PATENT SPECIFICATION

688,109

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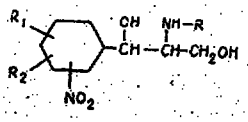
COMPLETE SPECIFICATION

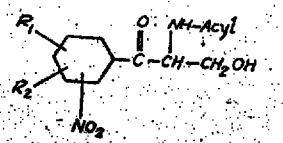
Process for the Manufacture of Amino Diols

We, PARKE, DAVIS & COMPANY, a corporation organised under the laws of the State of Michigan, one of the United States of America, of 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 a process for the manufacture of amino diol compounds. More particularly the invention relates to the production of amino diol compounds of formula



from ketonic compounds of formula



where R is hydrogen or an acyl radical, 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.

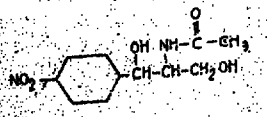
From inspection of the above formula, it will be readily appreciated by those skilled in the art that the acyl-amino diol and the amino diol compounds of the invention can exist in structural as well as optical isomeric forms. The term "structural" isomer or form as used herein refers to the cis or trans, that is, the planar relationship of the polar groups on the two asymmetric carbon atoms. The compounds having the cis structural configuration are those wherein the two most highly polar of the groups of the two asymmetric carbon atoms lie on the same side of the plane of the two carbon atoms. Conversely, the compounds having the trans configuration are those wherein the two most highly polar groups lie on opposite sides of the plane of the two carbon atoms. For convenience, the products having the trans structural form will hereinafter be referred to as "pseudo"-form to differentiate them from the products having the cis or "regular" structural form.

As is well known, most chemical methods for the production of organic compounds which can exist in diastereo isomeric forms lead to the formation of products containing primarily equal quantities of the two structural isomers. Where one particular diastereo isomer is desired, the separation of these mixed products into their two components is very difficult to achieve, and in all cases results in losses and increased production costs. For some inexplicable reason, the hereinafter described process for the conversion of the ketonic acyl amino alcohol compounds to the amino diol compounds of the invention results in the production of a mixture which contains a much larger quantity of the pseudo structural form of the amino diol products than of the amino diols having the cis configuration. In general, three to four times more pseudo product is present in the mixture than the corresponding cis product and where the quantities of material used in the process are small, the cis product can be eliminated, if desired, during the isolation of the reaction product from the reaction mixture. When large quantities of the starting materials

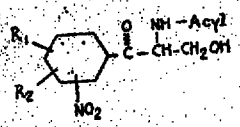
are employed, only very simple processing of the reaction mixture product is required to separate it into its components. Thus it is apparent that the avoidance of the mixture of diastereo isomers encountered as a general rule in the formation of compounds capable of existing in diastereo isomeric form is of great importance since it makes the separation of the isomeric mixture into its conponent parts much easier to accomplish, and reduces the losses characteristic of such separations to a minimum.

Because of the difficulty of representing the structural differences in the amino diol products by graphic formulae, the customary structural formulae have been used and the following convention adopted to designate the structural configuration. In those cases where the formula is that of one specific compound and no designation of its isomeric form is given, the product is the unseparated mixture of the two diastereo forms. When a designation is given, the product is the particular isomer designated. On the other hand, when the formula is general, that is, includes more than one specific compound, it represents not only the mixture of the diastereo isomers but the individual isomer as well. Thus for example, a general formula such as the first formula represents any one of three things, the unseparated mixture of the (*dl*)-pseudo and (*dl*)-regular amino diol compounds, the individual (*dl*)-pseudo isomers and the individual (*dl*)-regular isomers.

This convention is applied to specific compounds such as (*dl*)-1-*p*-nitrophenyl-2-acetamidopropane-1,3 diol, can be illustrated as follows: where the formula shown is

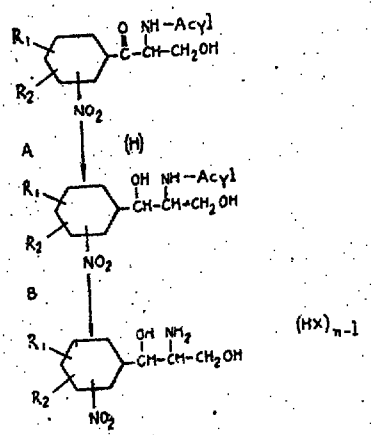


the mixture of the (*dl*)-pseudo and (*dl*)-regular isomers is meant. However, where a designation such as "(*l*)-ψ" appears below or to the side of the formula the product is a particular isomer, in this case, the pseudo isomer. In accordance with the invention a ketonic compound of formula,



is converted to the corresponding (*dl*)-acylamino diol by reduction with an oxidizable aluminum alkoxide in an organic solvent and the latter product if desired, hydrolyzed to the free (*dl*)-amino diol. Alternatively the (*dl*)-acylamino diol can be separated by fractional crystallisation or fractional solution into the regular and pseudo diastereo isomers and each isomer hydrolyzed separately to the corresponding (*dl*)-regular or (*dl*)-pseudo amino diol.

These transformations may be diagrammatically illustrated as follows:



where R_1 and R_2 have the same significance as given above, HX is one equivalent of a mineral acid and n is one or two.

The reduction of the α-acylamido-β-hydroxypropiophenone to the corresponding (*dl*)-acylamino diol compounds shown by A in the above diagram and using an oxidizable aluminum alkoxide as the reductant is carried out in an organic solvent which is usually a lower aliphatic alcohol and preferably, the one corresponding to the alkoxide. The use of alkoxides of secondary alcohols such as of isopropanol and secondary butanol is preferred since these alkoxides are more readily oxidised and hence milder reaction conditions can be employed. Alkoxides of tertiary alcohols such as that of tertiary butyl alcohol also produce good results. In general, the reaction can be effected over a wide temperature range, but for most purposes, a temperature between 20 and 125° C. has been found satisfactory. Similarly, the amount of the oxidizable aluminum alkoxide in relationship to the quantity of the ketonic compounds to be reduced can be varied within large limits. In most cases, it is seldom necessary to employ more than about three equivalents of the alkoxide, but, if desired, as little as one equivalent to as much as twenty or thirty equivalents can be used. When using an alkoxide derived from a secondary aliphatic alcohol in a solvent of the alcohol corresponding to the alkoxide, the preferred

method of bringing about the reaction is to reflux the reaction mixture containing one or slightly more equivalents of the aluminum alkoxide and to distill off the oxidized alcohol (a lower aliphatic ketone) as it is formed in the reaction mixture.

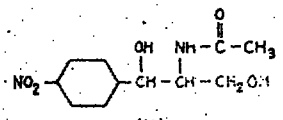
In some instances it is desired to hydrolyze the (*dl*)-acylamino diol products to the corresponding free (*dl*)-amino diol. This transformation which is illustrated by B in the above diagram can be carried out using either the purified acylamino diol mixture or the crude reaction mixture product from the reduction step as the starting material. If desired, the acylamino diol mixture can be first separated into the (*dl*)-ψ acylamino diol and the (*dl*)-reg. acylamino diol by recrystallisation from water, aqueous alcohols or alcohols and the individual isomers hydrolyzed to the corresponding (*dl*)-ψ or (*dl*)-reg. amino diol. The reaction can be effected with either alkaline or acidic hydrolysis catalysts or reagents. Dilute mineral acids such as dilute hydrochloric, hydrobromic, hydriodic, phosphoric and sulfuric acids are the preferred hydrolytic agents as they are more efficient in bringing about complete hydrolysis in a shorter time with less destruction of the final product. When acidic hydrolytic reagents such as the aforementioned mineral acids are employed the (*dl*)-1-(nitrophenyl) - 2 - aminopropane-1,3-diol product is present in the reaction mixture in the form of an acid addition salt, and it can either be isolated as such or the salt can be neutralized and the amino diol isolated as the free base. Among the many alkaline reagents which can be used to bring about the hydrolysis are the alkali and the alkaline earth metal hydroxides, oxides, carbonates, amides, alkoxides and phenolates; quaternary ammonium hydroxides and strong tertiary organic nitrogen bases.

The products of the invention are particularly useful in the synthesis of organic compounds possessing antibiotic activity. For example, the products produced in Examples 1, 2 and 7 can be converted to (*l*)-ψ-1-*p*-nitrophenyl-2-dichloroacetaminopropane-1,3-diol, a compound possessing outstanding and unique antibiotic properties. In addition to being useful in the preparation of antibiotics, some of the acylamino diol products prepared by the methods described above are themselves useful in the treatment of diseases. For example, the acylamino diol product of Example 7, (*dl*)-ψ-1-*p*-nitrophenyl - 2 - dichloroacetaminopropane-1,3-diol can be used in the treatment of typhus, Rocky Mountain spotty fever, various urinary infections and typhoid.

The invention is illustrated by the following examples:

EXAMPLE 1.

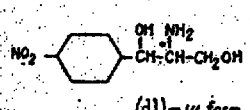
(a) 1.3 g. of *p*-nitro-α-acetamino-β-hydroxypropiophenone is added to 2 g. of aluminum isopropylate in 75 cc. of isopropanol at room temperature and the mixture stirred at room temperature for two days while a stream of nitrogen is passed through the solution. Most of the isopropanol is removed from the dark red-brown mixture under reduced pressure and the residue treated with 35 cc. of water. The mixture is heated to boiling, centrifuged to remove the aluminum hydroxide and the solution collected. The aluminum hydroxide is extracted with 35 cc. of hot water and the extract combined with the main reaction mixture solution. The combined extracts are cooled, filtered and the filtrate evaporated to dryness *in vacuo*. The residue is treated with a small amount of hot ethyl acetate and the crystalline material which fails to dissolve, collected. The crystalline material which consists principally of (*dl*)-ψ-1-*p*-nitrophenyl - 2 - acetaminopropane-1,3-diol of formula



(dl)-ψ form.

can be purified by recrystallisation from ethanol or ethanol-water mixtures to remove the small quantities of (*dl*)-cis product; m.p. 166—8° C.

(b) 3 g. of (*dl*)-ψ-1-*p*-nitrophenyl-2-acetaminopropane-1,3-diol is heated with 30 cc. of 5% hydrochloric acid on a steam bath for one-half hour. The solution is cooled, decolorized with charcoal and the decolorized solution made alkaline to pH 10—11 with sodium hydroxide solution. The free base of (*dl*)-ψ-1-*p*-nitrophenyl-2-aminopropane-1,3-diol of formula



(dl)-ψ form.

which separates upon standing is collected, washed with cold water and dried; m.p. 140—2° C. If desired, this product can be recrystallized from water.

The hydrochloride salt of (*dl*)-ψ-1-*p*-nitrophenyl-2-aminopropane-1,3-diol can be obtained by evaporating the decolorized solution obtained after hydrolyzing the (*dl*)-ψ-1-*p*-nitrophenyl-2-acet-

aminopropane-1,3-diol to dryness *in vacuo*. This salt has a melting point of 177.5—8.5° C.

(c) 2.5 g. of *p*-nitro-α-acetamino-β-hydroxypropiophenone is mixed with 1.5 g. of aluminum isopropylate and 25 cc. of dry isopropanol and the mixture heated under reflux for five hours. During the reflux period the acetone which is formed is distilled off and a stream of nitrogen is passed through the solution. The isopropanol is distilled from the reaction mixture under reduced pressure, the residue treated with about 50 cc. of water and the (*dl*)-ψ-1-*p*-nitrophenyl-2-acetaminopropane-1,3-diol isolated from the solution as described in (a) above.

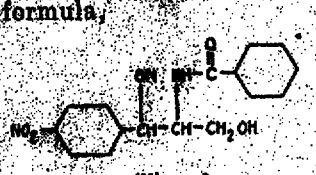
(d) 2.5 g. of *p*-nitro-α-acetamino-β-hydroxypropiophenone is mixed with 1.5 g. of aluminum isopropylate and 25 cc. of dry isopropanol and the mixture heated under reflux for five hours. During the reflux period, the acetone which is formed is distilled off and a stream of nitrogen is passed through the solution. The isopropanol is distilled from the reaction mixture under reduced pressure, the residue containing (*dl*)-ψ-1-*p*-nitrophenyl-2-acetaminopropane-1,3-diol treated with about 50 cc. of dilute hydrochloric acid. Sufficient strong sodium hydroxide solution is added to the solution to dissolve the aluminum hydroxide which forms upon neutralisation and after cooling, the solution is extracted with ethyl acetate. The ethyl acetate extracts are combined, dried and concentrated *in vacuo* to the point of crystallisation. The free base of (*dl*)-ψ-1-*p*-nitrophenyl - 2 - aminopropane-1,3-diol which separates on cooling is collected, washed with cold water and purified, if desired, by recrystallisation from water; m.p. 140—2° C.

(e) 50.6 g. of *p*-nitro-α-acetamino-β-hydroxypropiophenone is mixed with 41 g. of aluminum isopropylate and 600 cc. of dried isopropanol and the mixture heated under reflux for six hours. During the reflux period, the acetone which is formed is distilled off and a stream of nitrogen passed through the solution. The isopropanol is distilled from the reaction mixture *in vacuo* and the residue treated with 750 cc. of dilute hydrochloric acid. The mixture is saturated with sodium chloride and extracted exhaustively with ethyl acetate. The ethyl acetate extracts are dried and the ethyl acetate distilled *in vacuo*. The residue is extracted with several fresh portions of hot ethyl acetate, the mixture cooled and the residue collected. The ethyl acetate extracts are retained for further purification. The ethyl acetate insoluble residue (m.p. 158—63° C.) which consists of a mixture of (*dl*)-ψ-1-*p*-nitrophenyl - 2 - acetaminopropane-1,3-diol and the corresponding (*dl*)-reg. isomer is recrystallised from water to obtain 21 g. of (*dl*)-ψ-1-*p*-nitrophenyl-2-acetaminopropane-1,3-diol melting at 166—7° C. The aqueous filtrate is allowed to stand for two days and the crystals which have separated collected. The crystals are (*dl*)-reg.-1-*p*-nitrophenyl-2-acetamino-1,3-diol and melt at 185° C. before recrystallisation. After recrystallisation these crystals melt at 195° C. and weigh 3 g.

The ethyl acetate extract is evaporated to dryness *in vacuo* and the residue treated with about 75 cc. of hot absolute ethanol. The alcohol solution is allowed to stand and the crystalline material which separates, collected. This crystalline material is a mixture of the (*dl*)-ψ-(*dl*)-reg.-1-*p*-nitrophenyl - 2 - acetaminopropane-1,3-diol. In order to separate it into its two components it is recrystallized from water to obtain 3 g. of the crystalline (*dl*)-ψ-isomer and the (*dl*)-reg. isomer isolated from the filtrate by allowing it to crystallise on long standing. The yield of the (*dl*)-reg. isomer obtained at this point is 3 g.

EXAMPLE 2.

(a) 6.3 g. of *p*-nitro - α - benzamido-β-hydroxypropiophenone is added to 4 g. of aluminum isopropylate in 75 cc. of dried isopropanol and the mixture heated under reflux for about six hours. During the refluxing period, a portion of the reaction mixture is continuously distilled off and the distillate tested from time to time for acetone. The isopropanol is removed from the reaction mixture under reduced pressure and 150 cc. of water added to the residue. The mixture is heated to boiling, the aluminum hydroxide removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue is washed with several small portions of hot ethyl acetate and the crystalline solid which fails to dissolve collected. The crystalline solid which consists principally of (*dl*)-ψ-1-*p*-nitrophenyl-2-benzamidopropane-1,3-diol of formula,

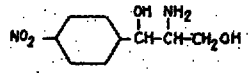


(dl)-ψ form.

is recrystallised from water to remove the (*dl*)-reg. isomer and the product collected. The (*dl*)-reg. isomer can be recovered, if desired, from the filtrate.

(b) 3 g. of (*dl*)-ψ-1-*p*-nitrophenyl-2-benzamidopropane-1,3-diol is heated on a

steam bath for one hour with 30 cc. of 5% hydrobromic acid. The reaction mixture is decolorised with charcoal and the decolorised solution made alkaline to pH 10 with sodium hydroxide solution. The (*dl*)-ψ-1-*p*-nitrophenyl - 2 - aminopropane-1,3-diol of formula,

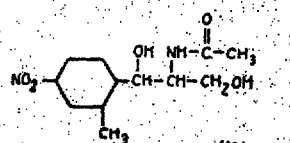


(dl)-ψ form.

which precipitates is collected, washed with cold water and purified, if desired by recrystallisation from water; m.p. 140—2° C.

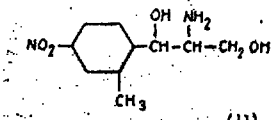
EXAMPLE 3.

(a) 5.32 g. of *o*-methyl-*p*-nitro-α-acetamino-β-hydroxypropiophenone is added to 4.8 g. of aluminum sec.-butylate in 75 cc. of dried sec.-butanol and the mixture refluxed under nitrogen while distilling off a small amount of the reaction mixture. The refluxing is continued until the distillate gives a negative test for methyl ethyl ketone (about six hours) and then the sec. butanol removed by distillation *in vacuo*. The residue is treated with 200 cc. of water, the mixture heated to boiling and aluminum hydroxide separated from the solution. The solution is evaporated to dryness and the residue extracted with several portions of hot ethyl acetate. The crystalline solid which fails to dissolve in the ethyl acetate is collected and dried *in vacuo*. This solid which consists of a mixture which is predominantly the (*dl*)-ψ-isomer together with minor amounts of the corresponding (*dl*)-reg. product is recrystallised from water to obtain the desired (*dl*)-ψ-1-(*o*-methyl-*p*-nitrophenyl)-2-acetaminopropane-1,3-diol of formula,



(dl)-ψ form.

(b) 2 g. of (*dl*)-ψ-1-(*o*-methyl-*p*-nitrophenyl)-2-acetaminopropane - 1,3 - diol is heated on a steam bath with 20 cc. of 5% hydrochloric acid for one hour. The solution containing the (*dl*)-ψ-1-(*o*-methyl-*p*-nitrophenyl) - 2 - aminopropane-1,3-diol hydrochloride is cooled, decolorised with charcoal and the decolorised solution made alkaline to pH 10 with sodium hydroxide solution. The free base of (*dl*)-ψ-1-(*o*-methyl-*p*-nitrophenyl) - 2 - aminopropane-1,3-diol which precipitates is collected, washed with cold water and dried *in vacuo*. This product which has the formula

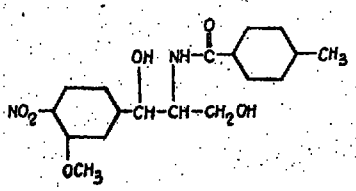


(dl)-ψ form

can be purified, if desired, by recrystallisation from water.

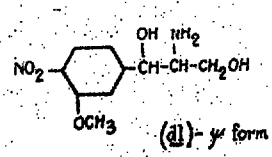
EXAMPLE 4.

(a) 7.1 g. of *m*-methoxy-*p*-nitro-α-*p*'-toluylamino-β-hydroxypropiophenone is added to 4 g. of aluminum isopropylate in 125 cc. of dried isopropanol and the resulting mixture refluxed under nitrogen while distilling off a small portion of the condensate. Refluxing is continued until the distillate gives a negative test for acetone and then the isopropanol is removed under reduced pressure. The residue is treated with 200 cc. of hot water, the aluminum hydroxide removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue is washed with several portions of hot ethyl acetate and the (*dl*)-1-(-*m*-methoxy-*p*-nitrophenyl)-2-*p*'-toluylaminopropane-1,3-diol of formula,



which fails to dissolve in the ethyl acetate collected. This product can be separated by the methods hereinbefore described into the (*dl*) - ψ - 1 - (*m*-methoxy-*p*-nitrophenyl)-2-*p*'-toluylaminopropane-1,3-diol and the corresponding (*dl*)-reg. isomer. As in the above examples, the mixture is composed principally of the (*dl*)-ψ-isomer.

(b) A mixture consisting of 3 g. of (*dl*)-ψ-1-(*m*-methoxy - *p* - nitrophenyl)-2-*p*'-toluylaminopropane-1,3-diol and 30 cc. of 5% hydrochloric acid is heated on a steam bath for about one hour and then evaporated to dryness *in vacuo*. The residue which consists of a mixture of *p*-toluic acid and the hydrochloride salt of (*dl*)-ψ-1-(*m* - methoxy-*p*-nitrophenyl)-2-aminopropane-1,3-diol is treated with 15 cc. of water, the mixture made alkaline to pH 10 with sodium hydroxide solution and the free base of (*dl*)-ψ-1-(*m*-methoxy-*p*-nitro-phenyl) - 2 - aminopropane-1,3-diol which precipitates, collected. This product which has the formula

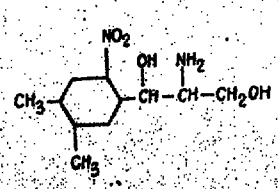


(dl)-ψ form

can be purified if desired, by recrystallisation from water.

EXAMPLE 5.

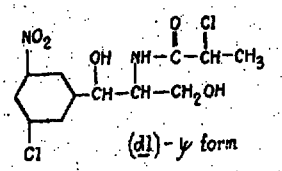
7.1 g. of 2-nitro-4,5-dimethyl-α-phenacetamino-β-hydroxypropiophenone is added to 4.5 g. of aluminum isopropylate in 150 cc. of dried isopropanol and the mixture refluxed under nitrogen for about five hours, during which time a small amount of the reaction mixture is continuously removed by distillation. After the reduction is completed, the isopropanol is removed by distillation *in vacuo*. The residue containing (*dl*)-1-(2¹-nitro-4¹,5¹-dimethylphenyl)-2-phenylacetaminopropane-1,3-diol is treated with 100 cc. of water and the mixture acidified with hydrochloric acid. Sufficient warm 10 N sodium hydroxide solution to dissolve the aluminum hydroxide which separates on neutralization is added, and, after cooling, the solution extracted with ethyl acetate. The combined ethyl acetate extracts are dried and then concentrated to the point of crystallisation. The (*dl*)-1-(2¹-nitro-4¹,5¹-dimethylphenyl)-2-aminopropane-1,3-diol of formula



which separates from the solution on cooling, is collected and dried *in vacuo*. If desired, this product can be recrystallised with water or alcohol to obtain the individual diastereo isomers of the amino diol.

EXAMPLE 6.

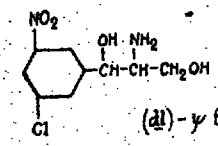
(a) 9.4 g. of 3-nitro-5-chloro-α-(α¹-chloropropionamino)-β-hydroxypropiophenone is added to 6 g. of aluminum isopropylate in 250 cc. of dry isopropanol and the mixture heated at 50° C. for about twenty-four hours, during which time a stream of nitrogen is passed through the solution. The isopropanol is removed by distillation *in vacuo* and the residue treated with about 200 cc. of water. The mixture is warmed to insure complete precipitation of the aluminum hydroxide, the aluminum hydroxide removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue is washed with several portions of hot ethyl acetate and the material which fails to dissolve, collected. The solid is recrystallised from water to obtain the desired (*dl*)-ψ-1-(3¹-nitro-5¹-chlorophenyl)-2-α-chloropropionaminopropane-1,3-diol of formula,



(dl)-ψ form

the aqueous filtrate is allowed to stand and the (*dl*)-reg. isomer which separates, collected and purified by recrystallisation. Further quantities of both isomers can be obtained from the ethyl acetate filtrate by the methods described in Example 1(e).

(b) A mixture consisting of 3 g. of (*dl*)-ψ-1-(3¹-nitro-5¹-chlorophenyl)-2-α-chloropropionaminopropane-1,3-diol and 30 cc. of 5% hydriodic acid is warmed on a steam bath for one-half hour. The solution is decolorised with charcoal and the decolorised solution made alkaline to pH 10 with sodium hydroxide solution. The free base of (*dl*)-ψ-1-(3¹-nitro-5¹-chlorophenyl)-2-aminopropane-1,3-diol of formula

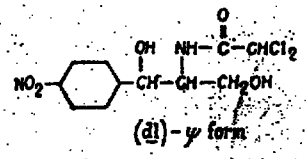


(dl)-ψ form

which precipitates, is collected and purified if desired by recrystallisation from water.

EXAMPLE 7.

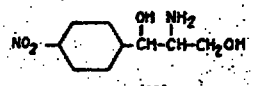
(a) 16 g. of *p*-nitro-α-dichloroacetamino-β-hydroxypropiophenone is added to 10 g. of aluminum isopropylate in 250 cc. of dry isopropanol, and the mixture refluxed for six hours. During the heating period, a stream of nitrogen is passed through the solution and a small amount of the reaction mixture is continuously distilled off. The isopropanol is removed by distillation *in vacuo*, the residue treated with 250 cc. of water and the mixture heated to boiling. The aluminum hydroxide is removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue is washed with several small portions of ethyl acetate and the crystalline solid containing (*dl*)-ψ-1-*p*-nitrophenyl-2-dichloroacetaminopropane-1,3-diol which fails to dissolve collected and recrystallised from water to obtain the desired (*dl*)-ψ-isomer. This product which has the formula



(dl)-ψ form.

can be recrystallised, if desired, from ethylene dichloride.

(b) 5 g. of (*dl*)-ψ-1-*p*-nitrophenyl-2-dichloroacetaminopropane-1,3-diol is heated on a steam bath with 50 cc. of 5% sulfuric acid for about 15 minutes. The mixture is decolorised with charcoal made alkaline to pH 10. to neutralise the sulfuric acid salt of the desired amino diol and the precipitated product collected. This product which is (*dl*)-ψ-1-*p*-nitrophenyl-2-aminopropane-1,3-diol of formula



(dl)-ψ form.

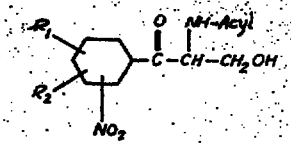
can be purified by recrystallisation from water; m.p. 140—2° C.

The ketonic acylamino alcohols employed as starting materials for the process of the present invention can be prepared by the process described in our copending Application No. 4142 of 1949 (Serial No. 688,023), of which the present Application is a Divisional Application.

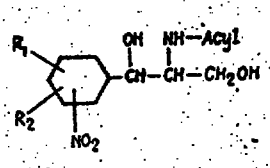
Throughout this Specification, and in the appended claims the term "lower" used in relation to an alkyl, alkoxy or aliphatic acyl radical denotes a radical containing not more than four carbon atoms.

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 reducing a compound of formula:



with an oxidizable aluminum alkoxide in an organic solvent to obtain a (*dl*)-acylamino diol 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 reduction is effected in a lower aliphatic alcohol which corresponds to the alkyl radical present in the oxidisable aluminum alkoxide.

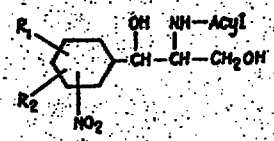
3. Process according to claims 1 or 2, wherein the oxidisable aluminum alkoxide is derived from a secondary aliphatic alcohol.

4. Process according to claims 1, 2 or 3, wherein the reduction is effected at a temperature between 20° and 125° C.

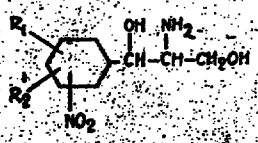
5. Process according to any of the preceding claims 1 to 4, wherein the compound which is reduced is *p*-nitro-α-dichloroacetamino-β-hydroxypropiophenone.

6. Process according to any of the preceding claims 1 to 4, wherein the compound which is reduced is *p*-nitro-α-acetamino-β-hydroxypropiophenone.

7. Process which comprises hydrolysing a (*dl*)-acylamino diol of formula



prepared by a process according to any of the preceding claims, to the corresponding free amino diol, or an acid addition salt thereof, said free amino diol having the formula



where R_1 and R_2 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals.

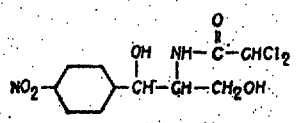
8. Process according to claim 7, wherein the hydrolysis is effected using an acidic hydrolytic agent.

9. Process according to claims 7 or 8, wherein the hydrolysis is carried out using a dilute mineral acid as the hydrolytic agent.

10. Process according to claims 7, 8 or 9, wherein the (*dl*)-acylamino diol is separated into its diastereoisomeric forms before hydrolysis by fractional crystallisation or fractional solution.

11. Process according to any of claims 7 to 10, wherein the (*dl*)-acylamino diol hydrolyzed is the pseudo-diasteroisomer.

12. Process according to any of the pre-



(dl)-ψ form

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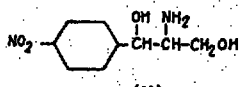
(b) 5 g. of (*dl*)-ψ-1-*p*-nitrophenyl-2-dichloroacetaminopropane-1,3-diol is heated on a steam bath with 50 cc. of 5% sulfuric acid for about 15 minutes. The mixture is decolorised with charcoal made alkaline to pH 10. to neutralise the sulfuric acid salt of the desired amino diol and the precipitated product collected. This product which is (*dl*)-ψ-1-*p*-nitrophenyl-2-aminopropane-1,3-diol of formula



(dl)-ψ form.

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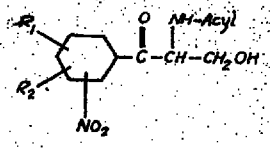
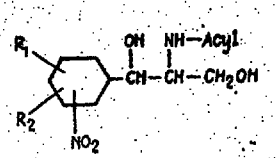
Having now particularly described and ascertained the nature of our said invention, and in what manner the same is to be performed, we declare that what we claim is:—

1. Process which comprises reducing a compound of formula:



with an oxidizable aluminum alkoxide in an organic solvent to obtain a (*dl*)-acylamino diol 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 reduction is effected in a lower aliphatic alcohol which corresponds to the alkyl radical present in the oxidisable aluminum alkoxide.

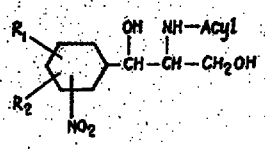
3. Process according to claims 1 or 2, wherein the oxidisable aluminum alkoxide is derived from a secondary aliphatic alcohol.

4. Process according to claims 1, 2 or 3, wherein the reduction is effected at a temperature between 20° and 125° C.

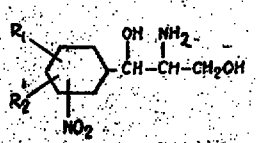
5. Process according to any of the preceding claims 1 to 4, wherein the compound which is reduced is *p*-nitro-α-dichloroacetamino - β - hydroxypropio - phenone.

6. Process according to any of the preceding claims 1 to 4, wherein the compound which is reduced is *p*-nitro-α-acetamino-β-hydroxypropiophenone.

7. Process which comprises hydrolysing a (*dl*)-acylamino diol of formula



prepared by a process according to any of the preceding claims, to the corresponding free amino diol, or an acid addition salt thereof, said free amino diol having the formula



where R_1 and R_2 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals.

8. Process according to claim 7, wherein the hydrolysis is effected using an acidic hydrolytic agent.

9. Process according to claims 7 or 8, wherein the hydrolysis is carried out using a dilute mineral acid as the hydrolytic agent.

10. Process according to claims 7, 8 or 9, wherein the (*dl*)-acylamino diol is separated into its diastereoisometric forms before hydrolysis by fractional crystallisation or fractional solution.

11. Process according to any of claims 7 to 10, wherein the (*dl*)-acylamino diol hydrolyzed is the pseudo-diasteroisomer.

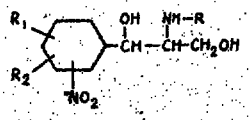
12. Process according to any of the pre-

* C L M S *

ceding claims 7 to 11 wherein R_1 and R_2 are hydrogen, and the aromatic-NO_2 substituent is in the para-position of the phenyl ring in relationship to the alcoholic residue.

13. Process according to the preceding claims 7 to 12, wherein the starting material is (*dl*)-ψ-1-*p*-nitrophenyl-2-acetaminopropane-1 : 3-diol.

14. Process for obtaining free amino diol and acylamino diol compounds of the formula



where R_1 and R_2 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals and R is hydrogen or an acyl radical, and acid addition salts of the products where R is hydrogen substantially as hereinbefore described with reference to any of the specific examples.

15. Free amino diol compounds, acylamino diol compounds, and acid addition salts of said free amino diols thereof when prepared or produced by the processes claimed in any of the preceding claims 1 to 14, or their obvious chemical equivalents.

16. The individual structural isomeric forms of the compounds claimed in claim 15 when prepared or produced by the methods or processes described herein or their obvious chemical equivalents.

17. (*dl*) - ψ-1-*p*-Nitrophenyl-2-dichloroacetamino-propane-1 : 3-diol when prepared or produced by any of the processes of claims 1 to 5 or 14 or an obvious chemical equivalent thereof.

18. (*dl*)-ψ-1-*p*-Nitrophenyl-2-acetaminopropane-1 : 3 diol when prepared or produced by any of the processes of claims 1 to 4, 6 or 14 or an obvious chemical equivalent thereof.

19. (*dl*)-ψ-1-*p*-Nitrophenyl-2-aminopropane-1 : 3-diol when prepared or produced by any of the processes of claims 7 to 14 or an obvious chemical equivalent thereof.

Dated this 31st day of January, 1952.

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