PATENTS ACT 1949

SPECIFICATION NO 1574583

The following corrections were allowed under Section 76 on 2 March 1983:

Page 3, line 33, *for* phenyloxazole *read* phenylthiazole

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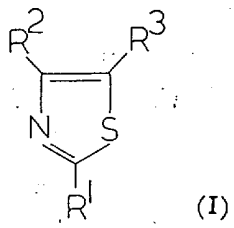
(19)

(54) PROCESS FOR PREPARING THIAZOLES

(71) We, JOHN WYETH & BROTHER LIMITED, a British Company, of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 0PH, 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 preparing a thiazole derivative having the formula



(I)

wherein R^1 and R^2 represent the same or different aryl radicals and R^3 represents a carboxyalkyl radical of up to 4 carbon atoms, or a pharmaceutically acceptable salt thereof.

The thiazole derivatives of formula I and their pharmaceutically acceptable salts are pharmaceutically useful. In particular they inhibit carrageenin-induced edema in the rat and are therefore indicated for use as anti-inflammatory agents.

Details of the pharmacology of such compounds and a method for their preparation from ketones and thioamides are reported in the Journal of Medicinal Chemistry, 1974, Vol. 17, No. 11, pages 1177 to 1181. Two such compounds are particularly noteworthy in that they were found to have an activity greater than phenylbutazone (a commercial anti-inflammatory agent) and comparable with indomethacin (another commercial anti-inflammatory agent). These two thiazole derivatives are 4 - (4 - chlorophenyl) - 2-phenylthiazole - 5 - acetic acid and 4 - (4-chlorophenyl) - 2 - (3 - methylphenyl)-thiazole - 5 - acetic acid. They were prepared by the following procedure which will be described with reference to 4 - (4 - chlorophenyl) - 2 - phenylthiazole - 5 - acetic acid as end product.

The procedure comprises:

(i) suspending 3 - (4 - chlorobenzoyl) propionic acid in diethyl ether at room temperature and adding one equivalent of bromine dropwise to form a solution containing 3-bromo - 3 - (4 - chlorobenzoyl)propionic acid;

(ii) evaporating the solvent from the solution and recrystallizing the residue from a mixture of petroleum ether of boiling point 60—80° and benzene to afford purified, solid 3 - bromo - 3 - (4 - chlorobenzoyl)propionic acid;

(iii) adding the 3 - bromo - 3 - (4 - chlorobenzoyl)propionic acid and an equimolar amount of thiobenzamide to dimethylformamide as solvent and stirring the solution for one hour at 70° whereby 4 - (4 - (4 - chlorophenyl) - 3 - phenylthiazole - 5 - acetic acid is formed in the solution; and

(iv) recovering and purifying the thiazole by cooling the solution, pouring it into water, filtering off the solid forming, washing the solid well with water, drying it and recrystallizing it from benzene to give 4 - (4 - chlorophenyl) - 2 - phenylthiazole - 5 - acetic acid as a purified solid.

The literature reference does not record the yield for the conversion of 3 - (4 - chlorobenzoyl)-propionic acid into its bromo derivative, but we have found that yields of 88% are usual. The yield for the conversion of this bromo compound into 4 - (4 - chlorophenyl) - 2 - phenylthiazole - 5 - acetic acid is reported to be 78% giving an overall yield of 69%.

The present invention is based upon the discovery that advantages can be obtained by modifying the procedure described above. In particular we have found that, by maintaining the 3 - bromo - 3 - (4 - chlorobenzoyl)-propionic acid intermediate in solution between its formation and use, instead of carrying out

step (ii) above the thiazole end product may be obtained in higher yield, for instance, a yield of about 90% for the overall procedure compared with the yield of 69% for the previous procedure.

The present invention provides a process for preparing a thiazole derivative having the formula I as defined and illustrated above or a pharmaceutically acceptable acid addition salt thereof, which comprises

(a) halogenating a ketone of the formula

$$R^2COCH_2R^3$$

(where R^2 and R^3 are as defined above) in a solvent to form an α-haloketone having the formula

$$R^2—CO—CH(Hal)—R^3$$

(where R^2 and R^3 are as defined above and Hal is a halogen atom).

(b) maintaining the α-haloketone in solution for the period from the formation of the α-haloketone until its use; and

(c) using the α-haloketone by reacting it with a thioamide having the formula

$$R^1CSNH_2$$

(where R^1 is as defined above) in a solvent to form a thiazole.

Where the thiazole obtained is in the form of an acid, the acid may be neutralised with a suitable base to form a pharmaceutically acceptable salt.

Symbols R^1 and R^2 represent the same or different aryl radicals. By the term "aryl" there is meant a monovalent radical of aromatic character including heterocyclic aromatic radicals. As examples of aryl there may be mentioned phenyl; phenyl substituted by one or two substituents selected from lower alkyl, trifluoromethyl, lower alkoxy, halogen and di(lower alkyl)amino; naphthyl; thienyl and pyridyl. R^1 and R^2 are preferably selected from phenyl, halophenyl, (lower alkoxy)-phenyl, trifluoromethylphenyl and (lower alkyl)phenyl. Symbol R^3 represents carboxyalkyl of 2 to 4 carbon atoms, preferably of 2 or 3 carbon atoms, e.g. carboxymethyl, 1-carboxyethyl or 2-carboxyethyl. R^3 preferably represents carboxymethyl. Symbol Hal represents a halogen atom, preferably bromine.

By the term "lower" as applied to such groups as alkyl or alkoxy there is meant that the group contains up to 6 carbon atoms, preferably up to 4 carbon atoms.

Step (a) of the process of the invention may be carried out in known manner, e.g. as described above, save that the α-haloketone is retained in the reaction solvent used rather than separated out as a solid and purified. As solvents for the reaction there may be used, for example, diethyl ether, methylene chloride or glacial acetic acid. Methylene chloride is preferred as solvent because then the yield of halogenation product may be very high indeed. The halogenation reaction may be carried out at ambient temperature or with moderate heating, for instance, at 30°C. We prefer to carry out the halogenation by adding one equivalent of bromine to a suspension of the ketone in a solvent. The addition should be gradual because otherwise the reaction mixture may become very exothermic.

The α-haloketone obtained by step (a) of the process of the invention is maintained in solution between steps (a) and (c). Normally the solvents used for the two reactions are different. Thus in accordance with the invention, the α-haloketone is maintained in solution whilst the solvent for the first step (a) is being removed and the solvent for the second reaction is being added. The α-haloketone can be retained in solution by various means, e.g. by distilling off the solvent used for the halogenation and simultaneous adding of a less volatile solvent. An advantage of the retention of the α-haloketone in solution between the two reactions is that it facilitates avoidance of any personal contact with the α-haloketone. Such contact is undesirable because we have discovered that 3 - bromo-3 - (4 - chlorophenyl) propionic acid, the preferred intermediate, is a skin irritant and a lachrymator.

Step (c) can be carried out in any suitable solvent. If an alcohol such as ethanol is used as the solvent, it is possible that the acid will be esterified during the thiazole formation. If this occurs the resultant ester can be converted into the desired acid or salt by an additional operation, hydrolysis or saponification. We recommend that this ester-formation be avoided because some esters have proved difficult to separate from starting materials and unwanted side products. Ester formation can be prevented by the presence of a base. In particular the reactants can be heated in isopropanol at 60°C in the presence of sodium carbonate. However, in our experience the yields arising from this procedure may be lower. It is therefore recommended to use an inert solvent for the reaction, for instance, dimethylformamide. The reaction is advantageously carried out at a temperature within the range of 50°C to 70°C.

The invention will be illustrated by the following Examples:—

EXAMPLE 1.

A 10 litre jacketed reaction vessel was equipped with stirrer, dropping funnel, thermometer and reflux condenser and was connected to a water scrubber. The reactor was charged with 4.65 litres of methylene chloride, 1.55 kilograms of 3 - (p - chlorobenzoyl)propionic acid and 15 millilitres of

hydrogen bromide in acetic acid. The suspension was stirred, heated to 30°C and a few millilitres of bromine were added. The colour was discharged within two minutes. The remaining bromine (the total being 1.224 kilogram, 395 millilitres) was added gradually over 1 to 1½ hours to give a solution of 3-bromo - 3 - (p - chlorobenzoyl)propionic acid. A small sample of the solution was taken for analysis. The yield of bromo acid was 98 to 100%.

The reactor was arranged for atmospheric distillation. The solution of the bromo acid was heated, the solvent being distilled off and replaced by 2 litres of dimethylformamide until a pot temperature of 98°C was attained. The solution of bromo acid in dimethylformamide was cooled to 60°C and a solution of 1.0 kilogram of thiobenzamide was added over 15 minutes at 50—60°C with occasional cooling as required. The reaction mixture was maintained at 50 to 60°C for 2 hours and was transferred to a 20 litre flanged top flask equipped with a stirrer. 9 litres of water was added and stirring was continued for two hours to solidify the resulting oil. The product was filtered off, washed with water (2 × 1 litre) and ethylene dichloride (2 × 250 millilitres) and was dried in an air oven at 60°C. The product was 2.16 to 2.18 kilograms of an off-white crystalline powder. The yield was 90% to 91% of 4 - (4 - chlorophenyl) - 2-phenyloxazole - 5 - acetic acid based upon the starting 3 - (p - chlorobenzoyl)propionic acid. The product can be purified by recrystallisation from ethylene dichloride.

EXAMPLE 2.

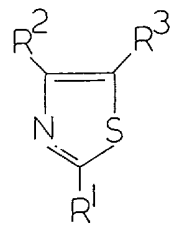
The keto acids defined below are brominated in a similar manner to Example 1 to form a bromo acid which is retained in solution prior to reaction with the thiamides defined below in a similar manner to Example 1 to form the thiazoles named.

KETO ACID	THIOAMIDE	THIAZOLE
3-(Benzoyl) propionic acid	3-Trifluoromethyl-thiobenzamide	4-Phenyl-2-(3-trifluoro-methyl)phenylthiazole-5-acetic acid, melting point 143–145°C.
3-(Benzoyl) propionic acid	4-Dimethylamino-thiobenzamide	2-(4-dimethylaminophenyl)-4-phenylthiazole-5-acetic acid, melting point 154–156°C.
3-(2-Thenoyl) propionic acid	2-Methylthio-benzamide	2-(2-Methylphenyl)-4-(2-thienyl)thiazole-5-acetic acid, melting point 136–138°C.
3-(4-Chloro-benzoyl)-propionic acid	Thionicotinamide	4-(*p*-Chlorophenyl)-2-(3-pyridyl)thiazole-5-acetic acid, melting point 238–239°C.
3-(2-Napthoyl)-propionic acid	4-Methoxythio-benzamide	2-(*p*-Methoxyphenyl)-4-(2-naphthyl)thiazole-5-acetic acid, melting point 160–162°C.
4-(4-Chloro-benzoyl)-butanoic acid	Thiobenzamide	3-[4-(*p*-Chlorophenyl)-2-phenylthiazol-5-yl] propionic acid, melting point 143–144°C.
3-(Benzoyl) propionic acid	4-Methoxy-2-methyl-thiobenzamide	2-(4-Methoxy-2-methyl-phenyl)-4-phenylthiazole-5-acetic acid, melting point 136–138°C.
3-(4-Bromo-benzoyl) propionic acid	Thiobenzamide	4-(*p*-Bromophenyl)-2-phenylthiazole-5-acetic acid, melting point 178–180°C
3-(4-Fluoro-benzoyl) propionic acid	4-Chlorothio-benzamide	2-(*p*-Chlorophenyl)-4-(*p*-fluorophenyl)thiazole-5-acetic acid, melting point 194–196°C.

The thiazole derivatives having formula I and their salts are described and claimed in our Patent No. 1,145,884.

WHAT WE CLAIM IS:—

1. A process for preparing a thiazole derivative having the formula



(I)

wherein R^1 and R^2 represent the same or different aryl radicals and R^3 represents a carboxyalkyl radical of up to 4 carbon atoms, or a pharmaceutically acceptable salt thereof, which comprises:

(a) halogenating a ketone having the formula

$$R^2COCH_2R^3$$

(wherein R^2 and R^3 are as defined above) in a solvent to form an α-haloketone having the formula

$$R^2—CO—CH(Hal)—R^3$$

(wherein R^2 and R^3 are as defined above and Hal is a halogen atom);

(b) maintaining the α-haloketone in solu-

tion for the period from the formation of the α-haloketone until its use; and

(c) using the α-haloketone by reacting it with a thioamide having the formula

$$R^1CSNH_2$$

(where R^1 is as defined above) in a solvent to form a thiazole and, if desired, a thiazole obtained in the form of an acid may be neutralised with a suitable base to form a pharmaceutically acceptable salt.

2. A process as claimed in Claim 1, where R^1 and R^2 are, independently, phenyl; phenyl substituted by one or two substituents selected from lower alkyl, trifluoromethyl, lower alkoxy, halogen and di(lower)alkylamino; naphthyl; thienyl or pyridyl and R^3 is carboxyalkyl of 2 or 3 carbon atoms.

3. A process as claimed in Claim 1, wherein R^1 is phenyl, R^2 is 4-chlorophenyl and R^3 is carboxymethyl.

4. A process as claimed in any one of Claims 1 to 3, wherein Hal is bromine.

5. A process as claimed in any one of Claims 1 to 4, wherein the solvents used for steps (a) and (c) are different and the β-haloketone is maintained in solution between its formation and use by distilling off solvent used for the halogenation and simultaneous adding of a less volatile solvent.

6. A process as claimed in any one of Claims 1 to 5, wherein methylene chloride is used as solvent for step (a).

7. A process as claimed in any one of Claims 1 to 6, wherein dimethylformamide is used as solvent for step (c).

8. A process as claimed in Claim 1, carried out substantially as described in Example 1 or 2 herein.

9. A thiazole derivative having the formula I as shown and defined in Claim 1 or a pharmaceutically acceptable salt thereof, whenever prepared by a process as claimed in any one of Claims 1 to 8.

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Agent for the Applicants.

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