PATENT SPECIFICATION

687,336

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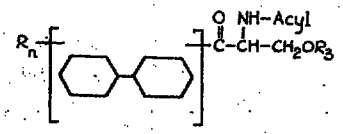
COMPLETE SPECIFICATION

Improvement in Biphenylyl-α-Acylamido-β-Hydroxyethyl Ketone Compounds

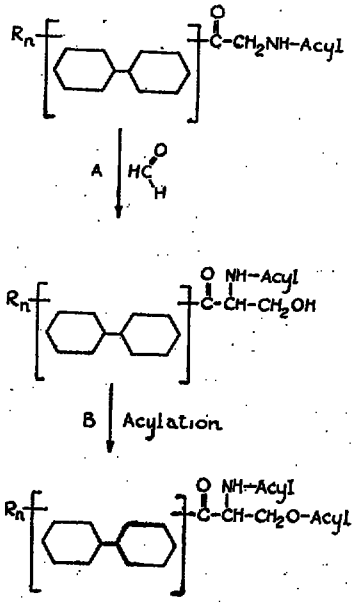
We, PARKE, DAVIS & COMPANY, a corporation organised under the laws of the State of Michigan, one of the United States of America, having a principal place of business at Joseph Campau at the River, in the City of Detroit, State of Michigan, United States of America, do hereby declare the invention, for 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 application relates to biphenylyl-α-acylamido-β-hydroxyethyl ketone compounds and to methods for obtaining the same. More particularly, the invention relates to biphenylyl-α-acylamido-β-hydroxyethyl ketone compounds having the formula,



where n is 1 or 2, R is the same or different when n is 2 and represents hydrogen, halogen, or nitro, lower alkyl or lower alkoxy radicals and R_3 is hydrogen or an acyl radical. The term acyl as used herein includes saturated and unsaturated lower aliphatic acyl, halogen substituted lower aliphatic acyl, carboxy substituted lower aliphatic acyl, cyano substituted lower aliphatic acyl, ether substituted lower aliphatic acyl, ester substituted lower aliphatic acyl, benzoyl, substituted benzoyl, araliphatic acyl, furoyl and pyridinoyl radicals. The term "lower" as used herein in connection with certain radicals means that such radicals contain not more than four carbon atoms.

The process for obtaining the products of the invention can be diagrammatically illustrated as follows:



where R and n have the same significance as given above.

In carrying out the reaction designated as A in the above diagram a biphenylyl acylamidomethyl ketone is condensed with formaldehyde in the presence of an alkaline condensation catalyst to obtain the corresponding biphenylyl-α-acylamido-β-hydroxylethyl ketone. In carrying out this condensation the formaldehyde may be supplied to the reaction mixture in a number of different forms. For

example, formaldehyde gas, aqueous or alcoholic solutions of formaldehyde, paraformaldehyde and other formaldehyde yielding polymers may be used. In most cases it has been found preferable to use an excess of formaldehyde usually up to about 4 or 5 mols in order to insure completeness of the condensation reaction.

A variety of solvents, alkaline condensation catalysts and reaction conditions may also be employed. As solvents, either aqueous or anhydrous lower aliphatic alcohols are particularly advantageous but moist dialkyl ethers and dioxane-water mixtures may also be used. The alkaline condensation catalysts used in this phase of the invention may be organic bases, inorganic bases or inorganic salts of acidic or pseudo acidic organic compounds. Some representative types of these catalysts are the hydroxides, oxides, carbonates, bicarbonates and amides of alkali or alkaline earth metals; alkali metal alkoxides; alkaline earth alkoxides; alkali metal phenolates; alkali metal salts of lower aliphatic carboxylic acids; organic tertiary amines and quaternary ammonium hydroxides of organic tertiary amines. In general, the weakly alkaline catalysts such as sodium bicarbonate, potassium bicarbonate, calcium hydroxide, pyridine, triethylamine, N-ethylmorpholine and N,N - dimethylaniline are preferred since they make the reaction much easier to control. When strongly alkaline catalysts such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium methylate and sodium ethylate are used, care must be taken to remove or inactivate the catalyst as soon as the reaction is completed in order to prevent the conversion of the desired product to the corresponding methylene bis compound by dehydration and coupling reaction. Although the amount of catalyst is not critical and can vary from a few hundredths or thousandths of a mol to one mol or more, per mol of biphenylyl acylamidomethyl ketone it is preferable from the standpoint of yields to use only enough to bring about a relatively rapid reaction. In most cases 0.05 mol or less is sufficient.

The temperature used in carrying out this methylolation reaction as well as the time required for its completion varies with the catalyst used. In general, the reaction can be carried out at a temperature between about 0 and 75° C. in a time varying from a few minutes to several hours. When strongly alkaline catalysts are used the reaction proceeds very rapidly and is usually complete in a few minutes at room temperature or below. However, when mildly alkaline catalysts are employed the reaction is not so rapid and usually requires from fifteen minutes to several hours at room temperature or slightly above, that is, at about 25 to 50° C.

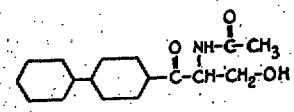
The conversion of the biphenylyl-α-acylamido-β-hydroxy ethyl ketone compounds to the corresponding β-acyloxy derivatives shown by B in the above diagram can be effected by treating the β-hydroxy ketone with an acyl halide or acyl anhydride under substantially anhydrous conditions either alone or in the presenceof an acylation catalyst such as an inorganic base, an alkaline salt of an organic acid, an organic tertiary base, an aromatic sulfonic acid or sulfuric acid. The acylation can, in general, be carried out at a temperature varying from about 10 to 140° C. but the preferred temperature for the reaction is between about 60 and 120° C. An inert organic solvent such as benzene, petroleum ether or toluene can be used for the reaction if desired, although in most cases it is more expedient to omit the use of a solvent and to merely use an excess of the acylating agent. Some of the catalysts which can be used to bring about the reaction in a shorter period of time are sodium hydroxide, potassium hydroxide, potassium carbonate, sodium acetate, pyridine, quinoline, triethylamine, N-ethylmorpholine, N-methylpiperidine, N,N-dimethylaniline, *p*-toluenesulfonic acid and sulfuric acid.

The products of the invention are useful as intermediates in the preparation of other organic compounds. They are of particular value in the preparation of organic compounds possessing antibiotic activity against microorganisms of the Rickettsia type.

The invention is illustrated by the following examples.

EXAMPLE 1.

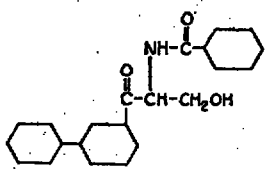
58 g. of 4-biphenylyl acetamidomethyl ketone is mixed with 300 cc. of methanol and 75 cc. of 40% neutral formalin, 2 g. of sodium bicarbonate is added and the mixture stirred at room temperature for about an hour during which time the desired solid product separates. The insoluble 4 - biphenylyl-α-acetamido-β-hydroxyethyl ketone of formula,



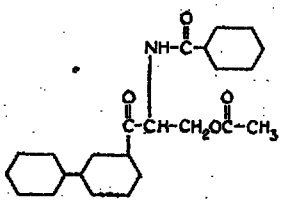
is collected and purified by recrystallization from ethyl acetate; m.p. 166—7° C.

EXAMPLE 2.

A mixture consisting of 31.5 g. of 3-biphenylbenzamidomethyl ketone, 1 g. of sodium bicarbonate and 6 g. of paraformaldehyde in 300 cc. of methanol is warmed at 45 to 50° C. for one-half hour. The reaction mixture is allowed to stand for one hour and then poured into 1½ liters of ice water. The precipitated product is collected, washed with water and purified by recrystallization from ethyl acetate or ethanol to obtain the pure 3-biphenylyl-α-benzamido - β - hydroxyethyl ketone of formula,



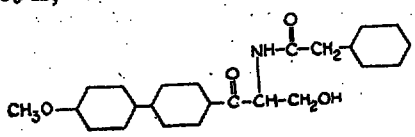
A mixture consisting of 3 g. of 3-biphenylyl-α-benzamido - β - hydroxyethyl ketone and 10 cc. of acetic anhydride is warmed to 40° C. and 1 drop of concentrated sulfuric acid added to the solution. The mixture is allowed to stand for one-half hour and then is evaporated to dryness *in vacuo*. The residue which consists of 3 - biphenylyl-α-benzamido-β-acetoxyethyl ketone of formula,



is washed with water and purified by recrystallization from ethanol.

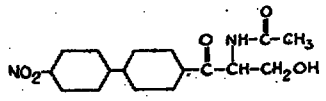
EXAMPLE 3.

A mixture consisting of 25 g. of 4¹-methoxy-4-byphenylyl phenylacetamidomethyl ketone, 0.2 g. of sodium bicarbonate and 6 g. of paraformaldehyde in 500 cc. of methanol is heated at 40° C. for about twenty minutes with stirring and then poured into 1500 cc. of ice water. The crude 4¹-methoxy - 4 - biphenylyl-α-phenylacetamido-β-hydroxyethyl ketone which separates is collected, washed with water and purified by recrystallization from alcohol. The formula of this product is,



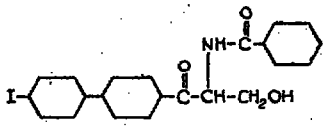
EXAMPLE 4.

2 g. of sodium bicarbonate is added to a solution of 50 g. of 4¹-nitro-4-biphenylyl acetamidomethyl ketone and 75 cc. of 40% neutral formalin in 450 cc. of methanol and the resulting mixture heated at 45 to 50° C. for about one-half hour. The reaction mixture is poured into 1½ litres of ice water and the crude 4¹-nitro - 4 - biphenylyl - α - acetamido-β-hydroxyethyl ketone which separates collected and washed with water. If desired, this product can be purified by recrystallization from methanol. Its formula is,



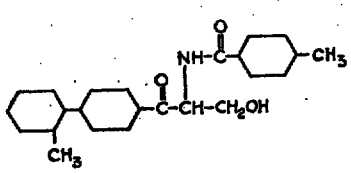
EXAMPLE 5.

33 g. of 4¹-iodo-4-biphenylyl benzamidomethyl ketone is mixed with 250 cc. of absolute methanol and 30 cc. of 38% aqueous formaldehyde. 0.6 g. of sodium bicarbonate is added and the mixture stirred at 35° C. for one and one-half hours during which time the solid product separates. The mixture is cooled, stirred for a short time and the solid 4¹-iodo - 4 - biphenylyl - α - benzamido - β-hydroxyethyl ketone collected, washed with water and dried. This product has the formula,



EXAMPLE 6.

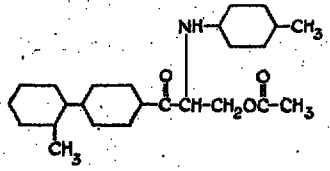
A mixture consisting of 65 g. of 2¹-methyl-4-biphenylyl - *p* - toluylamidomethyl ketone, 300 cc. of ethanol and 75 cc. of 40% neutral formalin is treated with 2 g. of sodium bicarbonate. The mixture is stirred at 35° C. for about one and one-half hours, cooled and the insoluble 2¹-methyl-4-biphenylyl-α-(*p*-toluylamido) - β - hydroxyethyl ketone collected. This product which has the formula,



is washed with water and dried *in vacuo*.

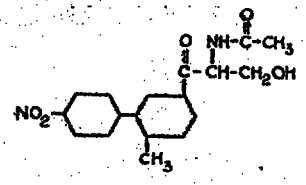
10 g. of 2¹ - methyl-4-biphenylyl-α-(*p*-

toluylamido)-β-hydroxyethyl ketone is heated at about 75° C. for one-half hour with 20 cc. of acetic anhydride containing one drop of concentrated sulfuric acid. The reaction mixture is evaporated to dryness *in vacuo*, the residue washed with ice water and purified by recrystallization from methanol or ethanol. The product thus obtained is 2¹ - methyl-4-biphenyl-α-(*p*-toluylamido)-β-acetoxyethyl ketone of formula,

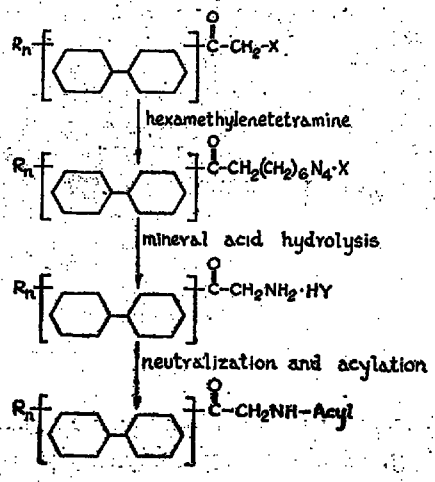


EXAMPLE 7.

A mixture consisting of 65 g. of 4¹-nitro-6-methyl-3-biphenylyl acetamidomethyl ketone, 350 cc. of methanol, 75 cc. of 40% neutral formalin and 2 g. of sodium bicarbonate is stirred for about two hours at room temperature. The solution is cooled and the 4¹-nitro-6-methyl-3-biphenylyl - α - acetamido - β - hydroxyethyl ketone collected, washed with a small amount of methanol and purified by recrystallization from ethyl acetate or methanol. The formula of this product is,



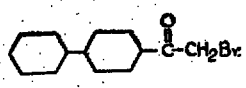
The starting materials used in the practice of the invention can be prepared in a number of different ways. One of these ways can be diagrammatically represented as follows:



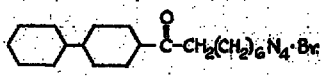
where X is a halogen atom, HY is one equivalent of a mineral acid and R and *n* have the same significance as given above.

A specific example of the above described method for preparing these starting materials is as follows:

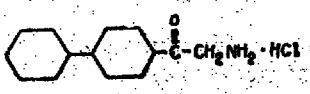
26 cc. of bromine is added slowly with stirring to 100 g. of 4-biphenylylmethyl ketone in 500 cc. of carbon tetrachloride at room temperature. As soon as the bromine color has been discharged from the solution the carbon tetrachloride is evaporated *in vacuo* to obtain the desired 4 - biphenylyl bromomethyl ketone of formula,



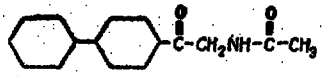
75 g. of hexamethylenetetramine dissolved in chloroform is added to the 4-biphenylyl bromomethyl ketone prepared in the above paragraph and the mixture allowed to stand at room temperature for about three hours. The 4-biphenylyl bromomethyl ketone - hexamethylenetetramine complex is collected, washed with a little chloroform and dried. The formula of this product is,



175 g. of the 4-biphenylyl bromomethyl ketone-hexamethylenetetramine complex is added to 200 cc. of concentrated hydrochloric acid in 1 liter of absolute alcohol and the mixture stirred overnight. The insoluble hydrochloride salt of 4-biphenylyl aminomethyl ketone is collected by filtration, washed with a small amount of cold water and dried at room temperature. The formula of this product is,

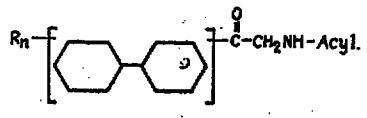


The 4-biphenylyl aminomethyl ketone hydrochloride prepared in the above paragraph is dissolved in 500 cc. of glacial acetic acid and 300 cc. of acetic anhydride. 150 g. of sodium acetate is added in small portions with stirring. After the addition has been completed the solution is diluted with water and the 4-biphenylyl acetamidomethyl ketone which separates collected and recrystallized from methanol; m.p. 154—5° C. The formula of this compound is,

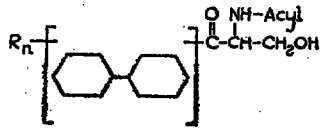


What we claim is:—

1. Process which comprises condensing a biphenylyl acylamidomethyl ketone compound of formula,



with formaldehyde in the presence of an alkaline condensation catalyst to obtain a biphenylyl α-acylamido-β-hydroxyethyl ketone compound of formula,

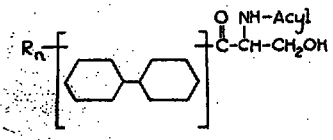


where n is 1 or 2 and R is the same or different when n is 2 and represents hydrogen, halogen, or nitro, lower alkyl or lower alkoxy radicals.

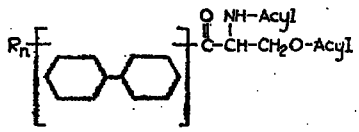
2. Process according to claim 1 wherein the condensation is carried out in a lower aliphatic alcohol-water reaction medium.

3. Process according to claims 1 and 2 wherein a weakly alkaline condensation catalyst is employed.

4. Process which comprises reacting a ~~biphenylyl - α - acylamino - β - hydroxy - ethyl~~ ketone compound of formula,



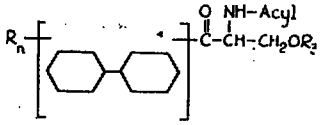
with an acyl anhydride or acyl halide under anhydrous conditions to obtain a biphenylyl - α - acylamido - β - acyloxy-ethyl ketone compound of formula,



where n is 1 or 2 and R is the same or different when n is 2 and represents hydrogen, halogen, or nitro, lower alkyl or lower alkoxy radicals.

5. Process according to claim 4 wherein the reaction is carried out in the presence of an acylation catalyst and an acyl anhydride is employed as the acylating agent.

6. Biphenylyl - α - acylamido - β-hydroxyethyl ketone compounds of formula,



where n is 1 or 2, R is the same or different when n is 2 and represents hydrogen, halogen, or nitro, lower alkyl or lower alkoxy radicals and R_2 is hydrogen or an acyl radical.

7. 4 - Biphenylyl - α - acetamido - β-hydroxyethyl ketone.

8. 3 - Biphenylyl - α - benzamido-β-hydroxyethyl ketone.

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biphenylyl - α - acylamido - β - hydroxy - ethyl

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* C L M S *