PATENT SPECIFICATION

688,023

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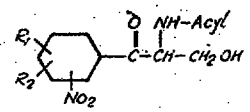
COMPLETE SPECIFICATION

Improvements in and relating to the Production of Ketonic Amino Alcohol Compounds

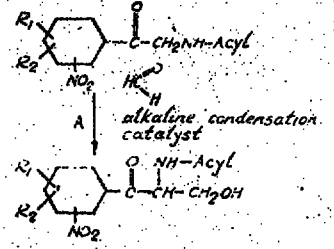
We, PARKE, DAVIS AND COMPANY, a corporation organised under the laws of the State of Michigan, one of the United States of America, and having our principal place of business at Joseph Campau at the River, in the City of Detroit, State of Michigan, United States of America, do hereby declare the nature of this invention and in what manner the same is to be performed to be particularly described and ascertained in and by the following statement:—

This invention relates to derivatives of organic amino alcohols and to methods for obtaining the same. In accordance with the invention an ω-acylamido acetophenone derivative containing a nitro group in the phenyl ring is condensed with formaldehyde in the presence of an alkaline condensation catalyst to obtain a ketonic compound of formula:



wherein R_1 and R_2 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals. The term "acyl" as used herein, includes lower aliphatic acyl, halogen-substituted lower aliphatic acyl, benzoyl, substituted benzoyl, and araliphatic acyl radicals.

This transformation may be diagrammatically illustrated as follows:—



In carrying out the condensation shown in the above diagram 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.

The relative quantities of the two reactants can be varied within rather wide limits but it is preferable to use an excess of the formaldehyde to insure completeness of the reaction. In general, best results seem to be obtained when about 3 to 5 mols of formaldehyde per mol of the nitro substituted ω-acylamidoacetophenone are used.

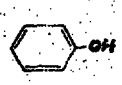
A variety of solvents, alkaline condensation catalysts and reaction conditions may be employed in the condensation reaction. As solvents, water and either aqueous or anhydrous lower aliphatic alcohols are particularly advantageous but moist dialkyl ethers and dioxane-water mixtures may also be used. 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 quarternary ammonium hydroxides of organic tertiary amines. In general, the weakly alkaline catalysts such as sodium bicarbonate, potassium bicarbonate, calcium hydroxide, pyridine, triethylamine, N-ethyl morpholine and N,N-dimethyl aniline 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 a dehydration and coupling reaction. Although the amount of the catalyst is not critical and can vary from a few hundredths or thousandths of a mol to one mol or more, 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 term " pseudo-acidic " employed above, refers to compounds which form metallic salts but which do not contain the classical organic acid structure



—C—OH. Among the compounds of this type are the phenols



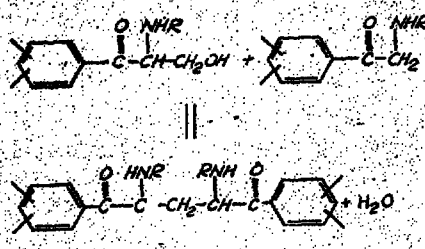


enols —CH=C—O—H, oximes R—C=NOH and aliphatic nitro compounds



R—CH=N—OH all of which form " salt " type compounds with alkali metal ions.

The undesired side reaction leading to a " methylene bis compound " takes place as follows and is irreversible.



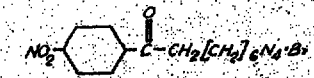
The temperature used in carrying out the methylolation reaction, as well as the time required for its completion, varies with the catalyst used. In general, the reaction can be carried out at a temperature between 0 and 75° C. in a time varying from a few minutes to several hours. When strongly alkaline 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 nitro - α - acylamido-β-hydroxypropiophenone compounds of the invention are particularly useful in the synthesis of other organic compounds. For example, these products can be converted to 1-nitrophenyl-2-acylamidopropane - 1,3 - diols, nitro - α - acylamido - β-acyloxypropiophenones and nitro - α - amino - β - hydroxypropionphenones in which connection reference is made to our copending Applications Nos. 2665/52 (Serial Nos. 688,108 and 688,109), 2666/52 and 26696/51 (Serial No. 688,107). The *p* - nitro - α - acylamido - β-hydroxypropionphenone products are particularly useful in the production of 1-*p*-nitrophenyl - 2 - acylamido - propane-1,3-diols which are important intermediates in the production of substances possessing antibiotic activity or themselves have antibiotic activity. Specifically, the product produced in Examples 1, 2 and 7 can be converted to (*l*)-ψ-1-*p*-nitrophenyl-2 - dichloracetamidopropane - 1,3 - diol (chloramphenicol) by reduction, hydrolysis, separation of the optical isomers and dichloroacetylation, the last two steps being performed, for example, by the processes described in Specifications Nos. 652,280 and 652,273. Additionally, the product of Example 7 can be reduced directly to (*dl*)-ψ-1-*p*-nitrophenyl-2-dichloroacetamidopropane - 1,3 - diol (optically racemic chloramphenicol).

The invention is illustrated by the following examples.

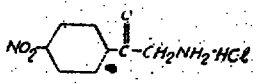
EXAMPLE 1.

[a] 71 g. of *p*-nitro-ω-bromoacetophenone dissolved in 300 cc. of chloroform is added to a solution of 46 g. of hexamethylene tetramine in 600 cc. of chloroform. The solid product begins to separate almost immediately and the temperature of the reaction mixture rises to about 50° C. After allowing the mixture to stand for about two hours the *p*-nitro - ω - bromoacetophenonehexamethylene tetramine complex is collected, washed with a little chloroform and dried. The formula of this product is:

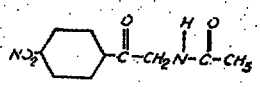


The *p* - nitro - ω - bromoacetophenone-

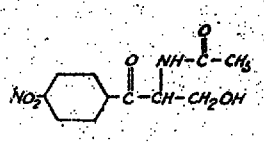
hexamethylene tetramine complex prepared above is mixed with a cold solution of 500 cc. of absolute ethanol and 100 cc. of concentrated hydrochloric acid and the mixture stirred overnight at room temperature. The solid product which consists of the hydrochloride salt of *p*-nitro-ω-aminoacetophenone contaminated with minor amounts of the hydrobromide salt and ammonium chloride is collected, washed with 200 cc. of ice cold water to remove the ammonium chloride and dried. The formula of this compound is:



46 g. of the *p* - nitro - ω - aminoacetophenone hydrochloride prepared above is mixed with 200 cc. of acetic anhydride and 25 g. of sodium acetate. The mixture is stirred at room temperature and small quantities of ice and water added from time to time. Stirring is continued until the mixture becomes clear and reaches a temperature of about 70° C. The solution is diluted with 900 cc. of water, cooled to 5° C. and the *p*-nitro-ω-acetamidoacetophenone collected, m.p. 158—161° C. *p*-Nitro-ω-acetamidoacetophenone has the formula,

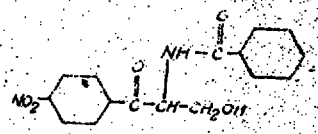


11.1 g. of *p*-nitro-ω-acetamidoacetophenone is mixed with 55 cc. of methanol and 17 cc. of 36—38% aqueous formaldehyde. 0.4 g. of sodium bicarbonate is added and the mixture stirred at 35° C. for about one hour and a half during which time the solid product separates. The mixture is cooled and stirred for one-half hour, the solid product collected, washed with water and dried at 60° C. The product thus obtained is *p*-nitro-α-acetamido - β - hydroxypropiophenone, m.p. 166—7° C., which has the formula,



Example 2.

[a] A mixture consisting of 7.1 g. of *p*-nitro-ω-benzamidoacetophenone, 0.2 g. of sodium bicarbonate and 1.5 g. of paraformaldehyde in 50 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 300—400 cc. of ice water. The precipitated product is collected, washed with water and purified by recrystallization from ethanol to obtain the pure *p*-nitro-α-benzamido-β-hydroxypropiophenone of formula,



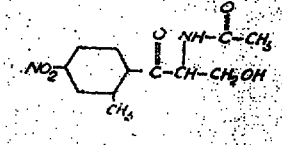
[b] A mixture consisting of 7.1 g. of *p*-nitro-ω-benzamidoacetophenone, 0.1 g. of sodium and 1.5 g. of paraformaldehyde in 50 cc. of methanol is allowed to stand at room temperature for about five minutes. The reaction mixture is immediately poured into 300 cc. of ice water and the desired *p*-nitro-α-benzamido-β-hydroxypropiophenone isolated and purified as described in [a].

[c] A mixture consisting of 7.1 g. of *p*-nitro-ω-benzamidoacetophenone, 0.2 g. of potassium carbonate and 3 g. of paraformaldehyde in a solvent mixture composed of 30 cc. of methanol and 10 cc. of water is stirred at room temperature for about ten minutes. The reaction mixture is poured into about 300 cc. of ice water and the crude *p*-nitro-α-benzamido-β-hydroxypropiophenone isolated and purified as described in [a].

[d] A mixture consisting of 7.1 g. of *p*-nitro-ω-benzamidoacetophenone, 0.2 g. of potassium carbonate and 3.75 g. of paraformaldehyde in 35 cc. of methanol is stirred at about 25° C. for five minutes, poured into 400 cc. of ice water and the crude *p* - nitro - α - benzamido-β-hydroxypropiophenone isolated and purified by recrystallization as described in [a].

Example 3.

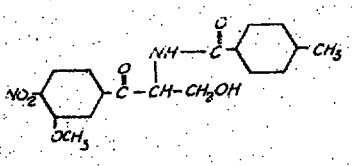
15 g. of *o*-methyl-p-nitro-ω-acetamidoacetophenone is mixed with 70 cc. of methanol, 10 cc. of water and 5.7 g. of paraformaldehyde. 0.5 g. of sodium bicarbonate is added and the mixture heated at 40° C. for one and a half hours. The mixture is poured in 600 cc. of ice water and the crude *o* - methyl - *p* - nitro-α-acetamido-β-hydroxypropiophenone collected and washed with water. This product which has the formula,



can be purified, if desired, by recrystallization from methanol.

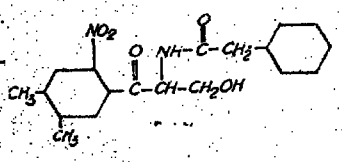
EXAMPLE 4.

A mixture consisting of 15 g. of *m*-methoxy-*p*-nitro-ω-*p*¹ - toluylamidoacetophenone, 4.1 g. of paraformaldehyde, 0.2 g. of pyridine and 150 cc. of ethanol is warmed at 35° C. for one-half hour and then poured into 750 cc. of ice water. The crude *m*-methoxy-*p*-nitro - α - *p*¹ - toluylamido - β - hydroxypropiophenone is collected, washed with water and purified by recrystallization from ethanol. The formula of this product is,



EXAMPLE 5.

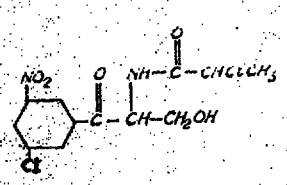
A mixture consisting of 16.3 g. of 2-nitro-4,5-dimethyl-ω - phenacetamidoacetophenone, 4.5 g. of paraformaldehyde and 0.2 g. of calcium hydroxide in 150 cc. of 95% ethanol is heated at 45° C. for about one-half hour. The reaction mixture is poured into 750 cc. of ice water and the crude 2-nitro-4,5-dimethyl-α-phenacetamido-β - hydroxypropiophenone collected. The crude product which has the formula,



is washed with water and purified by recrystallization from ethanol.

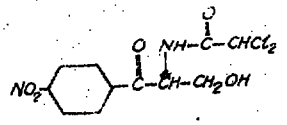
EXAMPLE 6.

A mixture consisting of 18 g. of 3-nitro-5-chloro-ω-[α-chloropropionamido] acetophenone, 6 g. of paraformaldehyde and 0.2 g. of sodium carbonate in 200 cc. of 70% aqueous methanol is stirred at room temperature for about one hour and then poured into 500 cc. of ice water. The precipitated product is collected, washed with water and purified by recrystallization from methanol or ethanol. The compound thus obtained is 3-nitro-5-chloro-α-[α¹-chloropropionamido] - β - hydroxypropiophenone of formula,



EXAMPLE 7.

A mixture consisting of 29 g. of *p*-nitro-ω - dichloroacetamidoacetophenone, 150 cc. of methanol, 50 cc. of 38% aqueous formaldehyde and 0.5 g. of sodium bicarbonate is heated at 35° C. for one and a half hours. The reaction mixture is cooled, the solid product collected and washed with water. The crude *p*-nitro-α-dichloroacetamido - β - hydroxypropiophenone thus obtained is purified by recrystallization from ethanol or methanol. The formula of this product is,

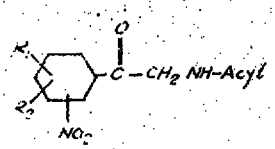


The ω-acylamidoacetophenone derivatives used as starting materials in the practice of the invention may be prepared by hydrolyzing a nitro - ω - haloacetophenone-hexamethylene tetramine complex to the corresponding nitro-ω-aminoacetophenone and acylating the amino ketone with the necessary acylating agent. A specific example of the preparation of *p*-nitro-ω-acetamidoacetophenone by this process is shown in Example 1 (a) above, whilst our co-pending Application (No. 4143 of 1949 No. 660,381), relates generally to the preparation of the ω-acylamidoacetophenone derivatives.

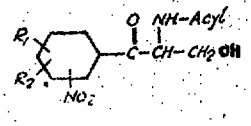
The term " lower " used in the specification and the appended claims, denotes an alcohol or an alkyl, alkoxy or aliphatic acyl radical containing not more than four carbon atoms.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. Process which comprises condensing a compound of formula,



with formaldehyde in the presence of an alkaline condensation catalyst to obtain a ketonic compound of formula,



where R_1 and R_2 are the same or different

can be purified, if desired, by recrystallization from methanol.

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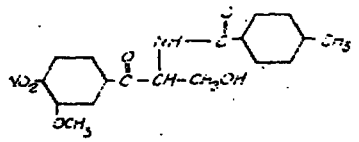

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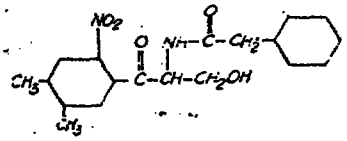

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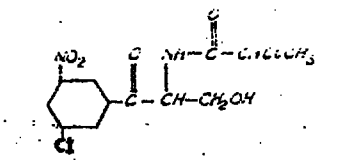

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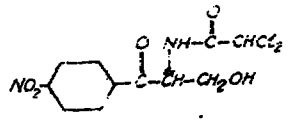

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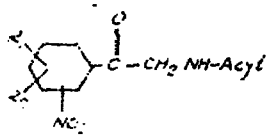
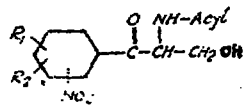


with formaldehyde in the presence of an alkaline condensation catalyst to obtain a ketonic compound of formula,



where R_1 and R_2 are the same or different

and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals.

2. Process according to claim 1, wherein the condensation is carried out in the presence of a solvent.

3. Process according to claims 1 and 2, wherein the condensation is carried out in water, a lower aliphatic alcohol or in a mixture of the same.

4. Process according to any of the preceding claims, wherein an excess of formaldehyde is employed in the condensation.

5. Process according to any of the preceding claims, wherein the condensation is carried out at a temperature between 0 and 75° C.

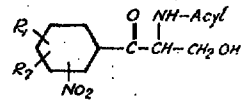
6. Process according to any of the preceding claims, wherein the condensation is carried out in the presence of a weakly alkaline compound.

7. Process according to any of claims 1 to 5, wherein the condensation is carried out in the presence of a strongly alkaline compound.

8. Process according to the preceding claims, wherein the acylamido nitroacetophenone compound used as a starting-material is *p*-nitro-α-dichloroacetamido-acetophenone.

9. Process according to the preceding claims 1 to 7, wherein the acylamido nitroacetophenone compound used as a starting material is *p*-nitro-α-acetamido-acetophenone.

10. Process for obtaining ketonic amino alcohol compounds of formula



where R_1 and R_2 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals substantially as hereinbefore described, with reference to any of the specific examples.

11. Ketonic amino alcohol compounds when prepared or produced by the processes claimed in any of the preceding claims 1 to 9 or their obvious chemical equivalents.

12. *p*-Nitro - α - dichloroacetamido - β-hydroxypropiophenone when prepared or produced by the processes of claims 1 to 8 or an obvious chemical equivalent thereof.

13. *p*-Nitro-α-acetamido - β - hydroxypropiophenone when prepared or produced by the processes of claims 1 to 7, 9, or an obvious chemical equivalent thereof.

Dated this 15th day of February, 1949.

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