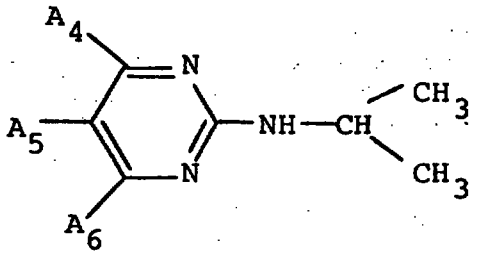
SPECIFICATION

Pyrimidine Derivatives

The invention relates to pyrimidine derivatives, to a method for their preparation, and to compositions containing them.

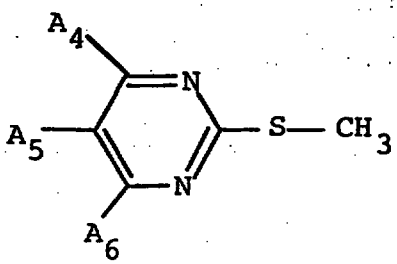
The invention provides a method for the preparation of a hydroxy derivative of 2-isopropylamino-pyrimidine of the general formula I

I



wherein each of A_4, A_5 and A_6 independently represents a hydrogen atom or a hydroxy group, with the proviso that at least one of A_4, A_5 and A_6 represents a hydroxy group, the method comprising reacting hydroxy derivatives of 2-methylthio-pyrimidine of the general formula II

II



wherein A_4, A_5 and A_6 are as above defined (including the proviso) with isopropylamine under pressure in a non-polar solvent at from 100°C to 120°C.

The compounds I as above defined are of special interest for their action in the field of nervous regeneration and for the treatment of muscular dystrophy. They are novel, with the exception of 4-hydroxy-2-isopropylamino-pyrimidine and hence the invention further provides a hydroxy derivative of 2-isopropylamino-pyrimidine of the general formula I wherein each of A_4, A_5 and A_6 independently represents a hydrogen atom or a hydroxy group, with the provisos that at least one of A_4, A_5 and A_6 represents a hydroxy group and that if only one of A_4, A_5 and A_6 represents a hydroxy group that one is A_5, and their acid addition salts.

The invention also provides 4-hydroxy-2-isopropylamino-pyrimidine or an acid addition salt thereof for use in nervous regeneration or the treatment of muscular distrophy.

Moreover, the invention also provides a therapeutical composition comprising a therapeutically effective amount of a hydroxy derivative of 2-isopropylamino-pyrimidine of the general formula I wherein each of A_4, A_5 and A_6 independently represents a hydrogen atom or a hydroxy group, with the proviso that at least one of A_4, A_5 and A_6 represents a hydroxy group or a therepeutically acceptable salt thereof in admixture with a therapeutically acceptable diluent or carrier.

The invention is illustrated by the following Examples.

EXAMPLE 1:

4-hydroxy-2-isopropylamino-pyrimidine

4-Hydroxy-2-methylthio-pyrimidine was obtained by reacting methyl iodide with 4-hydroxy-2-mercapto-pyrimidine (thiouracil) in the presence of sodium methanolate. The S-methyl-thiouracil thus obtained (20 g, 0.14 mol) was placed in a one litre pressurized reactor with 200 ml of dry toluene and 200 ml of isopropylamine. The reaction was carried on for 24 hours under pressure at 110°C to 120°C. The resulting mixture was evaporated to dryness, treated with acetone and diethyl ether (50/50), filtered, washed with water and recrystallized from isopropyl acetate. There were thus obtained 17 g (yield 84%) of a white crystalline product, insoluble in water but soluble in chloroform, melting at 140°C, elemental analysis of which showed a good correspondence with the formula $C_7H_{11}N_3O$ (molecular weight 153.18). The hydrochloride of this compound was also prepared; it was also a white crystalline product and had a melting point of 233°C to 234°C (Tottoli).

U.V. Spectral data for the base and hydrochloride were:

In water (for hydrochloride)	In Methanol (for base)
λ_{max} : 266 nm $E^{1\%}_{1CM}$ = 210	λ_{max} : 293 nm $E^{1\%}_{1cm}$ = 510
λ_{max} : 217 nm $E^{1\%}_{1cm}$ = 740	λ_{max} : 222 nm $E^{1\%}_{1cm}$ = 730
λ_{max} : 290 nm	

EXAMPLE 2:

5-hydroxy-2-isopropylamino-pyrimidine

The method described in Example 1 was repeated but 5-hydroxy-2-methylthio-pyrimidine was used instead of 4-hydroxy-2-methylthio-pyrimidine. Yield 83%. The temperature of reaction was 105°C. Melting point 161°C (Tottoli). U.V. Spectrum in water:methanol (60:40) :

λ_{max} : 341 nm $E^{1\%}_{1cm}$ = 205

λ_{max} : 241 nm $E^{1\%}_{1cm}$ = 1210

EXAMPLE 3:

4,6-dihydroxy-2-isopropylamino pyrimidine

The method described in Example 1 was repeated but 4,6-dihydroxy-2-methylthio-pyrimidine was used instead of 4-hydroxy-2-methylthio-pyrimidine. Yield 67%. Temperature of reaction 110°C. Melting point 215°C to 220°C with decomposition (Tottoli), for the hydrochloride of formula $C_7H_{11}N_3O_2$,HCl. This was a white crystalline product insoluble in water at room temperature.

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	Ex. 1	Ex. 2	Ex. 3
Route			
i.p.	200	240	260
per os	205	355	285

Pharmacology

The pharmacological activites of the compounds of the invention have been researched by the following comparative experimentation undertaken on the regeneration of the sciatic nerve of the male adult rat (Wistar).

A lesion is made on the sciatic nerve of the rats by application of a thermosound at -20°C for 20 minutes on the nerve. The rats are 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 are killed, the sciatic nerves are separated and placed in contact with a sery of 70 thin parallel platinum wires (interval 1 mm) and an electric signal applied upstream the lesion point is researched on the platinum wires: the more distant wire where the signal can be collected gives the regenerated length.

For each tested composition and each duration of treatment, a batch of 8 rats is used.

Four compositions have been tested i.p. : Example 1 compound, Example 2 compound, Example 3 compound, all at the i.p. dose of 10 mg/kg and, as a 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 Table 2 together with the figures obtained for control animals. The lengths of regenerated nerves are indicated in mm at 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 taken sample.

TABLE 2

Compound and dose i.p.	Duration (days) 7	11	14	17	21
Controls	5.1	10.2	12.8	17.8	22.4
Example 1 10 mg/kg	6.6	14.1	26.3	-	-
Example 2 10 mg/kg	6.8	14.4	26.1	-	-
Example 3 10 mg/kg	6.7	15.6	26.7	-	-
B1, B6, B12 500 mg/kg, 500 mg/kg 500 mg/kg	8.8	13.4	15.8	20.4	23.7

Presentation - Posology

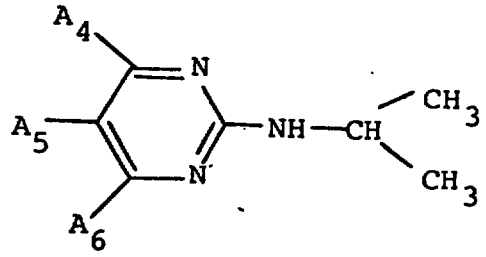
These derivatives may be presented in any therapeutically acceptable form, for instance, in tablets or in gelatine capsules containing 5 mg per dosage unit together with an excipient or in injectable form in phials containing at least 1 mg of active ingredient in the form of its hydrochloride dissolved in water. As to the posology for human use, oral administration requires from 20 mg to 1 g diem whereas the injectable form may be administered at does between 1 mg to 50 mg per diem.

An example of a suitable tablet formulation is given hereunder:

Compound of any of the Examples	5 mg
Lactose	70 mg
Talc	20 mg
Magnesium stearate	5 mg
	100 mg

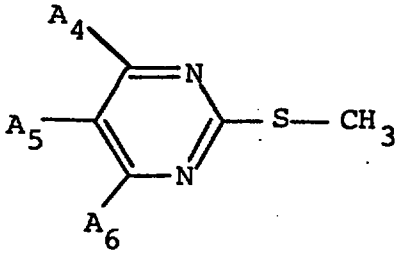
CLAIMS

1. A method for the preparation of a hydroxy derivative of 2-isopropylamino-pyrimidine of the general formula I



I

wherein each of A_4, A_5 and A_6 independently represents a hydrogen atom or a hydroxy group, with the proviso that at least one of A_4, A_5 and A_6 represents a hydroxy group, the method comprising reacting hydroxy derivatives of 2-methylthio-pyrimidine of the general formula II



II

wherein A_4, A_5 and A_6 are as above defined (including the proviso) with isopropylamine under pressure in a non-polar solvent at from 100°C to 120°C.

2. A hydroxy derivative of 2-isopropylamino-pyrimidine of the general formula I wherein each of A_4, A_5 and A_6 independently represents a hydrogen atom or a hydroxy group, with the provisos that at least one of A_4, A_5 and A_6 represents a hydroxy group and that if only one of A_4, A_5 and A_6 represents a hydroxy group that one is A_5, and their acid addition salts.

3. 5-Hydroxy-2-isopropylamino-pyrimidine or its hydrochloride.

TABLE 2

Compound and dose i.p.	Duration (days) 7	11	14	17	21
Controls	5.1	10.2	12.8	17.8	22.4
Example 1 10 mg/kg	6.6	14.1	26.3	-	-
Example 2 10 mg/kg	6.8	14.4	26.1	-	-
Example 3 10 mg/kg	6.7	15.6	26.7	-	-
B1, B6, B12 500 mg/kg, 500 mg/kg 500 mg/kg	8.8	13.4	15.8	20.4	23.7

Presentation - Posology

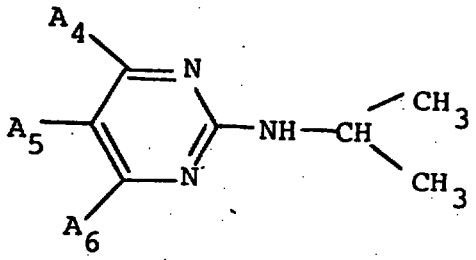
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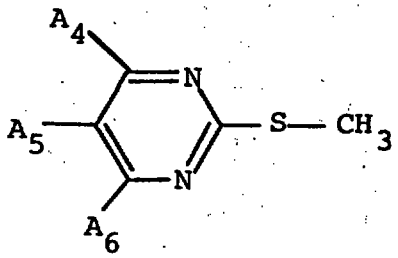
CLAIMS

1. A method for the preparation of a hydroxy derivative of 2-isopropylamino-pyrimidine of the general formula I



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wherein each of A_4, A_5 and A_6 independently represents a hydrogen atom or a hydroxy group, with the proviso that at least one of A_4, A_5 and A_6 represents a hydroxy group, the method comprising reacting hydroxy derivatives of 2-methylthio-pyrimidine of the general formula II



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wherein A_4, A_5 and A_6 are as above defined (including the proviso) with isopropylamine under pressure in a non-polar solvent at from 100°C to 120°C.

2. A hydroxy derivative of 2-isopropylamino-pyrimidine of the general formula I wherein each of A_4, A_5 and A_6 independently represents a hydrogen atom or a hydroxy group, with the provisos that at least one of A_4, A_5 and A_6 represents a hydroxy group and that if only one of A_4, A_5 and A_6 represents a hydroxy group that one is A_5, and their acid addition salts.

3. 5-Hydroxy-2-isopropylamino-pyrimidine or its hydrochloride.

4. 4,6-Dihydroxy-2-isopropylamino-pyrimidine or its hydrochloride.

5. 4-Hydroxy-2-isopropylamino-pyrimidine or an acid addition salt thereof for use in nervous regeneration or the treatment of muscular distrophy.

6. A method for the preparation of a hydoxy derivative of 2-isopropylamino-pyrimidine as defined in claim 1, the method being substantially as described herein with reference to any one of the Examples.

7. A therapeutical composition comprising a therapeutically effective amount of a hydroxy derivative of 2-isopropylamino-pyrimidine as defined in claim 1 or a therapeutically acceptable salt thereof in admixture with a therapeutically acceptable diluent or carrier.

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