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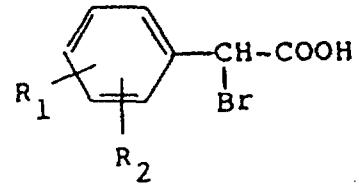
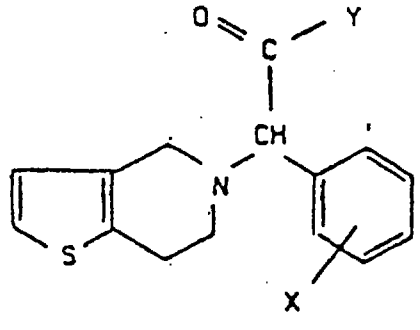
The present invention relates to a process for the preparation of thieno[3,2-c]pyridine derivatives, including clopidogrel, and the synthesising intermediates thereof, α-bromo-phenylacetic acids of formula



I

wherein R_1 and R_2, which may be identical or different, each represent a hydrogen or halogen atom. These acids are known products which are used as intermediates in the synthesis of various compounds, particularly in the pharmaceutical and agrochemical industries, possibly after esterification.

Thus, α-chloro-phenylacetic acid is used, for example, in the preparation of the semi-synthetic penicillins described in the Patent DE-A-2 624 064, antiulcerative thiazolium salts described in US-A-4 289 697, salts of thiazolo[2,3-b]thiazolium, which are metastasis inhibitors, described in US-A-4 327 221, or thieno[3,2-c]pyridine derivatives described in EP-A-99802, of formula II



II

wherein Y may represent the hydroxyl OH or the group OR

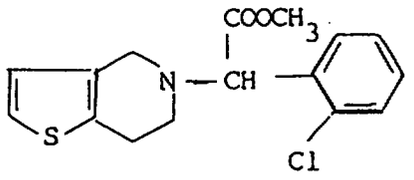
wherein R is a straight-chained or branched lower alkyl radical, or Y represents a group NR_1R_2, wherein R_1 and R_2 each independently of one another denote hydrogen or a straight-chained or branched lower alkyl group, or R_1 and R_2 together and with the nitrogen atom to which they are attached form a pyrrolidino, morpholino, piperidono or 4-benzyl-piperazino group, and X represents hydrogen, a halogen or a lower alkyl radical.

The publication J. Org. Chem. 45 (1980), pages 5214-5, describes the preparation of α-bromo-phenylacetic acid from (trihalomethyl)carbinol derivatives. The yields obtained are extremely poor and are all less than 25%.

The publication EP-0 011 279 relates to the preparation of arylacetic acid starting from an aromatic aldehyde, a trihalomethane and an alkanethiol. It is clear from the examples given in this document that the reaction is carried out at a temperature at least equal to ambient temperature.

Hitherto, the compounds of formula I have been prepared either from the corresponding phenylacetic acids by reacting with N-bromo-succinimide or with bromine, or from mandelic acid by reacting with a concentrated aqueous solution of hydrobromic acid. The phenylacetic acids themselves are prepared in a number of steps from toluene, via phenylacetonitrile as intermediate, whilst the mandelic acids may be prepared from benzaldehydes, which are reacted either with an alkali metal cyanide in a Strecker reaction in order to obtain mandelonitrile which is then hydrolysed in an aqueous medium, or with bromoform in the presence of potassium hydroxide.

These preparation methods, which involve the use of expensive or dangerous reagents, have poor yields and it was therefore desirable to find a new process for preparing, in particular, the compound of formula III

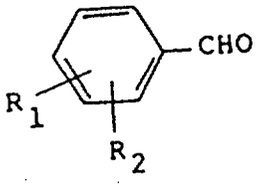


III

which inhibits platelet aggregation, under economic conditions, this compound previously having been prepared by reacting methyl alpha-chloro-(2-chloro)-phenylacetate with tetrahydrothieno[3,2-c]pyridine with moderate yields; in fact, in the course of preliminary tests, it had been found that by replacing the alpha-chloro derivative with a pure alpha-bromo derivative it was possible to increase the yield of the substitution of the heterocyclic nitrogen leading to compound III.

The invention makes it possible to prepare the compounds of formula I from the corresponding benzaldehydes in a single step and with good yields, using commercially available reagents, which can be handled without any special precautions.

In fact, according to a first aspect, the invention relates to a process for the preparation of alpha-bromophenylacetic acids (I) which consists in reacting a benzaldehyde of formula



IV

wherein R_1 and R_2 have the same meanings as in formula I, with tribromomethane and potassium hydroxide in water, in the presence of a third inert solvent, at a temperature of between -5 and +10°C.

The solvent may be a water-miscible solvent, especially an ether such as dioxane, 1,2-dimethoxyethane

or dimethoxymethane; the reaction mixture will consist of a mixture of about 50% by volume of solvent and water, but water may be added thereto during the reaction until a medium containing 90% water is obtained.

The solvent may also be a water-immiscible solvent such as an aromatic hydrocarbon, particularly benzene or toluene or an ether such as isopropyl ether. With these solvents, the reaction should be carried out in the presence of a phase transfer catalyst such as a quaternary ammonium salt, particularly a tetrabutylammonium or benzyl trimethylammonium halide or a phosphonium salt.

It is preferable to react the aldehyde and the bromoform in substantially equivalent quantities, specifically from 0.8 to 1.2 equivalents of $CHBr_3$ and in the presence of 3 to 4 equivalents of potassium hydroxide. The concentration of KOH in the aqueous medium is generally from 10 g to 50 g per 100 ml.

In order to restrict the production of acid, in particular, the reaction is carried out at a fairly low temperature, preferably between 0°C and 5°C. The reaction medium is stirred, depending on the temperature, for a period ranging from several hours to some days.

When the reaction is carried out in a homogeneous medium, at the end of the reaction the aqueous phase is washed with an immiscible solvent such as isopropyl ether or dichloromethane in order to eliminate the impurities, before acidifying and extracting the end product in a water-immiscible solvent using a conventional method. Any mandelic acid which may have formed is separated from the alpha-bromo derivative, for example by making use of the difference between their coefficients of partition between toluene and water.

The process is particularly suitable for the preparation of compounds of formula I wherein R_1 = H and

R_2 = Cl, Br or F; the yields of pure products are generally greater than 50% and frequently greater than 70%. On the other hand, it has been found that only very poor yields were obtained when the aromatic nucleus was substituted by alkyl or alkoxy groups. Similarly, it has not been possible to replace bromoform with chloroform to prepare the corresponding alpha-chloro acids under the same conditions.

The invention further relates to a process for preparing the compound of formula III and the pharmaceutically acceptable salts thereof, which consists in reacting the methylester of alpha-bromo(2-chloro)phenylacetic acid with 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in the presence of at least one equivalent of a base in a polar solvent conventionally used for this type of substitution, such as an alcohol, e.g. methanol or ethanol, a ketone, such as acetone or methylethyl ketone, an ester such as ethyl acetate, an ether such as tetrahydrofuran, or isopropyl ether, acetonitrile or dimethylformamide. The base used is preferably an alkali metal carbonate such as K_2CO_3, $NaHCO_3$ or Na_2CO_3.

At the end of the reaction, the solids are filtered and the solvent is evaporated under reduced pressure. The hydrochloride of the end product can then be prepared by reacting a concentrated aqueous solution of hydrochloric acid with the amine dissolved in ethyl acetate.

It is also possible to react the brominated acid with the nitrogenated heterocycle before esterifying the resulting product, but it is preferable to prepare the alpha-bromoester beforehand, for example by reacting the alcohol with the brominated acid in the presence of a strong acid.

In order to prepare clopidogrel (common international name), i.e. the dextrorotatory stereoisomer of the compound of formula III, the racemic

amine salts are subsequently recrystallised with an optically active acid such as camphor sulphonic acid, as mentioned in EP-A-0281459.

The following is a description of some examples of the embodiment of the invention. The products obtained are analytically pure and their physico-chemical characteristics are identical to those mentioned in the literature.

EXAMPLE 1 : α-bromo-(2-chloro)-phenylacetic acid

A solution of 100 g of 2-chloro-benzaldehyde and 198 g of tribromomethane in 60 ml of dioxane is added to a mixture of 160 g of ice, 160 g of potassium hydroxide and 100 ml of dioxane, with vigorous stirring, at a temperature of about 0°C.

After 1 hour, 1 litre of water is added and the reaction mixture is stirred for 18 hours at a temperature between 0°C and 5°C. It is then washed three times with 400 ml of cold isopropyl ether.

The aqueous phase is acidified by the addition of a concentrated aqueous solution of hydrochloric acid, before extracting twice with 400 ml aliquots of toluene. The end product is separated from the toluene phase after drying and evaporation of the solvent. After recrystallisation in toluene, 111 g of acid are isolated. Yield: 63%, based on the aldehyde.

EXAMPLES 2 to 6

Using the same procedure, the compounds listed in Table I were prepared:

TABLE I

EXAMPLE	R_1	R_2	YIELD
2	H	H	51%
3	H	Cl-4	74%
4	H	Br-2	71%
5	H	F-2	65%
6	Cl-2	Cl-4	68%

EXAMPLE 7 : α-bromo-(2-chloro)-phenylacetic acid

At a temperature below 0°C, a solution of 70.5 g of 2-chloro-benzaldehyde and 127 g of tribromomethane in 150 ml of isopropyl ether are added, with vigorous stirring, to a solution of 135 g of KOH and 12.5 g of benzyltrimethylammonium chloride in 400 ml of water.

The mixture is stirred for 26 hours at a temperature between -5°C and 0°C. Then 400 ml of water and 250 ml of isopropyl ether are added and the organic phase is separated off. After the aqueous phase has been washed with 300 ml of isopropyl ether, it is acidified by the addition of concentrated sulphuric acid and the end product is separated off by extracting twice with 400 ml aliquots of isopropyl ether. The organic solvent is then evaporated and the residue is dissolved in 300 ml of toluene; the toluene phase is washed twice with 60 ml of water and then concentrated *in vacuo* down to 60 ml. The end product slowly precipitates out in this medium.

In this way, 58.5 g of the desired acid are isolated: yield 47%.

EXAMPLE 8 : α-bromo-(2-chloro)-phenylacetic acid

To a solution of 270 g of potassium hydroxide and 34 g of tetrabutyl phosphonium bromide in 800 ml of water, is added a solution of 141 g of 2-chloro-benzaldehyde and 270 g of tribromomethane in 500 ml of ethyl ether. The mixture is kept at 0°C for 24 hours

with stirring.

After treating as in Example 2, 119 g of acid are obtained: yield 48%.

EXAMPLE 9: α-bromo-(2-chloro)-phenylacetic acid

A solution of 70.3 g of 2-chloro-benzaldehyde and 139 g of tribromomethane diluted in 50 ml of 1,2-dimethoxyethane is added, with vigorous stirring at a temperature of about -5°C, to a mixture of 131 ml of water, 114 g of potassium hydroxide (86% strength) and 50 ml of 1,2-dimethoxyethane. After 3 hours at about -5°C, 500 ml of water are added to the reaction medium at a temperature below or equal to 0°C, then the temperature is raised to +10°C and kept there for 10 hours.

The reaction mixture is then extracted four times with 95 ml of dichloromethane. The remaining aqueous phase is then acidified by the addition of concentrated hydrochloric acid and extracted twice with 100 ml aliquots of isopropyl ether. After drying and evaporation of the solvent and recrystallisation from toluene, 84.6 g of the pure acid desired are obtained: yield 67%.

A second batch can be isolated from the toluene solution, which contains a further 14.5 g of acid.

EXAMPLE 10 : Methyl α-[4,5,6,7-tetrahydro-thieno[3,2-c]-5-pyridyl]-(2-chloro)-phenylacetate

a) 55 g of α-bromo-(2-chloro)-phenylacetic acid obtained in Example 1 are dissolved in 200 ml of methanol; then 30 g of concentrated sulphuric acid are added and the medium is heated to reflux temperature, which is maintained for 4 hours.

The solvent is then eliminated under reduced pressure and 100 ml of isopropyl ether and 100 ml of water are poured onto the residue; after neutralisation, the ethereal phase is dried and concentrated and the

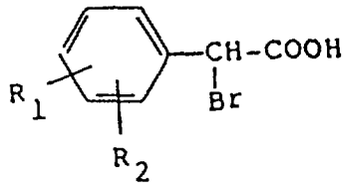
methyl ester distilled under reduced pressure to yield 53.5 g of product, which will be used as it is in the next step.

b) 7 g of pure 4,5,6,7-tetrahydro-thieno[3,2-c]-pyridine and 13.5 g of methyl α-bromo-(2-chloro)-phenyl acetate are added to 80 ml of methanol, with 6 g of sodium bicarbonate. The mixture is stirred for 6 hours at 80°C, then the solids are filtered off and the solvent is evaporated under reduced pressure.

Then 120 ml of ethyl acetate and 60 ml of water are poured onto the residue. The organic phase is decanted, washed with water and then cooled to about -10°C. A mixture of 20 g of ice and 10 ml of concentrated hydrochloric acid is then added thereto. The precipitate which forms is isolated by filtration and dried to yield 15.8 g of the hydrochloride of the desired product, which melts at 130°C.

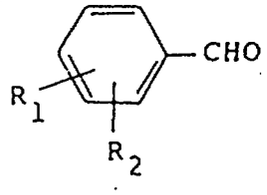
CLAIMS

1. A process for the preparation of compounds of formula I



I

wherein R_1 and R_2, which may be identical or different, each represent hydrogen or a halogen, characterised in that an aldehyde of formula



IV

wherein R_1 and R_2 have the same meaning as in formula I above, is reacted with $CHBr_3$ and KOH at a temperature between -5 and 10°C in a mixture of inert solvent and water.

2. A process according to claim 1, characterised in that R_1 is H and R_2 is 2-chloro.

3. A process according to claim 1 or claim 2, characterised in that the solvent is not miscible with water, and in that the reaction is effected in the presence of a phase transfer catalyst.

4. A process according to claim 3, characterised in that the solvent is selected from toluene and isopropyl ether.

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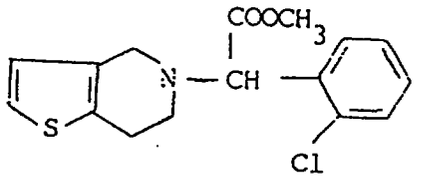
5. A process according to claim 1 or claim 2, characterised in that the solvent is an ether which is miscible with water.

6. A process for the preparation of a compound of formula III



III

comprising reacting the methyl ester of α-bromo-(2-chloro)-phenylacetic acid with 4,5,6,7-tetrahydro-thieno[3,2-c]pyridine in the presence of at least one equivalent of base in a polar solvent, characterised in that the α-bromo-(2-chloro)-phenylacetic acid is prepared according to the process of claim 1.

7. A process according to claim 6, characterised in that the base is selected from K_2CO_3, $NaHCO_3$ and Na_2CO_3.