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(71) Applicant *(for all designated States except US)*: **EGIS GYÓGYSZERGYÁR RT.** [HU/HU]; Keresztúri út 30-38, H-1106 Budapest (HU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MOLNÁRNÉ SAMU, Erika** [HU/HU]; Tungsram u. 55/a, H-1046 Budapest (HU). **SIMIG, Gyula** [HU/HU]; Hollósy S. u. 25., H-1126 Budapest (HU).

(74) Agent: **ADVOPATENT OFFICE OF PATENT AND TRADEMARK ATTORNEYS**; P.O. Box 11, H-1251 Budapest (HU).

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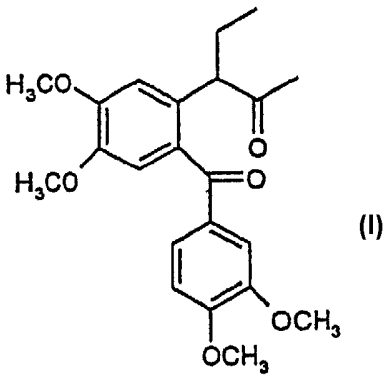
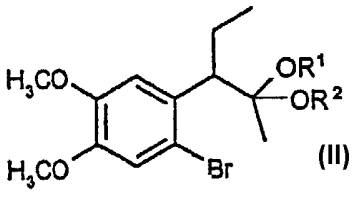
(54) **Title:** PROCESS FOR THE PREPARATION OF 3-[2-(3,4-DIMETHOXY-BENZOYL)-4,5-DIMETHOXY-PHENYL]-PENTAN-2-ONE



(I)



(II)

(57) **Abstract:** The invention relates to a process for the preparation of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula (I) starting from a compound of the general Formula (II) (wherein R^1 and R^2 each stands for C_{1-4}-alkyl or together form C_{2-6}-alkylene).

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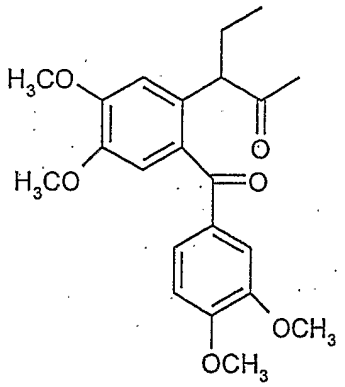
Process for the preparation of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one

FIELD OF THE INVENTION

The invention relates to a new process for the preparation of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula



I

TECHNICAL BACKGROUND OF THE INVENTION

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula I is an intermediate useful in the preparation of the anxiolytic active ingredient 1-(3,4-dimethoxy-phenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine having the International Non-Proprietory Name (INN) tofisopam.

According to HU 158,091 the compound of the Formula I is prepared from diisohomoeugenol by oxidation with chrome(VI)oxide; only low yields are obtained.

According to HU 194,529 1-(3,4-dimethoxy-phenyl)-3-methyl-4-ethyl-6,7-dimethoxy-isochromane is oxidized with chrome(VI)oxide into the corresponding benzopyrilium salt which is then converted into the title compound of the Formula I by alkaline-aqueous decomposition.

Both known procedures have the common disadvantage that in the oxidation reaction highly toxical chromium salts detrimental to the environment are formed. The storing, neutralization and recycling of said chromium salts represent a serious problem for the protection of the environment.

HU 187,161 aims the elimination of the above drawbacks of the known procedures. According to HU 187,161 the compound of the Formula I is prepared with the aid of a chromium-free process by reacting 3-(3,4-dimethoxy-phenyl)-pentan-2-one with 3,4-dimethoxy-benzoyl chloride in the presence of aluminium(III)chloride and decomposing the benzopyrilium salt formed in alkaline medium.

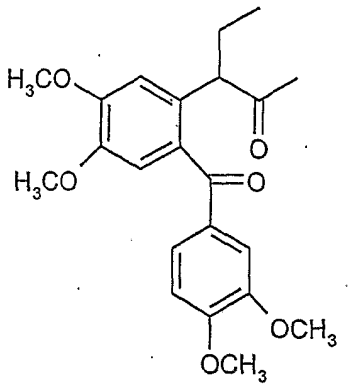
The disadvantage of the above process is that 3,4-dimethoxy-benzoyl chloride used as starting material is very susceptible to decomposition and the Friedel-Crafts product formed in the reaction is strongly contaminated, difficult to handle and the purification thereof encounters serious problems.

It is the object of the present invention to provide a chromium-free process for the preparation of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula I which eliminates the above drawbacks of the known procedures, is friendly to the environment and gives the desired compound of the Formula I with better yields and higher purity than the known methods.

The above object is solved by the process of the present invention.

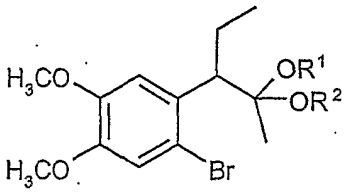
SUMMARY OF THE INVENTION

According to the present invention there is provided a process for the preparation of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula



I

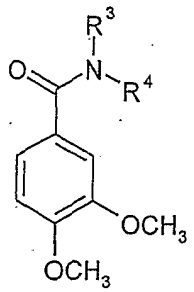
starting from a compound of the general Formula



II

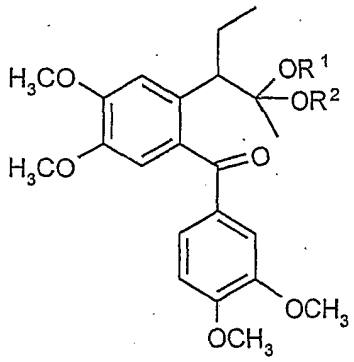
(wherein R^1 and R^2 each stands for C_{1-4}-alkyl or together form C_{2-6}-alkylene) which comprises

a) replacing the bromine atom in a compound of the general Formula II by an alkali or magnesium atom; reacting the alkali or magnesium compound thus obtained with an approximately equimolar amount of an acid amide of the general Formula



IIIa

(wherein R^3 and R^4 are C_{1-4}-alkyl) and hydrolysing the compound of the general Formula

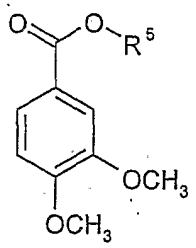


IV

thus obtained (wherein R^1 and R^2 are as stated above);

or

b) replacing the bromine atom in a compound of the general Formula II by an alkali or magnesium atom; reacting the alkali or magnesium compound thus obtained with an approximately equimolar amount of an ester of the general Formula



IIIb

(wherein R^5 is C_{1-4}-alkyl) and hydrolysing the compound of the general Formula IV thus obtained.

DETAILED DESCRIPTION OF THE INVENTION

The terms used in the present patent specification are to be interpreted as follows:

The term "C_{1-4}-alkyl" relates to straight or branched chain alkyl groups containing 1-4 carbon atoms (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl etc.).

The term "C_{2-6}-alkylene" relates to straight or branched chain alkylene groups containing 2-6 carbon atoms (e.g. ethylene, trimethylene etc.).

The synthesis and characterization of the 3-(2-bromo-4,5-dimethoxy-phenyl)-pentan-2-one ketals of the general Formula II is disclosed in co-pending Hungarian patent applications Ser. Nos. 01/05326 and 01/05327 filed on December 13, 2001.

According to a generally used process diaryl ketones are prepared from aryl metal compounds by reacting said aryl metal compound with an aromatic nitrile and hydrolysing the imine formed. However, said general process is not applicable for the preparation of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one because on the basis of prior art in the place of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-

pentan-2-one of the Formula I rather the formation of an isoquinoline derivative could be expected [Khim. Geterosikl. Soedin, (1988), (**1**), 134-5].

In the reaction of aryl metal compounds with the generally used Weinreb amides (N-methyl-N-methoxy-amide) the formation of a compound of the general Formula IV can be expected. However, the use of said reactant makes the synthesis very expensive and uneconomical [Bioorganic and Medicinal Chemistry Letters (1993), 1991-2].

The synthesis of the compounds of the general Formula IV by reacting aryl metal compounds with acid chlorides is not feasible either because acid chlorides are susceptible to easy decomposition and are generally contaminated with inorganic acids which considerably decreases the yield and increases the rate of side reactions.

It has been surprisingly found that the compounds of the general Formula IV can be readily prepared with the aid of amides of the general Formula IIIa and esters of the general Formula IIIb, whereby said compounds of the general Formulae IIIa and IIIb have not been hitherto generally used in metal organic chemistry for the formation of the ketone group.

The present invention is based on the recognition that the desired 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula I can be readily prepared by reacting an alkali or magnesium compound, formed from a 3-(2-bromo-4,5-dimethoxy-phenyl)-pentan-2-one ketal of the general Formula II, with a compound of the general Formula IIIa or IIIb and thereafter subjecting the 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one ketal of the general Formula IV thus obtained to hydrolysis.

According to variant a) of the process of the present invention the bromine atom in a compound of the general Formula II is replaced by an alkali or magnesium atom, whereupon the alkali or magnesium compound thus obtained is reacted with a 3,4-dimethoxy-benzoic acid-N,N-dialkyl-amide of the general Formula IIIa; said compound can be prepared from 3,4-dimethoxy-benzoic acid in a known manner.

The bromine atom in the compound of the general Formula II is replaced by an alkali (e.g. sodium, potassium or lithium) atom or by a magnesium atom with the aid of a Grignard-reaction. One may proceed preferably by carrying out a bromine → lithium exchange reaction. This may be performed by reacting the compound of the general Formula II with an alkyl lithium (preferably n-butyl lithium or n-hexyl lithium). The alkyl

lithium compound is preferably used in a solution formed with an alkane, preferably n-hexane. The replacement of the bromine atom by lithium can be carried out at a temperature between -78°C and -10°C - preferably at about -10°C - in anhydrous tetrahydrofurane. The alkali or magnesium compound formed - advantageously the lithium compound - is then reacted with an approximately equimolar amount (preferably 1.0-1.2 molar amount) of an amide of the general Formula IIIa. One may proceed preferably by reacting the lithium compound with the compound of the general Formula IIIa without isolation in the reaction mixture obtained during the preparation of said lithium compound. The reaction can be carried out at a temperature below 0°C, preferably at about -20°C. The compound of the general Formula IV thus formed can be isolated from the reaction mixture.

According to variant b) of the process of the present invention the bromine atom in the compound of the general Formula II is replaced by an alkali or magnesium atom, whereupon the alkali or magnesium compound thus obtained is reacted with an alkyl-3,4-dimethoxy-benzoate of the general Formula IIIb to yield a compound of the general Formula IV.

The compound of the general Formula IV obtained in reaction variant a) or b) can be optionally isolated and purified by

recrystallization. The isolated ketal of the general Formula IV is hydrolysed into the corresponding ketone of the Formula I with a mineral acid in a manner known per se.

Hydrolysis of the ketal of the general Formula IV can be preferably carried out by using a mineral acid, particularly diluted sulfuric acid or diluted hydrochloric acid, most advantageously diluted sulfuric acid. The reaction can be performed in a two-phase reaction mixture, preferably at 20-40°C. One phase of said two-phase system consists of a water non-miscible organic solvent (preferably an aromatic hydrocarbon, e.g. benzene, toluene or xylene; or an aliphatic halogenated hydrocarbon, e.g. dichloro methane) and the other phase consists of the aqueous acidic solution. The reaction can be promoted by adding kieselgel, used in a 2-5-fold amount related to the compound of the general Formula IV.

The compound of the Formula I can also be prepared directly, i.e. without isolating the intermediate of the general Formula IV. One may proceed by treating the in situ formed compound of the general Formula IV with an acid. In this case it is only the ketone of the Formula I which is isolated and purified.

The compound of the Formula I thus obtained can be purified, if desired, by recrystallization from a suitable solvent. As

recrystallization solvent preferably C_{1-4} straight or branched chain aliphatic alcohols can be used. The compound of the Formula I thus obtained has a purity above 98 % and is excellently suitable for the preparation of the pharmaceutically active tofisopam end-product.

The advantage of the process of the present invention is that it enables the preparation of the intermediate 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula I useful in the manufacture of tofisopam with high yields and by using environment-friendly compounds.

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

Example 1

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one-ethylene ketal (IV)

17.26 g (0.05 mole) of 3-(2-bromo-4,5-dimethoxy-phenyl)-pentan-2-one-ethylene ketal (II) is dissolved in 173 ml of anhydrous tetrahydrofurane, whereupon the solution is cooled to -78°C under external cooling with dry ice. A 2.5 molar solution of butyl lithium (0.06 mole) in 24 ml of hexane is added under stirring within 45 minutes. The addition having been completed the mixture is stirred for a further period of 2 hours at -78°C, whereupon 10.46 g (0.05 mole) of 3,4-dimethoxy-benzoic acid-N,N-dimethyl-amide (IIIa) is added. After a post-reaction of 20 minutes the temperature is slowly raised to room temperature. After a reaction period of 2 hours the mixture is admixed with a saturated ammonium chloride solution and extracted with ethyl acetate. The ethyl acetate phase is washed with a saturated sodium chloride solution, dried over magnesium sulfate, filtered and the filtrate is evaporated. The crude product is purified by recrystallization. Thus 9.0 g of the title compound is obtained.
Yield 42 %. M.p.: 165-166°C.
IR (KBr): 1638 cm^{-1}.
HNMR (DMSO-d_6, TMS, i400): 7.35 (d, J=1.9 Hz, 1H), 7.20 (dd, J=1.9, 8.4 Hz, 1H), 7.08 (s, 1H), 7.00 (d, J=8.5 Hz, 1H), 6.75 (s, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.65 (s,

3H), 3.80-3.50 (m, 4H), 3.02 (dd, J=3.7, 11.2 Hz, 1H), 1.76 (m, 1H), 1.62 (m, 1H), 1.00 (s, 3H), 0.56 (t, J=7.4 Hz, 3H) ppm. CNMR (DMSO-d_6, TMS, i400): 197.1, 154.6, 151.1, 149.9, 147.4, 134.8, 134.2, 132.1, 127.2, 113.1, 112.9, 112.7, 112.4, 112.0, 66.3, 65.5, 57.3, 57.0, 56.9, 50.8, 24.6, 24.0, 13.8 ppm.

Example 2

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one-ethylene ketal (IV)

One proceeds as described in Example 1 except that the reaction is carried out at -20°C. Thus 6.9 g of the title compound is obtained. Yield 32 %. M.p.: 164-166°C.

Example 3

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one-ethylene ketal (IV)

One proceeds as described in Example 1 except that the 2.5 molar hexane solution of butyl lithium is replaced by a 2.5 molar hexane solution of hexyl lithium; the reaction is carried out at -78°C. Thus 8.6 g of the title compound is obtained. Yield 40 %.

Example 4

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one-ethylene ketal (IV)

One proceeds as described in Example 1 except that the 2.5 molar hexane solution of butyl lithium is replaced by a 2.5 molar hexane solution of hexyl lithium and the reaction is carried out at -20°C. Thus 6.2 g of the title compound is obtained. Yield 29 %.

Example 5

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one-ethylene ketal (IV)

One proceeds as described in Example 1 except that in the place of 3,4-dimethoxy-benzoic acid-N,N-dimethyl amide (IIIa) 9.8 g (0.05 mole) of methyl-3,4-dimethoxy-benzoate is used. Thus 6.9 g of the title compound is obtained. Yield 32 %. M.p.: 164-166°C.

Example 6

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one (I)

To a mixture of 25.0 g of kieselgel, 100 ml of dichloro methane and 2.5 ml of a 15 % weight/volume sulfuric acid solution

6.46 g (0.015 mole) of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one-ethylene ketal is added. The reaction mixture is stirred at room temperature for 2 hours, whereupon the kieselgel is filtered off and washed with dichloro methane. The dichloro methane solution is dried over magnesium sulfate and evaporated. The crude product is recrystallized. Thus 5.4 g of the title compound is obtained. Yield 93 %. M.p.: 158-159°C.

Example 7

3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one (I)

One proceeds as described in Example 6 except that the compound of the general Formula IV is not purified, but for the acidic hydrolysis the crude product obtained by the process according to any of Examples 1-5 is used. It is only the compound of the Formula I which is purified by recrystallization. Thus 6.2-9.6 g of the title compound is obtained. Yield 32-50 % (related to the compound of the general Formula II).

Preparation of the starting materials

Example 8

3-(2-bromo-4,5-dimethoxy-phenyl)-pentan-2-one-ethylene ketal (II)

34.3 g (0.11 mole) of 3-(2-bromo-4,5-dimethoxy-phenyl)-pentan-2-one is dissolved in 250 ml of toluene. To the solution 11.2 ml (0.20 mole) of ethylene glycol and 1.5 g of p-toluene-sulfonic acid is added. The apparatus is equipped with a water separator and the reaction mixture is stirred under heating to boiling until the theoretical amount of water is separated. The water is removed, the toluene solution is washed acid free with a sodium carbonate solution, dried over magnesium sulfate, filtered and evaporated in vacuo. Thus 38 g of a crude product is obtained which is distilled off at 149-152°C/12 Pa. Thus 36.2 g of the chromatographically uniform title product is obtained. Yield 92 %. Mp.: 44-45°C.

IR (film): 2962 (CH_3O), 591 (C-Br) cm^{-1}.

HNMR (DMSO-d_6, TMS, i400): 7.09 (s, 1H), 7.01 (s, 1H), 3.94-3.77 (m, 4H), 3.72 (s, 3H), 3.71 (s, 3H), 3.27 (dd, J=3.4, 11.5 Hz, 1H), 1.92-1.85 (m, 1H), 1.64-1.56 (m, 1H), 1.07 (s, 3H), 0.63 (t, J=7.4 Hz, 3H) ppm.

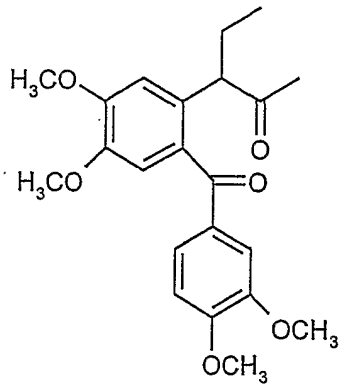
CNMR (DMSO-d_6, TMS, i400): 148.3, 148.1, 132.1, 116.6, 115.1, 111.9, 110.8, 65.2, 64.4, 55.8, 55.7, 53.3, 23.3, 22.8, 11.9 ppm.

Elemental analysis:

calc.:	C 52.19%, H 6.13%, Br 23.14%
found:	C 52.36%, H 6.12%, Br 23.23%

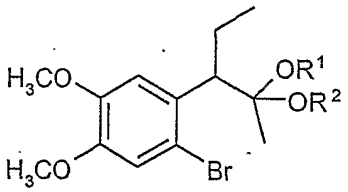
What we claim is,

1. Process for the preparation of 3-[2-(3,4-dimethoxy-benzoyl)-4,5-dimethoxy-phenyl]-pentan-2-one of the Formula



I

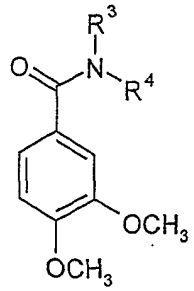
starting from a compound of the general Formula



II

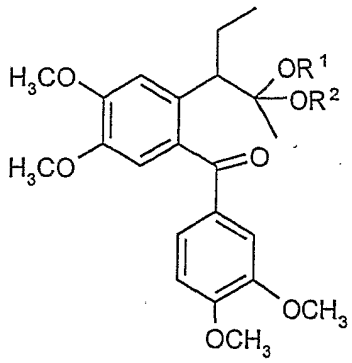
(wherein R^1 and R^2 each stands for C_{1-4}-alkyl or together form C_{2-6}-alkylene) which comprises

a) replacing the bromine atom in a compound of the general Formula II by an alkali or magnesium atom; reacting the alkali or magnesium compound thus obtained with an approximately equimolar amount of an acid amide of the general Formula



IIIa

(wherein R^3 and R^4 are C_{1-4}-alkyl) and hydrolysing the compound of the general Formula

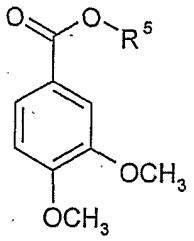


IV

thus obtained (wherein R^1 and R^2 are as stated above);

or

b) replacing the bromine atom in a compound of the general Formula II by an alkali or magnesium atom; reacting the alkali or magnesium compound thus obtained with an approximately equimolar amount of an ester of the general Formula



IIIb

(wherein R^5 is C_{1-4}-alkyl) and hydrolysing the compound of the general Formula IV thus obtained.

2. Process according to Claim 1 which comprises using as starting material a compound of the general Formula II wherein R^1 and R^2 each stands for methyl or ethyl, or R^1 and R^2 together form ethylene.

3. Process according to Claim 1 or 2 which comprises using a compound of the general Formula IIIa wherein R^3 and R^4 stand for methyl.

4. Process according to Claim 1 or 2 which comprises using a compound of the general Formula IIIb wherein R^5 is methyl.

5. Process according to any of Claims 1-4 which comprises replacing the bromine atom in a compound of the general Formula II by a lithium atom.

6. Process according to Claim 5 which comprises carrying out the reaction by using an alkyl lithium compound, preferably n-butyl-lithium or n-hexyl-lithium.

7. Process according to Claim 5 or 6 which comprises carrying out the reaction at a temperature between -78°C and -10°C.

8. Process according to Claim 1 which comprises using the compound of the general Formula IIIa in an amount of 1.0-1.2 molar equivalents.

9. Process according to any of Claims 1 and 5-8 which comprises reacting the alkali or magnesium compound without isolation with the compound of the general Formula IIIa.

10. Process according to Claim 9 which comprises carrying out the reaction at a temperature below 0°C.

11. Process according to Claim 1 which comprises using the compound of the general Formula IIIb in an amount of 1.0-1.2 molar equivalents.

12. Process according to Claim 1 or 11 which comprises reacting the alkali or magnesium compound without isolation with the compound of the general Formula IIIb.

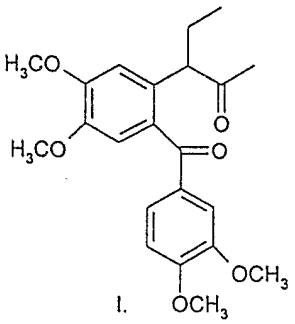
13. Process according to Claim 12 which comprises carrying out the reaction at a temperature below 0°C.

14. Process according to any of Claims 1-13 which comprises hydrolysing the compound of the general Formula IV with a mineral acid.

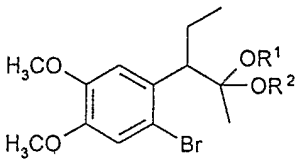
15. Process according to Claim 14 which comprises using hydrochloric acid or sulfuric acid.

16. Process according to any of Claims 1, 14 and 15 which comprises carrying out hydrolysis at 20-40°C.

17. Process according to any of Claims 1-16 which comprises hydrolysing the compound of the general Formula IV in situ in the reaction mixture obtained during the formation thereof.



I.



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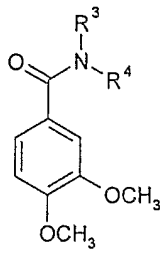
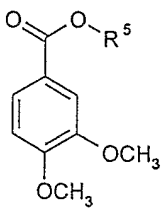
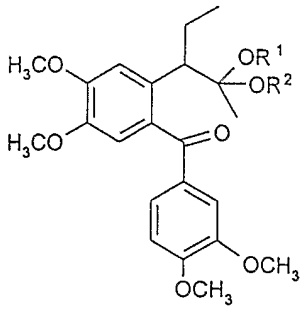


IIIa.



IIIb.



IV.

INTERNATIONAL SEARCH REPORT

Internatio[redacted] Application No
PCT/HU 02/00178

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C45/45 C07C49/84

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 7 C07C

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)

CHEM ABS Data, EPO-Internal, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; LANG, TIBOR ET AL: "2-Aroylphenylacetone derivatives" retrieved from STN Database accession no. 105:152712 CA XP002242492 cited in the application abstract & HU 194 529 B (GYOGYSZERKUTATO INTEZET, HUNG.) 29 February 1988 (1988-02-29) -----	1

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 May 2003	10/06/2003

Name and mailing address of the ISA	Authorized officer
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	Goetz, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 02/00178

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
HU 194529 B	28-02-1986	HU 37739 A2	28-02-1986