



(86) Date de dépôt PCT/PCT Filing Date: 1998/07/22
(87) Date publication PCT/PCT Publication Date: 1999/02/04
(45) Date de délivrance/Issue Date: 2007/08/28
(85) Entrée phase nationale/National Entry: 2000/01/24
(86) N° demande PCT/PCT Application No.: HU 1998/000068
(87) N° publication PCT/PCT Publication No.: 1999/005120
(30) Priorité/Priority: 1997/07/25 (HUP 97 01295)

(51) Cl.Int./Int.Cl. *C07D 235/02* (2006.01),
C07C 255/46 (2006.01)

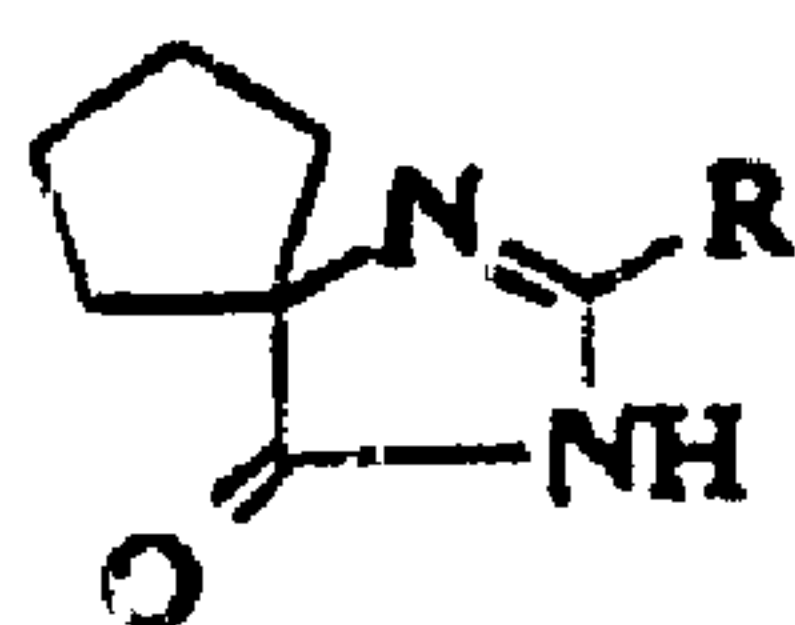
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(54) Titre : ELABORATION DE DERIVES 1,3-DIAZA-SPIRO (4.4) NON-1-EN-4-ONE ET D'INTERMEDIAIRES 1-CYANO-1-ACYLAMINOCYCLOPENTANE

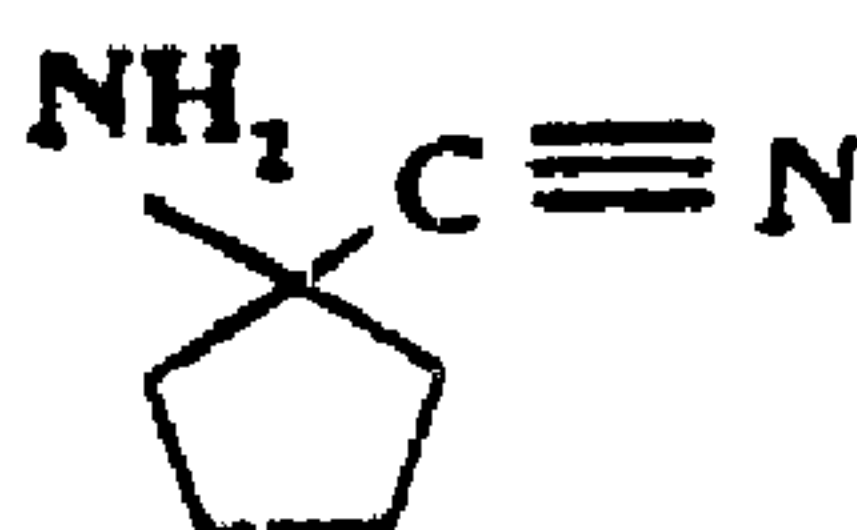
(54) Title: PROCESS FOR THE PREPARATION OF 1,3-DIAZA-SPIRO (4.4) NON-1-EN-4-ONE DERIVATIVES AND 1-CYANO-1-ACYLAMINOCYCLOPENTANE INTERMEDIATES



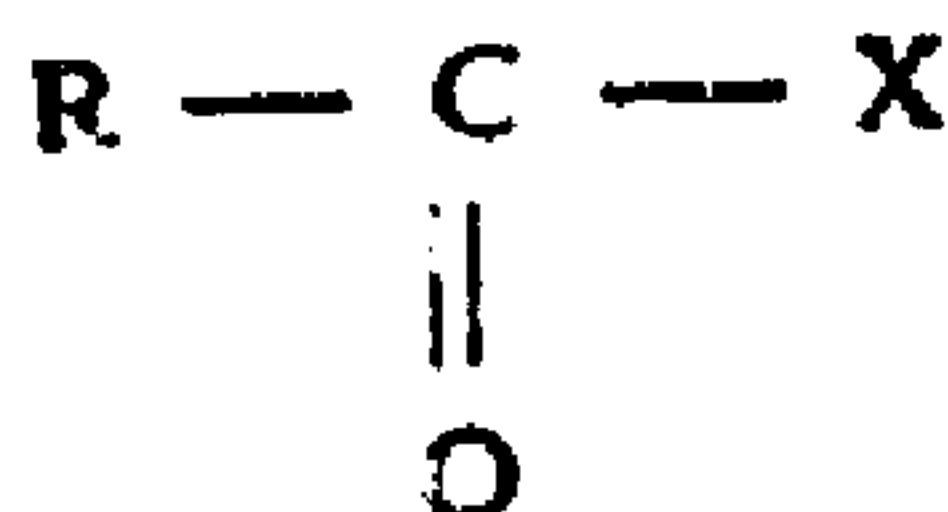
(I)



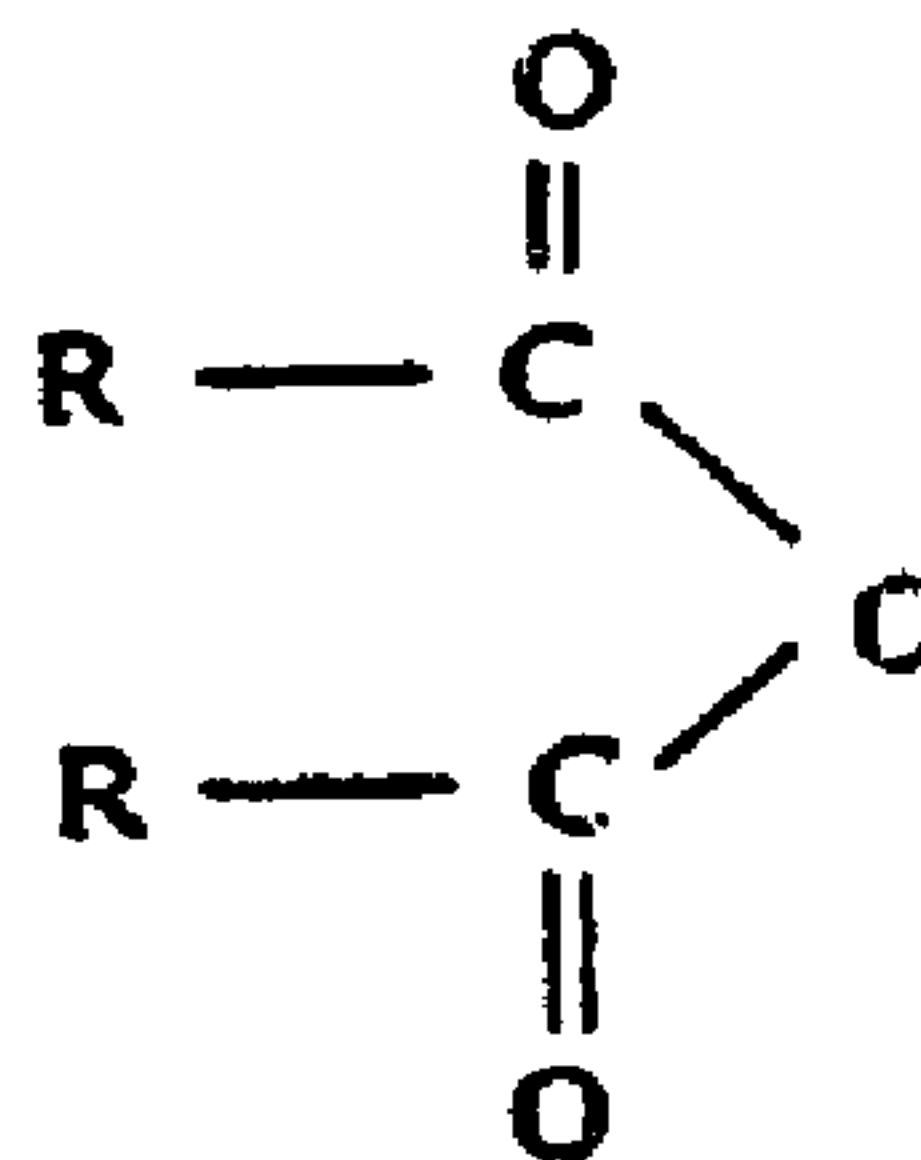
(II)



(III)



(IV)



(V)

(57) Abrégé/Abstract:

Process for the preparation of compounds of formula (I) wherein R means hydrogen atom, or C₁₋₆ alkyl group or C₇₋₁₂ aralkyl group or phenyl group, characterised in that a) the compound of formula (III) is reacted with a compound of formula (IV) wherein X means halogen atom or C₁₋₅ alkoxy group or hydroxyl group, and the resulting compound of formula (II) is transformed, in a reaction medium with pH above 7, into the compound of formula (I) or b) the compound of formula (III) is reacted with an anhydride of general formula (V) and the resulting compound of formula (II) transformed, in a reaction medium with pH above 7, into the compound of formula (I), or c) a compound of formula (II) is transformed, in a reaction medium with pH above 7, into the compound of formula (I), and if desired, the resulting compounds of formula (I), before or after isolation, are transformed into acid addition salts, or the compounds of formula (I) are liberated from their acid addition salts. Thus a process for the preparation of intermediates useful in synthesis of angiotensin II antagonists is disclosed.



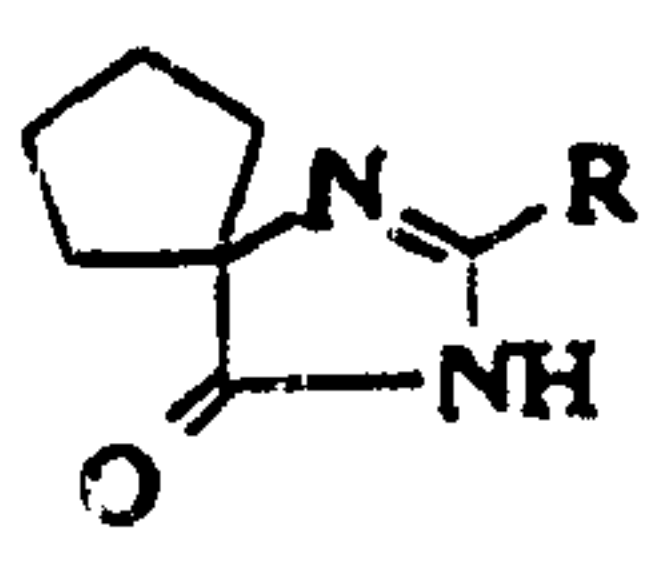
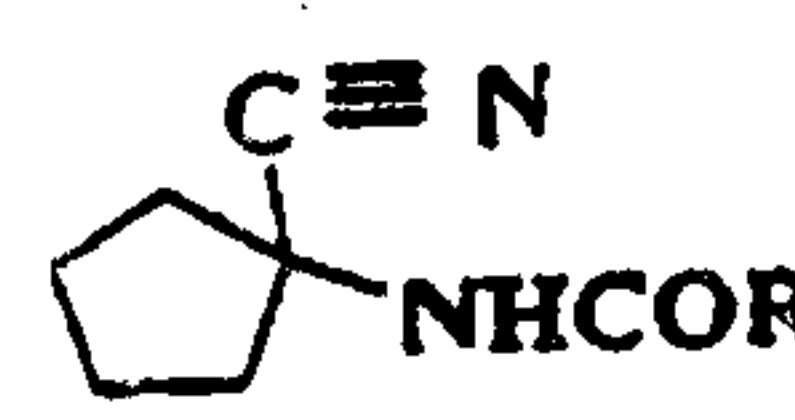
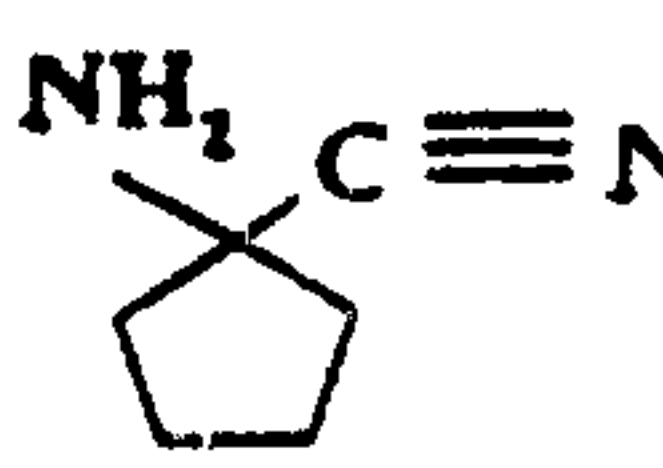
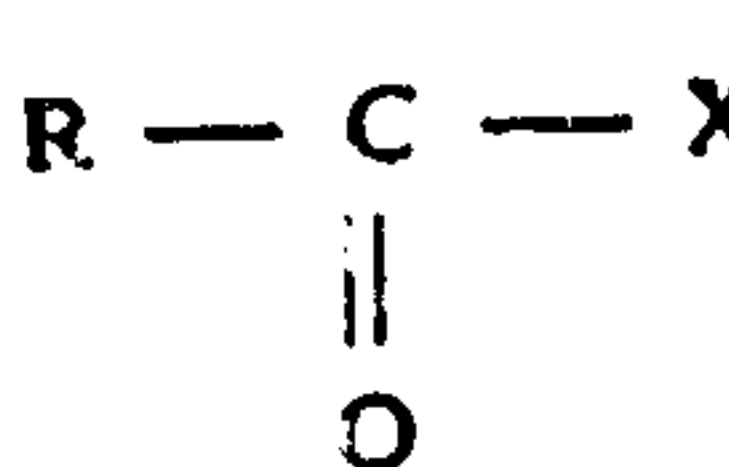
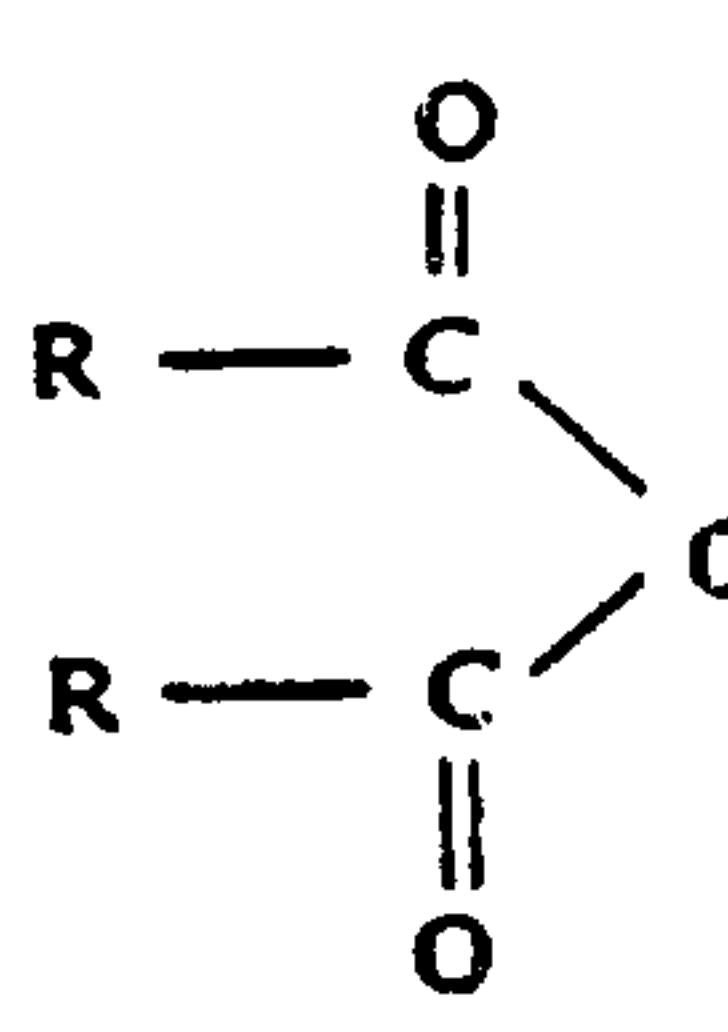
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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶: C07D 235/02, C07C 255/46	A1	(11) International Publication Number: WO 99/05120 (43) International Publication Date: 4 February 1999 (04.02.99)
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(54) Title: PROCESS FOR THE PREPARATION OF 1,3-DIAZA-SPIRO (4.4) NON-1-EN-4-ONE DERIVATIVES AND 1-CYANO-1-ACYLAMINOCYCLOPENTANE INTERMEDIATES		
(57) Abstract Process for the preparation of compounds of formula (I) wherein R means hydrogen atom, or C₁₋₆ alkyl group, or C₇₋₁₂ aralkyl group or phenyl group, characterised in that a) the compound of formula (III) is reacted with a compound of formula (IV) wherein X means halogen atom or C₁₋₅ alkoxy group or hydroxyl group, and the resulting compound of formula (II) is transformed, in a reaction medium with pH above 7, into the compound of formula (I) or b) the compound of formula (III) is reacted with an anhydride of general formula (V) and the resulting compound of formula (II) is transformed, in a reaction medium with pH above 7, into the compound of formula (I), or c) a compound of formula (II) is transformed, in a reaction medium with pH above 7, into the compound of formula (I), and if desired, the resulting compounds of formula (I), before or after isolation, are transformed into acid addition salts, or the compounds of formula (I) are liberated from their acid addition salts. Thus a process for the preparation of intermediates useful in synthesis of angiotensin II antagonists is disclosed.  (I)  (II)  (III)  (IV)  (V)		

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PROCESS FOR THE PREPARATION OF 1,3-DIAZA-SPIRO (4,4) NON-1-EN-4-ONE
DERIVATIVES AND 1-CYANO-1-ACYLAMINOCYCLOPENTANE INTERMEDIATES

The compounds of formulae (I) to (V), discussed
herein, are illustrated in Figure 1.

5 This invention relates to the new process for the preparation of compounds of
general formula (I) -wherein R means hydrogen atom or C₂₋₆ alkyl group - and to
the intermediates of general formula (II) -wherein the meaning of R is the same as
above. Compounds of general formula (I) are important intermediates used in the
course of preparation of active components of pharmaceuticals. They are e.g.
10 applied in the synthesis of angiotensine II antagonists (PCT application, publication
number WO-91/14679A).

Synthesis of 4-imidazolinones and their 2-substituted derivatives, constituting the
main skeleton of compounds of general formula (I) is known from the literature
15 (Bruckner: Szerves kémia Band III-1 page 296. Edition: Tankönyvkiadó, Budapest
1964). Takenaka and his co-workers described the preparation of 2-phenyl-4,4'-
dialkyl-5-oxo-2-imidazolines in tetrahydrofuran-water heterogeneous system by a 5-
12 hours reflux /Heterocycles 29 (6) p 1185 (1989)/. The above method is, however,
difficult to implement since preparation of the appropriate carboxamides is
20 problematic. The appropriate carboxamides are in general synthesised by partial
hydrolysis of α -aminonitriles, thus, by that of the α -aminonitrile (III). Taking into
account the sensitivity of the aminonitriles against alkalines and oxidants, from the
known methods only the partial hydrolysis performed in concentrated acidic
medium is considered as feasible.

25

The transformation of nitriles into carboxamides in strongly acidic medium,
preferably in concentrated sulfuric acid, raises, however, a number of problems. To
be able to stir the reaction mixture, sulfuric acid has to be applied in large excess.
As a consequence, heating up the reaction mixture to 70 °C and cooling it down
30 takes considerable time and keeping the reaction product for longer time in a

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concentrated sulfuric acidic medium will cause partial decomposition. This will cause the necessity of further purification steps. Since the aminocarboxamides are obtained in the form of sulfate salts, the amides have to be liberated. Neutralization of the large excess of acid means the addition of large amounts of base and also that of water, in order to keep the resulting salt in solution. The amino-carboxamide obtained is well solvated, its extraction from the reaction mixture requires a minimum 40-fold excess of the extracting solvent, even if the best - but from the aspect of health very unfavourable - chlorinated hydrocarbones are applied. These solvents, at that, can be recovered only with high losses.

Our aim was to work out a novel process for the preparation of the compounds of general formula (I) eliminating the above problems.

We have found that if

- a) the compound of formula (III) is reacted with a compound of general formula (IV) - wherein R means hydrogen atom or C₂₋₆ alkyl group, X means halogen atom, C₁₋₅ alkoxy group or hydroxyl group - and the resulting compound of general formula (II) - wherein the meaning of R is the same as given above - is transformed, in a reaction medium with pH above 7, into the compound of general formula (I) - wherein the meaning of R is as defined above -, or
- b) the compound of formula (III) is reacted with an anhydride of general formula (V) - wherein the meaning of R is the same as defined above -, and the resulting compound of general formula (II) - wherein the meaning of R is as given above - is transformed, in a reaction medium with pH above 7, into the compound of general formula (I), or
- c) a compound of general formula (II) - wherein the meaning of R is the same as defined above - is transformed, in a reaction medium with pH above 7, into the compound of general formula (I), and, if desired, the resulting compounds of general formula (I), before or after isolation, are transformed into acid addition salts, or the compounds of general formula (I) are liberated from their acid addition salts,

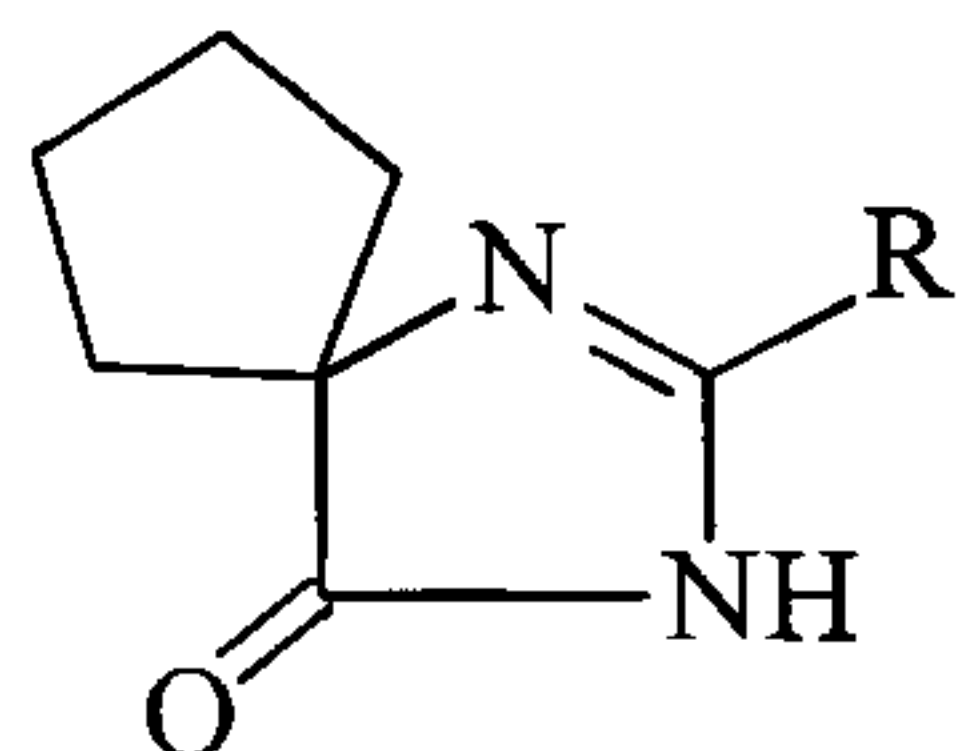
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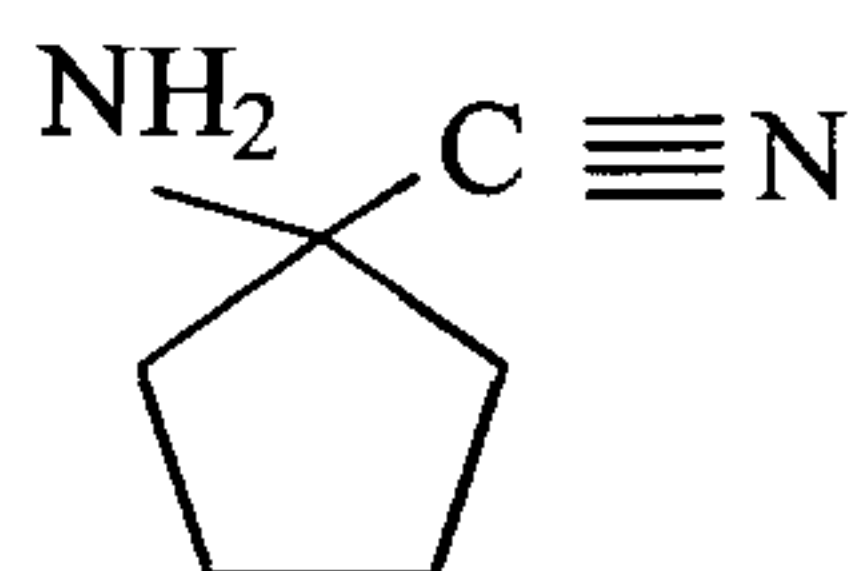
then the disadvantages of the known methods are avoided and the new method is also suitable for the "one-pot" synthesis of the compounds of general formula (I).

According to one aspect of the present invention,
5 there is provided a process for the preparation of a compound of general formula I



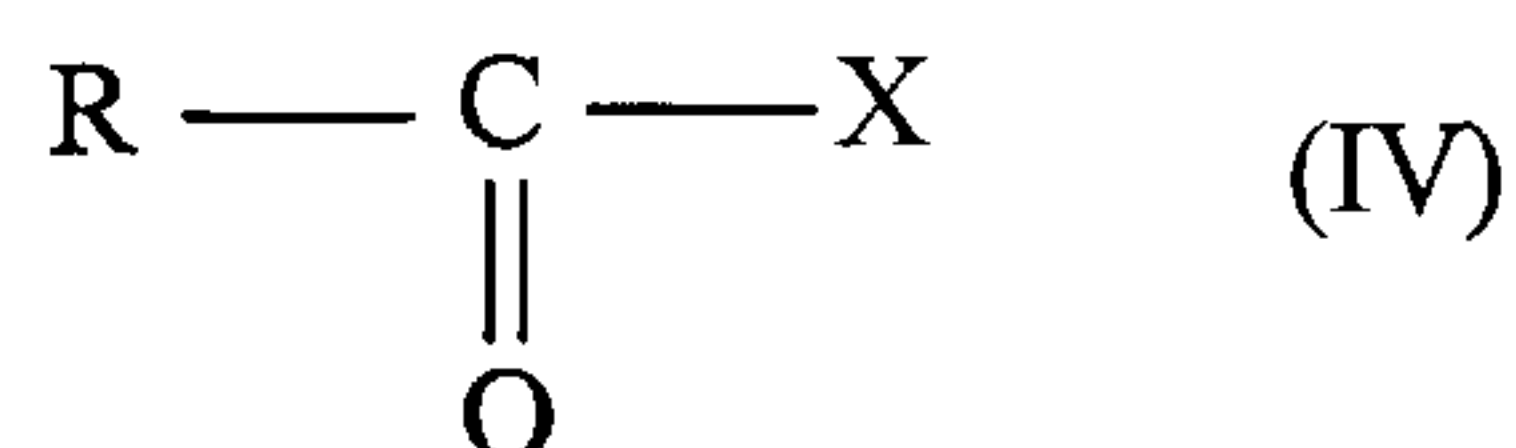
(I)

10 wherein R is hydrogen or C₂₋₆ alkyl, wherein: a) a compound of general formula (III)

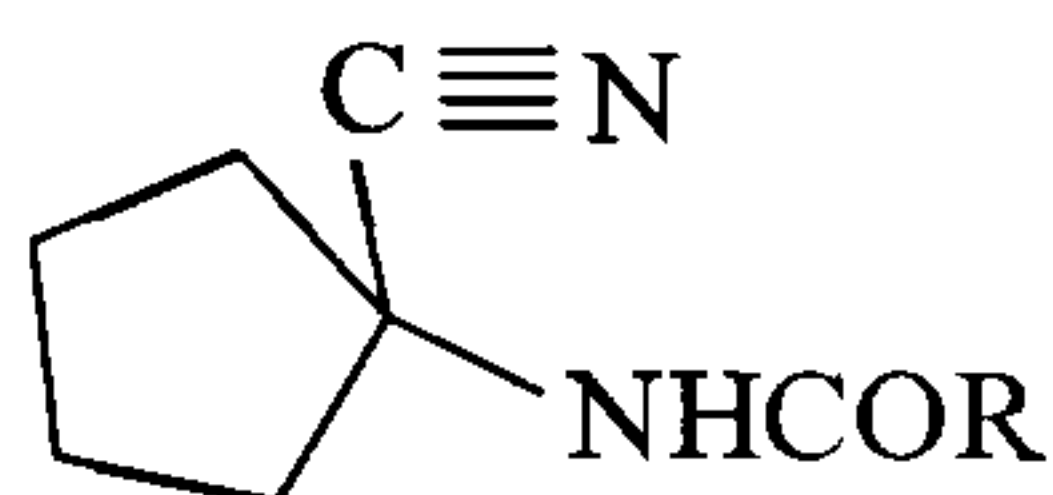


(III)

15 is reacted with a compound of general formula (IV)



wherein R is hydrogen or C₂₋₆ alkyl and X is halogen, C₁₋₅
20 alkoxy or hydroxyl, and the resulting compound of formula (II)



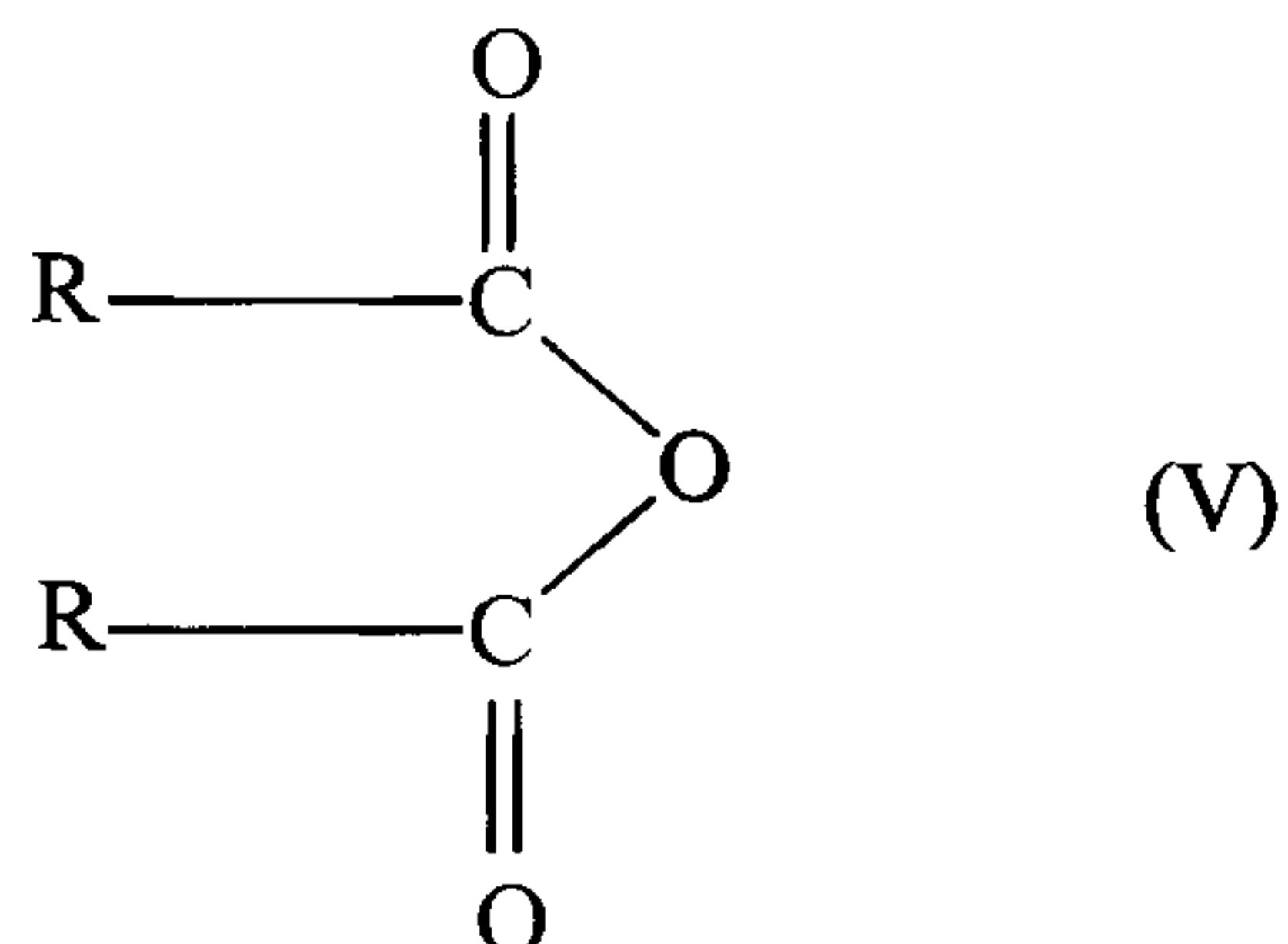
(II)

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3a

wherein R is hydrogen or C₂₋₆ alkyl, is transformed, in a reaction medium with pH above 7, into the compound of general formula (I); b) the compound of formula (III) is reacted with an anhydride of general formula (V)

5



wherein R is hydrogen or C₂₋₆ alkyl, and the resulting compound of general formula (II)



wherein R is hydrogen or C₂₋₆ alkyl is transformed, in a reaction medium with pH above 7, into the compound of general formula (I); or c) a compound of general formula (II)



wherein R is hydrogen or C₂₋₆ alkyl, is transformed, in a reaction medium with pH above 7, into the compound of general formula (I); and if desired, the resulting compound of general formula (I), before or after isolation, is transformed into an acid addition salt, or the compound of general formula (I) is liberated from its acid addition salt.

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3b

According to another aspect of the present invention, there is provided the process described herein, wherein the reaction is carried out in a homogeneous phase.

According to another aspect of the present invention, there is provided the process described herein, wherein the reaction is carried out in a heterogeneous phase.

According to still another aspect of the present invention, there is provided the process described herein, wherein one or more bases selected from alkali alcoholates, alkali metal hydroxides, alkali metal carbonates and anion-exchange resins are used to make the pH above 7.

According to yet another aspect of the present invention, there is provided the process described herein, wherein in the reaction taking place between the compound of formula (III) and a compound of general formula (IV) or (V) an acid binding agent is used.

According to a further aspect of the present invention, there is provided the process described herein, wherein the acid binding agent is an amine, an alkali-earth metal carbonate, an alkali-earth metal carbonate or an alkali-earth metal oxide.

According to yet a further aspect of the present invention, there is provided the process described herein, wherein the reaction takes place in one or more solvents selected from aromatic hydrocarbons, halogenated aliphatic hydrocarbons, aliphatic ethers, alcohols, or in a homogeneous or heterogeneous aqueous solvent system formed between water and one or more of said solvents.

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3c

According to still a further aspect of the present invention, there is provided the process described herein, wherein one or both of a phase transfer catalyst and dissolution transfer catalyst is used.

5 According to another aspect of the present invention, there is provided the process described herein, wherein the phase transfer catalyst is an alkyl ammonium hydrogen sulfate, a hydrogen halogenide or a hydroxide, and the dissolution transfer catalyst is an alcohol having a
10 chain length of up to 12 carbon atoms.

According to yet another aspect of the present invention, there is provided the process described herein, wherein the reaction is carried out without isolating the compounds of general formula (II).

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3d

In the first, acylation step the use of acid chlorides is the most advantageous, in the presence of an organic solvent and an acid binding agent. As for organic solvents for example ethers (methyl tert.-butyl ether), aromatic hydrocarbones e.g. toluene, xylene or chlorinated hydrocarbones e.g. dichloroethane can be applied, as for acid binding agents inorganic bases, for example alkali metal carbonates, alkali-earth metal oxides, organic bases e.g. trialkylamines may be employed.

The resulting, if desired isolated, compounds of general formula (II) are new, they are not known from the literature.

Transformation of the compounds of general formula (II) was carried out in homogenous phase, in mixtures of water and organic solvent, preferably in aqueous alcohols, most preferably in aqueous methanol. The reaction is carried out in basic medium, above pH=7, for example in the presence of sodium hydroxide, but other alkali metal hydroxides, as well as alkali metal carbonates, alkali-earth metal hydroxides, alkali-earth metal carbonates or anion-exchange resins may also be used.

Cyclisation may be accomplished in 0,5-2 hours.

The cyclisation step is preferably carried out at a temperature between 50-160 °C. The whole process can be carried out in one reaction pot and the resulting compounds of general formula (I) contain, at the highest. 0,1% amount of contamination. The yield of the process is over 70%, calculated on the starting compound of formula (III). The compounds of general formula (I) are preferably isolated in the form of their organic or inorganic acid addition salts. Synthesis of the starting compound of formula (III) is known from the literature /it was synthesised according to the method of the PCT application, publ. number WO-91/14679 and of Org. Synt. 1955 3; (MS: (m/z) 110, 95, 81, 68, 54, 41, 28)/.

Further details of the invention are illustrated by the following examples.

4 5 6 7 8 9

Example 1.**1-cyano-1-n-pentanoylaminocyclopentane**

To 11.0 g (0.1 mol) of 1-amino-1-cyanocyclopentane dissolved in 100 ml of dichloromethane, 15 ml 10. g (0.1 mol) of triethylamine was added, then dropwise 13 ml, 13 g (0.1 mol) of valeroyl chloride, while keeping the temperature at 25-35 °C. The reaction mixture was stirred at 30-35 °C for 2 hours, then it was washed with water. The phases were separated, the organic phase was evaporated to obtain the pure title compound as an oil. The compound was identified by elementary analysis, IR, NMR and GC-MS spectrometry.

¹H-NMR (CDCl₃): δ 0.81 (CH₃); 1.25 (CH₂); 1.51(CH₂); 2.14 (CH₂); 1.73 (m, ring, 1.2); 2.21 (ring 3H); 2.05 (ring 4H); 7.39 (1H, NH);

¹³C-NMR (CDCl₃): δ 13.4(CH₃); 21.9(CH₂); 27.3(CH₂); 35.4(CH₂); 22.7[2C(1,2)]; 38.4[2C(3,4)]; 54.6(C quaternary); 121.2(CN); 173.7(NH-CO);

IR ν max: 2238(CN); 1654 (CO); 3304(NH);

MS: (m/z) 194 (M+H), 165, 152, 137, 111, 102, 85, 51, 41, 29.

Example 2.**1-cyano-1-n-pentanoylaminocyclopentane**

11.0 g (0.1mol) of 1-amino-1-cyanocyclopentane and 20.5 g (0.11 mol) of valeric anhydride were refluxed for 3 hours. The reaction mixture was evaporated under vacuo to constant weight. The resulting 19,3 g oil (98.5 %) was identical with the product obtained in Example 1.

Example 3.**1-cyano-1-n-pentanoylaminocyclopentane**

11.0g (0.1 mol) of 1-amino-1-cyanocyclopentane and 20.4 g (0.2 mol) of valeric acid were placed in an apparatus equipped with water-separatory distillation head and boiled until 1.8 ml of water distilled off. The reaction mixture was then evaporated in fine vacuum to constant weight.

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19.1 g (97.4 %) of oily product was obtained, which was identical with the product obtained in Example 1.

Example 4.

5 1-cyano-1-n-pentanoylaminocyclopentane

11.0 g (0.1 mol) of 1-amino-1-cyanocyclopentane, 13.9 g (0.12 mol) of methyl valerate and 1.0 g sodium methylate were boiled for 16 hours. The volatile products were then distilled off in vacuo. To the residue 50 ml of water was added, the pH was adjusted to neutral by the addition of acetic acid and the mixture was extracted
10 with 70 ml followed by 2x50 ml of dichloroethane. The combined organic phases were dried over sodium sulfate and evaporated in vacuo to constant weight.

13.1 g (66.8 %) of oily product was obtained which was identical with the product obtained in Example 1.

15 Example 5.

1-cyano-1-formylaminocyclopentane

11.0 g (0.1 mol) of 1-amino-1-cyanocyclopentane and 10 ml of 85 % formic acid were placed in an apparatus equipped with water-separatory distillation head and boiled for 3 hours. The reaction mixture was then evaporated to constant weight in
20 vacuo.

12.4 g (90 %) of oily product was obtained which on investigation by GC-MS gave the following fragments of the title product M: 138, 137, 123, 111, 110, 109, 93, 81, 68, 66, 54, 46, 41 (R_t: 10.7')

25 Example 6.

2-butyl-1,3-diaza-spiro [4.4] non-1-en-4-one monohydrochloride

To 19.6 g (0.1 mol) of 1-cyano-1-n-pentanoylaminocyclopentane dissolved in 70 ml of methanol, 25 g (0.46 mol) of potassium hydroxide dissolved in 50 ml of water was added. The resulting solution was stirred and heated at 50-60 °C, then under
30 reflux conditions for 2,5 hours. The pH was decreased by the addition of 25 g of

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ammonium chlorid, then methanol was distilled off. The residue was extracted with 50 ml and 2 x 30 ml of toluene, the combined organic phases were evaporated to constant weight. The residual 16 g of title compound was dissolved in 100 ml of acetone, the pH of the resulting solution was adjusted to 1-2 with hydrochloric acid solution, the mixture was crystallized, the crystals were collected by filtration to obtain 14 g of the title compound, yield 60.8 %.

IR: 3600-2200 : vibr, NH; 1779 : γ c = o; 1642 γ c, 1517 : δ NH (IRFT Perkin Elmer)

¹H NMR: 0.9 ppm T (CH₃); 1.34 ppm S (CH₂); 1.73 ppm Q (CH₂);
1.78-2.01 ppm M cyclopentane (CH₂); 2.78 ppm T (CH₂); 9-15 ppm (NH, N)

MS: 194, 179, 166, 165, 152, 124, 84, 83, 54, 41

TLC: eluant: chloroform:methanol = 6:1, TLC plate: Kieselgel GF254

Detection by: I₂ vapors; R_f = 0,64

Example 7.

2-butyl-1,3-diaza-spiro [4.4] non-1-en-4-one

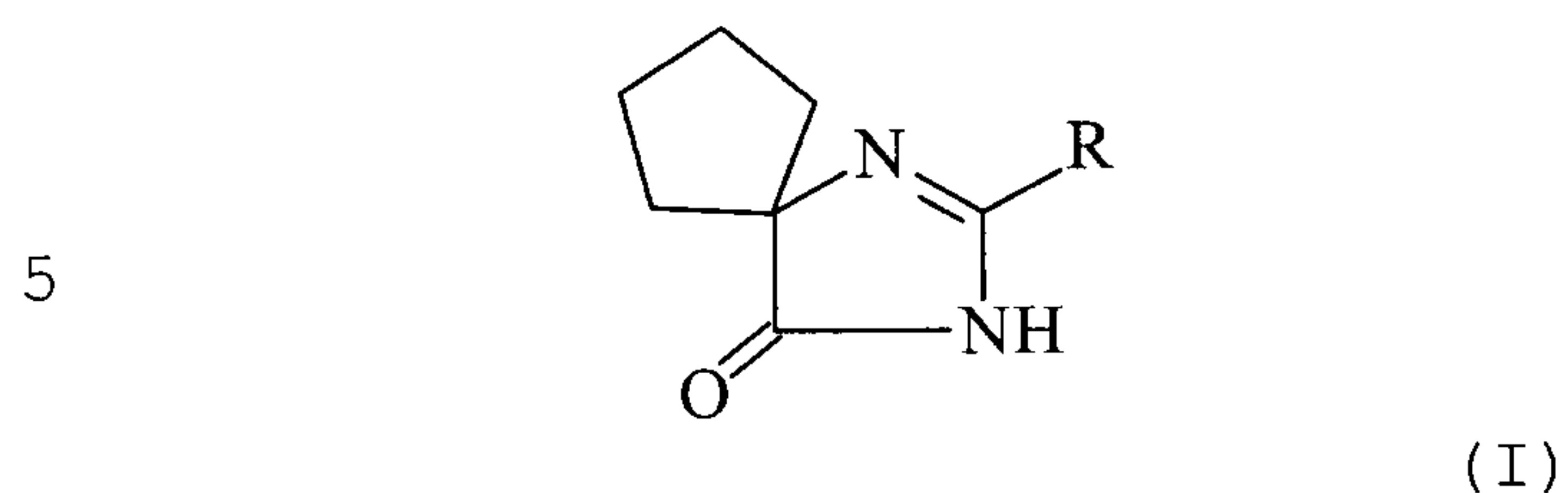
To 19.6 g (0,1 mol) of 1-cyano-1-n-pentanoylaminocyclopentane dissolved in 70 ml of methanol, 5 g of VarionTM AD resin was added the reaction mixture was heated under reflux conditions for 3 hours. After filtration and evaporation 16.5 g (71.7 %) of title compound was obtained, assay by GC: 92 %.

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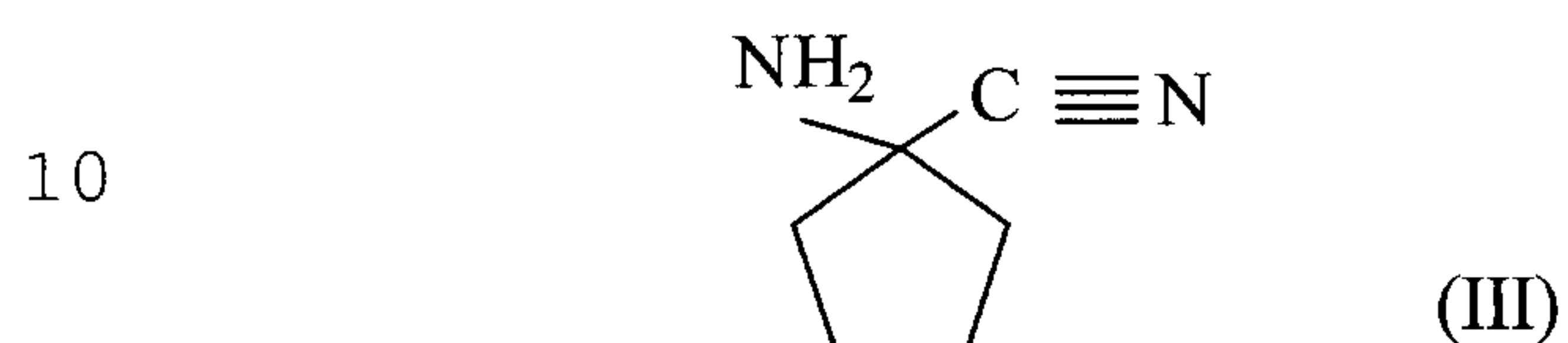
CLAIMS:

1. A process for the preparation of a compound of general formula I

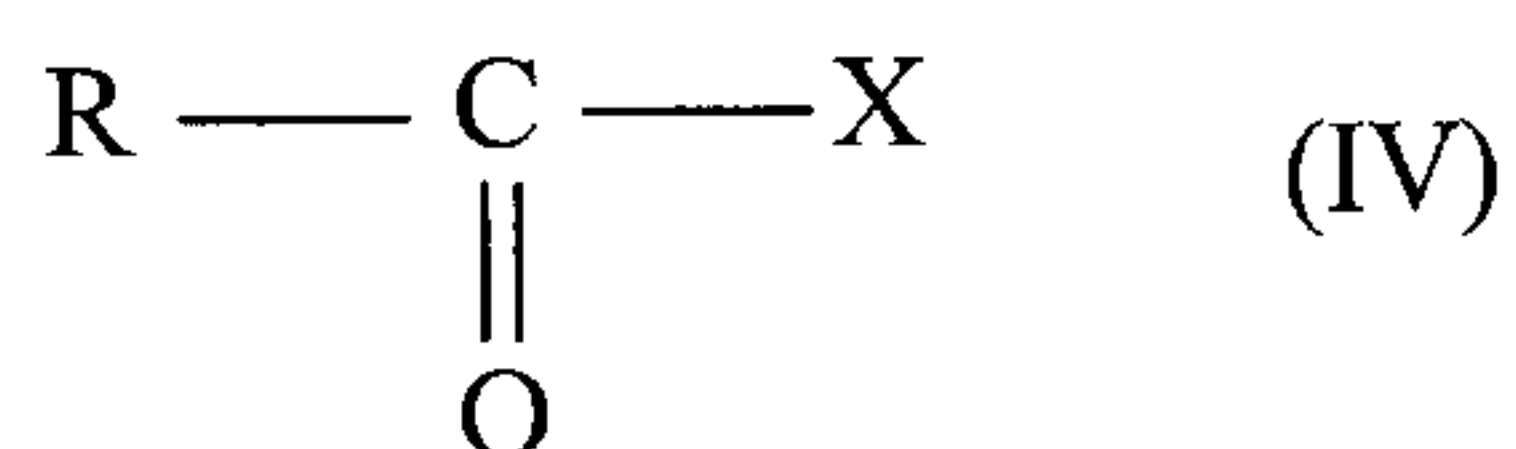


wherein R is hydrogen or C₂₋₆ alkyl, wherein:

a) a compound of general formula (III)



is reacted with a compound of general formula (IV)



15 wherein R is hydrogen or C₂₋₆ alkyl and X is halogen, C₁₋₅ alkoxy or hydroxyl, and the resulting compound of general formula (II)

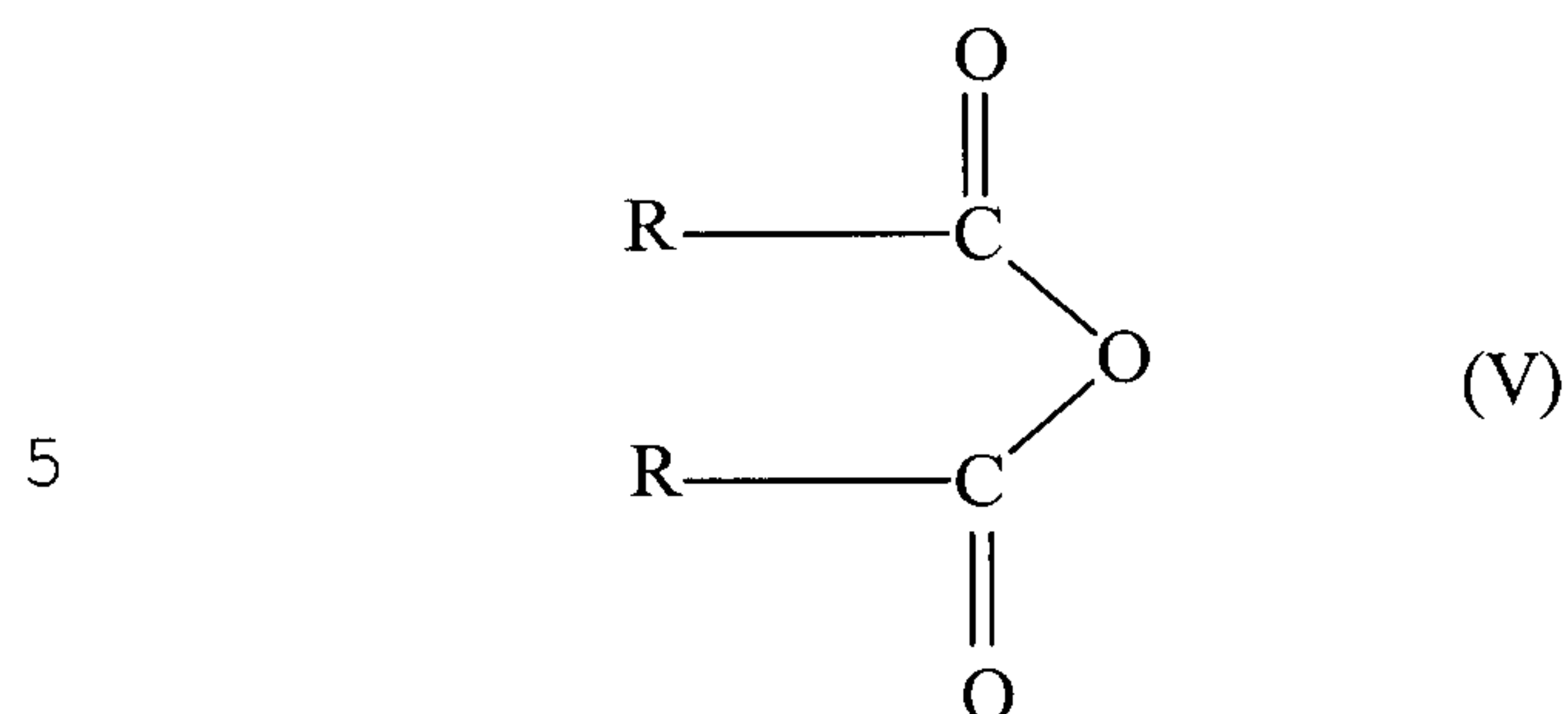


20 wherein R is hydrogen or C₂₋₆ alkyl, is transformed, in a reaction medium with pH above 7, into the compound of general formula (I);

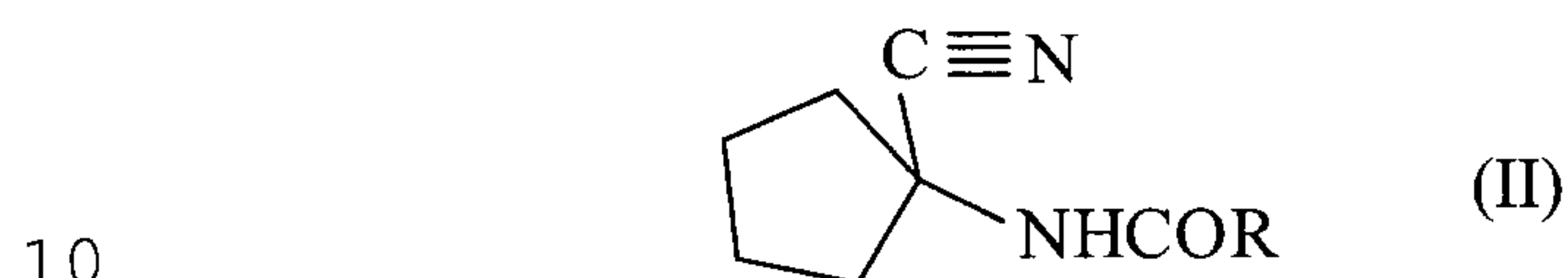
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b) the compound of formula (III) is reacted with an anhydride of general formula (V)

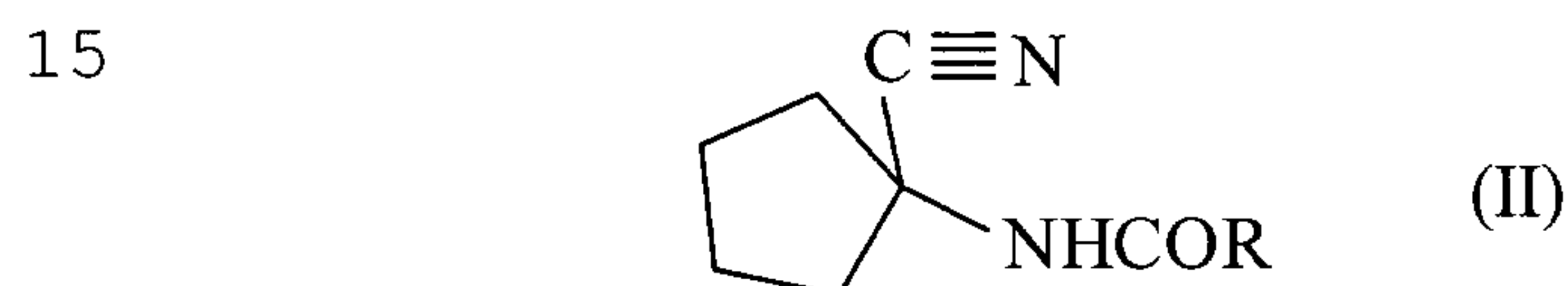


wherein R is hydrogen or C₂₋₆ alkyl, and the resulting compound of general formula (II)



wherein R is hydrogen or C₂₋₆ alkyl is transformed, in a reaction medium with pH above 7, into the compound of general formula (I); or

c) a compound of general formula (II)



wherein R is hydrogen or C₂₋₆ alkyl, is transformed, in a reaction medium with pH above 7, into the compound of general formula (I);

20 and if desired, the resulting compound of general formula (I), before or after isolation, is transformed into an acid addition salt, or the compound of general formula (I) is liberated from its acid addition salt.

2. The process according to claim 1, wherein the
25 reaction is carried out in a homogeneous phase.

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3. The process according to claim 1, wherein the reaction is carried out in a heterogeneous phase.

4. The process according to claim 1, wherein one or more bases selected from alkali alcoholates, alkali metal hydroxides, alkali metal carbonates and anion-exchange resins are used to make the pH above 7.

5. The process according to claim 1, wherein in the reaction taking place between the compound of formula (III) and a compound of general formula (IV) or (V) an acid binding agent is used.

6. The process according to claim 5, wherein the acid binding agent is an amine, an alkali-earth metal carbonate, an alkali-earth metal carbonate or an alkali-earth metal oxide.

7. The process according to claim 1, wherein the reaction takes place in one or more solvents selected from aromatic hydrocarbons, halogenated aliphatic hydrocarbons, aliphatic ethers, alcohols, or in a homogeneous or heterogeneous aqueous solvent system formed between water and one or more of said solvents.

8. The process according to claim 3, wherein one or both of a phase transfer catalyst and dissolution transfer catalyst is used.

9. The process according to claim 8, wherein the phase transfer catalyst is an alkyl ammonium hydrogen sulfate, a hydrogen halogenide or a hydroxide, and the dissolution transfer catalyst is an alcohol having a chain length of up to 12 carbon atoms.

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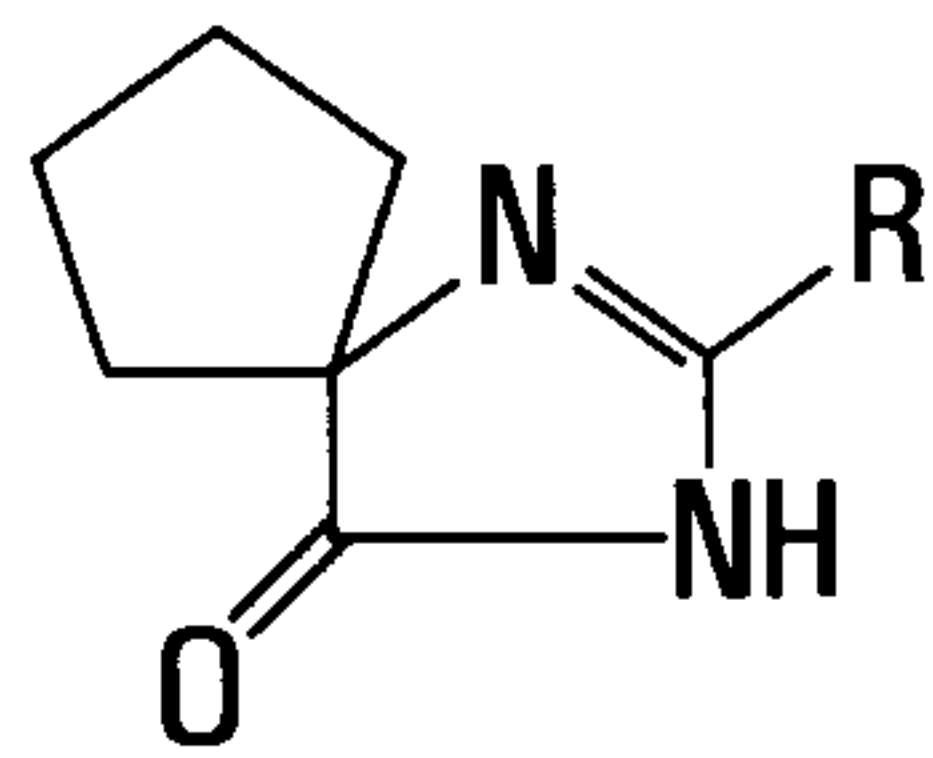
10. The process according to claim 1, wherein the reaction is carried out without isolating the compounds of general formula (II).

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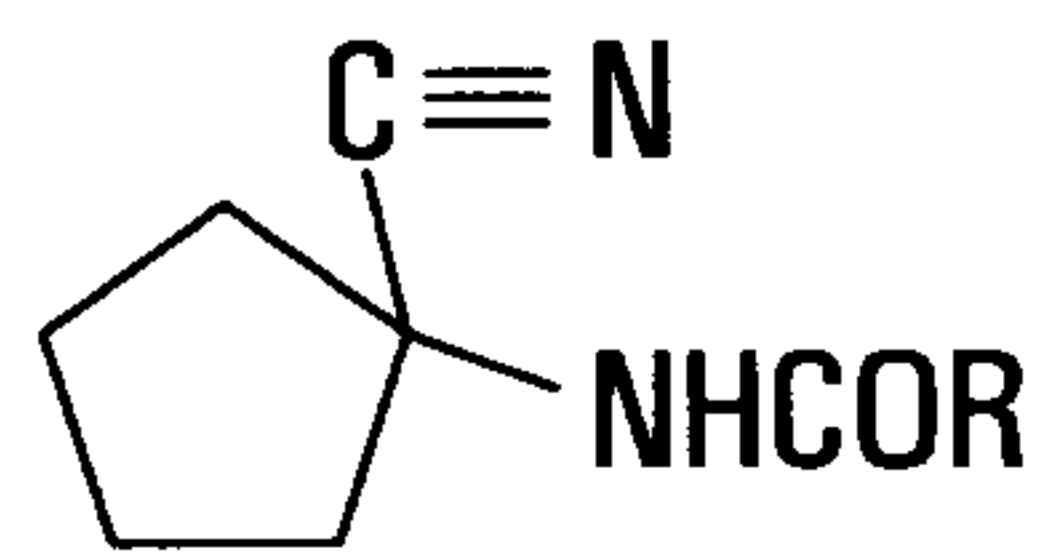
OTTAWA, CANADA

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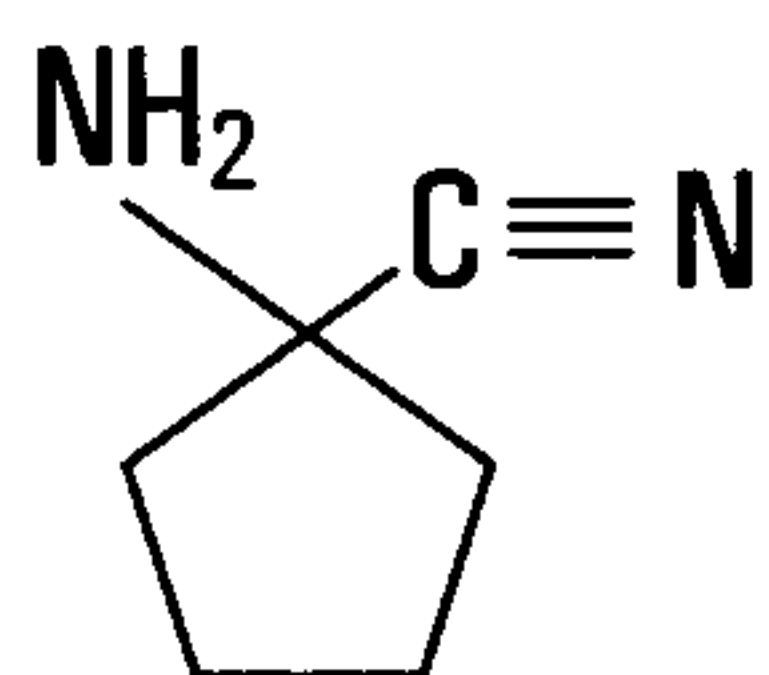
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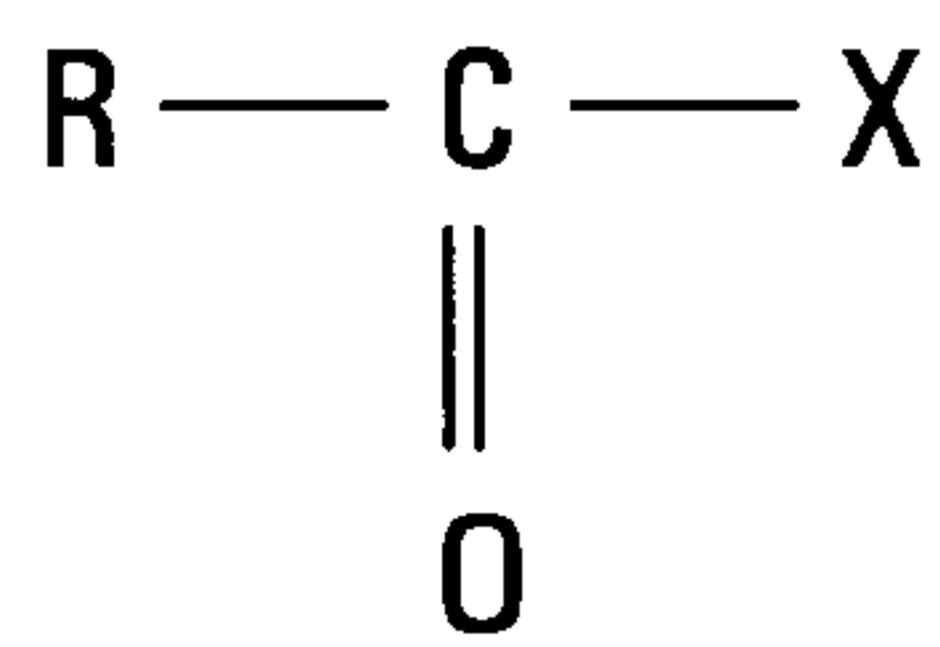
(I)



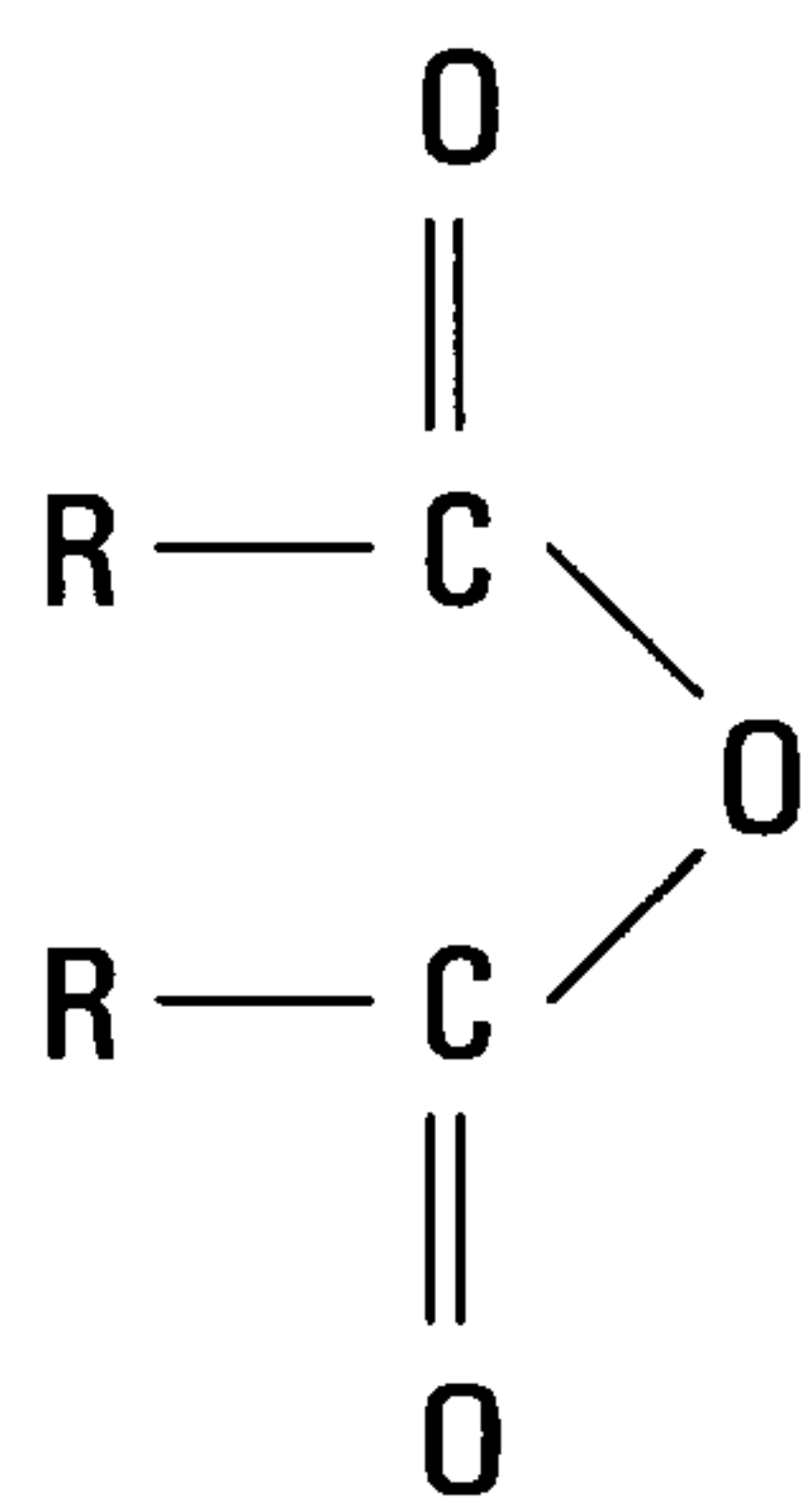
(II)



(III)

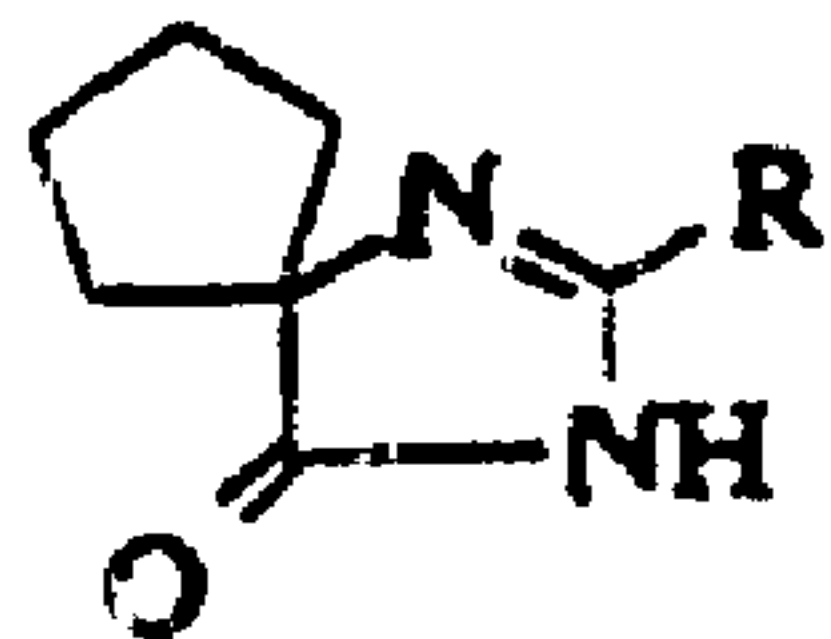


(IV)



(V)

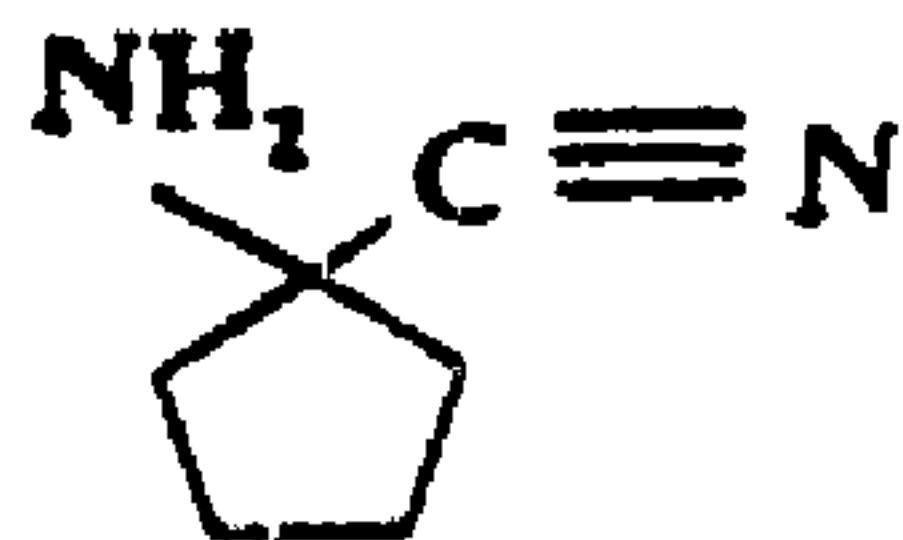
FIG. 1



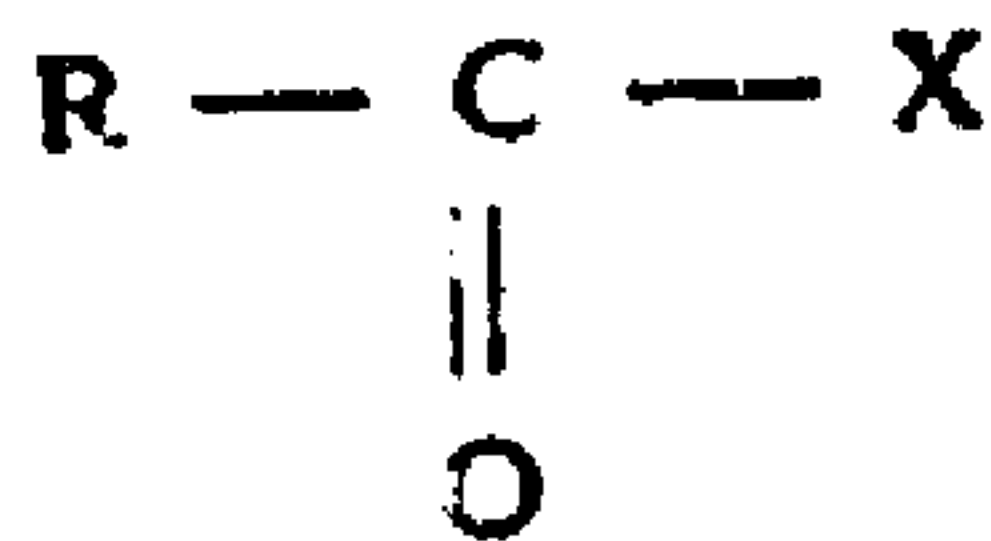
(I)



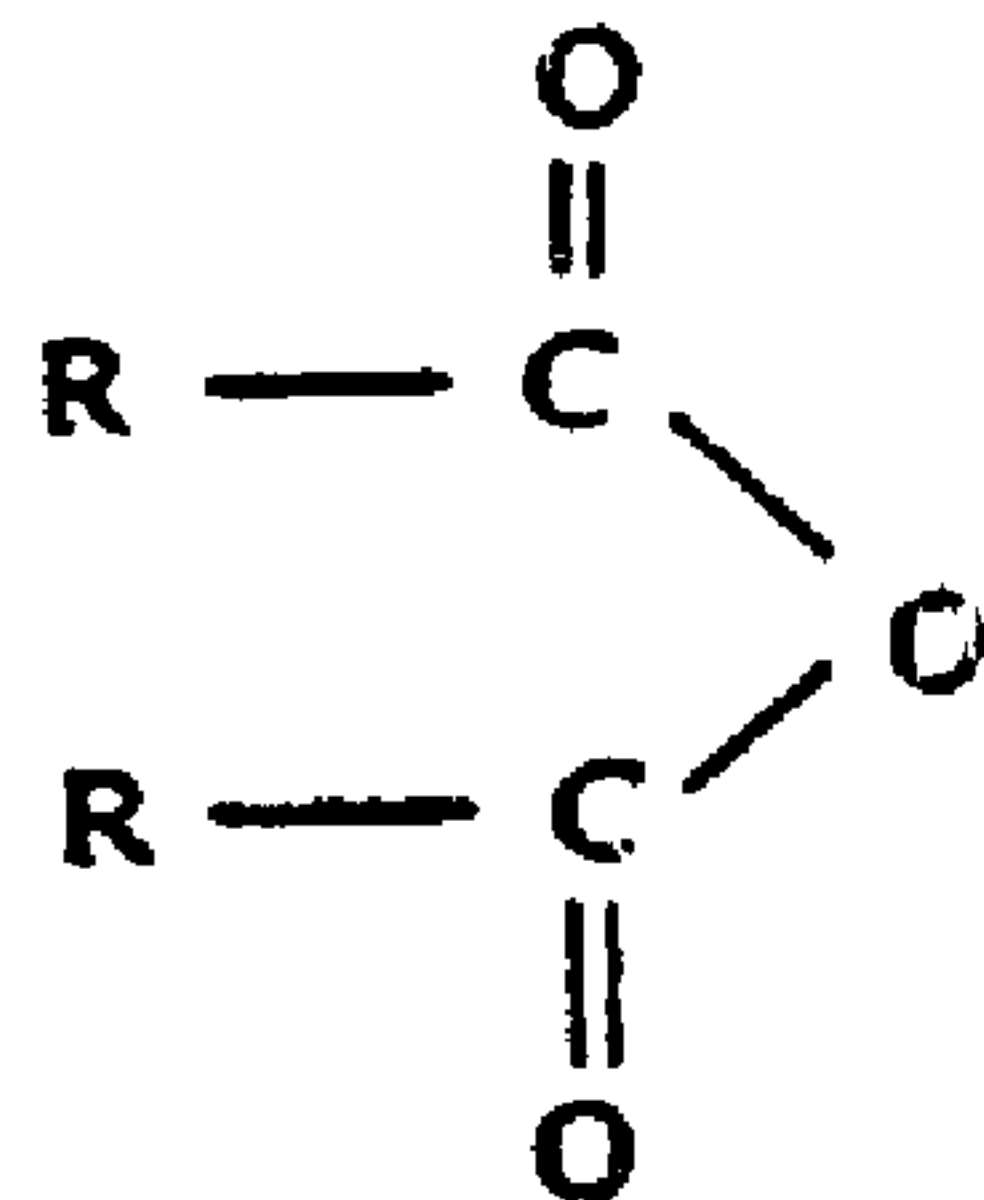
(II)



(III)



(IV)



(V)