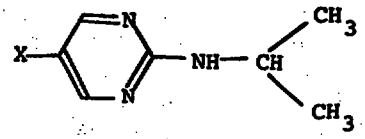
SPECIFICATION

**Isopropylamino-pyrimidine derivatives**

The invention relates to halogeno derivatives of isopropylamino-pyrimidine.

The invention provides 2-isopropylamino-5-halogeno-pyrimidines having the general formula:



in which X represents a fluorine, chlorine or bromine atom.

Those compounds in which X represents a chlorine or bromine atom may readily be prepared by reacting, preferably at room temperature and in stoichiometric proportions, 2-isopropylamino-pyrimidine with N-chloro- or bromo-succinimide in the presence of acetic acid. The yield is over 90%.

2-isopropylamino-5-fluoro-pyrimidine may be prepared by treating 2-isopropylamino-5-chloro or bromo-pyrimidine with an alkali metal fluoride, suitably potassium fluoride, preferably at 90°C for 2 to 6 hours in stoichiometric proportions.

The compounds according to the invention are useful as intermediates for the preparation of other derivatives of 2-isopropylamino-pyrimidine, such as the corresponding hydroxy derivative.

The invention is illustrated by the following Examples.

EXAMPLE 1

2-isopropylamino-5-bromo-pyrimidine

75 ml of acetic acid, 13.7 g (0.1 mole) of 2-isopropylamino-pyrimidine and 17.8 g (0.1 mole) of N-bromosuccinimide are poured into a 1 litre reaction vessel. The reaction mixture is stirred for 1 hour at room temperature and then poured into iced water. The resultant precipitate is filtered off, washed with water and dried. 20 g (yield 92%) of the title compound was obtained as a white powder melting at 90°C. Elemental analysis showed that the compound had the expected empirical formula of $C_7H_{10}N_3Br$.

EXAMPLE 2

2-isopropylamino-5-chloro-pyrimidine

Example 1 was repeated save that the N-bromosuccinimide was replaced by N-chlorosuccinimide. The title compound was obtained as a white powder in a yield of 96%. Elemental analysis showed that the compound had the expected empirical formula of $C_7H_{10}N_3Cl$.

EXAMPLE 3

2-isopropylamino-5-fluoropyrimidine

Stoichiometric proportions of 2-isopropylamino-5-bromo-pyrimidine, prepared as described in Example 1, and potassium fluoride were reacted together for 5 hours. After appropriate working up, the title compound was obtained as a white powder in a yield of 83%. Elemental analysis showed that the compound had the expected empirical formula of $C_7H_{10}N_3F$.

TOXICITY

The acute toxicity (mg/kg) of the compounds of the invention was determined on mice i.p. and per os and the values are reported in Table 1:

TABLE 1

| Compound / Route | Ex. 1 | Ex. 2 | Ex. 3 |
|---|---|---|---|
| i.p. | 310 | 325 | 460 |
| per os | 420 | 415 | 615 |

PHARMACOLOGY

The pharmacological activity of the compounds of the invention was studied by the following comparative experimentation undertaken on the regeneration of the sciatic nerve of the male adult rat (Wistar).

A lesion was made on the sciatic nerve of the rats by application of a thermosound at −20°C for 20 minutes on the nerve. The rats were then treated i.p. by the reference product or by the compounds of the invention for a predetermined duration. At the end of the treatment, the rats were sacrificed, the sciatic nerves were separated and placed in contact with a series of 70 thin parallel platinum wires (interval 1 mm) and an electric signal applied upstream the lesion point was researched on the platinum wires: the more distant wire where the signal can be collected gave the regenerated length.

Four compositions have been tested i.p.: the compounds of each of Examples 1, 2 and 3, each at the i.p. dose of 15 mg/kg and, as reference, a mixture of vitamins B1 (500 mg/kg), B6 (500 mg/kg) and B12 (5 mg/kg) which is known in the art to be the most effective composition in this field. Controls received no treatment at all. Five batches of 8 animals were used for each duration (7, 11, 14, 17 and 21 days) either for controls or for compounds 1, 2, 3 or reference mixture.

The results of this experimentation are summarized in the following Table 2 together with the figures obtained for control animals. The lengths of regenerated nerves are indicated in mm at the respective day columns as an average value of the lengths measured for all the animals of each batch. When no figure appears (17 and 21 days) this means that the regenerated length exceeded the length of the sample taken.

TABLE 2

| Duration (days) / Compound and dose i.p. | 7 | 11 | 14 | 17 | 21 |
|---|---|---|---|---|---|
| Controls | 5.4 | 10.4 | 13.0 | 17.9 | 23.0 |
| Example 1 10 mg/kg | 6.8 | 14.4 | 26.6 | – | – |
| Example 2 10 mg/kg | 6.7 | 14.4 | 26.2 | – | – |
| Example 3 10 mg/kg | 6.1 | 13.6 | 22.9 | 25.2 | – |
| B1, B6, B12 500 mg/kg, 500 mg/kg and 5 mg/kg | 8.6 | 13.5 | 16.1 | 20.9 | 24.8 |

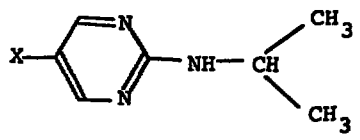
PRESENTATION—POSOLOGY

These derivatives may be presented in any therapeutically acceptable form. They may be admixed with a therapeutically acceptable diluent or carrier. A suitable presentation is in tables or in gelatine capsules containing 5 mg per dosage unit together with an excipient; for an injectable form, the product may be dosed in phials containing at least 1 mg of active ingredient in the form of its hydrochloride dissolved in water. As to the posology for human use, oral administration required from 30 mg to 1 g per diem whereas the injectable form may be administered at doses between 2 mg and 50 mg per diem. A therapeutic composition in unit dosage form may contain from 1 mg to 0.1 g of a pyrimidine derivative according to the invention. An example of a suitable table formulation is:

| | |
|---|---|
| Compound of any of the examples | 10 mg |
| Lactose | 70 mg |
| Talc | 15 mg |
| Magnesium stearate | 5 mg |
| | 100 mg |

CLAIMS

1. A compound having the general formula



in which X represents a fluorine, chlorine or bromine atom.

2. A process for the preparation of 2-isopropylamino-5-chloro or bromo-pyrimidine, the process comprising reacting 2-isopropylamino-pyrimidine with N-chloro or bromo-succinimide in the presence of acetic acid.

3. A process according to claim 2 in which the reactants are used in stoichiometric proportions and the reaction is carried out at ambient temperature.

4. A process for the preparation of 2-isopropylamino-5-fluoro-pyrimidine, the process comprising reacting 2-isopropylamino-5-chloro or bromo-pyrimidine with an alkali metal fluoride.

5. A process according to claim 4 in which the alkali metal fluoride is potassium fluoride.

6. A process according to claim 4 or claim 5 in which the reactants are used in stoichiometric proportions and the reaction is carried out at 90°C for from 2 to 6 hours.

7. A process for the preparation of 2-isopropylamino-5-chloro or bromo-pyrimidine, the process being substantially as described herein with reference to Example 1 or Example 2.

8. A process for the preparation of 2-isopropylamino-5-fluoro-pyrimidine, the process being substantially as described herein with reference to Example 3.

9. A therapeutic composition comprising a compound according to claim 1 in admixture with a therapeutically acceptable diluent or carrier.

10. A therapeutic composition according to claim 9 in unit dosage form and containing from 1 mg to 0.1 g of the compound according to claim 1.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1983. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

* C L M S *