

3 Jan 2000

**NEW NITROMETHYL KETONES. PROCESS FOR
PREPARING THEM AND COMPOSITIONS CONTAINING THEM**

BACKGROUND OF THE INVENTION

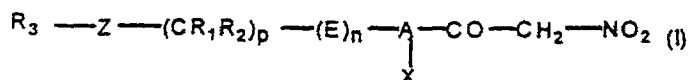
The present invention relates to new nitromethyl ketones, to their preparation and to their use as medicaments especially in the treatment or prevention of the complications of diabetes.

5 Diabetes is characterized by a high concentration of glucose in the blood. This glucose is normally metabolized by the enzyme hexokinase during the first stage of glycolysis, leading to the degradation into pyruvate. When the glucose concentration is
10 too high, hexokinase becomes saturated and a second pathway for glucose metabolism comes into play; it is the polyol pathway which involves two enzymes successively: aldose reductase which converts glucose to sorbitol and sorbitol dehydrogenase which converts
15 sorbitol to fructose. In the event of diabetes, the excess glucose accelerates the formation of sorbitol which tends to accumulate. This results in serious metabolic disturbances, such as for example an increase in osmotic pressure which can lead to tissue degene-
20 ration. Aldose reductase inhibitors are therefore useful for treating or preventing certain complications induced by diabetes.

Numerous products are described in the literature, such as aldose reductase inhibitors which are
25 active in vitro and in vivo.

They are mainly derivatives of hydantoins, of succinimides and of acetic acids and more recently derivatives of sulfonylnitromethanes.

The present invention relates to nitromethyl
30 ketone derivatives, their addition salts with physiologically acceptable bases, corresponding to the general formula (I):



in which

35 - A represents C₆-C₁₀ aryl or an optionally aromatic three- to ten-membered heterocycle in which one to





- 2 -

- four vertices are occupied by identical or different heteroatoms chosen from O, S and N;
- X represents halogen, cyano, C₁-C₇ alkyl, trifluoromethyl, C₂-C₇ alkoxy or trifluoromethoxy;
 - 5 - R₁ and R₂, which are identical or different, represent a hydrogen atom, a C₁-C₇ alkyl group, a C₃-C₁₂ cycloalkyl group, a trifluoromethyl group, a C₁-C₇ alkoxy group or R₁ or R₂ together form an alkylene chain of the -(CH₂)_r- type, where r is chosen from
10 2, 3 and 4;
 - p is chosen from 0, 1, 2, 3, 4 and 5;
 - Z represents a bond, the divalent radical -CO-NH- in which the carbonyl function is linked to R₃, the divalent radical -SO₂-NH- in which the sulfonyl
15 function is linked to R₃, a C₂-C₇ alkenylene radical, a sulfur atom, the sulfinyl group or a sulfonyl group;
 - R₃ represents a hydrogen atom; a halogen atom; a tri-
(C₁-C₇-alkyl)silyl group; a C₁-C₇ alkyl group
20 optionally substituted with one or more identical or different Y radicals; a C₆-C₁₀ aryl group optionally substituted with one or more identical or different Y radicals; a C₆-C₁₀ aryloxy group optionally substituted with one or more identical
25 or different Y radicals; a C₃-C₁₂ cycloalkyl group optionally substituted with one or more identical or different Y radicals; an optionally aromatic three- to ten-membered heterocycle in which one to
30 different heteroatoms chosen from O, S and N, the said heterocycle being optionally substituted with one or more identical or different Y radicals, or R₃ represents indanyl, 1,3-dihydro-1,3-dioxo-2H-iso-indol-2-yl, 1,3-benzodioxolyl, 2-oxopiperidinyl or
35 2-[(4-nitromethylcarbonyl-3-chlorophenyl)amino-carbonyl]-1-(phenyl)ethyl;
 - Y represents a halogen atom, C₁-C₇ alkyl, C₁-C₇ alkoxy, trifluoromethyl, carboxy, carbamoyl, (C₁-C₇)alkylcarbamoyl, di-(C₁-C₇)alkylcarbamoyl,

C₁-C₇ alkoxy carbonyl, amino, C₁-C₇-alkylamino, di-
(C₁-C₇)-alkylamino, nitro, cyano, hydroxy, tri-
fluoromethoxy, C₃-C₁₂ cycloalkyl, sulfo, C₁-C₇
alkylthio, C₁-C₇ alkylsulfinyl, C₁-C₇ alkyl-
sulfonyl, C₂-C₈ alkylcarbonyl, C₂-C₈ alkylthio-
carbonyl, C₂-C₈ alkylcarbonylamino, or C₆-C₁₀ aryl;

- E represents a divalent radical chosen from:

- (i) -CO-NR₄- in which the carbonyl group is linked
to -(CR₁R₂)_p- and R₄ represents the radical
-(CH₂)_q-R₅ where q is chosen from 0 and 1; and
where R₅ represents a hydrogen atom; a C₁-C₇ alkyl
group; a C₆-C₁₀ aryl group or an optionally
aromatic three- to ten-membered heterocycle in
which one to four vertices are occupied by identi-
cal or different heteroatoms chosen from O, N and
S; or R₅ and R₃ together form a bond;
(ii) -SO₂-NR₄- in which the sulfonyl group is
linked to -(CR₁R₂)_p- and R₄ is as defined above;
(iii) -NR₄- in which R₄ is as defined above;
(iv) -CH=N- in which the nitrogen atom is linked
to A; and
(v) an oxygen atom;

- n represents 0 or 1;

on the condition that -A(X)-(E)_n-(CR₁R₂)_p-Z-R₃ does not
represent halophenyl, methylphenyl, dichlorophenyl,
dimethylphenyl, 4-ethoxy-2-methylaminophenyl, methyl-
indolyl, dimethylindolyl, 2-hydroxyphenyl substituted
with a group X, 2-methoxyphenyl substituted with a
group X and optionally substituted 2-fluorophenyl as
defined above, and

on the condition that when A represents pyridyl, X
represents methyl and n is equal to 1, E does not
represent -NR₄-.

These compounds are inhibitors of the enzyme
aldose reductase and may be used in the treatment or
prevention of the complications of diabetes: neuro-
logical, peripheral and autonomous complications, renal
complications and ocular complications such as cataract
and retinopathy.





The physiologically acceptable salts of the compounds of formula (I) comprise the salts formed with metals (such as sodium, potassium, calcium, magnesium, aluminium), or with bases such as ammonium hydroxide or substituted amines (such as diethylamine, triethylamine, piperidine, piperazine, morpholine) or basic amino acids (such as lysine, arginine) or with osamines (such as meglumine) or with amino alcohols (such as 3-aminobutanol, 2-aminoethanol).

10 The term "aryl" represents an aromatic mono- or bicyclic group comprising 6 to 10 carbon atoms, such as phenyl or naphthyl.

The term "heterocycle" denotes a mono- or bicyclic ring with an aromatic character or otherwise, comprising 3 to 10 vertices of which 1 to 4 are occupied by identical or different heteroatoms chosen from oxygen, sulfur and nitrogen, such as for example the aziridinyl, oxiranyl, oxazolyl, furyl, tetrahydrofuryl, thienyl, imidazolyl, pyridyl, pyrazinyl, benzothienyl, benzopyranyl, benzofuryl, benzothiazolyl, pyrimidinyl, pyridazinyl, piperidinyl, quinolyl, tetrahydroquinolyl, tetrazolyl, phthalazinyl, purinyl, indolyl, chromenyl, chromanyl, isochromanyl and pyrrolyl.

25 The term "cycloalkyl" denotes saturated hydrocarbon groups containing 3 to 12 carbon atoms, preferably 3 to 8, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecenyl and cyclododecyl.

30 The term "halogen" represents a fluorine, chlorine, bromine or iodine atom.

The term "alkyl" denotes a linear or branched hydrocarbon radical such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, isobutyl, pentyl, hexyl, heptyl.

The term "alkoxy" denotes an alkyl group linked to an oxygen atom. Examples thereof are the methoxy, ethoxy, isopropoxy, butoxy, hexyloxy radicals.

Likewise, "aryloxy" denotes an aryl radical as defined above linked to an oxygen atom, such as phenoxy and naphthyloxy.

According to the invention, "alkenylene" radical is understood to mean, moreover, a divalent hydrocarbon radical carrying one or more ethylenic double bonds such as, for example, $-\text{CH}=\text{CH}-\text{CH}_2-$ or $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$.

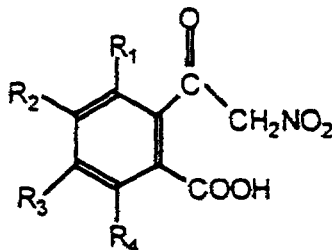
"Carbamoyl" radical denotes the monovalent radical of formula $-\text{CO}-\text{NH}_2$. The radical "(C₁-C₇)alkylcarbamoyl" denotes a carbamoyl radical substituted with a C₁-C₇ alkyl group on the nitrogen atom and the radical "di-(C₁-C₇)alkylcarbamoyl" denotes a carbamoyl radical substituted on the nitrogen atom with two C₁-C₇ alkyl groups.

The radical "(C₁-C₇)alkoxycarbonyl" denotes a radical $\text{R}-\text{O}-\text{CO}-$ in which R represents a C₁-C₇ alkyl group.

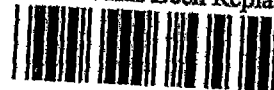
The radical "(C₁-C₇)alkylamino" denotes an amino group substituted on the nitrogen atom with a (C₁-C₇)alkyl radical and the radical "di-(C₁-C₇)alkylamino" denotes an amino group substituted on the nitrogen atom with two (C₁-C₇)alkyl radicals.

The terms "alkylthio", "alkylsulfinyl" and "alkylsulfonyl" represent an alkyl group linked to a sulfur atom which is respectively nonoxidized, mono-oxidized or di-oxidized, such as methylthio, methylsulfinyl or methylsulfonyl.

Some compounds of this type are known. For example, DE 2,415,350 describes antiallergic compounds of formula:



This Sheet Has Been Replaced

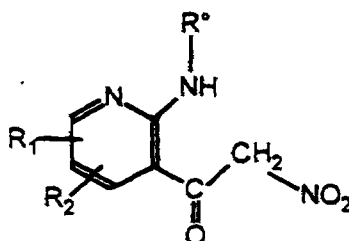




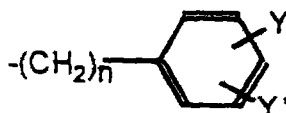
- 6 -

in which R_1 , R_2 , R_3 , R_4 , which are identical or different, may represent a hydrogen or halogen atom, an alkyl, alkoxy, aryl or arylalkyl group, a heterocycle or, two by two, a carbocycle or a heterocycle.

- 5 In patent DE 2,741,011, antihistaminic-antiallergic compounds are described, which are of the formula:



- 10 in which R' represents a hydrogen atom, a (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl- (C_1-C_2) alkyl, (C_3-C_6) alkenyl or (C_3-C_6) alkynyl group or a radical of formula



- 15 Nitromethyl ketone derivatives attached to polysubstituted naphthyridines and quinolones are described in patent EP 574 231 for an antibiotic activity.

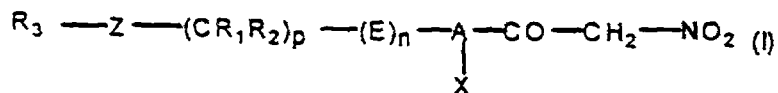
- Other nitromethyl ketone derivatives have been described in the literature, for example as synthesis intermediates, but the prior art does not refer at all to a potential therapeutic use of these compounds. There may be mentioned for example J. SETER, Israel J. Chem (1966) 4, 7-22 or BAKER D.C. and PUTT S.R., Synthesis (1978) 678-9 or FIELD G.F. and ZALLY W.J., Synthesis (1979) 295-6 or HAMADA Yasumasa et al., Chem. Pharm. Bull (1981) 29, 259-61.

- 30 The known nitromethyl ketone derivatives do not correspond to the formula (I) of the compounds of the invention; moreover, none of these compounds is described as having any inhibitory activity towards aldose reductase.

Preferred compounds of the invention are those for which, in the formula (I):

- A represents phenyl, n and p represent 0, Z represents a bond and R₃ represents a hydrogen atom, or
- 5 - A represents phenyl, n represents 1 and E represents -CO-NR₄-, and more particularly those for which p represents 1, R₁ and R₂ represent a hydrogen atom and Z represents a bond; or
- A represents phenyl, n represents 1, E represents
- 10 -SO₂-NR₄-; or
- A represents phenyl, n is equal to 1, E represents -CO-NR₄-, p is equal to 0 and Z represents -SO₂-NH-; or
- A represents an aromatic heterocycle such as benzothienyl or thienyl; or
- 15 - A represents naphthyl; or
- n represents 1 and E represents an oxygen atom.

Another group of preferred compounds consists of the compounds of formula:



- 20 in which
- A represents phenyl, naphthyl, benzothienyl or thienyl;
- X represents halogen, cyano, C₁-C₇ alkyl, trifluoromethyl, C₂-C₇ alkoxy or trifluoromethoxy;
- 25 - R₁ and R₂ represent a hydrogen atom, or R₁ and R₂ together form an alkylene chain of the -(CH₂)_r- type, where r is chosen from 2, 3 and 4;
- p is chosen from 0, 1, 2 and 3;
- Z represents a bond, the divalent radical -CO-NH- in
- 30 which the carbonyl function is linked to R₃ or the divalent radical -SO₂-NH- in which the sulfonyl function is linked to R₃;
- R₃ represents a hydrogen atom, C₁-C₇ alkyl optionally substituted with one or more identical or different Y
- 35 radicals; phenyl optionally substituted with one or more identical or different Y radicals; phenoxy





optionally substituted with one or more identical or different Y radicals; C₃-C₁₂ cycloalkyl optionally substituted with one or more identical or different Y radicals; benzothienyl; benzofuryl; or R₃ represents
5 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl or 2-oxo-piperidinyl;

- Y represents a halogen atom, C₁-C₇ alkoxy, trifluoromethyl, carboxy, trifluoromethoxy or phenyl;

- E represents a divalent radical chosen from:

10 (i) -CO-NR₄ in which the carbonyl group is linked to -(CR₁R₂)_p- and R₄ represents the radical (CH₂)_q-R₅ where q is chosen from 0 and 1, and where R₅ represents a hydrogen atom, a C₁-C₇ alkyl group or a phenyl group;

(ii) -SO₂-NR₄- in which the sulfonyl group is linked to
15 -(CR₁R₂)_p- and R₄ is as defined above;

(iii) -NR₄- in which R₄ is as defined above;

(iv) -CH=N- in which the nitrogen atom is linked to A;
and

(v) a hydrogen atom;

20 - n represents 0 or 1;

on the condition that -A(X)-(E)_n-(CR₁R₂)_p-Z-R₃ does not represent halophenyl, methylphenyl, dichlorophenyl, dimethylphenyl, 4-ethoxy-2-methylaminophenyl, methylindolyl, dimethylindolyl, 2-hydroxyphenyl substituted
25 with a group X, 2-methoxyphenyl substituted with a group X and optionally substituted 2-fluorophenyl as defined above, and

on the condition that when A represents pyridyl, X represents methyl and n is equal to 1, E does not
30 represent -NR₄-,

as well as their addition salts with pharmaceutically acceptable bases.

Among the preferred compounds of the invention, there may be mentioned:

- 35 (1) nitromethyl 2-trifluoromethoxyphenyl ketone;
(2) nitromethyl 2-cyanophenyl ketone;
(3) nitromethyl 2-ethylphenyl ketone;
(4) nitromethyl 2-trifluoromethylphenyl ketone;
(5) nitromethyl 2-ethoxyphenyl ketone;

- (6) nitromethyl 2-isopropoxyphenyl ketone;
(7) nitromethyl 2-methyl-1-naphthyl ketone;
(8) nitromethyl 3-chloro-2-naphthyl ketone;
(9) nitromethyl 3-chlorobenzo[b]thien-2-yl ketone;
5 (10) nitromethyl 6-methoxy-5-trifluoromethyl-1-naphthyl
ketone;
(11) 4-methyl-N-[2-nitromethylcarbonyl-3-methyl-
benzo[b]thien-5-yl]benzenesulfonamide;
(12) N-[3-chloro-4-nitromethylcarbonylphenyl]acetamide;
10 (13) nitromethyl 4-amino-2-chlorophenyl ketone;
(14) N-[3-chloro-4-nitromethylcarbonylphenyl]benzamide;
(15) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-chloro-
benzamide;
(16) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-methyl-
15 benzamide;
(17) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-
methoxybenzamide;
(18) N-[3-chloro-4-nitromethylcarbonylphenyl]-2-tri-
fluoromethylbenzamide;
20 (19) N-[3-chloro-4-nitromethylcarbonylphenyl]-2,2,3,3-
tetramethylcyclopropanecarboxamide;
(20) N-[3-chloro-4-nitromethylcarbonylphenyl]hexane-
amide;
(21) N-[3-chloro-4-nitromethylcarbonylphenyl]cyclo-
25 pentylacetamide;
(22) N-[3-chloro-4-nitromethylcarbonylphenyl]-3-phenyl-
propaneamide;
(23) N-[3-chloro-4-nitromethylcarbonylphenyl]-2-phenyl-
propaneamide;
30 (24) N-[3-chloro-4-nitromethylcarbonylphenyl]phenyl-
acetamide;
(25) N-[3-chloro-4-nitromethylcarbonylphenyl]benzo[b]-
thienyl-2-carboxamide;
(26) N-[3-chloro-4-nitromethylcarbonylphenyl]benzo-
35 furyl-2-carboxamide;
(27) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-chloro-
phenoxyacetamide;
(28) 2-chloro-N-[3-chloro-4-nitromethylcarbonyl-
phenyl]phenylacetamide;

This Sheet Has Been Replaced





- 10 -

- (29) N-[3-chloro-4-nitromethylcarbonylphenyl]-1-(4-chlorophenyl)cyclopropylcarboxamide;
- (30) N-[3-chloro-4-nitromethylcarbonylphenyl]-2-trifluoromethylphenylacetamide;
- 5 (31) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-chlorobenzenesulfonamide;
- (32) N-[3-chloro-4-nitromethylcarbonylphenyl]benzenesulfonamide;
- (33) nitromethyl 4-[N,N-di(phenylmethyl)amino]-2-chlorophenyl ketone;
- 10 (34) N-[2-chloro-3-nitromethylcarbonylphenyl]acetamide;
- (35) N-[2-chloro-3-nitromethylcarbonylphenyl]-2-methylphenylacetamide;
- (36) N-[4-chloro-3-nitromethylcarbonylphenyl]acetamide;
- 15 (37) N-[4-chloro-3-nitromethylcarbonylphenyl]-2-methylphenylacetamide;
- (38) N-[4-chloro-3-nitromethylcarbonylphenyl]benzenesulfonamide;
- (39) 2-[3-chloro-4-nitromethylcarbonylphenylamino-carbonylmethylaminocarbonyl]benzoic acid;
- 20 (40) N-[3-chloro-4-nitromethylcarbonylphenyl]-1,3-dihydro-1,3-dioxo-2H-isoindol-2-ylacetamide
- (41) 1-[3-chloro-4-nitromethylcarbonylphenyl]-3-phenylsulfonylurea;
- (42) nitromethyl 3-methyl-2-thienyl ketone;
- 25 (43) N-[3-chloro-4-nitromethylcarbonylphenyl]-2-methylphenylacetamide;
- (44) N-[3-chloro-4-nitromethylcarbonylphenyl]-2-oxopiperidine;
- 30 (45) N-[3-chloro-4-nitromethylcarbonylphenyl]-1-(4-chlorophenyl)cyclopentanecarboxamide;
- (46) N-[3-chloro-4-nitromethylcarbonylphenyl]indan-2-ylacetamide;
- (47) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-chlorophenylacetamide;
- 35 (48) N-[3-chloro-4-nitromethylcarbonylphenyl]-3-chlorophenylacetamide;
- (49) N-[3-chloro-4-nitromethylcarbonylphenyl]-3,4-dichlorophenylacetamide;

- (50) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-methyl-
phenylacetamide;
- (51) N-[3-chloro-4-nitromethylcarbonylphenyl]-3-methyl-
phenylacetamide;
- 5 (52) N-[3-chloro-4-nitromethylcarbonylphenyl]-3,4-di-
methylphenylacetamide;
- (53) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-tri-
fluoromethylphenylacetamide;
- (54) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-
10 methoxyphenylacetamide;
- (55) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-nitro-
phenylacetamide;
- (56) N-[3-chloro-4-nitromethylcarbonylphenyl]-2-fluoro-
4-bromophenylacetamide;
- 15 (57) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-fluoro-
phenylacetamide;
- (58) N-[3-chloro-4-nitromethylcarbonylphenyl]-3-phenyl-
2-propeneamide;
- (59) N-[3-methyl-4-nitromethylcarbonylphenyl]-2-methyl-
20 phenylacetamide;
- (60) N-[2-bromo-4-nitromethylcarbonylphenyl]-2-methyl-
phenylacetamide;
- (61) nitromethyl 2-chloro-4-methoxyphenyl ketone;
- (62) nitromethyl 2-isopropylphenyl ketone;
- 25 (63) N-[4-chloro-2-nitromethylcarbonylphenyl]-2-methyl-
phenylacetamide;
- (64) nitromethyl 2-chloro-4-phenylthiophenyl ketone;
- (65) N-[3-chloro-4-nitromethylcarbonylphenyl]-4-[3-
chloro-4-nitromethylcarbonylphenylaminocarbonyl]-
30 3-phenylbutaneamide;
- (66) nitromethyl 2-chloro-4-phenylsulfinylphenyl
ketone;
- (67) nitromethyl 4-chloro-2-trifluoromethoxyphenyl
ketone;
- 35 (68) N-[2-(3-chloro-4-nitromethylcarbonylphenylethyl)]-
2-methylbenzenesulfonamide;
- (69) N-[3-bromo-4-nitromethylcarbonylphenyl]-2-methyl-
phenylacetamide;

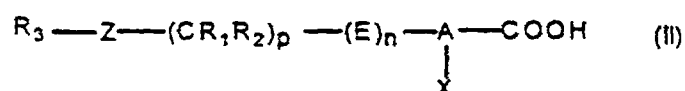
This Sheet Has Been Replaced



(70) N-[3-chloro-4-nitromethylcarbonylphenyl]-N-iso-propylbenzenesulfonamide.

The compounds of the invention are for example
5 prepared according to the following methods (A) and (B):

(A) The products of formula (I) may be prepared from the carboxylic acids (II)

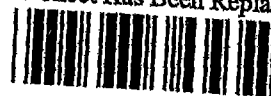


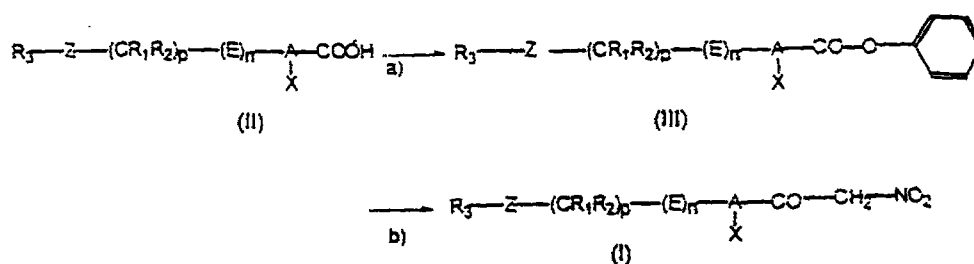
10 by the action of di-(C₁-C₇)alkyl cyanophosphonate and nitromethane in the presence of a base in a solvent which is inert towards the reaction, preferably in a polar aprotic solvent such as dimethylformamide or tetrahydrofuran. Advantageously, the molar ratio of the
15 carboxylic acid of formula (II) to the nitromethane varies between 0.6/1 and 2/1, preferably between 0.8/1 and 1.2/1. As base, use is preferably made of an amine, an alkyl lithium, an alkali metal hydride, an alkali metal carbonate, an alkali metal hydroxide or an alkali
20 metal alcoholate and especially triethylamine, pyridine, butyllithium, sodium hydride, potassium carbonate, potassium hydroxide or potassium tert-butoxide in a ratio of the carboxylic acid of formula (II) to the base of between 0.2/1 and 0.5/1, or better
25 still in a ratio of 0.4/1.

The reaction temperature is generally between -78°C and the reflux temperature of the solvent and preferably between -5°C and 80°C. Generally, the reaction is continued for 2 to 72 hours, preferably for
30 2 to 18 hours.

(B) As a variant, the product of formula (I) may be prepared from the carboxylic acids of formula (II) by prior conversion to the phenyl ester of formula (III) according to the following reaction scheme:

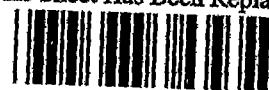
This Sheet Has Been Replaced





a) The preparation of the phenyl esters (III) may be carried out by reacting successively or simultaneously $SOCl_2$, or $POCl_3$, and phenol in the absence or in the presence of a solvent which is inert towards the reaction. When a solvent is used, it is preferably an aprotic solvent such as dichloromethane, benzene or toluene. In this first step, the molar ratio of $SOCl_2$, respectively $POCl_3$, to the carboxylic acid of formula (II) is preferably between 1/1 and 50/1, or better still the ratio is 10/1. Likewise, it is preferable that the molar ratio of the carboxylic acid to the phenol is between 1/0.9 and 1/1.2, or better still this ratio is 1/1.05. The reaction temperature is advantageously between -78°C and the reflux temperature of the solvent, preferably between 0°C and the reflux temperature of the solvent. This reaction is continued for 1 to 48 hours, preferably for 1 to 8 hours.

b) The phenyl esters of formula (III) thus formed are then treated with nitromethane in the presence of a base at a temperature of between 20°C and the boiling point of the solvent and, preferably, between 20°C and 40°C . The duration of the reaction varies advantageously between 2 and 72 hours, preferably between 2 and 48 hours. For this stage, the molar ratio of the compound of formula (III) to the nitromethane will be set at between 1/1 and 1/5, this ratio being preferably equal to 1/3. As appropriate base, there will be used for example an alkali metal hydroxide, an alkali metal carbonate, an alkali metal hydride, an alkyllithium, an amine or an alkali metal alcoholate. Thus, the base may be, for example, selected from potassium tert-butoxide, sodium hydroxide, potassium hydroxide, potassium



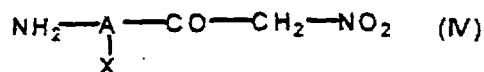


- 14 -

carbonate, sodium hydride, butyllithium and pyridine. The molar ratio of the phenyl ester of formula (III) to the base will be advantageously between 1/1 and 1/5, this ratio being preferably equal to 1/3.

5 Other procedures allow the preparation of the compounds of formula (I).

When in the formula (I) above, n is equal to 1 and E represents $-\text{CO}-\text{NR}_4-$, the compounds of the invention may be obtained by reacting an acid halide of
10 formula $\text{R}_3-\text{Z}-(\text{CR}_1\text{R}_2)_p-\text{CO}-\text{hal}$ where R_1 , R_2 , R_3 , Z and p are as defined above and hal is a halogen atom, with an amine of formula (IV):



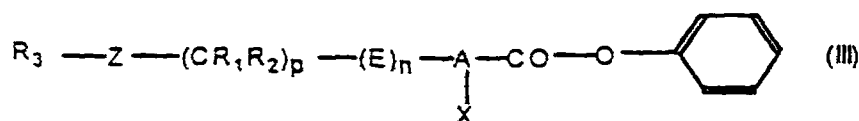
in which A and X are as defined above.

15 The procedure is carried out in the presence of a base, preferably an amine, such as pyridine, triethylamine or dimethylaminopyridine, in a solvent, preferably an aprotic solvent, at a temperature of between -20°C and the reflux temperature of the
20 solvent, for example between 0 and 40°C . The duration of the reaction is between 2 and 48 hours.

Examples of preferred solvents are dichloromethane, tetrahydrofuran, benzene or toluene.

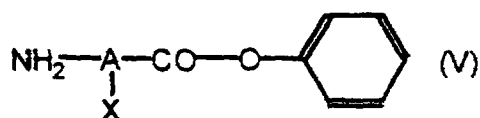
When, in the formula (I) above, n is equal to 1
25 and E represents $-\text{SO}_2-\text{NR}_4-$, the compounds of the invention may be obtained by reacting a sulfonyl halide of formula $\text{R}_3-\text{Z}-(\text{CR}_1\text{R}_2)_p-\text{SO}_2-\text{hal}$ where R_1 , R_2 , R_3 , Z and p are as defined above and hal is a halogen atom, with an amine of formula (IV) as defined above. Here again, the
30 procedure is advantageously carried out in the presence of a base in a solvent at a temperature of between -20°C and the reflux temperature of the solvent. The preferred operating conditions are the same as for the reaction of the acid chloride with the amine of formula
35 (IV) above.

As a variant, it is possible, in a first instance, to synthesize the benzyl ester of formula (III):



5 according to one of the reaction steps (i) to (vi) below, and then to treat the benzyl ester of formula (III) by the action of nitromethane in the presence of a base as described above:

10 - step (i) when n is equal to 1 and E represents $-CO-NR_4-$, an acid halide of formula $R_3-Z-(CR_1R_2)_p-CO-hal$, where R_1 , R_2 , R_3 , Z and p are as defined above and hal is a halogen atom, is reacted with an amine of formula (V):



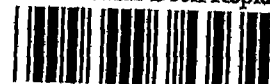
15 in which A and X are as defined above; or

- step (ii) when n is equal to 1 and E represents $-SO_2-NR_4-$, a sulfonyl halide of formula $R_3-Z-(CR_1R_2)_p-SO_2-hal$, where R_1 , R_2 , R_3 , Z and p are as defined above and hal is a halogen atom, is reacted with an amine of formula (V) as defined above; or

20 - step (iii) when n is equal to 1 and E represents $-NR_4-$, a compound of formula $R_3-Z-(CR_1R_2)_p-hal$, where R_1 , R_2 , R_3 , Z and p are as defined above and hal is a halogen atom, is reacted with an amine of formula (V) as defined above; or

25 - step (iv) when n is equal to 1 and E represents $-CH=N-$, an aldehyde of formula $R_3-Z-(CR_1R_2)_p-CHO$, where R_1 , R_2 , R_3 , Z and p are as defined above, is reacted with an amine of formula (V) as defined above; or

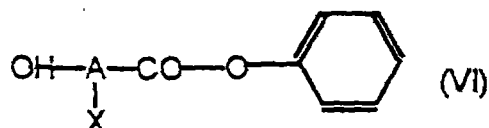
30 - step (v) when n is equal to 1 and E represents $-O-$, a compound of formula $R_3-Z-(CR_1R_2)_p-hal$, where R_1 , R_2 , R_3 , Z and p are as defined above and hal is





- 16 -

a halogen atom, is reacted with an alcohol of formula (VI):



in which A and X are as defined above;

5 - step (vi) when n is equal to 1, E represents -CO-NR₄-, p is 0 and Z represents -SO₂-NH-, an isocyanate of formula R₃-SO₂-N=C=O, in which R₃ is as defined above, is reacted with an amine of formula (V) as defined above;

10 - step (vii) when n is equal to 1 and E represents -CO-NR₄-, an acid of formula R₃-Z-(CR₁R₂)_p-COOH, where R₁, R₂, R₃, Z and p are as defined above, is reacted with an amine of formula (V) as defined above.

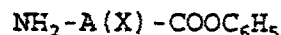
15 Some compounds of formula (I) may be obtained from compounds of formula (I) using simple conversion steps.

20 Thus, the compounds of formula (I) in which n is equal to 1, E represents -CO-NH-, p represents 1, R₁ and R₂ represent a hydrogen atom, Z represents a bond and R₃ represents 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl may be prepared from the corresponding compounds (having meanings of A and X which are identical) in which n is equal to 1, E represents -CO-NH-, p represents 1, R₁ and R₂ represent a hydrogen atom, Z represents -CO-NH- and R₃ represents 2-carboxyphenyl, 25 by the action of hydrochloric acid.

30 Likewise, the compounds in which n represents 1, E represents -CO-NH-, -(CR₁R₂)_p- represents CH₂ and R₃ represents 2-[(4-nitromethylcarbonyl-3-chlorophenyl)-aminocarbonyl]-1-(phenyl)ethyl may be prepared by reacting the dichloride of formula



with two equivalents of the ester of formula



35 in the presence of a base, and then treating the compound obtained with nitromethane in the presence of a base.

The compounds of formula (IV) are easily synthesized from commercially available compounds by methods known in the art.

By way of example, the compounds of formula (IV) may be obtained from the corresponding amines of formula (VII):



according to a procedure comprising the steps consisting of:

- 10 - protecting the amino function with a protective group such as a (C₁-C₇)alkylcarbonyl group, for example acetyl;
- reacting the amine thus protected with di(C₁-C₇)alkyl cyanophosphonate and nitromethane in the
- 15 presence of a base; and then
- deprotecting the amino function, for example by the action of sodium hydroxide when the protective group is an acetyl group.

20 The capacity of the compounds of the invention to inhibit the enzyme aldose reductase and to prevent the accumulation of sorbitol may be demonstrated during standard laboratory tests below:

1) Study in vitro: inhibition of aldose reductase

25 The aldose reductase used is obtained from male Wistar rat crystalline lenses according to a modification of the method of S. HAYMAN et al. (Journal of Biological Chemistry 240, p. 877, 1965). The enzymatic extract is diluted in a phosphate buffer in the

30 presence of NADPH and various concentrations of the test products. The reaction is initiated with L-glyceraldehyde and the reaction rate is measured by monitoring the disappearance of NADPH by spectrophotometry at 340 nm. The reaction rate is

35 calculated for each product concentration and then the concentration necessary for a 50% reduction in the reaction rate (IC₅₀) is evaluated by linear interpolation. The results are presented in Table 1 below.

This Sheet Has Been Replaced





- 18 -

2) Study in vivo: reduction of sorbitol accumulation

200 to 250 g male Wistar rats are made diabetic by intravenous injection of streptozotocin (60 mg/kg). They then receive an oral treatment of the test products, in the form of a suspension, 4 hours, 30 hours and 52 hours after the injection of streptozotocin. Eighteen hours after the last oral treatment, the rats are stunned and decapitated and then their sciatic nerves are removed. After extraction, the sorbitol level in the nerves is measured according to the enzymatic method described by H.U. BERGMEYER (Methods of enzymatic analysis. H.U. BERGMEYER ed., Academic Press New York 3, p. 1323, 1974).

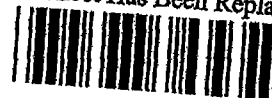
The percentage protection is calculated for each product relative to the batch of diabetic animals taking into account the sorbitol level in the sciatic nerves of nondiabetic rats.

By way of example, the results obtained for some of the test products are given in the following table:

TABLE 1

Example No.	Inhibition of aldose reductase in vitro IC ₅₀ (nM)	Protection against increase in sorbitol after administration 10 mg/kg/d (%)
1	41	70
23	7	40
24	7	45
28	7	58
30	7	61
43	7	70
59	6	52

The compounds of the invention may be used by way of medicaments as aldose reductase inhibitors, and are especially useful in the treatment of the complications of diabetes such as cataracts, retinopathies, neuropathies, nephropathies and certain vascular diseases. The daily dosages may vary from 5 mg to 200 mg of active ingredient.



These medicaments may be administered by the oral route in the form of tablets, gelatin capsules or granules affording immediate release or controlled release, by the intravenous route in the form of an injectable solution, by the transdermal route in the form of an adhesive transdermal device, by the local route in the form of a collyrium, solution, cream or gel.

A solid medicament for oral administration containing a compound of the present invention as active ingredient is prepared by supplementing the said compound with a filler and, where appropriate, a binder, a disintegrating agent, a lubricant, a colouring or a taste enhancer, and by forming the mixture into a tablet, a coated tablet, a granule, a powder or a capsule.

Examples of a filler comprise lactose, maize starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide, and examples of a binder comprise poly(vinyl alcohol), poly(vinyl ether), ethyl cellulose, methyl cellulose, acacia, tragacanth gum, gelatin, shellac, hydroxypropylcellulose, hydroxypropylmethylcellulose, calcium citrate, dextrin and pectin. Examples of lubricants comprise magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. The colouring may be any of those permitted for use in medicaments. Examples of taste enhancers comprise cocoa powder, mint in herb form, aromatic powder, mint in oil form, borneol and cinnamon powder. Of course, the tablet or granule may be suitably coated with sugar, gelatin and the like.

An injectable form containing the compound of the present invention as active ingredient is prepared, where appropriate, by mixing the said compound with a pH regulator, a buffering agent, a suspending agent, a solubilizing agent, a stabilizer, a tonic agent and/or a preservative, and by converting the mixture to a form injectable by the intravenous, subcutaneous or intramuscular route, according to a conventional process.



- 20 -

Where appropriate, the injectable form obtained may be freeze-dried by a conventional process.

Examples of suspending agents comprise methyl cellulose, polysorbate 80, hydroxyethylcellulose, acacia, tragacanth gum powder, sodium carboxymethyl-cellulose and polyethoxylated sorbitan monolaurate.

Examples of a solubilizing agent comprise castor oil solidified with polyoxyethylene, polysorbate 80, nicotinamide, polyethoxylated sorbitan monolaurate and the ethyl ester of castor oil fatty acid.

In addition, the stabilizer comprises sodium sulfite, sodium metasulfite and ether, whereas the preservative comprises methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate, sorbic acid, phenol, cresol and chlorocresol.

A few pharmaceutical formulations are given below by way of nonlimiting examples:

- Composition of an immediate-release tablet
Active ingredient 100 mg
Excipients: lactose, wheat starch, polyvidone, talc, magnesium stearate.
- Composition of a controlled-release tablet
Active ingredient 100 mg
Excipients: lactose, polyvidone, talc, magnesium stearate, polymer (cellulose or acrylic and methacrylic or vinyl or glyceride derivative).
- Composition of a gelatin capsule
Active ingredient 100 mg
Excipients: lactose, wheat starch, talc, magnesium stearate.
- Composition of an ampoule of injectable solution
Active ingredient 200 mg
Excipients: mannitol, water for injection.
- Composition of a cream
(composition per 100 g of cream)
Active ingredient 2 g
Excipients: self-emulsifiable cetylstearyl



alcohol, cetylaryloctanoate, nipasol,
sorbic acid, propylene glycol, carbapol.

• Composition of a collyrium

Active ingredient 15 mg

Excipients: sodium chloride, benzalkonium
chloride, water for injection.

The following examples illustrate the invention
with no limitation being implied.

In the nuclear magnetic resonance (NMR) data,
the following abbreviations are used: s for singlet, d
for doublet, t for triplet, q for quadruplet and m for
unresolved complex; the chemical shifts δ are expressed
in ppm; m.p. = represents the melting point and b.p.
the boiling point.

10

Example 1

Nitromethyl 2-trifluoromethoxyphenyl ketone

a) Phenyl 2-(trifluoromethoxyphenyl)benzoate

A mixture composed of 10 g (48.5 mmol) of
2-(trifluoromethoxy)benzoic acid, 50 ml of thionyl
chloride and a drop of dimethylformamide is heated
under reflux for 1.5 hours. After cooling and
concentrating the reaction mixture under vacuum, a
residue is obtained which is stirred for 2 hours at
100°C in the presence of 4.75 g (50 mmol) of phenol.
After cooling, the reaction medium is taken up in
dichloromethane, washed with a saturated NaHCO₃ solution
and then with water, dried over Na₂SO₄ and concentrated.

After distillation, 11 g of a colourless liquid
are obtained (yield = 80%).

b.p. = 100-110°C (under 1 mm of Hg)

NMR (CDCl₃): 7.15-7.4 (7H, m); 7.55 (1H, m); 8.05 (1H,
dd, J = 7.8 Hz and 1.8 Hz)

b) Nitromethyl 2-trifluoromethoxyphenyl ketone

4.2 ml (75 mmol) of nitromethane are added to a
solution composed of 8.5 g (75 mmol) of potassium tert-
butoxide and 115 ml of dimethyl sulfoxide, maintained
at 15°C. The mixture is stirred for 1 hour at 15°C



- 22 -

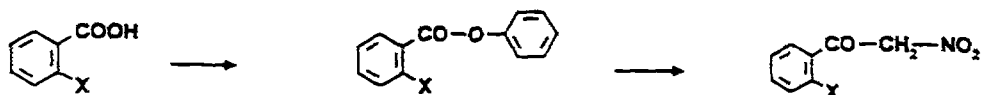
before adding, dropwise, 7 g (25 mmol) of the phenyl ester obtained in step a) above. After stirring for 3 hours at 15-20°C, 68 ml of ice-cold water and 6.8 ml of concentrated hydrochloric acid are added, with stirring, before pouring into 500 ml of an ice-water mixture. The precipitate formed is drained, washed with water and with hexane, before being dried. After recrystallization from an ethyl acetate-hexane mixture, 3 g of a cottony white solid are obtained (yield = 48%).

m.p. = 35-36°C

NMR (DMSO- d_6): 6.3 (2H, s, exchangeable with CF_3COOD); 7.55 (2H, m); 7.8 (1H, m); 7.95 (1H, dd, $J = 7.7$ Hz and 1.6 Hz).

15 Examples 2 to 6

By carrying out the procedure as in Example 1 (a and b), Examples 2 to 6 are obtained:



- 20 Nitromethyl 2-cyanophenyl ketone (Example 2)
 Nitromethyl 2-ethylphenyl ketone (Example 3)
 Nitromethyl 2-trifluoromethylphenyl ketone (Example 4)
 Nitromethyl 2-ethoxyphenyl ketone (Example 5)
 Nitromethyl 2-isopropoxyphenyl ketone (Example 6)



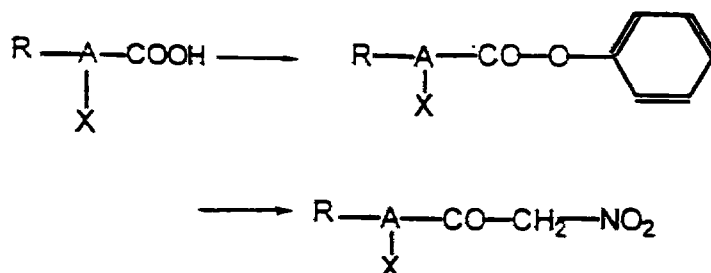
Examples	X	Phenyl esters	Compounds -CO-CH ₂ NO ₂
2	-CN	J. Am. Chem. Soc. (1962) 2196-2201	m.p. = 147-149°C NMR (DMSO-d ₆): 6.75 (2H, s, exchangeable with CF ₃ COOD); 8.1 (2H, m); 8.3 (2H, m)
3	-CH ₂ CH ₃	b.p. _{1.1} = 105-115°C NMR (CDCl ₃): 1.2 (3H, t, J = 7.5 Hz); 3.0 (2H, q, J = 7.5 Hz); 7.1-7.3 (5H, m); 7.35-7.45 (3H, m); 8.05 (1H, dd, J = 6.6 Hz and 1.3 Hz)	m.p. = 62-63°C NMR (DMSO-d ₆): 1.15 (3H, t, J=7.45 Hz); 2.85 (2H, q, J=7.45 Hz); 6.45 (2H, s, exchangeable with CF ₃ COOD); 7.40 (2H, m); 7.6 (1H, m); 7.7 (1H, dd, J = 7.75 Hz and 1.15 Hz)
4	-CF ₃	NMR (CDCl ₃): 7.15 (3H, m); 7.3 (2H, m); 7.55 (2H, m); 7.7 (1H, m); 7.8 (1H, m)	m.p. = 55-57°C NMR (CDCl ₃): 5.9 (2H, s, exchangeable with CF ₃ COOD); 7.75 (1H, m); 7.9 (2H, m); 8.0 (1H, m)
5	-OCH ₂ CH ₃	CA 95 168816 f	m.p. = 145-148°C NMR (DMSO-d ₆): 1.6 (3H, t, J = 7 Hz); 4.35 (2H, q, J = 7 Hz); 6.25 (2H, s, exchangeable with CF ₃ COOD); 7.25 (1H, m); 7.35 (1H, m); 8.15 (1H, m); 8.0 (1H, m)
6	-OCH(CH ₃) ₂	b.p. _{0.5} = 150°C NMR (CDCl ₃): 1.3 (6H, d, J = 6.1 Hz); 4.6 (1H, m, J = 6.1 Hz); 6.95 (2H, m); 7.15 (3H, m); 7.35 (3H, m); 7.85 (1H, dd, J = 7.7 Hz and 1.8 Hz)	m.p. = 78-80°C NMR (DMSO-d ₆): 1.4 (6H, d, J = 6 Hz); 4.9 (1H, m, J = 6 Hz); 6.1 (2H, s, exchangeable with CF ₃ COOD); 7.1 (1H, m); 7.2 (1H, d, J = 8.45 Hz); 7.7 (1H, m); 7.9 (1H, dd, J = 7.85 Hz and 1.8 Hz)

Examples 7 to 9

By carrying out the procedure as in Example 1
5 (a and b), the compounds of Examples 7 to 9 are
obtained:



- 24 -



where R represents $\text{R}_3\text{-Z-(CR}_1\text{R}_2)_p\text{-(E)}_n\text{-}$

Nitromethyl 2-methyl-1-naphthyl ketone (Example 7)

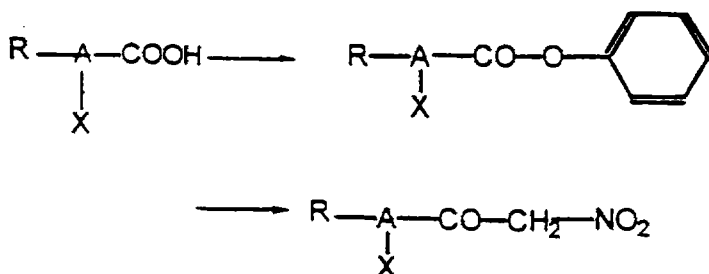
Nitromethyl 3-chloro-2-naphthyl ketone (Example 8)

5 Nitromethyl 3-chlorobenzo[b]thien-2-yl ketone (Example 9)

Examples	R-A- X	Phenyl esters	Compounds -CO-CH ₂ NO ₂
7		m.p. = 65-69°C NMR (CDCl ₃): 1.6 (3H, s); 7.2-7.5 (8H, m); 7.8 (2H, m); 7.95 (1H, m)	m.p. = 126-128°C NMR (CDCl ₃): 2.5 (3H, s); 5.9 (2H, s, exchangeable with CF ₃ COOD); 7.4 (2H, m); 7.7 (2H, m); 8.0 (1H, m); 8.6 (1H, d, J = 0.5 Hz)
8		NMR (DMSO-d ₆): 7.3 (3H, m); 7.5 (2H, m); 7.7 (2H, m); 8.0 (1H, d, J = 8.1 Hz); 8.15 (1H, d, J = 8 Hz); 8.2 (1H, s); 8.8 (1H, s)	m.p. = 109-113°C NMR (DMSO-d ₆): 6.6 (2H, s, exchangeable with CF ₃ COOD); 7.7 (2H, m); 8.0 (2H, m); 8.25 (1H, s); 8.65 (1H, s)
9		Z.Chem (1997) 17, 133-134	m.p. = 158-160°C NMR (DMSO-d ₆): 6.65 (2H, s, exchangeable with CF ₃ COOD); 7.8 (2H, m); 8.15 (1H, dd, J = 7.9 Hz and 0.8 Hz); 8.3 (1H, d, J = 7.9 Hz)

Examples 10 and 11

By carrying out the procedure as in Example 1 (a and b), the compounds of Examples 10 and 11 are obtained:



5

where R represents $\text{R}_3-\text{Z}-(\text{CR}_1\text{R}_2)_p-(\text{E})_n-$

Nitromethyl 6-methoxy-5-trifluoromethyl-1-naphthyl
ketone (Example 10)

4-Methyl-N-[2-nitromethylcarbonyl-3-methylbenzo[b]-
10 thien-5-yl]benzenesulfonamide (Example 11)

This Sheet Has Been Replaced





Examples	R-A- X	Phenyl esters	Compounds -CO-CH ₂ NO ₂
10		m.p. 137-139°C NMR (DMSO-d ₆): 4.1 (3H, s); 7.3-7.5 (3H, m); 7.6 (2H, m); 7.85 (2H, m); 8.4 (2H, m); 9.1 (1H, d, J = 9.75 Hz)	m.p. 146-148°C NMR (DMSO-d ₆): 4.05 (3H, s); 6.6 (2H, s); 6.6 (2H, s exchangeable with CF ₃ COOD); 7.8 (2H, m); 8.15 (1H, d, J= 7Hz) 8.35 (1H, m); 8.85 (1H, d, J = 9.75 Hz)
11		NMR (DMSO-d ₆): 2.35 (3H, s); 2.7 (3H, s); 6.8 (4H, m); 7.1-7.6 (5H, m) 7.9 (2H, m); 8.0 (1H, m); 10.5 (1H, s, exchangeable with CF ₃ COOD)	m.p. 185-190°C NMR (DMSO-d ₆): 2.3 (3H, s); 2.6 (3H, s); 6.45 (2H, s exchangeable with CF ₃ COOD); 7.3 (3H, m) 7.7 (3H, m); 7.9 (1H, d, J = 8.75 Hz); 10.45 (1H, s, exchange- able with CF ₃ COOD)

Example 12**N-[3-Chloro-4-nitromethylcarbonylphenyl]acetamide****a) Phenyl 4-amino-2-chlorobenzoate**

- 5 30 g of phenyl 2-chloro-4-nitrobenzoate prepared according to Makoto Suzuki, Yakugaku Zasshi (1959) 79, 286-90 (CA 53 14991 f) are added to a mixture of 800 ml of water, 60 ml of acetic acid and 96.5 g (1.728 mol) of iron. The reaction medium is heated for 1 hour under reflux. After cooling, the reaction medium is filtered and the solid recovered is washed with ethyl acetate. The aqueous phase is saturated with NaCl before being extracted with ethyl acetate. The combined organic phases are concentrated and purified by chromatography on a silica column with CH₂Cl₂ (yield = 82%).

m.p. = 127-128°C

- 20 NMR (DMSO-d₆): 6.35 (2H, s, exchangeable with CF₃COOD); 6.55 (1H, dd, J = 8.6 Hz and 2.2 Hz); 6.7 (1H, d, J = 2.2 Hz); 7.1-7.3 (3H, m); 7.45 (2H, m); 7.9 (1H, d, J = 8.6 Hz).

b) Phenyl 4-(acetaminol)-2-chlorobenzoate

37 ml (266 mmol) of triethylamine are added to a mixture composed of 60 g (242 mmol) of the amine obtained in step a) above and of 280 ml of dichloromethane, followed by 20.6 ml (290 mmol) of acetyl chloride. After stirring for 2 hours at room temperature, the medium is heated for 2 hours under reflux. After cooling, the reaction medium is thrown over an ice-hydrochloric acid mixture. The organic phase is decanted off and the aqueous phase is extracted with dichloromethane. The combined organic phases are washed with water, dried over Na_2SO_4 and concentrated, to give an oil which crystallizes. (Yield = quantitative)

m.p. = 84-86°C
15 NMR (DMSO-d_6): 2.15 (3H, s); 7.35 (3H, m); 7.5 (2H, m); 7.7 (1H, dd, $J = 8.7$ Hz and 2 Hz); 8.05 (1H, d, $J = 2$ Hz); 8.2 (1H, d, $J = 8.7$ Hz); 10.5 (1H, s, exchangeable with CF_3COOD).

c) N-[3-chloro-4-nitromethylcarbonylphenyl]acetamide

20 The title compound was obtained by carrying out the procedure as in Example 1b from the compound prepared in the preceding step b).

m.p. = 196°C (decomposition)

NMR (DMSO-d_6): 2.3 (3H, s); 6.55 (2H, s, exchangeable with CF_3COOD); 7.8 (1H, dd, $J = 8.7$ Hz and 1.8 Hz); 8.1 (2H, m); 10.7 (1H, s, exchangeable with CF_3COOD).

Example 13Nitromethyl 4-amino-2-chlorophenyl ketone

A mixture of 12.2 g (47.5 mmol) of N-[3-chloro-4-nitromethylcarbonylphenyl]acetamide prepared in Example 12, 11 g (274 mmol) of sodium hydroxide pellets and 161 ml of water is heated at 80°C for 1 hour. After cooling, the reaction medium is diluted with 900 ml of water and acidified to pH 5 by adding acetic acid. The precipitate formed is recovered, washed with water and air-dried before being recrystallized from ethyl acetate (Yield = 27%).

m.p. = 131-133°C



- 28 -

NMR (DMSO- d_6): 6.1 (2H, s, exchangeable with CF_3COOD);
6.45 (3H, m, of which 2H are exchangeable with CF_3COOD);
6.55 (1H, d, $J = 2$ Hz); 7.5 (1H, d, $J = 8.75$ Hz).

Example 145 N-[3-Chloro-4-nitromethylcarbonylphenyl]benzamidea) Phenyl 2-chloro-4-[(benzoylaminol)benzoate

A solution of 2.27 g (16.1 mmol) of benzoyl chloride in 30 ml of dichloromethane is added dropwise to a mixture composed of 4 g (16.1 mmol) of the compound prepared in Example 12a, of 2.26 ml (17.7 mmol) of triethylamine and 40 ml of dichloromethane, maintained at 0°C. The reaction medium is stirred for 1 hour at 0°C and then for 48 hours at room temperature. The dichloromethane is evaporated off. The residue is taken up in water, the solid filtered, washed with water and dried under vacuum at 80°C, to give 5 g of an off-white powder (Yield = 89%).

m.p. = 126-128°C

NMR (DMSO- d_6): 7.3 (3H, m); 7.5-7.7 (5H, m); 8.0 (3H, m); 8.2 (2H, m); 10.8 (1H, s, exchangeable with CF_3COOD).

b) N-[3-chloro-4-nitromethylcarbonylphenyl]benzoate

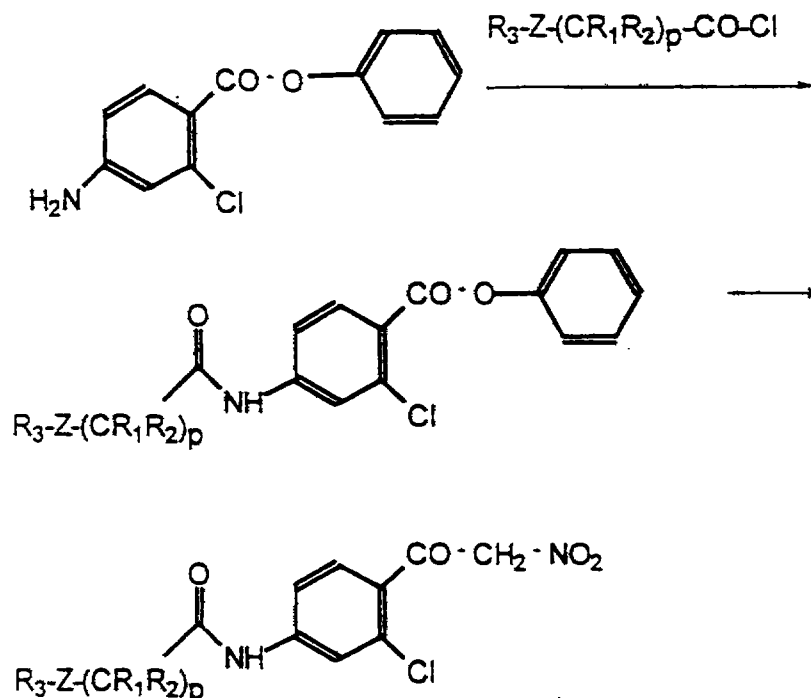
Obtained by carrying out the procedure as in Example 1b (Yield = 57%).

m.p. = 165-167°C

NMR (DMSO- d_6): 6.6 (2H, s, exchangeable with CF_3COOD); 7.7-7.8 (3H, m); 8.1 (4H, m); 8.3 (1H, d, $J = 0.8$ Hz); 10.9 (1H, s, exchangeable with CF_3COOD).

Examples 15 to 27

The compounds of Examples 15 to 27 were obtained from the amine prepared in Example 12a, the procedure being carried out as in Example 14.



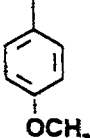
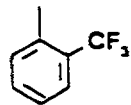
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-chloro-benzamide (Example 15)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-methyl-
5 benzamide (Example 16)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-methoxy-benzamide (Example 17)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-trifluoro-methylbenzamide (Example 18)
- 10 N-[3-Chloro-4-nitromethylcarbonylphenyl]-2,2,3,3-tetra-methylcyclopropanecarboxamide (Example 19)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]cyclopentyl-acetamide (Example 20)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]hexaneamide
15 (Example 21)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-3-phenyl-propaneamide (Example 22)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-phenyl-propaneamide (Example 23)
- 20 N-[3-Chloro-4-nitromethylcarbonylphenyl]phenylacetamide (Example 24)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]benzo[b]-thienyl-2-carboxamide (Example 25)

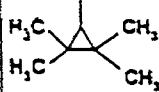
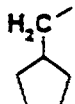


N-[3-Chloro-4-nitromethylcarbonylphenyl]benzofuryl-2-carboxamide (Example 26)

N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-chlorophenoxyacetamide (Example 27).

5

Examples	R3-Z- (CR ₂ R ₂) _p	Phenyl esters	Compounds -CO-CH ₂ NO ₂
15		m.p. 183-186°C NMR (DMSO-d ₆): 7.35 (3H,m); 7.55 (2H,m); 7.7 (2H,d, J = 8.6 Hz); 8.0 (1H,dd, J = 8.7 Hz and 2 Hz); 8.05 (2H,m); 8.25 (2H,m); 10.8 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 151-154°C NMR (DMSO-d ₆): 6.6 (2H,s, exchange- able with CF ₃ COOD); 7.9 (2H,d, J = 8.6 Hz); 8.15 (4H,m); 8.3 (1H,d, J = 1.85 Hz); 10.1 (1H,s, exchange- able with CF ₃ COOD)
16		m.p. 151-152°C NMR (DMSO-d ₆): 2.45 (3H, s); 7.35-7.55 (7H,m); 8.0 (3H,m); 8.25 (2H,m); 10.7 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 180-181°C NMR (DMSO-d ₆): 2.4 (3H,s); 6.4 (2H,s, exchange- able with CF ₃ COOD); 7.4 (2H, d, J = 8 Hz); 8.0 (4H,m); 8.15 (1H,d, J = 1.7 Hz); 10.65 (1H,s, exchangeable with CF ₃ COOD)
17		m.p. 128-131°C NMR (DMSO-d ₆): 3.90 (3H,s); 7.15 (2H,d, J = 8.9 Hz); 7.35 (3H,m); 7.55 (2H,m); 8.0 (3H,m); 8.2 (2H,m); 10.6 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 189-190°C NMR (DMSO-d ₆): 3.95 (3H,s); 6.5 (2H,s, exchange- able with CF ₃ COOD); 7.2 (2H,d, J = 8.8 Hz); 8.05 (4H,m); 8.25 (1H,d, J = 1.7 Hz); 10.7 (1H,s, exchange- able with CF ₃ COOD)
18		m.p. 150-152°C NMR (DMSO-d ₆): 7.5 (3H,m); 7.65 (2H,m); 7.9-8.05 (5H,m); 8.2 (1H,d, J = 1.9 Hz); 8.3 (1H,d, J = 8.6 Hz); 11.3 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 199-201°C NMR (DMSO-d ₆): 6.7 (2H,s, exchange- able with CF ₃ COOD); 8.0-8.3 (7H,m); 11.4 (1H,s, exchange- able with CF ₃ COOD)

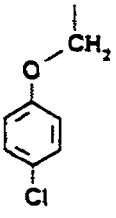
Examples	R3-Z- (CR ₁ R ₂) ₂	Phenyl esters	Compounds -CO-CH ₂ NO ₂
19		NMR (DMSO-d ₆): 1.2 (6H,s); 1.25 (6H,s); 7.3 (3H,m); 7.5 (2H,m); 7.6 (1H,dd, J = 8.7 Hz and 2.1 Hz); 8.0 (1H,d, J = 2.1 Hz); 8.1 (1H,d, J = 8.7 Hz); 10.5 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 94-96°C NMR (DMSO-d ₆): 1.25 (6H,s); 13.0 (6H,s); 1.4 (1H,s); 6.45 (2H,s, exchange- able with CF ₃ COOD); 7.65 (1H,dd, J = 8.7 Hz and 2 Hz); 7.95 (1H,d, J = 8.7 Hz); 8.05 (1H,d, J = 2 Hz); 10.2 (1H,s, exchange- able with CF ₃ COOD)
20	H ₃ C-(CH ₂) ₄ -	m.p. 60-63°C NMR (DMSO-d ₆): 0.95 (3H,t, J = 6.8 Hz); 1.35 (4H,m); 1.7 (2H,m); 2.4 (2H,t, J = 7.35 Hz); 7.35 (3H,m); 7.55 (2H,m); 7.7 (1H,dd, J = 8.7 Hz and 2 Hz); 8.1 (1H,d, J = 2 Hz); 8.2 (1H,d, J = 8.7 Hz); 10.4 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 80-83°C NMR (DMSO-d ₆): 0.90 (3H,t, J = 6.8 Hz); 1.35 (4H,m); 1.65 (2H,m); 2.4 (2H,t, J = 7.3 Hz); 6.45 (2H,s, exchange- able with CF ₃ COOD); 7.7 (1H,dd, J = 8.7 Hz and 1.8 Hz); 7.95 (1H,d, J = 8.7 Hz); 8.0 (1H,d, J = 1.8 Hz); 10.5 (1H,s, exchange- able with CF ₃ COOD)
21		NMR (DMSO-d ₆): 1.1 (2H,m); 1.45-1.7 (6H,m); 2.15 (1H,m); 2.3 (2H,d, J = 7.3 Hz); 7.25 (3H,m); 7.4 (2H,m); 7.6 (1H,dd, J = 8.7 Hz and 2.0 Hz); 8.0 (1H,d, J = 2.0 Hz); 8.05 (1H,d, J = 8.7 Hz); 10.3 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 113-115°C NMR (DMSO-d ₆): 0.95 (2H,m); 1.3 (4H,m); 1.5 (2H,m); 2.0 (1H,m); 2.1 (2H,d, J = 7.35 Hz); 6.15 (2H,s, exchange- able with CF ₃ COOD); 7.4 (1H,dd, J = 8.7 Hz and 2 Hz); 7.7 (2H,m); 10.2 (1H,s, exchange- able with CF ₃ COOD)

This Sheet Has Been Replaced





Examples	R3-Z- (CH ₂ R ₂) _p	Phenyl esters	Compounds -CO-CH ₂ NO ₂
22		NMR (DMSO-d ₆): 2.7 (2H, t, J = 7.7 Hz); 2.95 (2H, t, J = 7.7 Hz); 7.3 (8H, m); 7.5 (2H, m); 7.65 (1H, dd, J = 8.7 Hz and 2 Hz); 8.0 (1H, d, J = 2 Hz); 8.1 (1H, d, J = 8.7 Hz); 10.5 (1H, s, ex- changeable with CF ₃ COOD)	m.p. 122-123°C NMR (DMSO-d ₆): 2.7 (2H, t, J = 7.7 Hz); 2.9 (2H, t, J = 7.7 Hz); 6.4 (2H, s, exchange- able with CF ₃ COOD); 7.25 (5H, m); 7.6 (1H, dd, J = 8.7 Hz and 2 Hz); 7.9 (2H, m); 10.5 (1H, s, exchange- able with CF ₃ COOD)
23		NMR (DMSO-d ₆): 1.45 (3H, d, J = 7 Hz); 3.9 (1H, q, J = 7 Hz); 7.3-7.5 (10H, m); 7.7 (1H, dd, J = 8.7 Hz and 2 Hz); 8.0 (1H, d, J = 2 Hz); 8.1 (1H, d, J = 8.7 Hz); 10.55 (1H, s, ex- changeable with CF ₃ COOD)	m.p. 136-137°C NMR (DMSO-d ₆): 1.4 (3H, d, J = 7 Hz); 3.85 (1H, q, J = 7 Hz); 6.4 (2H, s, exchangeable with CF ₃ COOD); 7.3 (5H, m); 7.6 (1H, dd, J = 8.7 Hz and 2 Hz); 7.9 (2H, m); 10.6 (1H, s, exchange- able with CF ₃ COOD)
24		m.p. 121-124°C NMR (DMSO-d ₆): 3.8 (2H, s); 7.4 (8H, m); 7.5 (2H, m); 7.75 (1H, dd, J = 8.7 Hz and 2.05 Hz); 8.1 (1H, d, J = 2.05 Hz); 8.2 (1H, d, J = 8.7 Hz); 10.8 (1H, s, ex- changeable with CF ₃ COOD)	m.p. 105-107°C NMR (DMSO-d ₆): 3.85 (2H, s); 6.5 (2H, s, exchange- able with CF ₃ COOD); 7.4-7.5 (5H, m); 7.8 (1H, dd, J = 8.7 Hz and 2 Hz); 8.1 (2H, m); 10.9 (1H, s, exchange- able with CF ₃ COOD)
25		m.p. 176°C NMR (DMSO-d ₆): 7.4 (3H, m); 7.6 (4H, m); 8.0 (1H, dd, J = 8.7 Hz and 2 Hz); 8.15 (2H, m); 8.25 (2H, m); 8.5 (1H, s); 11.0 (1H, s, exchangeable with CF ₃ COOD)	m.p. 210-211°C NMR (DMSO-d ₆): 6.43 (2H, s, exchange- able with CF ₃ COOD); 7.5 (2H, m); 7.9-8.2 (5H, m); 8.45 (1H, s); 11.0 (1H, s, exchange- able with CF ₃ COOD)

Examples	R3-Z- (CR ₁ R ₂) _p	Phenyl esters	Compounds -CO-CH ₂ NC ₂
26		m.p. 186-188°C NMR (DMSO-d ₆): 7.35-7.60 (7H,m); 7.8 (1H,d, J = 8.4 Hz); 7.95 (2H,m); 8.1 (1H,dd, J = 8.7 Hz and 2 Hz); 8.25 (2H,m); 11.05 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 199-200°C NMR (DMSO-d ₆): 6.45 (2H,s, exchange- able with CF ₃ COOD); 7.4 (1H,m); 7.55 (1H,m); 7.85 (1H,m); 7.9 (2H,m); 7.95 (2H,m); 8.2 (1H,s); 11.0 (1H,s, exchangeable with CF ₃ COOD)
27		m.p. 162-164°C NMR (DMSO-d ₆): 4.8 (2H,s); 7.05 (2H,m); 7.25-7.6 (7H,m); 7.8 (1H,m); 8.1 (1H,d, J = 2 Hz); 8.15 (1H,d, J = 8.7 Hz); 10.65 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 190-192°C NMR (DMSO-d ₆): 4.8 (2H,s); 6.4 (2H,s, exchange- able with CF ₃ COOD); 7.0 (2H,m); 7.4 (2H,m); 7.7 (1H,dd, J = 8.75 and 2 Hz); 7.9 (2H,m); 10.6 (1H,s, exchange- able with CF ₃ COOD)

Example 28

2-Chloro-N-[3-chloro-4-nitromethylcarbonylphenyl]phenylacetamide

- 5 a) Phenyl 2-chloro-4-[(2-chlorobenzyl)carbonylamino]-benzoate

1.54 g (8 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride are added to a suspension composed of 2 g (8 mmol) of the compound prepared in Example 12a, of 1.28 g (10.4 mmol) of 4-dimethylaminopyridine, and 80 ml of dichloromethane. The solution obtained is stirred for 15 min at room temperature, before adding 1.45 g (8.4 mmol) of 2-chlorophenylacetic acid in 20 ml of dichloromethane. The solution is stirred for 18 hours at room temperature. 200 ml of water and 20 ml of concentrated HCl are then added. The decanted organic phase is washed with a 1 N HCl solution, and then with a sodium hydroxide solution, and with water until neutral, before being dried over Na₂SO₄ and concentrated. The residue is crys-





- 34 -

tallized from 95° ethanol to give 1.4 g of white powder (Yield = 43%).

m.p. = 160-163°C

NMR (DMSO- d_6): 3.95 (2H,s); 7.3-7.4 (5H,m); 7.5 (4H,m);
 5 7.7 (1H,dd, J = 8.7 Hz and 2.1 Hz); 8.05 (1H,d, J = 2.1 Hz); 8.2 (1H,d, J = 8.7 Hz); 10.8 (1H,s, exchangeable with CF_3COOD).

b) 2-Chloro-N-[3-chloro-4-nitromethylcarbonylphenyl]-phenylacetamide

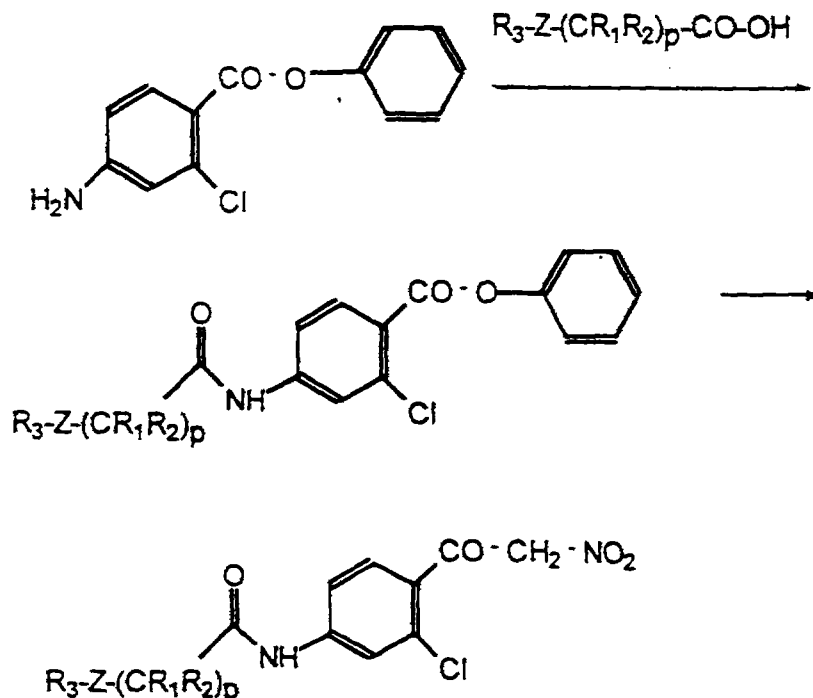
10 This compound was obtained by carrying out the procedure as in Example 1b.

m.p. = 154-156°C

NMR (DMSO- d_6): 3.95 (2H,s); 6.4 (2H,s, exchangeable with CF_3COOD); 7.35 (2H,m); 7.45 (2H,m); 7.7 (1H,dd,
 15 J = 8.7 Hz and 1.9 Hz); 7.95 (2H,m); 10.8 (1H,s, exchangeable with CF_3COOD).

Examples 29 and 30

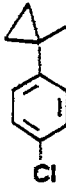
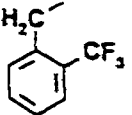
The compounds of Examples 29 and 30 were obtained by carrying out the procedure starting with
 20 the amine prepared in Example 12a as in Example 28.



N-[3-Chloro-4-nitromethylcarbonylphenyl]-1-(4-chlorophenyl)cyclopropylcarboxamide (Example 29)

N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-trifluoromethylphenylacetamide (Example 30)

5

Examples	R3-Z- (CR ₂ R ₂) _p	Phenyl esters	Compounds -CO-CH ₂ NO ₂
29		m.p. 119-121°C NMR (DMSO-d ₆): 1.25 (2H,m); 1.6 (2H,m); 7.3-7.55 (9H,m); 7.8 (1H,dd, J = 8.7 Hz and 2 Hz); 8.0 (1H,d, J = 2 Hz); 8.15 (1H,d, J = 8.7 Hz); 9.7 (1H,s, exchange- able with CF ₃ COOD)	m.p. 159-160°C NMR (DMSO-d ₆): 1.2 (2H,m); 1.5 (2H,m); 6.4 (2H,s, exchange- able with CF ₃ COOD); 7.4 (4H,s); 7.7 (1H,m); 7.9 (2H,m); 9.6 (1H,s, exchange- able with CF ₃ COOD)
30		m.p. 160-162°C NMR (DMSO-d ₆): 4.05 (2H,s); 7.35 (3H,m); 7.5-7.8 (7H,m); 8.05 (1H,d, J = 2 Hz); 8.2 (1H,d, J = 8.7 Hz); 10.8 (1H,s, ex- changeable with CF ₃ COOD)	m.p. 160-162°C NMR (DMSO-d ₆): 4.0 (2H,s); 6.4 (2H,s, exchange- able with CF ₃ COOD); 7.5-7.75 (5H,m); 7.9 (2H,m); 10.7 (1H,s, exchange- able with CF ₃ COOD)

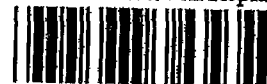
Example 31

N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-chloro-
benzenesulfonamide

10 A mixture composed of 2 g (9.3 mmol) of the
amine obtained in Example 13, 1.5 ml (18.5 mmol) of
pyridine, 2.95 g (13.9 mmol) of 4-chlorobenzenesulfonic
acid chloride and 80 ml of THF is heated for 16 h at
40°C. After cooling, 100 ml of water and 5 ml of con-
15 centrated hydrochloric acid are added before extracting
with ethyl acetate. The organic phase is washed with a
dilute sodium hydroxide solution. This aqueous phase is
then acidified with HCl and extracted with ethyl ace-
tate, which is then washed with water until neutral,
20 dried over Na₂SO₄ and concentrated under vacuum. The

This Sheet Has Been Replaced





- 36 -

residue is purified by chromatography on a silica column in a dichloromethane/methanol (98:2) mixture.

NMR (DMSO- d_6): 6.25 (2H, s, exchangeable with CF_3COOD); 7.0-7.3 (3H,m); 7.6-7.9 (4H,m); 11.2 (1H, broad s, exchangeable with CF_3COOD).

Example 32

N-[3-Chloro-4-nitromethylcarbonylphenyl]benzene-sulfonamide

a) Phenyl-2-chloro-4-[phenylsulfonylamino]benzoate

10 A mixture composed of 10 g (40.4 mmol) of the amine prepared in Example 12a, 6.5 ml (80.4 mmol) of pyridine, 10.7 g (60.5 mmol) of benzenesulfonic acid chloride and 200 ml of THF is stirred for 2 hours at room temperature, before being heated at 40°C for 14
15 hours. After cooling, 200 ml of water and 5 ml of concentrated HCl are added. The reaction medium is extracted with dichloromethane, which is then washed with water until neutral, dried over Na_2SO_4 and concentrated under vacuum. The residue, purified by chromatography
20 on a silica column with dichloromethane, gives 14.5 g of a light orange powder (Yield = 92%).

m.p. = 130-140°C

NMR (DMSO- d_6): 7.2-7.4 (5H,m); 7.5 (2H,m); 7.65 (3H,m); 7.8 (2H,dd, J = 7.5 Hz and 0.8 Hz); 8.1 (1H,d, J =
25 7.5 Hz); 11.25 (1H,s, exchangeable with CF_3COOD).

b) N-[3-Chloro-4-nitromethylcarbonylphenyl]benzene-sulfonamide

The compound was obtained by carrying out the procedure as in Example 1b.

30 NMR (DMSO- d_6): 6.4 (2H,s, exchangeable with CF_3COOD); 7.25 (2H,m); 7.7 (3H,m); 7.9 (3H,m); 11.2 (1H, broad s, exchangeable with CF_3COOD).

Example 33

Nitromethyl 2-chloro-4-[N,N-di(phenylmethyl)amino]-phenyl ketone

a) Phenyl 2-chloro-4-[N,N-di(phenylmethyl)amino]-benzoate

A mixture of 2.5 g (10 mmol) of the amine prepared in Example 12a, 2.7 g (20 mmol) of potassium car-

bonate, 6.8 g (40 mmol) of benzyl bromide, a few crystals of potassium iodide and 100 ml of dimethylformamide is heated at 80°C for 6 hours. After cooling, the reaction medium is poured into 300 ml of water, extracted with ethyl acetate, which is then washed with water, dried over Na₂SO₄ and concentrated. The residual oil is triturated in hexane and the solid obtained is recrystallized from ethanol, to give 1.6 g of an off-white solid (Yield = 37%).

10 m.p. = 133-135°C

NMR (DMSO-d₆): 4.8 (4H,s); 6.7-6.85 (2H,m); 7.1-7.5 (15H,m); 7.9 (1H,m)

b) Nitromethyl 2-chloro-4-[N,N-di(phenylmethyl)]-aminophenyl ketone

15 This compound was obtained by carrying out the procedure as in Example 1b (Yield = 40%).

m.p. 116-118°C

NMR (DMSO-d₆): 4.9 (4H,s); 6.25 (2H, s, exchangeable with CF₃COOD); 6.8-6.9 (2H,m); 7.2-7.5 (10H,m); 7.7

20 (1H,d, J = 9 Hz)

Example 34

N-[2-Chloro-3-nitromethylcarbonylphenyl]acetamide

a) Phenyl 3-amino-2-chlorobenzoate

25 This compound was obtained from phenyl 2-chloro-3-nitrobenzoate by carrying out the procedure as in Example 12a (Yield = 97%).

m.p. = 46-48°C

NMR (DMSO-d₆): 5.5 (2H,s, exchangeable with CF₃COOD); 6.85 (1H,dd, J = 7.45 Hz and 2.3 Hz); 7.0 (2H,m); 7.1

30 (3H,m); 7.3 (2H,m)

b) Phenyl 3-acetyl-amino-2-chlorobenzoate

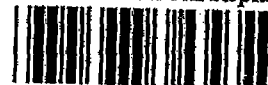
This compound was obtained by carrying out the procedure as in Example 12b (Yield = 60%).

m.p. = 120-122°C

35 NMR (DMSO-d₆): 2.2 (3H, s); 7.4 (3H, m); 7.55 (3H, m); 7.9 (1H, m); 8.0 (1H, m); 9.8 (1H, s, exchangeable with CF₃COOD)

c) N-[2-Chloro-3-nitromethylcarbonylphenyl]acetamide





- 38 -

This compound was obtained by carrying out the procedure as in Example 1b.

m.p. = 140-142°C

NMR (DMSO-d₆): 2.2 (3H, s); 6.5 (2H, s, exchangeable with CF₃COOD); 7.6 (1H, m); 7.8 (1H, dd, J = 8 Hz and 1.3 Hz); 8.1 (1H, dd, J = 8 Hz and 1.3 Hz); 9.8 (1H, s, exchangeable with CF₃COOD)

Example 35

N-[2-Chloro-3-nitromethylcarbonylphenyl]-2-methyl-phenylacetamide

a) Phenyl 2-chloro-3-[(2-methylbenzyl)carbonylamino]-benzoate

This compound was obtained from phenyl 3-amino-2-chlorobenzoate and (2-methylphenyl)acetic acid chloride, the procedure being carried out as in Example 14a (Yield = 78%).

m.p. = 123-125°C

NMR (CDCl₃): 2.3 (3H, s); 3.75 (2H, s); 7.1-7.4 (10H, m); 7.65 (1H, m); 7.8 (1H, broad s, exchangeable with CF₃COOD); 8.6 (1H, dd, J = 8.3 Hz and 1.55 Hz)

b) N-[2-Chloro-3-nitromethylcarbonylphenyl]-2-methyl-phenylacetamide

This compound was obtained by carrying out the procedure as in Example 1b (Yield = 45%).

m.p. = 130-132°C

NMR (DMSO-d₆): 2.25 (3H, s); 3.8 (2H, s); 6.4 (2H, s, exchangeable with CF₃COOD); 7.1 (3H, m); 7.2 (1H, m); 7.45 (1H, m); 7.6 (1H, dd, J = 7.75 Hz and 1.4 Hz); 7.9 (1H, dd, J = 8.1 Hz and 1.3 Hz); 9.8 (1H, s, exchangeable with CF₃COOD)

Example 36

N-[4-Chloro-3-nitromethylcarbonylphenyl]acetamide

a) Phenyl 2-chloro-5-nitrobenzoate

This compound was obtained from 2-chloro-5-nitrobenzoic acid, the procedure being carried out as in Example 1a (Yield = 92%).

m.p. = 83-85°C

NMR (DMSO- d_6): 7.4 (3H, m); 7.55 (2H, m); 8.0 (1H, d, J = 8.8 Hz); 8.5 (1H, dd, J = 8.8 Hz and 2.7 Hz); 8.95 (1H, d, J = 2.7 Hz)

b) Phenyl 5-amino-2-chlorobenzoate

5 18 g of Raney nickel are added to a solution of 59 g (212 mmol) of the compound prepared in step a) in 600 ml of dioxane. The mixture is hydrogenated at a pressure of 70 kg at 65°C. After filtration of the catalyst and concentration of the solvent, the residue
10 is purified by chromatography on a silica column in dichloromethane and then in a dichloromethane/hexane (1:1) mixture to give 29.3 g of a yellow solid (Yield = 55%).

m.p. = 84-86°C

15 NMR (CDCl₃): 3.8 (2H, broad s, exchangeable with CF₃COOD); 6.7 (1H, m); 7.2 (5H, m); 7.35 (2H, m)

c) Phenyl 5-acetylamino-2-chlorobenzoate

This compound was obtained from the amine prepared in step b), the procedure being carried out as in
20 Example 12b (Yield = 69%).

m.p. = 141-143°C

NMR (DMSO- d_6): 1.95 (3H, s); 7.2 (3H, m); 7.35 (2H, m); 7.5 (1H, d, J = 8.7 Hz); 7.75 (1H, dd, J = 8.7 Hz and 2.6 Hz); 8.25 (1H, d, J = 2.6 Hz); 10.25 (1H, s,
25 exchangeable with CF₃COOD)

d) N-[4-Chloro-3-nitromethylcarbonylphenyl]acetamide

The compound was obtained by carrying out the procedure as in Example 1b (Yield = 15%).

m.p. = 122-124°C

30 NMR (DMSO- d_6): 2.2 (3H, s); 6.45 (2H, s exchangeable with CF₃COOD); 7.7 (1H, d, J = 8.7 Hz); 7.9 (1H, dd, J = 8.7 Hz and 2.5 Hz); 8.2 (1H, d, J = 2.5 Hz); 10.5 (1H, s, exchangeable with CF₃COOD)

Example 37

35 N-[4-Chloro-3-nitromethylcarbonylphenyl]-2-methylphenyl-acetamide

a) Phenyl 2-chloro-5-[(2-methylbenzyl)carbonylamino]-benzoate

This Sheet Has Been Replaced





- 40 -

This compound was obtained from the amine prepared in Example 36b, and (2-methylphenyl)acetic acid chloride, the procedure being carried out as in Example 14a (Yield = 94%).

5 m.p. = 102-104°C

NMR (CDCl₃): 2.25 (3H, s); 3.75 (2H, s); 7.1-7.25 (9H, m, of which 1H is exchangeable with CF₃COOD); 7.35 (3H, m); 7.7 (1H, dd, J = 8.7 Hz and 2.2 Hz); 7.85 (1H, d, J = 2.2 Hz).

10 b) N-[4-Chloro-3-nitromethylcarbonylphenyl]-2-methyl-phenylacetamide

This compound was obtained by carrying out the procedure as in Example 1b (Yield = 38%).

m.p. = 148-150°C

15 NMR (DMSO-d₆): 2.3 (3H, s); 3.8 (2H, s); 6.4 (2H, s, exchangeable with CF₃COOD); 7.2 (4H, m); 7.6 (1H, d, J = 8.7 Hz); 7.8 (1H, dd, J = 8.7 Hz and 2.5 Hz); 8.2 (1H, d, J = 2.5 Hz); 10.6 (1H, s, exchangeable with CF₃COOD)

Example 38

20 N-[4-Chloro-3-nitromethylcarbonylphenyl]benzene-sulfonamide

a) Phenyl 5-[benzenesulfonylamino]-2-chlorobenzoate

This compound was obtained from the amine prepared in Example 36b by carrying out the procedure as in Example 32a (Yield = 97%).

25 in Example 32a (Yield = 97%).

m.p. = about 50°C

NMR (DMSO-d₆): 7.3-7.7 (10H, m); 7.8 (3H, m); 10.8 (1H, s, exchangeable with CF₃COOD)

30 b) N-[4-Chloro-3-nitromethylcarbonylphenyl]benzene-sulfonamide

This compound was obtained by carrying out the procedure as in Example 1b.

m.p. = 152-154°C

35 NMR (DMSO-d₆): 6.2 (2H, s, exchangeable with CF₃COOD); 7.2 (1H, m); 7.35-7.65 (5H, m); 7.75 (2H, m); 10.8 (1H, s, exchangeable with CF₃COOD)

Example 39

2-[(3-Chloro-4-nitromethylcarbonylphenyl)amino-carbonylmethylaminocarbonyl]benzoic acid



a) Phenyl 2-chloro-4-((1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)methylcarbonylamino)benzoate

This compound was obtained from the amine prepared in Example 12a, and (1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetic acid chloride (prepared from the corresponding acid and SOCl_2 , m.p. = 80-83°C), the procedure being carried out as in Example 14a (Yield = 54%).

m.p. = 220-222°C

10 NMR ($\text{DMSO}-d_6$): 4.55 (2H, s); 7.25 (3H, m); 7.4 (2H, m); 7.6 (1H, m); 7.8-8.0 (5H, m); 8.1 (1H, d, $J = 8.6$ Hz); 10.9 (1H, s, exchangeable with CF_3COOD)

b) 2-[(3-Chloro-4-nitromethylcarbonylphenyl)amino-carbonylmethylaminocarbonyl]benzoic acid

15 1.49 ml of nitromethane are added to a solution composed of 2.9 g (25.5 mmol) of potassium tert-butoxide and 50 ml of DMSO, maintained at a temperature below 20°C. The mixture is stirred for one hour at a temperature below 20°C before adding, dropwise, 3.7 g
20 (8.5 mmol) of the phenyl ester prepared in step a) dissolved in 90 ml of DMSO. After stirring for 16 hours at room temperature, the reaction medium is poured into 750 ml of water. This aqueous phase is washed with ethyl acetate and acidified with HCL. The precipitate
25 formed is filtered, washed with water and dried under vacuum before being recrystallized from acetonitrile to give 2.2 g of a white powder (Yield = 61%).

m.p. = 206-209°C

30 NMR ($\text{DMSO}-d_6$): 4.0 (2H, d, $J = 5.6$ Hz, is converted to singlet with CF_3COOD); 6.3 (2H, s, exchangeable with CF_3COOD); 7.4-8.0 (7H, m); 8.75 (1H, t, $J = 5.6$ Hz, exchangeable with CF_3COOD); 10.3 (1H, s, exchangeable with CF_3COOD); 13.1 (exchangeable with CF_3COOD)

Example 40

35 N-[3-Chloro-4-nitromethylcarbonylphenyl]-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetamide

HCl gas is bubbled for 1.5 hours through a suspension composed of 2 g (4.8 mmol) of the compound prepared in Example 39b and 30 ml of methanol. The heating



- 42 -

of the solution allows the dissolution of the solid at around 60°C. After cooling, the precipitate formed is filtered and recrystallized from acetonitrile to give 0.4 g of an off-white powder (Yield = 19%).

5 m.p. = 121°C (decomposition)

NMR (DMSO-d₆): 4.5 (2H, s); 6.3 (2H, s, exchangeable with CF₃COOD); 7.55 (1H, dd, J = 8.7 Hz and 2 Hz); 7.8-8.0 (6H, m); 10.9 (1H, s, exchangeable with CF₃COOD).

Example 41

10 1-[3-[Chloro-4-nitromethylcarbonylphenyl]-3-(phenylsulfonyl)urea

a) Phenyl 2-chloro-4-[phenylsulfonylaminocarbonyl-amino]benzoate

15 1.5 g (8.2 mmol) of phenylsulfonyl isocyanate in 20 ml of dichloromethane are added, dropwise, to a suspension of 2.08 g (8.4 mmol) of the amine prepared in Example 12a in 40 ml of dichloromethane. Complete solubilization is obtained upon addition of the first drops, followed by the formation of a thick precipitate. After stirring for 16 hours at room temperature, the precipitate is filtered and washed with dichloromethane and dried at 80°C under vacuum to give 2.2 g of a white powder (Yield = 62%).

m.p. = 183-185°C

25 NMR (DMSO-d₆): 7.0-7.9 (13H, m); 9.3 (1H, s, exchangeable with CF₃COOD); 11.0 (1H, s, exchangeable with CF₃COOD)

b) 1-[3-Chloro-4-nitromethylcarbonylphenyl]-3-(phenylsulfonyl)urea

30 This compound was obtained by carrying out the procedure as in Example 1b (Yield = 49%).

m.p. = 168-169°C

35 NMR (DMSO-d₆): 6.35 (2H, s, exchangeable with CF₃COOD); 7.35 (1H, m); 7.5-7.7 (4H, m); 7.8 (1H, d, J = 8.7 Hz); 8.0 (2H, m); 9.5 (1H, s, exchangeable with CF₃COOD); 11.3 (1H, broad s, exchangeable with CF₃COOD).

Example 42

Nitromethyl 3-methyl-2-thienyl ketone

A solution composed of 10 g (70 mmol) of 3-methyl-2-thiophenecarboxylic acid, 3.4 g (56 mmol) of nitromethane and 115 ml of DMF is cooled to 0°C. 11.9 g (72.8 mmol) of diethyl cyanophosphonate in 56 ml of DMF, and then 18.2 g (180 mmol) of triethylamine in 56 ml of DMF are added thereto successively. The medium is then stirred for 2 hours at 0°C and for 21 hours at room temperature. The reaction medium is poured over 1 litre of a toluene/ethyl acetate (1:1) mixture, and extracted with water. This aqueous phase, acidified with 40 ml of acetic acid, is extracted with a toluene/ethyl acetate (1:1) mixture. The organic extracts are washed with water and then with a saturated NaCl solution in water, before being dried over Na₂SO₄ and concentrated. The residue, purified by chromatography on a silica column in dichloromethane and then by recrystallization from an ethyl acetate-hexane mixture, gives 2 g of a pale yellow solid (Yield = 19%).

m.p. = 59-61°C

NMR (CDCl₃): 2.6 (3H, s); 5.7 (2H, s, exchangeable with CF₃COOD); 7.1 (1H, d, J = 4.9 Hz); 7.6 (1H, d, J = 4.9 Hz).

Example 43

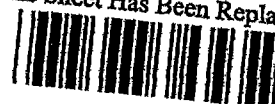
N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-methylphenyl-acetamide

a) 2-Chloro-4-[(2-methylbenzyl)carbonylamino]benzoic acid

19.56 g (116 mmol) of (2-methylphenyl)acetic acid chloride are added, over 1 hour, to a mixture of 20 g (116 mmol) of 4-amino-2-chlorobenzoic acid, 12.9 g (127 mmol) of triethylamine and 150 ml of DMF dried over a molecular sieve. After stirring for 16 h at room temperature, the DMF is removed by evaporation under vacuum. The residue is washed with water and with dichloromethane to give, after drying, 19 g of an off-white powder (Yield = 53%).

m.p. = 214-218°C

This Sheet Has Been Replaced





- 44 -

NMR (DMSO- d_6): 2.25 (3H, s); 3.8 (2H, s); 7.1-7.25 (4H, m); 7.55 (1H, dd, J = 8.6 Hz and 2 Hz); 7.8 (1H, d, J = 8.6 Hz); 7.9 (1H, d, J = 2 Hz); 10.6 (1H, s, exchangeable with CF_3COOD); 13.1 (1H, broad s, exchangeable with CF_3COOD).

b) N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-methyl-phenylacetamide

This compound was obtained by carrying out the procedure as in Example 42 starting with 19 g (62.5 mmol) of 2-chloro-4-[(2-methylbenzyl)carbonylamino]benzoic acid obtained in step a), 3.18 g of nitromethane, 11 g (67.6 mmol) of diethyl cyanophosphate, 16.8 g (167 mmol) of triethylamine in 205 ml of DMF dried over a molecular sieve. After chromatography on a silica column (eluent: dichloromethane-methanol 95:5) and recrystallization from a hexane-ethyl acetate mixture, 0.2 g (Yield = 1%) of a pale yellow powder is obtained.

m.p. = 133-135°C

NMR (DMSO- d_6): 2.3 (3H, s); 3.8 (2H, s); 6.45 (2H, s, exchangeable with CF_3COOD); 7.2-7.3 (4H, m); 7.75 (1H, dd, J = 8.7 Hz and 2 Hz); 7.9 (2H, m); 10.8 (1H, s, exchangeable with CF_3COOD).

Removal of the washings makes it possible to isolate 5.2 g (Overall yield = 30%) of a product identical to the first batch.

This compound is also obtained from the amine prepared in Example 12a by carrying out the procedure as in Example 28.

The phenyl ester intermediate (m.p. = 120-123°C, yield = 56%) is converted to the compound -CO-CH₂-NO₂ (m.p. = 141-143°C (acetonitrile)) with a yield of 43%.

Example 44

N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-oxo-piperidine

a) Phenyl 2-chloro-4-[5-chloropentanovlamino]benzoate

This compound was obtained by carrying out the procedure as in Example 14a, starting with the compound

prepared in Example 12a and 5-chloropentanoic acid chloride.

NMR (DMSO-d₆): 1.8 (4H, m); 2.5 (2H, t, J = 6.7 Hz); 3.75 (2H, t, J = 6.7 Hz); 7.3-7.6 (5H, m); 7.7 (1H, dd, J = 8.7 Hz and 2 Hz); 8.1 (1H, d, J = 2 Hz); 8.2 (1H, d, J = 8.7 Hz); 10.5 (1H, s, exchangeable with CF₃COOD).

b) N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-oxo-piperidine

This compound was obtained by carrying out the procedure as in Example 1b (Yield = 67%).

m.p. = 119-120°C

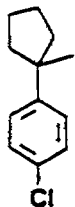
NMR (DMSO-d₆): 1.85 (4H, m); 2.45 (2H, t, J = 6.3 Hz); 3.7 (2H, t, J = 5.5 Hz); 6.4 (2H, s, exchangeable with CF₃COOD); 7.5 (1H, dd, J = 8.5 Hz and 2 Hz); 7.7 (1H, d, J = 2 Hz); 7.9 (1H, d, J = 8.5 Hz)

Examples 45 and 46

The following are obtained starting with the amine prepared in Example 12a, the procedure being carried out as in Example 14:

20 N-[3-Chloro-4-nitromethylcarbonylphenyl]-1-(4-chlorophenyl)cyclopentanecarboxamide (Example 45)

N-[3-Chloro-4-nitromethylcarbonylphenyl]-2,3-dihydro-1H-indene-2-acetamide (Example 46)

Examples	R ₁ -Z-(CR ₂ R ₃) _n	Phenyl esters	Compounds -CO-CH ₂ NO ₂
45		m.p. 118-120°C NMR (DMSO-d ₆): 1.7 (4H, m); 2.0 (2H, m); 2.7 (2H, m); 7.3 (3H, m); 7.5 (6H, m); 7.8 (1H, dd, J = 9 Hz and 2 Hz); 8 (1H, d, J = 2 Hz); 8.15 (1H, d, J = 9 Hz); 9.7 (1H, s, exchangeable with CF ₃ COOD)	m.p. = pasty solid NMR (DMSO-d ₆): 1.6 (4H, m); 1.9 (2H, m); 2.6 (4H, m); 6.4 (2H, s, exchangeable with CF ₃ COOD); 7.4 (4H, s); 7.75 (1H, dd, J = 9 Hz and 2 Hz); 7.9 (1H, d, J = 9 Hz); 7.95 (1H, d, J = 2 Hz); 9.7 (1H, s, exchangeable with CF ₃ COOD)

This Sheet Has Been Replaced



Examples	$R_1-Z-(CR_1R_2)_p$	Phenyl esters	Compounds $-CO-CH_2NO_2$
46		NMR (DMSO- d_6): 2.5 (4H,m); 2.8 (1H,m); 3.1 (2H,m) 7.35 (4H,m); 7.6 (1H,dd, $J = 9$ Hz and 2 Hz); 8 (1H,d, $J = 2$ Hz); 8.1 (1H,d, $J = 9$ Hz); 10.5 (1H,s, exchangeable with CF_3COOD)	m.p. 157-157.5°C NMR (DMSO- d_6): 2.5 (4H,m); 2.8 (1H,m); 3.1 (2H,m); 6.3 (2H,s, exchangeable with CF_3COOD); 7.1 (4H,m); 7.6 (1H,dd, $J = 9$ Hz and 2 Hz); 7.8 (1H,d, $J = 9$ Hz); 7.9 (1H,d, $J = 2$ Hz); 10.4 (1H,s, exchangeable with CF_3COOD)

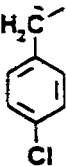
This Sheet Has Been Replaced



Examples 47 to 57

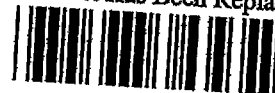
The following are obtained starting with the amine prepared in Example 12a, the procedure being carried out as in Example 28:

- 5 N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-chloro-benzeneacetamide (Example 47)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-3-chloro-benzeneacetamide (Example 48)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-3,4-dichloro-
- 10 benzeneacetamide (Example 49)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-methylbenzeneacetamide (Example 50)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-3-methylbenzeneacetamide (Example 51)
- 15 N-[3-Chloro-4-nitromethylcarbonylphenyl]-3,4-dimethylbenzeneacetamide (Example 52)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-trifluoromethylbenzeneacetamide (Example 53)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-methoxy-
- 20 benzeneacetamide (Example 54)
- N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-nitrobenzeneacetamide (Example 55)
- 4-Bromo-N-[3-chloro-4-nitromethylcarbonylphenyl]-2-fluorobenzeneacetamide (Example 56)
- 25 N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-fluorobenzeneacetamide (Example 57)

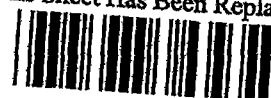
Examples	$R_1-Z-(CR_2R_2)_2$	Phenyl esters	Compounds $-CO-CH_2NO_2$
47		m.p. 140-142°C NMR (DMSO- d_6): 3.8 (2H,s); 7.4 (9H,m); 7.7 (1H,dd, J = 9 Hz and 2 Hz); 8.0 (1H,d, J = 2 Hz); 8.2 (1H,d, J = 9 Hz); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. 158-160°C NMR (DMSO- d_6): 3.6 (2H,s); 6.3 (2H,s, exchangeable with CF_3COOD); 7.4 (4H,m); 7.6 (1H,dd, J = 9 Hz and 2 Hz); 7.9 (2H,m); 10.7 (1H,s, exchangeable with CF_3COOD)



Examples	$R_1Z-(CR_1R_2)_p$	Phenyl esters	Compounds $-CO-CH_2NO_2$
48		m.p. 112-114°C NMR (DMSO- d_6): 3.8 (2H,s); 7.4 (9H,m); 7.75 (1H,dd, J = 9 Hz and 2 Hz); 8.0 (1H,d, J = 2 Hz); 8.2 (1H,d, J = 9 Hz); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. 131-134°C NMR (DMSO- d_6): 3.7 (2H,s); 6.35 (2H,s, exchangeable with CF_3COOD); 7.3 (4H,m); 7.6 (1H,dd, J = 9 Hz and 2 Hz); 7.9 (2H,m); 10.7 (1H,s, exchangeable with CF_3COOD)
49		m.p. 155-158°C NMR (DMSO- d_6): 3.8 (2H,s); 7.2-7.7 (9H,m); 8.0 (1H,d, J = 2 Hz); 8.2 (1H,d, J = 9 Hz); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. = 160-162°C NMR (DMSO- d_6): 3.7 (2H,s); 6.4 (2H,s, exchangeable with CF_3COOD); 7.3 (1H,dd, J = 8 Hz and 2 Hz); 7.6 (3H,m); 7.9 (2H,m); 10.7 (1H,s, exchangeable with CF_3COOD)
50		m.p. = 130-132°C NMR (DMSO- d_6): 2.0 (3H,s); 3.4 (2H,s); 7.1 (7H,m); 7.3 (2H,m); 7.4 (1H,dd, J = 9 Hz and 2 Hz); 7.8 (1H,d, J = 2 Hz); 7.95 (1H,d, J = 9 Hz); 10.4 (1H,s, exchangeable with CF_3COOD)	m.p. = 132-133°C NMR (DMSO- d_6): 2.3 (3H,s); 3.6 (2H,s); 6.3 (2H,s, exchangeable with CF_3COOD); 7.15 (4H,m); 7.6 (1H,dd, J = 9 Hz); 7.9 (2H,m); 10.6 (1H,s, exchangeable with CF_3COOD)
51		m.p. = 126-128°C NMR (DMSO- d_6): 2.3 (3H,s); 3.7 (2H,s); 7.2 (7H,m); 7.5 (2H,m); 7.7 (1H,dd, J = 9 Hz and 2 Hz); 8.1 (1H,d, J = 2 Hz); 8.2 (1H,d, J = 9 Hz); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. = 115-117°C NMR (DMSO- d_6): 2.2 (3H,s); 3.5 (2H,s); 6.3 (2H,s, exchangeable with CF_3COOD); 7.0 (4H,m); 7.55 (1H,dd, J = 7.6 Hz and 1.7 Hz); 7.8 (2H,m); 10.7 (1H,s, exchangeable with CF_3COOD)
52		m.p. = 156-158°C NMR (DMSO- d_6): 2.2 (6H, 2s); 3.7 (2H,s); 7.1 (3H,m); 7.3 (3H,m); 7.5 (2H,m); 7.7 (1H,dd, J = 9 Hz and 2 Hz); 8 (1H,d, J = 2 Hz); 8.15 (1H,d, J = 9 Hz); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. = 128-129°C NMR (DMSO- d_6): 2.1 (6H, 2s); 3.5 (2H,s); 6.25 (2H,s, exchangeable with CF_3COOD); 7.0 (3H,m); 7.5 (1H,dd, J = 9 Hz and 2 Hz); 7.85 (2H,m); 10.7 (1H,s, exchangeable with CF_3COOD)



Examples	$R_1-Z-(CR_2R_3)_p$	Phenyl esters	Compounds $-CO-CH_2NO_2$
53		m.p. = 135-137°C NMR (DMSO- d_6): 3.9 (2H,s); 7.3-7.8 (10H, m); 8.0 (1H,d, J = 2 Hz); 8.15 (1H,d, J = 9 Hz); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. = 164-165°C NMR (DMSO- d_6): 3.8 (2H,s); 6.4 (2H,s, exchangeable with CF_3COOD); 7.6 (5H,m); 7.9 (2H,m); 10.8 (1H,s, exchangeable with CF_3COOD)
54		m.p. = 147-149°C NMR (DMSO- d_6): 3.6 (2H,s); 3.8 (3H,s); 6.9 (2H,s); 7.3 (5H,m); 7.5 (2H,m); 7.7 (1H,dd, J = 8 Hz and 2 Hz); 8.0 (1H,d, J = 2 Hz); 8.15 (1H,d, J = 8 Hz); 10.7 (1H, s, exchangeable with CF_3COOD)	m.p. 147-149°C NMR (DMSO- d_6): 3.75 (2H,s); 3.8 (3H,s); 6.5 (2H,s, exchangeable with CF_3COOD); 7.0 (2H,m); 7.4 (2H,m); 7.7 (1H,dd, J = 9 Hz and 2 Hz); 8.1 (2H,m); 10.8 (1H,s, exchangeable with CF_3COOD)
55		m.p. 180-182°C NMR (DMSO- d_6): 4.0 (2H,s); 7.4 (3H,m); 7.5 (2H,m); 7.7 (3H,m); 8.0 (1H,d, J = 2 Hz); 8.15 (1H, J = 8.5 Hz); 8.25 (2H,m); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. 192-193°C NMR (DMSO- d_6): 3.9 (2H,s); 6.3 (2H, s, exchangeable with CF_3COOD); 7.6 (3H,m); 7.8 (2H, m); 8.2 (2H,m); 10.8 (1H,s, exchangeable with CF_3COOD)
56		m.p. = 173-175°C NMR (DMSO- d_6): 3.9 (2H,s); 7.5 (8H,m); 7.7 (1H,dd, J = 8.6 Hz and 1.9 Hz); 8.1 (1H,d, J = 1.9 Hz); 8.2 (1H,d, J = 8.6 Hz); 10.8 (1H,s, exchangeable with CF_3COOD)	m.p. 165-167°C NMR (DMSO- d_6): 3.8 (2H,s); 6.25 (2H,s, exchangeable with CF_3COOD); 7.3 (2H,m); 7.55 (2H,m); 7.8 (2H,m); 10.7 (1H,s, exchangeable with CF_3COOD)
57		m.p. 132-134°C NMR (DMSO- d_6): 3.75 (2H,s); 7.4 (9H,m); 7.7 (1H,dd, J = 9 Hz and 2 Hz); 8.0 (1H,d, J = 2 Hz); 8.15 (1H,d, J = 9 Hz); 10.7 (1H,s, exchangeable with CF_3COOD)	m.p. 139-141°C NMR (DMSO- d_6): 3.8 (2H,s); 6.5 (2H,s, exchangeable with CF_3COOD); 7.3 (2H,m); 7.5 (2H,m); 7.75 (1H,dd, J = 9 Hz and 2 Hz); 8.0 (2H,m); 10.8 (1H,s, exchangeable with CF_3COOD)

Example 58N-[3-Chloro-4-nitromethylcarbonylphenyl]-2-propenamide

Obtained by carrying out the procedure as in
5 Example 31, starting with the amine prepared in Example
13, in the presence of triethylamine and in
dichloromethane.

m.p. 140-144°C

NMR (DMSO-d₆): 6.35 (2H, s, exchangeable with CF₃COOD);
10 6.8 (1H, d, J = 12 Hz); 7.4 (3H, m); 7.65 (4H, m); 7.9
(1H, d, J = 9 Hz); 8.1 (1H, d, J = 2 Hz); 10.8 (1H, s,
exchangeable with CF₃COOD).

Example 59N-[3-Methyl-4-nitromethylcarbonylphenyl]-2-methylphenyl-
15 acetamidea) Phenyl 2-methyl-4-nitrobenzoate

Obtained by carrying out the procedure as in Exam-
ple 1a, starting with 2-methyl-4-nitrobenzoic acid.

b) Phenyl 4-amino-2-methylbenzoate

20 A mixture composed of 3.5 g (13.6 mmol) of the
nitro derivative prepared in Example 59a, 1 g of Raney
nickel and 35 ml of dioxane is subjected to a hydrogen
pressure of about 100 atm, for 2.5 h at 80°C. After
cooling, filtration of the reaction medium, and
25 concentration, 2.7 g of a pasty solid are obtained.

NMR (DMSO-d₆): 2.5 (3H, s); 6.1 (2H, s, exchangeable
with CF₃COOD); 6.5 (2H, m); 7.2 (3H, m); 7.4 (2H, m);
7.8 (1H, d, J = 8.3 Hz)

c) Phenyl 2-methyl-N-[(2-methylphenyl)carbonylamino]-
30 benzoate

Obtained by carrying out the procedure as in
Example 14a, starting with the amine prepared in
Example 59b and (2-methyl)phenylacetic acid chloride
(Yield = 86%).

35 NMR (DMSO-d₆): 2.3 (3H, s); 2.6 (3H, s); 3.7 (2H, s);
7.1-7.7 (11H, m); 8.1 (1H, d, J = 9 Hz); 10.5 (1H, s,
exchangeable with CF₃COOD).



d) N-[3-Methyl-4-nitromethylcarbonylphenyl]-2-methylphenylacetamide

Obtained by carrying out the procedure as in Example 1b, starting with the phenyl ester prepared in Example 59c.

m.p. 159-160°C

NMR (DMSO-d₆): 2.1 (3H, s); 2.25 (3H, s); 3.5 (2H, s); 6.15 (2H, s, exchangeable with CF₃COOD); 7.0 (4H, m); 7.3 (1H, d, J = 1.6 Hz); 7.45 (1H, dd, J = 8.5 Hz and 1.6 Hz); 7.6 (1H, d, J = 8.5 Hz); 10.4 (1H, s, exchangeable with CF₃COOD)

Example 60

N-[2-Bromo-4-nitromethylcarbonylphenyl]-2-methylphenylacetamide

a) 3-Bromo-4-[(2-methylphenyl)carbonylamino]benzoic acid

Obtained by carrying out the procedure as in Example 43a, starting with 4-amino-3-bromobenzoic acid and 2-methylphenylacetic acid chloride (Yield = 86%).

NMR (DMSO-d₆): 2.1 (3H, s); 3.6 (2H, s); 6.9 (3H, m); 7.0 (1H, m); 7.75 (1H, m); 7.9 (1H, d, J = 1.3 Hz); 9.3 (1H, s, exchangeable with CF₃COOD); 13.0 (1H, broad s, exchangeable with CF₃COOD)

b) Phenyl 3-bromo-4-[(2-methylphenyl)carbonylamino]benzoate

Obtained by carrying out the procedure as in Example 1a (Yield = 98%)

m.p. 139-141°C

NMR (DMSO-d₆): 2.4 (3H, s); 3.9 (2H, s); 7.2-7.5 (9H, m); 8.1 (2H, m); 8.3 (1H, d, J = 1.8 Hz); 9.7 (1H, s, exchangeable with CF₃COOD).

c) N-[2-Bromo-4-nitromethylcarbonylphenyl]-2-methylphenylacetamide

Obtained by carrying out the procedure as in Example 1b (Yield = 41%)

m.p. 125-127°C

NMR (DMSO-d₆): 2.2 (3H, s); 3.7 (2H, s); 6.3 (2H, s, exchangeable with CF₃COOD); 7.1 (4H, m); 7.8 (1H, dd, J



- 52 -

= 9 Hz and 2 Hz); 7.9 (1H, m); 8.1 (1H, d, J = 2 Hz);
9.5 (1H, s, exchangeable with CF₃COOD).

Example 61

Nitromethyl 2-chloro-4-methoxyphenyl ketone

5 a) Phenyl 2-chloro-4-methoxybenzoate

Obtained by carrying out the procedure as in
Example 1a, starting with 2-chloro-4-methoxybenzoic
acid (Yield = 77%)

NMR (CDCl₃): 3.8 (3H, s); 6.8 (1H, dd, J = 9 Hz and
10 2.5 Hz); 6.95 (1H, d, J = 2.5 Hz); 7.15 (3H, m); 7.3
(2H, m); 8.0 (1H, d, J = 9 Hz)

b) Nitromethyl 2-chloro-4-methoxyphenyl ketone

Obtained by carrying out the procedure as in
Example 1b.

15 NMR (DMSO-d₆): 3.9 (3H, s); 6.4 (2H, s, exchangeable
with CF₃COOD); 7.1 (1H, dd, J = 9 Hz and 2.5 Hz); 7.2
(1H, d, J = 2.5 Hz); 7.9 (1H, d, J = 9 Hz)

Example 62

Nitromethyl 2-isopropylphenyl ketone

20 a) Phenyl 2-isopropylbenzoate

Obtained by carrying out the procedure as in
Example 1a, starting with 2-(1-methylethyl)benzoic acid
(Yield = 85%).

NMR (CDCl₃): 1.2 (6H, m); 3.8 (1H, m); 7.1-7.25 (4H, m);
25 7.3-7.5 (4H, m); 7.9 (1H, dd, J = 8 Hz and 1.5 Hz)

b) Nitromethyl 2-isopropylphenyl ketone

Obtained by carrying out the procedure as in
Example 1b
(Liquid)

30 NMR (CDCl₃): 1.5 (6H, m); 3.4 (1H, m); 5.7 (1H, s,
exchangeable with CF₃COOD); 7.2-7.5 (4H, m)

Example 63

N-[4-Chloro-3-nitromethylcarbonylphenyl]-2-methyl-
phenylacetamide

35 a) 5-Chloro-2-[(2-methylphenyl)carbonylamino]benzoic
acid

Obtained by carrying out the procedure as in
Example 43a, starting with 2-amino-5-chlorobenzoic acid
and 2-methylphenylacetic acid chloride (Yield = 75%)

m.p. = 224-226°C NMR (DMSO- d_6): 2.3 (3H, s); 3.8 (2H, s); 7.2 (4H, m); 7.7 (1H, dd, J = 9 Hz and 2.5 Hz); 7.9 (1H, d, J = 2.5 Hz); 8.7 (1H, d, J = 9 Hz); 11.1 (1H, s, exchangeable with CF_3COOD); 14.0 (1H, broad s, exchangeable with CF_3COOD)

b) Phenyl 5-chloro-2-((2-methylphenyl)carbamoylamino)-benzoate

Obtained by carrying out the procedure as in Example 1a (Yield = 38%)

10 c) N-(4-Chloro-2-nitromethylcarbamoylphenyl)-2-methylphenylacetamide

Obtained by carrying out the procedure as in Example 1b.

m.p. = 128-130°C

15 NMR (DMSO- d_6): 2.4 (3H, s); 3.9 (2H, s); 6.5 (2H, s, exchangeable with CF_3COOD); 7.4 (4H, m); 7.9 (1H, dd, J = 9 Hz and 2 Hz); 8.1 (1H, d, J = 2 Hz); 8.3 (1H, d, J = 9 Hz); 10.9 (1H, s, exchangeable with CF_3COOD)

Example 64

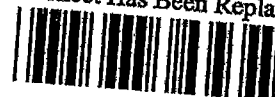
20 Nitromethyl 2-chloro-4-phenylthiophenyl ketone

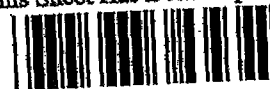
a) Phenyl 2-chloro-4-(phenylthio)benzoate

A solution of 4.15 g (60.5 mmol) of sodium nitrite in 20 ml of water is added, at 0°C, to a suspension of 15 g (60.5 mmol) of the amine prepared in Example 12a, in 12.1 ml of 10 N hydrochloric acid.

After stirring for one hour at 0°C, the medium is neutralized with a saturated sodium acetate solution. This mixture is poured, over 15 minutes, over a solution, at 70-80°C, composed of 8 g (72.6 mmol) of thiophenol, 3.85 g (96 mmol) of sodium hydroxide and 25 ml of water. At the end of the addition, the reaction medium is heated for 1 hour at 95°C. After cooling, the reaction medium is extracted with ethyl acetate. The organic phase, after washing with a dilute sodium hydroxide solution and then with water, is dried over Na_2SO_4 and concentrated under vacuum. The residue is purified by flash chromatography on silica (hexane) to give an orange-yellow liquid (Yield = 31%).

35 NMR (DMSO- d_6): 7.3-7.7 (12H, m); 8.1 (1H, m).



b) Nitromethyl 2-chloro-4-phenylthiophenyl ketone

Obtained by carrying out the procedure as in Example 1b.

m.p. = 77-78°C

5 NMR (DMSO-d₆): 6.5 (2H, s); 7.3 (2H, m); 7.7 (5H, m); 7.95 (1H, d, J = 8.5 Hz)

Example 65

N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-[(3-chloro-4-nitromethylcarbonylphenyl)aminocarbonyl]-3-phenyl-
10 butanamide

a) Phenyl 2-chloro-4-[[[3-chloro-4-(phenoxycarbonyl)phenyl]aminol-1,5-dioxo-3-phenylpentyl]-aminolbenzoate

Obtained by carrying out the procedure as in
15 Example 14, starting with the amine prepared in Example 12a and a 1/2 equivalent of 3-phenylglutaric acid dichloride.

NMR (DMSO-d₆): 2.8 (4H, m); 3.8 (1H, m); 7.1 - 7.6 (17H, m); 7.9 (2H, d, J = 2 Hz); 8.1 (2H, d, J = 9 Hz); 10.4
20 (2H, s, exchangeable with CF₃COOD).

b) N-[3-Chloro-4-nitromethylcarbonylphenyl]-4-[(3-chloro-4-nitromethylcarbonylphenyl)aminocarbonyl]-3-phenylbutanamide

Obtained by carrying out the procedure as in
25 Example 1b.

m.p. 195-196°C

NMR (DMSO-d₆): 2.8 (4H, m); 3.8 (1H, m); 6.4 (4H, s, exchangeable with CF₃COOD); 7.3 (5H, m); 7.5 (2H, dd, J = 9 Hz and 2 Hz); 7.9 (4H, m); 10.5 (s, exchangeable
30 with CF₃COOD).

Example 66

Nitromethyl 2-chloro-4-phenylsulfinylphenyl ketone

a) Phenyl 2-chloro-4-(phenylsulfinyl)benzoate

5 ml (40 mmol) of a 70% tert-butyl
35 hydroperoxide solution in water are added to a suspension of 2 g (5.9 mmol) of the compound prepared in Example 64a in 60 ml of water. The reaction medium is heated at 70° for 32 h. After cooling, the peroxides are destroyed by addition of a solution of 10 g of

sodium metabisulfite in 100 ml of water. After stirring for 2 hours and negative control for the peroxides, the reaction medium is extracted with dichloromethane. The organic phase is washed with a saturated NaCl solution in water and dried over Na_2SO_4 . After concentration of the dichloromethane and purification by flash chromatography on a silica column (hexane-ethyl acetate 4:1), 0.1 g of a colourless oil is obtained (Yield = 4%).

10 NMR ($\text{DMSO}-d_6$): 7.1 (3H, m); 7.2-7.4 (5H, m); 7.7 (3H, m); 7.8 (1H, d, $J = 1.6$ Hz); 8.0 (1H, m)

b) Nitromethyl 2-chloro-4-phenylsulfinyl ketone

Obtained by carrying out the procedure as in Example 1b.

15 (Oil).

NMR ($\text{DMSO}-d_6$): 6.4 (2H, s, exchangeable with CF_3COOD); 6.8 (3H, m); 7.2 (2H, m); 7.6 (3H, m)

Example 67

Nitromethyl 4-chloro-2-trifluoromethoxyphenyl ketone

20 a) Phenyl 4-chloro-2-trifluoromethoxybenzoate

In a hermetically closed steel container, a mixture composed of 21.5 g (112 mmol) of 4-chloro-2-hydroxybenzoic acid chloride, 59.8 g (336 mmol) of antimony trifluoride, 3.2 g of antimony pentafluoride and 258 ml of CCl_4 , is heated at 175°C for 6 h. After cooling, the reaction medium is taken up in about 3 l of dichloromethane. The organic phase is washed with water. The precipitate formed is washed with dichloromethane. The combined organic phases are dried over Na_2SO_4 and concentrated to give 19.2 g of a black liquid which is used without further purification.

35 The 19.2 g of the compound obtained above are mixed with 90 ml of toluene, 75 ml of thionyl chloride and a few drops of DMF, are stirred for 2 h at room temperature. The reaction medium is then concentrated under vacuum. The residue obtained is diluted with 200 ml of dichloromethane before being added to a mixture of 9.8 g of phenol, 16.2 g of triethylamine and 100 ml of dichloromethane. After stirring for 16 h at





room temperature, the reaction medium is poured over an ice + HCL mixture. The mixture is extracted with dichloromethane, which is then washed with a dilute sodium hydroxide solution, and with water before being
5 dried over Na_2SO_4 , and concentrated. The residue is purified with chromatography on silica (hexane-ethyl acetate 4:1) to give 9.2 g of an orange-coloured liquid (Yield = 37%).

b) Nitromethyl 4-chloro-2-trifluoromethoxyphenyl ketone

10 Obtained by carrying out the procedure as in Example 1b.

Pasty solid

NMR (CDCl_3): 5.7 (2H, s, exchangeable with CF_3COOD); 7.3-7.5 (2H, m); 8.0 (1H, d, $J = 9 \text{ Hz}$).

15 Example 68

N-[2-(3-Chloro-4-nitromethylcarbonylphenyl)-2-methyl-benzenesulfonamide

a) Ethyl 2-chloro-4-(cyanomethyl)benzoate

3.1 g (11.2 mmol) of ethyl 4-(bromomethyl)-2-chlorobenzoate are added dropwise to a solution
20 composed of 0.94 g (14.3 mmol) of potassium cyanide, 3.75 ml of water and 8.8 ml of ethanol, heated under reflux. After refluxing for 3 hours, the medium is poured over 200 ml of water, and extracted with ethyl
25 acetate. The organic phase is washed with a dilute HCL solution and then with water saturated with NaCl. The oil obtained after concentration of the organic phase is purified by flash chromatography on silica (hexane-ethyl acetate 1:0 to 1:1 gradient). 0.4 g of a brown
30 solid is obtained (Yield = 16%).

m.p. 60°C

NMR (CDCl_3): 1.4 (3H, t, $J = 7 \text{ Hz}$); 3.8 (2H, s); 4.5 (2H, q, $J = 7 \text{ Hz}$); 7.1 (1H, m); 7.5 (1H, d); 7.9 (1H, d)

35 b) Ethyl 4-(2-aminoethyl)-2-chlorobenzoate

A mixture composed of 1.9 g (8.5 mmol) of ethyl 2-chloro-4-(cyanomethyl)benzoate, 0.5 g of Raney nickel in 70 ml of methanol containing a few ml of liquid ammonia is subjected to a hydrogen pressure of about



60 kg/cm², at 50°C for 5 h, and then at 80°C for 4.5 h. After filtration of the reaction medium, 1.5 g of oil are obtained (Yield = 77%).

NMR (CDCl₃): 1.3 (3H, t, J = 7 Hz); 1.7 (2H, broad s, exchangeable with CF₃COOD); 2.6-3.0 (4H, m); 4.3 (2H, q, J = 7 Hz); 7.0 (1H, m); 7.2 (1H, m); 7.6 (1H, d, J = 6.3 Hz)

c) Ethyl 2-chloro-4-[2-(2-methylphenylsulfonfylamino)-ethyl]benzoate

10 Obtained by carrying out the procedure as in Example 32c (Yield = 43%).

(Oil).

NMR (CDCl₃): 1.3 (3H, t, J = 7 Hz); 2.4 (3H, s); 2.7 (2H, m); 3.1 (2H, m); 4.3 (2H, q, J = 7 Hz); 4.4 (1H, broad s, exchangeable with CF₃COOD); 6.9 (1H, m); 7.0 (1H, m); 7.1-7.4 (3H, m); 7.7 (1H, m); 7.8 (1H, dd, J = 8 Hz and 1.25 Hz)

d) 2-Chloro-4-[2-(2-methylphenylsulfonfylamino)-ethyl]benzoic acid

20 A mixture composed of 1 g (2.6 mmol) of the ethyl ester previously prepared, 18 ml of methanol, 18 ml of water and 0.2 g (5.2 mmol) of NaOH pellets, is heated for 4 h at 40°C. After concentration of the methanol and addition of 30 ml of water, the medium is washed with CH₂Cl₂. The aqueous phase is then acidified to give 0.675 g of a white precipitate (Yield = 72%).

m.p. 122-124°C

NMR (DMSO-d₆): 2.3 (3H, s); 2.7 (2H, m); 3.0 (2H, m); 7.0-7.8 (8H, m, of which 1H is exchangeable with CF₃COOD); 13.1 (1H, broad s, exchangeable with CF₃COOD)

30 e) Phenyl 2-chloro-4-[2-(2-methylphenylsulfonfylamino)-ethyl]benzoate

Obtained by carrying out the procedure as in 1a as the whole (Yield = 61%).

35 (Oil).

NMR (CDCl₃): 2.4 (3H, s); 2.7 (2H, m); 3.2 (2H, m); 4.1 (1H, m, exchangeable with D₂O); 7.0-8.0 (12H, m)



- 58 -

f) N-[2-(3-Chloro-4-nitromethylcarbonylphenyl)ethyl]-2-methylbenzenesulfonamide

Obtained by carrying out the procedure as in Example 1b.

5 (Oil).

NMR (CDCl₃): 2.5 (3H, s); 2.7 (2H, t, J = 5 Hz); 3.2 (2H, t, J = 5 Hz); 4.4 (1H, broad s, exchangeable with CF₃COOD); 5.8 (2H, s, exchangeable with CF₃COOD); 7.0-7.5 (5H, m); 7.6 (1H, m); 7.9 (1H, m)

10 Example 69

N-[3-Bromo-4-nitromethylcarbonylphenyl]-2-methylphenyl-acetamide

a) 2-Bromo-4-[(2-methylbenzyl)carbonylamino]benzoic acid

15 Obtained by carrying out the procedure as in Example 43, starting with 4-amino-2-bromobenzoic acid (Yield = 23%).

m.p. = decomposition at 205°C

20 NMR (DMCO-d₆): 2.4 (3H, s); 3.9 (2H, s); 7.2 (4H, m); 7.6 (1H, dd, J = 9 Hz and 2 Hz); 7.9 (1H, d, J = 9 Hz); 8.2 (1H, d, J = 2 Hz); 10.7 (1H, s, exchangeable with CF₃COOD); 13.0 (1H, broad s, exchangeable with CF₃COOD)

b) Phenyl 2-bromo-4-[(2-methylbenzyl)carbonylamino]benzoate

25 Obtain by carrying out the procedure as in Example 14a (Yield = quantitative) (Oil).

30 NMR (DMSO-d₆): 2.0 (3H, s); 3.7 (2H, s); 6.8-7.3 (9H, m); 7.5 (1H, dd, J = 8 Hz and 2 Hz); 7.8 (1H, d, J = 8 Hz); 8.0 (1H, d, J = 2 Hz); 10.5 (1H, s, exchangeable with CF₃COOD)

c) Phenyl 2-bromo-4-[(2-methylbenzyl)carbonylamino]benzoate

35 Obtained by carrying out the procedure as in Example 1b (Oil).

NMR (DMSO-d₆): 2.4 (3H, s); 3.8 (2H, s); 6.5 (2H, s, exchangeable with CF₃COOD); 7.2-7.6 (4H, m); 7.8 (1H,

dd, $J = 9$ Hz and 2 Hz); 8.0 (1H, d, $J = 9$ Hz); 8.3 (1H, d, $J = 2$ Hz); 10.9 (1H, s, exchangeable with CF_3COOD)

Example 70

N-[3-Chloro-4-nitromethylcarbonylphenyl]-N-isopropyl-
5 benzenesulfonamide

a) Phenyl 2-chloro-4-[(isopropyl)(phenylsulfonyl)-
aminol]benzoate

10 10.1 g (25.5 mmol) of sodium hydride (at 55% in oil) are added to a solution of 9.9 g (25.5 mmol) of the compound prepared in Example 32a, in 100 ml of DMF. After stirring for 1 hour at room temperature, 9.4 g (76.5 mmol) of 2-bromopropane are added and the medium is stirred at room temperature for 16 hours before heating at 60°C for 34 hours. 5.1 ml (51 mmol) of
15 2-iodopropane are then added. The reaction medium is then heated for 4 hours at 60°C before being poured over a water-ice-HCl mixture. The medium is extracted with ethyl acetate, which is then dried and concentrated to give an oil. After purification by
20 chromatography on a silica column (CH_2Cl_2) 1.9 g of off-white crystals are obtained (Yield = 17%).

m.p. 120°C

NMR ($\text{DMSO}-d_6$): 1.0 (6H, d, $J = 6.5$ Hz); 4.4 (1H, m); 7.1-7.9 (12H, m); 8.0 (1H, d, $J = 8$ Hz)

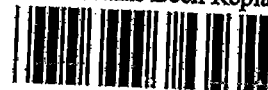
25 b) N-[3-Chloro-4-nitromethylcarbonylphenyl]-N-
isopropylbenzenesulfonamide

Obtained by carrying out the procedure as in Example 1b, starting with the phenyl ester prepared in Example 65a.

30 (Oil)

NMR (CDCl_3): 1.0 (6H, d, $J = 7$ Hz); 4.5 (1H, q, $J = 7$ Hz); 5.8 (2H, s, exchangeable with CF_3COOD); 7.0 (1H, dd, $J = 9$ Hz and 2 Hz); 7.15 (1H, m); 7.35-7.7 (6H, m)

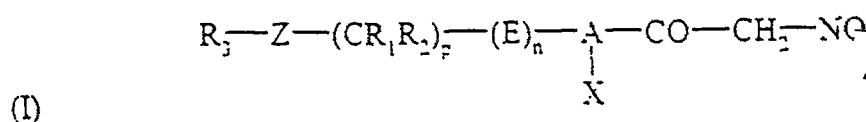
This Sheet Has Been Replaced



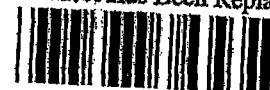


THE CLAIMS :

1. A method of treating a condition by inhibition of aldose reductase which comprises administering to a patient in need thereof an aldose reductase inhibiting amount of a compound of the formula:



This Sheet Has Been Replaced



in which

A represents C_6-C_{10} -aryl or an optionally aromatic three- to ten-membered heterocycle in which one to four ring atoms are identical or different heteroatoms chosen from O, S and N; X represents halogen, cyano, C_1-C_7 -alkyl, trifluoromethyl, C_2-C_7 -alkoxy or trifluoromethoxy;

R_1 and R_2 , which are identical or different, represent a hydrogen atom, a C_1-C_7 -alkyl group, a C_3-C_{12} -cycloalkyl group, a trifluoromethyl group, a C_1-C_7 -alkoxy group or R_1 and R_2 together form an alkylene chain $-(CH_2)_r-$, where r is chosen from 2, 3 and 4;

p is chosen from 0, 1, 2, 3, 4 and 5;

Z represents a bond, the divalent radical $-CO-NH-$ in which the carbonyl function is linked to R_3 , the divalent radical $-SO_2-NH-$ in which the sulfonyl function is linked to R_3 , a C_2-C_7 -alkenylene radical, a sulfur atom, the sulfinyl radical or the sulfonyl radical;

R_3 represents a hydrogen atom; a halogen atom; a tri- $(C_1-C_7$ -alkyl)silyl group; a C_1-C_7 -alkyl group optionally substituted with one or more identical or different Y radicals; a C_6-C_{10} -aryl group optionally substituted with one or more identical or different Y radicals; a C_6-C_{10} -aryloxy group optionally substituted with one or more identical or different Y radicals; a C_3-C_{12} -cycloalkyl group optionally substituted with one or more identical or different Y radicals; an optionally aromatic three- to ten-membered heterocycle in which one to four ring atoms are identical or different heteroatoms chosen from O, S and N, the heterocycle being optionally substituted with one or more identical or different Y radicals, or R_3 represents indanyl, 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl, 1,3-benzodioxolyl, 2-oxopiperidinyl or 2-[(4-nitromethylcarbonyl-3-



chlorophenyl)aminocarbonyl]-1-(phenyl)ethyl;

Y represents a halogen atom, C_1 - C_7 -alkyl, C_1 - C_7 -alkoxy, trifluoromethyl, carboxy, carbamoyl, $(C_1$ - C_7)alkylcarbamoyl, di- $(C_1$ - C_7)alkylcarbamoyl, C_1 - C_7 -alkoxycarbonyl, amino, C_1 - C_7 -alkylamino, di- $(C_1$ - C_7)-alkylamino, nitro, cyano, hydroxy, trifluoromethoxy, C_3 - C_{12} -cycloalkyl, sulfo, C_1 - C_7 -alkylthio, C_1 - C_7 -alkylsulfinyl, C_1 - C_7 -alkylsulfonyl, C_2 - C_8 -alkylcarbonyl, C_2 - C_8 -alkylthiocarbonyl, C_2 - C_8 -alkylcarbonylamino, or C_6 - C_{10} -aryl;

E represents a divalent radical chosen from:

(i) $-\text{CO}-\text{NR}_4-$ in which the carbonyl group is linked to $-(\text{CR}_1\text{R}_2)_p-$ and R_4 represents the radical $-(\text{CH}_2)_q-\text{R}_5$ where q is chosen from 0 and 1; and where R_5 represents a hydrogen atom; a C_1 - C_7 -alkyl group, a C_6 - C_{10} -aryl group or an optionally aromatic three- to ten-membered heterocycle in which one to four ring atoms are identical or different heteroatoms chosen from O, N and S; or R_5 and R_3 together form a bond;

(ii) $-\text{SO}_2-\text{NR}_4-$ in which the sulfonyl group is linked to $-(\text{CR}_1\text{R}_2)_p-$ and R_4 is as defined above;

(iii) $-\text{NR}_4-$ in which R_4 is as defined above;

(iv) $-\text{CH}=\text{N}-$ in which the nitrogen atom is linked to A; and

(v) an oxygen atom;

n represents 0 or 1;

— with the proviso that:

A is an optionally aromatic three- to ten-membered heterocycle in which one to four ring atoms are identical or different heteroatoms chosen from O, S and N,

Z is a sulfur atom, sulfinyl radical or sulfinyl radical,

R^3 is an optionally aromatic three- to ten-membered heterocycle in which one to four ring atoms are identical or different heteroatoms chosen from O, S and N, the heterocycle being optionally substituted with one or more identical or different Y radicals, or R^3 is indanyl, 1,3-dihydro-1,3-dioxo-2H-isindol-2-yl, 1,3-benzodioxolyl or 2-oxopiperidinyl; and/or

E is an optionally aromatic three- to ten-membered heterocycle in which one to four ring atoms are identical or different heteroatoms chosen from O, S and N, or E is $-\text{NR}_4-$, $-\text{CH}=\text{N}-$ or an oxygen atom; when n is 1,

This Sheet Has Been Replaced





- with the proviso that $-A(X)-(E)_n-(CR_1R_2)_p-Z-R_3$ does not represent halophenyl, methylphenyl, dichlorophenyl, dimethylphenyl, 4-ethoxy-2-methylaminophenyl, methylindolyl, dimethylindolyl, 2-hydroxyphenyl substituted with a group X, 2-methoxyphenyl substituted with a group X and optionally substituted 2-fluorophenyl as defined above, and
- with the proviso that when A represents pyridyl, X represents methyl and n is equal to 1, E does not represent $-NR_4-$;
- or an addition salt thereof with a pharmaceutically acceptable base.

2. The method of claim 1, wherein the condition is a complication from diabetes.
3. The method of claim 2, wherein the complication is cataract, retinopathy, neuropathy, nephropathy and/or a vascular disease.
4. A method according to claim 1, in which A represents phenyl and n and p represent 0, Z represents a bond and R_3 represents a hydrogen atom.
5. A method according to claim 1, in which A represents phenyl, n and p are equal to 1, E represents $-CO-NR_4-$, R_1 and R_2 represent a hydrogen atom and Z represents a bond.
6. A method according to claim 1, in which A represents phenyl, n is equal to 1 and E represents $-SO_2-NR_4-$.
7. A method according to claim 1, in which A represents phenyl, n is equal to 1, E represents $-CO-NR_4-$, p is equal to 0 and Z represents the divalent radical $-SO_2-NH-$ in which SO_2 is linked to R_3 .
8. A method according to claim 1, in which A represents an aromatic heterocycle.

This Sheet Has Been Replaced





9. A method according to claim 1, in which A represents naphthyl.
10. A method according to claim 1, in which n is 1 and E represents an oxygen atom.
11. A method according to claim 1, in wherein the compound is chosen from:
nitromethyl 3-methyl-2-thienyl ketone, or
4-methyl-N-[2-nitromethylcarbonyl-3-methylbenzo[b]thien-5-yl]benzenesulfonamide. --

This Sheet Has Been Replaced

