

1.037.375



PATENT SPECIFICATION

NO DRAWINGS

1.037.375

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Date of Application and filing Complete Specification: Aug. 7, 1964.

No. 32291/64.

Complete Specification Published: July 27, 1966.

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Index at acceptance:—C2 C(1E6K4, 1E6K6, 1F2C2, 1F2D2, 1Q4, 1Q6C, 1Q7A, 1Q8A, 1Q8B, 1Q8C, 1Q9B, 1Q11D, 1Q11J, 2B31, 3A14A3A, 3A14A5, 3A14A8C, 3A14A8D)

Int. Cl.:—C 07 d 53/06

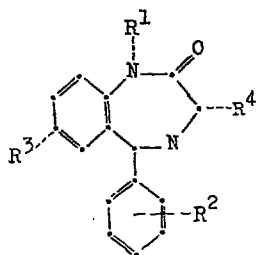
COMPLETE SPECIFICATION

A 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:—

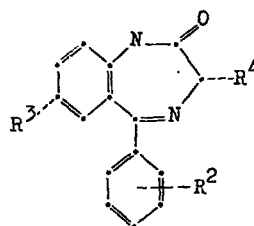
This invention is concerned with a process for the manufacture of certain benzodiazepine derivatives.

The benzodiazepine derivatives with the manufacture of which the invention is concerned are compounds of the general formula



I

wherein R^1 and R^4 each represent a lower-alkyl group, R^2 represents a halogen atom or a nitro or trifluoromethyl group, R^3 represents a halogen atom or a trifluoromethyl, nitro or cyano group and the bonds shown as broken lines denote that the substituents attached thereby are optional, and the corresponding 4,5-unsaturated 1-unsubstituted compounds of the formula

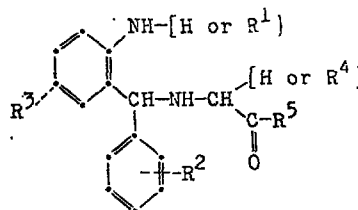


25

II

wherein R^2 , R^3 , R^4 and the broken lines have the significance given earlier, and acid-addition salts of both groups of compounds.

The process of the invention comprises the intramolecular condensing of a compound of the general formula



III

wherein R^1 , R^2 , R^3 and R^4 and the broken lines have the meanings already given and R^5 represents a lower-alkoxy, hydroxy or aryloxy group, and, if desired in the case where R^1 is absent, oxidising the product obtained by means of an oxidising system the oxidation potential of which is greater than 0.32 volt and/or converting the product into

an acid addition salt if required.

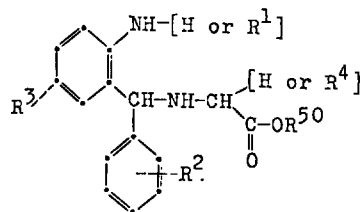
As used in this description and in the claims appended hereto, the term 'lower-alkyl' means straight and branched chain alkyl groups containing not more than seven carbon atoms; for example, methyl, ethyl, propyl and *isopropyl*. Similarly, the term 'lower alkoxy' means straight and branched chain alkoxy groups containing not more than seven carbon atoms. The term 'halogen' comprehends all four halogens; that is to say, iodine, bromine, fluorine and chlorine (the last three being preferred). Aryloxy comprehends aromatic hydrocarbonoxy groups such as phenoxy. The preferred products are 7-chloro - 1,3,4,5 - tetrahydro - 5 - phenyl-2H - 1,4 - benzodiazepin - 2 - one, 7-nitro - 1,3,4,5 - tetrahydro - 5 - phenyl-2H - 1,4 - benzodiazepin - 2 - one and 7-chloro - 1,3,4,5 - tetrahydro - 5 - (2 - fluoro-phenyl) - 2H - 1,4 - benzodiazepin - 2 - one and it will be appreciated that the preferred starting materials are those which lead to the aforementioned preferred products.

It will have been gathered that the invention essentially consists in the intramolecular condensation of compounds of formula III which, depending on the meaning of R^5 , are amino-acetic acids or amino-acetates (i.e. esters). While the intramolecular condensation can be effected with any of these, it is preferred to effect the intramolecular condensation using the aminoacetic acids (i.e. compounds of formula III in which R^5 is hydroxy). In such instances the intramolecular condensation constitutes a dehydration.

The intramolecular condensation can suitably be effected by heating a starting compound of formula III in an inert organic solvent. The dehydration embodiment (i.e. where R^5 in the compound used as the starting compound is hydroxy) can be effected by any suitable means but is preferably effected by heating in an inert organic solvent at temperatures from about 25° C to about 300° C, temperatures from about 80° C to about 200° C being especially preferred. Exemplary of useful organic solvents are hydrocarbons, for example, aromatic hydrocarbons such as xylene, halogen-containing hydrocarbons such as methylene chloride, ethers such as diethyl ether, diglyme and tetrahydrofuran and basic nitrogen-containing heterocycles such as pyridine and piperidine. Mixtures of inert organic solvents can also be used with advantage.

Compounds of formula III which are (2-amino - benzhydryl)amino - acetic acids are preferred starting materials for the process

and can be prepared by a variety of methods. More particularly, they can be prepared by hydrolysis of corresponding esters of the formula:

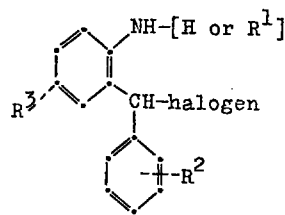


(IV)

wherein R^1 , R^2 , R^3 and R^4 have the same meaning as in formula III, R^5 is a lower-alkoxy or aryloxy group and the broken lines have the significance given earlier.

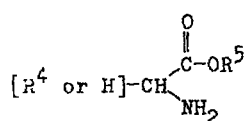
The compounds of formula III in general (that is, including those of formula IV) can be prepared by reaction of corresponding 2-amino-benzhydryl amines with a lower-alkyl or aryl halo-acetate (the bromoacetate and chloroacetate are especially preferred) or a haloacetic acid. This reaction can be effected at room temperature or above or below room temperature. Moreover, it is suitably effected in an inert organic solvent (for example, a hydrocarbon such as benzene or toluene), preferably in the presence of an acid binding agent (i.e. an acid accepting agent). Either inorganic or organic acid binding agents may be used; for example, carbonates such as sodium carbonate and amines such as lower-alkyl amines (e.g. triethyl amine).

Again, compounds of formula III can be prepared from benzhydryl halides of the formula:



(V)

wherein R^1 , R^2 , R^3 and the broken lines have the same meaning as in formula I, by reaction with a glycine compound of the formula



(VI)

in which R^4 and R^5 have the same meaning as in formula III.

5 The benzhydryl halides of formula V can be prepared by treatment of corresponding benzhydrols with a halogenating agent (iodinating, chlorinating and brominating agents being preferred, chlorinating agents being especially preferred). As examples of
10 halogenating agents there can be named thionyl halides (such as thionyl chloride and thionyl bromide), phosphorus trihalides or pentahalides (such as phosphorus trichloride, phosphorus tribromide or phosphorus penta-
15 chloride), hydrogen halides (such as hydrogen chloride or hydrogen bromide). The so-formed benzhydryl halide can then be isolated (advantageously in the form of its acid addition salt; for example, as the acid
20 addition salt formed during the halogenation reaction) or, preferably, is further reacted by adding the glycine compound of formula VI directly to the reaction mixture in which the benzhydryl halide of formula V has been
25 formed. A preferred embodiment of the reaction with a benzhydryl halide of formula V constitutes using as the glycine compound of formula VI a glycine ester (i.e. R^5 is lower-alkoxy or aryloxy).

30 The hydrolysis of the aminoacetate ester of formula IV to the acetic acid of formula III is suitably carried out either by alkaline or by acid hydrolysis and can be carried out at room temperature or above or below room
35 temperature. Preferably, it is carried out above room temperature by refluxing the ester of formula IV in an acidic or basic aqueous medium.

40 Products of general formula I in which R^1 is absent can be oxidised by means of an oxidising system the oxidation potential of which is greater than 0.32 volt to give a product of formula II. This oxidation results in
45 the loss of one mol of hydrogen from 5-phenyl - 1,3,4,5 - tetrahydro - 2H - 1,4-benzodiazepin-2-one of formula I with the resultant formation of a corresponding 1,3-dihydro - 5 - phenyl - 2H - 1,4 - benzo-
diazepin-2-one of formula II.

50 The removal of a mol of hydrogen from a compound of formula I in which R^1 is absent can be effected with weak or strong oxidants. The expression "weak oxidant" as used
55 herein means an oxidising system the potential of which is between 0.32 and 0.74 volt and

the expression "strong oxidant" means an oxidising system the potential of which is greater than 0.74 volt. With strong oxidants the result is suitably achieved by means of an agent containing in combination with oxygen
60 or in an anion a metal at a valence higher than its principal valence—said metal being vanadium, chromium, manganese or lead. By principal valence is meant that valence of the metal in which it has the largest number of
65 stable compounds. Thus, the principal valence for vanadium and chromium is 3 and that of manganese and lead is 2. Examples of suitable oxidants are lead peroxide, vanadium pentoxide, chromic acid and the
70 permanganate ion. Preferred oxidants are those formed from chromium and manganese in combination with oxygen at their higher valences; for example, chromic acid or the permanganate ion. Chromic acid is especially
75 preferred, and the term is used herein to include H_2CrO_4 (i.e. an aqueous solution of chromium trioxide) as well as chromium trioxide dissolved in organic solvents (e.g. in acetic acid or pyridine).

80 The oxidants referred to can be added to a solution containing the compound to be oxidized, or the compound to be oxidized can be added to a solution containing the oxidant, or the oxidant can be formed *in situ*.
85 Especially preferred is the use of chromic acid formed *in situ*. This can be effected, for example, by the addition of chromium trioxide and an acid (for example, sulphuric acid) to the mixture containing the compound to be
90 oxidized.

The conversion of a compound of formula I to a compound of formula II can also be effected with weak oxidants. Suitable weak oxidants are, for example, mercuric acetate,
95 ferric chloride, ferricyanide ions, mercuric oxide, selenium dioxide and silver oxide.

Selenium dioxide, silver oxide and chromic acid are the preferred oxidants. Manganese dioxide may also be mentioned as another
100 oxidant which is useful in the present process.

The concentration of the reactants is not critical but the oxidant should preferably be used in a slight stoichiometric excess of the compound of formula I which is being
105 oxidized. By a slight stoichiometric excess is meant an amount in excess of one stoichiometric equivalent but less than two stoichiometric equivalents. The temperature suitable
110 for the reaction will vary with the specific compound and, especially, with the specific oxidant being used. The oxidants *per se* are known in the art and have been used previously in oxidation reactions. It has been
115 found that the conditions conventionally employed in the art for the use of these oxidants will successfully effect dehydrogenation of the 4,5-position of a compound of formula I without concomitant splitting of the benzo-
diazepine moiety. The reaction media 120

utilized can suitably be those generally used in the art for the particular oxidant being used. Preferably, the reaction medium should be inert to the oxidant. It should be noted that the choice of temperature (in terms of yield and facility of reaction) at which to conduct the reaction is also dependent upon the reaction medium selected.

Products obtainable by the process of this invention are useful as sedatives, tranquilizers, anticonvulsants and muscle relaxants. Those compounds of formulae I and II in which R² (when present) represents a halogen atom or a trifluoromethyl group and R³ (when present) represents a halogen atom or a nitro or trifluoromethyl group and their acid-addition salts are claimed *per se* in the specification of our Letters Patent No. 972,968. Those compounds of formula II in which R³ is present and represents the cyano group and their acid-addition salts are claimed *per se* in the specification of our Letters Patent No. 985,657. Those compounds of formula II in which R² is present and represents a nitro group in the ortho-position and R³ (when present) represents a nitro group and their acid addition salts are claimed *per se* in the specification of our Letters Patent No. 1,000,507. The compounds of formula I in which R² (when present) represents a halogen atom, R³ is present and represents the cyano group and R⁴ is absent and their acid addition salts are claimed *per se* in the specification of our copending application for Letters Patent No. 51389/64 (now Serial No. 1,028,617).

The following Examples are illustrative of the invention:

EXAMPLE 1.

A solution of 2 - [1 - (2 - amino - 5-chloro - phenyl) - 1 - phenyl - methylamino] - acetic acid (1.00 g) in anhydrous pyridine (10 ml) and piperidine (0.02 ml) was heated under reflux for 17 hours. The mixture was evaporated *in vacuo* and the residue was partitioned between diluted hydrochloric acid and ether. The aqueous acid layer was made basic with sodium hydroxide solution and the resulting precipitate was filtered off and recrystallized from ethanol, giving 7-chloro-1,3,4,5 - tetrahydro - 5 - phenyl - 2H - 1,4-benzodiazepin-2-one as colourless prisms of melting point 183°—185° C.

A mixture of 1.28 g of 7-chloro-1,3,4,5-tetrahydro - 5 - phenyl - 2H - 1,4 - benzodiazepin-2-one, 1.0 g of selenium dioxide, 1.4 ml of pyridine and 100 ml of tertiary butanol was heated at 60° C for 30 minutes. The mixture was then cooled and filtered over a filter aid. Evaporation of solvents yielded a pink residue which was recrystallized from methanol yielding 7-chloro-1,3-dihydro-5-phenyl - 2H - 1,4 - benzodiazepin-2-one melting at 216°—217° C.

The starting material can be prepared as follows:

2 - Amino - 5 - chloro - benzhydrylamine dihydrochloride (30.6 g) was dissolved in water (150 ml), and made basic with 20% sodium hydroxide solution. Extraction of the mixture with methylene chloride gave 2-amino-5-chloro-benzhydryl amine as a pale yellow viscous oil.

2 - Amino - 5 - chloro - benzhydryl amine (11.64 g, 0.050 mol), dissolved in dry benzene (100 ml), was treated with triethyl amine (7.2 ml, 10.1 g, 0.100 mol). The reaction mixture was then stirred in an ice-bath at 0°—5° C during the dropwise addition (in the course of 20—30 minutes) of a solution of ethyl bromo-acetate (5.52 ml, 8.35 g, 0.050 mole) in dry benzene (20 ml). Stirring was then continued for 16 hours at room temperature, which was followed by heating the mixture on a steam-bath for one hour. After cooling, the reaction mixture was poured into water and extracted with methylene chloride to give a bright yellow oil. This was partitioned between dilute hydrochloric acid and ether, the aqueous acid layer was made basic with sodium hydroxide solution and extracted with methylene chloride to give the crude product as a viscous yellow gum. Trituration with hexane, followed by several recrystallizations from hexane and from ethanol gave 2 - [1 - (2 - amino - 5-chloro - phenyl) - 1 - phenylmethylamino] - acetic acid ethyl ester as colourless rods of melting point 103°—104° C.

2 - [1 - (2 - amino - 5 - chloro - phenyl) - 1 - phenylmethylamino] - acetic acid ethyl ester (1.81 g) was heated under reflux in a mixture of saturated methanolic barium hydroxide (30 ml, about 1-N) and water (10 ml) for 17 hours. The resulting precipitated barium salt was filtered off after cooling the mixture and recrystallized from water, giving colourless needles (melting point 206°—210° C). The barium salt was then dissolved in N,N-dimethyl-formamide (20 ml), and converted to the free acid by addition of the calculated amount of 1-N sulphuric acid, followed by filtration to remove the precipitated barium sulphate. Concentration of the filtrate and dilution with water gave 2-[1-(2 - amino - 5 - chloro - phenyl) - 1 - phenylmethylamino] - acetic acid as pale yellow prisms (from methanol). The melting point was rather indefinite, but about 234°—242° C (decomposition).

EXAMPLE 2.

A suspension of 2-[1-(2-amino-5-chloro-phenyl) - 1 - phenylmethylamino] - acetic acid (1.00 g) in dry xylene (20 ml) was stirred and heated under reflux for six hours, some solid material remaining undissolved. The mixture was cooled and filtered, giving 7 - chloro - 1,3,4,5 - tetrahydro - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one as colourless prisms of melting point 181°—185° C.

5 A suspension of 1.43 g of 7-chloro-1,3,4,5-tetrahydro - 5 - phenyl - 2H - 1,4 - benzodiazepin-2-one in a solution of 1.8 g of silver nitrate in 0.4 ml of ethanol and 4.0 ml of water was treated with a solution of 0.8 g of sodium hydroxide in 5.6 ml of water. The mixture was shaken at room temperature for 18 hours. The solids were then removed by filtration and washed with dichloro-methane.

10 The filtrate was made acidic with dilute sulphuric acid and extracted with dichloro-methane. All the organic fractions were combined, washed with water and concentrated. Recrystallization of the residue from methanol yielded 7 - chloro - 1,3 - dihydro - 5 - phenyl-2H - 1,4 - benzodiazepin - 2 - one melting at 216°—217° C.

The starting material can be prepared as follows:

20 A solution of 2-amino-5-chloro-benzhydrol (23.4 g, 0.100 mol) in ethylene dichloride (250 ml) was stirred and treated with dry hydrogen chloride, which was bubbled through the mixture until excess was present.

25 Then pyridine (2 drops) and thionyl chloride (14.4 ml, 23.8 g, 0.200 mol) was added, and the mixture was heated under reflux until evolution of sulphur dioxide virtually ceased (0.5 hour). The mixture was then evaporated *in vacuo*, with protection from atmospheric moisture. The residue was dissolved in methylene chloride (200 ml) and evaporated again to remove excess thionyl chloride. The residue obtained by evaporation of the reaction mixture, was dissolved in methylene chloride (60 ml). The solution was then stirred and cooled in an ice-bath, while a solution of freshly distilled glycine ethyl ester (10.3 g, 100 millimol) in methylene chloride (25 ml) was added dropwise over the course of 30 minutes. The mixture was then stirred for 1 hour at room temperature, and poured into ice-water. The organic layer was then evaporated giving the crude product as a brown, partly crystalline residue. This was partitioned between ether and dilute hydrochloric acid, the acid layer was made basic with sodium hydroxide solution, and extracted with methylene chloride, to give the almost pure product, 2 - [1 - (2 - amino - 5-chloro - phenyl) - 1 - phenylmethylamino]-acetic acid ethyl ester as a tan-coloured crystalline residue. One recrystallization from (methylene chloride)/hexane gave colourless prisms of melting point 102°—105° C. The ester can be hydrolyzed as described in the last paragraph of the foregoing example.

EXAMPLE 3.

60 2 - Amino - 5 - chloro - benzhydrol amine dihydrochloride (30.6 g, 0.100 mol) suspended in ethanol (200 ml) was treated with anhydrous sodium carbonate (21.2 g, 0.200 mol). The mixture was heated under reflux and treated dropwise in the course of

1 hour with a solution of ethyl bromoacetate (11.1 ml, 16.7 g, 0.100 mol) in ethanol (25 ml). Stirring and heating under reflux were continued for 24 hours, then the mixture was filtered, and the combined filtrates were concentrated *in vacuo*. The resulting residue was worked up in the manner described in example 2 for the preparation of 2 - [1 - (2 - amino - 5 - chloro - phenyl)-1-phenylmethylamino]-acetic acid ethyl ester giving a yellow oil. This was hydrolyzed by heating it under reflux with a mixture of aqueous 1-N sodium hydroxide solution (120 ml) and ethanol (240 ml) for 3 hours. The resulting solution was concentrated *in vacuo*, diluted with water, and acidified with 3-N acetic acid (pH 5—6), to give cream-coloured prisms containing 2 - [1 - (2 - amino - 5-chloro - phenyl) - 1 - phenylmethylamino]-acetic acid. The resulting crude product was cyclised to 7 - chloro - 1,3,4,5 - tetrahydro-5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one by treatment with refluxing xylene as described in example 2 giving tan-coloured prisms of melting point 182°—186° C.

A solution of 2.0 g of chromium trioxide in a small amount of water (2 ml) was added to a solution of 5.45 g of 7-chloro-1,3,4,5-tetrahydro - 5 - phenyl - 2H - 1,4 - benzodiazepin-2-one in 50 ml of glacial acetic acid. The mixture was allowed to stand at room temperature for 12 hours, diluted with ice-water and made basic (pH 8) with ammonium hydroxide. The precipitate was filtered and dissolved in dichloro-methane. The resultant dichloro-methane solution was then washed with water, dried and concentrated. Recrystallization of the residue from acetone gave 7 - chloro - 1,3 - dihydro - 5 - phenyl - 2H-1,4 - benzodiazepin - 2 - one melting at 216°—217° C.

The following compounds can be prepared in analogy to any one of the foregoing examples:

5 - Phenyl - 1,3,4,5 - tetrahydro - 2H - 1,4-benzodiazepin-2-one, recrystallized from a mixture of acetone/(petroleum ether), colourless needles of melting point 147°—148° C.

7 - Nitro - 1,3,4,5 - tetrahydro - 2H - 5-phenyl - 1,4 - benzodiazepin - 2 - one, recrystallized from a mixture of N,N-dimethylformamide and water as colourless needles of melting point 236°—237° C (decomposition).

7 - Chloro - 1,3,4,5 - tetrahydro - 2H - 5-(2 - chloro - phenyl) - 1,4 - benzodiazepin-2-one, recrystallized from a mixture of acetic acid and water, melting point 235°—237° C.

7 - Bromo - 1,3,4,5 - tetrahydro - 2H - 5-(2 - fluoro - phenyl) - 1,4 - benzodiazepin-2-one, recrystallized from methanol, colourless needles, melting point 224°—225° C.

EXAMPLE 4.

According to the procedure described in the last paragraph of example 3, 5-(3-nitro-

- phenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 1,3 - dihydro - 5 - (3 - nitro-phenyl) - 2H - 1,4 - benzodiazepin - 2 - one melting at 224°—227° C.

EXAMPLE 5.

- According to the procedure described in the last paragraph of example 3, 1,3,4,5-tetrahydro - 5 - (4 - nitro - phenyl) - 2H-1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 1,3 - dihydro - 5 - (4 - nitro-phenyl)-2H-1,4-benzodiazepin-2-one melting at 279°—281° C.

EXAMPLE 6.

- According to the procedure described in the last paragraph of example 3, 7-fluoro-1,3,4,5 - tetrahydro - 5 - (4 - chloro - phenyl)-2H-1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 7-fluoro-1,3-dihydro-5 - (4 - chloro - phenyl) - 2H - 1,4 - benzodiazepin-2-one melting at 230°—232° C.

EXAMPLE 7.

- A solution of 0.01 mol of 1,3,4,5-tetrahydro - 5 - (3 - nitro - phenyl) - 2H - 1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) in 200 ml of glacial acetic acid was oxidized at room temperature with a solution of 0.075 mol of chromium trioxide in 2 ml of water. The mixture was allowed to stand for 17 hours, diluted with water (0° C) and made basic (pH 8) with ammonium hydroxide. The resulting product was extracted into dichloro-methane and the extract washed, dried, filtered and evaporated. The residue was then recrystallized from methanol giving 1,3 - dihydro - 5 - (3 - nitro - phenyl)-2H - 1,4 - benzodiazepin - 2 - one as white prisms melting at 224°—227° C.

EXAMPLE 8.

- 5 - (4 - nitro - phenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one (prepared in analogy to any one of examples 1 to 3) was oxidized according to the procedure of example 7 yielding 1,3-dihydro-5-(4-nitro - phenyl) - 2H - 1,4 - benzodiazepin-2-one as pale yellow prisms melting at 279°—281° C.

EXAMPLE 9.

According to the procedure of the last

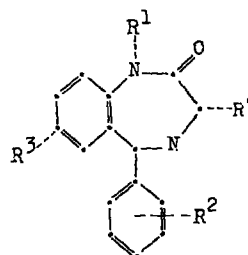
paragraph of example 3, 7-chloro-5-(2-fluoro-phenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 3.5 hours. There was thus obtained 7 - chloro - 1,3 - dihydro - 5 - (2-fluoro - phenyl) - 2H - 1,4 - benzodiazepin-2-one melting at 205°—206° C.

EXAMPLE 10.

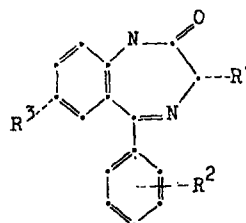
According to the procedure of the last paragraph of example 3, 5-(4-chloro-phenyl)-1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 5 - (4 - chloro - phenyl) - 1,3-dihydro - 2H - 1,4 - benzodiazepin - 2 - one melting at 268°—271° C (decomposition).

WHAT WE CLAIM IS:—

- 1) A process for the manufacture of compounds of the general formula



wherein R¹ and R⁴ each represent a lower-alkyl group, R² represents a halogen atom or a nitro or trifluoromethyl group, R³ represents a halogen atom or a trifluoromethyl, nitro or cyano group and the bonds shown as broken lines denote that the substituents attached thereby are optional and the corresponding 4,5-unsaturated 1-unsubstituted compounds of the formula



wherein R², R³, R⁴ and the broken lines have the significance given earlier, and acid-addition salts of both groups of compounds, which process comprises intramolecularly condensing a compound of the formula

phenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 1,3 - dihydro - 5 - (3 - nitro-phenyl) - 2H - 1,4 - benzodiazepin - 2 - one melting at 224°—227° C.

EXAMPLE 5.

According to the procedure described in the last paragraph of example 3, 1,3,4,5-tetrahydro - 5 - (4 - nitro - phenyl) - 2H-1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 1,3 - dihydro - 5 - (4 - nitro-phenyl)-2H-1,4-benzodiazepin-2-one melting at 279°—281° C.

EXAMPLE 6.

According to the procedure described in the last paragraph of example 3, 7-fluoro-1,3,4,5 - tetrahydro - 5 - (4 - chloro - phenyl)-2H-1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 7-fluoro-1,3-dihydro-5 - (4 - chloro - phenyl) - 2H - 1,4 - benzo-diazepin-2-one melting at 230°—232° C.

EXAMPLE 7.

A solution of 0.01 mol of 1,3,4,5-tetrahydro - 5 - (3 - nitro - phenyl) - 2H - 1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) in 200 ml of glacial acetic acid was oxidized at room temperature with a solution of 0.075 mol of chromium trioxide in 2 ml of water. The mixture was allowed to stand for 17 hours, diluted with water (0° C) and made basic (pH 8) with ammonium hydroxide. The resulting product was extracted into dichloro-methane and the extract washed, dried, filtered and evaporated. The residue was then recrystallized from methanol giving 1,3 - dihydro - 5 - (3 - nitro - phenyl)-2H - 1,4 - benzodiazepin - 2 - one as white prisms melting at 224°—227° C.

EXAMPLE 8.

5 - (4 - nitro - phenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4 - benzodiazepin - 2 - one (prepared in analogy to any one of examples 1 to 3) was oxidized according to the procedure of example 7 yielding 1,3-dihydro-5-(4-nitro - phenyl) - 2H - 1,4 - benzodiazepin-2-one as pale yellow prisms melting at 279°—281° C.

EXAMPLE 9.

According to the procedure of the last

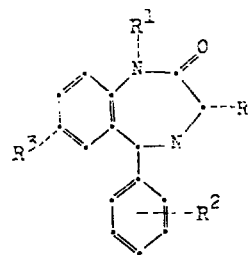
paragraph of example 3, 7-chloro-5-(2-fluoro-phenyl) - 1,3,4,5 - tetrahydro - 2H - 1,4-benzodiazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 3.5 hours. There was thus obtained 7 - chloro - 1,3 - dihydro - 5 - (2-fluoro - phenyl) - 2H - 1,4 - benzodiazepin-2-one melting at 205°—206° C.

EXAMPLE 10.

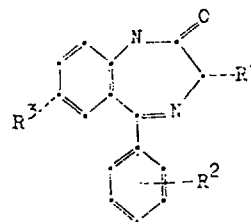
According to the procedure of the last paragraph of example 3, 5-(4-chloro-phenyl)-1,3,4,5 - tetrahydro - 2H - 1,4 - benzo-diazepin-2-one (prepared in analogy to any one of examples 1 to 3) was reacted with chromium trioxide in glacial acetic acid. The reaction time was 12 hours. There was thus obtained 5 - (4 - chloro - phenyl) - 1,3-dihydro - 2H - 1,4 - benzodiazepin - 2 - one melting at 268°—271° C (decomposition).

WHAT WE CLAIM IS:—

1) A process for the manufacture of compounds of the general formula

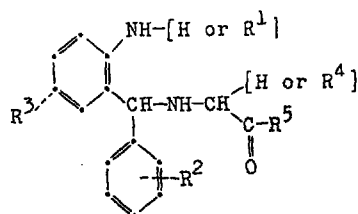


wherein R¹ and R⁴ each represent a lower-alkyl group, R² represents a halogen atom or a nitro or trifluoromethyl group, R³ represents a halogen atom or a trifluoromethyl, nitro or cyano group and the bonds shown as broken lines denote that the substituents attached thereby are optional and the corresponding 4,5-unsaturated 1-unsubstituted compounds of the formula



wherein R², R³, R⁴ and the broken lines have the significance given earlier, and acid-addition salts of both groups of compounds, which process comprises intramolecularly condensing a compound of the formula





wherein R¹, R², R³, R⁴ and the broken lines have the meanings already given and R⁵ represents a lower-alkoxy, hydroxy or aryloxy group, and, if desired in the case wherein R¹ is absent, oxidising the product by means of an oxidising system the oxidation potential of which is greater than 0.32 volt, and/or converting the product into an acid addition salt if required.

2) A process in accordance with claim 1 insofar as R⁵ is a hydroxy group, wherein the intramolecular condensation is carried out by heating the starting material in an inert organic solvent.

3) A process in accordance with claim 2, wherein the inert organic solvent is an aromatic hydrocarbon.

4) A process in accordance with claim 3, wherein the aromatic hydrocarbon is xylene.

5) A process in accordance with claim 2, wherein the inert organic solvent is a basic nitrogen-containing heterocycle.

6) A process in accordance with claim 5, wherein the said nitrogen-containing heterocycle is piperidine or pyridine or a mixture thereof.

7) A process in accordance with any one of claims 1 to 6 inclusive, wherein 2-[1-(2-amino-5-chloro-phenyl)-1-phenylmethylamino]-acetic acid, 2-[1-(2-amino-5-nitro-phenyl)-1-phenylmethylamino]-acetic acid or 2-[1-(2-amino-5-chloro-phenyl)-1-(2-fluoro-phenyl)-methylamino]-acetic acid is used as the starting material.

8) A process as claimed in any one of the preceding claims, wherein the oxidation is effected by means of an agent containing in

combination with oxygen or in an anion a metal at a valence higher than its principal valence, said metal being vanadium, chromium, manganese or lead.

9) A process in accordance with claim 8, wherein the oxidation is effected using chromic acid or manganese dioxide.

10) A process in accordance with claim 9, wherein chromic acid is used as the oxidising agent.

11) A process in accordance with claim 10, wherein the chromic acid is used in the form of chromium trioxide.

12) A process in accordance with claim 10, wherein the chromic acid is formed *in situ*.

13) A process in accordance with claim 12, wherein the chromic acid is formed from chromium trioxide and sulphuric acid.

14) A process in accordance with any one of claims 1 to 7 inclusive, wherein the oxidation is effected by means of mercuric acetate, mercuric oxide, selenium dioxide, ferric chloride, ferricyanide ions or silver oxide.

15) A process in accordance with claim 14, wherein the oxidation is effected by means of selenium dioxide.

16) A process in accordance with claim 14, wherein the oxidation is effected by means of silver oxide.

17) A process in accordance with any one of claims 8 to 16 inclusive, wherein the oxidizing agent is used in a slight excess over the stoichiometric amount.

18) A process for the manufacture of the compounds of the first two formulæ given in claim 1 and acid addition salts thereof, substantially as described with reference to the Examples.

19) Compounds of the first two formulæ given in claim 1 and acid addition salts thereof, when manufactured by the process claimed in any one of claims 1 to 18 inclusive.

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