resulting 7-nitro-5-phenyl-1,

* C L M S *

form of yellow crystals of melting point 175°—177°C, can be obtained in a similar manner to that described in this Example.

EXAMPLE 4

200 g of 2 - chloro - 5 - trifluoromethyl - benzophenone were dissolved in 250 ml of anhydrous pyridine and treated with 210 g of ethylene-diamine. The solution was stirred and heated under reflux for 5 hours, with protection from atmospheric moisture. The dark coloured mixture was then evaporated *in vacuo* and the oily residue was dissolved in 1 litre of methylene chloride. This solution was washed with 0.5 litre of water containing sufficient sodium carbonate to make the aqueous layer strongly basic. The methylene chloride extract was further washed with water until the washings were neutral, then dried over anhydrous sodium sulphate and evaporated *in vacuo*. This gave the crude product as a light brown oil which was dissolved in 200 ml of methanol and the resulting solution slowly poured into 4 litres of stirred ice-cold 1-*N* hydrochloric acid, resulting in precipitation of a yellow hydrochloride. The mixture was stirred for *ca* 16 hours at *ca* 20°C and then the yellow precipitate was filtered off and washed with ether. The aqueous and ether filtrates were shaken together and separated, and the ether layer was washed with water until neutral. The aqueous acid layer, together with the yellow-coloured washings, were combined with the precipitated hydrochloride, and the mixture was carefully made basic by dropwise addition of 5-*N* sodium hydroxide solution, with cooling and stirring of the mixture. The resulting precipitate was extracted with methylene chloride, the extract was washed with water, dried over sodium sulphate and evaporated to give a yellow-brown gum which consisted mostly of the desired base, 5-phenyl-7 - trifluoromethyl - 1, 2 - dihydro - 3H - 1, 4-benzodiazepine, and another compound, 2-(2 - amino - ethylamino) - 5 - trifluoro - methyl-benzophenone. This mixture was dissolved in 600 ml of pyridine and the solution was heated under reflux for 3 hours in order to effect cyclisation of the amino-ketone. Evaporation of the pyridine solution yielded a brown gum which was purified by dissolving it in methylene chloride, washing the solution three times with 250 ml of water each time, drying over sodium sulphate, followed by filtration of the solution through a short, wide, chromatography column containing 125 g of "WOELM" neutral alumina (activity III). Evaporation of the eluates and recrystallization of the residue from a mixture of 150 ml of benzene and 1 litre of hexane yielded 5-phenyl - 7 - trifluoromethyl - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine as yellow prisms which, upon recrystallization from hexane, formed pale yellow prisms of melting point 116°—118°C. This material appeared to be a dimorphic crystalline form of the compound described in Example 1. The two compounds had identical infrared spectra in chloroform solution, identical R_f values in thin-layer chromatography and were interconvertible by recrystallization from hexane. The said interconversion was surprising in view of the fact that hexane had already been used in their purification, but appears to be a peculiarity of the compound in question. Both forms of the compound formed the same monohydrochloride described in Example 1.

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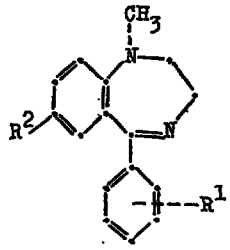
1) A process for the manufacture of benzodiazepine derivatives of the general formula



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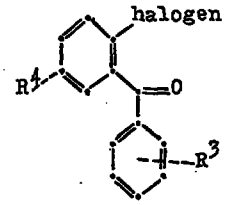

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2) A process in accordance with claim 1, wherein 2 - chloro - 5 - trifluoromethyl - benzophenone, 2, 5 - dichloro - benzophenone or 2 - chloro - 5 - nitro - benzophenone is used as the starting material.

3) A process in accordance with claim 1 or claim 2, wherein 2 - chloro - 5 - nitro - benzophenone is reacted with ethylene-diamine, the resulting 7-nitro-5-phenyl-1,

2 - dihydro - 3H - 1, 4 - benzodiazepine is methylated, the methylation product is reduced to form 1 - methyl - 7 - amino - 5 - phenyl - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine which is then diazotised and treated with hydrochloric acid to form 1 - methyl - 7 - chloro - 5 - phenyl - 1, 2 - dihydro - 3H - 1, 4 - benzodiazepine.

4) A process as claimed in claim 1, substantially as described with reference to the Examples.

5) Compounds of the formula first written in claim 1, and acid addition salts thereof, when manufactured by the process claimed in any one of claims 1 to 4 inclusive.

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