

1

3,320,282

PROCESS FOR PREPARING ESTERS OF 2-HYDROXY-3-(3-INDOLYL)ALKANOIC ACIDS

Manfred Schach von Wittenau and Billie Kenneth Koe, Gales Ferry, Conn., assignors to Chas. Pfizer & Co., Inc., New York, N.Y., a corporation of Delaware

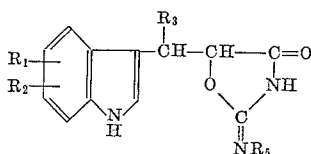
No Drawing. Original application Oct. 29, 1962, Ser. No. 233,911. Divided and this application Feb. 24, 1965, Ser. No. 444,481

4 Claims. (Cl. 260—326.13)

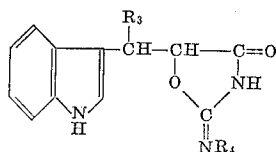
This application is a division of our application Ser. No. 233,911, filed Oct. 29, 1962, said latter application being a continuation-in-part of our application Ser. No. 136,173, filed Sept. 6, 1961, both now abandoned.

This invention is concerned with new and useful antimicrobial agents and with the methods for their synthesis. Each of these new and novel products is useful in combating pathogenic microorganisms, including Gram-positive and Gram-negative bacteria. They are also useful as disinfecting agents against pathogenic microorganisms, in separating mixtures of microorganisms and in classifying microorganisms for diagnostic research purposes.

The compounds of this invention comprise:



and



wherein

R₁ is selected from the group consisting of hydrogen, chloro, fluoro, nitro, amino, alkyl of one to four carbon atoms and alkoxy of one to four carbon atoms;

R₂ is selected from the group consisting of chloro, fluoro, nitro, amino, alkyl of one to four carbon atoms and alkoxy of one to four carbon atoms;

R₃ is alkyl of one to three carbon atoms;

R₄ is selected from the group consisting of hydrogen, phenyl, anisyl, toluidyl and alkyl of two to four carbon atoms; and

R₅ is selected from the group consisting of hydrogen, phenyl, anisyl, toluidyl and alkyl of one to four carbon atoms;

provided that when R₃ is methyl, R₄ is other than alkyl and R₅ is other than methyl.

Among the typical member compounds of this invention are such novel compounds as:

1-[3-(4,7-dichloro)indolyl]-1-[5-(2-ethylimino-4-keto)oxazolidinyl]ethane;

1-[3-(5-amino)indolyl]-1-[5-(2-(iso)-propylimino-4-keto)oxazolidinyl]propane and

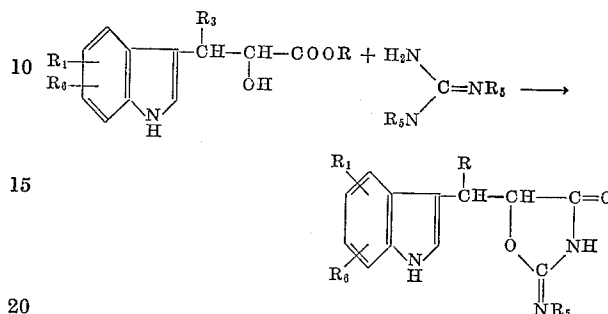
1-[3-(4-methoxy)indolyl]-1-[5-(2-imino-4-keto)oxazolidinylethane.

A general preparative method which is applicable to the synthesis of these compounds involves the reaction of a substituted guanidine with a hydroxy indole acid ester. Another method of synthesis involve the reaction of 3-acyl indoles with iso-hydantoin and subsequent reduction of the resulting product to yield the desired compounds of the present invention. Still another method

2

of preparing these compounds is the condensation of a hydroxy indole acid ester with a 2-substituted-2-isothio-pseudo-urea to yield the desired product.

The preferred synthetic route, involves the reaction of a hydroxy indole acid ester with a substituted guanidine, as represented by the following equations:



wherein R₁, R₃, R₄ and R₅ are defined as aforementioned; R is lower alkyl containing from one to three carbon atoms and R₆ is selected from the group consisting of hydrogen, chloro, fluoro, nitro, amino, alkyl of one to four carbon atoms and alkyl of one to four carbon atoms. This reaction may also be employed to produce compounds wherein the 3-position of the oxazolidine ring is substituted.

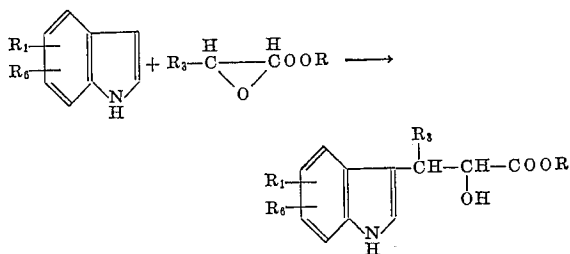
This reaction is preferably conducted in the presence of an inert polar organic solvent, such as lower oxygenated aliphatic compounds. Typical organic solvents which may be employed are ethers, esters, ketones and alcohols. In particular, lower aliphatic alcohols containing from one to four carbon atoms are the solvents of choice. It is desirable that this solvent be present in sufficient amounts to dissolve each of the starting materials. The reactants are preferably present in substantially equimolar quantities, although the reaction may be conducted in the presence of higher quantities of the appropriate guanidine.

In general, the reaction is preferably carried out within the temperature range of about 20° C. to about reflux temperatures for a period of about one-half to forty-eight hours. Recovery of the desired product is most conveniently accomplished by evaporation of the organic solvent. Alternatively, the reaction product may be recovered by extraction with an immiscible solvent which subsequently is removed by evaporation. Still another procedure for the separation of the products of this invention is by the use of column chromatography.

The starting substituted guanidines necessary for the process of this invention can either be commercially obtained or they can be prepared by the reaction of a cyanamide with a primary amine. This procedure was described by H. King and I. Tonkin in the Journal of the Chemical Society, 1946, page 1063. Many of the commercially available guanidines are obtained as the inorganic acid salts. The guanidine salts so obtained are easily converted to the corresponding base employed in this reaction by any number of standard and convenient procedures. For example, methyl guanidine may be prepared by dissolving the commercially available methyl guanidine sulfate in an anhydrous, sodium alcoholate. When the reaction is complete, the solution is filtered to remove the insoluble sodium sulfate and the filtrate is concentrated. This solution contains methyl guanidine as the free base. It is even possible to employ the guanidine acid salts, as such, by adding this compound and the hydroxy indole acid ester to the alcoholic solution of a sodium alkoxylate; in this case, the guanidine base is formed in situ and then reacts with the hydroxy indole acid ester.

The hydroxy indole acid esters which are the other starting materials for the preparation of the compounds of this invention are obtained by a number of synthetic routes.

The preferred method of synthesizing the hydroxy indole acid esters which are utilized in the preparation of the compounds of this invention is a novel, one-step synthesis which involves the reaction of indole or a substituted indole with an alkyl 2,3-epoxyalkylate, as represented by the following equations:



wherein R, R₁, R₃ and R₆ are defined as aforementioned.

This reaction may be conducted in the presence of an inert polar organic solvent, such as benzene, chloroform and lower oxygenated aliphatic compounds. Normally, it is preferable that this solvent is present in sufficient amounts to dissolve each of the starting materials which are preferably present in substantially equimolar quantities.

This reaction when conducted in the presence of the aforesaid solvent may be carried out within the temperature range of about 50° C. to about 160° C. with a preferred temperature range from about 100° C. to about 140° C. The reaction time varies with the temperature. Generally, the higher the reaction temperature the shorter the reaction time. Reaction times vary from about one-half to forty-eight hours. This reaction may be acid catalyzed. The catalysts which may be employed are phenol, 2,6-dimethylphenol and inorganic acids including Lewis acid such as aluminum chloride, aluminum bromide, tin chloride, etc. When phenol is employed as the catalyst, the reaction can also be conducted by admixing the reactants when phenol at temperatures as high as 265° C. for about one to three hours, without the use of the aforesaid solvents.

The aforementioned reaction may also be conducted by simple admixing an indole or a substituted indole with an alkyl 2,3-epoxyalkylate in a sealed container and heating said container until the reaction is complete. This reaction may be carried out at a temperature of about 180° C. to about 275° C. with a preferred temperature range from about 240° C. to about 265° C. The reaction time varies with the temperature from one to ten hours.

Another preferred method of synthesizing the hydroxy indole acid esters of this invention is an adaptation of the method employed by Gortatowski and Armstrong, in the Journal of Organic Chemistry, volume 22, page 1217 (1957), for the synthesis of indole lactic acid. Generally, this method involves the reaction of a substituted indole with an aldehyde and isopropylamine to produce the corresponding 3-(isopropylaminoalkylidene)-substituted indole. Reacting this compound with diethylacetoxy-malonate in the presence of metallic sodium or sodium methoxide as a catalyst, there is obtained the diethyl [3 - (substituted) - indolyl alkylidene]acetoxy-malonate. When this product is hydrolyzed and subsequently decarboxylated, the resulting product is α-hydroxy-β-alkyl-β[3-(substituted) indolyl]propionic acid which is reacted with a diazoalkane to produce the desired starting ester. The length of the R₅ alkyl moiety in the hydroxy indole acid esters will be determined by the aldehyde employed in the first reaction of the heretofore discussed reaction sequence. For example, when it is desired that R₅ be a propyl group, the aldehyde employed is butylaldehyde.

Still another procedure for the synthesis of the hydroxy indole acid esters employed in the formation of the compounds of this invention involves the reaction of a substituted indolyl magnesium iodide with an alkionyl chloride by the procedure described in Beilstein, volume 21, I, 302. The 3-alkionyl(substituted)indole obtained in this manner is then heated with glycolylurea in the presence of piperidine or acetic anhydride and sodium acetate to obtain the corresponding hydantoin compound. Hydrolyzing this compound by the procedure described in Chemical Reviews 38, 526, and, thereafter, reacting this product with sodium borohydride, the corresponding α-hydroxy-β[3-(substituted)-indolyl]alkanoic acid is obtained. The desired starting ester is formed by reacting the aforementioned compound with an appropriate diazoalkane.

When it is desired to form the compounds of this invention in which the R₁, R₂, are hydrogen and R₃ is methyl, the starting hydroxy indole acid ester may be obtained by the degradation of an antibiotic which is obtained by the fermentation of *Streptomyces albus*. This antibiotic was isolated by March et al. and reported in Antibiotics and Chemotherapy, volume X, No. 5, page 315. Its physical and chemical properties have been described by K. Rao in Antibiotics and Chemotherapy, volume X, No. 5, page 312. When this antibiotic is hydrolyzed by alkali, there is obtained the desired 2-hydroxy-3-(3-indolyl)butyric acid which may be esterified as heretofore described. More particularly, this hydrolysis is conducted by refluxing 1 gram of the antibiotic in a mixture of 40 milliliters of a 10% sodium hydroxide solution and 10 milliliters of a 5% barium hydroxide solution. The basic hydrolysis products are distilled off by a stream of nitrogen as they are formed during the refluxing period. When the hydrolysis is complete, the reaction mixture is filtered to remove the precipitated barium carbonate and the filtrate acidified with 1 N hydrochloric acid to a pH of 2. This solution is extracted with three 150 milliliter portions of ether and when the ether is evaporated the residue is 2-hydroxy-3-(3-indolyl)butyric acid. After several recrystallizations from an ether-chloroform mixture, this acid melts between 175–177° C. and is obtained in approximately a 46% yield. Subsequently, an ethanolic solution of this acid is reacted with an excess of diazomethane and the resulting product is the desired hydroxy indole acid ester which is employed in the synthesis of some of the compounds of this invention.

The antibiotic compounds of this invention have activity against a variety of microorganisms, including both Gram-positive and Gram-negative bacteria which are resistant to many of the commonly employed antibiotics, for example, when compounds of this invention are administered to mice which have been infected with an otherwise lethal dose of tetracycline resistant strains of *Staphylococcus aureus*, they afforded life-saving protection to the infected mice. Another advantage of these antibiotics is that they are remarkably non-toxic when they are administered to mice by the oral, intraperitoneal and subcutaneous routes.

In connection with the use of the previously described compounds of this invention as antimicrobial agents, they may be administered alone or, preferably in combination with a pharmaceutically acceptable carrier, and as such can be given in single or multiple doses. More particularly, the antimicrobial compounds of this invention may be administered in suitable dosage forms providing a dosage unit of the active ingredient in an amount that is adjusted to the particular needs of the individual. When large doses of these antimicrobial agents are to be used, it is preferable to administer two or more doses at various time intervals, as selected by the attending physician.

These antimicrobial compounds may be administered in a variety of dosage formulations, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of capsules, tablets, lozenges, troches,

5

hard candies, suspensions, solutions, elixirs, parenteral solutions and suspensions, ointments, soaps and powders. The carriers employed include, solid diluents, ointment bases, aqueous vehicles, non-toxic organic solvents and the like. In general, the compounds of this invention are present in various dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired dosage.

For purposes of oral administration, tablets containing various excipients, such as sodium citrate, calcium carbonate and dicalcium phosphate may be employed along with various disintegrants such as alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, gelatin, and acacia; in addition, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft elastic and hard-shelled gelatin capsules, preferred materials in this connection would also include polyethylene glycol and glycerin as they not only may be used in this particular type of pharmaceutical dosage form as diluents, but also as plasticizing agents serving to protect the capsule against any leakage that might possibly occur due to denaturation of the gelatin protein. When aqueous suspensions and elixirs are desired for oral administration, the antimicrobial ingredient may be combined with various sweetening and flavoring agents, coloring matter or dyes and, if so desired, emulsifying and suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

Solutions or suspensions of these antimicrobial compounds in pyrogen-free, sterile distilled water containing a preservative such as butyl paraben, propyl paraben, chlorobutanol, phenol and the like may be utilized for parenteral administration by intramuscular or intravenous injection. Similar aqueous preparations, where the concentration of active ingredients are normally lower, may be employed as ophthalmic solutions.

For use as a dusting powder, the active ingredients of this invention are mixed with any of a number of extending agents either organic or inorganic in nature which are suitable for the manufacture of pulverulent preparations. These include, for example, tricalcium phosphate, calcium carbonate, kaolin, talcum, boric acid and others. These mixtures may be used in the dry form or, by the addition of wetting agents, the dry powder can be rendered wettable by water so as to be suitable as a topical suspension.

For special purposes, the agents of this invention can be worked into the form of a paste or an ointment by the use of such semi-solid extending agents as soap petroleum jelly, carbowax, glycerin or lanolin with or without the aid of solubility promoters or dispersing agents.

In all these various formulations, the active antimicrobial agents can be one or a plurality of the compounds of this invention. The compounds may also be advantageously employed in combination with other antimicrobial agents or in combination with other pharmaceutical compounds. There may be mentioned by way of example, acetylsalicylic acid, salicylamide, antihistamines, and ascorbic acid. In this manner, it is possible to obtain mixtures which will combat the microorganisms and produce an overall well-being in the patient.

The following examples are given solely for the purpose of illustration only and are not to be construed as limitations of this invention many variations of which are possible without departing from the spirit or scope thereof.

Example I

To 40 milliliters of absolute ethanol in which there are dissolved 225 mg. of metallic sodium, there are added 1.22 g. of methyl guanidine sulfate and the mixture is

6

stirred for 30 minutes. After filtration to remove the insoluble sodium sulfate, 850 mg. of methyl-2-hydroxy-3-(3-indolyl)butyrate are added to the filtrate and the mixture is held at room temperature for 48 hours. When the ethanolic solvent is removed under vacuum, the remaining residue is a mixture of 1-(3-indolyl)-1-[5-(2-methylimino-4-keto)oxazolidinyl]-ethane and 1-(3-indolyl)-1-[5-epi-(2-methylimino-4-keto)oxazolidinyl]ethane which are separated by paper chromatography.

Example II

An absolute propanol solution containing 0.20 M of phenyl guanidine and 0.10 M of ethyl-2-hydroxy-3-(3-indolyl)valerate is refluxed for 1 hour. Thereafter, the propanol is removed under reduced pressure and the residue crystallized from ethanol. The crystalline product is a mixture of 1-(3-indolyl)-1-[5-(2-phenylimino-4-keto)oxazolidinyl]propane and 1-(3-indolyl)-1-[5-epi(2-phenylimino-4-keto)oxazolidinyl]propane which are separated by paper chromatography.

Example III

To 100 milliliters of absolute methanol containing 1.84 g. of propyl guanidine, there are added 2.6 g. of propyl-2-hydroxy-3-[3-(5,6-dimethoxy)-indolyl]butyrate. The resulting mixture is held for 20 hours at 50° C. When the methanol is removed by evaporation, the remaining solid is a mixture of 1-[3-(5,6-dimethoxy)indolyl]-1-[5-[2-(n-propylimino-4-keto)-oxazolidinyl]ethane and 1-[3-(5,6-dimethoxy)indolyl]-1-[5-epi[2-(n-propylimino-4-keto)-oxazolidinyl]ethane which are separated by fractional crystallization.

Example IV

With stirring 50 ml. of absolute butanol containing 1.5 g. of anisyl guanidine are added to 50 ml. of an absolute butanol solution containing 1.0 g. of methyl-2-hydroxy-3-[3-(4-fluoro)indolyl]-4-methyl-valerate. The resulting mixture agitated for 10 hours at 65° C. Subsequently, the butanol is removed under reduced pressure and the residue crystallized from absolute ethanol. The crystalline material obtained is a mixture 1-[3-(4-fluoro)indolyl]-1-[5-(2-anisylimino-4-keto)oxazolidinyl]-2-methyl propane and 1-[3-(4-fluoro)indolyl]-1-[5-(2-anisylimino-4-keto)oxazolidinyl]-2-methyl propane which are separated by fractional crystallization.

Example V

The procedure described in Example II is repeated using other starting materials and reagents in place of those specifically mentioned. For the sake of convenience and in order to avoid unnecessary repetition of experimental details other compounds which can be prepared in this manner are listed below:

- (1) 1 - [3 - (6 - methyl)indolyl] - 1 - [5 - (2 - imino-4-keto)oxazolidinyl]butane
- (1) 1 - [3 - (7 - nitro)indolyl] - 1 - [5 - (2 - ethylimino-4-keto)oxazolidinyl]ethane
- (3) 1 - [3 - (4,7 - dichloro)indolyl] - 1 - [5 - (2 - toluidylimino-4-keto)oxazolidinyl]ethane
- (4) 1 - [3 - (5 - amino)indolyl] - 1 - [5 - (2 - (iso) - propylimino-4-keto)oxazolidinyl]propane
- (5) 1 - [3 - (4 - chloro)indolyl] - 1 - [5 - (2 - methylimino-4-keto)oxazolidinyl]ethane
- (6) 1[3 - [7 - (iso)-propyl]indolyl] - 1 - [5 - (2 - phenylimino-4-keto)oxazolidinyl]ethane
- (7) 1 - [3 - (5 - butyl)indolyl] - 1 - [5 - (2 - butyl - 4 - keto)oxazolidinyl]propane

Example VI

With stirring, 28.2 g. of phenol and 70.2 g. of indole are dissolved in 39.0 g. of ethyl-2 3-epoxy butyrate. The resulting solution is heated at 140° C. for 18 hours and, thereafter, diluted with 1000 ml. of diethyl ether. This mixture is extracted with four 50 ml. portions of a chilled

7

0.5 N sodium hydroxide solution. The diethyl ether phase is dried over sodium sulfate and evaporated. The residue is dissolved in 75 ml. of ethyl acetate and chromatographed on an aluminum oxide column. The column is developed by the addition of 6000 ml. ethyl acetate, followed by elutions with 4000 ml. of a 1% ethanol-99% ethyl acetate mixture. The first 6000 ml. eluate portion is discarded and the last 4000 ml. portion is distilled under a 0.5 mm. vacuum.

The product had a boiling point of 170°-180° C. This material was rechromatographed by the procedure described above and the product obtained was ethyl-2-hydroxy-3-(3-indolyl)butyrate.

Example VII

A mixture containing 13 g. of ethyl-2,3-epoxy butyrate, 11.7 g. of indole and 9 g. of toluene sulfonic acid were heated at 140° C. for ½ hour. The residue is dissolved in 100 ml. of ethyl alcohol to which there is added 250 ml. of a 2 N sodium hydroxide solution. This mixture was refluxed for one hour during which 500 ml. of water were gradually added to the mixture. Thereafter, the reaction mixture was extracted with three 500 ml. portions of ethyl acetate. The combined ethyl acetate portions are dried over sodium sulfate and evaporated under vacuum. The 5.3 g. of residue was shown to contain by paper chromatography ethyl-2-hydroxy-3-(3-indolyl)butyrate.

Example VIII

A mixture of 12.6 g. of 4,7-dichloro indole, 13 g. of trifluoro acetic acid and 13 g. of ethyl-2,3-epoxy propionate is refluxed for 30 minutes. Thereafter, the mixture was admixed with 50 ml. of ethyl alcohol and 250 ml. of a 2 N sodium hydroxide solution and the resulting mixture is refluxed for an additional hour. Thereafter, the reaction mixture is extracted with three 500 ml. portions of ethyl acetate. The aqueous phase is acidified to a pH of 2 by the addition of concentrated hydrochloric acid and is again extracted with three 500 ml. portions of ethyl acetate. The combined ethyl acetate portions are dried over sodium sulfate and subsequently evaporated under vacuum. The resulting residue was shown to consist mainly of 4.86 g. of ethyl-2-hydroxy-3-[3-(4,7-dichloro)indolyl]propionate.

Example IX

To 150 ml. of benzene there is added 12.7 g. of 5-methoxy indole, 13 g. of methyl-2,3-epoxy butyrate and 9 g. of aluminum chloride. This mixture is refluxed for one hour and the residue is admixed with 100 ml. of ethyl alcohol 250 ml. of a 2 N sodium hydroxide solution and 250 ml. of water. The benzene is removed by evaporation under reduced pressure and the residue is refluxed for one hour. Subsequently, the mixture is extracted three times with 500 ml. portions of ethyl acetate. The aqueous phase is acidified to a pH of 2 by the addition with stirring of concentrated hydrochloric acid. This acidified solution is again extracted with three 500 ml. portions of ethyl acetate. The combined ethyl acetate portions are dried over sodium sulfate and evaporated under vacuum. The residue remaining weighed 2.7 g. and was shown by paper chromatography to consist mainly of methyl-2-hydroxy-3-[3(5-methoxy)indolyl]butyrate.

The procedure described above was repeated employing zinc chloride as the catalyst.

Example X

The procedure described in Example VI is repeated using other starting materials and reagents in place of those specifically mentioned. For the sake of convenience, and in order to avoid unnecessary repetition of experimental detail, other compounds which can be prepared in this manner are listed below:

8

- (1) methyl-2-hydroxy-3-[3-(5-methoxy)indolyl]butyrate
- (2) methyl-2-hydroxy-3-[3-(5,6-dimethoxy)indolyl]butyrate
- (3) ethyl-2-hydroxy-3[3-(5-chloro)indolyl]butyrate
- (4) ethyl-2-hydroxy-3(3-indolyl)butyrate
- (5) propyl-2-hydroxy-3(3-indolyl)butyrate
- (6) ethyl-2-hydroxy-3(3-indolyl)-4-methyl valerate
- (7) methyl-2-hydroxy-3[3-(5-chloro)indolyl]-4-methyl valerate
- (8) ethyl-2-hydroxy-3[3-(7-fluoro)indolyl]butyrate
- (9) methyl-2-hydroxy-3[3-(6-amino)indolyl]butyrate
- (10) propyl-2-hydroxy-3[3-(5-ethyl)indolyl]butyrate

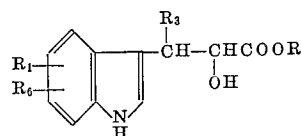
Example XI

The procedure described in Example II is repeated using as starting materials the compounds listed in Example X and the appropriate guanidines. The compounds prepared in this manner are listed below:

- (1) 1-[3-(5-methoxy)indolyl]-1-[5-(2-imino-4-keto)-oxazolidinyl]ethane
- (2) 1-[3-(5,6-dimethoxy)indolyl]-1-[5-(2-imino-4-keto)oxazolidinyl]ethane
- (3) 1-[3-(5-chloro)indolyl]-1-[5-(2-imino-4-keto)-oxazolidinyl]ethane
- (4) 1-(3-indolyl)-1-[5-(2-anisylimino-4-keto)oxazolidinyl]ethane
- (5) 1-(3-indolyl)-1-[5-(2-imino-4-keto)oxazolidinyl]ethane
- (6) 1-(3-indolyl)-1-[5-(2-imino-4-keto)oxazolidinyl]-2-methyl propane
- (7) 1-[3-(5-chloro)indolyl]-1-[5-(2-imino-4-keto)-oxazolidinyl]-2-methyl propane
- (8) 1-[3-(7-fluoro)indolyl]-1-[5-(2-imino-4-keto)-oxazolidinyl]ethane
- (9) 1-[3-(6-amino)indolyl]-1-[5-(2-imino-4-keto)oxazolidinyl]ethane
- (10) 1-[3-(5-ethyl)indolyl]-1-[5-(2-imino-4-keto)-oxazolidinyl]ethane

What is claimed is:

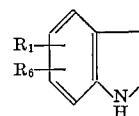
1. A process for the production of a compound of the formula:



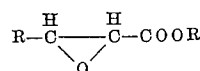
wherein

R_1 and R_6 are selected from the group consisting of hydrogen, chloro, fluoro, nitro, amino, alkyl of one to four carbon atoms and alkoxy of one to four carbon atoms;

R_3 and R are alkyl of one to three carbon atoms; which comprises contacting a compound of the formula:



wherein R_1 and R_6 are as previously defined; with a compound of the formula:



wherein R_3 and R are as previously defined.

2. The process of claim 1 conducted in the presence of an acid catalyst.

3. The process of claim 2 wherein the acid catalyst is phenol.

4. The process of claim 2 wherein the acid catalyst is a Lewis acid. 5

References Cited by the Examiner

UNITED STATES PATENTS

3,076,814 2/1963 Speeter et al, ----- 260—319 10

OTHER REFERENCES

Bentley et al.: Biochem. Jour., vol. 64, September 1956, pp. 44-49.

Oda: Chemical Abstracts, vol. 48, 1954, p. 1935d.

Rodd, Ed., Chemistry of Carbon Compounds, vol. IV, part A, Elsevier Publishing Co., New York, 1957, p. 92.

ALEX MAZEL, *Primary Examiner*.

HENRY R. JILES, *Examiner*.

MARY O'BRIEN, *Assistant Examiner*.