

PATENT SPECIFICATION

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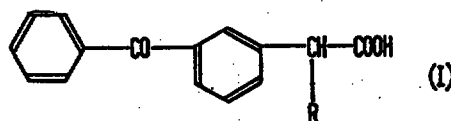


(54) NEW PROCESS FOR THE PREPARATION OF (3-BENZOYLPHENYL)ALKANOIC ACIDS

(71) We, RHONE-POULENC S.A., a French Body Corporate of 22 Avenue Montaigne, Paris 8e, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new process for the preparation of therapeutically useful (3 - benzoylphenyl) - alkanolic acids.

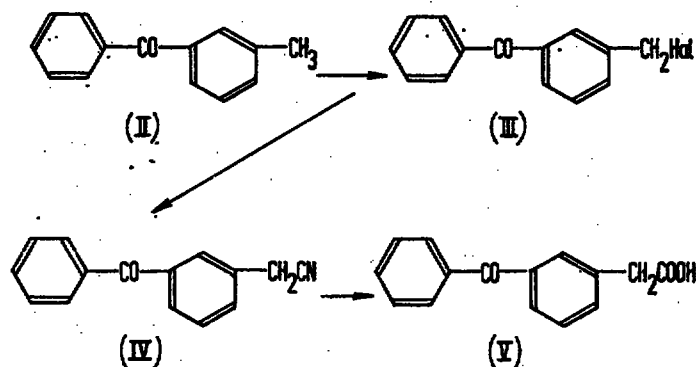
It is known from the specifications of French Patent No. 1,546,478 and its Addition No. 94,930 granted to Societe des Usines Chimiques Rhone-Poulenc on applications filed 27th January, 1967 and 15th December, 1967 respectively that (3 - benzoylphenyl) - alkanolic acids of the general formula:



(wherein R represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, and the benzene rings can optionally be substituted by one or more halogen atoms or alkoxy or alkylthio radicals containing 1 to 4 carbon atoms, or trifluoromethyl radicals) and salts thereof possess useful pharmacodynamic properties and are particularly useful as anti-inflammatory agents.

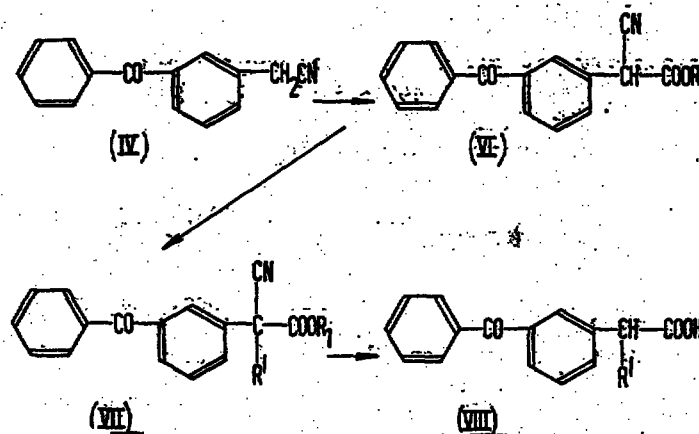
In the aforesaid French patent specifications there are described processes for the preparation of the (3 - benzoylphenyl)alkanoic acids of general formula I, the processes involving

(1) when the product required is one wherein R represents a hydrogen atom and the benzene rings are unsubstituted or substituted as aforementioned conversion of a 3 - methylbenzophenone into a 3 - halomethylbenzophenone, replacement of the halo-methyl substituent of the intermediate by a cyanomethyl radical, and hydrolysis of the resulting (3 - benzoylphenyl) - acetonitrile to the corresponding acid, according to the reaction scheme;—

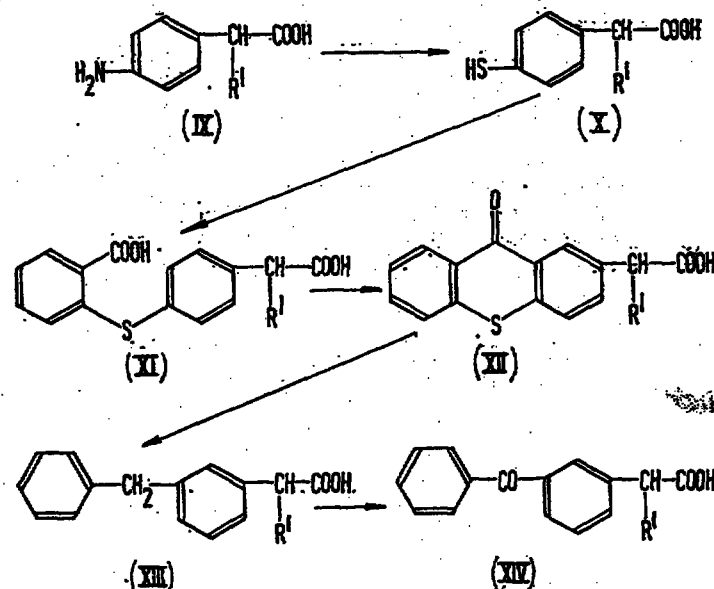


wherein Hal represents a halogen, e.g. chlorine or bromine, atom;

(2) when the product required is one wherein R represents an alkyl radical and the benzene rings are unsubstituted or substituted as aforementioned, converting a (3 - benzoylphenyl)acetonitrile into an alkyl (3 - benzoylphenyl) - cyanoacetate, alkylating the carbon atom in the α - position to the ester group, and hydrolysing and decarboxylating the (3 - benzoylphenyl)acetic acid derivative so obtained, according to the reaction scheme:—



wherein R' and R, each represent an alkyl radical containing 1 to 4 carbon atoms, or
 (3) when the product required is one wherein R represents an alkyl radical and the benzene rings are unsubstituted, replacing the amino substituent in a (4 - aminophenyl) alkanic acid by a mercapto radical, reacting the (4 - mercaptophenyl)alkanoic acid with 2 - iodobenzoic acid to obtain a diphenylsulphide, cyclising the diphenylsulphide to a 2 - (2 - thiazanthonyl) - alkanic acid, subjecting that compound to desulphuration to yield a (3 - benzylphenyl)alkanoic acid and oxidising the methylene group between the two benzene rings to a carbonyl group, according to the reaction scheme:—



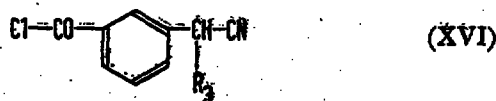
wherein R' is as hereinbefore defined.

It has now been found as a result of research and experimentation that compounds of general formula I wherein the *para* - position of the benzoyl group is unsubstituted or substituted by a halogen (preferably chlorine) atom and R represents a hydrogen atom or a methyl radical, which are outstanding anti-inflammatory agents, can be prepared by a new process which involves fewer stages than the hitherto known processes for obtaining those compounds and utilises readily available and inexpensive starting materials.

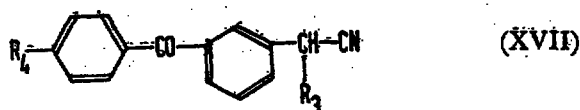
The process of the present invention for the preparation of (3 - benzoylphenyl)-alkanoic acids of the general formula:



(wherein R₃ represents a hydrogen atom or a methyl radical and R₄ represents a hydrogen or halogen, preferably chlorine, atom) comprises carrying out a Friedel-Crafts reaction between a (3 - chlorocarbonylphenyl) - alkanonitrile of the general formula:



(wherein R₃ is as hereinbefore defined) and benzene or a halogenobenzene, and hydrolysing the resulting nitrile of the general formula:

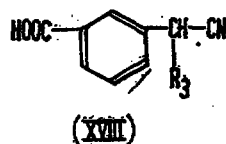


(wherein R₃ and R₄ are as hereinbefore defined) to the corresponding (3 - benzoylphenyl)alkanoic acid of general formula (XV).

The reaction between the compound of general formula (XVI) and benzene or a halogenobenzene is carried out under conditions suitable for a Friedel-Crafts reaction, generally employing an excess of benzene or the halogenobenzene reactant, in the presence of a Friedel-Crafts catalyst, preferably aluminium chloride, and advantageously at the reflux temperature of the reaction mixture.

Hydrolysis of the nitriles of general formula (XVII) can be effected by methods known *per se* for converting a nitrile to an acid. It is particularly advantageous to heat the nitrile of general formula (XVII) in water or an organic solvent (e.g. methanol or ethanol) in the presence of a base such as sodium hydroxide or potassium hydroxide, or of an acid such as sulphuric acid. It is preferable to effect the hydrolysis in an inert atmosphere such as a nitrogen atmosphere.

The acid chlorides of general formula (XVI) employed as starting materials in the process of the invention can be prepared from the corresponding acids of the general formula:



(wherein R₃ is as hereinbefore defined) by methods known *per se* for the preparation of acid chlorides from acids. Preferably thionyl chloride is used in an inert organic solvent (e.g. carbon tetrachloride), and the reaction is carried out at the reflux temperature of the reaction mixture.

The acids of general formula (XVIII) can be obtained by reacting acetonitrile or propionitrile with 2 - chlorobenzoic acid, which are all readily available and inexpensive compounds, according to the method described by E. R. Biehl, J. Org. Chem., 31, 602 (1966).

The (3 - benzoylphenyl)alkanoic acids of general formula (XV) can be converted into metal salts or addition salts with nitrogenous bases by application of methods known *per se*. Thus, these salts can be prepared by the action of an alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal base, ammonia or amine, on the acid of general formula (XV) in an appropriate solvent such as an alcohol, an ether, a ketone or water; the salt formed is precipitated, if necessary after concentration of the solution, and is separated by filtration or decantation.

In this specification the term "methods known *per se*" means heretofore used or described in the chemical literature.

The following Examples illustrate the process of the present invention.

EXAMPLE 1

(a) A suspension of 2 - (3 - carboxyphenyl) - propionitrile (19.4 g.) [prepared according to E. R. Biehl, J. Org. Chem. 31, 602 (1966)] in carbon tetrachloride (250 cc.) containing thionyl chloride (26 g.) is heated under reflux for 4 hours. After cooling, the solvent is evaporated under reduced pressure (20 mm.Hg) at 50°C. and then the residue obtained is distilled. 2 - (3 - Chlorocarbonylphenyl) - propionitrile (13 g.), b.p. 138°C/0.1 mm.Hg, is thus obtained.

(b) A solution of 2 - (3 - chlorocarbonylphenyl) - propionitrile (11.9 g.) in anhydrous benzene (20 cc.) is added to a suspension of anhydrous aluminium chloride (16.4 g.) in anhydrous benzene (50 cc.). The reaction mixture is heated under reflux for 1 hour. After cooling, the reaction mixture is hydrolysed with crushed ice (100 g.) associated with 10N hydrochloric acid (10 cc.).

After decanting, the organic layer is washed with distilled water, dried over anhydrous sodium sulphate, filtered and then concentrated to dryness under reduced pressure to yield 2 - (3 - benzoylphenyl)propionitrile (14 g.) melting at 49°C.

After recrystallisation from diisopropyl ether (35 cc.), there is obtained 2 - (3 - benzoylphenyl)propionitrile (11.8 g.) melting at 51°C.

(c) A solution of 2 - (3 - benzoylphenyl) - propionitrile (1.2 g.) in a methanol/water mixture (1/1 v/v; 10 cc.) containing 85% pure potassium hydroxide pellets (0.3 g.) is heated under reflux for 24 hours. After cooling, the solution obtained is concentrated under reduced pressure (20 mm.Hg) at 50°C. The resulting residue is dissolved in distilled water (30 cc.) and the solution obtained is washed with diethyl ether (2×20 cc.). The aqueous phase is acidified with 10N hydrochloric acid (2 cc.). The product which crystallises is filtered off, washed with distilled water (10 cc.) and then dried to give 2 - (3 - benzoylphenyl)propionic acid (0.9 g.), m.p. 92°C.

EXAMPLE 2

(a) A suspension of 3 - carboxyphenyl - acetonitrile (16.1 g.) [prepared according to E. R. Biehl, *loc cit.*] in anhydrous carbon tetrachloride (150 cc.) containing thionyl chloride (23.6 g.) is heated under reflux for 4 hours. After cooling, the solvent is evaporated under reduced pressure (20 mm.Hg) at 50°C. and then the residue obtained is distilled. 3 - Chlorocarbonylphenyl - acetonitrile (11.8 g.), b.p. 140—142°C./0.2 mm.Hg, is thus obtained.

(b) 3 - Chlorocarbonylphenyl - acetonitrile (11.5 g.) is added over the course of 20 minutes to a suspension of aluminium chloride (16.7 g.) in anhydrous chlorobenzene (120 cc.). The reaction mixture is heated under reflux for 3 hours. After cooling, the reaction mixture is hydrolysed with crushed ice (300 g.) associated with concentrated hydrochloric acid (d=1.19; 60 cc.). After extraction with diethyl ether (3×100 cc.), the organic layer is washed with distilled water, dried over anhydrous sodium sulphate and then concentrated under reduced pressure (20 mm.Hg) at 50°C. to give 3 - (4 - chlorobenzoyl)phenyl - acetonitrile (16.7 g.), m.p. 93°C.

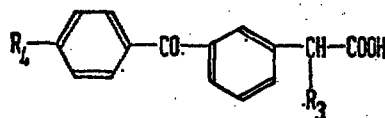
(c) A suspension of 3 - (4 - chlorobenzoyl)phenyl - acetonitrile (16.5 g.) in 3N sodium hydroxide solution (150 cc.) is heated reflux for 18 hours. After cooling, the solution is diluted with water (600 cc.) and then acidified by adding concentrated hydrochloric acid (d=1.19; 50 cc.). The product which crystallises is filtered off, washed with water (4×50 cc.) and then dried to give 3 - (4 - chlorobenzoyl)phenyl - acetic acid (14.7 g.), m.p. 144°C.

After recrystallisation from benzene (100 cc.), there is obtained 3 - (4 - chlorobenzoyl)phenyl - acetic acid (12 g.) melting at 148°C.

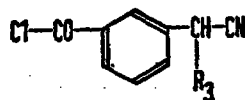


WHAT WE CLAIM IS:—

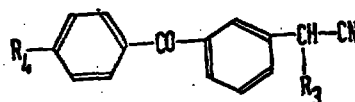
1. Process for the preparation of (3 - benzoylphenyl)alkanoic acids of the general formula:



(wherein R_3 represents a hydrogen atom or a methyl radical and R_4 represents a hydrogen or halogen atom) which comprises carrying out a Friedel-Crafts reaction between a (3 - chlorocarbonylphenyl)alkanonitrile of the general formula:



(wherein R_3 is as hereinbefore defined) and benzene or a halogenobenzene, and hydrolysing the resulting nitrile of the general formula:



(wherein R_3 and R_4 are as hereinbefore defined) to the corresponding (3 - benzoylphenyl)alkanoic acid.

2. Process according to claim 1 in which an excess of benzene or the halogenobenzene is employed in relation to the (3 - chlorocarbonylphenyl)alkanonitrile reactant.

3. Process according to claim 1 or 2 in which the Friedel-Crafts catalyst employed is aluminium chloride.

4. Process according to claim 1, 2 or 3 in which the reaction between the (3 - chlorocarbonylphenyl) - alkanonitrile and benzene or a halogenobenzene is carried out at the reflux temperature of the reaction mixture.

5. Process according to any one of the preceding claims in which hydrolysis of the intermediate nitrile to the corresponding (3 - benzoylphenyl)alkanoic acid is effected by heating the nitrile in water or an organic solvent in the presence of a base or of an acid.

6. Process according to claim 5 in which the base is sodium hydroxide or potassium hydroxide, and the acid is sulphuric acid.

7. Process according to any one of claims 1 to 6 in which a Friedel-Crafts reaction is carried out between 2 - (3 - chlorocarbonylphenyl)propionitrile and benzene, and 2 - (3 - benzoylphenyl)propionitrile thus obtained is hydrolysed to 2 - (3 - benzoylphenyl)propionic acid.

8. Process according to any one of the preceding claims followed by the step of converting by methods known *per se* the (3 - benzoylphenyl)alkanoic acid obtained into a metal salt or an addition salt with a nitrogenous base.

9. Process for the preparation of (3 - benzoylphenyl)alkanoic acids according to claim 1 substantially as described in Example 1.

10. Process for the preparation of (3 - benzoylphenyl)alkanoic acids according to claim 1 substantially as described in Example 2.

11. (3 - Benzoylphenyl)alkanoic acids of the general formula depicted in claim 1, and metal salts and addition salts with nitrogenous bases, when prepared by the process claimed in any one of claims 1 to 10.

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