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(54) IMPROVED PROCESS FOR THE PREPARATION OF PURE DIGOXIN MONOMETHYL ETHERS

(71) We, BOEHRINGER MANNHEIM G.M.B.H., of Mannheim-Waldhof, Germany, a corporation organised under the laws of Germany, 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:—

The present invention is concerned with an improved process for the preparation of pure digoxin monomethyl ethers.

It is known that derivatives of digoxin in which one or two hydroxyl groups of the three digitoxosyl radicals thereof are etherified by alkyl radicals containing 1 or 2 carbon atoms, are better absorbed enterally than digoxin itself and, therefore are outstandingly suitable therapeutic agents for oral administration in the treatment of human cardiac insufficiencies (see our British Patent Specification No. 1,168,970).

From animal experiments and extensive clinical observations, we have, in the meantime, ascertained that two monomethyl ethers of digoxin are of especially great value for the treatment of weakness of cardiac muscle, namely 3''' - O - methyl - digoxin and, in particular, 4''' - O - methyl - digoxin.

Both compounds are described and claimed in our above-mentioned British Patent Specification No. 1,168,970 and can be prepared by the process described therein by reacting digoxin with conventional O-methylation agents, for example with dimethyl sulphate or diazomethane, using conventional process conditions. However, when the invention was first made which is disclosed in our above-mentioned British Patent Specification the exact constitution of the digoxin monomethyl ethers was not known. Furthermore, it was not possible to restrict the methylation reaction to the monomethyl stage without the use of the poisonous and explosive diazomethane, the use of which scarcely be considered on a large scale.

In the case of conventional methylation

processes, for example, with dimethyl sulphate, digoxin polyethers are formed in considerable amounts (20—30%) but these cannot be demethylated to give digoxin or monomethyl-digoxin. This means a considerable loss of expensive starting material, which loss is increased still more because the desired monomethyl ether must be separated from the polymethyl ethers by chromatography. In the working up of the reaction mixture according to the process of our British Patent Specification No. 1,168,970, it can also happen that digitoxose is split off to give the therapeutically useless digoxigenin.

We have now found that, with the avoidance of the above-described disadvantages, the above-mentioned digoxin monomethyl ethers can be obtained in pure form by means of the known reaction of digoxin with dimethyl sulphate in dimethylformamide in the presence of barium hydroxide when, surprisingly, there is added to the reaction mixture either (a) aluminium oxide and an inert organic solvent or (b) aluminium isopropylate, and the reaction mixture, after being diluted with chloroform, is mixed with pyridine, evaporated in a vacuum and the desired product separated in from unreacted digoxin by a method in actual use or described in the literature on the subject.

The important advantages of the new process according to the present invention are that the use of diazomethane is completely avoided, polymethyl-digoxins are formed to such a minor amount that a chromatographic purification can be omitted and, by selection of the process conditions, the methylation can be directed, as desired, exclusively to the 3'''- or 4'''-hydroxyl group of the digitoxose side chain.

The process according to the present invention also reduces the cost of preparation of these valuable cardiac glycosides because the return of the separated digoxin to the methylation process ensures an almost complete conversion of the valuable digoxin start-

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Price 33p

ing material into the desired monomethyl ethers.

The elucidation of the structure of the monomethyl ethers of digoxin obtained by the process according to the present invention by partial hydrolysis with 0.05N hydrochloric acid to give digoxigenin monodigitoxoside, digoxigenin-bis-digitoxoside and digoxigenin, as well as complete acidic splitting with 0.1N sulphuric acid and detection of the cymarose and 4 - O - methyl - digitoxose split off, showed that the use, according to the process of the present invention, of aluminium oxide and an inert organic solvent results in the formation of the 4''' - O - methyl - digoxin, whereas the reaction with the use of aluminium isopropylate leads to the formation of 3''' - O - methyl - digoxin.

As inert solvent, there can be used any solvent which is miscible with dimethylformamide and which is not attacked by the dimethyl sulphate under the reaction conditions; the amount of solvent to be added must be determined from case to case. An amount corresponding to the amount of dimethylformamide used has proved to be favourable and toluene has proved to be especially useful for this purpose. Furthermore, there can also be used benzene, dioxan, chlorinated hydrocarbons, such as ethylene chloride and chloroform, or cyclohexane.

The working up and purification of the mixture obtained of digoxin monomethyl ether and unreacted digoxin can be carried out, after evaporation of the crude product in a vacuum with the addition of pyridine, by means of multiplicative partition, for example, with chloroform-carbon tetrachloride-methanol-water (1:1:1:1), the O-methyl ether of digoxin in question being obtained in pure form by evaporation of the organic phase and recrystallisation of the residue, for example from acetone. The digoxin present in the aqueous phase is extracted with chloroform and returned to another methylation reaction.

The following Examples are given for the purpose of illustrating the present invention:—

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EXAMPLE 1.

1 g. digoxin and 300 mg. aluminium isopropylate are dissolved in 8 ml. dimethylformamide and, after the addition of 580 mg. barium hydroxide, mixed at ambient temperature and while stirring, with 0.8 ml. dimethyl sulphate. Thereafter, the reaction mixture is stirred for 4 hours at ambient temperature, diluted with 50 ml. chloroform, suction filtered through kieselguhr, washed with chloroform, mixed with 4 ml. pyridine and evaporated in a vacuum. The residue is taken up in chloroform and shaken out three times with water. The collected wash waters are shaken out once with chloroform

and the combined chloroform phases, after drying over anhydrous sodium sulphate, are evaporated in a vacuum. For the separation of unreacted digoxin, the dry residue is subjected to a multiplicative partition with the phase mixture chloroform-carbon tetrachloride-methanol-water (1:1:1:1). The organic phase, after evaporation and recrystallisation of the residue from acetone, gives 510 mg. 3''' - O - methyl - digoxin; m.p. 226—229°C.

The digoxin present in the aqueous phase is extracted with chloroform and returned to a further methylation reaction.

EXAMPLE 2

100 g. digoxin are dissolved, with slight warming, in 800 ml. dimethylformamide. Thereafter, the solution is distilled with 800 ml. toluene, mixed with 60 g. barium hydroxide and 80 g. aluminium oxide (Brockmann) and, while stirring at ambient temperature, 80 ml. dimethyl sulphate in 800 ml. toluene added dropwise within the course of 60 minutes. Subsequently, the reaction mixture is stirred at ambient temperature for 20—24 hours, then diluted with 2.4 litres chloroform, suction filtered through 100 g. kieselguhr, washed with 2.4 litres chloroform, mixed with 400 ml. pyridine and evaporated in a vacuum to give a viscous residue. This is taken up in 3 litres chloroform and shaken out three times with 500 ml. amounts of water. The collected washed waters are again shaken out with 500 ml. chloroform and the combined chloroform phases are dried over anhydrous sodium sulphate and evaporated in a vacuum. Subsequently, for the separation of methyl-digoxin and digoxin, the residue is subjected to a multiplicative partition with the phase mixture chloroform-carbon tetrachloride-methanol-water (1:1:1:1). The organic phase, after evaporation and recrystallisation of the residue from acetone, yields 46 g. 4''' - O - methyl - digoxin; m.p. 226—229°C.

The digoxin present in the aqueous phase is extracted with chloroform and returned to a further methylation reaction.

WHAT WE CLAIM IS:—

1. A process for the preparation of pure 3''' - and 4''' - O - methyl - digoxin by the reaction of digoxin with dimethyl sulphate in dimethylformamide in the presence of barium hydroxide wherein either (a) aluminium oxide and an inert organic solvent are added or (b) aluminium isopropylate is added to the reaction mixture, the reaction mixture thereafter diluted with chloroform and, the addition of pyridine, evaporated in a vacuum and the residue then separated into unreacted digoxin and (a) 4''' - O - methyl - digoxin or (b) 3''' - O - methyl -

ing material into the desired monomethyl ethers.

The elucidation of the structure of the monomethyl ethers of digoxin obtained by the process according to the present invention by partial hydrolysis with 0.05N hydrochloric acid to give digoxigenin monodigitoxoside, digoxigenin-bis-digitoxoside and digoxigenin, as well as complete acidic splitting with 0.1N sulphuric acid and detection of the cymarose and 4 - O - methyl - digitoxose split off, showed that the use, according to the process of the present invention, of aluminium oxide and an inert organic solvent results in the formation of the 4''' - O - methyl - digoxin, whereas the reaction with the use of aluminium isopropylate leads to the formation of 3''' - O - methyl - digoxin.

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digoxin by a method in actual use or described in the literature on the subject.

2. Process according to claim 1, wherein the inert organic solvent used is toluene, benzene, dioxan, a chlorinated hydrocarbon or cyclohexane.

3. Process according to claim 1 or 2, wherein the final vacuum evaporation residue obtained is separated into unreacted digoxin and the methyl-digoxin by multiplicative partition.

4. Process according to claim 3, wherein the multiplicative partition is carried out with the phase system chloroform-carbon tetrachloride-methanol-water (1:1:1:1).

5. Process according to claim 4, wherein the unreacted digoxin present in the aqueous

phase is extracted with chloroform and re-used.

6. Process according to claim 1 for the preparation of pure 3'''- and 4''' - O - methyl - digoxin, substantially as hereinbefore described and exemplified.

7. 3''' - O - Methyl - digoxin, whenever prepared by the process according to any of claims 1 and 3—6.

8. 4''' - O - Methyl - digoxin, whenever prepared by the process according to any of claims 1—6.

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