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PATENT SPECIFICATION

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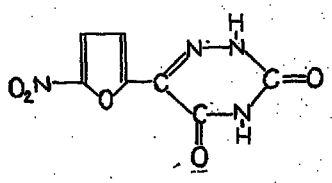
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COMPLETE SPECIFICATION

Improvements in or relating to a Derivative of Nitrofuran

We, THE NORWICH PHARMACAL COMPANY, a Company organised under the Laws of the State of New York, United States of America, of Norwich, State of New York, United States of America, 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 is for improvements in or relating to a derivative of nitrofuran, namely 5 - (5 - nitro - 2 - furyl) - 4 - azauracil having the formula:



to the preparation thereof, and to 5-(2-furyl)-4-azauracil useful as an intermediate in the preparation of said nitrofuran.

We have discovered that the said nitrofuran derivative is inimical, in small amounts, to a variety of micro-organisms as shown in the following table:

Microorganism	Minimum Inhibiting Concentration in Mg. Percent
Streptococcus pyogenes	0.2
Staphylococcus aureus	3.0
Salmonella typhosa	3.0
Escherichia coli	0.4
Salmonella choleraesuis	6.0
Pasteurella avicida	2.0
Erysipelothrix rhusiopathiae	0.8

The said nitrofuran derivative is not restricted to *in vitro* antimicrobial effects since we have found that it exerts systemic activity when administered in far less than toxic amount to animals. Mice lethally infected with *Salmonella typhosa* are protected; a total dose of 210 mg/Kg. in increments of 70 mg/Kg. spaced at 0.5, 4.5 and 8 hours after infection serves to protect 70% of the mice without manifesting any toxic effect on the host.

We have also found that the said nitrofuran derivative is remarkably resistant to metabolic destruction when ingested by animals since it appears in the urine in the amount of about 53% of the administered

[*Price 4s. 6d.*]

dose. Such urine itself shows antibacterial activity against many organisms associated with urinary tract infections.

Another valuable characteristic which is exhibited by the compound is the relative absence of emetic properties upon oral administration, thus permitting more flexible dosage without incurring rejection due to regurgitation, a response which is manifested by an appreciable percentage of sensitive subjects to which other drugs of this type have been administered. A dose of 100 mg./Kg. administered to dogs, a very emetic-sensitive species, produces vomiting in only about 50%, a relatively high tolerance at such a high drug dosage level.

The said nitrofuran derivative is readily adapted to pharmaceutical compounding and formulation in various forms such as tablets, suspensions, lozenges, capsules and the like in accordance with conventional practice in the art.

The process for the preparation of the said nitrofuran derivative comprises the nitration of 5 - (2 - furyl) - 4 - azauracil which we have found to be a particularly valuable synthetic intermediate. As nitrating agents, those acids and mixtures of acids and anhydrides may be used which are known to accomplish furan nitration without damage to the furan nucleus. Among these are mixtures of fuming or concentrated nitric acid and acetic anhydride and/or acetic acid and sulphuric acid. In the case of a concentrated nitric acid-acetic anhydride nitrating mixture, the sulphuric acid may, if desired, be present in catalytic amounts only.

The nitrated compound can be readily recovered from the nitration mixture by filtration in accordance with conventional isolation procedures.

The preferred process consists in treating the semi-carbazone of 2-furoyl formic acid with an alkaline agent such as sodium ethoxide, in an inert medium and under the influence of heat, to effect cyclization. The intermediate thus produced is nitrated with a mixture of nitric acid and acetic anhydride containing a catalytic quantity of sulphuric acid and the nitro compound, 5-(5-nitro-2-furyl)-4-azauracil, is recovered from the reaction mixture by treating it with a base, quenching and filtering.

The following illustrative example is given to illustrate the manner in which the invention may be carried into effect.

EXAMPLE

44 g. of 2-furoyl cyanide is hydrolysed with concentrated hydrochloric acid at room temperature to crude 2-furoyl formic acid by the method of Fischer Ber. *46* 892 (1913). The crude acid is dissolved in 50 ml. of ethanol and added to a solution of 44 g. of semi-carbazide hydrochloride in 450 ml. of water. The 2-furoyl formic acid semicarbazone precipitates rapidly and is collected and dried. The semicarbazone may be purified by treatment with charcoal in a solution of 100 ml. of concentrated ammonium hydroxide in 1500 ml. of water followed by precipitation with 100 ml. of concentrated hydrochloric acid. The white solid is collected, washed with water and dried at 110° C; yield—33 gms.; melting point 191° C (dec.).

20 g. of the 2-furoyl formic acid semicarbazone produced as above described in 450 ml. of propylene glycol is treated with a solution of sodium ethoxide prepared by dissolving 7.5 g. of metallic sodium in 150 ml. of ethanol. The solution is refluxed for twenty-four hours after which the solvents are removed by distillation *in vacuo*. The residual yellow solid is dissolved in 110 ml. of hot water and acidified with 30 ml. of concentrated hydrochloric acid. The solid is collected, washed well with water and dried at 75° C to constant weight giving 16.1 g. (melting point 308° C; (uncorrected, sealed tube)) of white 5-(2-furyl)-4-azauracil.

5 - (2 - furyl) - 4 - azauracil (7.2 gms.) prepared as above described is added in small increments, so as to maintain the temperature at 25—30° C, to a nitration mixture prepared by admixing 8.4 ml. 70% nitric acid containing two drops of concentrated sulphuric acid to 38 ml. of acetic anhydride. After one hour at 25—30° C, the nitration mixture is treated with 18 g. of anhydrous potassium acetate. The mixture is held at 45—50° C for one-half hour. The suspension is poured into 250 ml. of cold water. The light yellow solid is filtered, washed with water and dried at 110° C to constant weight. The yield of 5 - (5 - nitro - 2 - furyl) - 4 - azauracil is 6.4 gm.; melting point 318—319° C; (uncorrected; sealed tube). It may be recrystallised from a mixture of 1 volume of dimethylformamide and 5 volumes of nitromethane and then from acetonitrile.

	C	H	N
Calculated	37.51%	1.80%	25.00%
Found	37.71	1.92	24.88

WHAT WE CLAIM IS:—

1. A process for the production of 5-(5-nitro-2-furyl)-4-azauracil which comprises the steps of forming 5-(2-furyl)-4-azauracil by treating 2-furoyl-formyl semicarbazone with an alkaline ring-closure agent in an inert solvent under the influence of heat to cyclize said semicarbazone, and subjecting the 5-(2-furyl)-4-azauracil so formed to the action of a nitrating mixture including nitric acid whereby said 5-(2-furyl)-4-azauracil is converted into 5-(5-nitro-2-furyl)-4-azauracil.

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2. A process according to claim 1 wherein said nitrating mixture comprises concentrated nitric acid and acetic anhydride.

3. A process according to claim 1 wherein said nitrating mixture comprises concentrated nitric acid, acetic anhydride and a catalytic quantity of sulphuric acid.

4. A process according to any of the preceding claims wherein said ring-closure agent is sodium ethoxide.

5. A process according to any of the preceding claims wherein said cyclizing is effected by heating under reflux, whereafter the solvent is evaporated and the residue is dissolved in water and the furylazauracil precipitated by acidification of the solution.

6. The process for the production of 5-(5-nitro-2-furyl)-4-azauracil substantially as described in the Example.

7. 5-(2-furyl)-4-azauracil.

8. 5-(5-nitro-2-furyl)-4-azauracil.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

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