

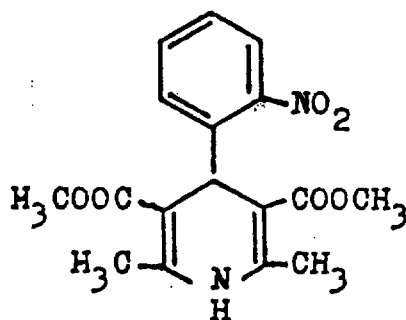
2216521

- 1 -

PROCESS FOR THE PREPARATION OF 1,4-DIHYDRO-PYRIDINE
DERIVATIVES,

This invention relates to a new and improved process for the preparation of a 1,4-dihydro-pyridine derivative, to new intermediates useful in the preparation thereof and to a process for the preparation of the said new intermediates.

More particularly, the invention is concerned with new and improved processes for the preparation of dimethyl-1,4-dihydro-2,6-dimethyl-4-(2'-nitrophenyl)-pyridine-3,5-dicarboxylate of the Formula I



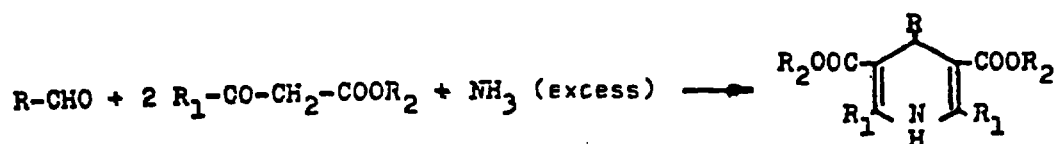
(I)

(referred to further on as "nifedipine").

It is known that nifedipine is a valuable calcium antagonist, widely used in the treatment of hyper-

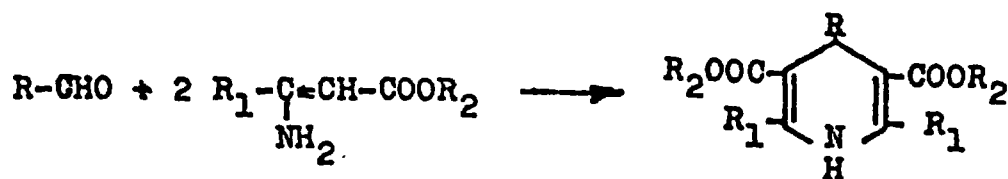
tension of all kinds and of heart muscle diseases
(US patent No. 3,485,847).

Several methods are known for the preparation of nifedipine. A. Hantzsch [Justus Liebigs Annalen der Chemie 215, 1 (1882)] described a general method for the preparation of 1,4-dihydro-pyridine derivatives by reacting an aldehyde with a 3-keto-carboxylic acid ester in the presence of an excess of ammonia. The reaction is illustrated in reaction scheme A.



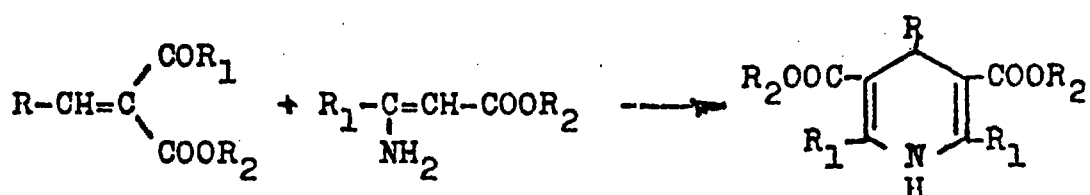
reaction scheme A

A further general process of A. Hantzsch-Beyer [C. Beyer, Ber. Dtsch. Chem. Ges. 24, 1662 (1891)] is shown in reaction scheme B.



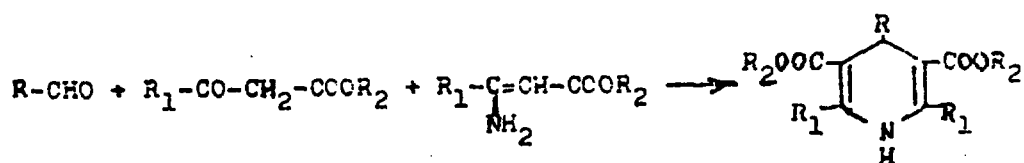
reaction scheme B

According to this process an aldehyde is reacted with two equivalents of an enamino-carboxylic acid ester. E. Knoevenagel [Ber. Dtsch. Chem. Ges. 31, 743 (1898)] elaborated the reaction of ylidene carboxylic acid esters and enamino carboxylic acid esters. This reaction is illustrated in reaction scheme C.



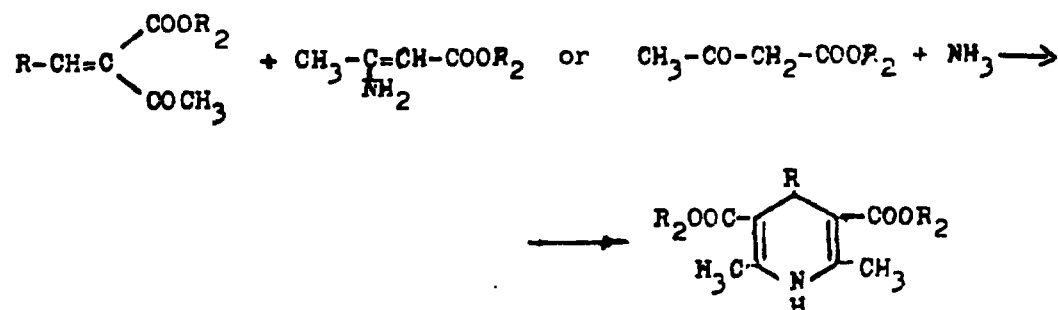
reaction scheme C

H. H. Fox et al. [J. Org. Chem. 16, 1259 (1951)] studied the reaction of aldehydes, 3-keto-carboxylic acid esters and enamino carboxylic acid esters. The reaction is shown in reaction scheme D.



reaction scheme D

According to DOS No. 2,117,571 dihydro-pyridines are prepared by reacting a nitro-phenyl-benzylidene-acetoacetate with a β -amino-crotonic acid ester or with ammonia and an acetoacetate. The reaction is illustrated in reaction scheme E.



reaction scheme E

The above methods were applied for the preparation of nifedipine. Thus, according to German patent No. 1,620,827 nifedipine is prepared by reacting 2-nitro-benzaldehyde with methyl acetoacetate in methanol in the presence of an excess of ammonia. The process yields, however, red-brown nifedipine contaminated by numerous by-products. Hungarian patent No. 192,546 contains a critical evaluation of this process and it is disclosed herein that on reproducing Example 1 of German patent No. 1,620,827 nifedipine contaminated by seven by-products is obtained.

Hungarian patent No. 192,546 relates to a modified and improved form of the above-mentioned Knoevenagel-synthesis applied to the preparation of symmetrical 1,4-dihydro-pyridine-dicarboxylates, including nifedipine.

In the first step of the synthesis 2-nitro-benzaldehyde is reacted with methyl acetoacetate in the presence of a catalytic amount (0.01-0.7 mole, related to 1 mole of methyl acetoacetate) of piperidine acetate to give methyl-

2-nitro-benzylidene-acetoacetate with a high yield of about 97%. This product is reacted after or without isolation with methyl-3-amino-crotonate. The yield of the second step is 87%, the total yield of both steps amounts to 84.4 %. According to the disclosure of the cited Hungarian patent the thin layer chromatogram of the nifedipine thus obtained shows no by-products (Merck-type plate coated with kieselgel; developed with a 3:2:5 mixture of chloroform, acetone and petrolether).

In the course of the earlier procedures - particularly in case of the Hantzsch-type synthesis - if free ammonia is present during the complete reaction period undesired reactions may take place and by-products contaminating the end-product may be formed. Since the requirements of Pharmacopoeia against nifedipine are very high and quality standards for drugs are more and more increasing, there is a great demand for the preparation of nifedipine of high purity, free of contaminations.

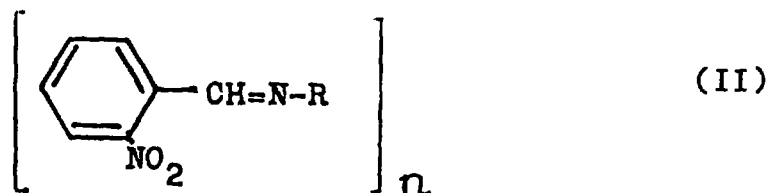
The industrial scale use of the process disclosed in Hungarian patent No. 192,546 has several drawbacks. From the economical point of view it is unfavourable that the half amount of the ester component used in the reaction is constituted by the expensive methyl-3-amino-crotonate. A further disadvantage is the long overall reaction time. In the first step the reaction time of the formation of the methyl-2-nitro-benzylidene-acetoacetate amounts to 16 hours, while in the second stage the said ylidene compound is converted into nifedipine in a reaction which requires

36 hours. Thus the total reaction time amounts to 52 hours. The methyl-3-amino-crotonate used must be prepared separately and is more expensive.

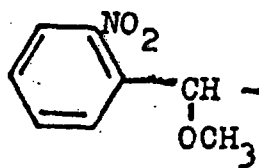
It is the object of the present invention to provide an economical industrial scale process for the preparation of nifedipine, whereby the reaction time is shortened and a pure product free of contaminations is obtained.

The process of the present invention is suitable for the economical and high yield industrial scale production of nifedipine of high purity.

According to the present invention there is provided a process for the preparation of dimethyl-1,4-dihydro-2,6-dimethyl-4-(2'-nitro-phenyl)-pyridine-3,5-dicarboxylate of the Formula I, which comprises reacting a compound of the general Formula II

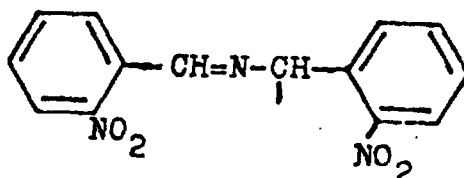


(wherein n is 1 or 3; if n is 1, then R stands for a group of the Formula (a))



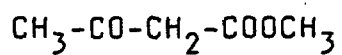
(a)

or (b)



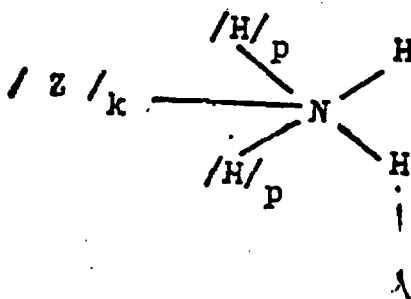
(b)

and if n is 3, then R represents hydrogen) with methyl acetoacetate of the Formula III



(III)

and optionally with an amino compound of the general Formula IV



(IV)

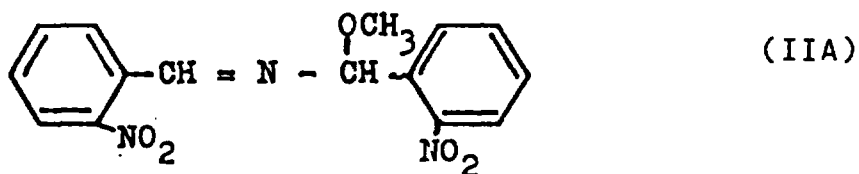
(wherein Z is a group of the Formula (c),



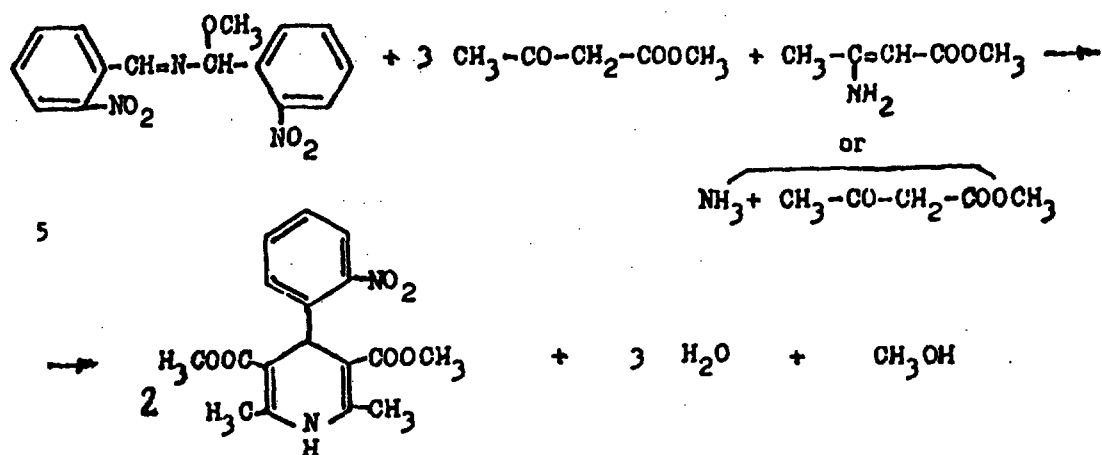
k is 1 and both symbols p are 0; or Z stands for a C₁₋₅ straight or branched chain alkanoyloxy group or a carbonate, hydrocarbonate or hydroxy anion, k is 1 and both symbols p are 1; or k is 0, one of both symbols p is 0 and the other is 1) in an inert solvent.

According to the process of the present invention,

1-methoxy-1-(2'-nitro-phenyl)-N-(2'-nitro-phenyl)-methylene-methaneamine of the Formula IIA



is used as starting material; this is a compound of the general Formula II, wherein R is a group of the Formula (a) and n is 1. The reaction is shown in reaction scheme F.



reaction scheme F

In the course of the reaction 1 mole of the compound of Formula IIA is reacted with 3 moles of methyl acetoacetate and 1 mole of methyl-3-amino-crotonate. The latter component may also be prepared in situ by reacting methyl acetoacetate with ammonia. For this purpose aqueous ammonium hydroxide or methanolic ammonia may be used. The reaction can be carried out in an inert solvent or solvent mixture. As reaction medium any suitable inert solvent may be used which does not interact with the starting materials under the reaction conditions used. Thus, polar protic solvents (e.g. water; alcohols, e.g. methanol, ethanol etc; amides, e.g. formamide, acetamide) or dipolar aprotic solvents (e.g. acetonitrile, acetone, dimethyl sulfoxide, nitrobenzene)

may be used. It is very preferred to work in methanol as medium. The reaction may be accomplished in a broad temperature range, preferably at a temperature between -10°C

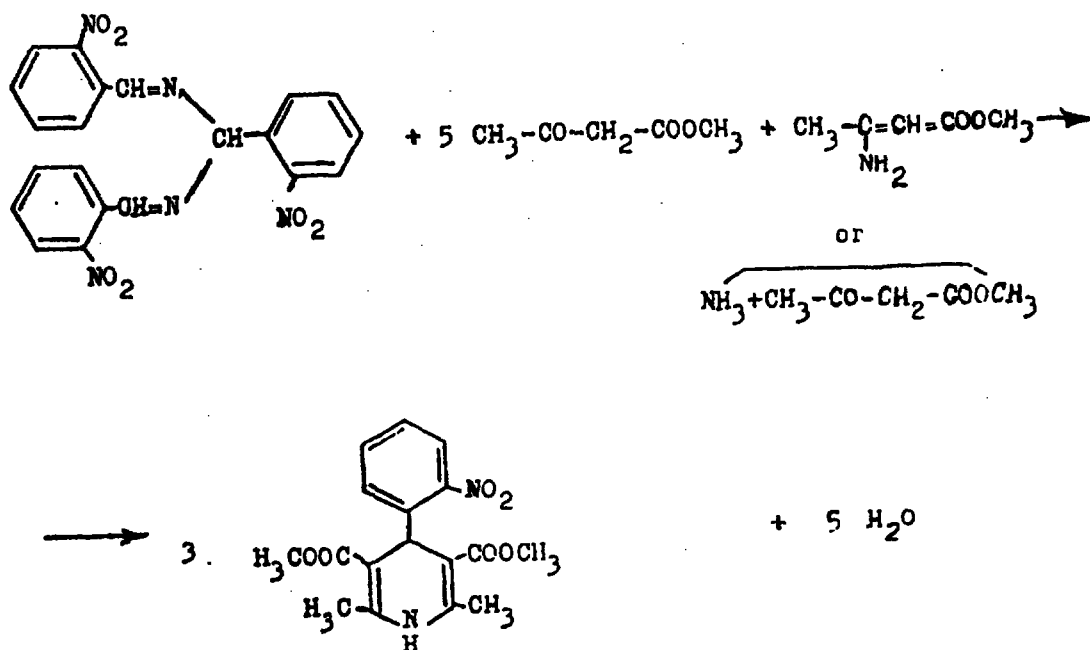
and +120 °C, advantageously at 5-100 °C, particularly at 25-80 °C. The reaction time depends on the temperature and may take 12-60 hours, preferably 25-55 hours. The reaction is generally completed within 36 hours with high yields.

One may proceed preferably by adding to a suspension of 1 mole of the compound of the Formula IIA in methanol 3 moles of methyl acetoacetate and subsequently 1 mole of methyl-3-amino-crotonate and heating the reaction mixture to boiling for 36 hours.

One may also proceed by converting the compound of the Formula IIA to nifedipine without isolation in the same apparatus.

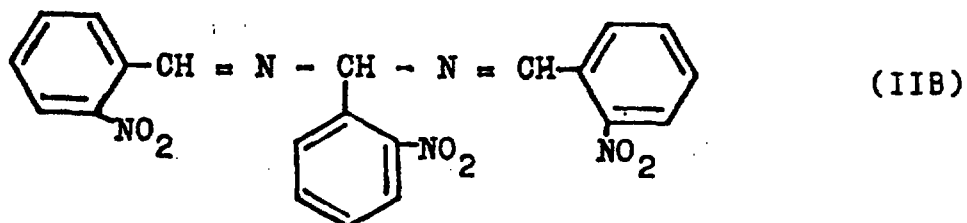
The reaction having been completed, nifedipine may be isolated from the reaction mixture by simple methods. The reaction mixture is cooled, the precipitated nifedipine filtered off, dissolved in warm acetic acid, precipitated with water, washed and dried. The product meets the requirements of Pharmacopoeia and no recrystallization is required.

According to a further form of realization of the process of the present invention, 1-(2'-nitro-phenyl)-N,N'-bis-(2'-nitro-phenyl)-methylene-methanediamine of the formula IIB is used as starting material. This is a compound of the Formula II, wherein n is 1 and R is a group of the Formula (b). The reaction is illustrated in reaction scheme G.



reaction scheme G

In the course of the reaction 1 mole of the compound of the Formula IIB



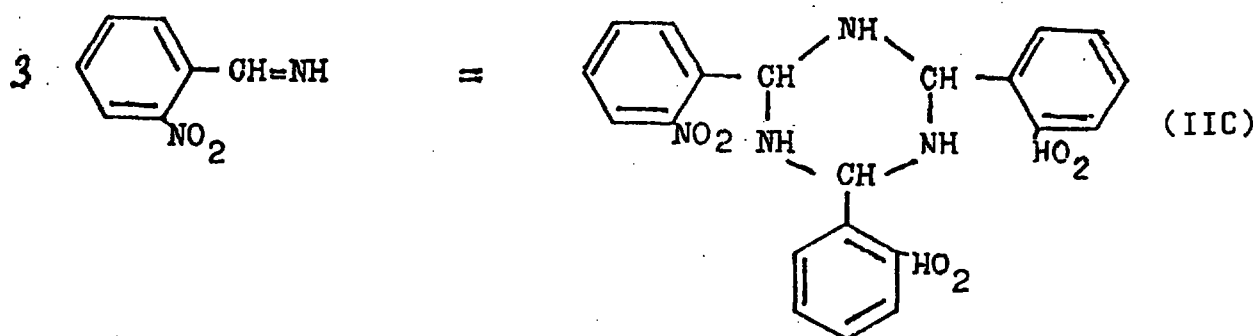
is reacted with 5 moles of methyl acetoacetate and 1 mole of methyl-3-amino-crotonate. This is a compound of the general Formula IV, wherein Z is a group of the Formula (c), k is 1 and both symbols p are 0. The latter component may also be prepared in situ by reacting methyl acetoacetate and ammonia. For this purpose aqueous ammonium hydroxide or methanolic ammonia may be used. The reaction can be carried out in an inert solvent or solvent mixture. As reaction medium any inert solvent which does not interact with the starting material under the reaction conditions may be used. The inert solvents enumerated in connection with the use of the starting material of the Formula IIA may be used. It is particularly preferred to work in methanolic medium. The reaction may be carried out in a broad temperature interval. The reaction temperature may vary between -10°C and $+120^{\circ}\text{C}$, preferably at $5-100^{\circ}\text{C}$, particularly $25-80^{\circ}\text{C}$. The reaction time depends on the temperature and the reaction takes generally 12-60 hours, preferably 25-55 hours. The reaction is generally completed with a high yield within 36-40 hours.

One may also proceed by converting the compound of the Formula IIB to nifedipine without isolation in the same apparatus.

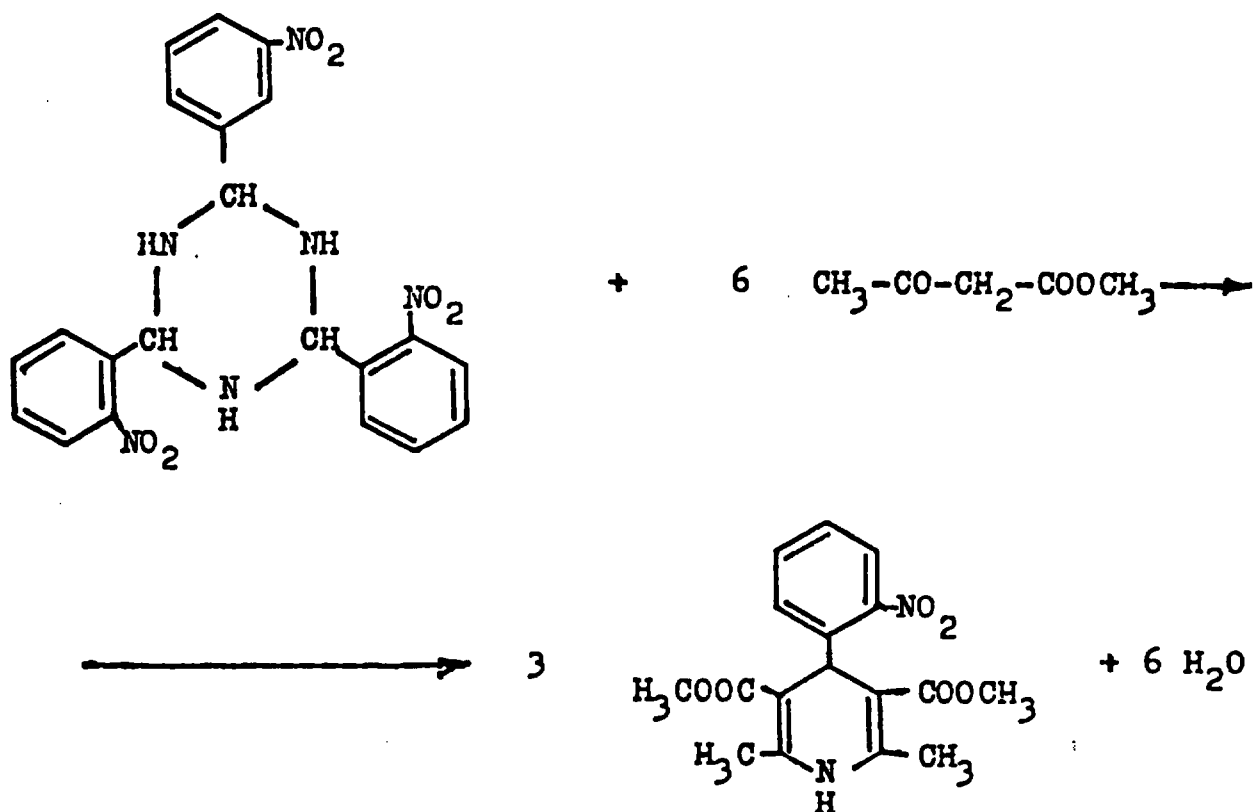
The reaction having been completed, nifedipine may be isolated from the reaction mixture by simple methods. One may preferably proceed by filtering the precipitated nifedipine, washing and drying the product. One may also proceed preferably by dissolving nifedipine in acetic acid

under warming and precipitating the product by adding water. The nifedipine thus obtained meets the requirements of Pharmacopoeia and no recrystallization is required.

According to a further form of realization of the process of the present invention, trimeric 2-nitrobenzalimine of the Formula IIC



is used as starting material. This compound exists in monomeric form too and is a compound of the general Formula II wherein n is 3 and R stands for hydrogen. The reaction is illustrated in reaction scheme H.



reaction scheme H

In the course of the reaction 1 mole of a compound of Formula IIC is reacted with 6 moles of methyl acetoacetate. The reaction is carried out in an inert solvent which does not interact with the starting materials under the reaction conditions used. As reaction medium a solvent or solvent mixture enumerated in connection with the use of the starting material of the Formula IIA may be used. One may work particularly advantageously in methanol as medium. The reaction temperature may vary between wide ranges. One may work generally at a temperature between -10 °C and

+120 °C, preferably at 5-100 °C, particularly preferably at 25-80 °C. The reaction time depends on the temperature and the reaction takes generally 12-60 hours, preferably 25-55 hours. The particularly preferred reaction time amounts to 36-50 hours.

One may also proceed by converting the compound of the Formula IIC to nifedipine without isolation in the same apparatus.

The nifedipine thus obtained may be isolated from the reaction mixture by simple methods. One may proceed by cooling the reaction mixture, separating the nifedipine by filtration or centrifuging, or dissolving nifedipine in warm acetic acid, precipitating by addition of water, washing and drying. The nifedipine thus obtained meets the requirements of Pharmacopoeia.

The starting materials of the general Formula II are new compounds, not described in prior art.

According to a further aspect of the present invention there is provided a process for the preparation of compounds of the general Formula II, which comprises
A) for the preparation of a compound of the general Formula II, wherein n is 1 and R stands for a group of the Formula (a), reacting 2-nitro-benzaldehyde with an ammonium salt of the general Formula $R_1\text{-COONH}_4$ (wherein R_1 is hydrogen or C_{1-4} alkyl) in methanol; or

- B) for the preparation of the compounds of the general Formula II, wherein n is 1 and R stands for the group of the Formula (b), reacting 2-nitro-benzaldehyde with an ammonium salt of the general Formula $R_1\text{-COONH}_4$ (wherein R_1 is as stated above) in isopropanol or with ammonium hydroxide in methanol; or
- C) for the preparation of the compounds of the general Formula II, wherein n is 3 and R stands for hydrogen, reacting 2-nitro-benzaldehyde with ammonia in an inert solvent;

and, if desired, isolating the compound of the general Formula II thus obtained from the reaction mixture.

According to the above process A) 2-nitro-benzaldehyde is reacted with an ammonium salt of the general Formula $R_1\text{-COONH}_4$ and methanol. R_1 may be a straight or branched chain alkyl group having 1-4 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl). As ammonium salt of the general Formula $R_1\text{-COONH}_4$ preferably ammonium acetate may be used. The methanol used as reactant may also be preferably applied in an excess whereby it acts as reaction medium, too. The reaction may be accomplished in a broad temperature range. One may work at a temperature between -10°C and $+80^\circ\text{C}$, preferably at $15\text{-}40^\circ\text{C}$. The reaction is accomplished within a relatively short time, it takes

1.5 - 7 hours. The desired compound of the Formula IIA is obtained with excellent yields in a reaction period of about 7 hours.

The reaction may also be carried out in any other inert solvent, which does not interact with the starting materials under the conditions used.

The compound of the Formula IIA thus obtained may be isolated from the reaction mixture by known methods. The product may be very simply isolated by cooling the reaction mixture, filtration or centrifuging and subsequent washing and drying. One may also proceed by converting the compound of the Formula IIA directly, without isolation, to nifedipine in the same apparatus.

According to process B) 2-nitro-benzaldehyde is reacted with an ammonium salt of the Formula $R_1\text{-COONH}_4$ or ammonium hydroxide. As ammonium salt of the general Formula $R_1\text{-COONH}_4$ preferably ammonium acetate may be used. The reaction of 2-nitro-benzaldehyde and ammonium acetate may be carried out in an inert solvent as medium. For this purpose any inert solvent may be used which does not interact with the starting materials under the reaction conditions used. Thus, preferably polar protic solvents (e.g. water; aliphatic alcohols having at least two carbon atoms, such as ethanol, isopropanol; amides, e.g. formamide, acetamide) or dipolar aprotic solvents (e.g. acetonitrile, acetone, dimethyl sulfoxide, nitrobenzene) may be used. The reaction can be preferably performed in isopropanol as medium.

One may also proceed by reacting 2-nitro-benzaldehyde with ammonium hydroxide. As reaction medium preferably methanol can be used.

The reaction of process B) may be carried out in a broad temperature range. The reaction may be preferably accomplished at a temperature between -10°C and $+80^{\circ}\text{C}$, particularly at $15-40^{\circ}\text{C}$. The reaction takes place within a relatively short period of time and takes generally 6-7 hours. The compound of the Formula IIB is obtained with excellent yields with a reaction time of about 7 hours.

The compound of the Formula IIB thus obtained may be isolated by known and simple methods, e.g. as described in connection with the isolation of the compound of the Formula IIA.

One may also proceed by converting the compound of the Formula IIB to nifedipine without isolation in the same apparatus.

According to process C) 2-nitro-benzaldehyde is reacted in an inert solvent with ammonia. One may proceed preferably by reacting a solution of 2-nitro-benzaldehyde and methanol with a methanolic ammonium solution. The reaction may, however, also be accomplished in any inert solvent which does not interact with the starting materials under the conditions used. Thus the solvents enumerated in connection with the use of the starting material of the Formula IIB (process B) may be used.

The reaction may be performed in a broad temperature interval. One may work at a temperature between -10°C and $+80^{\circ}\text{C}$, preferably at $15-40^{\circ}\text{C}$. The reaction takes generally 5-25 hours.

The compound of the Formula IIC may be isolated by simple methods, e.g. as disclosed in connection with process A). One may also proceed by converting the compound of the Formula IIC to nifedipine without isolation, in the same apparatus.

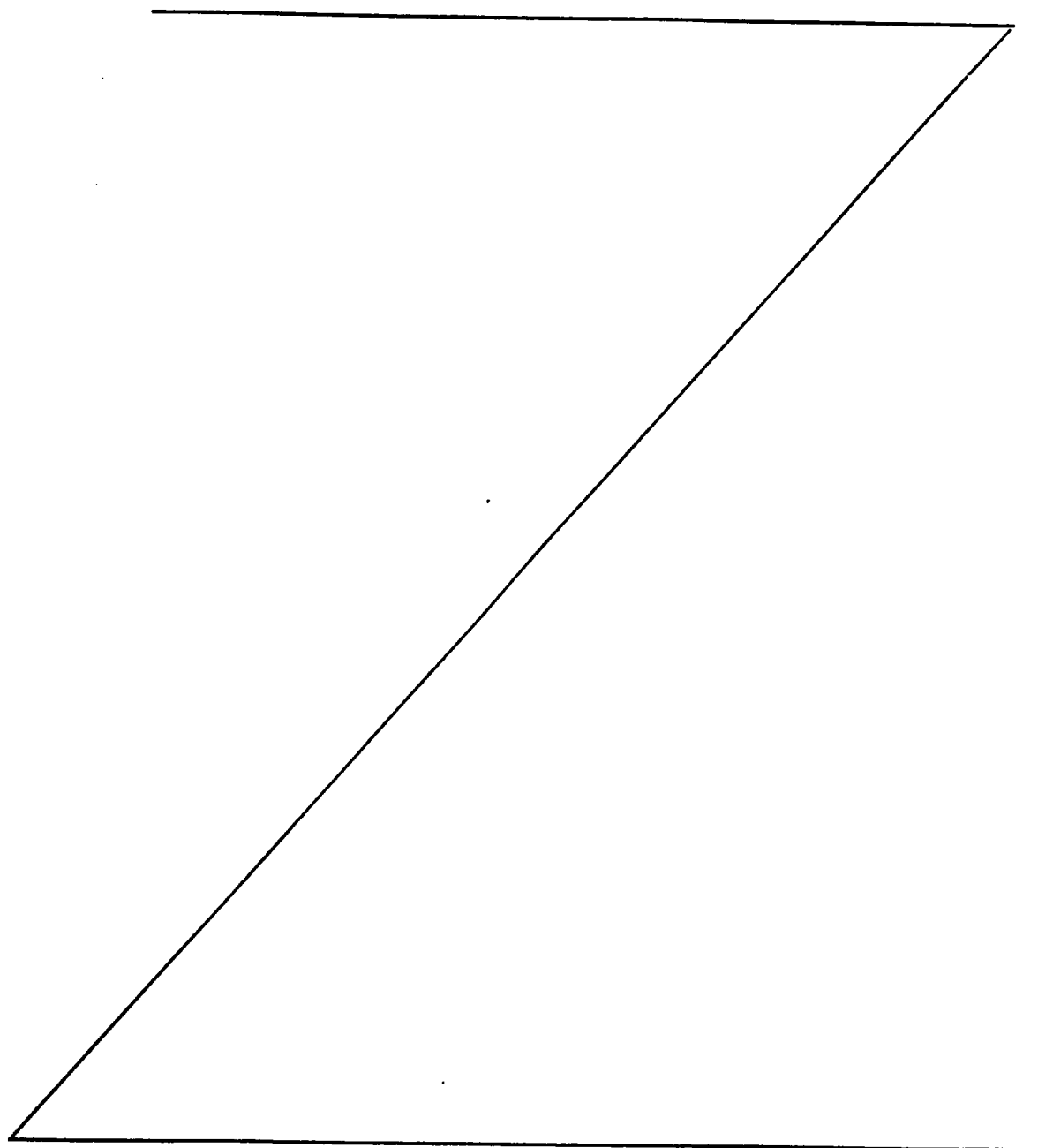
It has been found that the compounds of the general Formula II may be prepared with excellent yields and in such purity that they can be converted directly without recrystallization to highly pure nifedipine which meets the requirements and quality standards of Pharmacopoeia.

It has been found in a surprising manner that if 2-nitro-benzaldehyde is reacted in the same organic solvent - in methanol -, the structure of the compound of the general Formula II formed depends on the character of the ammonia-source used. The relationship between the ammonia source and the structure of the compound of the general Formula II obtained is shown in Table I.

Table I

Ammonia source	Structure of product	Yield
Ammonium acetate	IIA	98%
Ammonium hydroxide	IIB	92%
Anhydrous ammonia	IIC	75%

The starting materials used (2-nitro-benzaldehyde, ammonium salts of the general Formula $R_1\text{-COONH}_4$, ammonium hydroxide, methanol) are commercially available products.



The process is highly suitable for industrial scale manufacture.

The advantages of the present invention may be summarized as follows:

In course of those known methods which are not Hantzsch-type reactions (i.e. if in addition to the β -keto-carboxylic acid esters more expensive enamino carboxylic acid esters are also used), the said expensive enamino carboxylic acid ester component constitutes exactly one half of the total amount of the ester starting materials used. Thus, according to the process disclosed in Hungarian patent No. 192,546 1 mole of methyl-3-amino-crotonate is used, related to 1 mole of methyl acetoacetate.

On the other hand, according to the process of the present invention enamino carboxylic acid esters (methyl-3-amino-crotonate) are used either not at all (in case of the starting material of the Formula IIC) or the amount thereof is only one-sixth of that of the total ester components used (in case of the starting material of the Formula IIB) or but one-fourth of that of the total ester-components used (in case of the starting material of the Formula IIA).

The reaction time is shorter than in case of the process disclosed in Hungarian patent No. 192,546. In the first step of the said known synthesis the formation of the ylidine derivative requires 16 hours, while the starting

materials of the process of the present invention are formed practically quantitatively and more rapidly, within about 7 hours (see particularly reaction schemes G and F). The conversion of the compound of the general Formula II to nifedipine requires approximately the same time as the second step of the process set forth in Hungarian patent No. 192,546 (conversion of the ylidene intermediate to nifedipine).

It is surprising and unforeseeable that despite of the complicated reaction-mechanism the new synthesis route according to the present invention provides with such excellent yields highly pure nifedipine being suitable for pharmaceutical purposes without further crystallization and purification steps.

Further details of the present invention are to be found in the Examples without limiting the scope of protection.

to the said Examples.

Example 1

To a suspension of 315.3 g (1 mole) of 1-methoxy-1-(2'-nitro-phenyl)-N-(2'-nitro-phenyl)-methylene-methane-amine and 1 litre of methanol 348.3 g (3 mole) of methyl acetoacetate and thereafter 115.1 g (1 mole) of methyl-3-amino-crotonate are added. The reaction mixture is heated to boiling for 36 hours whereupon it is cooled. The precipitated product is filtered, sucked dry, dissolved in acetic acid under warming and the product is precipitated with water. The product is filtered, washed with methanol and dried. Thus 572 g of nifedipine are obtained, yield 82.6 %, m. p.: 172-174 °C.

The product thus obtained is dissolved in chloroform and subjected to thin layer chromatography on HPTLC Kieselgel 60 plates in a bath containing diisopropyl ether for 2 hours. The chromatogram shows no additional (strange) spots.

The starting material can be prepared as follows:

151.1 g (1 mole) of 2-nitro-benzaldehyde are dissolved in 250 ml methanol whereupon 80 g (1.04 mole) of ammonium acetate are added under stirring. The reaction mixture is stirred at 40 °C for 15 minutes and thereafter at room temperature for 7 hours. The reaction mixture is cooled, the precipitated product filtered, washed with water and dried. Thus 154.5 g of 1-methoxy-1-(2'-nitro-phenyl)-N-(2'-nitro-phenyl)-methylene-methaneamine are obtained, yield 98%, m. p.: 117-118 °C.

Example 2

31.5 g (0.1 mole) of 1-methoxy-1-(2'-nitro-phenyl)-N-(2'-nitro-phenyl)-methylene-methane-amine are suspended in 100 ml of methanol. 46.45 g (0.4 mole) of methyl acetoacetate are added, whereupon ammonium hydroxide comprising an equivalent amount of ammonia is added dropwise. The reaction mixture is heated to boiling for 14 hours, then cooled. The precipitated product is filtered, washed with cold methanol and water and dried. Thus 49.2 g of nifedipine are obtained, yield 71 %, m. p.: 170-172 °C.

Example 3

To a mixture of 31.5 g (0.1 mole) of 1-methoxy-1-(2'-nitro-phenyl)-N-(2'-nitro-phenyl)-methylene-methane-amine and 68 ml of methanol first 46.45 g (0.4 mole) of methyl acetoacetate and subsequently a methanolic ammonia solution comprising 1.7 g (0.1 mole) of ammonia are added. The reaction mixture is heated to boiling for 36 hours, then cooled. The precipitated product is filtered, sucked dry, dissolved in acetic acid under warming, precipitated with water, filtered, washed with water and dried. Thus 51.2 g of nifedipine are obtained, yield 74%, m. p.: 171-175 °C.

Example 4

To a suspension of 433.4 g (1 mole) of 1-(2'-nitro-phenyl)-N,N'-bis-(2'-nitro-phenyl)-methylene-methanediamine and 1.5 litre of methanol 580.6 g (5 moles) of methyl acetoacetate and 115.1 g (1 mole) of methyl-3-amino-crotonate

are added under stirring. The reaction mixture is heated to boiling for 46 hours, then cooled. The precipitated product is filtered, sucked dry, dissolved in acetic acid under warming, precipitated with water, filtered and dried. Thus 810.2 g of nifedipine are obtained, yield 78.5%, m. p.: 173-174 °C.

The starting material can be prepared as follows:

a) To 500 ml of isopropanol first 151.1 g (1 mole) of 2-nitro-benzaldehyde and subsequently 80 g (1.04 mole) of ammonium acetate are added. The reaction mixture is stirred at 40 °C for 15 minutes and then at room temperature for 7 hours. The reaction mixture is cooled, the precipitated product is filtered, washed with water and dried. Thus 141.6 g of 1-(2'-nitro-phenyl)-N,N'-bis-(2'-nitro-phenyl)-methylene-methane-diamine are obtained, yield 98%, m. p.: 124-127 °C.

b) To a solution of 15.1 g (0.1 mole) of 2-nitro-benzaldehyde and 40 ml of methanol under stirring an ammonium hydroxide solution containing 1.7 g (0.1 mole) of ammonia is added. The solution is stirred at room temperature for 25 hours, then cooled, the precipitated product is filtered, washed with methanol and dried. Thus 13.3 g of 1-(2'-nitro-phenyl)-N,N'-bis-(2'-nitro-phenyl)-methylene-methane-diamine are obtained, yield 92%, m. p.: 123-126 °C.

Example 5

To a suspension of 43.3 g (0.1 mole) of 1-(2'-nitro-phenyl)-N,N'-bis-(2'-nitro-phenyl)-methylene-methane-

-diamine and 140 ml of methanol 69.7 g (0.6 mole) of methyl acetoacetate and 8.7 ml of a 25% ammonium hydroxide solution are added under stirring. The reaction mixture is stirred at 45 °C for 42 hours, then cooled. The precipitated product is filtered, dissolved in acetic acid under warming, precipitated with water and dried. Thus 79.0 g of nifedipine are obtained, yield 76%, m. p.: 172-173 °C.

Example 6

9 g (0.02 mole) of trimeric 2-nitro-benzaldehyde-imine and 14 g (0.12 mole) of methyl acetoacetate are dissolved in 25 ml of methanol. The reaction mixture is stirred under boiling for 25 hours, then cooled. The precipitated crystals are dissolved in acetic acid under warming, precipitated with water, cooled, filtered, washed with water and methanol and dried. Thus 12.4 g of nifedipine are obtained, yield 60%, m. p.: 170-173 °C.

The starting material can be prepared as follows:

To a solution of 15.1 g (0.1 mole) of 2-nitro-benzaldehyde and 40 ml of methanol a methanolic solution of 1.7 g (0.1 mole) of ammonia is added dropwise under stirring. The reaction mixture is stirred at room temperature for 20 hours, then cooled, the precipitated product is filtered, washed with methanol and dried. Thus 11.3 g of trimeric 2-nitro-benzaldehyde-imine are obtained, yield 75.3 %, m. p.: 117-119 °C.

Reference should be made to divisional patent application

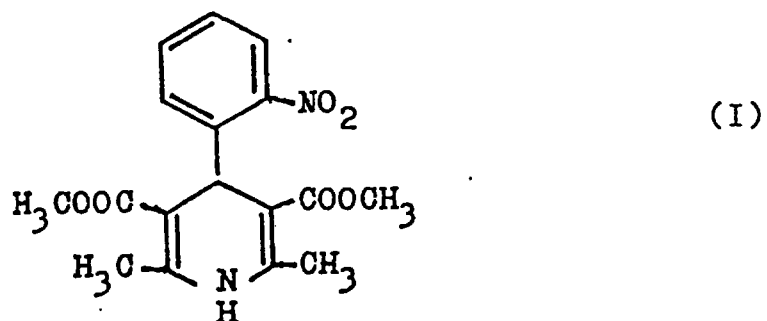
43 9105770.0 (Publication No. 224 3605) which discloses and claims an alternative process for preparing nifedipine.



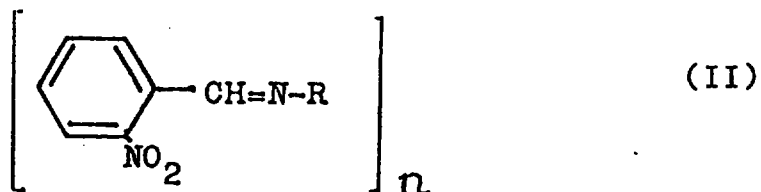
- 27 -

CLAIMS

1. Process for the preparation of dimethyl-1,4-dihydro-2,6-dimethyl-4-(2'-nitro-phenyl)-pyridine-3,5-dicarboxylate of the Formula I,



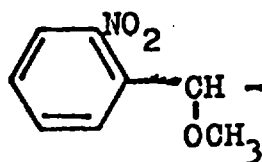
which comprises reacting a compound of the general Formula II



(wherein n is 1 or 3; if n is 1, then R stands for a group of the Formula (a))

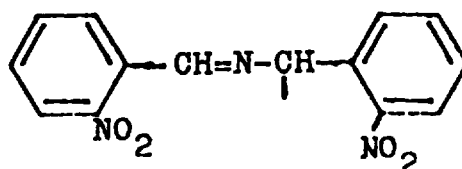


- 28 -



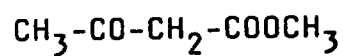
(a)

or (b)



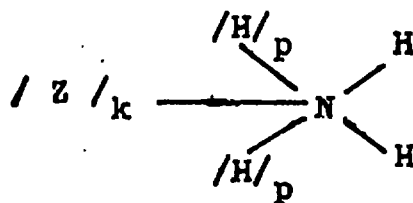
(b)

and if n is 3, then R represents hydrogen) with methyl acetoacetate of the Formula III



(III)

and optionally with an amino compound of the general Formula IV



(IV)

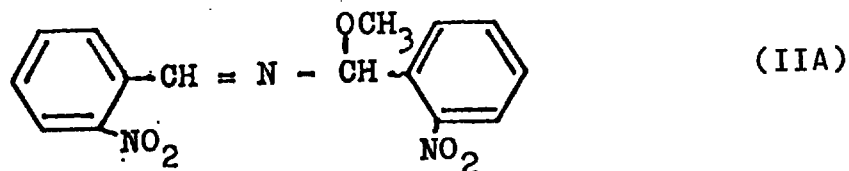


(wherein Z is a group of the Formula (c),



k is 1 and both symbols p are 0; or Z stands for a C₁₋₅ straight or branched chain alkanoyloxy group or a carbonate, hydrocarbonate or hydroxy anion, k is 1 and both symbols p are 1; or k is 0, one of the symbols p is 0 and the other is 1) in an inert solvent.

2. Process according to Claim 1, which comprises using as starting material a compound of the general Formula II, wherein R is a group of the Formula (a) and n is 1, i.e. the 1-methoxy-1-(2'-nitro-phenyl)-N-(2'-nitro-phenyl)-methylene-methaneamine of the Formula IIA.





- 30 -

3. Process according to Claim 2, which comprises reacting 1 mole of the compound of the Formula IIA with 3 moles of methyl acetoacetate and 1 mole of a compound of the general Formula IV, wherein Z is a group of the Formula (c), $k = 1$ and both symbols p are 0, i.e. with methyl-3-amino-crotonate.

4. Process according to Claim 3, which comprises forming the methyl-3-amino-crotonate of the Formula IV in situ by reacting methyl acetoacetate with ammonia.

5. Process according to Claim 4, which comprises using aqueous ammonium hydroxide or methanolic ammonia.

6. Process according to Claim 2, which comprises reacting a compound of the Formula IIA without isolation with methyl acetoacetate and methyl-3-amino-crotonate.

7. Process according to any of Claims 2-6, which comprises using methanol as inert solvent.

8. Process according to any of Claims 2-7, which comprises carrying out the reaction at a temperature between -10°C and $+120^{\circ}\text{C}$.

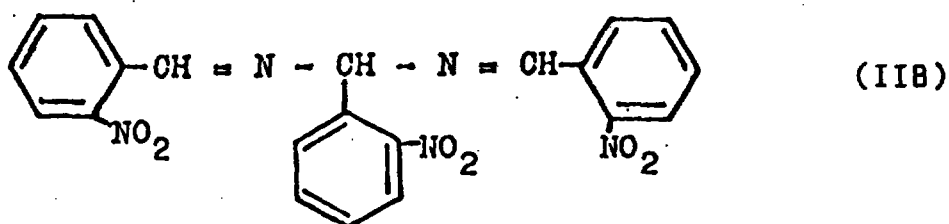
9. Process according to Claim 8, which comprises carrying out the reaction at a temperature of $5-100^{\circ}\text{C}$.

10. Process according to claim 9, wherein the said temperature is in the range of from 25 to 80°C .



- 31 -

11. Process according to Claim 1, which comprises using as starting material a compound of the general Formula II, wherein R is a group of the Formula (b) and n is 1, i.e. the 1-(2'-nitro-phenyl)-N,N'-bis-(2'-nitro-phenyl)-methylene-methane-diamine of the Formula IIB.



12. Process according to Claim 11, which comprises reacting 1 mole of the compound of the general Formula IIB with 5 moles of methyl acetoacetate and 1 mole of methyl-3-amino-crotonate (compound of the general Formula IV, wherein Z is a group of the Formula (c), k is 1 and both symbols p are 0).

13. Process according to Claim 12, which comprises forming methyl-3-amino-crotonate in situ by reacting methyl-acetoacetate with ammonia.

14. Process according to Claim 13, which comprises using aqueous ammonium hydroxide or methanolic ammonia.

15. Process according to Claim 11, which comprises reacting the compound of the Formula IIB without isolation with methyl acetoacetate and methyl-3-amino-crotonate.



32.

16. Process according to any of Claims 11 to 15, which comprises carrying out the reaction in a lower aliphatic alcohol.

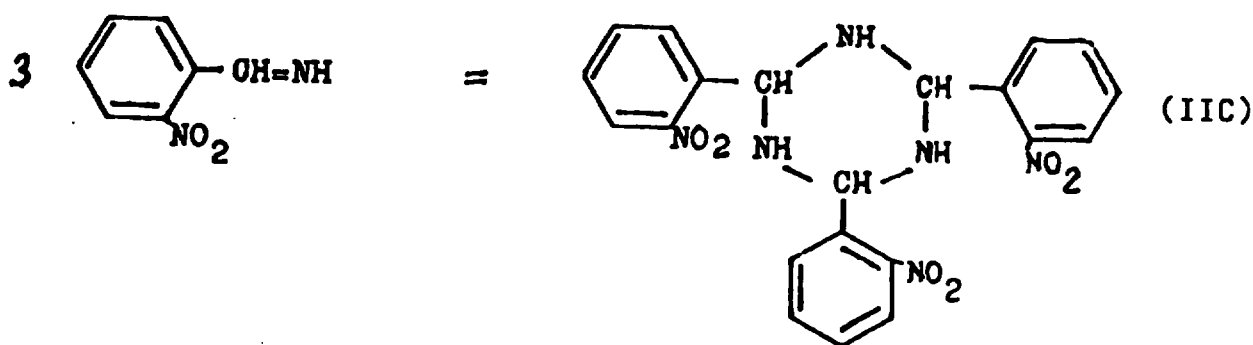
17. Process according to claim 16, wherein the alcohol is methanol or iso-propanol.

18. Process according to any of Claims 11-17, which comprises carrying out the reaction at a temperature between -10°C and 120°C .

19. Process according to Claim 18, which comprises carrying out the reaction at $5-100^{\circ}\text{C}$.

20. A process according to Claim 19, wherein the reaction is conducted at a temperature within the range of from $25-80^{\circ}\text{C}$.

21. Process according to Claim 1, which comprises using as starting material trimeric 2-nitro-benzaldimine of the Formula IIC,



i.e. a compound of the general Formula II, wherein R is hydrogen and n is 3.



22. Process according to Claim 21, which comprises reacting 1 mole of the compound of Formula IIC with 6 moles of methyl acetoacetate.
23. Process according to Claim 22, which comprises using methanol as inert solvent.
24. Process according to any of Claims 20-23, which comprises reacting the compound of the Formula IIC without isolation with methyl acetoacetate.
25. Process according to any of Claims 20-24, which comprises carrying out the reaction at a temperature between -10°C and $+120^{\circ}\text{C}$.
26. process according to Claim 25, which comprises carrying out the reaction at $5-100^{\circ}\text{C}$.
27. Process as claimed in claim 26, wherein the reaction is carried out at a temperature of 25 to 80°C .
28. Compounds of the general Formula II (wherein n is 1 or 3, and if n is 1 then R stands for a group of the Formula (a) and (b) and if n is 3 then R stands for hydrogen).
29. Process for the preparation of compounds of the general Formula II (wherein R and n are as stated in Claim 28), which comprises
- A) for the preparation of a compound of the general Formula II, wherein n is 1 and R stands for a group of the Formula (a), reacting 2-nitro-benzaldehyde with an ammonium salt of the general Formula $R_1\text{-COONH}_4$ (wherein R_1 is hydrogen or C_{1-4} alkyl) in methanol; or
- B) for the preparation of the compounds of the general Formula II, wherein n is 1 and R stands for the group



of the Formula (b), reacting 2-nitro-benzaldehyde with an ammonium salt of the general Formula $R_1\text{-COONH}_4$ (wherein R_1 is as stated above) in isopropanol or with ammonium hydroxide in methanol;

or

C) for the preparation of the compounds of the general Formula II, wherein n is 3 and R stands for hydrogen,

reacting 2-nitro-benzaldehyde with ammonia in an inert solvent;

and, if desired, isolating the compound of the general Formula II thus obtained from the reaction mixture.

30. A process of making Nifedipine substantially as hereinbefore described in any one of Examples 1 to 6.

31. Nifedipine prepared by a process as claimed in any one of claims 1 to 27 or 30.

32. A process as claimed in claim 29 which is substantially as hereinbefore described in Example 1, 4 or 6.
