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NITROPHENYL-OXAZOLINES AND PROCESSES OF PREPARING THE SAME

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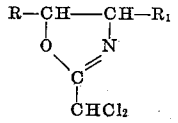
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Claims priority, application Great Britain December 14, 1949

9 Claims. (Cl. 260—307)

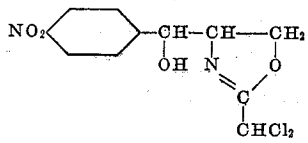
This invention relates to new chemical compounds and to processes for their preparation. In particular, it is concerned with the provision of new oxazolines useful as therapeutic agents or as intermediates in the production of therapeutic agents.

The new oxazolines of the present invention are compounds of the formula:



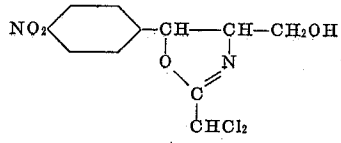
where R represents a para-nitrophenyl group and R_1 represents an hydroxymethyl group or R represents a hydrogen atom and R_1 represents a para-nitrophenyl-hydroxymethyl group.

These compounds can be regarded as having either the structure:



II

or the analogous structure:



III

The compounds of the present invention each contain two asymmetric carbon atoms and can exist in structural as well as optical isomeric forms. The term "structural" refers to the spatial relationship of the polar groups respectively attached to the two asymmetric carbon atoms.

By analogy with the nomenclature adopted by Rebstock et al. (J. A. C. S., vol. 71, pp. 2458–2473) in connection with the diastereoisomeric amino diol, 2-dichloracetamido-1-p-nitrophenylpropane 1:3-diol (also known by the common name "Chloramphenicol") the structural isomeric forms are herein referred to as "erythro" and "threo" respectively.

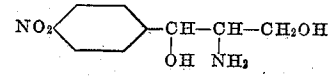
Both the erythro and the threo forms can exist as racemates of optically active isomers from which it will be appreciated that, strictly speaking, the compounds of the present invention can each exist in six different forms and that, accordingly, for a given structural formula of conventional type as used herein, there are included the complete mixture of all six forms, the racemates of the erythro and threo series and the four individual isomers L-erythro, D-erthyro, L-threo and D-threo.

It should be noted that the configurational representation of the isomers as D and L bears no relation to the

actual sign of the rotation but refers to the configuration about the alpha carbon atom. The D-threo isomer of Formula II has the same configuration with respect to the alpha carbon atom as the therapeutically active isomer of chloramphenicol which has been designated D(-)-threo 2-dichloracetamido-1-p-nitrophenylpropane 1:3-diol.

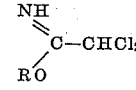
The DL- and D-threo compounds of Formula III are of direct therapeutic interest in that they possess an activity similar to that of, and are therefore useful in the same therapeutic fields as, the DL and D forms of 2-dichloracetamido-1-p-nitrophenylpropane 1:3-diol. Their degree of tolerance is comparable to that of the known substance. Furthermore, they also exhibit an advantage thereover in that they are substantially tasteless while chloramphenicol and the racemic mixture containing it are intensely bitter. The corresponding forms of the threo compounds of Formula II similarly have therapeutic application though they are less active than those of type III. Furthermore, the compounds of the present invention, especially the DL- and D-threo and DL- and L-erthyro forms, are of importance as intermediates for the production of chloramphenicol and the DL-mixture of which it is the D-component (see the specification of co-pending application No. 199,937, now abandoned) of even date herewith. The erythro forms of Formulae II and III may also be converted into the corresponding threo forms by a process of epimerisation involving the formation of an intermediate in the form of chloramphenicol or its erythro epimer.

According to a feature of the present invention compounds of Formula I are prepared by reacting an amino-diol of the formula:



IV

with an imino-ether of the type:



V

(where R represents the residue of an alcohol R.OH) which may be employed in the form of an acid addition salt. The resultant reaction mixture contains corresponding compounds of both types II and III which can be separated as, for example, by fractional crystallisation or chromatography.

The amino-diol starting material, of course, contains two asymmetric carbon atoms and can exist in erythro and threo forms each of which can occur as racemate or D or L isomers. In the process above described there is no substantial inversion of erythro to threo form, or vice versa. There is, however, a substantial difference between the two series erythro and threo as to the relative proportions of isomers of type II and type III produced. In the threo series, the proportion is substantially 2:3 while in the erythro series the product is substantially entirely erythro compound of type II with a minor percentage of erythro compound of type III.

If pure D-threo isomer of Formula III is required it is preferred to employ as the starting material pure D-threo amino diol of Formula IV since the oxazolines of the present invention are somewhat unstable and therefore difficult to resolve by conventional methods.

The present invention is illustrated by the following examples.

Example I

D(—)-threo 2-amino-1-p-nitrophenyl-propane 1:3 diol as prepared by the method described by Rebstock et al. (J. A. C. S., vol. 71, pp. 2458–2473) (1.65 g.) was dissolved in warm dry pyridine (10 cc.) and treated with dichloracetiminoethyl ether hydrochloride (1.8 g.). The

mixture was allowed to stand at room temperature for some hours, and the pyridine hydrochloride was then removed by filtration. Evaporation of the solvent and crystallisation of the residue from methanol gave a crude oxazoline. Recrystallisation of this from methanol gave the pure compound, D-threo 2-dichloromethyl-4-p-nitrophenylhydroxymethyl-Δ^2-oxazoline, M. P. 143–144° C. and $(\alpha)_D^{20}=-176.85°$ (C=1% in ethyl acetate). Found: C, 43.8; H, 3.04; N, 9.09; Cl, 22.8.

$C_{11}H_{10}O_4N_2Cl_2$

requires C, 43.25; H, 3.18; N, 9.17; Cl, 23.2%. The original filtrate from the first crystallisation was evaporated to dryness and the residue fractionally crystallised from benzene to give the oxazoline D-threo 2-dichloromethyl - 5 - p - nitrophenyl - 4 - hydroxymethyl - Δ^2-oxazoline, M. P. 132–133° C. and $(\alpha)_D^{20}=-13.65°$ (C=6.5% in ethyl acetate). Found: C, 42.9; H, 3.18; N, 9.15; Cl, 23.2. $C_{11}H_{10}O_4N_2Cl_2$ requires C, 43.25; H, 3.18; N, 9.17; Cl, 23.2%.

Example II

DL-threo 2 - amino - 1 - p- nitrophenylpropane 1:3 - diol as prepared by the method described by Rebstock et al. (J. A. C. S., vol. 71, pp. 2458–2473) (6.7 g.) was dissolved in warm dry pyridine (40 cc.)3 and treated with dichloracetiminoethyl ether hydrochloride (6.7 g.). The mixture was allowed to stand at room temperature for some hours, and the pyridine hydrochloride was then removed by filtration. Evaporation of the solvent and crystallisation of the residue from methanol gave the oxazoline DL - threo 2 - dichloromethyl-4-p-nitrophenyl-hydroxymethyl-Δ^2-oxazoline, M. P. 163–164° C. Found: C, 43.2; H, 3.3; N, 9.3; Cl, 23.0. $C_{11}H_{10}O_4N_2Cl_2$ requires C, 43.25; H, 3.18; N, 9.17; Cl, 23.2%. The mother liquors from this crystallisation were evaporated to dryness and the residue fractionally crystallised from methanol, ethyl acetate, and finally benzene, to give the oxazoline DL-threo 2-dichloromethyl-5-p-nitrophenyl-4-hydroxymethyl-Δ^2-oxazoline, M. P. 128°–129° C. Found: C, 43.3; H, 3.3; N, 9.1. $C_{11}H_{10}O_4N_2Cl_2$ requires C, 43.25; H, 3.18; N, 9.17%.

Example III

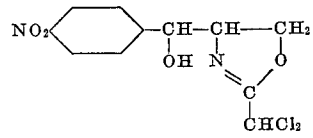
3.75 g. of L-erythro 2-amino-1-p-nitrophenylpropane 1:3-diol hydrochloride melting at 190–200° C. (cap.) and having $(\alpha)_D^{28}=+17.8°$ (C=6% in water) were dissolved in 30 cc. of anhydrous pyridine. 3.47 g. of dichloracetiminoethyl ether hydrochloride were added to the solution at ordinary temperature. The mixture was left overnight at ordinary temperature. The salts which crystallised were filtered off and the filtrate obtained was evaporated to dryness under 3 mm. mercury (maximum temperature of heating bath=30° C.). The residue was treated with 37 cc. of water and the product which crystallised was washed with water and then dried in vacuo in the presence of sulphuric acid. There was thus obtained 3.29 g. of L-erythro 2-dichloromethyl-4-p-nitro-phenylhydroxymethyl-Δ^2-oxazoline, M. P. (cap.)= 132–136° C. which after recrystallisation in 14 cc. of boiling ethanol had the following characteristics: M. P. (cap.)=143° C.; $(\alpha)_D^{25}=-37.0°$ (C=4% in acetone.

Example IV

1.93 g. of racemic erythro 2-amino-1-p-nitrophenylpropane 1:3-diol hydrochloride of M. P. 206–208° C. were dissolved in 15 cc. of anhydrous pyridine. To this solution there was added 1.8 g. of dichloracetiminoethyl ether hydrochloride of M. P. 80° C. The solution was left for 2-hours at room temperature when pyridine hydrochloride precipitated. The mixture was then poured into 100 cc. of water. A product crystallised rapidly and was filtered off, washed with water and dried at 100° C. It was racemic erythro 2-dichloromethyl-4-p-nitrophenylhydroxymethyl-Δ^2-oxazoline, M. P.=167–168° C. Yield 1.5 g.

I claim:

1. The erythro forms of the oxazoline



2. 2 - dichloromethyl - 4 - hydroxymethyl-5-p-nitrophenyl-Δ^2-oxazoline.

3. 2-dichloromethyl-4-p-nitrophenylhydroxymethyl-Δ^2-oxazoline.

4. An oxazoline of the class consisting of 2-dichloromethyl - 4 - hydroxymethyl - 5 - p - nitrophenyl - Δ^2-oxazoline and 2 - dichloromethyl - 4 - p-nitrophenylhydroxymethyl-Δ^2-oxazoline.

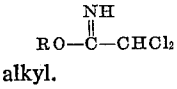
5. DL - threo - 2 - dichloromethyl - 4 - hydroxymethyl-5-p-nitrophenyl-Δ^2-oxazoline.

6. D - threo - 2 - dichloromethyl - 4 - hydroxymethyl-5-p-nitrophenyl-Δ^2-oxazoline.

7. DL - threo - 2 - dichloromethyl - 4 - p - nitrophenylhydroxymethyl-Δ^2-oxazoline.

8. D - threo - 2 - dichloromethyl - 4 - p - nitrophenylhydroxymethyl-Δ^2-oxazoline.

9. Process for the production of an oxazoline of the class consisting of 2-dichloromethyl-4-hydroxymethyl-5-p-nitrophenyl-Δ^2-oxazoline and 2-dichloromethyl-4-p-nitrophenylhydroxymethyl-Δ^2-oxazoline which comprises reacting in an anhydrous organic solvent at substantially room temperature a 1-p-nitrophenyl-2-aminopropane-1,3-diol with an acid addition salt of an imino ether of the formula



where R is lower alkyl.

References Cited in the file of this patent

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