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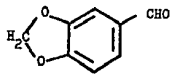
(19)

(54) PROCESS FOR THE PREPARATION OF HELIOTROPIN

(71) We, SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B.V., a company organised under the laws of The Netherlands, of 30 Carel van Bylandtlaan, The Hague, The Netherlands, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to a process for the preparation of heliotropin and to heliotropin prepared by this process.

Heliotropin (also known as piperonal, or 3,4 - methylenedioxybenzaldehyde and having the structural formula



is an important aroma and flavour chemical and is also an intermediate in syntheses of other aroma chemicals and some pharmaceutical chemicals.

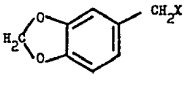
In general heliotropin is manufactured from safrole, which is a component of many essential oils, of which the most important are those of camphor, sassafras, and *Ocotea pretiosa* (Brazil). Safrole is isomerized to isosafrole which is then oxidized to heliotropin, usually with chromic acid or ozone.

It has also been suggested to manufacture heliotropin starting from catechol (J. Gen. Chem., USSR, 1938, 8, 1975). This method involves a 3-step process which comprises 1) the preparation of methylenedioxybenzene from catechol, 2) the conversion of methylenedioxybenzene with paraformaldehyde and hydrogen chloride to heliotropyl chloride and 3) the reaction of the latter with hexamethylene tetramine in ethanol to obtain heliotropin with an overall yield of 11—28% based on catechol. An improvement in the yield of step 1), and thus overall yield, can be obtained by employing a process for preparation of methylenedioxybenzene from catechol as described in U.K. patent specification 1,097,270 which involves the reaction of catechol with a methylene dihalide under alkaline conditions in the presences of a highly polar, aprotic solvent.

It has now been found that heliotropin can be obtained in good yields if the conversion of heliotropyl halide to heliotropin is carried out with an alkali metal salt of 2-nitropropane in the presence of an alcohol having 1—6 carbon atoms.

Accordingly the present invention provides a process for the preparation of heliotropin which comprises reacting a heliotropyl halide with an alkali metal salt of 2-nitropropane in the presence of an alcohol having 1—6 carbon atoms.

The heliotropyl halide, which is represented by the formula



wherein X represents a halogen atom, preferably is heliotropyl chloride. The reaction is preferably carried out at a temperature of 20—100°C, a temperature range of 40—60°C being particularly preferred.

Very good results are obtained if the akali metal salt of 2-nitropropane is potassium 2-propanenitronate and the alcohol having 1—6 carbon atoms is tertiary butanol. As will be shown in the Examples the selection of potassium 2 - propanenitronate together with tertiary butanol surprisingly leads to further improvements in the yield of heliotropin. In this specification the expression "potassium 2 - propanenitronate" is used to designate the potassium salt of 2 - nitropropane ($(CH_3)_2C=NO_2K$). Potassium 2 - propanenitronate may be provided by the addition of a solution of potassium

hydroxide in water to a solution of 2 - nitropropane in tertiary butanol.

Heliotropyl halide may be prepared by the halomethylation of methylenedioxybenzene which, in the case of heliotropyl chloride, may be performed with paraformaldehyde and aqueous hydrochloric acid. It is possible and convenient to use the chloromethylated mixture thus obtained without further purification. The chloromethylated mixture is preferably added to the solution of potassium 2 - propanenitronate.

Methylenedioxybenzene is preferably obtained by a process as described in U.K. patent specification 1,097,270.

The process of the invention is further illustrated in the following Examples.

Example I

Heliotropin from methylenedioxybenzene by cloromethylation and reaction with 2-nitropropane in ethanolic sodium ethoxide.

(a) Paraformaldehyde (3.0 g, 0.1 mole) was suspended in cold (0°C) aqueous hydrogen chloride (20 ml) that had been saturated at 0°C. Methylenedioxybenzene, hereinafter referred to as MDOB, (12.2 g, 0.1 mole) was added and the reaction mixture was stirred at 0°C for 4 hours. The oil was separated, the aqueous layer extracted three times with methylene chloride (10 ml portions), the total organic layers dried with $MgSO_4$ and the solvent removed *in vacuo*.

(b) To a solution of sodium (1.84 g, 0.08 mole) in ethanol (60 ml) was added 2 - nitropropane (7.12 g; 0.08 mole) to obtain a thick but stirrable white slurry. The chloromethyl mixture prepared as in (a) was added dropwise over a few minutes, the reaction mixture becoming bright orange in colour, this colour fading rapidly once the addition had been completed. The reaction mixture was stirred at room temperature for 64 hours over which time it became much thinner in consistency. The pH was adjusted from about 9.0 to about 6.0 by the addition of a little HCl, and the reaction mixture was subjected to steam distillation, collecting first the ethanol, then water containing heliotropin. Distillation was continued until the distillate no longer gave a positive reaction with 2,4 - dinitrophenylhydrazine, some $3\frac{1}{2}$ litres of distillate being collected. The distillate was saturated with sodium chloride, extracted three times with methylene chloride, the combined extracts dried with $MgSO_4$ and evaporated to leave 9.5 g residue.

The ethanol initially separated was evaporated to dryness at room temperature *in vacuo* to yield a further 0.2 g. Distillation at 15 mm produced a 1:1 mixture of acetoxime and MDOB (0.5 g), b.p. 26—46°C/15 mm, a further 2.5 g of MDOB, b.p. 60—65°C/15 mm, and finally 5.85 g, b.p. 128—132°C/15 mm of heliotropin together with a small amount of heliotropyl ethyl ether. The yield of crude heliotropin was 55% based on unrecovered MDOB.

Example II

Heliotropin from methylenedioxybenzene by chloromethylation and reaction with sodium 2-propanenitronate in isopropanol-water

(a) Paraformaldehyde (4.5 g, 0.15 mole) was suspended at 0°C in saturated aqueous hydrogen chloride (20 ml). MDOB (12.2 g, 0.1 mole) was added and the reaction mixture stirred between 17° and 20°C with a slow stream of hydrogen chloride passing through the mixture. Stirring was continued for 1.5 hours when almost all the MDOB had disappeared. The mixture, composed mainly of heliotropyl chloride together with some bischloromethyl-methylenedioxybenzene and MDOB was separated, the aqueous layer extracted twice with 10 ml portions of methylene chloride and the total organic layer evaporated at 30°—35°C *in vacuo*.

(b) To a stirred mixture of water (5 ml) and 2 - nitropropane (8.9 g, 0.1 mole) at 20°C was added a solution of sodium hydroxide (4.1 g, 0.1 mole, 98% purity) in water (5.0 ml) over 2—3 minutes and the mixture was stirred at 20—30°C for 60 minutes during which time it became homogeneous. Isopropyl alcohol (10 ml) was added, followed by the chloromethylated mixture prepared as in (a), the transfer being completed by use of isopropyl alcohol (2 ml). Sodium hydroxide (0.1 g) was added to ensure neutralization of any hydrogen chloride, then the whole was stirred rapidly on a bath at 35—40°C. The reaction mixture thinned rapidly and an exotherm (7—8° above the oil bath temperature) ceased after $\frac{3}{4}$ hours. The oil bath temperature was raised to 50°C and after a total time of $2\frac{1}{2}$ hours GLC analysis indicated virtual completion of reaction.

The reaction mixture was pumped in vacuo to remove volatile material at 80°C, first at 15 mm, then at 30°C and 0.5 mm. The residue was stirred rapidly with sodium metabisulphite (10 g) and water (12 ml). Further addition of metabisulphite (5 g) and water (15 ml) ensured completion of the bisulphite addition reaction after $2\frac{1}{2}$ hours. Ethanol (20 ml) was then added, the whole filtered and the solid washed with ethanol (3x25 ml) and methylene chloride (2x25 ml). The solid was suspended in water (50 ml) and methylene chloride (30 ml) and decomposed with saturated sodium

carbonate solution below pH 8.5. The layers were separated, the aqueous layer extracted with methylene chloride and the total organic solution dried with $MgSO_4$, decolorized with charcoal and evaporated *in vacuo* to give 7.0 g crude heliotropin; yeild 46% on total MDOB.

Example III

Heliotropin from methylenedioxybenzene by chloromethylation and reaction with sodium 2-propanenitronate in tertiary butanol-water

(a) Paraformaldehyde (4.5 g) was suspended in saturated aqueous hydrogen chloride (20 ml) at 0°C. MDOB (12.2 g) was added and the reaction mixture stirred rapidly at 18—25°C for 2 hours with a slow stream of hydrogen chloride passing through the reaction mixture. The layers were separated, the aqueous layer extracted twice with 10 ml portions of methylene chloride, then the combined organic layer and extracts evaporated free of solvent at 30—35°C *in vacuo*.

(b) To a mixture of 2 - nitropropane (10.68 g) and water (5 ml) was added with stirring a solution of sodium hydroxide (5.0 g) in water (5.5 ml), the addition time being 5 minutes. The temperature was controlled below 45°C for 20 minutes after which time solution was complete. Tertiary butanol (10 ml) was added and the reaction mixture heated to 40°C. The heat source was removed and the chloromethyl mixture prepared as in (a) added over 15 minutes maintaining a temperature of 48—49°C without heating or cooling. The transfer was completed with t-butanol (2 ml), then the mixture was stirred at 40°C for 3 hours. The volatile materials were removed into a cooled (−70°C) trap *in vacuo* and the residue treated at room temperature with sodium metabisulphite (10 g) and water (20 ml). When stirring became difficult, ethanol (20 ml) was added and stirring continued for 4.5 hours at room temperature. The solid was filtered off, washed with ethanol then methylene chloride and finally decomposed with saturated sodium bicarbonate solution from a suspension in water and methylene chloride to yield heliotropin; yield 52.5% on total MDOB (57.5% on MDOB not recovered).

The volatile distillate was treated with concentrated hydrochloric acid (10 ml) and water (8 ml), distilling off the acetone via a short column. When acetone was no longer detectable the residue was evaporated to dryness to yield crude hydroxylamine hydrochloride in 49% yield based on total MDOB (53% on MDOB not recovered). The acetone containing distillate was extracted with methylene chloride to recover approximately 8—9% of the MDOB used.

Example IV

Preparation of heliotropin from methylenedioxybenzene by chloromethylation and reaction with potassium 2-propane-nitronate in aqueous t-butanol

(a) To hydrochloric acid (1 litre, saturated at 0°) was added paraformaldehyde (52.5 g); when this had been dissolved by stirring a further quantity (52.5 g) of paraformaldehyde was added, followed by MDOB (535 g). The mixture was stirred vigorously and kept at 19—20°C by occasional cooling. After 65 minutes the mixture was allowed to settle and the heavy organic layer was washed once with water (250 ml). The separated acid and water washings were extracted twice with carbon tetrachloride (50 ml) to yield on evaporation a further 11 g of oil which was added to the main product.

(b) A solution of 2-nitropropane (288.75 g; 3.2 mole) in tertiary butanol (750 ml) was stirred rapidly and a solution of potassium of potassium hydroxide (215 g of 85%) in water (112 ml) was added at such a rate that the temperature did not exceed 50°C. To this stirred solution the chloromethylation product prepared as in (a) was added during 45 minutes; a temperatre of 50—55°C was maintained without heating. Tertiary butanol (100 ml) was used for rinsing in the last of the chloromethylation product and the mixture was stirred at 50—55°C until a Beilstein halogen test on an extract of a test portion was negative (90 minutes). The tertiary butanol was recovered from the reaction mixture, along with a little water, in 97.5% yield by distillation at 150 mm through a 40 cm Vigreux column; the internal temperature of the distillant was 43—45°C.

Water (400 ml) and carbon tetrachloride (250 ml) were added to the reaction mixture and after shaking the layers were separated and the aqueous layer was re-extracted with carbon tetrachloride (50 ml). The carbon tetrachloride solutions were extracted twice with hydrochloric acid (5N) in 150 ml portions, then once with aqueous sodium bicarbonate solution (50 ml); a little dried magnesium sulphate was then added and the mixture filtered and washed through with carbon tetrachloride (100 ml). The carbon tetrachloride was recovered almost quantitatively by distillation through a 25 cm Widmer column and the residue was fractionated at 15 mm pressure. MDOB (229 g) was recovered at 69—100°C (nearly all around 70°C) and the heliotropin fraction (285.2 g) at 140—146°C. This fraction was

recrystallized from a mixture of isopropanol (330 ml) and water 150 ml) with cooling finally to −20°C to yield pure heliotropin (216.3 g); m.p. 33—36°C; congealing point after melting 37°C. The mother liquors and the higher fraction on distillation contained a further 30.6 g of heliotropin and 8 g of MDOB; the total yield of heliotropin based on unrecovered MDOB was 67.5% (59% recrystallized).

WHAT WE CLAIM IS:—

1. A process for the preparation of heliotropin which comprises reacting a heliotropyl halide with an alkali metal salt of 2 - nitropropane in the presence of an alcohol having 1—6 carbon atoms.

2. A process according to Claim 1 wherein the heliotropyl halide is heliotropyl chloride.

3. A process according to Claim 1 or 2 wherein the reaction is carried out at a temperature of 20—100°C.

4. A process according to any one of Claims 1—3 wherein the alkali metal salt of 2 - nitropropane is potassium 2 - propanenitronate.

5. A process according to any one of Claims 1—4 wherein the alcohol is tertiary butanol.

6. A process according to Claim 1 substantially as hereinbefore described with reference to the Examples.

7. Heliotropin when prepared by a process claimed in any one of Claims 1—6.

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