Patented Oct. 4, 1949

2,483,884

UNITED STATES PATENT OFFICE

2,483,884

METHOD FOR MAKING NITROPHENYL ACYLAMIDO ALKANE DIOLS

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No Drawing. Application March 16, 1948, Serial No. 15,264

10 Claims. (Cl. 260—562)

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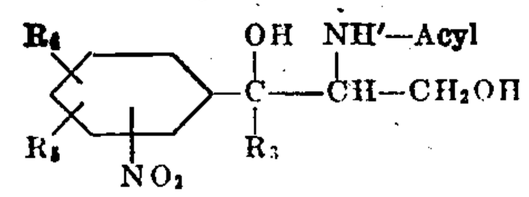
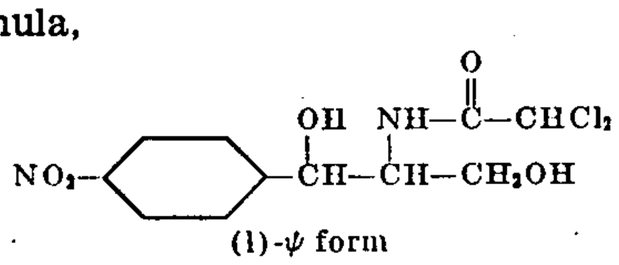
The invention relates to a method for the manufacture of nitrophenyl acylamido alkane diols represented by the formula,



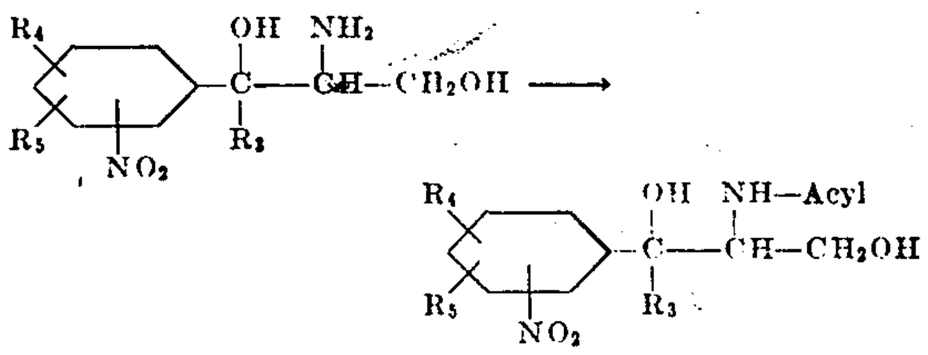
where R_4 and R_5 are the same or different and represent hydrogen, halogen, lower alkyl and lower alkoxy radicals and R_3 is hydrogen or a lower alkyl radical, which compounds are claimed in our copending application, Serial No. 76,179, filed February 12, 1949, as a continuation-in-part of the instant application. A representative compound within said class is the antibiotic compound, (l) - ψ-1-p-nitrophenyl - 2 - dichloroacetamidopropane-1,3-diol, chloramphenicol, having the formula,



(l)-ψ form

The new nitrophenyl acylamido alkane diols are so unique in chemical constitution that their synthesis from previously known compounds requires a series of steps to accomplish the purpose. In our research, we have extensively explored the entire field of syntheses and in so doing we have not only discovered many different synthetic processes which can be successfully used to obtain the nitrophenyl acylamido alkane diols, but have also discovered many new intermediate compounds, the existence of which has not heretofore been known, or even contemplated.

Some of the subject matter originally disclosed herein is now disclosed and claimed in our copending applications, Serial Nos. 76,172, 76,173, 76,174, 76,175, 76,176, 76,177, 76,178, 76,179 and 76,180, all filed February 12, 1949 as continuations-in-part of the instant application and the present application is directed more particularly to that step in the process diagrammatically represented as follows:



where R_4 and R_5 are the same or different and represent hydrogen, halogen, lower alkyl and lower alkoxy radicals, R_3 is hydrogen or a lower

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alkyl radical and acyl represents a radical such as lower aliphatic acyl, halogen substituted lower aliphatic acyl, benzoyl, substituted benzoyl and like radicals.

It will be readily appreciated by those skilled in the art that the compounds represented by the above formulae may 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. To differentiate between these two possible forms we will subsequently refer to the cis compounds as the "regular" series or form and the trans compounds as the "pseudo" (ψ) series or form. Such cis compounds are products wherein the two most highly polar of the groups on the two asymmetric carbon atoms lie on the same side of the plane of the two carbon atoms. Conversely, the trans or pseudo compounds are those wherein the two most highly polar groups lie on opposite sides of the plane of the two carbon atoms.

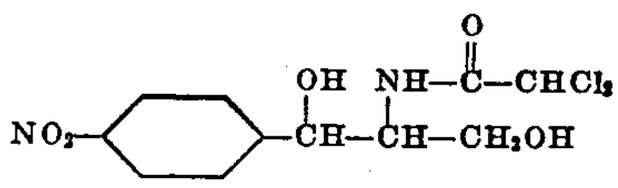
Both the regular and pseudo forms exist as racemates of optically active isomers which can be resolved into the dextro (d) and levo (l) rotatory isomers by the methods hereinafter described.

From the above it will be apparent that, strictly speaking, the starting materials and final products of the process claimed herein, as well as the products used in the production of the starting materials, exist in four different forms. However, the lability of the nitro group in the phenyl nitro diols, produced in step I below and used in the production of the starting materials, is such that the products cannot be separated into their individual forms. On the other hand, the phenylamino diols and phenyl acylamido diols are stable and the four forms of the product are separable. Such a separation is often desirable because of the differing degrees of physiological activity of the isomers.

Because of the difficulty of representing these structural differences in graphic formulae we have used the customary structural formulae and adopted the following convention in order to designate its structural and optical 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 total unseparated mixture of the four forms. When a designation is given the product is the particular isomer or mixture designated. On the other hand, when the formula is general, that is, includes more than one specific compound, it represents not only the complete mixture of the four forms but the individual isomers and mix-

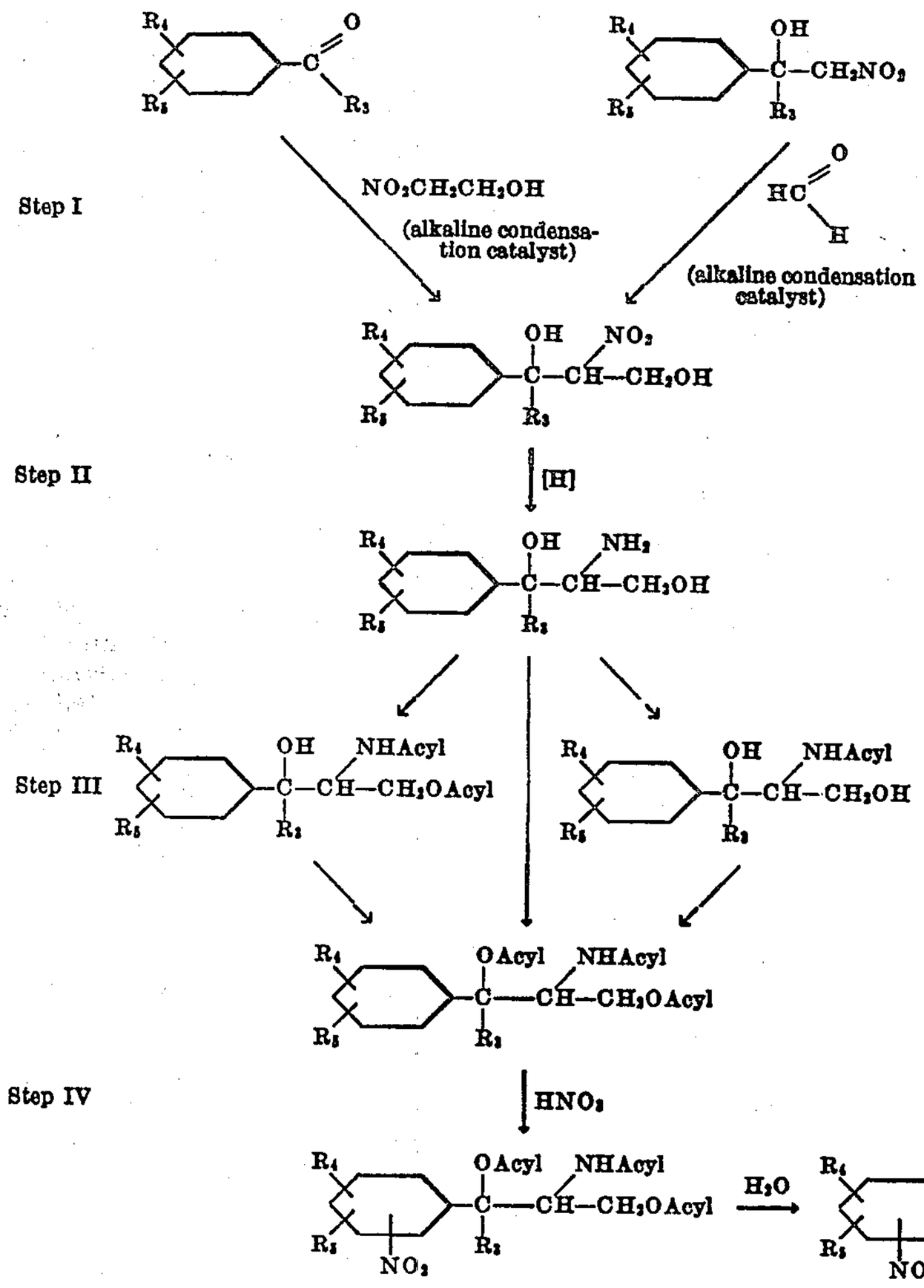
tures of two of these individual isomers. Thus, for example, general formulae such as appear above include seven things, the complete mixture of the four forms, the racemic regular and pseudo mixtures and the four individual isomers. The racemic mixtures are the (dl) regular mixture and the (dl)-pseudo mixture while the four individual isomers are the (d)-regular, the (l)-regular, the (d)-pseudo and the (l)-pseudo forms.

Our convention as applied to specific compounds such as 1 - p - nitrophenyl - 2 - dichloroacetamidopropane-1,3-diol can be illustrated as follows: Where the formula shown is:



the complete mixture of the four forms, the (d)-regular, the (l)-regular, the (d)-pseudo and the (l)-pseudo, is meant. However, where a designation such as "(l)-ψ" appears below or to the side of the formula the product is the particular isomer, in this case, the levo rotatory optical isomer of the pseudo form.

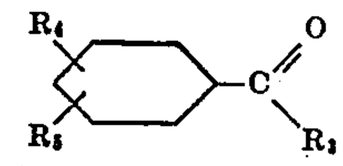
Using the above conventions, one of our processes for obtaining the starting materials for use in the process claimed herein, may be diagrammatically represented as follows:



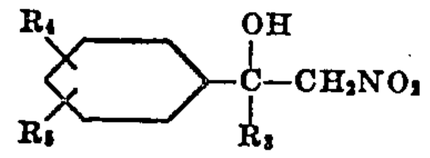
where R_3, R_4 and R_5 have the same significance as given above and acyl- in each case represents

the same or different acyl radical. Included in the term "acyl" are radicals such as lower aliphatic acyl, halogen substituted lower aliphatic acyl, benzoyl, substituted benzoyl and the like radicals.

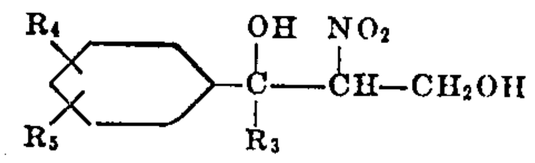
Step I of our process comprises condensing a phenyl carbonyl compound of formula,



or formaldehyde with β-nitroethanol or an α-phenyl β-nitroethanol of the formula,



respectively, in the presence of an alkaline condensing catalyst such as an alkali metal oxide, an alkali metal hydroxide, a metal alkoxide or an alkali metal amide to obtain a 1-phenyl-2-nitropropane-1,3-diol of formula,



In either case the condensation is effected in the same manner and is preferably carried out in an inert organic solvent such as a lower aliphatic alcohol and at a temperature below about 50° C.

The next step of the process, step II, comprises reducing the 1-phenyl-2-nitropropane-1,3-diol

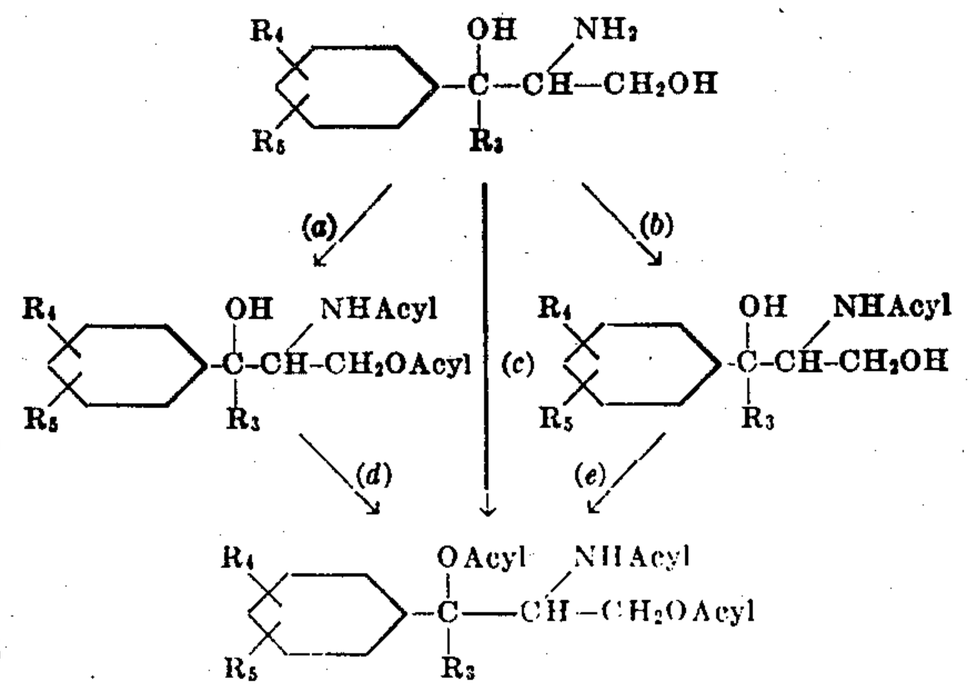
compound obtained in step I to the corresponding 1-phenyl-2-aminopropane-1,3-diol compound. This is preferably accomplished by catalytic means using catalysts and conditions which do not cause hydrogenolysis of benzyl alcohol. Some of the catalysts which have been found suitable for this purpose are palladium oxide, palladium on carbon and Raney nickel. When the foregoing hydrogenation catalysts are used the hydrogenation can be carried out under hydrogen pressures varying from atmospheric, about 15 lbs. per sq. in., to about 2000 lbs. per sq. in. and at temperatures ranging from about 20 to 50° C. As media for the hydrogenation a variety of different organic solvents, such as acetic acid and lower aliphatic alcohols, may be used.

Another method of effecting this transformation consists in reducing the 1-phenyl-2-nitropropane-1,3-diol compound by chemical means such as by the use of reducing salts or acid-metal combinations. Some of the reducing salts which may be used are stannous chloride, sodium hydrosulfite, ferrous sulfate and the like while iron-acetic acid and zinc-sulfuric acid are examples of the metal-acid reductants. Still another metal-acid combination which has proved advantageous is a nickel-aluminum alloy, such as "Raney nickel catalyst powder," in combination with acetic acid.

Where one particular isomeric or racemic form of the final product is desired it is usually advantageous to separate the regular from the pseudo structural form at this point. This can usually be accomplished quite readily and completely by utilization of the differences in solubility of the two forms in organic solvents such as chloroform. However, in some cases the solvent solubility differential of the two forms is not great enough to afford a clean-cut separation of the two structural isomers and in these cases it is preferable to convert the isomer mixture of the 1-phenyl-2-aminopropane-1,3-diol to either an N-acyl or an O,N-diacyl derivative whose structural isomers differ more markedly in their solubility characteristics. The structural isomers of these acylated derivatives can then be separated by fractional crystallization from a solvent such as an aliphatic alcohol, acetone, chloroform, ethyl acetate and aqueous mixtures of the same. This alternate method of separating these structural isomers is also very useful in further purification of the individual isomeric forms separated in the form of their free base by the differential solvent solubility method.

Where a particular optical isomer of the final product is desired the corresponding individual regular or pseudo structural form of the 1-phenyl-2-aminopropane-1,3-diol can be resolved into its optical isomers at this point or at a later stage in the process. This resolution may be carried out by forming an acid addition salt of the racemic amine with an optically active acid such as d-tartaric, l-tartaric, d-mandelic, l-mandelic, d-brom-camphor sulfonic acid and l-brom-camphor sulfonic acid, separating the two isomeric salts by recrystallization from a solvent such as a lower aliphatic alcohol or mixtures of the same with water or other organic solvents and then regenerating the individual optical isomers from the separated optically active acid addition salts by neutralizing each one separately. When carrying out this resolution it is desirable, but not absolutely necessary, to choose the form of the optically active acid so that the desired optical isomer will separate from the crystallization solution first.

The third step of our process involves converting the 1-phenyl-2-aminopropane-1,3-diol compound produced in step II to the completely acylated amino diol. This can be accomplished in a number of different ways as will be apparent by reference to the following diagram:



The choice of one of the above methods depends, of course, upon many factors but primarily upon the nature of the final product desired and the methods used to carry out the final steps of the process.

When it is necessary to separate the structural forms of the 1-phenyl-2-aminopropane-1,3-diol compound through an N-acyl or an O,N-diacyl derivative or when such derivatives are prepared for purification of the structural isomers, it is, of course, preferable to use either one of the two step-wise acylation procedures rather than hydrolyze the acyl groups and then totally reacylate the base in one-step.

In order to effect the O,N-diacylation designated as (*a*) in the above diagram we heat the 1-phenyl-2-aminopropane-1,3-diol compound with an excess of an acyl anhydride or acyl halide for a short period of time. In most cases the reaction mixture need only be heated for five to thirty minutes at 60 to 135° C.

The N-mono-acylation of 1-phenyl-2-aminopropane-1,3-diol [(*b*) in the above diagram] can be carried out by heating the base with an acyl ester under substantially anhydrous conditions at a temperature above the boiling point of the alcohol formed from the acylating ester during the reaction. Thus when methyl esters are employed the temperature should be maintained substantially above 65° C. and preferably in the neighborhood of 100° C. The time required for completion of the reaction depends to a large extent upon the nature of the acid portion of the acylating ester. For example, in the case of α-dihalo acetic esters the reaction is substantially complete within one-half hour while a longer period of time is required when the corsponding α-monohalo acetic ester is used.

An alternative method of carrying out this N-mono acylation of the 1-phenyl-2-aminopropane-1,3-diol compounds consists in treating an alkaline aqueous solution of the amino diol with a substantial excess of an acyl anhydride or halide. During the reaction the mixture is kept below the boiling point and the pH is maintained above 7.

The complete acylation of the amino diol in one step as well as the complete acylation of the mono- and di-acyl derivatives (see *c*, *d* and *e* in

the above diagram) can be accomplished by treatment of the starting material with an acyl anhydride or halide in conjunction with an inorganic or tertiary organic base under substantially anhydrous conditions. In general, this transformation can be effected by heating the reaction mixture at about 60 to 130° C. for about one-half to several hours. Some examples of the tertiary bases which may be used with the acyl anhydrides or halides in this case are pyridine, quinoline, dimethylaniline, triethylamine, N-ethylpiperidine and the like.

Step IV, the next step of our process, involves ring nitration of the completely acylated 1-phenyl-2-aminopropane-1,3-diol compound of step III to produce the corresponding completely acylated 1-(nitrophenyl)-2-aminopropane-1,3-diol. This nitration can be carried out using mixed acid, that is, a mixture of concentrated nitric and sulfuric acids; 100% nitric acid or fuming nitric acid. In all cases the temperature of the reaction mixture should be kept between −20 and +10° C. and preferably in the neighborhood of 0° C. The next step is to hydrolyze off all the acyl groups in the completely acylated 1-(nitrophenyl)-2-aminopropane-1,3-diol.

In hydrolyzing off all of the acyl groups from the completely acylated 1-(nitrophenyl)-2-aminopropane-1,3-diol acidic or alkaline conditions can be used. However, we prefer to hydrolyze using dilute mineral acid since it is more efficient in bringing about complete hydrolysis in a shorter time. When acidic hydrolytic conditions are used the 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 in this form or it can be neutralized and isolated as the free base.

If a particular optical isomer of the final compound is desired, the racemic optical isomer mixture of one of the structural forms is resolved at this point. As mentioned above, this resolution or separation can also be carried out on the free base of the 1-phenyl-2-aminopropane-1,3-diol compound and if this has been done it, of course, is not necessary to repeat the resolution at this point. The conditions, reagents and methods used to separate the optical isomers at this stage of the process are the same as those described for the resolution of a racemic mixture of one of the structural forms of the 1-phenyl-2-aminopropane-1,3-diol compounds.

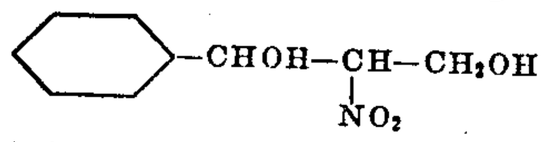
The re-acylation of the amino group in the 1-(nitrophenyl)-2-aminopropane-1,3-diol compound, the process to which the instant invention is directed, can be effected by treating the free base with an acylating agent under mild acylating conditions. In order to eliminate the possibility of di-acylation at this point it is preferable to use either an ester type acylating agent under substantially anhydrous conditions or an acyl anhydride or halide in a mildly alkaline aqueous reaction medium. In general, the reaction is carried out in the same manner as described above for the conversion of the 1-phenyl-2-aminopropane-1,3-diol compounds to the corresponding N-monoacyl products (see reaction *b*).

When an acyl group containing at least one α-halogen atom is desired on the amino nitrogen atom in the final product, it is preferable to use the corresponding halogenated acyl ester as the acylating agent. Thus, for example, when the desired product is a 1-(nitrophenyl)-2-dichloroacetamidopropane-1,3-diol compound the acylating agent of choice is a lower alkyl ester of dichloroacetic acid. When acylating agents of this type are used the reaction is usually effected by heating a mixture of the two reactants at a temperature sufficiently high to distill off the alcohol liberated during the reaction from the acylating ester.

The invention is illustrated by the following examples.

Example 1

1.1 g. of sodium is dissolved in 20 cc. of methanol and the resulting solution added to a solution of 5 g. of benzaldehyde and 4.5 g. of β-nitroethanol in 20 cc. of methanol. After standing at room temperature for a short time the gel which forms on the mixing of the reactants changes to a white insoluble powder. The precipitate is collected, washed with methanol and ether and then dried. The product thus produced is the sodium salt of 1-phenyl-2-nitropropane-1,3-diol. If desired, the free nitro-diol having the formula

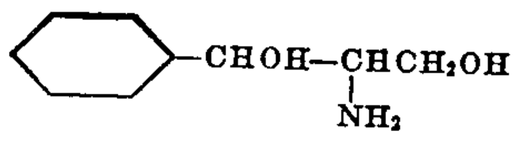


can be obtained by acidification of the salt.

An alternative method of preparing the sodium salt of 1-phenyl-2-nitropropane-1,3-diol is as follows:

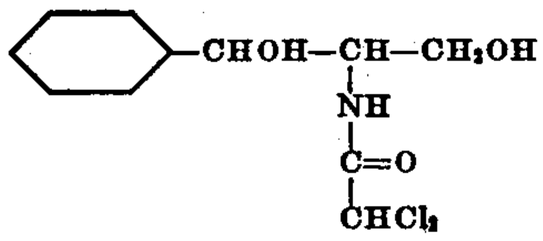
1.65 g. of formaldehyde in 10 cc. of methanol is added to a solution of 9.2 g. of 1-phenyl-2-nitroethane-1,2-diol in 20 cc. of methanol. A solution of 1.1 g. of sodium dissolved in 10 cc. of methanol is added slowly to the reaction mixture with stirring and the mixture stirred at room temperature until the desired sodium salt of 1-phenyl-2-nitropropane-1,3-diol precipitates. The precipitated product is collected, washed with methanol and ether and then dried.

18 g. of the sodium salt of 1-phenyl-2-nitropropane-1,3-diol is dissolved in 200 cc. of glacial acetic acid. 0.75 g. of palladium oxide hydrogenation catalyst is added and the mixture shaken at room temperature under three atmospheres pressure of hydrogen overnight. The reaction vessel is opened, 2.5 g. of 10% palladium on carbon hydrogenation catalyst added and the mixture shaken under three atmospheres pressure of hydrogen for three hours. The catalyst is removed from the reaction mixture by filtration and the filtrate concentrated under reduced pressure. 50 cc. of n-propanol is added to the residue and the insoluble inorganic salt removed by filtration. The filtrate is treated with excess hydrochloric acid and evaporated to obtain a pale yellow oil. 5 g. of the oil thus obtained is treated with 15 cc. of saturated potassium carbonate solution and the mixture extracted with 50 cc. of ether, then with 30 cc. of ethyl acetate and finally with two 30 cc. portions of ethanol. Evaporation of the solvent from the extract gives the following quantities of the desired 1-phenyl-2-aminopropane-1,3-diol: 0.5 g., 1.0 g. and 3.1 g. The formula of this product is:



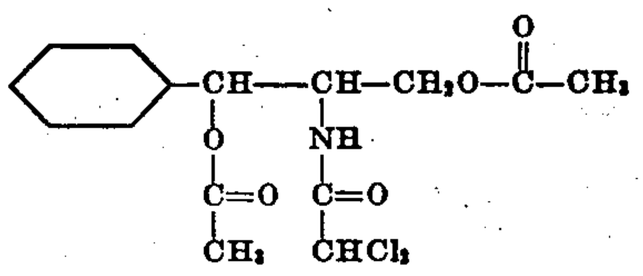
1.7 g. of 1-phenyl-2-aminopropane-1,3-diol is treated with 1.6 g. of methyl dichloroacetate and the mixture heated at 100° C. for one and a quarter hours. The residue is washed with two 20 cc. portions of petroleum ether and the insoluble product collected. Recrystallization from ethyl acetate yields the desired (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol in

pure form; M. P. 154–6° C. This product's formula is:



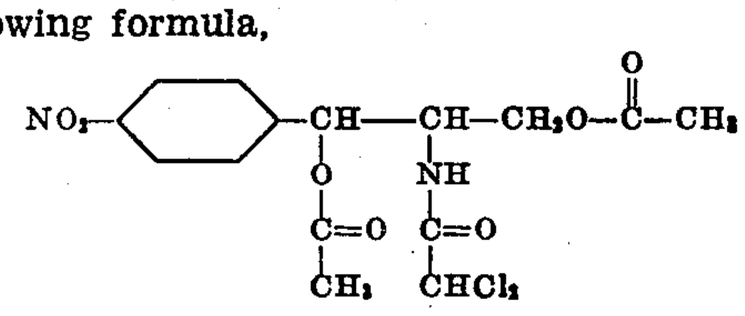
(dl)-reg. form

500 mg. of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol is added to a solution consisting of 1 cc. of pyridine and 1 cc. of acetic anhydride and the resulting reaction mixture heated at 100° C. for one-half hour. The reaction mixture is evaporated to dryness under reduced pressure and the residue taken up in and crystallized from methanol. Recrystallization from methanol produces the pure diacetate of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol (M. P. 94° C.) having the formula,



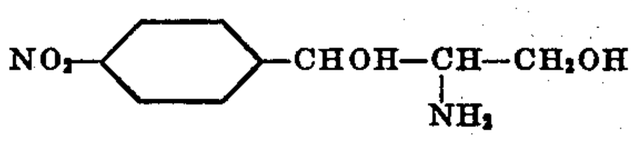
(dl)-reg. form

200 mg. of the diacetate of (dl)-reg.-1-phenyl-2-dichloroacetamidopropane-1,3-diol is added to a mixture consisting of 0.25 cc. of concentrated nitric acid and 0.25 cc. of concentrated sulfuric acid at 0° C. The reaction mixture is stirred until solution is complete, poured onto 25 g. of ice and the mixture extracted with ethyl acetate. The ethyl acetate extracts are evaporated under reduced pressure and the diacetate of (dl)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol so produced purified by recrystallization from ethanol; M, P. 134° C. This compound has following formula,



(dl)-reg. form

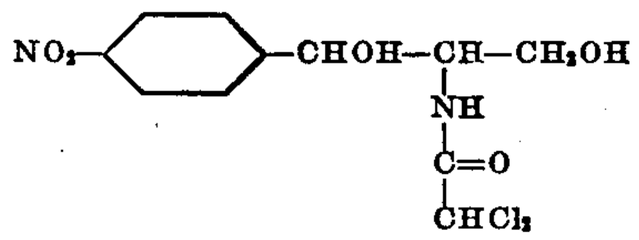
100 mg. of the diacetate of (dl)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol is heated with 5 cc. of 6 N hydrochloric acid for about three hours. The reaction mixture is evaporated to dryness under reduced pressure to obtain the desired hydrochloride salt of (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol; M. P. of pure salt 216–8° C. The free base can be obtained by dissolving the hydrochloride in water and neutralizing the solution with sodium hydroxide to pH 9. The solution is extracted with ethyl acetate and the ethyl acetate evaporated to obtain the free base of (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol; M. P. 107–9° C. when crystallized from ethanol or ethylene dichloride. The formula of this product is



(dl)-reg. form

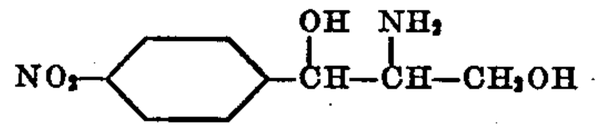
The triacetate of (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol (produced by treatment of the free base with acetic anhydride in pyridine) melts at 154–5° C.

500 mg. of the diacetate of (dl)-reg.-1-p-nitrophenyl - 2-dichloroacetamidopropane-1,3-diol is dissolved in a mixture consisting of 25 cc. of acetone and an equal volume of 0.2 N sodium hydroxide solution at 0° C. and the mixture allowed to stand for one hour. The reaction mixture is neutralized with hydrochloric acid and evaporated under reduced pressure to dryness. The residue is extracted with several portions of hot ethylene dichloride, the extracts concentrated and then cooled to obtain the crystalline (dl)-reg. - 1 - p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol; M. P. 171° C. The formula of this compound is:



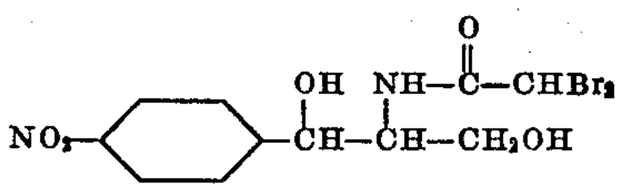
(dl)-reg. form

600 mg. of (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol is dissolved in a warm solution of 900 mg. of (d)-camphor sulfonic acid in 18 cc. of n-butanol. Solution is cooled, the crystals which separate collected and recrystallized twice from n-butanol. The crystalline acid addition salt obtained in this manner, the (d)-camphor sulfonate of (d)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol, is dissolved in water containing excess sodium hydroxide and the free base of the desired (d)-reg.-isomer recovered by extraction with ethyl acetate. After drying, the ethyl acetate is distilled in vacuo to obtain the free base of (d) - reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol in crystalline form. Its formula is:



(d)-reg. form

A mixture consisting of 75 mg. of (d)-reg.-1-p-nitrophenyl-2-aminopropane-1,3 - diol and 0.1 cc. of methyl dibromo-acetate is heated on a steam bath for about one hour, cooled and petroleum ether added to precipitate the desired amide. The solid is collected and purified by recrystallization from ethylene dichloride. This product which has the formula,



(d)-reg. form

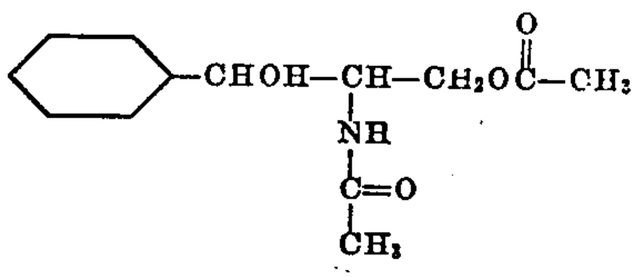
is (d) - reg.-1-p-nitrophenyl-2-dibromoacetamidopropane-1,3-diol.

Example 2

(*a*) 20 g. of the sodium salt of 1-phenyl-2-nitropropane-1,3-diol (prepared by either of the methods described in Example 1) is dissolved in 200 cc. of glacial acetic acid. 0.75 g. of palladium oxide hydrogenation catalyst is added and the mixture shaken with hydrogen under three atmospheres pressure for about twelve hours. The catalyst is removed by filtration, the filtrate concentrated to about one-tenth volume in vacuo and diluted with fi[illegible] volumes of water. The solution is extracted with one volume of ethyl acetate or ether and the extract discarded. The aqueous phase is made alkaline to pH 12 with strong sodium hydroxide solution and extracted with five 100 cc. portions of ethyl acetate. The combined extracts are dried, the ethyl acetate

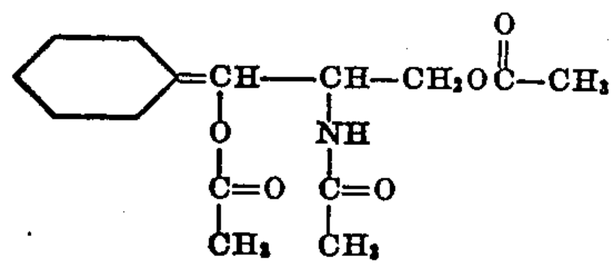
evaporated and the residue recrystallized from chloroform. The white crystalline product thus obtained is (dl)-reg.-1-phenyl-2-aminopropane-1,3-diol; M. P. 103–4° C.

The chloroform filtrate from the crystallization of the (dl)-reg-1-phenyl-2-aminopropane-1,3-diol is evaporated to dryness and the residue heated with an excess of acetic anhydride at 70° C. for fifteen minutes. The reaction mixture is evaporated to dryness in vacuo and the residue recrystallized from ethanol. This white crystalline product which melts at 167–8° C. is (dl)-ψ-1-phenyl-2-acetamido-3-acetoxypropane - 1 - ol. It can be represented by the following formula,



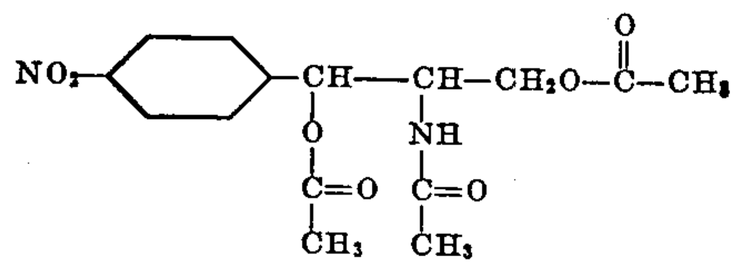
(dl)-ψ-form

2 g. of (dl)-ψ-1-phenyl-2-acetamido-3-acetoxy propane-1-ol is added to a mixture composed of 4 cc. of acetic anyhdride and 4 cc. of dry pyridine and the resulting mixture heated at 100° C. for about one-half hour. The reaction mixture is evaporated in vacuo and the residue recrystallized from methanol to obtain the triacetate of (dl)-ψ-1-phenyl-2-aminopropane-1,3-diol melting at 79° C. Its formula is:



(dl)-ψ-form

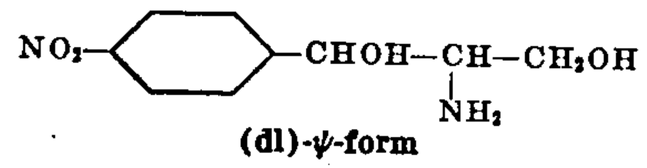
2 g. of the triacetate of (dl)-ψ-1-phenyl-2-aminopropane-1,3-diol is added in small portions to a mixture composed of 2.5 cc. of concentrated nitric acid and 2.5 cc. of concentrated sulfuric acid. The temperature of the nitrating mixture is maintained at about 0° C. and the reaction continued until solution of the aminodiol derivative is complete. The reaction mixture is poured onto 250 g. of ice and the resulting solution extracted with several portions of ethyl acetate. After washing with sodium carbonate solution the ethyl acetate is distilled from the combined extracts in vacuo and the residual triacetate of (dl)-ψ-1-p-nitrophenyl-2-aminopropane-1, 3-diol purified by recrystallization from ethanol. This product which melts at 145° C. has the formula,



(dl)-ψ-form

2 g. of the triacetate of (dl)-ψ-1-p-nitrophenyl-2-aminopropane-1, 3-diol is heated with 100 cc. of 5% hydrochloric acid for two to three hours on a steam bath and then the reaction mixture evaporated to dryness in vacuo. The crystalline hydrochloride salt of (dl)-ψ-1-p-nitrophenyl-2-aminopropane-1, 3-diol (M. P. 177.5–8.5° C.) thus obtained is taken up in a small amount of water and the solution made alkaline to pH 9 with sodium hydroxide solution. The solution is extracted with ethyl acetate, the combined extracts

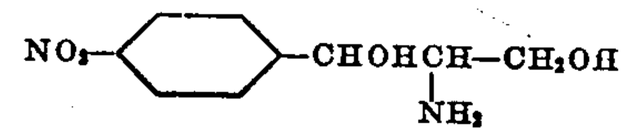
dried and the ethyl acetate evaporated to obtain the desired free base of (dl)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol; M. P. 140.5° C. The formula of this compound is:



(dl)-ψ-form

The (dl)-ψ-1-p-nitrophenyl-2-aminopropane-1, 3-diol prepared above is dissolved in a small amount of water and treated with an aqueous solution containing an equivalent amount of (d)-tartaric acid. The solution is evaporated to dryness in vacuo and the residue fractionally crystallized from the minimum amount of hot methanol. The first isomer to separate from the solution in crystalline form is the (d)-tartaric acid salt of (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol; M. P. 198–200° C. The (d)-tartaric acid salt of (d)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol is recovered from the filtrates after removal of the salt of the (l)-isomer.

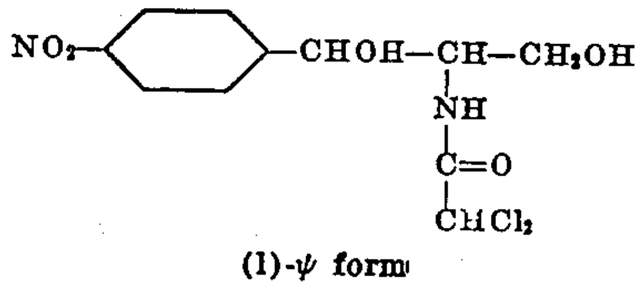
The (d)-tartaric acid salt of (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol obtained above is dissolved in water, the solution made alkaline to pH 9 with sodium hydroxide solution and extracted with several portions of ethyl acetate. The combined ethyl acetate extracts are dried and the ethyl acetate evaporated to obtain the free base of (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol (M. P. 157° C.) having the formula,



(l)-ψ form

By decomposing the (d)-tartaric acid salt of (d) - ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol in the same manner as described above for the (l)-isomer, one obtains the free base of (d)-ψ-1-p-nitrophenyl - 2 - aminopropane-1,3-diol. In an analogous manner the (dl)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol may be resolved into its isomeric forms via the (d)-camphor sulfonic acid salt. This is accomplished by reacting the optically active acid with the racemic base in butanol and separating the isomers by recrystallization from n-butanol. The salt of the (l) isomer which separates from the solution first has an M. P. of 172° C.

A mixture consisting of 1.5 g. of the free base of (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol and 1.5 g. of methyl dichloroacetate is heated at 100° C. for one and a half hours. The reaction mixture is cooled and treated with 25 cc. of petroleum ether. The residue which fails to dissolve is collected, washed with two additional 10 cc. portions of petroleum ether and dried. The product thus obtained is (l)-ψ-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol. This product which has the formula,



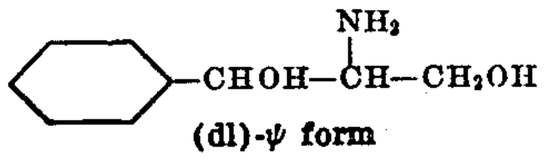
(l)-ψ form

can be purified by recrystallization from ethylene dichloride; M. P. 147.5–148.5° C. Repeated recrystallization raises the melting point to about 150–151° C.

By treating the free base of (d)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol in an analogous

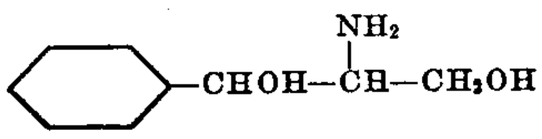
manner, (d)-ψ-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol is obtained.

4 g. of (dl)-ψ-1-phenyl-2-acetamido-3-acetoxypropane-1-ol in 25 cc. of 3 N hydrochloric acid is refluxed for about three hours and the reaction mixture evaporated to dryness. The residual hydrochloride salt is taken up in a small amount of water, the solution made alkaline with sodium hydroxide and extracted with ethyl acetate. After drying, the ethyl acetate is evaporated from the extracts in vacuo to obtain the free base of (dl)-ψ-1-phenyl-2-aminopropane-1,3-diol; M. P. 81–3° C. This product has the formula,



(dl)-ψ form

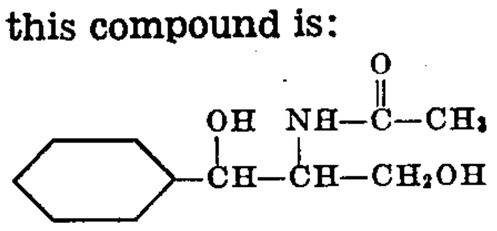
The free base of (dl)-ψ-1-phenyl-2-aminopropane-1,3-diol obtained above is dissolved in 60 cc. of warm n-butanol containing 5 g. of (d)-camphor sulfonic acid and the mixture cooled. The solid which separates is collected, recrystallized twice from n-butanol and dissolved in a small amount of water containing an excess of sodium hydroxide. The solution is extracted with ethyl acetate, the ethyl acetate extracts dried and the solvent distilled in vacuo. The residue which consists of (l)-ψ-1-phenyl-2-aminopropane-1, 3-diol has the formula,



(l)-ψ form

0.5 g. of (l-ψ-1-phenyl-2-aminopropane-1, 3-diol is dissolved in 5 cc. of dry pyridine and 3 g. of benzoic anhydride added to the resulting solution. The mixture is heated on a steam bath for four hours, cooled and 20 cc. of water added. The insoluble product is collected, washed with water and purified by recrystallization from ethanol. The product obtained in this manner is the tri-benzoate of (l)-ψ-1- phenyl-2-aminopropane-1, 3-diol.

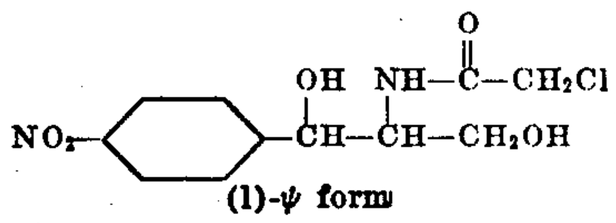
500 mg. of (dl)-ψ-1-phenyl-2-acetamido-3-acetoxypropane-1, 3-diol is added to a solution consisting of 25 cc. of 0.1 N sodium hydroxide solution and an equal volume of acetone at 0° C. and the resulting mixture stirred for one hour. The solution is neutralized with hydrochloric acid and the acetone evaporated under reduced pressure. The residual aqueous solution is extracted with ethyl acetate, the extracts dried and the ethyl acetate distilled in vacuo. The residue which consists of (dl)-ψ-1-phenyl-2-acetamidopropane-1,3-diol is purified by recrystallization from ethyl acetate or alcohol; M. P. 132.5° C. The formula of this compound is:



(dl)-ψ form

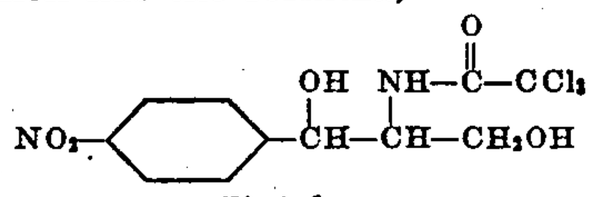
2 g. of (dl)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol and an equal amount of (+) (d) mandelic acid is dissolved in 80 cc. of boiling absolute ethanol and the solution allowed to cool slowly. The (+) (d) mandelate salt of l(—)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol which separates from the solution first is collected and purified by recrystallization from absolute ethanol. The (+) (d)-mandelate salt of the d(+)-ψ-isomer can be recovered from the filtrates. Each of the salts is then dissolved separately in water, neutralized and the optical isomeric free bases recovered from the solutions by extraction with ethyl acetate.

A two-phase mixture consisting of 50 cc. of 0.5 N potassium hydroxide solution, an equal volume of ethyl acetate, 1.06 g. of (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol and 1.13 g. of chloroacetyl chloride is shaken for about 10 to 15 minutes at 0° C. The ethyl acetate layer is separated and the aqueous phase extracted with several portions of ethyl acetate. The combined extracts and ethyl acetate layer are evaporated to dryness under reduced pressure and the residual (l)-ψ-1-p-nitrophenyl-2-chloroacetamidopropane-1,3-diol (M. P., crude, 83–6° C.) purified by recrystallization from alcohol-petroleum ether mixture. The formula of this product is:



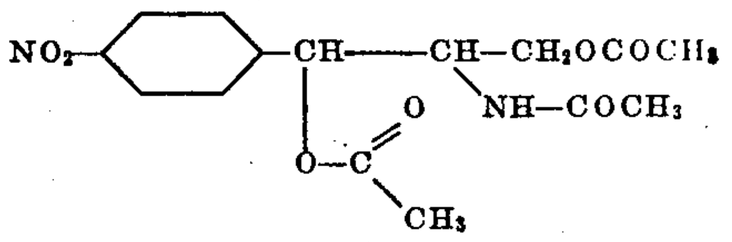
(l)-ψ form

A mixture consisting of 1.06 g. of (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol and 2 g. of methyl trichloroacetate is heated at about 100° C. for about one and a half hours, cooled and the 50 cc. of petroleum ether added to the solution. The insoluble material is collected, washed with petroleum ether and purified by recrystallization from ethylene dichloride. This product is (l)-ψ-1-p-nitrophenyl-2-trichloroacetamidopropane -1, 3-diol which has the formula,



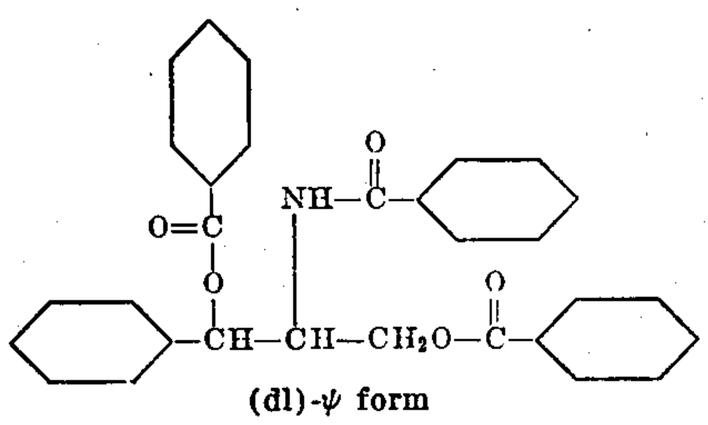
(l)-ψ form

A solution of 500 mg. of (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol in 5 cc. of acetic anhydride is refluxed 3 hours. The reaction mixture is evaporated to dryness in vacuo and the residue recrystallized from methanol; M. P. 109–11° C. This compound has the formula,



(l)-ψ form

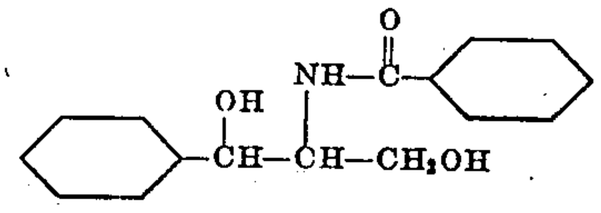
A mixture consisting of 2 g. of (dl)-ψ-1-phenyl-2-aminopropane-1,3-diol, 10 cc. of dry pyridine and 10 cc. of benzoyl chloride is allowed to stand for twenty-four hours, poured into about 300 cc. of ice water and the precipitate collected. The crude tribenzoate of (dl)-ψ-1-phenyl-2-aminopropane-1,3-diol thus obtained is washed with sodium bicarbonate solution, water, dilute hydrochloric acid and finally with water. This product which has the formula,



(dl)-ψ form

may be purified by recrystallization from methanol.

1 g. of the tribenzoate of (dl)-ψ-1-phenyl-2-aminopropane-1,3-diol in 50 cc. of acetone is added to 50 cc. of 0.1 N sodium hydroxide solution at 0° C. and the mixture allowed to stand for one hour at 0° C. The excess alkali is exactly neutralized and the solution evaporated to dryness in vacuo. The residue is washed with water to remove the salt and recrystallized from alcohol. The product thus obtained is (dl)-ψ-1-phenyl-2-benzamidopropane-1,3-diol which has the formula,



(dl)-ψ form

(*b*) 10 g. of (dl)-reg.-1-phenyl-2-aminopropane-1,3-diol, prepared as described in (*a*) above, is heated with a mixture consisting of 20 cc. of pyridine and 20 cc. of acetic anhydride for one-half hour at 100° C. The reaction mixture is evaporated to dryness in vacuo to obtain the desired triacetate of (dl)-reg.-1-phenyl-2-aminopropane-1, 3-diol. This same compound can also be obtained by first diacylating the (dl)-reg.-1-phenyl-2-aminopropane-1, 3-diol on the amino and terminal hydroxyl groups with acetic anhydride and then subsequently 0-acylating the (dl)-reg.-1-phenyl-2-acetamido-3-acetoxypropane-1-ol so obtained with acetic anhydride and pyridine.

10 g. of the triacetate of (dl)-reg.-1-phenyl-2-aminopropane-1,3-diol is added in small portions to a mixture composed of 12.5 cc. of concentrated nitric acid and 12.5 cc. of concentrated sulfuric acid at 0° C. After the addition has been completed the temperature is maintained at 0° C. until solution is complete and then the reaction mixture poured onto 1250 g. of ice. The solution is extracted with several portions of ethyl acetate, the ethyl acetate extracts washed with dilute sodium carbonate solution and the ethyl acetate removed by distillation in vacuo. The residue which consists of the triacetate of (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1, 3-diol is purified by recrystallization from ethanol.

8 g. of the triacetate of (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol is heated with 400 cc. of 5% hydrochloric acid for about three hours and the reaction mixture evaporated to dryness in vacuo. The residual (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol hydrochlochloride is taken up in a small amount of water, the solution made alkaline to pH 9 with sodium hydroxide solution and the mixture extracted with ethyl acetate. The combined extracts are dried and the ethyl acetate removed by distillation in vacuo to obtain the desired (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol.

5 g. of (dl)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol is dissolved in water and treated with an equivalent amount of d-tartaric acid. The reaction mixture is evaporated to dryness and the mixture of the d-tartaric acid salts of the (d) and (l) forms of reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol separated by fractional crystallization.

The d-tartaric acid salt of (d)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol is dissolved in water, the solution made alkaline to pH 9 with sodium hydroxide solution and extracted with ethyl acetate. The extracts are dried and the ethyl acetate distilled to obtain the free base of

(d)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol.

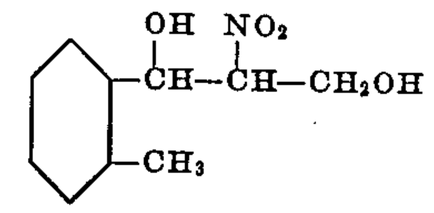
In a similar manner, the free base of (l)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol may be obtained by decomposing the corresponding d-tartaric acid salt with sodium hydroxide.

2 g. of (d)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol is heated at 100° C. with 2 g. of methyl dichloroacetate for one and a half hours, the reaction mixture cooled and extracted with 35 cc. of petroleum ether. The insoluble residue which consists of the desired (d)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol is washed with petroleum ether and dried.

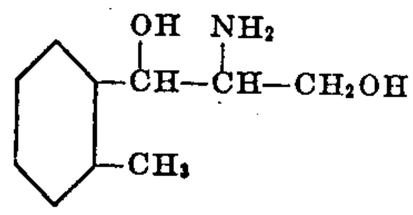
By treating the free base of (l)-reg.-1-p-nitrophenyl-2-aminopropane-1,3-diol in the same manner one obtains (l)-reg.-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol.

Example 3

(*a*) 2.2 g. of sodium dissolved in 40 cc. of methanol is added to a solution of 12 g. of o-methyl benzaldehyde and 9 g. of β-nitroethanol in 40 cc. of methanol. The reaction mixture is allowed to stand at room temperature for a short time and then the white insoluble sodium salt of 1-o-methylphenyl-2-nitropropane-1,3-diol removed by filtration, washed with ether and dried. Acidification of this sodium salt produces the corresponding free nitro compound, 1-o-methylphenyl-2-nitropropane-1,3-diol, which has the formula,



18 g. of the sodium salt of 1-o-methylphenyl-2-nitropropane-1,3-diol is dissolved in 175 cc. of glacial acetic acid, 0.75 g. of palladium oxide hydrogenation catalyst added and the mixture hydrogenated under three atmospheres pressure of hydrogen for about twelve hours. The catalyst is removed by filtration, the filtrate concentrated to a small volume in vacuo and then the residue diluted with five volumes of water. The solution is extracted with one volume of ethyl acetate or ether and the extract discarded. The aqueous phase is made alkaline to pH 12 with strong sodium hydroxide solution and extracted with five volumes of ethyl acetate. The ethyl acetate extracts are combined, dried and the ethyl acetate evaporated in vacuo. The residue which consists of a mixture of the (dl)-regular and (dl)-pseudo 1-o-methylphenyl-2-aminopropane-1,3-diol is taken up in and crystallized from chloroform to obtain the (dl)-reg.-1-o-methylphenyl-2-aminopropane-1,3-diol in crystalline form. Its formula is:

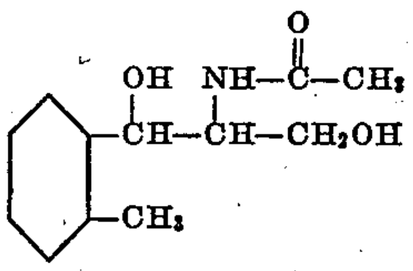


(dl)-reg. form

The chloroform filtrate from which the (dl)-reg.-1-o-methylphenyl-2-aminopropane-1,3-diol has been removed is evaporated in vacuo to obtain the crude (dl)-ψ-1-o-methylphenyl-2-aminopropane-1,3-diol. If desired, the crude (dl)-pseudo product can be converted directly to the triacetate by treatment with acetic anhydride and pyridine but we have found it preferable to purify this product through an acyl derivative such as the N-mono acetate or the N, 3-o-diace-

tate before proceeding further in the synthesis of our new antibiotics. This purification may be carried out as follows:

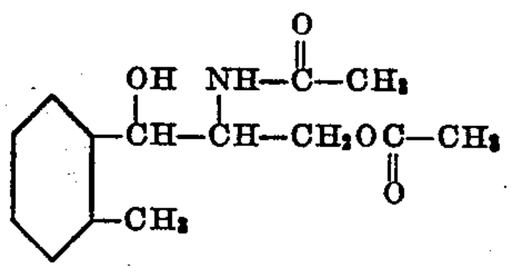
1. The crude (dl)-ψ-1-o-methylphenyl-2-aminopropane-1,3-diol is treated with an excess of acetyl chloride at about room temperature in a solvent of dry benzene. When a considerable amount of the hydrochloride salt of (dl)-ψ-1-o-methylphenyl-2-aminopropane-1,3-diol has separated from the solution the reaction is stopped by the addition of 300 cc. of water. After thorough mixing the aqueous solution is removed and saved for recovery of the unacetylated amino diol. The benzene solution is washed with dilute sodium bicarbonate solution and then dried. The benzene is removed by distillation in vacuo and the crude (dl)-ψ-1-o-methylphenyl-2-acetamidopropane-1,3-diol taken up in alcohol and purified by recrystallization from alcohol. The formula of this product is:



(dl)-ψ form

2. An alternative method for purifying the crude (dl)-ψ-amino diol is as follows:

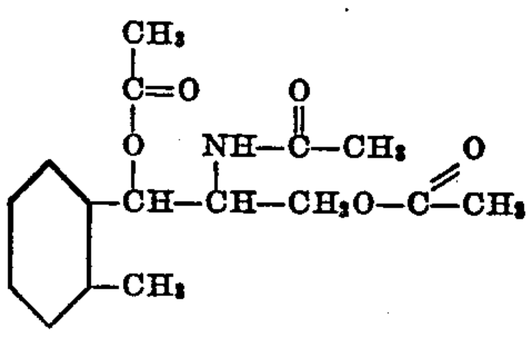
The crude (dl)-ψ-1-o-methylphenyl-2-aminopropane-1,3-diol is heated with an excess of acetic anhydride at about 70 to 80° C. for fifteen minutes and then the reaction mixture evaporated in vacuo. The residue which consists of (dl)-ψ-1-o-methylphenyl-2-acetamido-3-acetoxypropane-1-ol has the formula:



(dl)-ψ form

and is purified by recrystallization from ethanol.

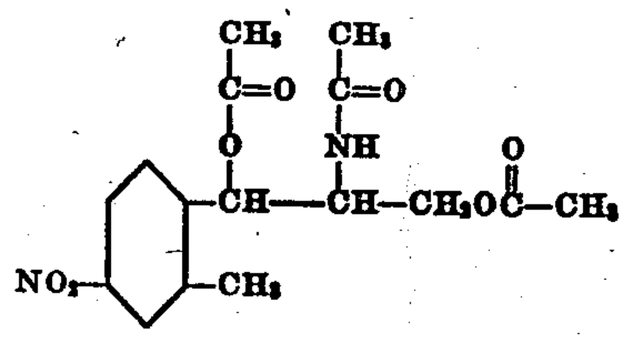
5 g. of either (dl)-ψ-1-o-methylphenyl-2-acetamidopropane-1,3-diol or (dl)-ψ-1-o-methylphenyl-2-acetamido-3-acetoxypropane-1-ol is added to a mixture consisting of 10 cc. of acetic anhydride and 10 cc. of pyridine and the resulting mixture heated at 100° C. for about one-half hour. The reaction mixture is concentrated to dryness in vacuo and the residual triacetate of (dl)-ψ-1-o-methylphenyl-2-aminopropane-1,3-diol recrystallized from methanol. The formula of this product is:



(dl)-ψ form

6 g. of the triacetate of (dl)-ψ-1-o-methylphenyl-2-aminopropane-1,3-diol is added in small portions to a nitrating mixture composed of 7.5 cc. of concentrated nitric and 7.5 cc. of concentrated sulfuric acid while keeping the temperature at about 0° C. The reaction mixture is stirred until solution is complete and then poured onto 750 g.

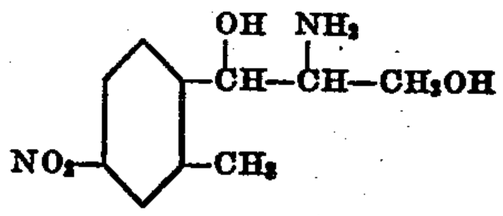
of ice. The solution is extracted with several portions of ethyl acetate, the extracts washed with sodium carbonate solution and the ethyl acetate distilled. The residue which consists principally of the triacetate of (dl)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol of formula,



(dl)-ψ form

can be purified by recrystallization from ethanol.

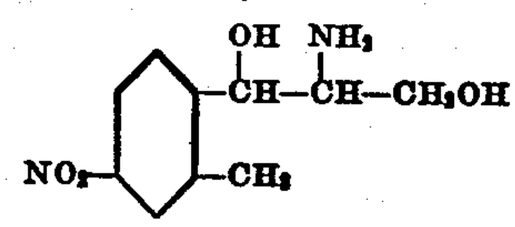
5 g. of the triacetate of (dl)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol is heated with 250 cc. of 5% hydrochloric acid for about three hours and then the reaction mixture evaporated to dryness in vacuo. The residue which consists of (dl)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol hydrochloride is taken up in water, the solution made alkaline to pH 9 with sodium hydroxide and then extracted with several portions of ethyl acetate. The ethyl acetate extracts are dried and the ethyl acetate distilled to obtain the free base of (dl)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol which has the formula,



(dl)-ψ form

4 g. of (dl)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane is dissolved in a small amount of water and added to an aqueous solution containing an equivalent amount of d-tartaric acid. The solution is evaporated to dryness in vacuo and the residue fractionally crystallized from hot methanol. The first isomer to separate from the solution is the (d)-tartaric acid salt of (l)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol. After removal of the (d)-acid salt of the (l)-isomer the corresponding (d)-acid salt of the (d)-isomeric diol is recovered from the combined filtrates.

The (d)-tartaric acid salt of (l)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol obtained above is dissolved in water and the solution made alkaline to pH 9 with sodium hydroxide. The solution is extracted with ethyl acetate, the extracts dried and the ethyl acetate evaporated to obtain the free base of (l)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol. This compound has the formula,

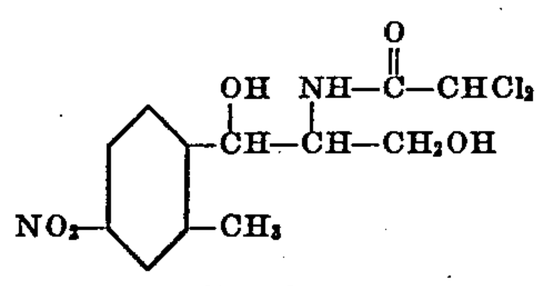


(l)-ψ form

By neutralization of the (d)-tartaric acid salt of the (d)-ψ-isomer one obtains the free base of (d)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol.

2.2 g. of (l)-ψ-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol is mixed with 1.75 g. of methyl dichloroacetate and the mixture heated at 100° C. for one and a half hours. The reaction

mixture is cooled, extracted with two 25 cc. portions of petroleum ether and the residue which fails to dissolve collected. The residue which consists of (l) - ψ - 1-o-methyl-p-nitrophenyl-2-dichloroacetamidopropane - 1,3 - diol is washed with two additional 10 cc. portions of petroleum ether and purified by recrystallization from ethylene dichloride. Its formula is:



(l)-ψ form

By similar treatment of the free base of (d)-ψ-1-o-methyl-p-nitrophenyl - 2-aminopropane-1,3-diol with methyl dichloroacetate, one obtains (d)-ψ-1-o-methyl - p - nitrophenyl - 2 - dichloroacetamidopropane-1,3-diol.

(*b*) 6 g. of the (dl)-reg.-1-o-methylphenyl-2-aminopropane-1,3-diol obtained in (*a*) above is heated with 8 cc. of pyridine and 8 cc. of acetic anhydride for one hour at 100° C. and then the reaction mixture evaporated to dryness in vacuo. The residue thus obtained consists of the triacetate of (dl)-reg.-1-o-methylphenyl-2-aminopropane-1,3-diol.

5 g. of the triacetate of (dl)-reg.-1-o-methylphenyl-2-aminopropane-1,3-diol is nitrated by adding the solid to a mixture consisting of 6 cc. of concentrated sulfuric acid at 0° C. The mixture is stirred at 0° C. until solution is complete and then poured onto 600 g. of ice. The solution is extracted with ethyl acetate, the extracts washed with sodium bicarbonate solution and dried. Distillation of the ethyl acetate in vacuo yields principally the desired triacetate of (dl)-reg. - 1 - o - methyl - p - nitrophenyl - 2 - aminopropane-1,3-diol. This product can be purified by recrystallization from ethanol.

4 g. of the triacetate of (dl)-reg.-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol is heated with about 200 cc. of 5% hydrochloric or hydrobromic acid for about three to four hours and the reaction mixture evaporated to dryness in vacuo. The residue which consists of the corresponding hydrohalide salt of (dl)-reg.-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol is taken up in water, the solution made alkaline to pH 9 with potassium hydroxide and the solution extracted with ethyl acetate. The combined extracts are dried and the ethyl acetate removed by distillation in vacuo to obtain the desired (dl)-reg.-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol.

3 g. of (dl)-reg.-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol is dissolved in water and the solution treated with an aqueous solution containing one equivalent of (d)-tartaric acid. The aqueous reaction mixture is evaporated to dryness in vacuo and the optical isomers separated by fractional crystallization of their salts from methanol. The (d)-tartaric acid salt of the (d)-reg. isomer separates first from the mixture while the (d)-tartaric acid salt of the (l)-reg. isomer is recovered from the filtrates.

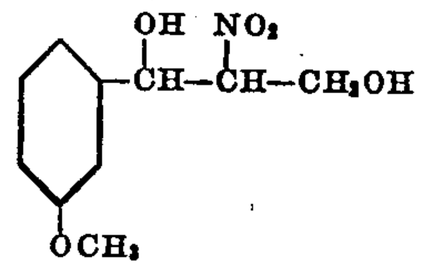
Each of the isomeric salts of the reg.-1-o-methyl - p - nitrophenyl - 2 - aminopropane-1,3-diol is decomposed separately by dissolving it in water, treating the solution with alkali and extracting the solution with ethyl acetate to obtain the respective free base.

1.2 g. of the free base of (d)-reg.-1-o-methyl-p-nitrophenyl-2-aminopropane-1,3-diol is heated at 100° C. for one and a half hours with 1.3 g. of methyl dichloroacetate. The residue is extracted twice with a small amount of petroleum ether, the extracts discarded and the residue consisting of (d)-reg.-1-o-methyl-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol collected. The product is washed with petroleum ether and purified by recrystallization from ethylene dichloride.

By treating the free base of (l)-reg.-1-o-methyl-p-nitrophenyl-2-aminopropane in a similar manner one obtains (l)-reg.-1-o-methyl-p-nitrophenyl - 2 - dichloroacetamidopropane-1,3-diol.

Example 4

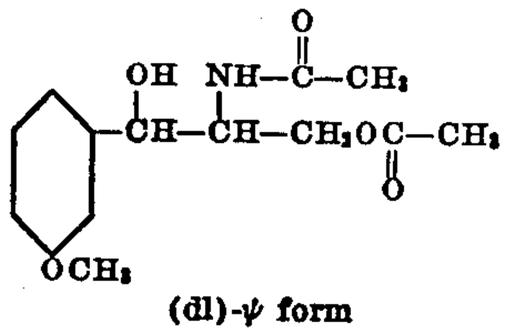
A solution of 2.2 g. of sodium in 40 cc. of methanol is added to a solution of 13.6 g. of m-methoxybenzaldehyde and 9 g. of β-nitroethanol in 40 cc. of methanol. The reaction mixture is allowed to stand at room temperature for a short time and then the white, insoluble sodium salt of 1-m-methoxyphenyl-2-nitropropane-1,3-diol collected. The product is washed with ether and dried. If desired, the free nitro compound, 1-m-methoxyphenyl-2-nitropropane-1,3-diol, having the formula,



can be obtained by acidification of the salt.

20 g. of the sodium salt of 1-m-methoxyphenyl-2-nitropropane-1,3-diol is dissolved in 200 cc. of glacial acetic acid. 0.75 g. of palladium oxide hydrogenation catalyst is added and the mixture hydrogenated under three atmospheres pressure of hydrogen for about twelve hours. The catalyst is removed by filtration, the filtrate concentrated in vacuo to about one-tenth of its original volume and the residue diluted with five volumes of water. The solution is extracted with ethyl acetate and the extract discarded. The aqueous solution is made alkaline to pH 12 with strong sodium hydroxide, extracted with ethyl acetate and the combined extracts dried. The ethyl acetate is removed by distillation in vacuo and the residue recrystallized from chloroform to obtain the (dl)-reg.-1-m-methoxyphenyl-2-aminopropane-1,3-diol in crystalline form. The corresponding (d) and (l)-pseudo isomers remain dissolved in the chloroform solution and are recovered by evaporation of the filtrate.

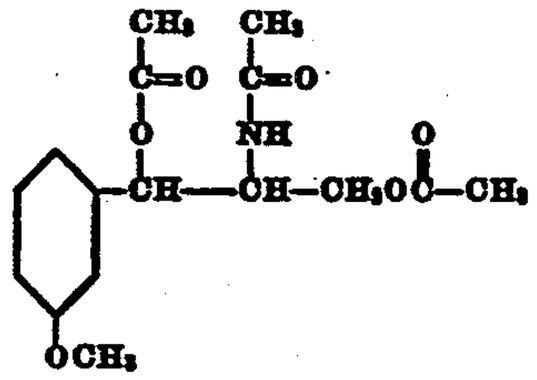
The crude (dl) - ψ - 1 - m - methoxyphenyl-2-aminopropane-1,3-diol is heated at about 70° C. with an excess of acetic anhydride for one-half hour and then the excess acetic anhydride and liquid reaction products removed by distillation in vacuo. The residue which consists of (dl) - ψ - 1 - m - methoxyphenyl - 2 - acetamido-3-acetoxypropane-1-ol of the formula,



(dl)-ψ form

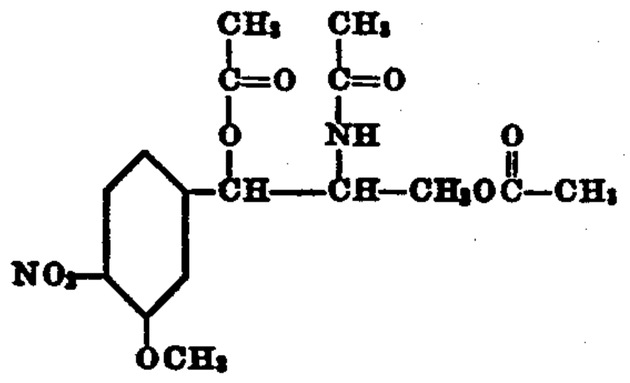
is taken up in ethanol and purified by recrystallization from this solvent.

5 g. of (dl)-ψ-1-m-methoxyphenyl-2-acetamido-3-acetoxypropane-1-ol is added to a mixture of 10 cc. of acetic anhydride and 10 cc. of pyridine. The resulting mixture is heated at 100° C. for one-half hour and then concentrated to dryness in vacuo. The residual triacetate of (dl)-ψ-1-m-methoxyphenyl - 2 - aminopropane-1,3-diol is purified by recrystallization from ethanol. Its formula is:



(dl)-ψ form

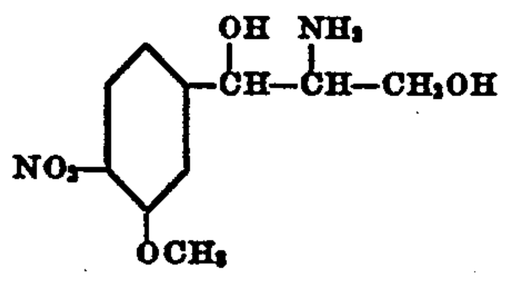
4 g. of the triacetate of (dl)-ψ-1-m-methoxyphenyl-2-aminopropane-1,3-diol is added to a mixture consisting of 5 cc. of concentrated nitric acid and 5 cc. of concentrated sulfuric acid while maintaining the temperature at 0° C. The reaction mixture is stirred until solution is complete and then poured onto 500 g. of ice. The solution is extracted with ethyl acetate, the extracts washed with sodium carbonate solution and the ethyl acetate distilled. The residue consists principally of the desired triacetate of (dl)-ψ-1-m-methoxy-p-nitrophenyl - 2 - aminopropane-1,3-diol which has the formula,



(dl)-ψ form

The contaminating isomeric nitration products can be removed from the desired product by fractional recrystallization from alcohol.

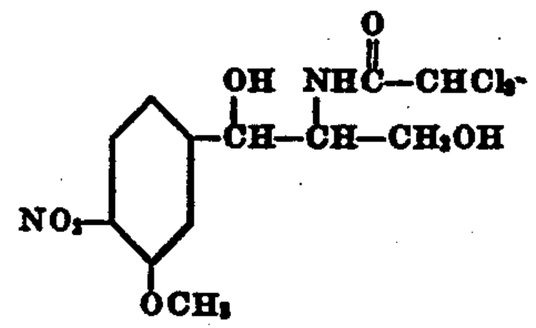
4 g. of the triacetate of (dl)-ψ-1-m-methoxy-p-nitrophenyl-2-aminopropane - 1,3-diol is refluxed with 200 cc. of 5% hydrochloric acid for three hours and then the reaction mixture evaporated to dryness in vacuo. The residual (dl)-ψ-1 - m-methoxy-p-nitrophenyl-2-aminopropane-1,3-diol hydrochloride is taken up in water, the solution made alkaline to pH 9 with sodium hydroxide and then extracted with ethyl acetate. The combined extracts are dried and the ethyl acetate removed by distillation under reduced pressure to obtain the desired (dl)-ψ-1 - m-methoxy-p-nitrophenyl-2-aminopropane-1,3-diol. This product's formula is



(dl)-ψ form

A mixture consisting of 1.2 g. of (dl)-ψ-1-m-methoxy - p - nitrophenyl-2-aminopropane-1,3-diol and 1 g. of methyl dichloroacetate is heated at 100° C. for one hour and a half. The residue is cooled, extracted with two 25 cc. portions of

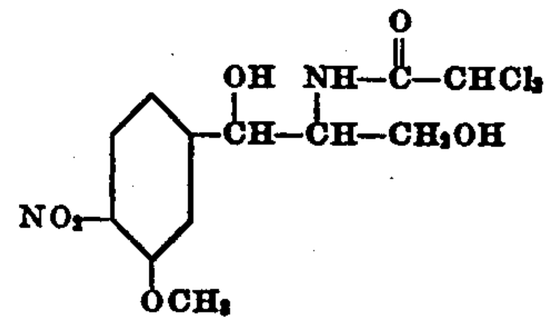
petroleum ether and the material which fails to dissolve collected. This crystalline material which consists of (dl)-ψ-1-m-methoxy-p-nitrophenyl - 2 - dichloroacetamidopropane-1,3-diol of formula,



(dl)-ψ form

is washed with two 10 cc. portions of petroleum ether, dried and then purified by recrystallization from ethylene dichloride.

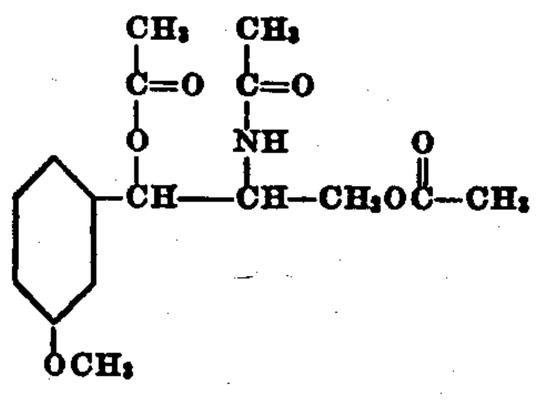
2 g. of (dl)-ψ-1-m-methoxy-p-nitrophenyl-2-aminopropane-1,3-diol is resolved into the respective (d)- and (l)-isomers through the d-tartaric acid salts as described in the preceding examples for the resolution of similar compounds. 0.75 g. of the (l)-ψ-1-m-methoxy-p-nitrophenyl-2-aminopropane-1,3-diol thus obtained is converted to the corresponding 2-dichloroacetamido derivative of formula,



(l)-ψ form

by heating with 0.6 g. of methyl dichloroacetate at 100° C. for one and a half hours followed by leaching the impurities out of the residual product with petroluem ether. The insoluble product can then be purified further, if desired, by recrystallization from ethylene dichloride.

(*b*) A mixture consisting of 8 g. of (dl)-reg.-1 - m-methoxyphenyl-2-aminopropane-1,3-diol (from (*a*) above), 16 cc. of acetic anhydride and 16 cc. of pyridine is heated at 100° C. for one-half hour and then the reaction mixture concentrated to dryness under reduced pressure. The residual triacetate of (dl)-reg.-1-m-methoxyphenyl-2-aminopropane-1,3-diol of formula,

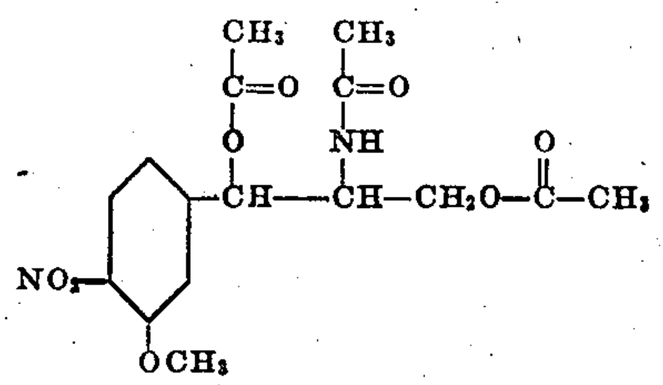


(dl)-reg. form

is purified by recrystallization from ethanol.

8 g. of the triacetate of (dl)-reg.-1-m-methoxyphenyl-2-aminopropane-1,3-diol is added to a nitrating mixture composed of 10 cc. of concentrated nitric acid and 10 cc. of concentrated sulfuric acid while maintaining the temperature at 0° C. The reaction mixture is stirred until solution is complete and then poured onto 1000 g. of ice. The crude triacetate of (dl)-reg.-1-m-methoxy-p-nitrophenyl-2-aminopropane-1,3-diol is recovered from the solution by extraction with ethyl acetate and the ethyl acetate distilled from

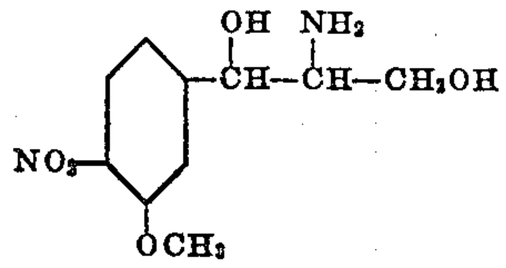
the extracts. This product which has the formula,



(dl)-reg. form

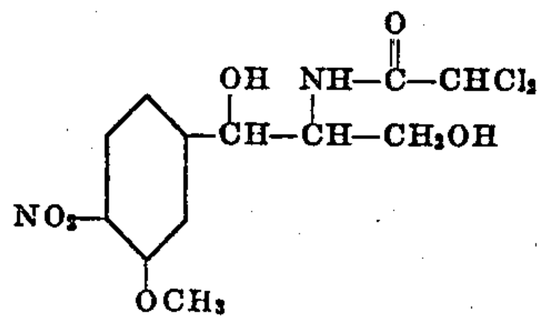
can be purified by recrystallization from ethanol.

6 g. of the triacetate of (dl)-reg.-1-m-methoxy-p-nitrophenyl-2-aminopropane-1,3-diol is hydrolyzed by refluxing with 300 cc. of 5% hydrochloric acid for three hours. The reaction mixture is evaporated to dryness in vacuo and the residue which consists of the hydrochloride of the desired amino diol taken up in water. The solution is made alkaline to pH 9 with sodium hydroxide solution, extracted with ethyl acetate and the solvent distilled from the extracts to obtain the desired free base of (dl)-reg.-1-m-methoxy - p - nitrophenyl - 2 - aminopropane-1,3-diol. Its formula is:



(dl)-reg. form

A mixture consisting of 4 g. of (dl)-reg.-1-m-methoxy - p - nitrcphenyl - 2 - aminopropane-1,3-diol and 3.3 g. of methyl dichloroacetate is heated at 100° C. for about two hours, cooled and the residue washed well with petroleum ether. The undissolved residue which consists of (dl)-reg. - 1 - m - methoxy - p - nitrophenyl - 2 - dichloroacetamidopropane-1,3-diol of formula,

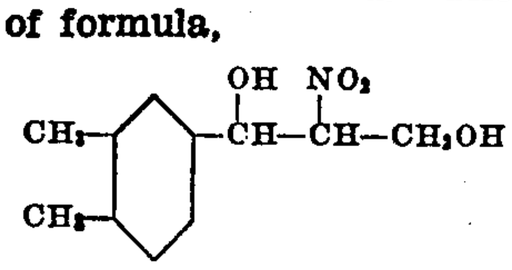


(dl)-reg. form

is collected and purified by recrystallization from ethylene dichloride.

Example 5

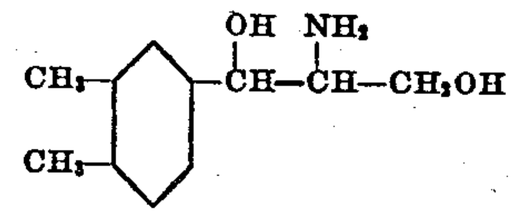
2.2 g. of sodium dissolved in 40 cc. of methanol is added to a solution consisting of 13.4 g. of 3,4-dimethylbenzaldehyde and 9 g. of β-nitroethanol in 40 cc. of methanol and the reaction mixture allowed to stand at room temperature until the gel which forms initially is converted to a white insoluble powder. The precipitate which consists of the sodium salt of 1-(3',4'-dimethylphenyl) - 2 - nitropropane - 1,3 - diol is collected, washed with ether and dried. The free nitro compound of formula,



can be obtained by acidification of the sodium salt.

A mixture consisting of 20 g. of the sodium

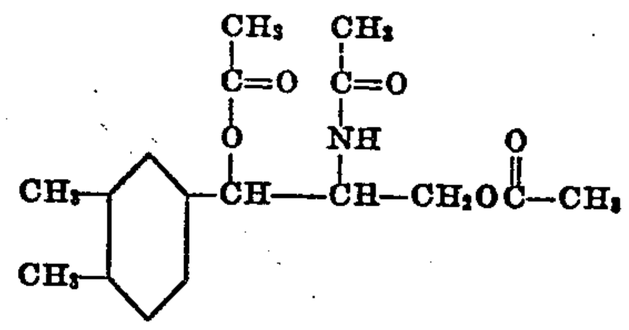
salt of 1-(3',4'-dimethylphenyl)-2-nitropropane-1,3-diol, 175 cc. of glacial acetic acid and 0.75 g. of palladium oxide hydrogenation catalyst is shaken under three atmospheres pressure of hydrogen for about fifteen hours. The catalyst is removed by filtration and the filtrate concentrated to about one-tenth volume in vacuo. The residue is diluted with five volumes of water, the solution extracted with one volume of ethyl acetate and the extract discarded. The aqueous solution is made alkaline to about pH 12 with sodium hydroxide, extracted with ethyl acetate and the combined extracts dried. The ethyl acetate is evaporated in vacuo and the residue taken up in and crystallized from chloroform to obtain (dl) - reg. - 1 - (3',4' - dimethylphenyl) - 2-aminopropane-1,3-diol in crystalline form. Its formula is:



(dl)-reg. form

The corresponding (dl)-ψ-form can be recovered from the chloroform filtrate.

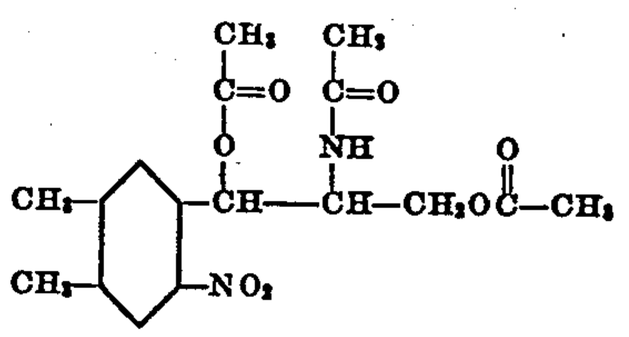
8 g. of (dl)-reg.-1-(3',4'-dimethylphenyl)-2-aminopropane-1,3-diol is heated at 100° C. for one-half hour with a mixture consisting of 16 cc. of acetic anhydride and 16 cc. of pyridine and the mixture evaporated to dryness in vacuo. The residue which consists of the desired triacetate of (dl) - reg. - 1 - (3',4' - dimethylphenyl) - 2-aminopropane-1,3-diol of formula,



(dl)-reg. form

is collected and purified by recrystallization from ethanol.

8 g. of the triacetate of (dl)-reg.-1-(3',4'-dimethylphenyl)-2-aminopropane-1,3-diol is nitrated at 0° C. with a mixture consisting of 10 cc. of concentrated nitric acid and 10 cc. of concentrated sulfuric acid, the reaction mixture poured onto 1000 g. of ice and the desired triacetate of (dl)-reg.-1-(2'-nitro-4',5'-dimethylphenyl)-2-aminopropane-1,3-diol recovered from the solution by extraction with ethyl acetate followed by distillation of the solvent from the extracts. This product which can be purified by recrystallization from ethanol has the formula,

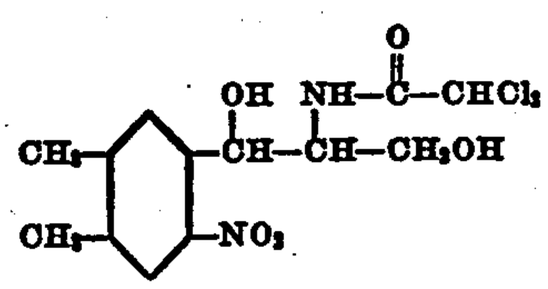


(dl)-reg. form

6 g. of the triacetate of (dl)-reg.-1-(2'-nitro-4',5'-dimethylphenyl)-2-aminopropane-1,3 - diol is refluxed for three of four hours with about 300 cc. of 5% hydrochloric acid and then the reaction mixture evaporated to dryness in vacuo. The residue is dissolved in water, the solution made alkaline to about pH 12 with sodium hy-

droxide and extracted with ethyl acetate. The ethyl acetate is distilled from the extracts in vacuo to obtain the desired (dl)-reg.-1-(2'-nitro-4',5'-dimethylphenyl)-2-aminopropane-1,3-diol.

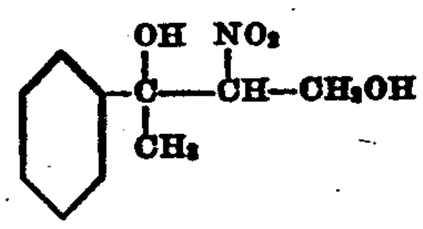
4 g. of (dl)-reg.-1-(2'-nitro-4',5'-dimethylphenyl)-2-aminopropane-1,3-diol is heated at 100° C. for one and a half hours with 3.2 g. of methyl dichloroacetate. The residue is cooled, washed with several portions of petroleum ether and purified by recrystallization from ethylene dichloride. The product thus obtained is (dl)-reg.-1-(2'-nitro-4',5'-dimethylphenyl)-2-dichloroacetamidopropane-1,3-diol of formula,



(dl)-reg. form

Example 6

A solution of 2.2 g. of sodium in 40 cc. of methanol is added to a solution of 12 g. of acetophenone and 9 g. of β-nitroethanol in 40 cc. of methanol and the mixture allowed to stand at room temperature until the sodium salt of the desired 2-nitro-3-phenylbutane-1,3-diol separates from the solution. The salt is collected, washed with ether and dried. If desired, the free nitro compound having the formula,

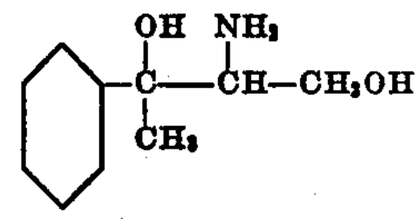


can be obtained by acidification of the salt.

20 g. of the sodium salt of 2-nitro-3-phenylbutane-1,3-diol is dissolved in 200 cc. of glacial acetic acid, 0.75 g. of palladium oxide hydrogenation catalyst added to the solution and the mixture shaken under three atmospheres pressure of hydrogen for about fifteen hours. The catalyst is removed by filtration and the filtrate concentrated to one-tenth volume in vacuo. The residue is diluted with five volumes of water, the solution extracted with one volume of ethyl acetate and the extract discarded. The aqueous solution is made alkaline with sodium hydroxide (pH 12) and extracted with ethyl acetate. After drying, the ethyl acetate is evaporated in vacuo from the combined extracts to obtain the desired 2-amino-3-phenylbutane-1,3-diol of formula,

If desired, this product can be separated into its regular and pseudo structural forms and each of these forms in turn separated into the d and l optical isomers. However, we have found that it is preferable to only separate the two structural forms at this point rather than to resolve the total mixture into its four components. The separation of the regular and pseudo forms is accomplished by crystallization from chloroform in which the pseudo form has a higher solubility than the regular form.

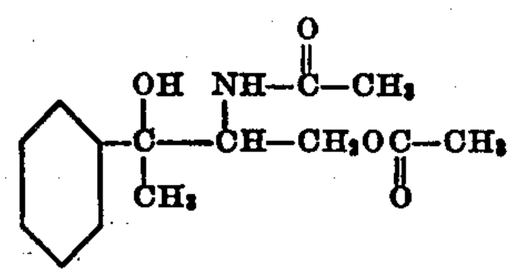
The unresolved 2-amino-3-phenylbutane-1,3-diol is taken up in and crystallized from the minimum amount of hot chloroform and the crystalline (dl)-reg.-2-amino-3-phenylbutane-1,3-diol removed by filtration. The filtrate is evaporated to dryness to obtain the crude (dl)-ψ-2-amino-3-phenylbutane-1,3-diol of formula,



(dl)-ψ form

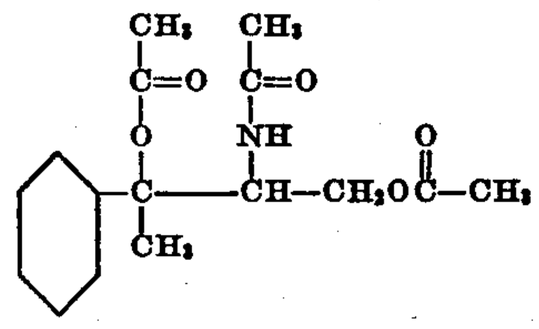
which is purified via the N, 3-O-diacetate as follows:

The crude (dl)-ψ-2-amino-3-phenylbutane-1,3-diol is heated at 80° C. for one-half hour with an excess of acetic anhydride and then the reaction mixture evaporated to dryness in vacuo. The residual (dl)-ψ-1-acetoxy-2-acetamido-3-phenylbutane-3-ol is purified by recrystallization from ethanol. The formula of this product is:



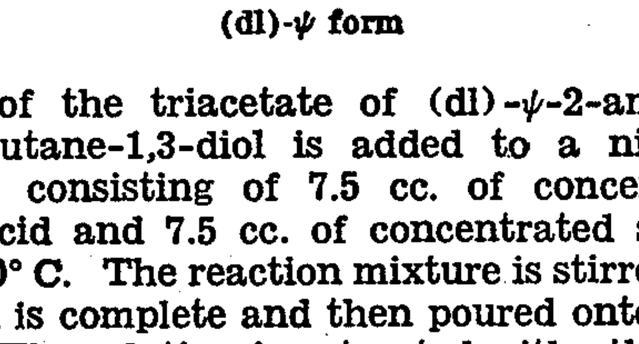
(dl)-ψ form

8 g. of (dl)-ψ-1-acetoxy-2-acetamido-3-phenylbutane-3-ol is heated for one hour at 100° C. with a mixture consisting of 16 cc. of acetic anhydride and 16 cc. of pyridine and then the reaction mixture evaporated to dryness in vacuo. The residue which consists of the triacetate of (dl)-ψ-2-amino-3-phenylbutane-1,3-diol is purified by recrystallization from ethanol. The formula for this product is:



(dl)-ψ form

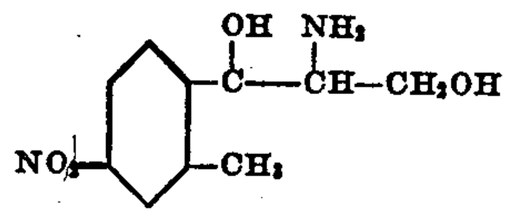
6 g. of the triacetate of (dl)-ψ-2-amino-3-phenylbutane-1,3-diol is added to a nitrating mixture consisting of 7.5 cc. of concentrated nitric acid and 7.5 cc. of concentrated sulfuric acid at 0° C. The reaction mixture is stirred until solution is complete and then poured onto 750 g. of ice. The solution is extracted with ethyl acetate, the extracts washed with sodium carbonate solution and dried. Distillation of the ethyl acetate yields the desired triacetate of (dl)-ψ-2-amino-3-p-nitrophenylbutane-1,3-diol of formula,



(dl)-ψ form

5 g. of the triacetate of (dl)-ψ-2-amino-3-p-nitrophenylbutane-1,3-diol is refluxed with 250 cc. of 5% hydrobromic acid for about two hours

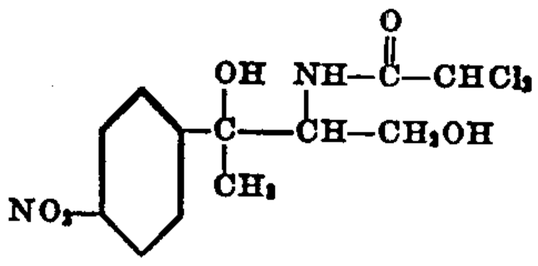
and then the reaction mixture evaporated to dryness in vacuo. The residue is taken up in water, the solution made alkaline with sodium hydroxide and extracted with ethyl acetate. The ethyl acetate is distilled from the combined extracts to obtain the free base of (dl)-ψ-2-amino-3-p-nitrophenylbutane-1,3-diol of formula,



(dl)-ψ form

If desired, this product may be resolved into the (d) and (l) optical isomers by fractional crystallization of the (d)-tartaric acid or d-bromcamphor sulfonic acid salts followed by decomposition of the salts in each case with alkali.

A mixture consisting of 2 g. of (dl)-ψ-2-amino-3-p-nitrophenylbutane-1,3-diol and 1.7 g. of methyl dichloroacetate is heated at 100° C. for about two hours and the reaction mixture cooled. The solid product is extracted with petroleum ether and the material which fails to dissolve collected. This insoluble product consists of (dl)-ψ-2-dichloroacetamido-3-p-nitrophenylbutane-1,3-diol. This compound, whose formula is,

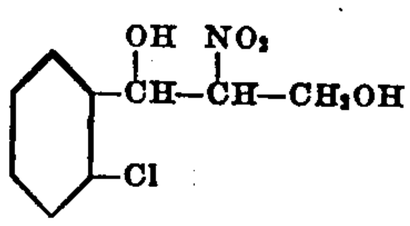


(dl)-ψ form

can be purified by recrystallization from ethylene dichloride.

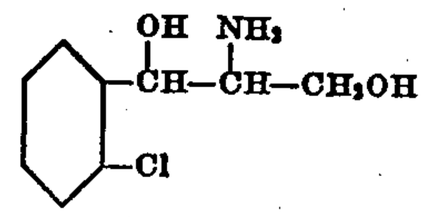
Example 7

2.2 g. of sodium dissolved in about 35 cc. of methanol is added to a solution of 14 g. of o-chlorobenzaldehyde and 9 g. of β-nitroethanol in 40 cc. of methanol. The reaction mixture is allowed to stand at room temperature for a short time and then the white, insoluble, sodium salt of 1-o-chlorophenyl-2-nitropropane-1,3-diol collected. The salt is washed with ether and dried. If desired, the free nitro diol can be obtained by acidification of this salt. The formula of the nitro diol is:

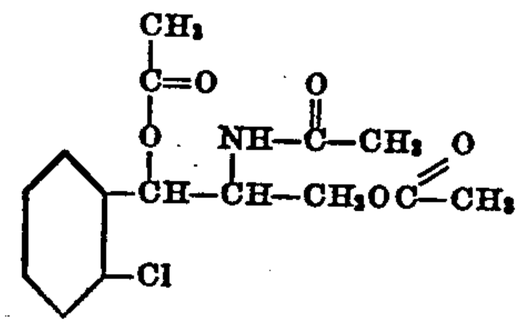


20 g. of sodium salt of 1-o-chlorophenyl-2-nitropropane-1,3-diol or an equivalent amount of the free nitro diol is dissolved in 175 cc. of glacial acetic acid. About 1 g. of palladium oxide hydrogenation catalyst is added and the nitro diol reduced to the corresponding amino compound by shaking the solution under three atmospheres pressure of hydrogen for ten hours. The catalyst is removed by filtration, the filtrate concentrated to a small volume in vacuo and the residue diluted with about five volumes of water. The solution is extracted with one volume of ethyl acetate and the extract discarded. The aqueous solution is made alkaline to pH 10 to 12 with sodium hydroxide solution and extracted with ethyl acetate. The extracts are dried and the ethyl acetate distilled in vacuo to obtain the free

base of 1-o-chlorophenyl-2-aminopropane-1,3-diol. This product has the following formula,

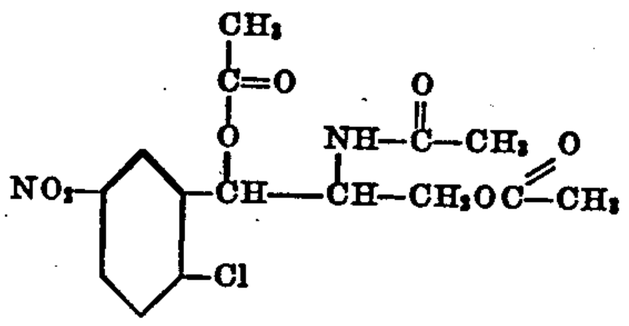


10 g. of 1-o-chlorophenyl-2-aminopropane-1,3-diol is heated with a mixture composed of 30 cc. of pyridine and 30 cc. of acetic anhydride for about one-half hour at 100° C. The reaction mixture is concentrated to dryness in vacuo and the residue washed with water. The water insoluble product thus obtained is the triacetate of 1-o-chlorophenyl-2-aminopropane-1,3-diol. This compound which has the formula,



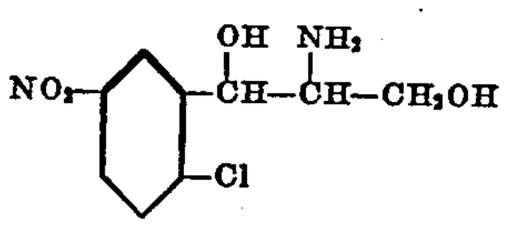
can be purified by recrystallization from ethanol.

10 g. of the triacetate of 1-o-chlorophenyl-2-aminopropane-1,3-diol is added in small portions to a nitrating mixture composed of 15 cc. of concentrated nitric acid and 15 cc. of concentrated sulfuric acid keeping the temperature in the neighborhood of 0° C. When solution of the solid is complete the reaction mixture is poured onto 1500 g. of ice and the solution extracted with several portions of ethyl acetate. The ethyl acetate extracts are washed with sodium carbonate solution, dried and the ethyl acetate removed by distillation in vacuo. The residual triacetate of 1-(2'-chloro-5'-nitrophenyl)-2-aminopropane-1,3-diol of formula,



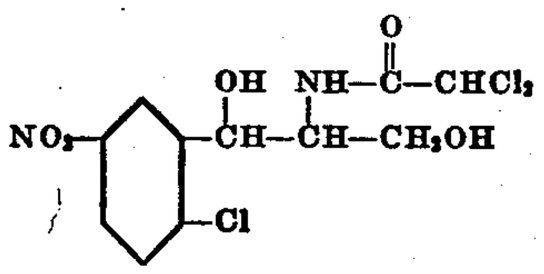
is purified, if desired, by recrystallization from alcohol.

5 g. of the triacetate of 1-(2'-chloro-5'-nitrophenyl)-2-aminopropane-1,3-diol is heated with 250 cc. of 5% hydrochloric acid for about three hours and then the reaction mixture evaporated to dryness in vacuo. The residue which consists of 1-(2'-chloro-5'-nitrophenyl)-2-aminopropane-1,3-diol hydrochloride is taken up in water, the solution made alkaline to about pH 9 or 10 with sodium hydroxide and extracted with ethyl acetate. The extracts are dried and the ethyl acetate distilled in vacuo to obtain the free base of 1-(2-chloro-5'-nitrophenyl)-2-aminopropane-1,3-diol. This product has the formula,



About 4 g. of 1-(2'-chloro-5'-nitrophenyl)-2-aminopropane-1,3-diol is heated with 4.5 g. of methyl dichloroacetate at 100° C. for two hours. The reaction mixture is cooled, treated with 75 cc. of petroleum ether and the insoluble product collected. The crude 1-(2'-chloro-5'-nitro-

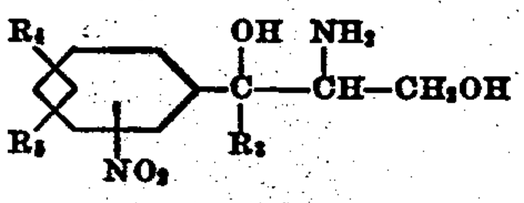
phenyl)-2-dichloroacetamidopropane-1,3-diol is washed with several more portions of petroleum ether and purified further, if desired, by recrystallization from ethylene dichloride. The formula of this product is:



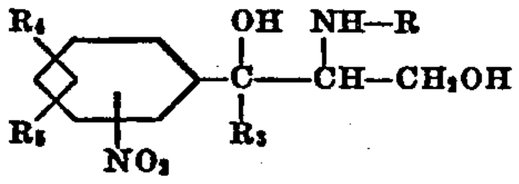
Attention is called to the following copending applications relating to microbiological methods for preparing chloramphenicol, Bartz Serial No. 15,265, filed March 16, 1948 and Ehrlich et al. Serial No. 15,255, filed March 16, 1948.

What we claim as our invention is:

1. Process which comprises reacting a compound of formula,

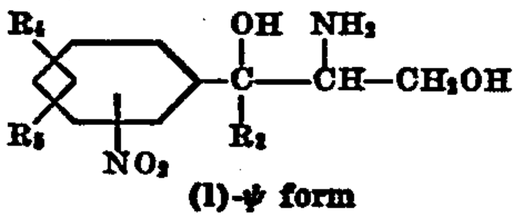


with a lower alkyl ester of a halogenated lower aliphatic carboxylic acid under anhydrous conditions to obtain a compound of formula,



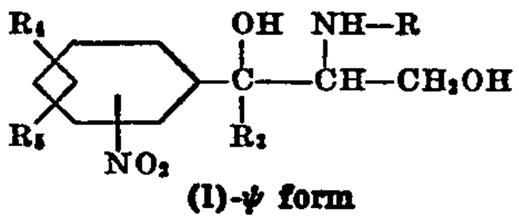
where R is a halogenated lower aliphatic carboxylic acid acyl radical, R_3 is a member of the class consisting of hydrogen and lower alkyl radicals and R_4 and R_5 are members of the class consisting of hydrogen, halogen, lower alkyl and lower alkoxy radicals.

2. Process which comprises reacting a compound of formula,



(l)-ψ form

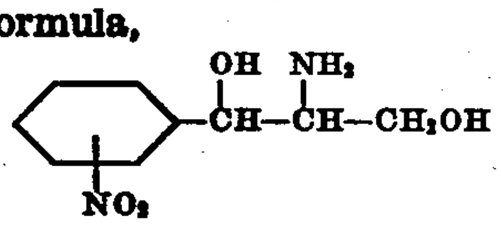
with a lower alkyl ester of a halogenated lower aliphatic carboxylic acid to obtain a compound of the formula,



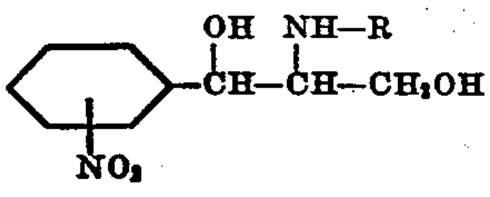
(l)-ψ form

where R is a halogenated lower aliphatic carboxylic acid acyl radical, R_3 is a member of the class consisting of hydrogen and lower alkyl radicals and R_4 and R_5 are members of the class consisting of hydrogen, halogen, lower alkyl and lower alkoxy radicals.

3. Process which comprises reacting a compound of formula,

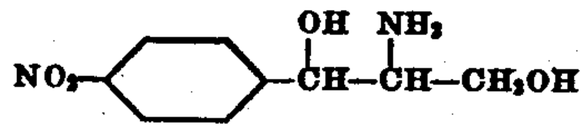


with a lower alkyl ester of a halogenated lower aliphatic carboxylic acid under anhydrous conditions to obtain a compound of formula,

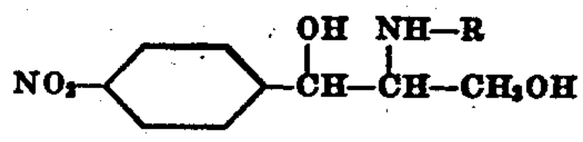


where R is a halogenated lower aliphatic carboxylic acid acyl radical.

4. Process which comprises reacting a compound of formula,

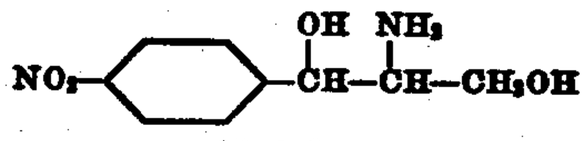


with a lower alkyl ester of a halogenated lower aliphatic carboxylic acid under anhydrous conditions to obtain a compound of formula,



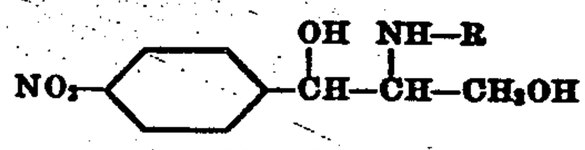
where R is a halogenated lower aliphatic carboxylic acid acyl radical.

5. Process which comprises reacting a compound of formula,



(l)-ψ form

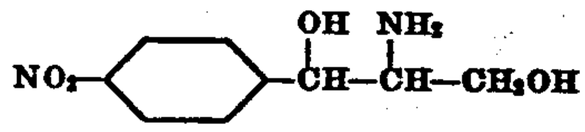
with a lower alkyl ester of a halogenated lower aliphatic carboxylic acid under anhydrous conditions to obtain a compound of formula,



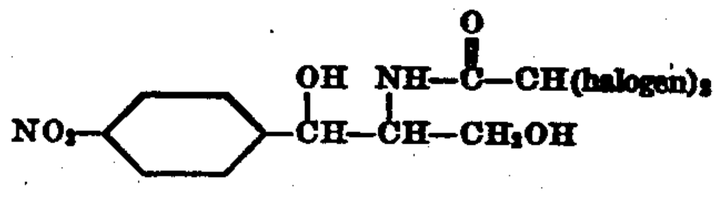
(l)-ψ form

where R is a halogenated lower aliphatic carboxylic acid acyl radical.

6. Process which comprises reacting a compound of formula,

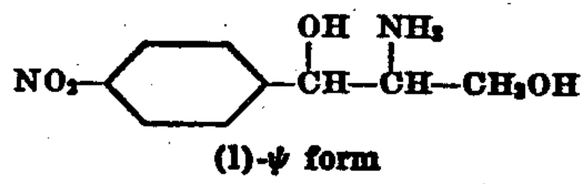


with a lower alkyl ester of a dihalo acetic acid under anhydrous conditions to obtain a compound of formula,



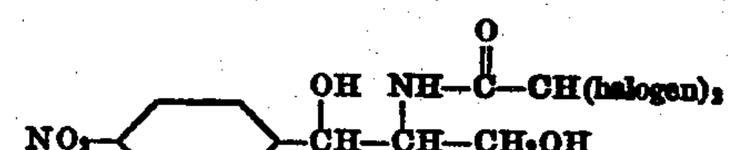
7. Process which comprises reacting (l)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol with a lower alkyl ester of dichloroacetic acid under anhydrous conditions to obtain (l)-ψ-1-p-nitrophenyl-2-dichloroacetamidopropane-1,3-diol.

8. Process which comprises reacting a compound of formula,



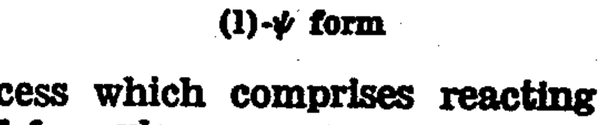
(l)-ψ form

with a lower alkyl ester of a dihalo acetic acid under anhydrous conditions to obtain a compound of formula,



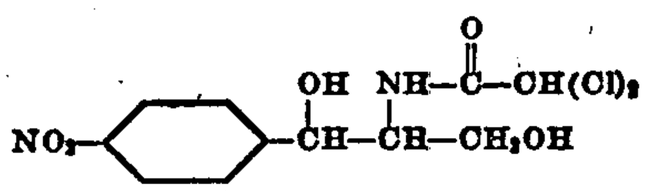
(l)-ψ form

9. Process which comprises reacting a compound of formula,



with a lower alkyl ester of dichloroacetic acid

under anhydrous conditions to obtain a compound of formula,



10. Process which comprises reacting (1)-ψ-1-p-nitrophenyl - 2 - aminopropane - 1,3 - diol with methyl dichloroacetate under anhydrous conditions to obtain (1)-ψ-1-p-nitrophenyl-2-aminopropane-1,3-diol.

HARRY M. CROOKS, JR.
MILDRED C. REBSTOCK.
JOHN CONTROULIS.
QUENTIN R. BARTZ.

REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
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