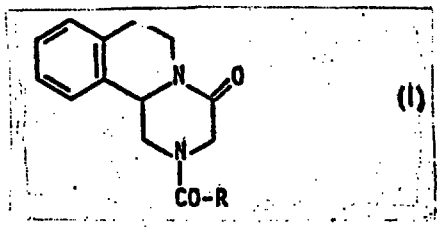
Description

The present invention relates to a process for the preparation of 2-acyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino-[2,1-a]-4-isoquinolinones.

More particularly, the present invention has for its object a new process for the preparation of compounds of the formula:



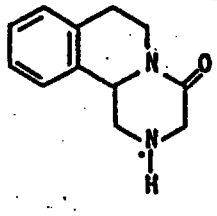
(I)

in which R represents a lower alkyl group, cycloalkyl having 3 to 8 carbon atoms, phenyl or substituted phenyl.

The 2-acyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino [2,1-a]-4-isoquinolinones of above formula 1 are well known products which are described in the German Patents Nos. 1795728 and 2362539 as powerful anthelmintics or as intermediaries in the preparation of products having anthelmintic activity.

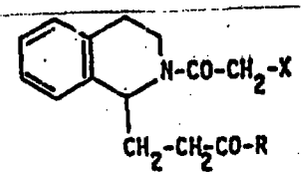
The above compound of formula 1, in which R is a cyclohexyl group, has been given the Common International Denomination of "Praziquantel" and it has been indicated as having a broad anthelmintic spectrum with an excellent activity against all the species of pathogenic Schistosomes in humans and the Cestodes (Experientia 1977, 1036).

The German Patents Nos. 2362539 and 2441261 describe a process which may be used for the preparation of the compounds of the above general formula I, the said process being characterised in that 4-oxo-1,2,3,6,7,11b-hexahydro-2H-pyrazino-[2,1-a]-isoquinoline of formula



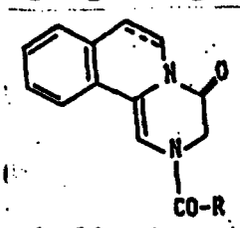
(II)

is reacted with the acid R-COOH or one of its functional derivatives, or even that a compound of formula



(III)

in which X represents a halogen, a methylsulphonyloxy group or an arylsulphonyloxy group containing 6 to 10 carbon atoms, is treated in the presence of a cyclising agent, or even, when it is a question of preparing diastereoisomers, a compound of formula

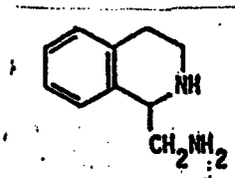


(IV)

in which the dotted line indicates that it may a double bond in the 6,7-position, is treated with a reducing agent.

According to German Patent No. 2504250, the starting product III has the disadvantage of only being available with very low yields from the isoquinoline, the R-COCl acid chloride and cyanides.

The same Patent visualises a process which is characterised in that a compound of formula:

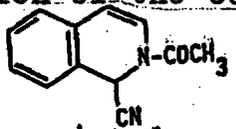


(V)

in the form of addition mono-salts, is treated with the chloride R-COCl in the presence of a weak base, which is more weakly basic than the product which is obtained, and then the compound which is obtained is transformed into the above compound III by action of a halogenoacetyl halide.

The compounds III are then transformed into the compounds of formula I as indicated above, using the process of German Patent No. 2362539.

The compound of formula V is, in its turn, prepared by catalytic hydrogenation of the compound of formula



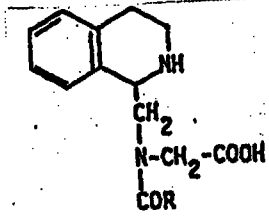
(VI)

preferably using Raney nickel as catalyst (Helv. Chim. Acta, 1939, 22, 673-683), and then by hydrolysis. However, this

(11)

hydrogenation, already for quantities of 150 to 200 mg., comprises an operation at high temperature and at a very high pressure (of at least 150 to 250 atmospheres), and this constitutes a disadvantage at the industrial level, especially when the quantities are even larger.

German Patent No. 2457971 described another process for the preparation of the compounds of the above formula I, which consists in cyclising a compound of formula

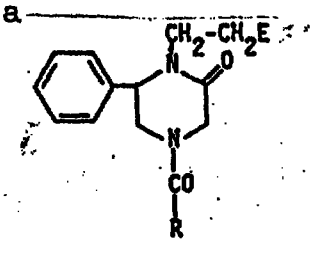


VII

or one of its functional groups on the carboxyl.

However, the compounds VII are prepared from the above product V, the obtaining of which requires high temperatures and pressures.

According to the same Patent, it is also possible to cyclise a compound of formula



VIII

in which E is a halogen or a hydroxyl group, but this procedure is not the one which is preferred in relation to that which comprises the cyclising of the product VII.

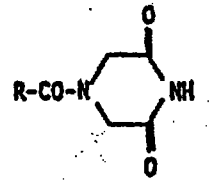
In all cases, all the methods which lead to the products of formula I with suitable yields comprise, primarily, either a hydrogenation at very high pressures and temperatures, in the presence of catalysts such as Raney Nickel, which necessitate careful preparation, or other processes which comprise, for example, the use of hydrofluoric gases or other expensive silicon-containing intermediaries.

It has now been found that the compounds of general formula I as indicated above can be prepared with high overall yields by the process of the present invention, which makes use of novel intermediaries and chemical reactions which are easy

(12)

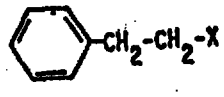
to use, the transfer of such process to an industrial level being simple.

Thus, according to one of its aspects, the present invention is concerned with a process for the preparation of 2-acyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino- [2,1-a] -4-isoquinolinones of formula I as above, the said process being characterised in that a 4-acyl-2,6-dioxopiperazine of formula:



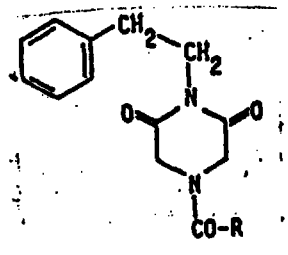
IX

is treated with an alkylating agent of formula:



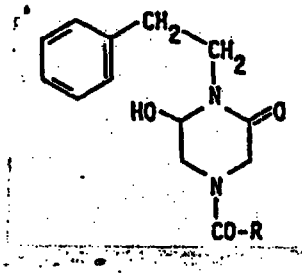
X

in which X represents chlorine, bromine, iodine or a nucleophobic group, in the presence of an alkaline condensation agent and in an inert organic solvent; one of the imidic carbonyls of the compound thus obtained and of formula:



XI

is selectively reduced by a complex metal hydride in the presence of a metallic chloride catalyst chosen from $CuCl_2$, $CoCl_2$, $NiCl_2$, $CrCl_3$, $FeCl_3$, $SnCl_2$, $SrCl_2$, $MnCl_2$, $CeCl_2$, $HgCl_2$, and the compound thus obtained and of formula

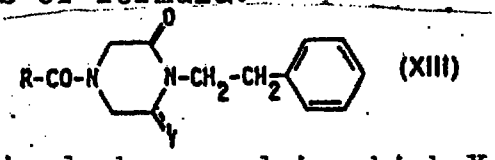


XII

is cyclised by the action of a strong organic or mineral acid at a temperature which is between 0 and 25°C.

According to another of its aspects, the present invention

has for its object, as intermediaries, novel 4-acyl-6-oxo-1-phenethyl piperazines of formula:



(XIII)

in which R is as defined above and in which Y is O or H.OH.

The steric configuration of the hydroxyl in the 2-position of the above compounds XII is of no importance in the process of the present invention, because the cyclisation passes through a carbocation, which destroys the asymmetric centre in the 2-position and the final products are obtained with a practically quantitative yield.

The term "lower alkyl" which is used here designates a straight-chain or branched-chain saturated aliphatic hydrocarbon radical which contains up to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, isobutyl, sec.butyl, tert.-butyl and similar radicals.

The term "substituted phenyl" which is used here designates a phenyl group which is monosubstituted or disubstituted by an atom or a radical which is inert under the above reaction conditions, for example, a halogen, such as fluorine, chlorine or bromine, a free or etherified hydroxy group with a lower alkyl as defined above, a hydroxy group which is free or monosubstituted or disubstituted by a lower alkyl, such as defined above, a mercapto group which is free or thioetherified with a lower alkyl group, such as defined above, a cyano group, a trifluomethoxy or trifluomethylthio group.

The reaction between the starting compound of the above formula IX and the reagent of formula X is an alkylation conducted in the presence of an alkaline condensation agent, such as an alkali metal hydride, for example, of sodium, an alkaline alcoholate and the like. The nucleophobic group indicated by X in the above formula X is preferably the methane-sulphonyloxy (mesyloxy) group or p-toluosulphonyloxy (tosyloxy) group, but the benzene-sulphonyloxy, β-naphthalene-sulphonyloxy and similar groups may also be used. The particularly preferred alkylating agents are phenethyl bromide and phenethyl iodide.

According to a preferred operating procedure, the reaction mixture is heated for 2 to 8 hours to a temperature which is between 50 and 100°C in an inert organic solvent, such as dimethyl formamide, dimethyl acetamide, dioxane or dimethoxyethane. With completion of the reaction, the product thus obtained is isolated by a conventional procedure and it can be purified or directly used for the following stage.

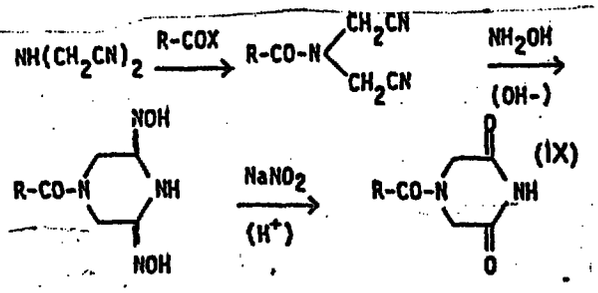
The 4-acyl-2,6-dioxo-1-phenethyl piperazine of formula XI is then reduced with a complex metal hydride, such as the double hydride of an alkali metal and an alkaline-earth metal, such as sodium borohydride, lithium borohydride or the hydride of lithium and aluminium or even other complex metal hydrides, such as the borohydride of potassium and tri-sec.-butyl, in the presence of a catalytic metal hydride. The operation is generally carried out in the presence of an inert solvent like an ether, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane, at a temperature which is between -70°C and the boiling point of the solvent being used. If sodium borohydride is used, the reaction may take place in aqueous or hydroalcoholic solution at a temperature close to ambient temperature.

According to one preferred operating procedure, this is carried out with an excess of sodium borohydride in an alcoholic solvent, such as methanol or ethanol, at a temperature between 0 and 25°C, using the cupric chloride ($CuCl_2$) as catalyst. After having destroyed the excess of reducing agent, the compound thus obtained, which is the 4-acyl-2-hydroxy-6-oxo-1-phenethyl piperazine of formula XII, is isolated in accordance with the conventional methods and purified, or even used as such for the cyclisation.

The cyclisation is carried out by treatment with a strong organic or mineral acid, such as hydrochloric acid, sulphuric acid, phosphoric acid, trifluoracetic acid and similar acids at a temperature which is between 0 and 25°C., preferably from 0 to 5°C. The final product of formula I as above is isolated by pouring the reaction mixture into iced water and by extraction with an appropriate solvent.

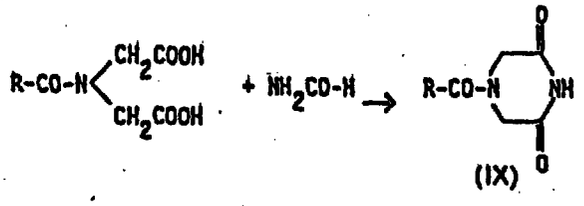
(15)

The 4-acyl-2,6-dioxopiperazines of formula IX used as starting compound in the process of the present invention are products which are known in the literature or which are easily prepared from iminodiacetonitrile by reaction with an acid halide, by subsequent treatment of the N-acyl iminodiacetonitrile thus obtained with hydroxylamine, and diazotisation in accordance with the following diagram:



described in J.Chem.Soc.Perkins I, 1972, 1009.

The 4-acyl-2,6-dioxopiperazines of formula IX being used as starting compounds may also be prepared by causing the reaction of an N-acyl-iminodiacetic acid or the corresponding diamine with formamide, while eliminating the water which is formed azeotropically in accordance with the following diagram:



as described in Belgian Patent No. 624686.

The following examples illustrate the invention.

Preparation:

a) N-(cyclohexylcarbonyl) iminodiacetonitrile

50 g (0.52 mol) of iminodiacetonitrile, 160 g (0.78 mol) of potassium carbonate, 150 ml. of water and 400 ml. of dichloromethane are mixed while stirring. After cooling the reaction mixture to 0°C., 96.5 g (0.65 mol) of cyclohexyl carbonyl are added dropwise. The temperature is allowed to return to ambient temperature in two hours, while continuing to stir. The organic phase is decanted, and the aqueous phase is extracted twice with dichloromethane. The combined organic

phases, dried over sodium sulphate, leave an oily residue after evaporation. By trituration with cyclhexane, crystals are recovered and these are recrystallised from the cyclohexane. White crystals, m.p. = 82°C., yield 85%.

b) 4-(cyclohexylcarbonyl)-2,6-bis-(hydroxyimino)-piperazine

To a mixture of 19.4 g (0.28 mol) of hydroxylamine hydrochloride and 7.42 g (0.07 mol) of potassium carbonate in 60 ml of methanol and 20 ml of water are added, in portions, 14.4 g (0.07 mol) of N-(cyclohexylcarbonyl) iminodiacetonitrile. The mixture is refluxed, in inert atmosphere, for 2½ hours. After cooling, the crystals are filtered off. These crystals are suspended in a mixture of 120 ml of ethanol and 50 ml of water and refluxed for one hour. The crystals are filtered off while hot and they are recrystallised in a mixture of water and ethanol. White crystals, m.p. > 260°C, yield: 84%.

c) 4-(cyclohexylcarbonyl)-2,6-dioxopiperazine

6 g (0.023 mol) of 4-(cyclohexylcarbonyl)-2,6-bis-(hydroxyimino) piperazine are suspended in a mixture of 20 ml of water and 20 ml of acetic acid. After cooling the reaction medium to between 0 and 5°C, a solution of 5 g (0.069 mol) of sodium nitrite in 25 ml of water is added dropwise in an inert atmosphere. The mixture is left for 24 hours at ambient temperature. Evaporation to dryness leaves a residue, which is purified by filtration on a silica bed (eluant: dichloromethane/methanol 9/1). The crystals obtained are recrystallised from ethanol. White crystals, m.p. 180°C, yield; 83%.

In the same manner, by causing reaction of iminodiacetonitrile with cyclopropylcarbonyl choride, cyclobutylcarbonyl chloride, cyclopentylcarbonyl chloride, cycloheptylcarbonyl chloride and cyclooctylcarbonyl chloride, treating the products thus obtained with hydroxylamine hydrochloride and subjecting the dioximes to a diazotisation in accordance with the operating procedure described above, there are respectively obtained 4-(cyclopropylcarbonyl) 2,6-dioxopiperazine, 4-(cyclobutylcarbonyl)-2,6-dioxopiperazine, 4-(cyclopentylcarbonyl)-2,6-dioxopiperazine, 4-(cycloheptylcarbonyl)-2,6-dioxopiperazine and 4-(cyclooctylcarbonyl)-2,6-dioxopiperazine.

(17)

Example 1

a) 4-cyclohexylcarbonyl)-2,6-dioxo-1-phenethyl piperazine

15 g (0.067 mol) of 4-(cyclohexylcarbonyl)-2,6-dioxo-piperazine are dissolved in 200 ml of dimethyl formamide. 4 g (0.073 mol) of sodium methylate are added and the mixture left for 1 hour at ambient temperature. In an inert atmosphere, the mixture has added thereto, dropwise, a solution of 19 g (0.081 mol) of (2-iodoethyl) benzene in 50 ml of dimethyl formamide and is brought for 5 hours to 80°C. The solution is evaporated to dryness in vacuo and the residue is taken up in a mixture of water and dichloromethane. The decanted organic phase is dried over dry sodium sulphate. Evaporation of the solvent leaves an oily residue which is purified by chromatography on a silica column (eluant: toluene/ethyl acetate 7/3). The crystals which are obtained are recrystallised in cyclohexane. White crystals, m.p. 90°, yield: 86%.

b) 4-cyclohexylcarbonyl)-2-hydroxy-6-oxo-1-phenethyl piperazine

15.2 g (0.046 mol) of 4-(cyclohexylcarbonyl)-2,6-dioxo-1-phenethyl piperazine are dissolved in 600 ml of ethanol. In an inert atmosphere, at 0°C., 8.7 g (0.0509 mol) of cupric chloride dihydrate are added and left for 1 hour at 0°C. The reaction mixture, kept at 0°C., has added thereto, in portions, 8.8 g (o.23 mol) of sodium hydroboride and is left for 45 minutes at 0°C. The excess of reducing agent is destroyed by adding acetone. The insoluble salts are filtered off and the filtrate is evaporated to dryness. The obtained residue is treated with a mixture of water and dichloromethane. The organic phase is decanted, dried over dry sodium sulphate and evaporated to dryness. The residue as obtained is purified by filtration on a silica bed (eluant: ethyl acetate). Beige crystals, m.p. = 134°C, yield: 73%.

c) 2-(cyclohexylcarbonyl)-1,3,4,5,6,11b-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4 (Praziquantel).

12.25 g (0.037 mol) of 4-(cyclohexylcarbonyl)-2-hydroxy-6-oxo-1-phenethyl piperazine are added portion-wise to 150 ml of 12N hydrochloric acid, previously cooled to 0°C, and left

overnight at ambient temperature. The reaction medium is poured into iced water and extracted with dichloromethane. The organic phase, dried over dry sodium sulphate and evaporated to dryness, leaves an oil which crystallises slowly on standing. The "praziquantel" crystals thus obtained are recrystallised from a mixture of petroleum ether and acetone. White crystals, m.p. = 138-140°C, yield: 95%. The total yield of praziquantel from iminodiacetonitrile, starting compound of the preparation, is 35%.

Example 2:

0.067 mol of 4-(cyclopropylcarbonyl)-2,6-dioxopiperazine are dissolved in 200 ml. of dimethyl acetamide. 0.073 mol of sodium methylate are added and the mixture is left for 1 hour at ambient temperature. The reaction mixture has added thereto, dropwise and in inert atmosphere, a solution of 0.081 mol of (2-tosyloxyethyl) benzene in 50 ml of dimethyl acetamide and is brought to 90°C for 4 hours. Evaporation to dryness under reduced pressure is carried out, the residue is taken up in a mixture of water and methylene chloride and the decanted organic phase is dried over dry sodium sulphate. The solvent is evaporated and the residue, constituted by 4-(cyclopropylcarbonyl)-2,6-dioxo-1-phenethyl piperazine in crude form, is dissolved in 600 ml of ethanol. Added to the solution thus obtained, at 0°C and in inert atmosphere, are 0.059 mol of manganese chloride and it is then left for 1 hour at 0°C. 0.23 mol of sodium borohydride is added in portions to the reaction medium, kept at 0°C, and the reaction medium is left for 45 minutes at 0°C. The excess of reducing agent is destroyed by adding acetone. The insoluble salts are filtered, the filtrate is evaporated to dryness and the residue is treated with a mixture of water and methylene chloride. The decanted organic phase is dried over dry sodium sulphate and evaporated to dryness. The residue is purified by filtration on a silica bed and the product thus obtained, formed by the 4-(cyclopropylcarbonyl)-2-hydroxy-6-oxo-1-phenethyl piperazine, is added in portions to 150 ml of hydrochloric acid, previously cooled to 0°C. After one night at ambient temperature, the reaction medium is poured into iced water and extracted with dichloromethane. The

organic phase is dried on anhydrous sodium sulphate and the solvent evaporated. In this way, there is obtained the 2-(cyclopropylcarbonyl)-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4; m.p. = 148-149°C, yield: 57%.

In the same manner, using 4-(cyclobutylcarbonyl)-2,6-dioxopiperazine, 4-(cyclopentylcarbonyl)-2,6-dioxopiperazine, 4-(cycloheptylcarbonyl)-2,6-dioxopiperazine and, respectively, 4-(cyclooctylcarbonyl)-2,6-dioxopiperazine, there are obtained;

the 2-(cyclobutylcarbonyl)-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a) isoquinolinone-4; m.p. = 153-156°C; yield 55%;

the 2(cyclopentylcarbonyl)-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4, m.p. 127-128°C; yield 60%;

the 2-(cycloheptylcarbonyl)-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4, m.p. 88-91°C, yield 57%;

and respectively;

the 2-(cyclooctylcarbonyl)-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4; m.p. = 107-108°C; yield: 55%.

Example 3:

7.8 g (0.050 mol) of 4-acetyl-2,6-dioxopiperazine are dissolved in 200 ml of dimethoxyethane. 3.2 g (0.060 mol) of sodium methylate are added and the mixture left for 1 hour at ambient temperature. To the reaction medium is added, dropwise and in an inert atmosphere, a solution of 13 g (0.070 mol) of 2-(bromoethyl) benzene in 50 ml of dimethoxyethane and the mixture is brought to 85°C for 5 hours. It is evaporated to dryness under vacuum and the residue is taken up in a mixture of water and dichloromethane. The oily residue which is obtained is purified by chromatography on a silica column (eluant: toluene/ethyl acetate 7/3). Obtained in this way is the 4-acetyl-2,6-dioxo-1-phenethyl piperazine which, after recrystallation in a mixture of ethyl acetate/isopropanol, melts at 130°C.

The product thus obtained is dissolved in 500 ml of ethanol. 7.15 g (0.055 mol) of $CoCl_2$ are added at 0°C in an inert atmosphere and the mixture left for 1 hour at this temperature. The reaction medium has added thereto, in portions and at 0°C, 9.5 g (0.25 mol) of sodium borohydride and left for 45 minutes at 0°C. The excess ofreducing agent is destroyed by acetone,

the insoluble salts are filtered and the filtrate is evaporated to dryness. The residue obtained is treated with a mixture of water and dichloromethane. The organic phase is decanted, then dried on dry sodium sulphate and evaporated to dryness. The residue obtained is purified by filtration on a silica bed (eluant: ethyl acetate), the product thus obtained is added in portions to 150 ml of 12N-hydrochloric acid cooled beforehand to 0°C and left overnight at ambient temperature. The reaction medium is poured into iced water and extracted with dichloromethane. The organic phase is dried on dry sodium sulphate, and evaporated to dryness. There is thus obtained the 2-acetyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4 which, after recrystallisation in a mixture of petroleum ether and acetone, melts at 140-141°C. Total yield: 60%.

Example 4:

12 g (0.055 mol) of 4-benzoyl-2,6-dioxopiperazine are dissolved in 200 ml of dimethyl formamide. 3.5 g (0.064 mol) of sodium methylate are added and left for 1 hour at ambient temperature. To the reaction medium is added, dropwise and in an inert atmosphere, a solution of 16 g (0.080 mol) of (2-methanesulphonyl-ethyl) benzene in 50 ml of dimethyl formamide and the medium is brought to 70°C for 5 hours. It is evaporated to dryness under vacuum and the residue is taken up in a mixture of water and dichloromethane. The decanted organic phase is dried on dry sodium sulphate. Evaporation of the solvent leaves an oily residue, which is purified by chromatography on a silica column (eluant: toluene/ethyl acetate 7/3). Obtained in this way is the 4-benzoyl-2,6-dioxo-1-phenethyl piperazine which, after recrystallisation from a mixture of cyclohexane/ethyl acetate, melts at 102°C.

16.1 g (0.050 mol) of the product thus obtained are dissolved in 600 ml of ethanol. In an inert atmosphere, at 0°C, there are added 8.94 g (0.055 mol) of ferric chloride and the mixture is left for 1 hour at 0°C. To the reaction medium, kept at 0°C, there are added in small quantities 9.5 g (0.25 mol) of sodium borohydride and it is left for 1 hour at 0°C. The excess of reducing agent is destroyed by adding

acetone. The insoluble salts are filtered and the filtrate is evaporated to dryness. The residue obtained is treated with a mixture of water and dichloromethane. The organic phase is decanted, dried on dry sodium sulphate and evaporated to dryness. The residue is purified by filtration on a silica bed (eluant: ethyl acetate). 10.78 g (0.035 mol) of the product thus obtained are then added in small quantities to 150 ml of 12N hydrochloric acid previously cooled to 0°C and left overnight at ambient temperature. The reaction medium is poured into iced water and extraction takes place with dichloromethane. The organic phase is dried on dry sodium sulphate and evaporated to dryness. In this way, there is obtained the 2-benzoyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4, m.p. = 160-162°C, Total yield: 58%.

Example 5:

In an inert atmosphere, 15 g (0.050 mol) of 4-parabromo-benzoyl-2,6-dioxopiperazine are dissolved in 300 ml of dimethyl formamide. 3.25 g (0.060 mol) of sodium methylate are added and left for 1½ hours at ambient temperature. To the reaction mixture is added dropwise a solution of 21 g (0.090 mol) of (2-iodoethyl) benzene in 50 ml of dimethyl formamide and brought to 120°C for 8 hours.

After cooling, the reaction medium is poured on to 3000 ml of iced water and extracted 3 times with ethyl acetate. The united organic phases are washed with water for eliminating the residual dimethyl formamide, dried on sodium sulphate and evaporated to dryness. The oily residue which is obtained is crystallised in isopropyl ether, filtered and dried under vacuum in order to give the 4-parabromo-benzoyl-2,6-dioxo-1-phenethyl piperazine, which is presented in the form of grey crystals. M.p. = 110-120°C.

14 g (0.035 mol) of the product thus obtained are dissolved in inert atmosphere in 500 ml of ethanol and the solution is cooled to 0°C. 6.5 g (0.038 mol) of cupric chloride dihydrate are then added and the mixture is maintained at 0°C for 1 hour. 6.6 g (0.175 mol) of $NaBH_4$ are added in small

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portions, keeping a temperature which is below 5°C, and the medium is left for 45 minutes at 0°C. The excess of reducing agent is then destroyed with acetone, the insoluble salts are filtered off and the filtrate is evaporated to dryness.

The oily residue which is obtained is treated with a mixture of dichloromethane and water. The organic phase is decanted, dried over sodium sulphate and evaporated to dryness.

The residue is purified by filtration on a silica bed (eluant: ethyl acetate) and evaporated to dryness. The 4-parabromobenzoyl-2-hydroxy-6-oxo-1-phenethyl piperazine crystallises in isopropyl ether in the form of white crystals. M.p.= 136-138°C.

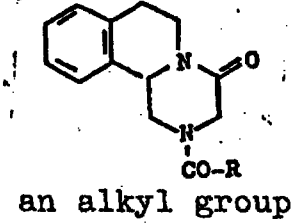
9.9 g (0.024 mol) of the product obtained above are added in small quantities to 150 ml of 12N-hydrochloric acid cooled to 0°C and left overnight at ambient temperature.

The medium is poured into iced water and extracted with methylene chloride. The organic phase is dried on sodium sulphate and evaporated to dryness. The oily resi e which slowly crystallises is recrystallised in a hexane-acetone mixture to give 6.6 g of 2-parabromobenzoyl-1,3,4,6,7,11-hexahydro-2H-pyrazino-(2,1-a)-isoquinolinone-4. M.p. 204-206°C (Köfler); yield, starting with the 4-parabromobenzoyl-2,6-dioxopiperazine: 35%.

CLAIMS for the contracting countries BE, CH, DE, GB, IT, LI, FR, LU, NL, SE.

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1. Process for the preparation of 2-acyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-4-isoquinolinones of formula:



in which R represents an alkyl group containing up to 6 carbon atoms, cycloalkyl having from 3 to 8 carbon atoms, a phenyl or phenyl group substituted by a halogen atom, a hydroxy group, alcoxy containing up to 6 carbon atoms, amino, alkylamino containing up to 6 carbon atoms, mercapto, alkylthio containing up to 6 carbon atoms, cyano, trifluoromethoxy,

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portions, keeping a temperature which is below 5°C, and the medium is left for 45 minutes at 0°C. The excess of reducing agent is then destroyed with acetone, the insoluble salts are filtered off and the filtrate is evaporated to dryness.

The oily residue which is obtained is treated with a mixture of dichloromethane and water. The organic phase is decanted, dried over sodium sulphate and evaporated to dryness.

The residue is purified by filtration on a silica bed (eluant: ethyl acetate) and evaporated to dryness. The 4-parabromobenzoyl-2-hydroxy-6-oxo-1-phenethyl piperazine crystallises in isopropyl ether in the form of white crystals. M.p.= 136-138°C.

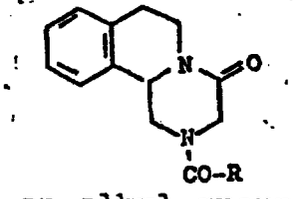
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CLAIMS for the contracting countries BE, CH, DE, GB, IT, LI, FR, LU, NL, SE.

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1. Process for the preparation of 2-acyl-1,3,4,6,7,11b-hexahydro-2H-pyrazino-(2,1-a)-4-isoquinolinones of formula:



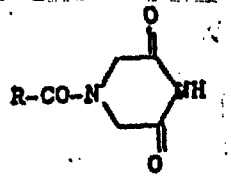
in which R represents an alkyl group containing up to 6 carbon atoms, cycloalkyl having from 3 to 8 carbon atoms, a phenyl or phenyl group substituted by a halogen atom, a hydroxy group, alcoxy containing up to 6 carbon atoms, amino, alkylamino containing up to 6 carbon atoms, mercapto, alkylthio containing up to 6 carbon atoms, cyano, trifluoromethoxy,



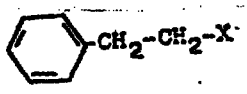
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or trifluoromethylthio, characterised in that:

a) a 4-acyl-2,6-dioxopiperazine of formula:

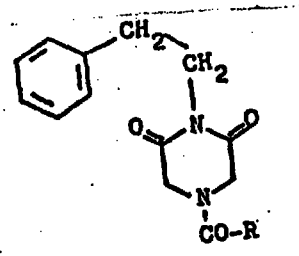


in which R is as defined above, is treated with an alkylating agent of formula:



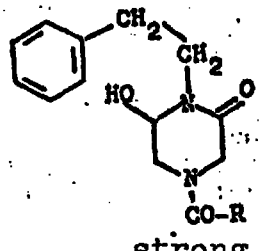
in which X represents chlorine, bromine, iodine or a nucleophobic group, in the presence of an alkaline condensation agent in an inert organic solvent,

b) one of the imidic carbonyl groups of the compounds thus obtained and of formula



is selectively reduced by a complex metal hydride in the presence of a metallic chloride catalyst selected from $CuCl_2$, $CoCl_2$, $NiCl_2$, $CrCl_3$, $FeCl_3$, $SnCl_2$, $SrCl_2$, $MnCl_2$, $CeCl_2$, $HgCl_2$, and

c) the compound thus obtained, having the formula



is cyclised by action of a strong mineral or organic acid at a temperature which is between 0 and 25°C.

2. Process according to claim 1, characterised in that, as alkylating agent, there is used the chloride, bromide or iodide of phenethyl or the mesylate or tosylate of phenethyl.

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3. Process according to claim 1, characterised in that the alkaline condensation agent used in the condensation reaction of the stage a is an alkaline metal hydride or an alkaline metal alcoholate.

4. Process according to any one of claims 1 to 3, characterised in that the solvent of the stage a is dimethyl formamide, dimethyl acetamide, dioxan or dimethoxyethane and the reaction is effected under heat at 50-100°C.

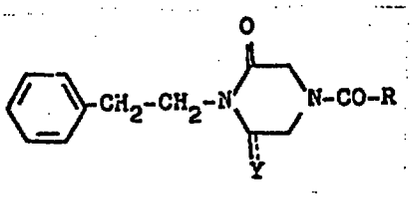
5. Process according to claim 1, characterised in that the complex metal hydride used as reducing agent in the stage b is a double hydride of an alkaline metal and an alkaline-earth metal, possibly containing an alkyl fraction.

6. Process according to claim 5, characterised in that sodium borohydride is used as complex metallic hydride.

7. Process according to claim 1, characterised in that cupric chloride is used as metallic chloride catalyst.

8. Process according to claim 1, characterised in that the cyclising acid used in the stage c is selected from hydrochloric acid, sulphuric acid, phosphoric acid and trifluoracetic acid.

9. A compound of formula :



in which Y represents O or H,OH and R represents an alkyl group containing up to 6 carbon atoms, cycloalkyl having 3 to 8 carbon atoms, phenyl or phenyl substituted by a halogen atom, a hydroxy group, alcoxy containing up to 6 carbon atoms, amino, alkylamino containing up to 6 carbon atoms, mercapto, alkylthio containing up to 6 carbon atoms, cyano, trifluoromethoxy or trifluoromethylthio.

10. Compound according to claim 9, selected from 4-acetyl-2,6-dioxo-1-phenethyl piperazine, 4-benzoyl-2,6-dioxo-1-phenethyl piperazine, 4-(cyclohexylcarbonyl)-2,6-dioxo-1-phenethyl piperazine and 4-(4-bromobenzoyl)-2,6-dioxo-1-phenethyl piperazine.

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