

PATENT SPECIFICATION

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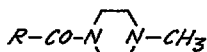
COMPLETE SPECIFICATION

Carboxylic acid-N-methyl-piperazides and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT, vormals Meister Lucius & Brüning, a Body Corporate recognised under German Law, of 6230 Frankfurt (M)-Hoechst, Germany, 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 new carboxylic acid-N-methyl-piperazides and with their manufacture and use.

The present invention provides carboxylic acid-N-methylpiperazides of the general formula (I)



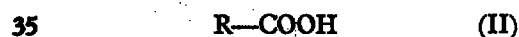
(I)

and their physiologically tolerable acid addition salts.

In the general formula I, R represents a linear or branched alkyl group containing 3 carbon atoms, or a cyclic group containing 5 to 7 ring carbon atoms which may contain as well as methylene groups, one or more bond systems, ring members and substituents selected from double bonds, endomethylene groups, oxygen or sulphur atoms, imino groups and methyl groups, which bond systems, ring member and substituents may be the same or different.

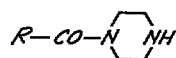
The present invention also provides a process for the manufacture of the aforesaid compounds, which comprises

a) reacting a reactive derivative of a carboxylic acid of the formula II



with N-methyl-piperazine, or

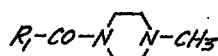
b) reacting a carboxylic acid-piperazide of the formula III



(III)

with a methylating agent, or

c) selective catalytic hydrogenation of a carboxylic acid-N-methyl-piperazide of the formula IV



(IV),

in which R₁ represents an unsaturated group which is capable of conversion into the group R by catalytic hydrogenation, and, if desired, converting a resulting free base into a physiologically tolerable acid addition salt thereof or converting a resulting acid addition salt into the free base.

As reactive derivatives of carboxylic acids which are used as starting materials for the method mentioned under paragraph (a) above, there are particularly suitable the acid chlorides, but other reactive derivatives such, for example, as carboxylic acid fluorides, carboxylic acid bromides, carboxylic acid esters, carboxylic acid anhydrides, carboxylic acid azides, mixed anhydrides with carbonic acid semi-esters, or carboxylic acid imidazolides may also be used. They are derived, for example, from butyric acid, isobutyric acid, cyclopentane-carboxylic acid, cyclohexane-carboxylic acid or cyclohexene-carboxylic acid and their methyl-substituted homologues, endomethylene-cyclohexane-carboxylic acid or tetrahydropyran-carboxylic acid.

When reacting acid chlorides with N-methyl-piperazine, the presence of a solvent is preferred. As solvents there are used, for example, aliphatic or aromatic hydrocarbons such as petroleum ether, benzene or toluene, ethers such, for example, as diethyl ether, diisopropyl ether, anisole, tetrahydrofuran or

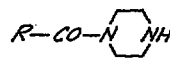
dioxan, esters such, for example, as ethyl or butyl acetate, ketones such, for example, as acetone or methyl ethyl ketone, amides such, for example, as dimethylformamide or nitriles such, for example, as acetonitrile. The reaction can be carried out at a low as well as at an elevated temperature, for example at the boiling temperature of the solvent. It is advantageously to start the reaction at room temperature and to complete it by heating, for example at the boiling point of the solvent.

If the reactants are used in equimolar amounts, the hydrochlorides of the piperazides are formed, which, according to the solvent selected, usually separate out in a crystalline form and are isolated by filtration. It is also possible to remove the hydrogen halide liberated in the course of the reaction by means of an acid-binding agent, for example an inorganic base for example sodium carbonate or sodium hydroxide or a tertiary amine such as, for example, triethylamine, dimethylaniline or pyridine, or alternatively an excess amount of the piperazine. When operating in this way, the free carboxylic acid piperazides are formed, which in most cases remain in a dissolved state and which can be recovered in the usual manner, for example by evaporation of the solution. If necessary, traces of oily by-products are removed by filtration. The carboxylic acid-N-methyl-piperazides are purified by distillation under reduced pressure.

The piperazine starting material can also be used for the reaction in the form of an acid addition salt. In this case, the acid-binding agent is used in excess so that the corresponding free base is formed from the piperazine salt. The free carboxylic acid piperazides so obtained can be isolated as described above. The other reactive carboxylic acid derivatives mentioned above can be reacted with N-methyl-piperazine in an analogous manner.

If, according to the method described under paragraph (a) above, mixed anhydrides with carbonic acid semi-esters are used as starting materials, an advantageous procedure is to react an appropriate carboxylic acid in a suitable solvent, for example dioxan or tetrahydrofuran, at a temperature between -20 and $+30^{\circ}\text{C}$, preferably at -10°C , in the presence of a tertiary base, for example triethylamine, with a carbonic acid semi-ester, for example chloroformic acid-tert.-butyl ester and to allow the mixed anhydride so formed to react with N-methyl-piperazine. The latter reaction step can be performed at a temperature between -20 and $+50^{\circ}\text{C}$. It is advantageous to start the reaction at a temperature below 0°C and to complete it at room temperature.

The compounds of the present invention can also be obtained, according to the method mentioned under paragraph (b) above, by methylation of a carboxylic acid-piperazide of the formula



As methylating agents, there may be employed, for example, the methyl esters of strong inorganic acids (for example methyl iodide, methyl bromide, and dimethyl sulphate) and *p*-toluene-sulphonic acid methyl ester.

The methylation may be carried out in neutral solvents, for example alcohol, dioxan or nitro-benzene. It is, however, also possible to operate in an alkaline solution by adding the methylating agent to an alkaline solution of the carboxylic acid piperazide.

A further method for preparing the carboxylic acid-N-methyl-piperazides, according to the method mentioned under paragraph (c) above, comprises the catalytic hydrogenation of compounds of the formula IV which in the carboxylic acid radical contain one or several unsaturated linkages. The carboxylic acid part may be derived, for example, from unsaturated aliphatic carboxylic acids, for example, crotonic acid, or from cyclic carboxylic acids containing double bonds, for example benzoic acid, cyclohexene-carboxylic acid or cyclohexadiene-carboxylic acid. Triple bonds may likewise be present in the carboxylic acid part.

The catalytic hydrogenation is performed in a known manner with Adams catalysts, or platinum, palladium or nickel catalysts, in appropriate solvents, for example, water, alcohols, acetic ester, glacial acetic acid or mixtures of these solvents, if desired with the addition of a mineral acid at a preferably elevated temperature and under an elevated pressure in an atmosphere of hydrogen.

The carboxylic acid piperazides of the present invention are monobasic and form salts with inorganic and organic acids which are usually obtained in a crystalline form. As acids suitable for the formation of salts there may be mentioned, for example, hydrochloric acid, acetic acid, citric acid and maleic acid. The salts are readily soluble in water to a greater or lesser degree.

The compounds of the present invention possess a strong anthelmintic activity, particularly on filariae. Filariasis is widely spread, particularly in tropical countries. Compared with the hitherto known N:N-diethyl-4-methyl-1-piperazine-carboxamide, the compounds of the present invention show an increased efficiency against the filaria *Litosmoides carinii* as is shown by the following comparison:

Cotton rats infected with *Litosmoides carinii* were treated orally or subcutaneously on five successive days with varying doses of the compound to be examined. After a certain number of days following the start of the

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treatment, the decrease in per cent of the micro filariae was determined in comparison with the initial value and the average value was ascertained from the values found.

h in %...

Preparation	Dose	Decrease of micro filariae days after start of treatment				Average value
		6	12	18	24	
cyclohexane-carboxylic acid-N-methyl-piperazide	5 × 30 mg/kg subcutaneously	96.8	93.9	74.6	86.5	88.2
N:N-diethyl-4-methyl-1-piperazine-carboxylic amide	5 × 30 mg/kg subcutaneously	93.2	75.2	67.6	63.1	74.7



10 It can thus be seen from these results that the compounds of the present invention are distinctly superior to N:N-diethyl-4-methyl-1-piperazine carboxylic amide. Moreover, the toxicity of the compounds of the present invention is weaker than that shown by N:N-diethyl - 4 - methyl - 1 - piperazine - carboxamide. The toxicity was determined by treating 10 mice each orally or 10 rats each subcutaneously with varying high doses and determining the rates at which the animals died.

1a
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Dose subcutaneously administered	Cotton rats: rates at which animals died as a % cyclohexane- carboxylic acid N- methyl-piperazide	Cotton rats: rates at which animals died as a % N:N-diethyl-4- methyl-1-piperazine carboxamide
5 × 450	0	10
5 × 550	0	80
5 × 650	0	
5 × 750	30	
dosis tolerata maxima/kg	5 × 650 mg	5 × 400

Dose orally administered	Mice: rates at which animals died as a % tetrahydro- pyran-4-carboxy- lic acid-N-methyl- piperazide	Mice: rates at which animals died as a % N:N-diethyl-4- methyl-1- piperazine- carboxamide
1 × 1 500	0	100
1 × 1 750	20	100
1 × 2 000	20	
dosis tolerata maxima/kg	1 × 1 500	1 × 580



The carboxylic acid-N-methyl-piperazides of the present invention can be employed as the free bases or in the form of their physiologically tolerable acid addition salts, if desired in the form of pharmaceutical preparations containing them in admixture or conjunction with a pharmaceutically suitable carrier, preferably a carrier suitable for oral or parenteral, but more preferably oral, administration. They are preferably administered in unit dosage form, for example in the form of tablets or suspendable powders which when given to animals can be mixed with their food. Powders suspendable in water may contain, in addition to the compounds of the present invention, as carrier and auxiliary substances, for example, finely divided silicic acid or coconut lorol-sulphonate as dispersing agent. For the preparation of tablets the usual substances employed for the manufacture of tables, such, for example, as maize starch, lactose, pectins, particularly ultra-amylopectin (Na-amylopectin-glycollate), and talc are used. For some therapeutical applications, other anthelmintics and/or antibiotics may be admixed with compounds of the invention. The pharmaceutical preparations are produced according to the usual methods.

The following Examples illustrate the invention:

EXAMPLE 1.

To a mixture consisting of 20 grams of N-methyl-piperazine, 20 grams of triethylamine and 400 ml of ethyl acetate, is added dropwise, while stirring, a solution of 21.4 grams of butyric acid chloride in 50 millilitres of acetic ester. Upon the termination of the addition, stirring is continued for a further 2 hours, the triethylamine-hydrochloride which separates out is filtered off with suction and the solvent is evaporated from the filtrate under reduced pressure. 200 Millilitres of absolute ether are added to the residue, the brownish oily substance which is thereby formed in a small amount is removed by treating the ethereal solution with charcoal and then filtering the ether is evaporated and the residue is distilled. 28 Grams of butyric acid-(N-methyl-piperazide) are obtained.

In order to convert this product into the maleate, the free base as isolated above is added to a solution of 19 grams of maleic acid in 200 millilitres of ethyl acetate, whereby the maleate separated out. The yield is 42 grams and the melting point is 94°C (from ethyl acetate).

In the same manner the following N-methyl-piperazides, which may be converted into their maleates in an analogous manner by treatment with equimolar amounts of maleic acid, are obtained by reacting equimolar quantities of the corresponding acid-chloride and N-methyl piperazine:

Formula of the chloride	Formula of the N-methyl-piperazine	Boiling point of the base mm	Melting point of the maleate
b)		100—102°/4	137°
c)		138—140°/4	141°
d)		146°/3	156°
e)		176—178°/7	149°
f)		153°/4	134°
g)		156—159°/5	177°

Instead of the maleates, the citrates can be prepared in an analogous manner by reaction of the free bases with equimolar amounts of citric acid: for example, 10.5 grams of cyclohexane-carboxylic acid-(N-methyl-piperazide) are added to a solution of 9.6 grams of citric acid in 150 millilitres of acetone. The citrate which at first separates out as an oil becomes solid when heated again on a steam bath. After filtering with suction and recrystallization from alcohol, the yield of the desired product is 18 grams and the melting point is 125°C.

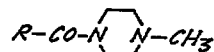
EXAMPLE 2.

To a solution of 20 grams of N-methyl-piperazine in 200 millilitres of ethyl-acetate is added, while stirring, a solution of 21.4 grams of butyric acid chloride in 50 millilitres of ethyl acetate. The temperature spontaneously rises to 58°C and an oil which precipitates solidifies after some time. After cooling, the solid is filtered off with suction and washed with ethyl acetate. In order to remove the admixed N-methyl-piperazine-hydrochlor-

ide, the crude product is taken up in 300 millilitres of chloroform, the undissolved N-methyl-piperazine-hydrochloride is filtered off and the filtrate is concentrated by evaporation. Upon the addition of ethyl acetate pure butyric acid-(N-methyl-piperazide)-hydrochloride separates out, is then recrystallized from a mixture of butanol and ethyl acetate. After drying on a steam bath, the yield of the desired product is 14 grams and the melting point is 157—159°C.

WHAT WE CLAIM IS:—

1. A carboxylic acid-N-methyl-piperazide of the general formula (I)



(I)
in which R represents a branched or unbranched alkyl group containing 3 carbon atoms or a cyclic group containing 5 to 7 ring



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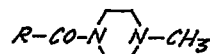
EXAMPLE 2.

To a solution of 20 grams of N-methyl-piperazine in 200 millilitres of ethyl-acetate is added, while stirring, a solution of 21.4 grams of butyric acid chloride in 50 millilitres of ethyl acetate. The temperature spontaneously rises to 58°C and an oil which precipitates solidifies after some time. After cooling, the solid is filtered off with suction and washed with ethyl acetate. In order to remove the admixed N-methyl-piperazine-hydrochlor-

ide, the crude product is taken up in 300 millilitres of chloroform, the undissolved N-methyl-piperazine-hydrochloride is filtered off and the filtrate is concentrated by evaporation. Upon the addition of ethyl acetate pure butyric acid-(N-methyl-piperazide)-hydrochloride separates out, is then recrystallized from a mixture of butanol and ethyl acetate. After drying on a steam bath, the yield of the desired product is 14 grams and the melting point is 157—159°C.

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(I)
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carbon atoms which may contain as well as methylene groups, one or more bond systems, ring members and substituents selected from double bonds, endomethylene groups, oxygen atoms, sulphur atoms, imino groups and methyl groups, which bond systems ring members and substituents may be the same or different.

2. A physiologically tolerable acid addition salt of a compound as claimed in claim 1.

3. Butyric acid-N-methyl-piperazide.

4. A physiologically tolerable acid addition salt of the compound claimed in claim 3.

5. Cyclohexane-carboxylic acid-N-methyl-piperazide.

6. A physiologically tolerable acid addition salt of the compound claimed in claim 5.

7. Tetrahydropyran-4-carboxylic acid-N-methyl piperazide.

8. A physiologically tolerable acid addition salt of the compound claimed in claim 7.

9. Any one of the physiologically tolerable acid addition salts as claimed in claim 2 and described in the Examples herein.

10. A pharmaceutical preparation which comprises a compound as claimed in claim 1 in admixture or conjunction with a pharmaceutically suitable carrier.

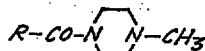
11. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 2, in admixture or conjunction with a pharmaceutically suitable carrier.

12. A pharmaceutical preparation which comprises the compound claimed in claims 3, 5 or 7, in admixture or conjunction with a pharmaceutically suitable carrier.

13. A pharmaceutical preparation which comprises a physiologically tolerable acid addition salt as claimed in claim 4, 6, 8 or 9, in admixture or conjunction with a pharmaceutically suitable carrier.

14. A pharmaceutical preparation as claimed in any one of claims 10 to 13, which is in a unit dosage form.

15. A process for the manufacture of a carboxylic acid-N-methyl-piperazide of the general formula (I)



(I)

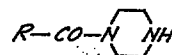
or a physiologically tolerable salt thereof, in which R represents a branched or unbranched group containing 3 to 6 carbon atoms or a cycloaliphatic group containing 5 to 7 ring carbon atoms, which comprises

a) reacting a reactive derivative of a carboxylic acid of the formula II



with N-methyl-piperazine, or

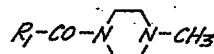
b) reacting a carboxylic acid-piperazide of the formula III



(III)

with a methylating agent, or

c) selective catalytic hydrogenation of a carboxylic acid-N-methyl-piperazide of the formula IV



(IV),

in which R₁ represents an unsaturated group which is capable of conversion into the group R, where R has the meaning given above, by catalytic hydrogenation, or and, if desired, converting a resulting free compound into a physiologically tolerable acid addition salt thereof or converting a resulting salt into a free compound.

16) A process for the manufacture of a compound as claimed in claim 1 or 2, conducted substantially as described in Example 1 or 2 herein.

ABEL & IMRAY, ~~✗~~
Chartered Patent Agents,
Quality House,
Quality Court,
Chancery Lane,
London, W.C.2.



Abel - Imray