die Lösung filtriert, im Reaktionsdünnschichtverdampfer i. V. eingeengt auf ca. 8 l und der Rückstand mit 24 l Wasser verdünnt und bis zur Kristallisation gerührt. Die weitere Reinigung erfolgt durch Umkristallisation aus Wasser Ausbeute 75 bis 80 % der Theorie.

Erfindungsanspruch

1. Verfahren zur Herstellung von 4-[1-Methyl-5-bis(2-chloräthyl)-benzimidazolyl-2]-buttersäure durch Reaktion von 4-[1-Methyl-5-bis-(2-hydroxyäthyl)-benzimidazolyl-2]-buttersäureestern mit Thionylchlorid und anschließende Verseifung des Esters dadurch gekennzeichnet, daß man die Reaktion bei Temperaturen von -5 bis 30 °C, bis zum vollständigen Umsatz der Hydroxyäthylgruppen führt, indem man an die bei 0 bis 5 °C durchgeführte Hauptreaktion eine 10 bis 30stündige Nachreaktion bei Temperaturen zwischen 20 bis 25 °C anschließt und daß man zum gezielten Abbruch der Reaktion das überschüssige Thionylchlorid durch Einrühren des Reaktionsgemisches in wässrige Chlorwasserstoffsäure hydrolysiert, vorzugsweise bei 15 bis 25 °C.

2. Verfahren nach Punkt 1 dadurch gekennzeichnet, daß die Nachreaktion vorzugsweise 15 bis 16 Stunden dauert.

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Method for preparing 4-[1-methyl-5-bis(2-chloroethyl)amino-benzimidazolyl-2]-butyric acid

Title of the invention

Method for preparing 4-[1-methyl-5-bis(2-chloroethyl)amino-benzimidazolyl-2]-butyric acid.

Field of the invention

The invention relates to an improved method for preparing 4-[1-methyl-5-bis(2-chloroethyl)amino-benzimidazolyl-2]-butyric acid. The compound is known as a highly effective chemotherapeutic for treating the growth of tumors.

Characteristics of the known technical solution

The preparation of 4-[1-methyl-5-bis(2-chloroethyl)amino-benzimidazolyl-2]-butyric acid results from reaction of 4-[1-methyl-5-bis-(2-hydroxyethyl)-amino-benzimidazolyl-2]-butyric acid ester with inorganic acid chlorides, preferably thionyl chloride (DDR-WP 34 727). The method provides very unsteady yields decreasing in addition by increased starting amounts. At the same it is necessary to remove excess thionyl chloride by costly distillation processes to achieve the desired purity of the final product, wherein in addition by-products formed during the reaction have to be separated by a cost intensive and labour intensive chromatographic purification on aluminium oxide.

Object of the invention

Object of the invention is the preparation of 4-[1-methyl-5-bis-(2-chloroethyl)amino-benzimidazolyl-2]-butyric acid according to a method with reproducible good yields independent of the scheduled quantity wherein on the one hand

the removal of the excessive chlorinating agent is simplified and wherein in particular the extensive chromatographical purification can be omitted.

Demonstration of the inventive subject matter

On the one hand, there was the object to reveal and delete the reasons for the highly unsteady yields and furthermore to modify the working up of the reaction mixture so that the removal of the excessive thionyl chloride and of the by-products was simplified in order to eliminate the cost intensive chromatographic purification. By extensive examination of the method according to the state of the art it was surprisingly found that the reaction was very uncompleted after the indicated reaction time and at this time only traces of the bis-chloroethyl compound were contained in the reaction mixture besides equal amounts of mono-chloroethyl compound and starting compound. Progression of the reaction occurs during distillation of the solvent leading the reaction sometimes to the right final point depending on the distillation conditions, often being uncompleted and forming an increased amount of by-products due to reaction time that was too long, respectively. A solution of the problems could not be achieved by changing the reaction times only, as no adequate conversion of the reaction was achieved using stoichometric amounts of thionyl chloride and excessive thionyl chloride caused uncontrolled preparation of by-products during distillation. Surprisingly all described problems could be solved by introducing the mixture in aqueous hydrochloric acid for stopping of the reaction. Thereby, on the one hand, excessive thionyl chloride was decomposed in non-exothermic reaction and at the same time the reaction product was dissolved in aqueous hydrochloric acid. Achieving the exact definite stopping of the reaction, the reaction with the thionyl chloride could be

conducted to a complete conversion by thin film chromatographic control. It was found that after a defined period of time of the main reaction a minimum after-reaction of 10 hours was necessary but 30 hours should not be exceeded. Particular advantageous are 16 hours. At the same time the solvent of the chlorinating reaction is distilled and contaminations precipitate in an insoluble form following the esterification of the ester group. Further processing of the hydrochloric solution can be done in a known manner. The following example indicates the preferred embodiment of the invention.

Example

4.305 kg of 4-[1-methyl-5-bis-(2-hydroxyethyl)-amino-benzimidazolyl]butyric acid ester (or the corresponding amounts of methyl, propyl or butyl ester) are dissolved in 36 l chloroform. After cooling to 0°C 2.175 kg thionyl chloride are added within 40 min maintaining the temperature at 0-5°C by cooling. It is stirred for 1 hour at the same temperature, increased to room temperature within 2.5 to 3 hours and left for 15 to 16 hours at room temperature.

The solution is dispersed by strong agitation in 37.5 l concentrated sulphuric acid decomposing excessive thionyl chloride with heavy formation of HCl and SO_2. Subsequently the chloroform is distilled and afterwards it is stirred for 3 hours at about 95°C. After addition of 0.78 kg of activated carbon it is stirred for further 30 min at 95°C, the solution is filtered, concentrated to 8 l in the thin-film evaporator and the residue is diluted with 24 l water and is stirred until crystallisation starts. The further purification is achieved by re-crystallisation from water, yielding 75 to 80% of the theory.

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