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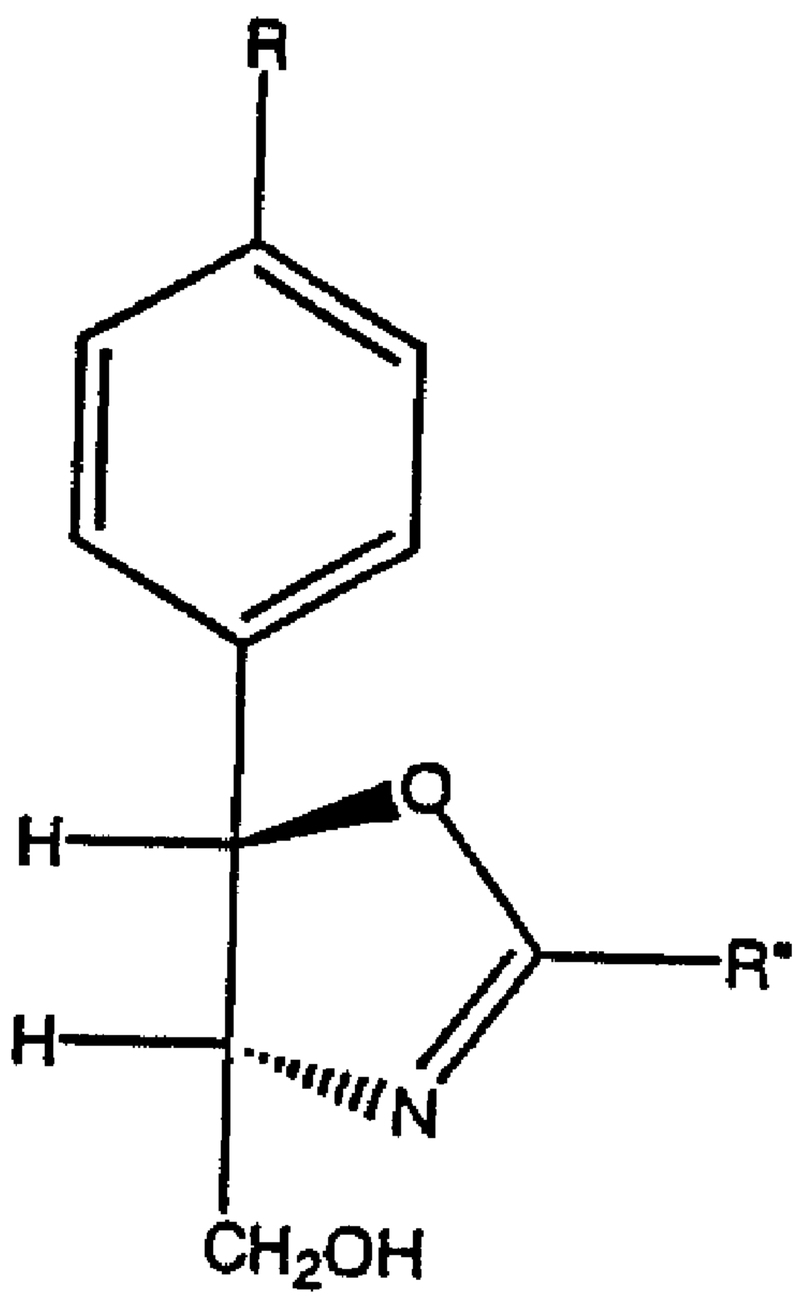
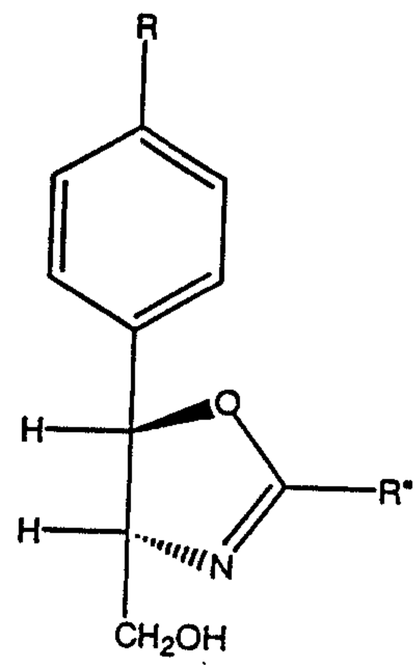
(54) Titre : PROCEDE DE PREPARATION D'INTERMEDIAIRES DU FLORFENICOL
(54) Title: PROCESS FOR PREPARING INTERMEDIATES TO FLORFENICOL



(57) Abrégé/Abstract:
A process for preparing a compound of formula (I) wherein R and R" are as described herein. Compounds of formula (I) are useful as intermediates in the preparation of florfenicol.

ABSTRACT OF THE DISCLOSURE

A process for preparing a compound of formula (I) wherein R and R" are as described herein. Compounds of formula (I) are useful intermediates in the preparation of florfenicol.



PROCESS FOR PREPARING INTERMEDIATES TO FLORFENICOL

FIELD OF THE INVENTION

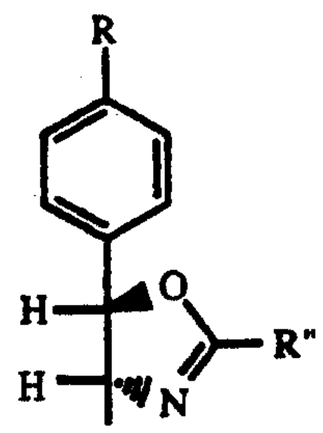
The present invention relates to intermediates to florfenicol and to a novel process for preparing them.

BACKGROUND OF THE INVENTION

Florfenicol, also known as [R-(R*,S*0]-2,2-Dichloro-N-[1-(fluoro-methyl)-2-hydroxy-2-[4-(methylsulfonyl)phenyl]ethyl]acetamide, is a broad spectrum antibacterial agent useful in the treatment of gram positive, gram negative and rickettsial infections as disclosed in U.S. Patent 4,361,557. The present invention relates to intermediates to florfenicol and to a novel process for preparing them. The intermediates described in the present specification can be used to prepare florfenicol as can be seen, for example, in US Patent 4,876,352.

SUMMARY

In one embodiment, the present invention is directed toward a process for preparing a compound of formula I:

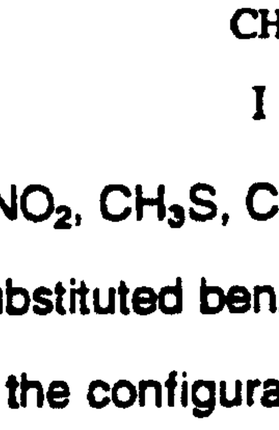


I

wherein R is H, NO_2, CH_3S, CH_3SO_2, or C_4 to C_6 alkyl; and R" is aryl, halo aryl, benzyl, substituted benzyl, C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, and haloalkyl, and the configuration of the oxazoline ring is 4R trans:

which comprises

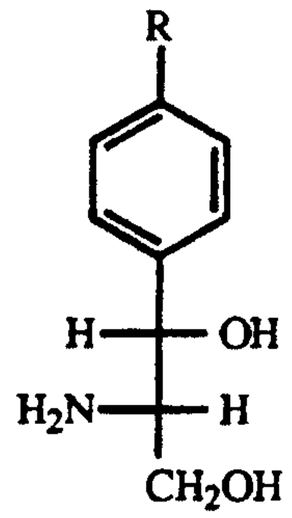
a) contacting a compound of formula II:



II

wherein R is as described above, and R' is H, C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl, benzyl, substituted benzyl or aryl;

with a reducing agent such as potassium borohydride, in a suitable reaction vessel, to obtain a compound of formula III:



III

wherein R is as described above, and b) then in the same reaction vessel reacting a compound of formula III, with a compound of the formula IV:

IV

wherein R" is as described above so as to obtain compound of the formula I.

The present invention has the advantage of being an efficient and economical process for preparing florfenicol, its analogs and oxazoline intermediates thereto.

DETAILED DESCRIPTION OF THE EMBODIMENTS

When utilized in the present specification and in the appended claims, the terms listed hereinbelow, unless otherwise indicated, are defined as follows:

The term "protic solvent" is intended to mean hydrogen-bonding solvent, as defined in James B. Hendrickson, Cram, Donald J., and Hammond, George S., *Organic Chemistry*, Mcgraw Hill Book Company, New York, New York, (1970), 1279 pp. The solvent should preferably, but not necessarily, be capable of precipitating oxazoline (I) out of solution. Such solvents include, but are not limited to, water, C_1 to C_{10} alkanoic acids such as formic acid, acetic acid and the like, C_1 to C_{10} alcohols such as methanol and ethanol and mixtures thereof, C_2 to C_{10} dialcohols such as ethylene glycol and C_1 to C_{10} trialcohols such as glycerin. Alternatively, the protic solvent can be admixed with any suitable cosolvent in order to effect precipitation of oxazoline compound (I). Such cosolvents can include other protic solvents which are miscible with the protic solvent such as C_4 to C_{10} alkanes, aromatic solvents such as benzene, toluene, xylenes, halobenzenes such as chlorobenzene, and ethers such as diethylether, tert-butylmethylether, isopropylether and tetrahydrofuran, or mixtures of any of the above solvents or cosolvents.

The term "alkyl" means a straight or branched alkyl such as methyl, ethyl, propyl, or sec-butyl. Alternatively, the number of carbons in alkyl may be specified. For example, C_1 to C_6 alkyl means an alkyl as described above containing 1 to 6 carbon atoms. "Haloalkyl" means an

"alkyl" as described above wherein one or more hydrogens are replaced by halo.

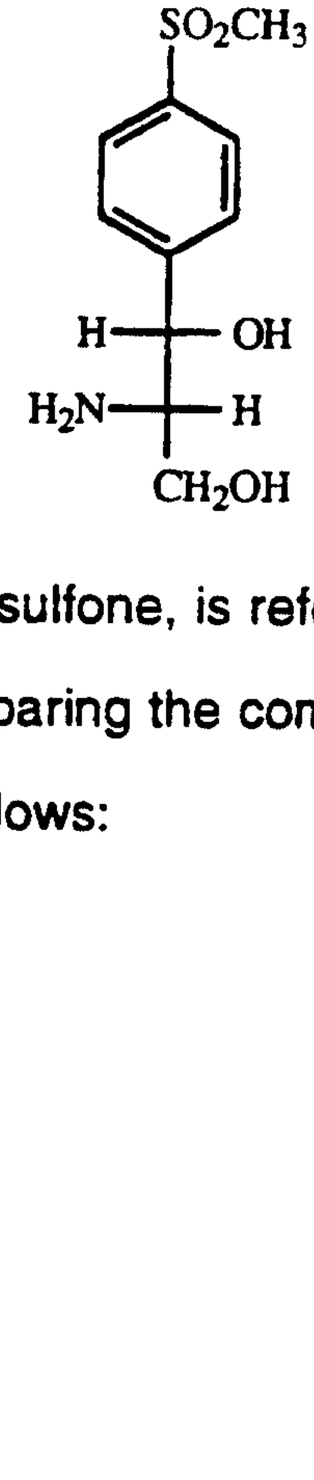
The term "aryl" means phenyl, or phenyl substituted by C_1 to C_6 alkyl or halo.

Substituted benzyl means benzyl substituted by C_1 to C_6 alkyl, or halo.

The term "halo" means fluoro, chloro, bromo, or iodo.

The term "halo aryl" means phenyl substituted by halo.

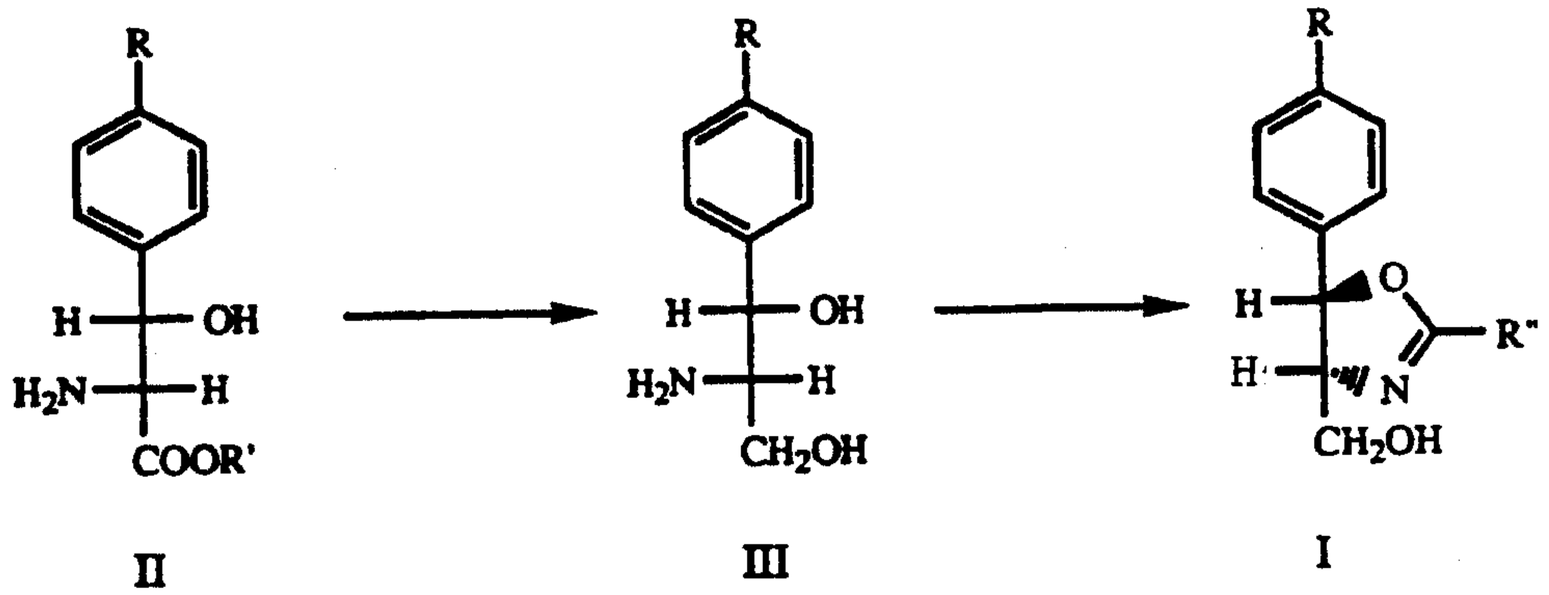
In the present specification,



which is an aminodiol sulfone, is referred to as ADS.

The procedure for preparing the compounds of the invention can be represented as follows:

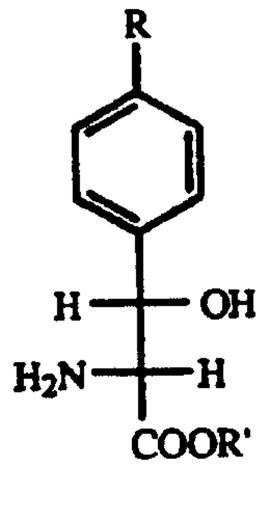
Formula Scheme



II III I

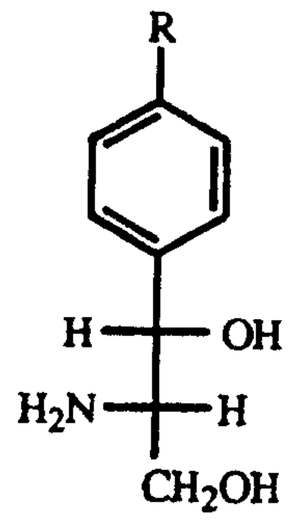
wherein R, R' and R" are as described herein.

With reference to the formula scheme above, a compound of formula I may be prepared as follows. A compound of formula II



II

wherein R and R' are as described above is treated with a reducing agent such as $NaBH_4$, $Ca(BH_4)_2$, $LiBH_4$ or more preferably KBH_4 in a protic solvent such as ethanol, ethylene glycol, or more preferably methanol, at a temperature in the range of about 0 °C to about 30 °C more preferably room temperature for a period of about 2 to about 8 hours, more preferably about 4 hours to obtain a compound of formula III:



III

wherein R is as described above.

If, for example, in the reaction described just above, methanol is employed as the solvent in the reduction, it may be recovered by distillation for reuse in subsequent reactions. Removing methanol can also improve the yield of the compound of formula I.

In the same reaction vessel, the compound of formula III is contacted with a compound of formula IV,

$$R''—C\equiv N$$

IV

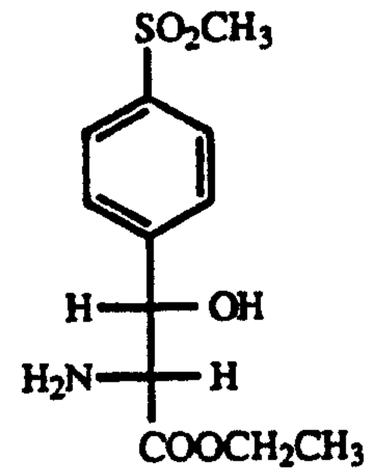
wherein R" is as described above, in the amount of about 1.1 to about 2.5 equivalents, preferably about 1.7 equivalents as compared to the compound of formula III.

Compounds of formula IV can be, for example, benzonitrile or dichloroacetonitrile. The reaction is run at a temperature between 25°C and 115°C depending upon the nitrile and the solvent employed. The reaction is run from about 6 hours to about 30 hours, preferably 18 hours. The reaction mixture is then cooled, for example, by the addition of cold water and worked up by conventional means such as filtration and washing to afford a compound of formula I. Preferably this step of the reaction is run at a pH in a range of about 6 to about 7.

An advantage of the present process is that it eliminates the need to isolate ADS, since both reaction steps are run in the same vessel.

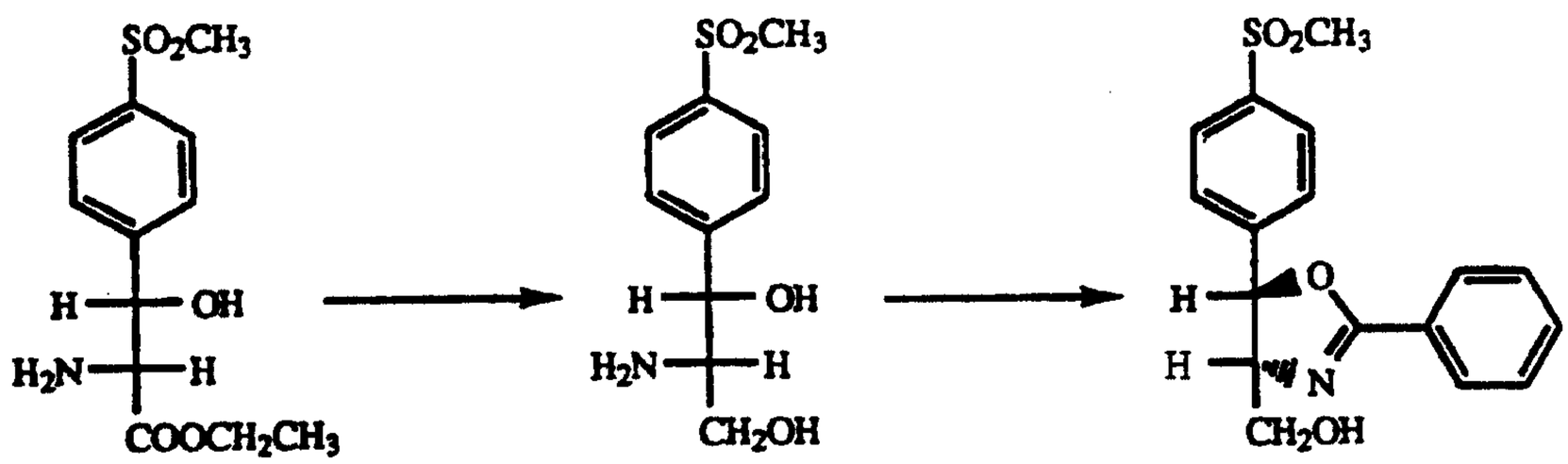
Formation of the dichloromethyl oxazoline is preferred and the formation of the phenyl oxazoline is most preferred.

The serine ethyl ester, as shown below, is the preferred starting material of formula II.



The following examples illustrate the present invention in a manner by which it can be practiced but, as such, should not be construed as limitations on the scope of the invention.

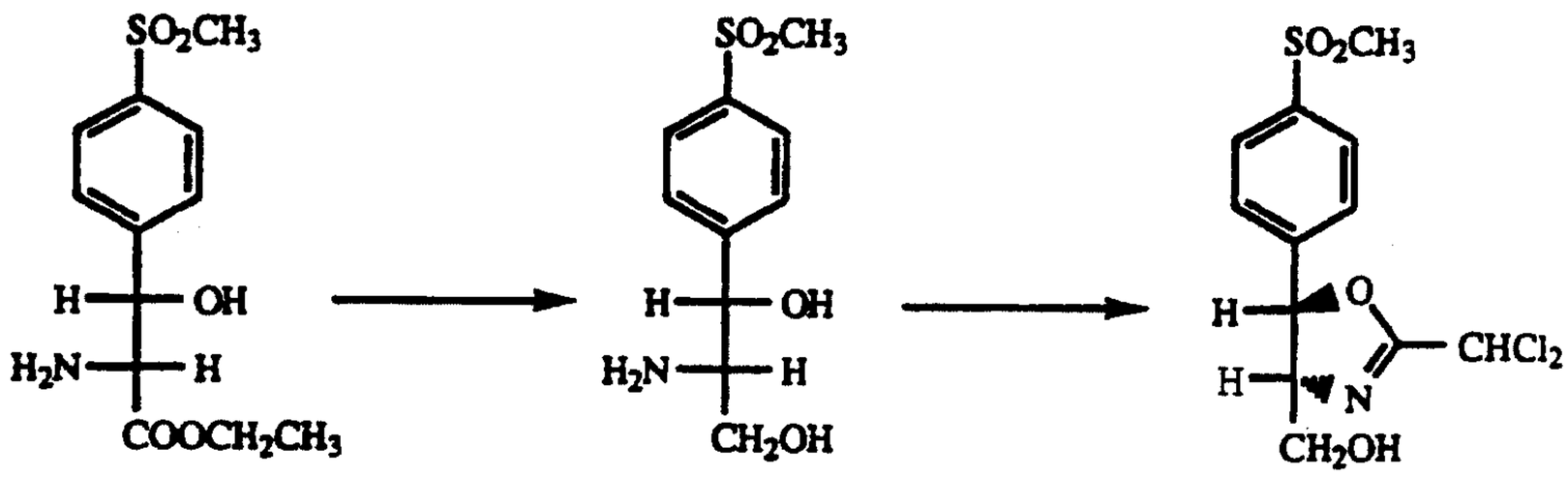
EXAMPLE 1



KBH_4 (1g) is placed in about 40 mL of methanol. D-Threo p-methylsulfonyl phenyl serine ethyl ester (5 g) is added with stirring. The reduction to ADS is complete in several hours and can be monitored by HPLC. When the reaction is complete, 20 mL of glycerin is

added to destroy any excess reducing agent and methanol is removed by distillation. After the methanol has been removed, the resulting mixture is heated to 105 °C and benzonitrile (3.1 mL) is added while continuing heating for about 18 hours. Formation of the desired oxazoline can be monitored by HPLC. The reaction is cooled to room temperature and worked up by addition of cold water, filtration of the resulting solids, washing of the solids with methanol then drying under vacuum. The yield is about 4.7 g (81 %) of material that is identical to an authentic sample of the phenyl oxazoline.

EXAMPLE 2



KBH_4 (1g) is placed in about 40 mL of methanol. D-Threo p-methylsulfonylphenyl serine ethyl ester (5 g) is added with stirring. The reduction to ADS is complete in several hours and can be monitored by HPLC. When the reaction is complete, 20 mL of glycerin is added to destroy any excess reducing agent and methanol is removed by distillation. After the methanol has been removed, the resulting mixture is acidified to a pH of about 6 to 7 with H_2SO_4 and dichloroacetonitrile (2.4 g) is added. The reaction is stirred at 50°C for about 18 hours. Formation of the desired oxazoline can be monitored by HPLC. The reaction is cooled to room temperature and worked up by

filtration of the solids, washing of the solids with isopropanol and 2 % $NaHCO_3$ then drying under vacuum. The yield is about 3.8 g (65 %) of material that is identical to an authentic sample of the dichloro oxazoline.

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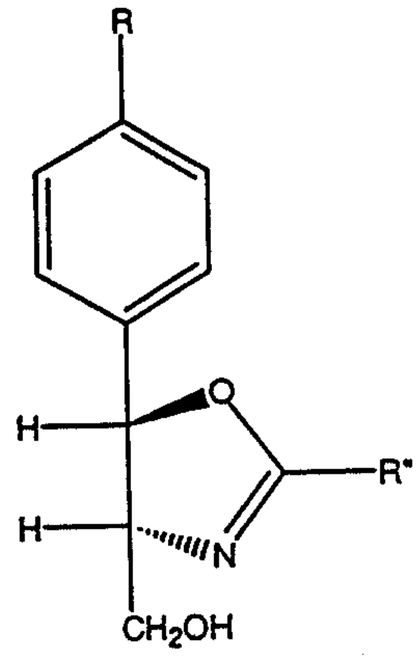
THE STARTING MATERIALS

The starting materials of formula (II) and (IV) are known to those skilled in the art.

CLAIMS

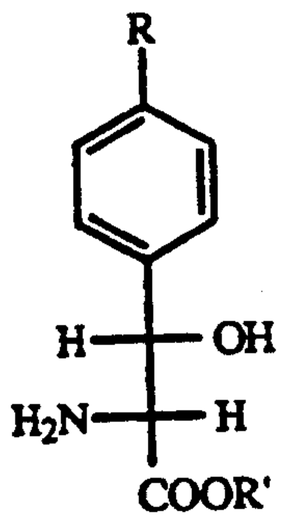
1. A process for preparing a compound of formula (I):



Wherein R is H, NO_2, CH_2S, CH_3SO_2 or C_4 to C_6 alkyl; and R″ is aryl, halo aryl, benzyl, substituted benzyl, C_1- to C_6 alkyl, C_3 to C_7 cycloalkyl, and haloalkyl, and the configuration of the oxazoline ring is 4R trans:

which comprises:

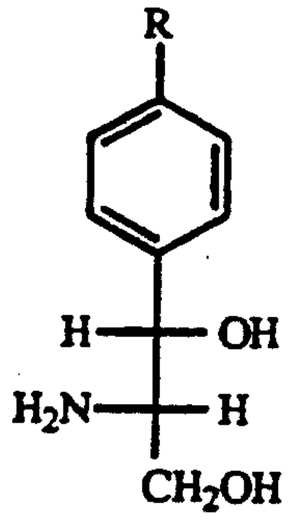
a) contacting a compound of formula II:



II

wherein R is as described above, and R' is H, C_1 to C_6 alkyl, C_3 to C_7 cycloalkyl; benzyl, substituted benzyl, or aryl;

with a reducing agent, in a suitable reaction vessel, to obtain a compound of formula III:



III

wherein R is as described above, and b.) then in the same reaction vessel reacting a compound of formula III, with a compound of the formula IV:

$$R'' - C \equiv N$$

IV

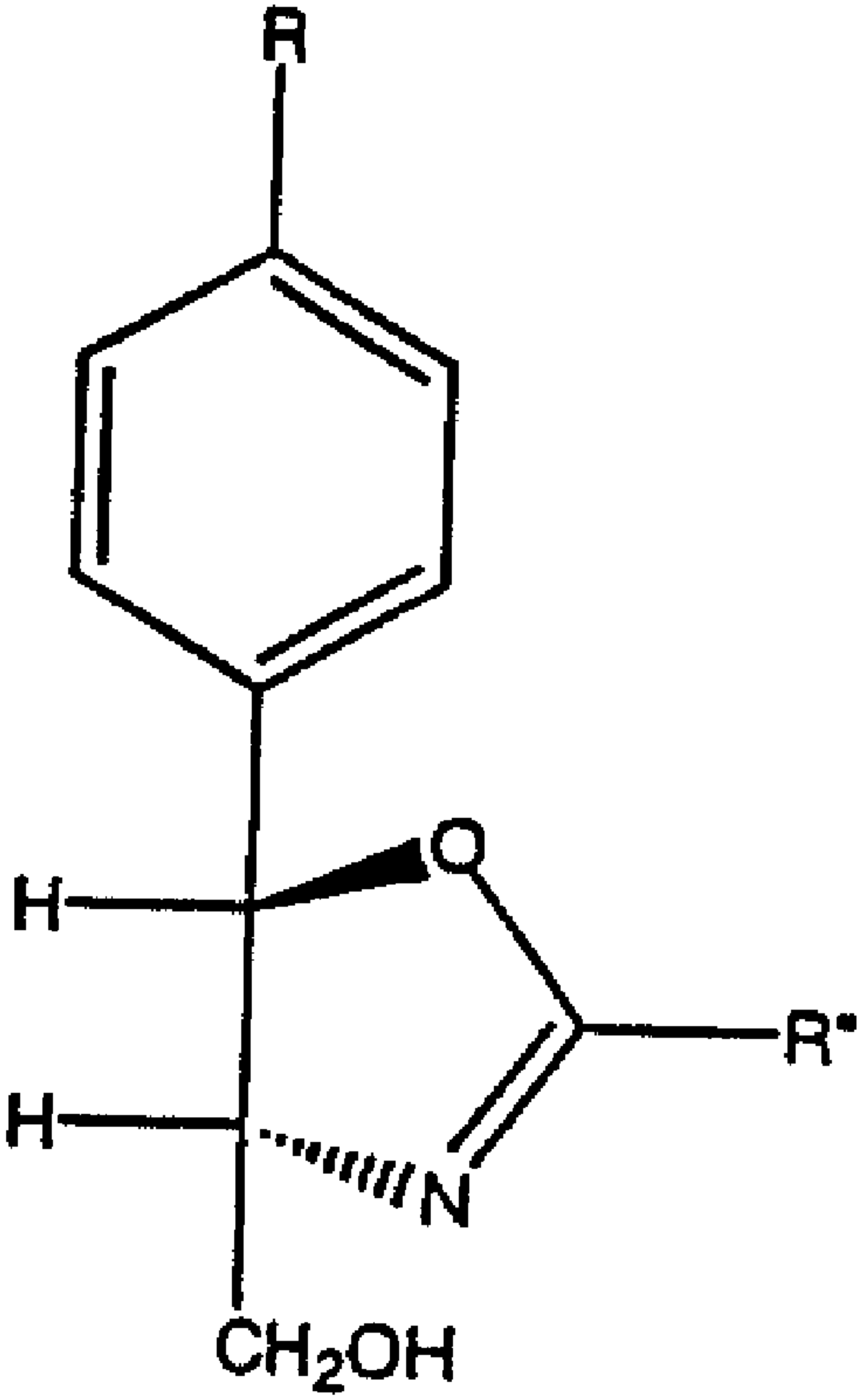
to obtain a compound of the formula I.

2. A process according to claim 1, wherein the reducing agent is potassium borohydride.

3. A process according to claim 1 or 2, wherein R is CH_3SO_2-.

4. A process according to claim 3, wherein R″ is $-CHCl_2$.

5. A process according to claim 3, wherein R″ is phenyl.


R
H
O
R'
H
N
CH2OH