

680096

AUSTRALIA
Patents Act 1990

NOTICE OF ENTITLEMENT

I Dr Carlo KOS

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AUSTRIA

being the applicant and the nominated person in respect of an application for a patent for an invention entitled PROCESS FOR PREPARING N-SUBSTITUTED GLYCINIC ACIDS OR GLYCINE ESTERS AND USE OF SAID PROCESS IN INDIGO SYNTHESIS (Application No. 14141/95), state the following:

Part 1 - I am the actual inventor of the invention. I was an employee of the original applicant DSM CHEMIE LINZ GMBH and the said original applicant subsequently assigned the application to me.

Parts 2 and 3 - (Not applicable)

Part 4 - The basic application AT 2625/93 was filed by CHEMIE LINZ GMBH which subsequently changed its name to DSM CHEMIE LINZ GMBH. The basic application was listed in the declaration made under Article 8 of the PCT in respect of PCT/EP94/04259, of which the present application is the Australian national phase, and was the first application made in a Convention country in respect of the invention.

Parts 5, 6 and 7 - (Not applicable)

DATE: 7 May 1997

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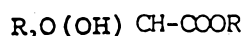
- (54) Title
PROCESS FOR PREPARING N-SUBSTITUTED GLYCINIC ACIDS OR GLYCINE ESTERS AND USE OF SAID PROCESS IN INDIGO SYNTHESIS
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- (56) Prior Art Documents
US 4073804
EP 99981
- (57) Claim

1. A process for the preparation of an N-substituted glycine ester or an N-substituted glycine acid of the formula



I

in which R is hydrogen or a straight-chain or branched alkyl group having 1 to 10 C atoms and R₁ and R₂ independently of one another are hydrogen, a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group where R₁ and R₂ are not simultaneously hydrogen, which comprises reacting a glyoxylic acid ester half-acetal or glyoxylic acid half-acetal of the formula



II

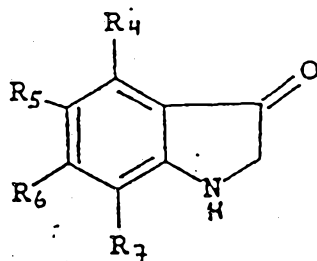
in which R has the abovementioned meaning and R₃ is an alkyl group having 1 to 4 C atoms, with an amine of the formula



III

in which R_1 and R_2 have the abovementioned meaning, in a diluent at temperatures from 0°C up to the reflux temperature of the diluent used, and treating the resulting intermediate product with hydrogen under pressure in the presence of a hydrogenation catalyst and a diluent, the N-substituted glycine ester or the N-substituted glycine acid of the formula I being formed, and, if desired, isolating this from the reaction mixture and if appropriate converting it into a salt or, in the case of the glycine ester, into the free acid.

8. A process for the preparation of an indoxyl derivative of the formula



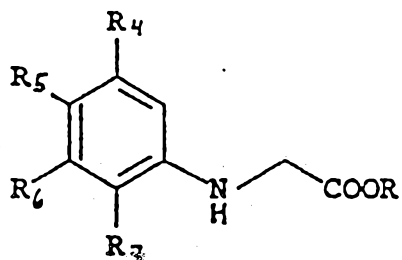
IV,

in which R_4 , R_5 , R_6 and R_7 independently of one another are hydrogen, halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, or R_5 and R_6 or R_6 and R_7 , together with the two particular C atoms on which they are substituted, are a benzene ring which is unsubstituted or substituted by halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, which comprises preparing an N-arylglycine ester of the

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formula



1b,

in which R has the meaning given in the formula I as claimed in claim 1 and R₄, R₅, R₆ and R₇ have the above-mentioned meaning, as claimed in one of claims 1 to 6 and cyclizing it, in the presence of molten alkali metal hydroxide or alkaline earth metal hydroxide, with or without addition of an alkali metal amide, at temperatures from 150 to 300°C to give the indoxyl of the formula IV .

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(21) Internationales Aktenzeichen: PCT/EP94/04259 (22) Internationales Anmeldedatum: 21. December 1994 (21.12.94) (30) Prioritätsdaten: A 2625/93 27. December 1993 (27.12.93) AT DSM CHEMIE LINZ GMBH (71) Anmelder (für alle Bestimmungsstaaten ausser US): CHEMIE LINZ GMBH [AT/AT]; St. Peter-Strasse 25, A-4021 Linz (AT); Dr. Carlo Kos Gernlandweg 9, A-4060 Leonding Austria AUSTRIA (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): KOS, Carlo [AT/AT]; Gernlandweg 9, A-4060 Leonding (AT). (74) Anwalt: KUNZ, Ekkehard; St.Peter-Strasse 25, A-4021 Linz (AT).		(81) Bestimmungsstaaten: AU, BR, CA, CN, CZ, HU, JP, KP, KR, PL, SI, SK, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Veröffentlicht Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.	
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(54) Title: PROCESS FOR PREPARING N-SUBSTITUTED GLYCINIC ACIDS OR GLYCINE ESTERS AND USE OF SAID PROCESS IN INDIGO SYNTHESIS			
(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON N-SUBSTITUIERTEN GLYCINSÄUREN ODER GLYCINESTERN UND VERWENDUNG DES VERFAHRENS ZUR INDIGOSYNTHESE			
(57) Abstract <p>A process is disclosed for preparing a N-substituted glycine ester or a N-substituted glycinic acid by reacting a glyoxylic acid ester or hemiacetal with an amine, then hydrating the resulting intermediate product. Also disclosed is the use of the process in a process for preparing indoxyl and indigo derivatives by ring closure of a N-arylglycine ester produced according to the above-mentioned process in molten alkaline or alkaline earth carbonate, with or without the admixture of an alkali amide, followed if required by oxidising the resulting indoxyl derivative into the corresponding indigo derivative.</p>			
(57) Zusammenfassung <p>Verfahren zur Herstellung eines N-substituierten Glycinesters oder einer N-substituierten Glycinsäure durch Reaktion eines Glyoxylsäureester- bzw. Glyoxylsäurehalbacetals mit einem Amin und Hydrierung des dabei entstehenden Zwischenproduktes, sowie die Verwendung des Verfahrens in einem Verfahren zur Herstellung von Indoxyl- und Indigoderivaten durch Ringschluß eines gemäß obigem Verfahren hergestellten N-Arylglycinesters in geschmolzenem Alkali- oder Erdalkalicarbonat mit oder ohne Zusatz eines Alkalamids und gegebenenfalls Oxidation des dabei entstehenden Indoxylderivates zum entsprechenden Indigoderivat.</p>			

see
folio
4

Process for the preparation of N-substituted glycine acids or glycine esters and the use of the process for indigo synthesis

Indigo has been prepared worldwide for a long time from N-phenylglycine, which is oxidized via indoxyl to give indigo. According to Ullmann, Volume A 14, 149 to 156, the N-phenylglycine needed for this is prepared essentially either by reaction of monochloroacetic acid with aniline or anthranilic acid or by hydrolysis of N-cyanomethylaniline. For preparation of N-cyanomethylaniline, hydrocyanic acid or sodium cyanide is reacted with dianilinomethane here. However, working with monochloroacetic acid or with cyanides is undesirable for safety and environmental protection reasons.

It has now been found, unexpectedly, that indoxyl can be prepared not only from N-phenylglycine but also from N-phenylglycine esters, and that N-substituted glycine esters and also N-substituted glycine acids can be prepared by an environment-friendly route by reaction of an amine with a glyoxylic acid ester half-acetal or a glyoxylic acid half-acetal. Glyoxylic acid ester half-acetals and glyoxylic acid half-acetals can be produced on a large industrial scale by an environment-friendly route by ozonolysis of maleic acid derivatives and hydrogenation of the peroxidic reaction solution, for example in accordance with EP B-0 099 981.

The invention therefore relates to a process for the preparation of N-substituted glycine acids or glycine esters of the formula

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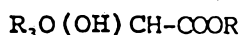
I

in which R is hydrogen or a straight-chain or branched alkyl group having 1 to 10 C atoms and R_1 and R_2 independently of one another are hydrogen, a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group where R_1 and R_2 are not simultaneously hydrogen, which comprises reacting a glyoxylic acid ester

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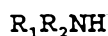


half-acetal or glyoxylic acid half-acetal of the formula



II

in which R has the abovementioned meaning and R_3 is an alkyl group having 1 to 4 C atoms, with an amine of the formula



III

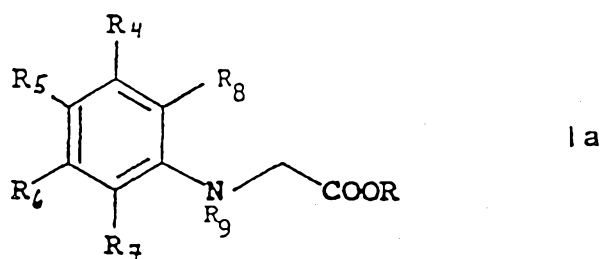
in which R_1 and R_2 have the abovementioned meaning, in a diluent at temperatures from 0°C up to the reflux temperature of the diluent used, and treating the reaction product with hydrogen under pressure in the presence of a hydrogenation catalyst and a diluent, the N-substituted glycine ester or the N-substituted glycine acid of the formula I being formed, and, if desired, isolating this from the reaction mixture and if appropriate converting it into a salt or, in the case of the glycine ester, into the free acid.

In the formulae I to III, R is hydrogen or a straight-chain or branched alkyl group having 1 to 10 C atoms, preferably having 1 to 4 C atoms, especially preferably having 1 or 2 C atoms, and R_3 is an alkyl group having 1 to 4 C atoms, preferably having 1 or 2 C atoms, where R and R_3 particularly preferably have the same meaning. R_1 and R_2 independently of one another are hydrogen, an alkyl group or an aryl group, where R_1 and R_2 are not simultaneously hydrogen. Alkyl group here is to be understood as a straight-chain, branched or cyclic alkyl group having 1 to 22 C atoms, which can be unsubstituted or substituted by alkoxy groups having 1 to 4 C atoms or by phenyl groups, for example the methyl, ethyl, n-propyl, butyl, octyl, dodecyl or hexadecyl group or isomers thereof, such as iso-propyl, iso-butyl, 2-ethylhexyl or iso-dodecyl groups, or benzyl or ethylphenyl groups. Alkoxy groups are, for example, methoxy, ethoxy, butoxy or iso-butoxy groups. An aryl group is a phenyl or naphthyl group which is unsubstituted or substituted by



halogen, by alkyl groups, preferably having 1 to 6 atoms, particularly preferably having 1 to 4 C atoms, or by alkoxy groups, preferably having 1 to 4 C atoms, a phenyl group being preferred. Halogen is fluorine, chlorine or bromine. Preferably, R_1 is hydrogen and R_2 is an aryl group, preferably a phenyl or naphthyl group which is unsubstituted or substituted by halogen, by alkyl groups having 1 to 4 C atoms or by alkoxy groups having 1 to 4 C atoms, particularly preferably a phenyl or naphthyl group which is unsubstituted or substituted by alkyl groups.

The preferred N-substituted glycine acids and glycine esters accordingly include compounds of the formula



in which R has the meaning given in the formula I, R_4 , R_5 , R_6 , R_7 and R_8 independently of one another are hydrogen, halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, or R_5 and R_6 or R_6 and R_7 or R_4 and R_8 , together with the two particular C atoms on which they are substituted, are a benzene ring which is unsubstituted or substituted by halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, and R_9 is hydrogen, an alkyl radical having 1 to 6 C atoms, which can optionally be substituted, or an aryl radical, which can optionally be substituted by halogen, alkyl groups or alkoxy groups.

To prepare the compounds of the formula I, a glyoxylic acid ester half-acetal or glyoxylic acid half-acetal of the formula II is first heated and reacted with an amine of the formula III at temperatures from 0°C , preferably from room temperature, up to the reflux temperature of the diluent used, if appropriate under



pressure. Diluents are preferably to be understood as meaning alcohols, such as methanol, ethanol, iso-propanol and butanol. That alcohol in which the alkyl part corresponds to the alkyl parts in the glyoxylic acid ester half-acetal preferably used is preferably employed as the diluent.

At least 1 mol, but in general 1 to 5 mol, preferably 1 to 3 mol, particularly preferably 1 to 1.5 mol, of amine of the formula III are employed here per mol of glyoxylic acid ester half-acetal or glyoxylic acid half-acetal of the formula II. The reaction is preferably carried out under normal pressure, but pressures from 1 to 20 bar can be applied.

The reaction is monitored in the customary manner, preferably by chromatography. When the reaction has ended, which is detected by the disappearance of the particular half-acetal from the reaction mixture, the reaction mixture is cooled. The intermediate compound formed, which has not been identified chemically, but is probably a compound of the formula $R_1R_2-N-C(OH)(OR_3)-COOR$, $R_1R_2-N-CH(OH)-COOR$, $R_1R_2-N-CH(OR_3)-COOR$ or, in the case where, for example, R_2 is a hydrogen atom, a compound of the formula $R_1N=CH-COOR$, in which R , R_1 , R_2 and R_3 in the compounds mentioned have the abovementioned meaning, can be isolated by evaporating off the diluent and if appropriate purified, for example with the aid of extraction, distillation or chromatography. However, it has proved to be advantageous that the reaction mixture can be subjected to the hydrogenation directly and without isolation of the intermediate product.

The hydrogenation of the intermediate compound is carried out with the aid of hydrogen in a diluent in the presence of a hydrogenation catalyst. Suitable diluents are diluents which are inert under the reaction conditions, for example aliphatic hydrocarbons, such as hexane or pentane, aromatic hydrocarbons, such as toluene or xylenes, ethers, such as iso-propyl ether, methyl-tert-butyl ether, tetrahydrofuran or dioxane, pyridine, water and alcohols or mixtures of such diluents, preferably



aliphatic alcohols having 1 to 8 C atoms, for example methanol, ethanol, iso-propanol, butanol, hexanol or octanol. The diluent is employed in an excess relative to the intermediate compound, preferably in a 5- to 30-fold excess, based on the weight. The intermediate compound must be soluble in the diluent.

Catalysts which are capable of catalyzing the splitting off of half-acetal, hydroxyl or alkoxy groups from a C atom when hydrogen is supplied or which are capable of catalyzing the hydrogenation of enamines to give amines are used as the hydrogenation catalyst. Such catalysts contain, as the active component, metals, such as, for example, nickel, cobalt, platinum or palladium, or chemical compounds of such metals, for example oxides, which can be alloyed, intermingled or coated with one another and/or with other metals or metal compounds, for example iron, rhodium or copper. The catalyst preferably comprises nickel as the active constituent. The catalyst can be employed here as such, in a form applied to a customary support material or to a monolithic support, or if appropriate as a fixed bed catalyst, and is preferably employed in a form applied to a support.

In general, at least 0.5 g of catalyst is used per mol of intermediate compound. Since the optimum amount of the catalyst depends on its efficiency, however, it may be of advantage to employ larger or smaller amounts of catalyst.

The optimum catalyst and the optimum amount of catalyst can easily be determined by simple preliminary experiments with various amounts of catalysts of known specificity.

The hydrogen is introduced into the reaction mixture in the customary manner, and the hydrogen is advantageously forced onto the reaction mixture comprising the intermediate compound, diluent and hydrogenation catalyst. A hydrogen pressure from 1 to 120 bar, preferably from 20 to 100 bar, particularly preferably from 40 to 80 bar, is established here.

The hydrogenation is carried out at temperatures



from about 10°C to about 150°C, preferably between about 20°C and 130°C.

5 The N-substituted glycine ester or the N-substituted glycine acid of the formula 1 is formed in high yields in this reaction. The reaction is monitored with the aid of suitable methods, preferably by chromatography. When the reaction has ended, the N-substituted glycine ester or the N-substituted glycine acid can be isolated from the reaction mixture by evaporation of the
10 diluent and if appropriate purified with the aid of customary methods, such as extraction, chromatography or distillation. In general, however, the purity of the resulting N-substituted glycine ester and the N-substituted glycine acid is very high and therefore adequate
15 for most purposes without a purification step. The reaction mixture, which comprises, for example, the N-phenylglycine ester, can therefore be employed directly in any desired further reaction.

20 If appropriate, the N-substituted glycine ester and the N-substituted glycine acid can be converted into a salt, for example an alkali metal or alkaline earth metal salt, in a known manner. Preferred salts are the Na and the K salt. The glycine ester can furthermore be converted, if desired, into the free acid in a known
25 manner.

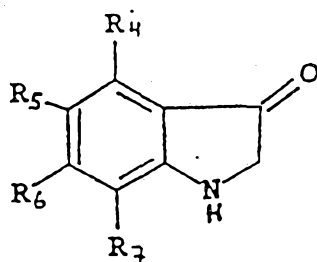
30 In a particularly preferred embodiment of the process, a glyoxylic acid ester half-acetal in which the two alkyl groups are identical and in each case are a straight-chain alkyl group having 1 to 4 C atoms is heated at the reflux temperature under normal pressure with an amine of the formula R_1NH_2 in which R_1 is a phenyl or naphthyl group which is unsubstituted or substituted by halogen, by alkyl groups having 1 to 4 C atoms or by alkoxy groups having 1 to 4 C atoms in a molar ratio of
35 1:1 to 1.5 in an alkyl alcohol in which the alkyl part corresponds to the alkyl parts in the glyoxylic acid ester half-acetal employed. The reaction is monitored by chromatography. When the glyoxylic acid ester half-acetal has disappeared from the reaction mixture, a



hydrogenation catalyst which comprises nickel as the active constituent and is applied to a support is introduced into the reaction mixture and hydrogen is forced in with a pressure of 40 to 80 bar. The reaction is monitored by chromatography. When the reaction has ended, the N-phenylglycine ester formed is isolated, if appropriate, by evaporating off the diluent and if appropriate is further purified in the customary manner, for example by extraction, distillation or chromatography, or the reaction mixture which comprises the N-phenylglycine ester is employed directly in any desired further reaction.

The N-substituted glycine ester and the N-substituted glycine acid of the formula I can be used for synthesis of the most diverse chemical compounds, for example for intermediate products for herbicides, or for synthons or pharmaceutical intermediate products. N-arylglycine esters prepared by the process according to the invention are preferably employed for the preparation of corresponding indoxyl derivatives and furthermore for the preparation of corresponding indigo derivatives. In fact, it has been found, unexpectedly, that it is possible to carry out cyclization of an N-arylglycine to give indoxyl directly, that is to say without prior hydrolysis of the ester groups.

The invention therefore also relates to a process for the preparation of an indoxyl derivative of the formula

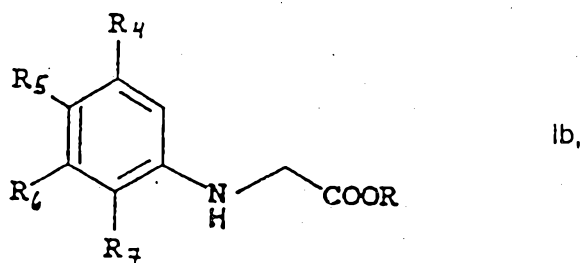


IV,

in which R_4 , R_5 , R_6 and R_7 , independently of one another are hydrogen, halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, or R_5 and R_6 or R_6 and R_7 , together with the two particular C atoms on which



they are substituted, are a benzene ring which is unsubstituted or substituted by halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, which comprises preparing an N-arylglycine ester of the
5 formula



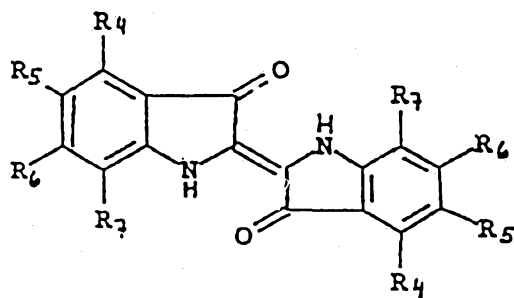
in which R has the meaning given in the formula I and R₄, R₅, R₆ and R₇ have the abovementioned meaning, as described above and cyclizing it with or without isolation, in the presence of molten alkali metal hydroxide or
10 alkaline earth metal hydroxide, with or without addition of an alkali metal amide, at temperatures from 150 to 300°C to give the indoxyl of the formula IV .

Preferably, in the formula IV, R₄, R₅, R₆ and R₇ are hydrogen, halogen, alkyl groups having 1 to 4 C atoms or alkoxy groups having 1 to 4 C atoms, particularly
15 preferably hydrogen or alkyl groups.

The cyclization of the N-arylglycine ester can be carried out here unexpectedly as with arylglycines themselves, for example in the manner described according to
20 Römpps Chemie Lexikon [Römpps Chemical Dictionary], page 1861 et seq., the alkyl ester group of the N-substituted glycine ester being split off as an alcohol.

The invention furthermore relates to a process for the preparation of an indigo derivative of the
25 formula





V.

in which R_4 , R_5 , R_6 and R_7 have the meaning given in formula IV, which comprises preparing, according to the invention, an indoxyl derivative of the formula IV in which R_4 , R_5 , R_6 and R_7 have the abovementioned meaning and oxidizing this in the customary manner, preferably, for example, in accordance with Chemische Berichte, Volume 99, 1966, pages 2146 - 2154, to give the indigo derivative of the formula V.

N-Substituted glycine esters and indoxyl and indigo compounds can be prepared in good yields by an environment-friendly route in the manner described. The process according to the invention therefore represents an enrichment of the art.

Examples

General preparation instructions:

0.375 mol of the amine of the formula III was dissolved in about 9 to 13 times the amount by weight of methanol, 0.375 mol of glyoxylic acid methyl ester methyl hemi-acetal (GMHA) (45 g) or 0.375 mol of glyoxylic acid methyl hemi-acetal (GAHA) (39.75 g), dissolved in about 12 times the amount by weight of methanol, is added and the mixture is allowed to react at 25 to 45°C. The progress of the reaction was monitored by means of thin layer chromatography. When the reaction had ended, the reaction solution was fed into a hydrogenation reactor and subjected to hydrogenolysis at a temperature of about 115°C under a hydrogen pressure of about 60 bar by means



of a nickel catalyst, which was applied to a support (Ni 6458 from Engelhardt). The reaction was monitored by thin layer chromatography. When the reaction had ended, the catalyst was filtered off and the diluent was distilled off. Since the purity of the N-substituted glycine esters obtained in this reaction was very high and in some cases exceeded 99%, it was possible to omit further purification. N-substituted glycine esters or glycine acids prepared in accordance with the general preparation instructions and the yields obtained are shown in Table 1. The resulting N-substituted glycine esters and glycine acids and their purity were characterized by gas chromatography, by comparison with the chemically pure substances.



Table 1

	Ex- ample	A	B	P	Yield
	1	34.8 g of aniline	45 g of GMHA	62 g of N-phenylgly- cine acid methyl ester	100
5	2	40.9 g of 4-hydroxy- aniline	45 g of GMHA	67 g of N-4- hydroxy- phenyl- glycine methyl ester	99
	3	56.6 g of anthranilic acid methyl ester	45 g of GMHA	56 g of N-2- carbometh- oxy-phenyl- glycine acid methyl ester	99
	4	53.6 g of 1- naphthyl- amine	45 g of GMHA	62 g of N-naphthyl- glycine acid methyl ester	69
	5	40.1 g of benzylamine	45 g of GMHA	67 g of N-benzylgly- cine acid methyl ester	100
	6	34.8 g of aniline	39.75 g of GAHA	53.7 g of N-phenyl- glycine acid	95

10 In Table 1 the abbreviations are as follows .

- A: Amount and nature of the amine of the formula III
- B: Amount of glyoxylic acid ester half-acetal or glyoxylic acid half-acetal
- P: Amount and nature of the N-substituted glycine ester obtained as the product



Yield: Yield in % of theory, based on the amine of the formula III employed

Example 7

0.5 g of N-phenylglycine acid methyl ester,
5 prepared in the manner described in Example 1, was introduced into a hot melt of 2.5 g of potassium hydroxide, into which 0.3 g of sodium amide had been introduced and which had a temperature of about 260 to 270°C, and allowed to react for a few minutes. The indoxyl/potassium
10 hydroxide melt formed by this procedure was introduced into ice-water. 0.3 g of indigo was obtained by introducing air into the aqueous suspension and filtering off and drying the precipitate formed.

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What I claim is

1. A process for the preparation of an N-substituted glycine ester or an N-substituted glycine acid of the formula



in which R is hydrogen or a straight-chain or branched alkyl group having 1 to 10 C atoms and R_1 and R_2 independently of one another are hydrogen, a substituted or unsubstituted alkyl group or a substituted or unsubstituted aryl group where R_1 and R_2 are not simultaneously hydrogen, which comprises reacting a glyoxylic acid ester half-acetal or glyoxylic acid half-acetal of the formula



in which R has the abovementioned meaning and R_3 is an alkyl group having 1 to 4 C atoms, with an amine of the formula



in which R_1 and R_2 have the abovementioned meaning, in a diluent at temperatures from 0°C up to the reflux temperature of the diluent used, and treating the resulting intermediate product with hydrogen under pressure in the presence of a hydrogenation catalyst and a diluent, the N-substituted glycine ester or the N-substituted glycine acid of the formula I being formed, and, if desired, isolating this from the reaction mixture and if appropriate converting it into a salt or, in the case of the glycine ester, into the free acid.

2. The process as claimed in claim 1, wherein a compound of the formula II in which R and R_3 are identical and are alkyl groups having 1 to 4 C atoms is employed.

3. The process as claimed in one of claims 1 or 2,



wherein a compound of the formula III in which R_1 is a phenyl or naphthyl group which is unsubstituted or substituted by halogen, by alkyl groups having 1 to 6 C atoms or by alkoxy groups having 1 to 4 C atoms and R_2 is hydrogen is employed.

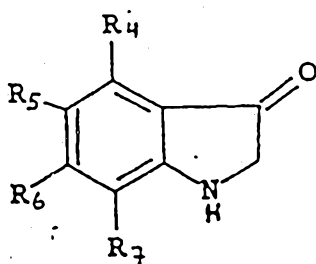
4. The process as claimed in one of claims 1 to 3, wherein a pressure of 40 to 80 bar and a temperature of 20 to 130°C is maintained during the hydrogenolysis.

5. The process as claimed in one of claims 1 to 4, wherein a compound of the formula III in which R_1 is a phenyl or naphthyl group which is unsubstituted or substituted by alkyl groups having 1 to 4 C atoms and R_2 is hydrogen is employed.

6. The process as claimed in one of claims 1 to 5, wherein 1 to 1.5 mol of the compound of the formula III are employed per mol of the compound II.

7. The process as claimed in one of claims 1 to 6, wherein an aliphatic alcohol having 1 to 4 C atoms, the alkyl part of which corresponds to the alkyl parts in the glyoxylic acid ester half-acetal employed is employed as the diluent.

8. A process for the preparation of an indoxyl derivative of the formula

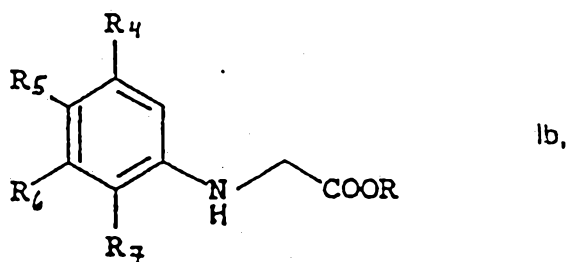


IV,

in which R_4 , R_5 , R_6 and R_7 , independently of one another are hydrogen, halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, or R_5 and R_6 or R_6 and R_7 , together with the two particular C atoms on which they are substituted, are a benzene ring which is unsubstituted or substituted by halogen, alkyl groups having 1 to 6 C atoms or alkoxy groups having 1 to 4 C atoms, which comprises preparing an N-arylglycine ester of the



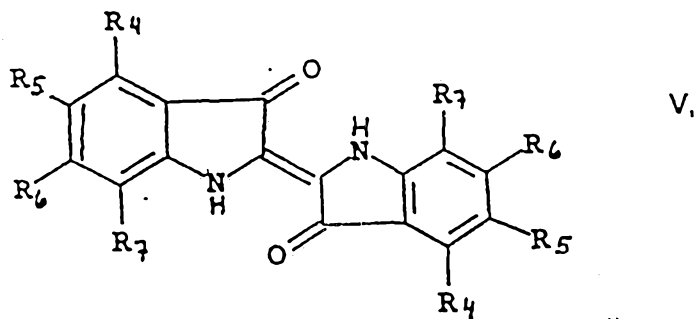
formula



in which R has the meaning given in the formula I as claimed in claim 1 and R₄, R₅, R₆ and R₇ have the above-mentioned meaning, as claimed in one of claims 1 to 6 and cyclizing it, in the presence of molten alkali metal hydroxide or alkaline earth metal hydroxide, with or without addition of an alkali metal amide, at temperatures from 150 to 300°C to give the indoxyl of the formula IV.

9. The process as claimed in claim 8, wherein an N-arylglycine ester of the formula Ia in which R is an alkyl group having 1 to 4 C atoms and R₄, R₅, R₆ and R₇ independently of one another are hydrogen, halogen, alkyl groups having 1 to 4 C atoms or alkoxy groups having 1 to 4 C atoms is employed.

10. A process for the preparation of an indigo derivative of the formula



in which R₄, R₅, R₆ and R₇ have the meaning given in formula IV as claimed in claim 8, which comprises preparing, as claimed in claim 8, an indoxyl derivative of the formula IV as claimed in claim 8 and oxidizing this in



INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/EP 94/04259

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07C227/08 C07C229/18 C07C229/14 C07D209/36		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07C C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 073 804 (HEARON ET. AL.) 14 February 1978 siehe das ganze Dokument ---	1-7
A	EP,A,0 099 981 (CHEMIE LINZ AKTIENGESELLSCHAFT) 8 February 1984 cited in the application siehe das ganze Dokument -----	1-7
<div style="display: flex; justify-content: space-between;"> ☐ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex. </div>		
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-size: 1.2em;">12 April 1995</div>		Date of mailing of the international search report <div style="text-align: center; font-size: 1.2em;">28.04.95</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016		Authorized officer <div style="text-align: center; font-size: 1.2em;">Helps, I</div>

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4073804	14-02-78	NONE	
EP-A-0099981	08-02-84	DE-A- 3224795	05-01-84
		CA-A- 1217780	07-02-87
		JP-C- 1628823	20-12-91
		JP-B- 2053426	16-11-90
		JP-A- 59021643	03-02-84
		US-A- 5015760	14-05-91