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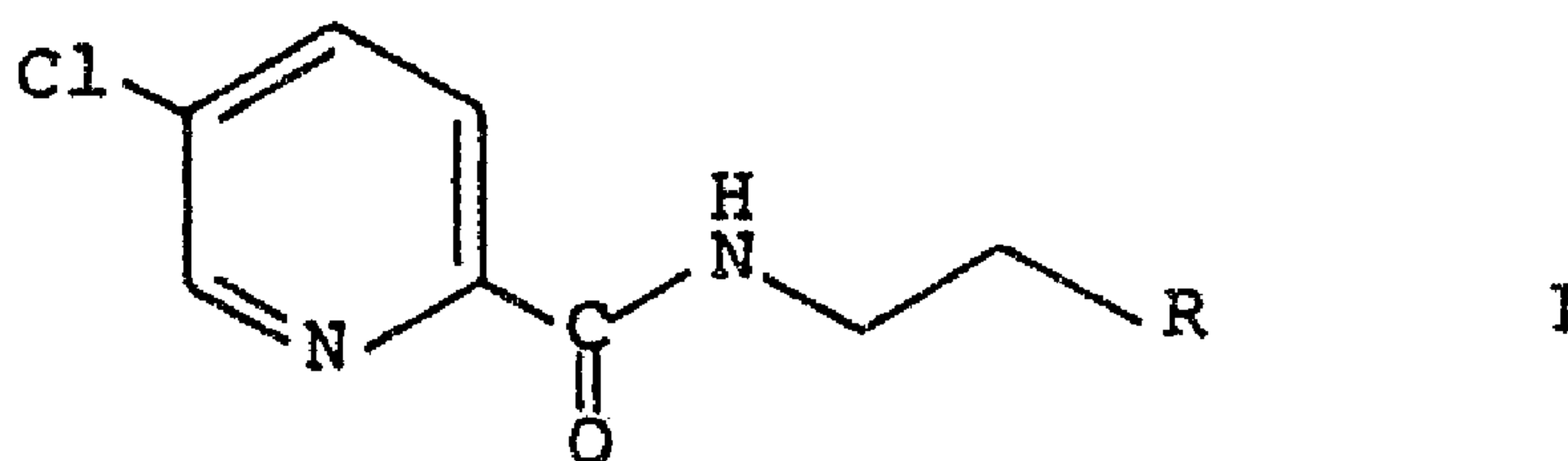
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(54) Titre : PROCEDE DE PREPARATION DE PYRIDINE-2-CARBOXAMIDES

(54) Title: PROCESS FOR PREPARING PYRIDINE-2-CARBOXAMIDES



III



VI

(57) Abrégé/Abstract:

It has been found that pyridine-2-carboxamides of the formula (see formula I) wherein R signifies amino or a residue convertible into amino, and pharmaceutically usable acid addition salts of that carboxamide in which R signifies amino can be manufactured in a simple manner and in good yield by reacting 2,5-dichloropyridine in the presence of a palladium-phosphine catalyst with an alkyne of the formula (see formula III) wherein R¹ signifies hydrogen, lower-alkyl, trimethylsilyl or the group -(R²)(R³)-COH and R² and R³ each independently signify hydrogen or lower-alkyl or together signify cyclopentyl or cyclohexyl, oxidizing the resulting alkyne to give 5-chloropyridine-2-carboxylic acid and reacting this acid or a reactive functional derivative thereof with an amino compound of the formula (see formula VI) or with carbon monoxide and an amino compound of formula VI or with carbon monoxide and a lower alkanol which is optionally mixed with water and reacting the resulting acid or the resulting ester with an amino compound of formula VI. The compounds of formula I in which R signifies amino are known, reversible and highly active MAO-B inhibitors.

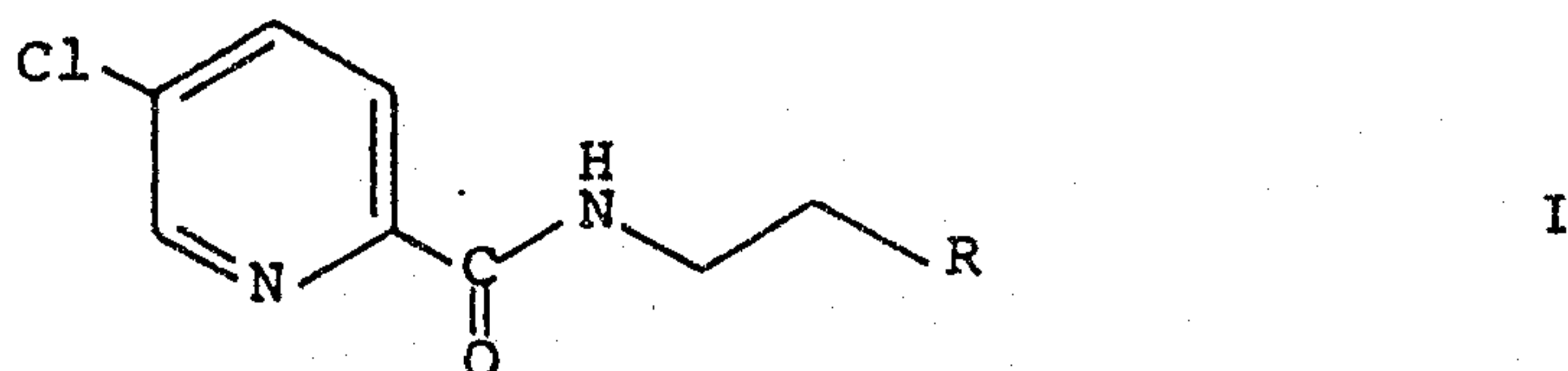


5

Abstract

It has been found that pyridine-2-carboxamides of the formula

10



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wherein R signifies amino or a residue convertible into amino,

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and pharmaceutically usable acid addition salts of that carboxamide in which R signifies amino can be manufactured in a simple manner and in good yield by reacting 2,5-dichloropyridine in the presence of a palladium-phosphine catalyst with an alkyne of the formula

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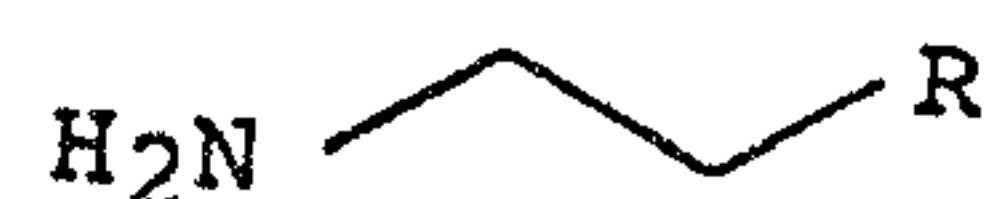
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wherein R^1 signifies hydrogen, lower-alkyl, trimethylsilyl or the group $-(R^2)(R^3)-COH$ and R^2 and R^3 each independently signify hydrogen or lower-alkyl or together signify cyclopentyl or cyclohexyl,

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oxidizing the resulting alkyne to give 5-chloropyridine-2-carboxylic acid and reacting this acid or a reactive functional derivative thereof with an amino compound of the formula

5



VI

10

15

or with carbon monoxide and an amino compound of formula VI or with carbon monoxide and a lower alkanol which is optionally mixed with water and reacting the resulting acid or the resulting ester with an amino compound of formula VI. The compounds of formula I in which R signifies amino are known, reversible and highly active MAO-B inhibitors.

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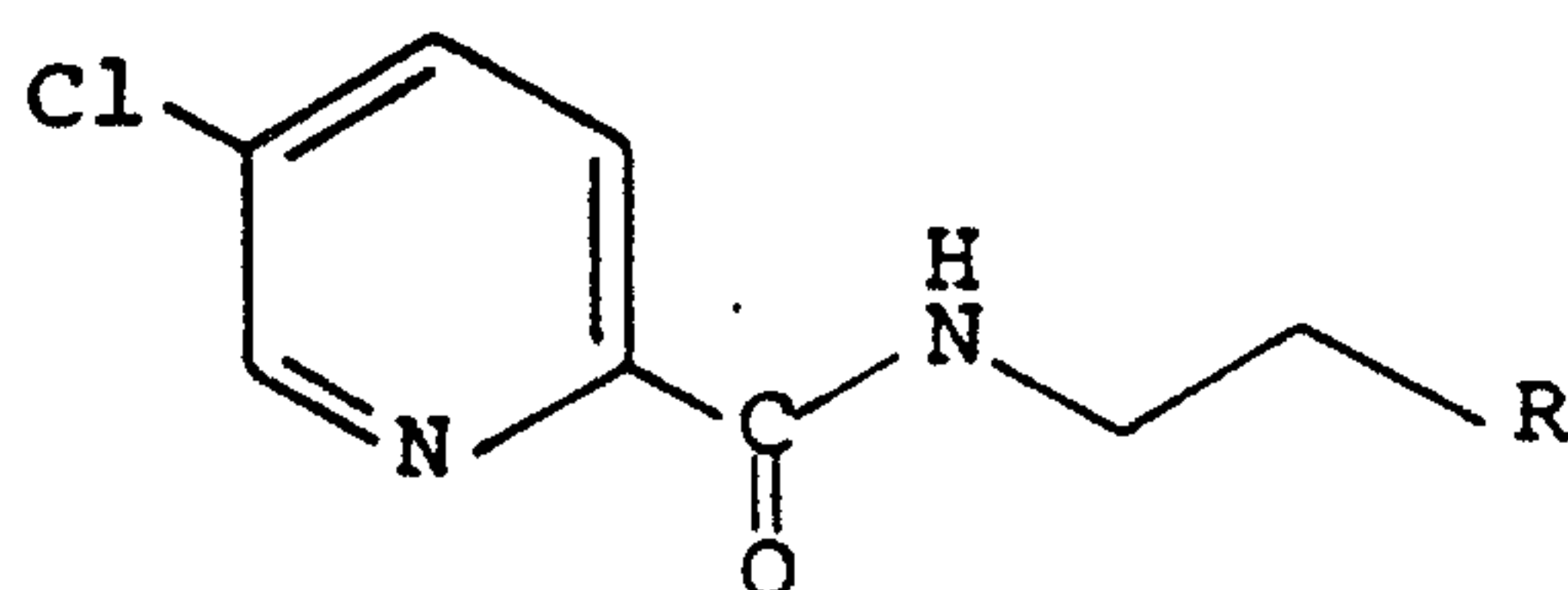
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The present invention is concerned with a novel process for the manufacture of pyridine-2-carboxamides of the general formula

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wherein R signifies amino or a residue convertible into amino,

and of pharmaceutically usable acid addition salts of that compound in which R signifies amino.

20

The compounds of formula I above in which R signifies a residue convertible into amino are valuable intermediates and can be used, for example, for the manufacture of N-(2-aminoethyl)-5-chloropyridine-2-carboxamide, i.e. the compound of formula I in which R signifies amino. This compound as well as its pharmaceutically usable acid addition salts have a pronounced, reversible and highly selective monoamine oxidase B (MAO-B) inhibiting property and are accordingly suitable for the treatment of depressive states, Parkinsonism and cognitive disorders. A process for the manufacture of N-(2-aminoethyl)-5-chloropyridine-2-carboxamide and its pharmaceutically usable salts - inter alia from compounds of formula I above in which R signifies a residue convertible into amino - as well as their interesting pharmacological properties are described, for example, in British Patent Specification

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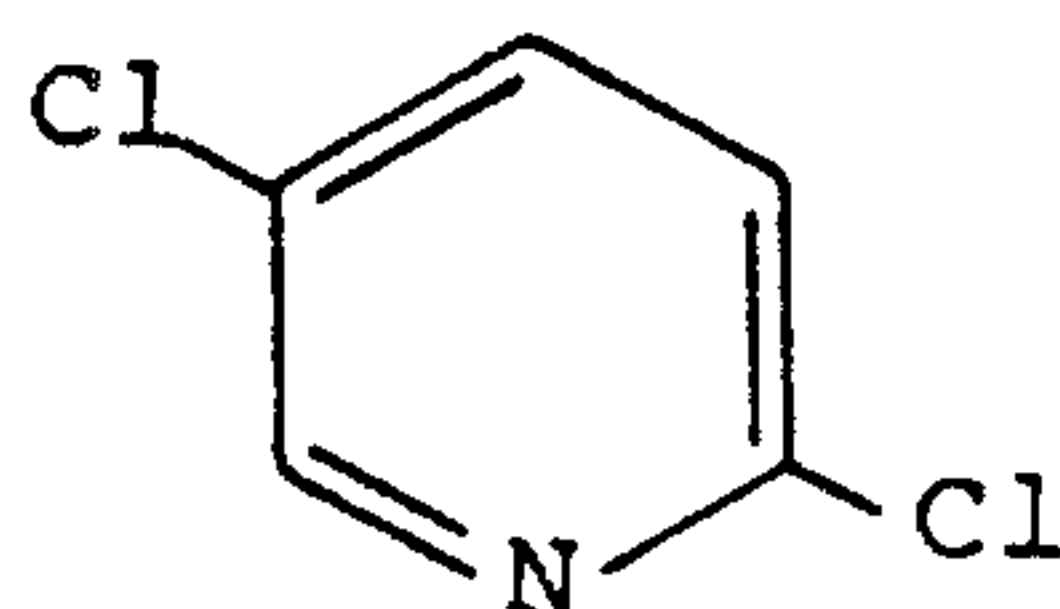
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No. 2163746.

5 The term "lower-alkyl" used in the present description
relates to straight-chain and branched hydrocarbon
residues with 1-7, preferably 1-4, carbon atoms such as
methyl, ethyl, propyl, isopropyl, butyl, isobutyl,
sec.-butyl, t-butyl, pentyl, hexyl, heptyl and the like.
10 In a similar manner, the terms "C₁₋₈-alkyl" and
"C₁₋₄-alkyl" refer to corresponding hydrocarbon residues
with 1-8 and, respectively, 1-4 carbon atoms. The term
"C₁₋₄-alkoxy" signifies alkyl ether groups in which
"C₁₋₄-alkyl" has the above significance. Ther term
15 "halogen" embraces the four halogens fluorine, chlorine,
bromine and iodine.

20 The process in accordance with the invention comprises
reacting 2,5-dichloropyridine of the formula



II

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in the presence of a palladium-phosphine catalyst

30 (a) with an alkyne of the general formula

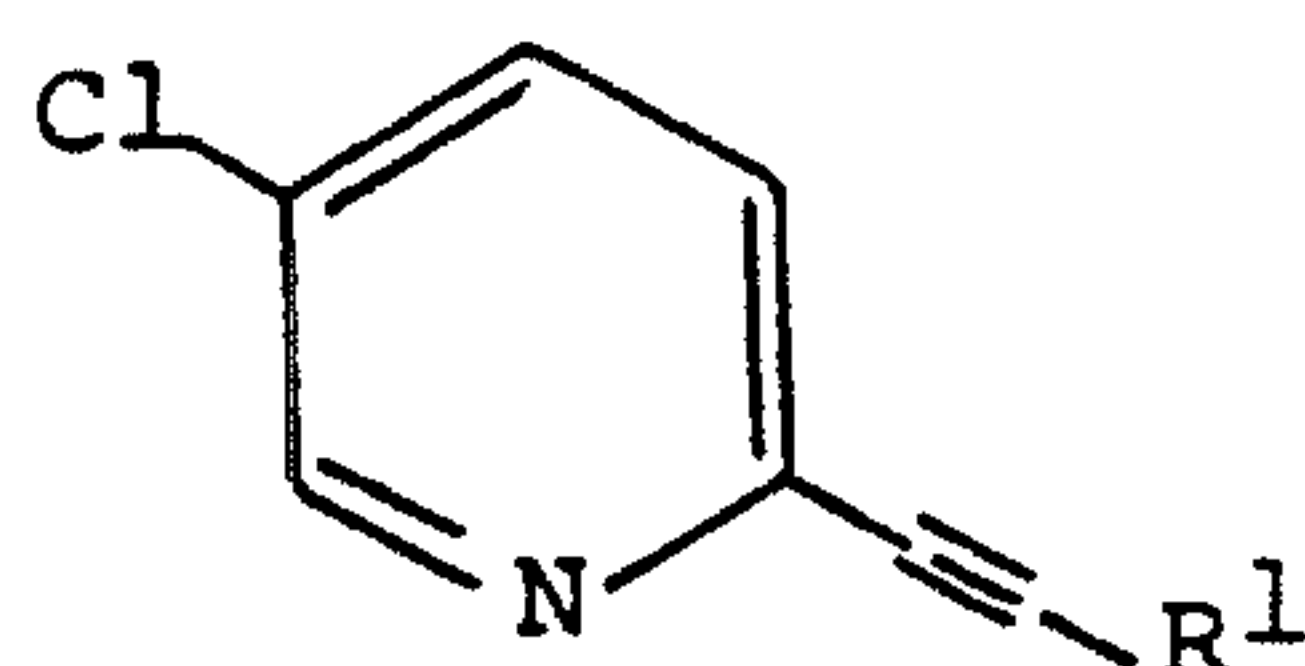


III

35 wherein R¹ signifies hydrogen, lower-alkyl,
trimethylsilyl or the group -(R²)(R³)-COH and R²
and R³ each independently signify hydrogen or
lower-alkyl or together signify cyclopentyl or
cyclohexyl.

oxidizing the resulting alkyne of the general formula

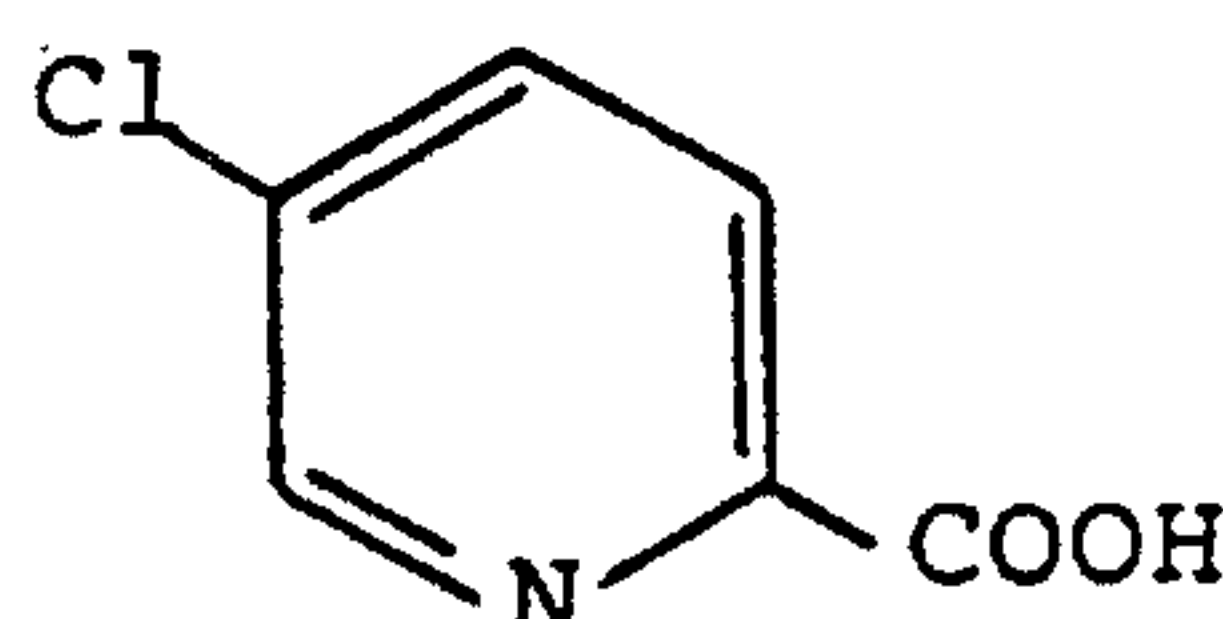
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IV

10 wherein R¹ has the significance given above,
to give 5-chloropyridine-2-carboxylic acid of the formula

15



V

and reacting this or a reactive functional derivative thereof with an amino compound of the general formula

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VI

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wherein R has the significance given above,

or

30

b) with carbon monoxide and an amino compound of formula VI above or with carbon monoxide and a lower alkanol optionally mixed with water to give 5-chloropyridine-2-carboxylic acid of formula V above or a lower alkyl ester thereof and reacting the resulting acid or the resulting lower alkyl ester or another reactive functional derivative of this acid with an amino compound of formula VI above,

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c) where the compound of formula I in which R signifies

amino is desired, if necessary converting into amino the residue R in a resulting compound of formula I in which R signifies a residue convertible into amino, and

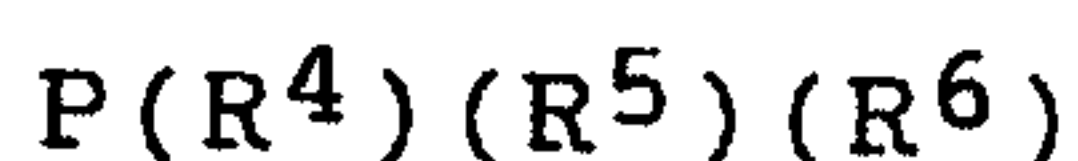
- 5 d) if desired converting the resulting compound into a pharmaceutically usable acid addition salt.

The alkynylation of 2,5-dichloropyridine of formula II with an alkyne of formula III in the presence of a
10 palladium-phosphine catalyst can be carried out in a manner known per se. Thus, the reaction can be carried out e.g. under anhydrous and oxygen-free conditions in an inert gas atmosphere in the presence of a base and a catalytic amount of copper-(I) iodide in a solvent or
15 solvent mixture which is inert under the reaction conditions at a temperature between about 40° and 150°C, preferably between about 60° and 100°C. Suitable bases are organic bases such as secondary or tertiary amines, e.g. dialkylamines or trialkylamines such as dimethylamine,
20 diethylamine, methylethylamine, trimethylamine, triethylamine, ethyldiisopropylamine and the like, and inorganic bases such as sodium hydroxide or potassium hydroxide, calcium carbonate and the like, whereby excess amine can also serve as the solvent. If the reaction is
25 carried out in the presence of an inorganic base, the use of a phase transfer catalyst or of a crown ether can be of advantage. Diethylamine is the preferred base. As solvents there come into consideration aliphatic and aromatic hydrocarbons such as hexane, benzene, toluene, xylene and
30 the like, halogenated aliphatic and aromatic hydrocarbons such as methylene chloride, chlorobenzene and the like, ethers such as diethyl ether, tetrahydrofuran, dioxan and the like, ketones such as acetone, methyl propyl ketone and the like, carboxylic acid esters such as methyl
35 acetate, ethyl acetate and the like, alcohols such as t-butanol and the like, dimethylformamide, dimethyl sulphoxide and the like. The pressure is not critical in

the reaction in accordance with the invention and therefore the reaction can be carried out at atmospheric pressure or elevated pressures, preferably at atmospheric pressure.

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The catalyst is a palladium-phosphine complex compound which, if desired, can also be formed in situ from a palladium component and a phosphine ligand. As palladium components there come into consideration in this case
10 metallic palladium, which is optionally supported on a carrier material such as carbon, or a complex or a salt of 0-, 2- or 4-valent palladium such as palladium-dichloro-bis(acetonitrile), palladium-bis(dibenzylideneacetone), palladium chloride, palladium acetate and the like. The
15 amount of palladium component conveniently amounts to 0.2-2.0 mol%, preferably 0.2-0.5 mol%. As phosphine ligands there come into consideration chiral and non-chiral mono- and diphosphorus compounds such as are described in Houben-Weyl, Methoden der organischen Chemie,
20 volume E1, page 106 et. seq. Georg Thieme Verlag Stuttgart, 1982, and Aspects Homog. Catal., 4, 145-202 (1981), especially those of the general formula



25

wherein R^4 , R^5 and R^6 each independently signify C_{1-8} -alkyl, cyclohexyl, benzyl, phenyl or phenyl which is substituted by C_{1-4} -alkyl, C_{1-4} -alkoxy, halogen, trifluoromethyl or phenyl

30

The amount of phosphine ligand conveniently amounts to 0.01-100 mol per mol of palladium, preferably 0.1-10 mol per mol of palladium. For the in situ preparation of the palladium-phosphine complex compound there is preferably
35 used palladium-dichloro-bis(acetonitrile), palladium-(II) chloride or palladium-(II) acetate.

5 However, the use of an already formed palladium-phosphine complex compound such as palladium-dichloro-bis(triphenylphosphine), palladium-tetrakis(triphenylphosphine) and the like is preferred, with palladium-dichloro-bis-(triphenylphosphine) being the preferred complex compound.

10 The oxidation of a resulting alkyne of formula IV can also be carried out in a manner known per se with permanganate. Thus, the reaction can be carried out in a solvent or solvent mixture which is inert under the reaction conditions at a temperature between about 40° and 120°C, preferably between about 60° and 100°C. Suitable
15 solvents are water and mixtures of water with water-miscible ethers such as tetrahydrofuran, dioxan and the like, ketones such as acetone, methyl ethyl ketone and the like, acetonitrile and the like. The pressure for this reaction step is not critical and therefore the reaction
20 can be carried out at atmospheric pressure or elevated pressures, but preferably at atmospheric pressure.

25 The reaction of 5-chloropyridine-2-carboxylic acid with an amino compound of formula VI has been described previously, for example in the above-mentioned British Patent Specification No. 2163746.

30 The amidation of 2,5-dichloropyridine of formula II with carbon monoxide and an amino compound of formula VI in the presence of a palladium-phosphine catalyst can be carried out in a manner known per se. Thus, the reaction can be carried out e.g. under anhydrous and oxygen-free conditions in the presence of a base in a solvent or solvent mixture which is inert under the reaction
35 conditions at a temperature between about 60° and 150°C, preferably between about 100° and 130°C. Suitable bases are organic bases such as tertiary amines, e.g. trialkylamines such as trimethylamine, triethylamine, ethyldiiso-

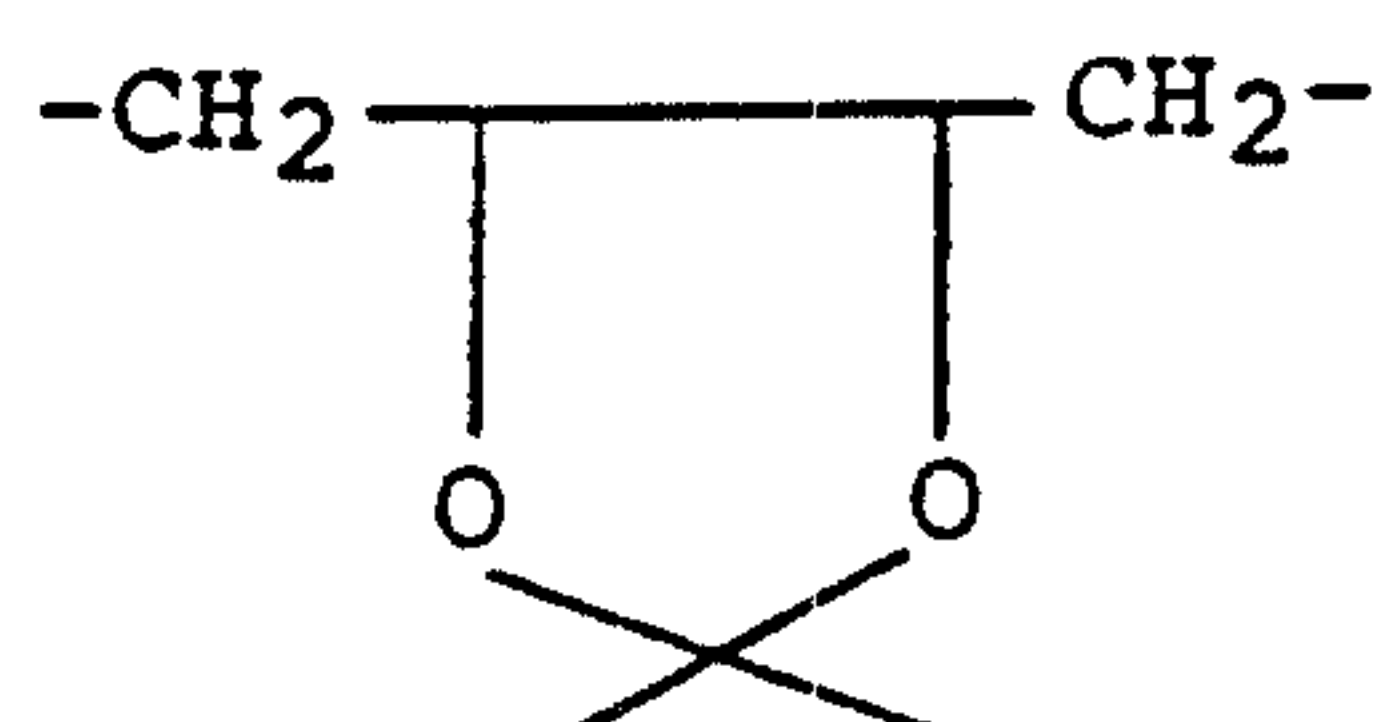
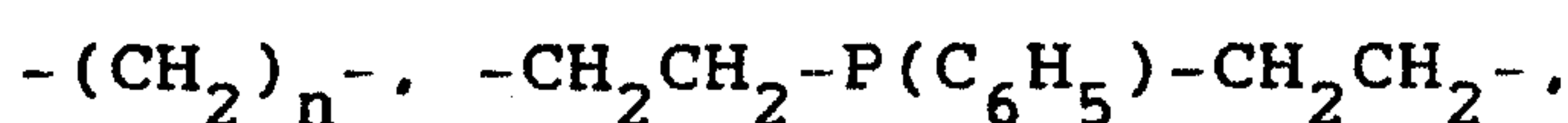
propylamine and the like, dialkylarylamines such as N,N-dimethylaniline and the like, triarylamines such as triphenylamine, tritolylamine and the like and inorganic bases such as sodium bicarbonate, potassium bicarbonate, calcium carbonate and the like, whereby excess amine of formula VI can also serve as the base. If the reaction is carried out in the presence of an inorganic base, the use of a phase transfer catalyst or of a crown ether can be of advantage. Triethylamine is the preferred base. As solvents there come into consideration aliphatic and aromatic hydrocarbons such as hexane, benzene, toluene, xylene and the like, halogenated aliphatic and aromatic hydrocarbons such as methylene chloride, chlorobenzene and the like, ethers such as diethyl ether, tetrahydrofuran, dioxan and the like, ketones such as acetone, methyl propyl ketone and the like, carboxylic acid esters such as methyl acetate, ethyl acetate and the like, alcohols such as t-butanol and the like, dimethylformamide, dimethyl sulphoxide and the like. The pressure is not critical in the reaction in accordance with the invention and therefore the reaction can be carried out at atmospheric pressure or elevated pressures, preferably at about 10^6 Pa.

The catalyst is a palladium-phosphine complex compound which is conveniently formed in situ from a palladium component and a phosphine ligand. As palladium components there come into consideration metallic palladium, which is optionally supported on a carrier material such as carbon, or a complex or a salt of 0-, 2- or 4-valent palladium such as palladium-bis(dibenzylideneacetone), palladium chloride, palladium acetate and the like. The amount of palladium component conveniently amounts to 0.0001-0.5 mol%, preferably 0.01-0.1 mol%. As phosphine ligands there come into consideration chiral and non-chiral mono- and diphosphorus compounds such as are described in

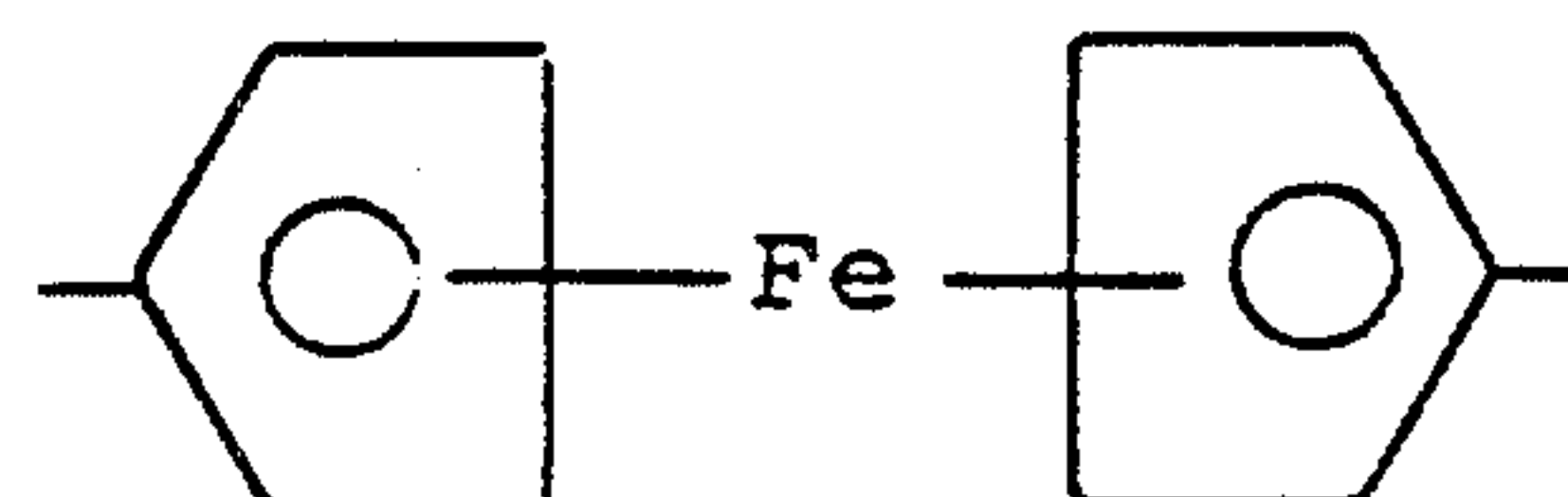
Houben-Weyl, Methoden der organischen Chemie, volume E1, page 106 et. seq. Georg Thieme Verlag Stuttgart, 1982, and Aspects Homog. Catal., 4, 145-202 (1981), especially those of the general formulae



wherein R^4 , R^5 and R^6 have the significance given above and X signifies binaphthyl or one of the groups



or



and n signifies a number of 1-8.

The amount of phosphine ligand conveniently amounts to 0.01-100 mol per mol of palladium, preferably 0.1-10 mol per mol of palladium. For the in situ preparation of the palladium-phosphine complex compound there is preferably used palladium-(II) chloride or palladium-(II) acetate, palladium-dichloro-bis(acetonitrile) and a bis(diphenylphosphino)alkane, preferably 1,3-bis(diphenylphosphino)propane.

The conversion of compounds of formula I in which R signifies a residue convertible into amino into the compound of formula I in which R signifies amino as well as the conversion of the last-mentioned compound into pharmaceutically usable acid addition salts have - as already mentioned above - been described previously, for example in British Patent Specification No. 2163746.

The 2,5-dichloropyridine which is used as the starting material as well as the compounds of formulae III and VI

which are used as starting materials are known or can be prepared in analogy to the known compounds.

The following Examples illustrate the present invention in more detail; all temperatures are given in degrees Celsius.

Example 1

10 A 250 ml autoclave is charged under an argon atmosphere with 50 ml of toluene, 5.2 ml (37.2 mmol) of triethylamine, 1.2 mg (0.0067 mmol) of palladium chloride, 5.6 mg (0.0135 mmol) of 1,3-bis(diphenylphosphino)propane, 6.5 g (40.56 mmol) of t-butyl (2-aminoethyl)carbamate and 15 5.0 g (33.8 mmol) of 2,5-dichloropyridine. After repeated evacuation and pressurization with 10^6 Pa of nitrogen the autoclave is gassed with 10^6 Pa of carbon monoxide and heated to 130° while stirring. After heating to 130° for 24 hours the autoclave is cooled, opened and 20 discharged and the orange-brown suspension is filtered through 50 g of silica gel with a 1:1 mixture of toluene and ether as the eluting agent. The fractions containing the desired product (determined by thin-layer chromatography) are combined, evaporated to about 150 ml and 25 stirred vigorously at 70° overnight with a solution of 2 mg of sodium cyanide in 25 ml of water in order to separate the palladium. Thereafter, the organic phase is separated, washed with water and evaporated. Crystallization of the solid residue from toluene/hexane yields 30 8.51 g (84%) of t-butyl [2-(5-chloropyridine-2-carboxamido)ethyl]carbamate as white crystals, m.p. 106-108°.

Example 2

35 The amidation of 5 g (33.8 mmol) of 2,5-dichloropyridine in the presence of 475 mg of palladium-dichloro-

-bis(triphenylphosphine) and 355 mg of triphenylphosphine is carried out in a manner analogous to Example 1.

5 Working-up of the crude product as described in Example 1 yields 8.83 g (87.2%) of pure t-butyl [2-(5-chloro-pyridine-2-carboxamido)ethyl]carbamate which is identical with the product obtained in Example 1.

10

Example 3

The amidation of 5 g (33.8 mmol) of 2,5-dichloro-pyridine in the presence of 2.0 mg of palladium chloride and 4.8 mg of 1,3-bis(diphenylphosphino)propane is carried
15 out at 110° in a manner analogous to Example 1. Working-up of the crude product as described in Example 1 yields 9.45 g (93.3%) of pure t-butyl [2-(5-chloropyridine-2-carboxamido)ethyl]carbamate which is identical with the product obtained in Example 1.

20

Example 4

The amidation of 5 g (33.8 mmol) of 2,5-dichloro-pyridine in the presence of 11.4 mg of palladium acetate
25 and 75 mg of 1,3-bis(diphenylphosphino)propane is carried out in a manner analogous to Example 1. Working-up of the crude product as described in Example 1 yields 9.66 g (95.4%) of pure t-butyl [2-(5-chloropyridine-2-carbox-amido)ethyl]carbamate which is identical with the product
30 obtained in Example 1.

Example 5

The amidation of 5 g (33.8 mmol) of 2,5-dichloro-pyridine in the presence of 27 mg of bis(palladium)-tris-
35 (dibenzylideneacetone)chloroform adduct and 75 mg of 1,3-bis(diphenylphosphino)propane is carried out in a manner analogous to Example 1. Working-up of the crude

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product as described in Example 1 yields 9.20 g (90.8%) of pure t-butyl [2-(5-chloropyridine-2-carboxamido)ethyl]-carbamate which is identical with the product obtained in Example 1.

5

Example 6

1.0 g (6.75 mmol) of 2,5-dichloropyridine are reacted with 2.49 g (15.54 mmol) of t-butyl (2-aminoethyl)-
10 carbamate, 197 mg of palladium-bis(dibenzylideneacetone) and 147 mg of 1,3-bis(diphenylphosphino)propane in 10 ml of toluene in a round flask at 120° under a carbon monoxide atmosphere for 2.7 hours. Working-up of the crude product carried out analogously to Example 1 yields 1.7 g
15 (83%) of pure t-butyl [2-(5-chloropyridine-2-carbox-amido)ethyl]carbamate which is identical with the product obtained in Example 1.

Example 7

20

The amidation of 5 g (33.8 mmol) of 2,5-dichloro-pyridine in the presence of 13.5 mg of palladium-dichloro-bis(acetonitrile) and 80 mg of 1,3-bis(diphenyl-phosphino)propane in 50 ml of tetrahydrofuran is carried
25 out in a manner analogous to Example 1. Working-up of the crude product as described in Example 1 yields 9.15 g (90.3%) of pure t-butyl [2-(5-chloropyridine-2-carbox-amido)ethyl]carbamate which is identical with the product obtained in Example 1.

30

Example 8

The amidation of 5 g (33.8 mmol) of 2,5-dichloro-pyridine in the presence of 13.5 mg of palladium-dichloro-bis(acetonitrile) and 80 mg of 1,3-bis(diphenyl-phosphino)propane in 50 ml of ethyl acetate is carried out
35

in a manner analogous to Example 1. Working-up of the crude product as described in Example 1 yields 9.51 g (93.9%) of pure t-butyl [2-(5-chloropyridine-2-carboxamido)ethyl]carbamate which is identical with the product obtained in Example 1.

Example 9

The amidation of 5 g (33.8 mmol) of 2,5-dichloropyridine in the presence of 137 mg of tetrabutylammonium iodide and 3.12 g of sodium bicarbonate is carried out in a manner analogous to Example 2. Working-up of the crude product as described in Example 1 yields 7.53 g (74.3%) of pure t-butyl [2-(5-chloropyridine-2-carboxamido)ethyl]carbamate which is identical with the product obtained in Example 1.

Example 10

The amidation of 5 g (33.8 mmol) of 2,5-dichloropyridine in the presence of 12.1 g (202 mmol) of ethylenediamine, 8.8 mg of palladium-dichloro-bis(acetonitrile) and 21 mg of 1,3-bis(diphenylphosphino)propane is carried out at 110° in a manner analogous to Example 1. After the addition of 1.91 g (35.5 mmol) of sodium methylate and evaporation of the reaction mixture there are obtained, by extraction with 3N hydrochloric acid and subsequent basification of the acidic-aqueous solution, 5.05 g (75%) of N-(2-aminoethyl)-5-chloropyridine-2-carboxamide; content according to HPLC: 98.2 wt.%, content of N,N'-ethylene-bis(5-chloro-2-pyridinecarboxamide): <1% (GC). Conversion of the free base with hydrogen chloride in methanol into the hydrochloride and crystallization from methanol/ether yields N-(2-aminoethyl)-5-chloropyridine-2-carboxamide hydrochloride as white crystals, m.p. 191-195°.

Example 11

5 The amidation of 10 g (67.6 mmol) of 2,5-dichloro-
pyridine in the presence of 13.2 g (87.8 mmol) of N-
-benzylethylenediamine, 11.5 g of palladium chloride and
26.5 mg of 1,3-bis(diphenylphosphino)propane is carried
10 out at 110° in a manner analogous to Example 1. By
extraction of the reaction mixture with 1N hydrochloric
acid and subsequent basification of the acidic-aqueous
solution there is obtained N-[2-(benzylamino)ethyl]-5-
-chloropyridine-2-carboxamide as a pale yellow oil which,
by stirring in hexane, yields 16.61 g (85%) of pure N-[2-
15 -(benzylamino)ethyl]-5-chloropyridine-2-carboxamide as
pale yellow crystals, m.p. 45-46°.

Example 12

20 A 10 litre sulphonation flask, equipped with a
mechanical stirrer, thermometer, intensive condenser,
dropping funnel, gas inlet arrangement and calcium
chloride tube, is charged under argon with 1.850 kg
(12.5 mol) of 2,5-dichloropyridine, 4.600 l of diethyl-
25 amine and 1.395 kg (16.25 mol) of 2-methyl-3-butyne-2-ol.
To the yellow solution obtained there are added while
stirring 1.4 g (7.5 mmol) of copper-(I) iodide as well as
26.3 g (37.5 mmol) of palladium-dichloro-bis(triphenyl-
phosphine). The fine suspension is subsequently heated to
30 reflux (about 70°) and the course of the reaction is
followed by thin-layer chromatography and gas chroma-
tography. After 24 hours the reaction mixture is cooled to
20° with an ice bath. The solid (diethylamine hydro-
chloride) is filtered off and rinsed three times with
35 700 ml of diethylamine each time. The solid contains
neither product nor palladium (<4 ppm) and is discarded.
The filtrates are combined and evaporated at 40° under
reduced pressure. There are thus obtained 2.905 kg of a

dark brown residue which becomes solid at 20°, its purity in accordance with GC (ISTD) amounts to 76.1% (g/g).

5

950 g of crude alkynol are dissolved in 2.300 l of toluene and this solution is placed in a 5 litre separating funnel. Then, two 3 litre separating funnels are each charged with 500 ml of toluene. Subsequently, 10 three 1 l portions of deionized water are allowed to flow through the three separating funnels, in each case with good intermixing. The aqueous phases are discarded and the organic phases are treated in a 6 litre 4-necked round flask, equipped with a mechanical stirrer and thermometer, 15 with 12 g (0.25 mol) of sodium cyanide, 600 ml of deionized water and 1.2 g of tetrabutylammonium bromide. The 2-phase mixture obtained is stirred vigorously at 25° for 24 hours. Then, the two phases are separated and the aqueous phase is washed with 1 l of toluene. The two 20 organic phases are washed in succession with 2.5 l of deionized water. The organic phases are combined and dried over 250 g of sodium sulphate, and the suspension obtained is filtered. The solid is washed with 250 ml of toluene and the combined filtrates are evaporated at 40° under 25 reduced pressure, whereby there are obtained 921 g of 4-(5-chloro-2-pyridyl)-2-methyl-3-butyne-2-ol as a dark brown oil which crystallizes upon standing. This crude product (crude yield; 115%; GC content about 87%) is used directly in the next step.

30

450 g (2.0 mol) of alkynol in a 10 litre sulphonation flask, equipped with a mechanical stirrer, thermometer, reflux condenser and gas inlet arrangement, are treated under argon with 7 l of warm, deionized water (70-80°), whereby a yellow emulsion results upon stirring. Then, 35 1.043 kg (6.6 mol) of potassium permanganate are added in 50 to 75 g portions in such a manner that the internal temperature amounts to 70° to 80°, duration of the

addition: about 2 hours. The course of the reaction is followed by thin-layer chromatography. The reaction mixture is held at about 80° with a hot oil bath (100°) until a complete reaction has been determined. Then, the reaction mixture is filtered while hot and the manganese dioxide is washed six times with 1 l of hot deionized water (about 90°) each time. The filtrate is concentrated to a volume of 7 l at 40° under reduced pressure. Traces of manganese dioxide in the concentrate are removed by filtration over fine paper.

To the filtrate in a 10 litre sulphonation flask, equipped with a mechanical stirrer, thermometer, reflux condenser, pH electrode, dropping funnel and gas inlet arrangement, are slowly added dropwise under argon and while stirring at 20° 365 ml of hydrochloric acid (pure) until pH 3 is attained. After completion of the addition of the hydrochloric acid (about 45 minutes) the suspension is cooled to 4° in an ice bath and stirred for one hour. The solid is subsequently filtered off and washed with 2.100 l of deionized water (ice-cold). The residue is dried at 50° overnight under reduced pressure. There are obtained 289 g (90%) of 5-chloropyridine-2-carboxylic acid as a pale beige powder.

567 g (3.6 mol) of 5-chloropyridine-2-carboxylic acid are mixed with 4.540 l of 2-butanol under argon in a 10 litre 4-necked sulphonation flask, equipped with a mechanical stirrer, thermometer, reflux condenser, dropping funnel with pressure balance and gas inlet arrangement. To the solution obtained there are added while stirring 67 ml of conc. sulphuric acid and the mixture is subsequently heated to reflux, whereby the course of the reaction is followed by gas chromatography. After 3.5 hours about 4% of acid are still present in the mixture in accordance with GC. The ascending condenser is replaced by a descending condenser and 1 l of 2-butanol is

added dropwise within 2.5 hours while simultaneously 2 l of solvent are distilled off from the reaction mixture. 5 97% of ester and 1.5% of acid are detected in the reaction mixture by GC. After distilling off a further 1.5 l of solvent the reaction mixture is cooled to 25° with an ice bath and treated in a 20 litre stirring vessel with 4 l of toluene and a solution of 303 g of sodium bicarbonate in 10 4 l of deionized water. A further three 20 litre stirring vessels are each charged with 1 l of toluene and the organic phases are washed in sequence with the aqueous phase from the first stirring vessel as well as three times with 1 l of deionized water each time. The aqueous 15 phases are discarded. The organic phases are combined and dried over 1 kg of sodium sulphate. The drying agent is filtered off and the filtrate is evaporated at 30°-50° under reduced pressure. There are obtained 809 g of brown oil as the crude product. 767 g of crude product are 20 subjected to a distillation in a high vacuum. The main fraction boils at 86-89°/0.1 Pa. There are obtained in this manner 693 g of pale yellow distillate (94%) of 2-butyl 5-chloropyridine-2-carboxylate which forms an oily solid mass at 25°, GC purity: 98.3%.

25 A 10 litre four-necked sulphonation flask, equipped with a mechanical stirrer, thermometer and gas inlet arrangement, is charged under argon with 692 g (3.2 mol) of 2-butyl 5-chloropyridine-2-carboxylate and 7 l of 30 ethylene diamine and the clear solution obtained is stirred, whereby the internal temperature rises slowly from 22° to a maximum of 30° during the stirring. The course of the reaction is followed by gas chromatography. After a reaction period of 3 hours (the internal 35 temperature still amounts to 27°) the reaction solution is evaporated at 30-40° under reduced pressure. The evaporation residue - a clear, yellow oil - weighs 753 g. A 20 litre stirring vessel as well as two 5 litre

separating funnels are charged with, respectively, 2.250 l of ice-cold 3N hydrochloric acid, 750 ml of 1.5N hydrochloric acid and 750 ml of deionized water. The evaporation residue (753 g of a clear, yellow oil) is subsequently treated with 1.500 l of methylene chloride and the solution obtained is added to the stirring vessel. After intermixing of the two phases the pH value of the aqueous phase amounts to about 1. Subsequently, the organic phase from the stirring vessel as well as two 1.5 l portions of methylene chloride are passed in sequence and with good intermixing through the stirring vessel and the two separating funnels. The aqueous phases are combined in the stirring vessel and adjusted to about pH 11 by the addition of 3 l of ice-cold 3N sodium hydroxide solution. The two separating funnels are charged with two 750 ml portions of semi-saturated sodium chloride solution. Then, in each case with good intermixing, six 1.5 l portions of methylene chloride are passed through the stirring vessel and the two separating funnels. The organic phases are combined and dried over 500 g of sodium sulphate. The drying agent is filtered off and the filtrate is evaporated at 30°-40° under reduced pressure. The yellow, oily residue is dried at 40°/0.1 Pa for a further 15 hours and thereafter weighs 616 g (3.08 mol). It crystallizes upon standing at 20°. The crystallizate is dissolved in 3.2 l of methanol at 20°. 688 ml of 4.48N methanolic hydrochloric acid (3.08 mol) are added in one portion to the solution while cooling in an ice bath. The reaction mixture is stirred for 15 minutes and the resulting suspension is subsequently heated to 50°, whereby a clear solution again results. Thereto there are added within 30 minutes 5.8 l of t-butyl methyl ether (pre-heated to 50°). The suspension obtained is left to cool to 20° (duration about 1.5 hours) and it is subsequently cooled to 0°-5° with an ice bath. The solid is subsequently filtered off and rinsed with 1.100 l of petroleum ether (low-boiling). The crystallizate is sub-

sequently dried to constant weight at 40° in a vacuum drying oven and thereafter weighs 693 g (95% crystallization yield). For further purification, the crystallizate is heated to 55° in 3.6 l of methanol and dissolved. While stirring vigorously there are allowed to drop in within 1.5 hours 5.500 l of t-butyl methyl ether (pre-heated to 50°), whereby the mixture is seeded with pure crystals of the end product after the addition of 1.5 l of solvent. The suspension obtained is left to cool to about 20° (duration about 1.5 hours), whereupon it is cooled to 0°-5° with an ice bath. The crystallizate is filtered off and washed with 1.1 l of pentane. The N-(2-aminoethyl)-5-chloropyridine-2-carboxamide hydrochloride obtained is dried in a high vacuum at 50°/1 Pa for two days and thereafter weighs 665 g (87%), m.p. 197-199°.

Example 13

9.0 ml (80 mmol) of 1-hexyne and 6.0 g (40 mmol) of 2,5-dichloropyridine in 80 ml of diethylamine are placed under argon, whereby a pale yellow solution results. Thereto there are added 0.40 g (1.5 mmol) of triphenylphosphine, 0.04 g (0.02 mmol) of copper-(I) iodide as well as 0.24 g (0.9 mmol) of palladium-dichloro-bis(triphenylphospine). The orange solution obtained is subsequently heated to reflux for 24 hours while stirring. Thereafter, the reaction mixture is cooled to 25° and evaporated at 40° under reduced pressure. The brown residue is then treated with 50 ml of ethanol and again evaporated. The crude product is filtered over 50 g of silica gel with 700 ml of hexane/toluene (1:1) and the eluate is evaporated at 50° under reduced pressure. The residue is subsequently distilled in a bulb tube at 190°/2600 Pa. There are obtained 6.8 g of 2-hexynyl-5-chloropyridine as a yellow oil.

Example 14

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1.2 ml (10 mmol) of trimethylsilylacetylene, 40 ml of diethylamine and 1.5 g (10 mmol) of 2,5-dichloropyridine are stirred at 20° under argon. To the colourless solution obtained there are added 0.1 g (0.4 mmol) of triphenylphosphine, 0.01 g (0.05 mmol) of copper-(I) iodide as well as 0.06 g (0.25 mmol) of palladium-dichloro-bis(acetonitrile). The reaction solution is subsequently heated to reflux for 5 hours while stirring. After cooling to 25° the reaction solution is evaporated at 40° under reduced pressure. 50 ml of ethanol are subsequently added to the residue and the mixture is again evaporated. The crude product is filtered over 30 g of silica gel with ethyl acetate and the eluate is evaporated, whereby 1.6 g of brown liquid remain behind. 1.0 g thereof is distilled in a bulb tube at 70°/0.1 Pa, whereby there are obtained as the main fraction 0.6 g of 2-trimethylsilylethynyl-5-chloropyridine which solidifies upon standing.

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0.10 g (0.5 mmol) of 2-trimethylsilylethynyl-5-chloropyridine, 0.01 g of sodium lauryl sulphate and 2 ml of deionized water are placed under an inert gas atmosphere. Subsequently, 0.25 g (15 mmol) of potassium permanganate is added thereto at 23° while stirring. After 2 hours the reaction mixture is treated with aqueous sodium bisulphite solution (about 40 percent) until, after filtration of a sample over filter paper, the violet colour of the permanganate has disappeared. The suspension is filtered over a layer of Dicalite* and the filtrate is adjusted to pH 3 with 1N aqueous hydrochloric acid, whereby a white suspension results. This is cooled in an ice bath and the crystals are filtered off. The crystals are treated with 1 ml of deionized water, the suspension is again cooled to 0° and the crystals are filtered off. These are evaporated twice from methanol/toluene under reduced pressure and the

* Trademark

- 20 -

residue is dried in a high vacuum. There are obtained
17 mg of 5-chloropyridine-2-carboxylic acid as a white,
5 solid residue, m.p. 171-172°.

Example 15

10 The carbonylation of 5.0 g (33.8 mmol) of 2,5-di-
chloropyridine in 50 ml of methanol/triethylamine 1:1 in
the presence of 0.47 g of palladium dichloro-bis(tri-
phenylphosphine) at 110° is carried out in a manner
analogous to Example 1. Working-up of the crude product as
in Example 1 yields 2.86 g (49%) of crude methyl 5-chloro-
15 pyridine-2-carboxylate which, by crystallization from
hexane, yields pure methyl 5-chloropyridine-2-carboxy-
late in the form of white crystals, m.p. 83-86°.

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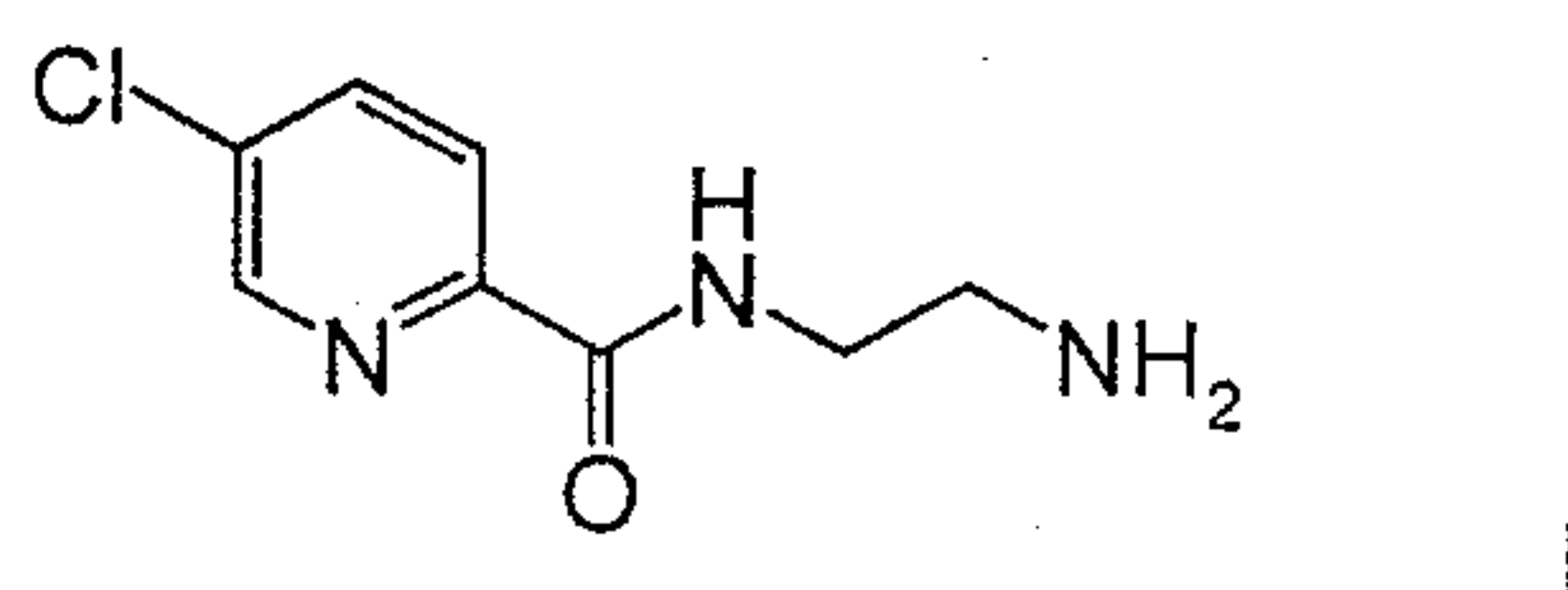
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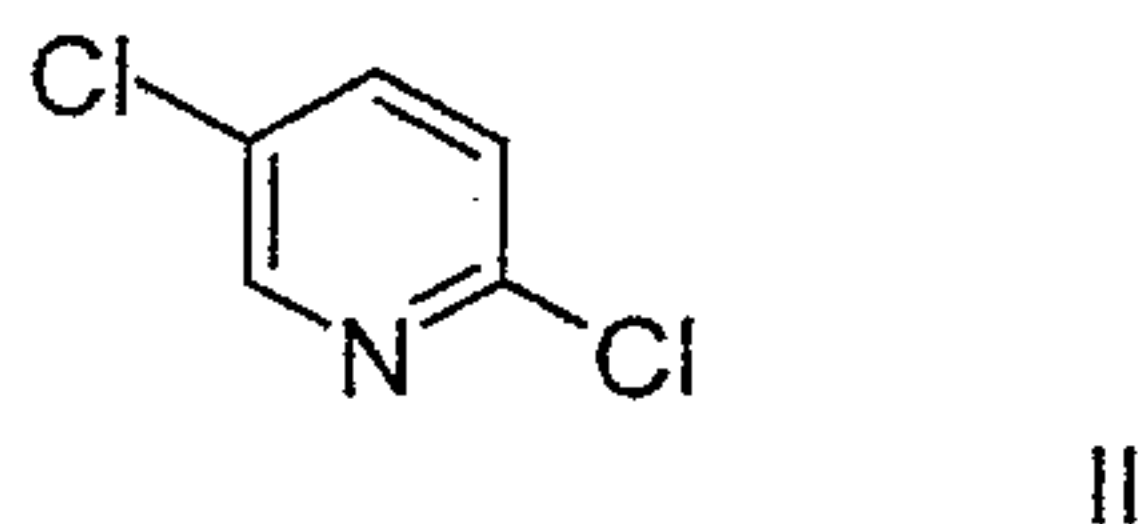
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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the manufacture of pyridine-2-carboxamides of the general formula



- and of pharmaceutically usable acid addition salts of that compound, which process
5 comprises reacting 2,5-dichloropyridine of the formula

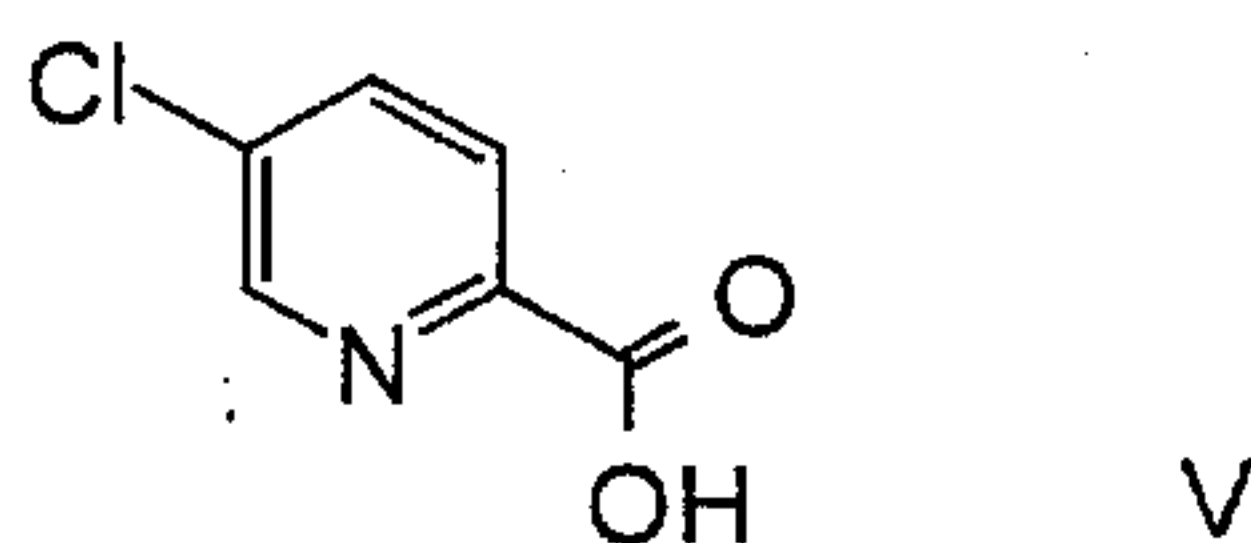


in the presence of a palladium-phosphine catalyst which is formed in situ from a palladium component and a phosphine ligand

- a) with carbon monoxide and an amino compound of formula



- b) or with carbon monoxide and a lower alkanol optionally mixed with water to give 5-chloropyridine-2-carboxylic acid of formula V



-22 -

or a lower alkyl ester thereof and reacting the resulting acid or the resulting lower alkyl ester with an amino compound of formula VI above.

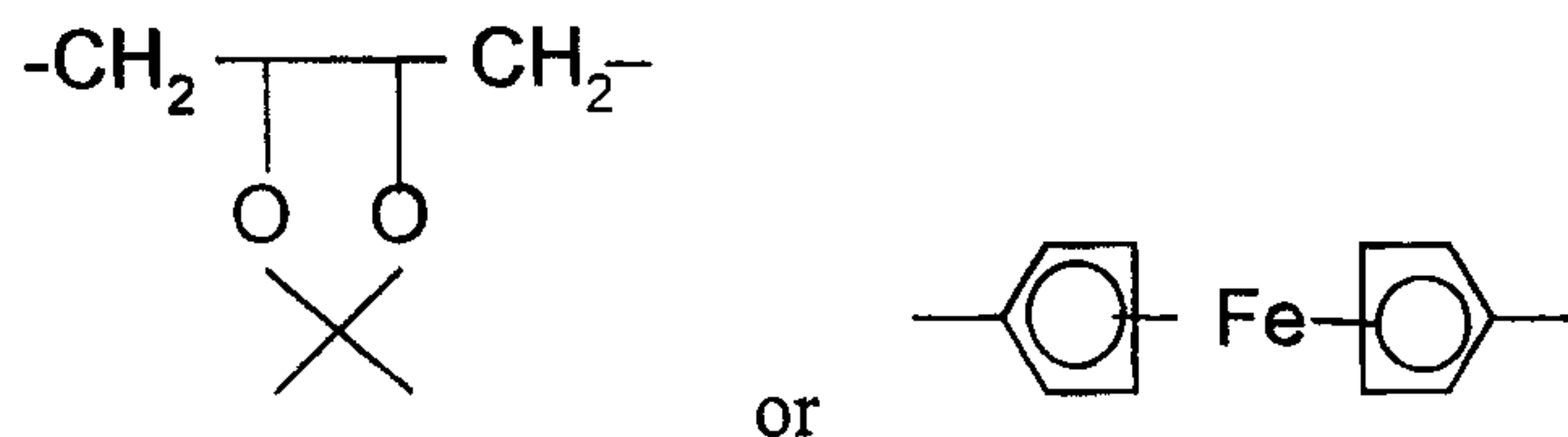
2. A process according to claim 1a), wherein the reaction is carried out in the presence of a base.
- 5 3. A process according to claim 2, wherein triethylamine is used as the base
4. A process according to any one of claims 1 – 3, wherein the reaction in accordance with process variant a) is carried out in an aromatic hydrocarbon, an ether or a carboxylic acid ester.
- 10 5. A process according to claim 4, wherein the reaction is carried out in toluene, tetrahydrofuran or ethyl acetate.
6. A process according to any one of claims 1-5, wherein the reaction in accordance with process variant a) is carried out at a temperature between about 60° and 150°.
7. A process according to claim 6, wherein the reaction is carried out at a temperature between about 60° and 100°.
- 15 8. A process according to any one of claims 1 - 7, wherein the reactions are carried out at a pressure of about 10⁵ to about 10⁷ Pa.
9. A process according to claim 8, wherein the process variant a) is carried out at a pressure of about 10⁶ Pa.
- 20 10. A process according to claim 1, wherein the reactions are carried out in the presence of palladium-dichloro-bis(triphenylphosphine).
11. A process according to claim 1, wherein the palladium-phosphine catalyst is prepared from 0.0001 – 0.5 mol% of metallic palladium or a complex or salts of 0-, 2- or 4-valent palladium and 0.01 – 100 mol per mol of palladium of a phosphorus compound of the general formulae

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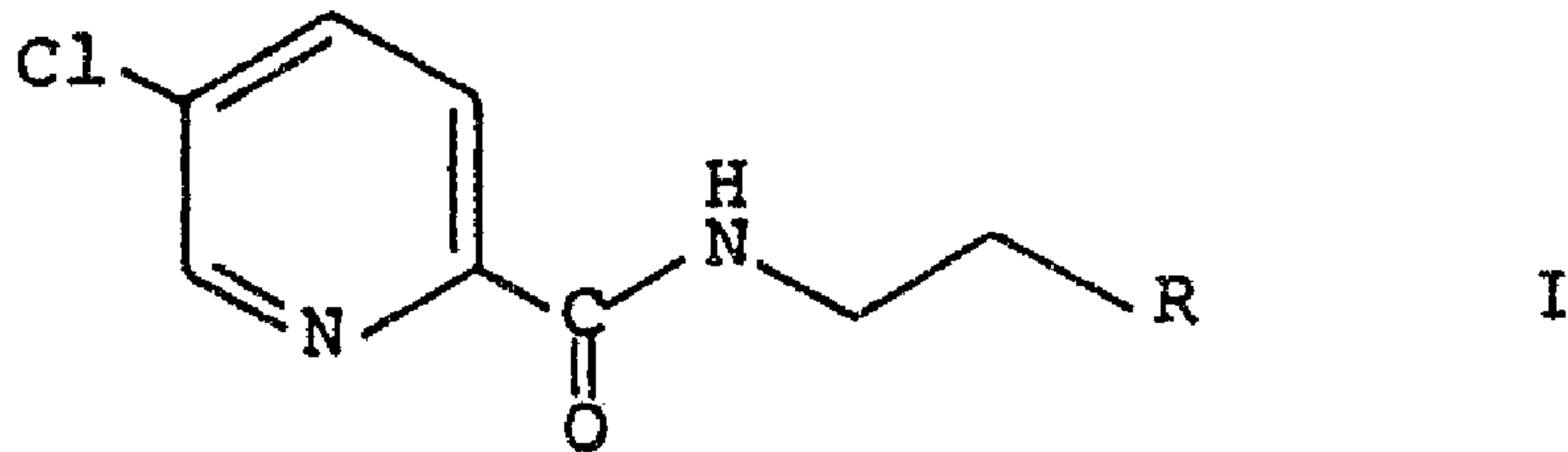
- 23 -

wherein R^4 , R^5 and R^6 each independently signify C_{1-8} -alkyl, cyclohexyl, benzyl, phenyl or phenyl, which is substituted by C_{1-4} -alkyl, C_{1-4} -alkoxy, halogen, trifluoromethyl or phenyl and X signifies binaphthyl or one of the groups $-(CH_2)_n-$, $-CH_2CH_2-P(C_6H_5)-CH_2-CH_2-$,



5 and n signifies a number of 1 – 8.

12. A process according to claim 11, wherein palladium-(II) chloride or palladium-(II) acetate and a bis(diphenylphosphino)alkane is used for the preparation of the palladium-phosphine catalyst.
13. A process according to claims 11 or 12, wherein 0.01 - 0.1% of palladium
10 component and 0.1 - 10 mol of phosphine ligand are used per mol of palladium.
14. A process according to claim 6, wherein the reaction is carried out at a temperature between about 100° and 130°.
15. A process according to claim 12, wherein the bis(diphenylphosphino)alkane is
15 1,3-bis-(diphenylphosphino) propane for the preparation of the palladium-phosphine catalyst.



III



VI