PATENT SPECIFICATION

652,278

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(Divided out of No. 652,275)
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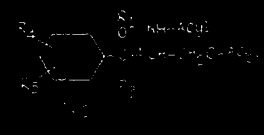
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COMPLETE SPECIFICATION

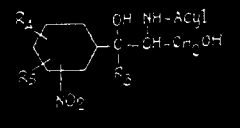
Process for the Manufacture of Organic N-Acylamido Diols

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 organic N-acylamido diols. More particularly, the invention relates to a process for selectively hydrolyzing a polyacylated amino diol of formula



to the corresponding N-acylamido diol of formula.



...re R_1 is an acyl radical, R_3 is ...rogen or a lower alkyl radical, R_4 and R_5 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals.

It will be readily appreciated by those skilled in the art that the compounds represented by the above formulæ 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.

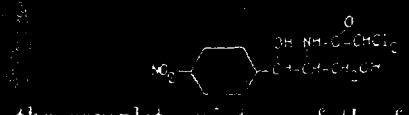
Both the regular and pseudo forms exist as racemates of optically active isomers which can be resolved into the dextro (*d*) and levo (*l*) rotatory isomers.

Because of the difficulty of representing these structural differences in graphic formulæ we have used the customary structural formulæ 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 mixtures of two of these individual isomers. Thus, for example, a general formula such as appears above includes 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

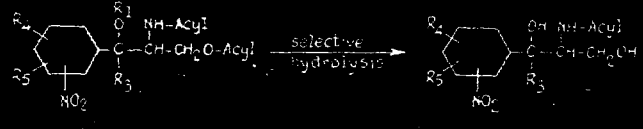
[Price 2/-]

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, our process for obtaining these new products may be diagrammatically represented as follows:



where R_1, R_3, R_4, R_5 have the same significance as given above.

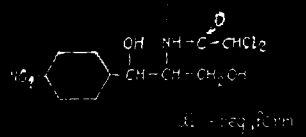
In order to carry out the selective hydrolysis depicted above the polyacylated amino diol is treated with an alkali metal hydroxide dissolved in an aqueous solution containing a lower aliphatic ketone at about −20 to +15° C. The best results are obtained using a temperature of about 40°C. and about a 50% aqueous solution of a ketone.

The products prepared in accordance with the process of the invention find use as antibiotics or intermediates for the preparation of chemical compounds possessing antibiotic activity. For example, one of the products which can be produced by the instant process is (*l*) - ψ - 1 - *p* - nitrophenyl - 2 - dichloroacetamidopropane-1,3-diol. This product is known as chloramphenicol and is of particular value in the treatment of typhus, typhoid fever, urinary infections and other diseases.

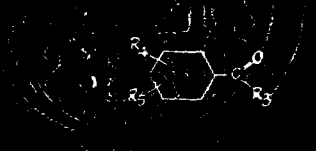
The invention is illustrated by the following example.

EXAMPLE

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 is 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:



The polyacylated organic amino diols used as starting materials for the process of the invention can be prepared in a number of different ways. One method for obtaining the polyacylated amino diols consists in condensing a carbonyl compound of formula:



where R_4, R_5 and R_3 have the same significance as given above; with β-nitroethanol in the presence of an alkaline condensation catalyst, reducing the nitro group in the 1-phenyl-2-nitroalkane-1,3-diol compound so obtained to an amino group, separating, if desired, the structural forms of the amino diol by fractional crystallization and polyacylating the free amino diol compound by treatment with an acyl halide or anhydride under anhydrous conditions in the presence of an alkaline catalyst such as pyridine. Where one particular optical isomer is desired, one of the structural forms of the free amino diol is resolved into its optical isomers via an acid addition salt with an optically active organic acid prior to the polyacylation step.

Nitration of the completely acylated amino diols wields the desired starting materials. This nitration can be carried out using a mixture of equal parts of concentrated nitric and sulfuric acids at about 0° C.

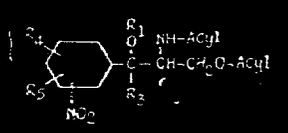
Throughout this Specification and in the appended claims by the use of the terms "lower" alkyl and alkoxy radicals, there are meant radicals containing not more than four carbon atoms.

The present invention is related to the inventions forming the subject of our copending Patent Applications Nos. 32506 of 1948, 13744 of 1950, 13745 of 1950, 13746 of 1950, 13747 of 1950,

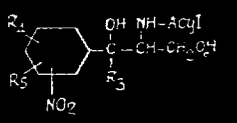
13748 of 1950, 13750 of 1950 and 13751 of 1950 (Serial Nos. 652,275, 652,272, 652,273, 652,274, 652,276, 652,277, 652,279 and 652,280).

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. A process which comprises hydrolyzing directly and in one step a polyacylated compound of formula



by subjecting said polyacylated compound to alkaline hydrolysis under such mild temperature conditions as will produce an N-acylamido diol compound of formula



where R_1 is an acyl radical, R_3 is hydrogen or a lower alkyl radical, R_4 and R_5 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals.

2. Process as claimed in claim 1, wherein the hydrolysis is effected by means of an alkali metal hydroxide.

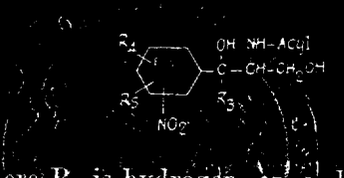
3. Process as claimed in claim 1 or 2, wherein the solvent for the reaction is an aqueous solution containing a lower aliphatic ketone.

4. Process as claimed in claim 3, wherein the lower aliphatic ketone is acetone.

5. Process as claimed in any preceding claim, wherein the temperature is kept at about −20 to +15° C. and is preferably about 0° C.

6. Process for hydrolyzing a polyacylated compound substantially as described hereinbefore with reference to the specific Example.

7. N-Acylamido diols of formula



where R_3 is hydrogen or a lower alkyl radical, R_4 and R_5 are the same or different and represent hydrogen, halogen, lower alkyl or lower alkoxy radicals whenever prepared or produced by the process of the preceding claims or by an obvious chemical equivalent thereof.

Dated this 1st day of June, 1950.

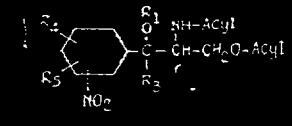
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Agents for the Applicants.

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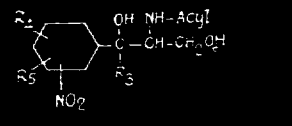
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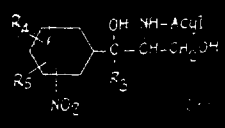
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