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RACEMIZATION OF OPTICALLY ACTIVE COMPOUNDS

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Our invention relates to the racemization of optically active compounds of the type of ephedrine and more particularly optically active ephedrine and pseudo-ephedrine or mixtures of these compounds.

In the synthetic production of racemic ephedrine dextrorotatory ephedrine (d-ephedrine) is obtained in addition to the more valuable levorotatory compound (l-ephedrine). It is an object of our invention to convert the d-ephedrine thus obtained, which cannot successfully be utilized for pharmaceutical purposes, into the racemic substance, from which the l-ephedrine may be separated according to any one of the known methods for resolving racemic substances into their optically active components, and may thus be recovered.

It is another object of our invention to utilize optically active pseudo-ephedrine, which is known to be of less value in pharmacology. When racemizing optically active pseudo-ephedrine, part of this compound is re-arranged into racemic ephedrine, from which product the valuable l-ephedrine may be recovered.

Numerous efforts have been made for racemizing optically active ephedrine. Schmidt (244 Archiv der Pharmazie 239–240) tried to inactivate l-ephedrine by heating it with the 10-fold quantity of hydrochloric acid. However by proceeding in this manner he obtained dextrorotatory pseudo-ephedrine (d-ps-ephedrine). This was confirmed by Emde (l. c., page 244). Further attempts to racemize ephedrine were described by Schmidt 250 Archiv der Pharmazie 154. When acting with baryta on the active material at temperatures up to 210° C., no inactivation of l-ephedrine, but only a decomposition of the material took place. Apparently d-ps-ephedrine, when acted upon with baryta, was converted into l-ephedrine, but Spaeth and Göhring (41 Monatshefte für Chemie, 319) were not in a position to confirm this statement.

It has further been found that l-ephedrine is not changed by an alcoholic solution of potassium hydroxide. When treated with diluted sulphuric acid, it was converted into d-ps-ephedrine. l-Ephedrine and d-ps-ephedrine, when treated with acetic anhydride, yielded d-ps-acetyl-ephedrine. By treating l-ephedrine with nitrous acid d-ps-ephedrine is obtained.

Racemization could not be observed in any of these cases.

Spaeth (58 Berichte der Deutschen Chemischen Gesellschaft 197:1268) did not succeed either in racemizing optically active ephedrine or ps-ephedrine.

We have now found that optically active ephedrine as well as optically active pseudo-ephedrine or mixtures thereof can be completely racemized by treating them at a temperature above normal with an alkali alcoholate. d-l-Ephedrine and d-l-pseudo-ephedrine, result in this treatment. The sodium and potassium alcoholates of methyl-, ethyl-, propyl-, butyl-, and amyl-alcohol or of aromatic alcohols such as benzyl alcohol or cycloaliphatic alcohols, such as cyclohexanol, have been found to be suitable for this treatment. In order to be enabled to distil off any excess of alcohol after the conversion has been completed, we prefer using compounds of alcohols, which boil at moderate temperatures, preferably below 167–168° C. under a pressure of 15 mm. mercury column. In such case the alcohol can easily be distilled off without any losses in ephedrine, since under a pressure of 15 mm. mercury column ephedrine boils only at 167–168° C. Mixtures of alkali alcoholates of different alcohols may be employed as well.

The quantities of alkali alcoholate used in the racemizing treatment may be very small; they influence the temperature and time of conversion and may range between $\frac{1}{10}$ and 2 mols per mol of the optically active ephedrine substance to be treated. The greater the quantity of alkali alcoholate and the higher the temperature, the more rapidly does conversion proceed, but the greater is also the danger of suffering losses by decomposition of the starting material.

The racemization may be carried through in the molten state, i. e. without the addition of a solvent. We prefer however to carry out the racemizing treatment with the materials in solution, since this mode of operation allows a better control of the reaction. As solvents we may use in the first line inert hydrocarbons, preferably such as boil at a sufficiently high temperature, for instance above 140° C., which includes decahydronaphthalene, tetrahydronaphthalene, naphthalene, cymene, high boiling benzene- or benzine-hydrocarbons and the like. High boiling alcohols such as benzyl alcohol may be used as well.

The range of temperatures within which conversion may be carried through, extends from about 135 to 210° C. Temperatures between 170 and 190° C. have been found to be most suitable.

We are now going to explain our invention more in detail by giving some examples, but we do not intend to limit the invention to the spe-

cific starting materials, or temperatures, quantities and duration recited in these examples.

Example 1

1 gram metallic sodium is dissolved in 20 ccm. methanol; 500 ccm. decahydronaphthalene (known under the trade name "Dekalin") and 60 grams d-ephedrine are added to the solution. 120 ccm. decahydronaphthalene are distilled off under atmospheric pressure and the liquid is heated 4 hours to boiling in a flask at an inner temperature of about 195° C. The mass is now cooled down and the bases extracted from the Dekalin solution by shaking with dilute sulphuric acid. The sulphuric acid solution thus obtained is rendered strongly alkaline and the basic precipitate is dissolved in ether. The ether is distilled off and the residue is dissolved in hydrochloric acid to form a neutral solution to which is added a solution of potassium oxalate. The oxalate crystallizing from this solution is d-l-ephedrine oxalate. By means of caustic potash solution d-l-ps-ephedrine may be precipitated from the mother liquor, the yield amounting to 53% d-l-ps-ephedrine and 42% d-l-ephedrine.

Example 2

2 grams metallic sodium are dissolved in 40 ccm. methanol; 30 grams d-ps-ephedrine and 300 ccm. Dekalin are added and 120 ccm. Dekalin are then distilled off and the remainder boiled 2 hours. The liquid is treated further as described with reference to Example 1. The yield is 50.7% d-l-ps-ephedrine and 42.7% d-l-ephedrine.

Example 3

1 gram metallic sodium is dissolved in 20 ccm. methanol and 30 grams d-ephedrine are added to the solution. The methyl alcohol is distilled off, the residue is melted and the clear melt heated 2 hours to 190° C. The melt is now dissolved in hydrochloric acid to form a neutral solution, which is treated further with oxalate as described with reference to Example 1. The yield is 49% d-l-ps-ephedrine and 45% d-l-ephedrine.

Example 4

40 grams metallic sodium are dissolved in 1800 ccm. amyl alcohol. 1000 ccm. amyl alcohol are distilled off, 80 grams d-ephedrine are added to the concentrated solution of sodium amylate and the whole is boiled 42 hours. After cooling the bases formed in the reaction are extracted by shaking with sulphuric acid. From the sulphuric acid solution the bases are recovered by precipitating with caustic soda solution and shaking with ether and are separated in a known manner by means of the oxalate. The yield is 59 grams d-l-ephedrine oxalate and 15 grams d-l-ps-ephedrine base.

Various changes may be made in the details disclosed in the foregoing specification without departing from the invention or sacrificing the advantages thereof.

We claim:

1. The method of racemizing optically active compounds of the type of ephedrine, which comprises acting at a temperature ranging between 135 and 210° C. on a member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine with an alkali metal alcoholate the alcohol of which, under a pressure of 15 mm. mercury column, boils below 167–168° C.

2. The method of racemizing optically active compounds of the type of ephedrine, which comprises acting at a temperature ranging between 135 and 210° C. on a member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine with a mixture of alkali metal alcoholates formed from alcohols which, under a pressure of 15 mm. mercury column, boil below 167–168° C.

3. The method of racemizing optically active compounds of the type of ephedrine, which comprises heating to a temperature ranging between 135 and 210° C. a melt consisting of a member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine and of an alkali metal alcoholate, the alcohol constituent of which, under a pressure of 15 mm. mercury column, boils below 167–168° C.

4. The method of racemizing optically active compounds of the type of ephedrine, which comprises heating to a temperature ranging between 135 and 210° C. a solution consisting of a member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine and of an alkali metal alcoholate, the alcohol of which, under a pressure of 15 mm. mercury column, boils below 167–168° C.

5. The method of racemizing optically active compounds of the type of ephedrine, which comprises heating to a temperature ranging between 135 and 210° C. a solution, in an inert hydrocarbon solvent, of a member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine and of an alkali metal alcoholate, the alcohol of which, under a pressure of 15 mm. mercury column, boils below 167–168° C.

6. The method of racemizing optically active compounds of the type of ephedrine, which comprises acting at a temperature ranging between 135 and 210° C. on at least one member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine with a molar quantity, ranging from one tenth to twice that of the ephedrine substance present, of alkali metal alcoholate, the alcohol constituent of which, under a pressure of 15 mm. mercury column, boils below 167–168° C.

7. The method of racemizing optically active compounds of the type of ephedrine, which comprises acting at a temperature ranging between 170 and 190° C. on a member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine with an alkali metal alcoholate, the alcohol of which, under a pressure of 15 mm. mercury column, boils below 167–168° C.

8. The process of preparing l-ephedrine, which comprises acting at a temperature ranging between 135° and 210° C. on d-ephedrine with an alkali metal alcoholate, the alcohol constituent of which, under a pressure of 15 mm. mercury column, boils below 167–168° C., and separating the l-ephedrine from the racemic substance formed in the reaction.

9. The process of converting optically active pseudo-ephedrine into the more valuable ephedrine, which comprises acting at a temperature ranging between 135 and 210° C. on optically active pseudo-ephedrine with an alkali metal alcoholate, the alcohol constituent of which, under a pressure of 15 mm. mercury column, boils below 167–168° C., and separating the ephedrine thus produced from the pseudo-ephedrine present.

10. The process of converting optically active

pseudo-ephedrine into more valuable ephedrine, which comprises acting at a temperature ranging between 135 and 210° C. on optically active pseudo-ephedrine with alkali metal alcoholate, the alcohol constituent of which, under a pressure of 15 mm. mercury column, boils below 167–168° C., and recovering the l-ephedrine thus produced in racemic mixture with d-ephedrine.

11. The method of racemizing optically active compounds of the type of ephedrine, which comprises heating to a temperature ranging between 135 and 210° C. a solution, in dekahydronaphthalene, of a member of the group constituted by optically active ephedrine and optically active pseudo-ephedrine and of an alkali metal alcoholate, the alcohol of which, under a pressure of 15 mm. mercury column, boils below 167–168° C.

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