

PATENT SPECIFICATION

(11) 1290303

NO DRAWINGS

1290303

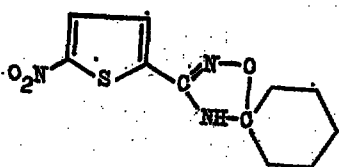
- (21) Application No. 11174/71 (22) Filed 23 April 1971
 (31) Convention Application No. 6171 (32) Filed 24 April 1970 in
 (33) Switzerland (CH)
 (45) Complete Specification published 27 Sept. 1972
 (51) International Classification C07D 99/02 A61K 27/00
 (52) Index at acceptance

C2C 170—27X—288 174—271—276 211 215 221 225 226
 22Y 246 254 255 25Y 28X 305 30Y 332 621
 671 681 708 790 79Y ML

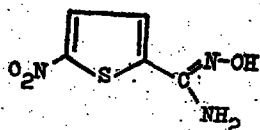


(54) A 1,2,4-OXADIAZOLINE DERIVATIVE AND A PROCESS FOR THE MANUFACTURE THEREOF

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESSELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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:—
 The present invention is concerned with a 1,2,4-oxadiazoline derivative and a process for the manufacture thereof.
 The 1,2,4-oxadiazoline derivative provided by the present invention is 3 - (5 - nitro - 2 - thienyl) - 1 - oxa - 2,4 - diazasp[4,5]dec - 2-ene which has the following formula



According to the process provided by the invention, the 1,2,4 - oxadiazoline derivative aforesaid is manufactured by reacting the amidoxime of the formula



with cyclohexanone or a ketal thereof.

The reaction parameters such as solvent, temperature, reaction time and pressure are variable in a manner which will be readily apparent to one skilled in the art. Thus, the reaction can be undertaken in an inert organic solvent or, on the other hand, in the absence of a solvent. It will, of course, be evident

[Price 25p]

that the reaction is carried out in a closed system (e.g. in an autoclave or in a bomb-tube) when a solvent whose boiling point lies below the reaction temperature is used. If the boiling point of the solvent lies in the region of the reaction temperature the reaction can be carried out under reflux conditions and if it lies above the reaction temperature it suffices just to heat to this temperature. Examples of inert organic solvents are ethers such as diisopropyl ether and tetrahydrofuran, alcohols such as methanol and ethanol, hydrocarbons such as benzene and toluene, halogenated hydrocarbons such as chloroform and dichloroethylene and highly polar solvents such as dimethylformamide.

The pressure is not a critical feature of the reaction since, as mentioned earlier, the reaction can be carried out in an open or closed system. Therefore, the reaction can be carried out at normal pressure or at an elevated pressure.

A temperature which is favourable for the reaction of the amidoxime of formula II with cyclohexanone or a ketal thereof is a temperature between 70°C and 150°C. Particularly preferred are temperatures between 90°C and 120°C. Temperatures below 20°C do not come into consideration for technical purposes since the rate of reaction then becomes too slow. Quite generally, however, an upper limit is set as regards the temperature, namely a temperature at which decomposition of the starting material and/or of the reaction product occurs.

Examples of ketals of cyclohexanone with which the amidoxime of formula II can be reacted are the lower alkyl ketals in which the alkyl group contains from 1 to 4 carbon atoms, preferably the diethyl ketal.

The 1,2,4-oxadiazoline derivative provided by this invention is useful as a medicament. It is active against protozoa, especially trypanosomes and amoebae. A particularly marked activity against *Trypanosoma cruzi*

The 1,2,4-oxadiazoline derivative and the other ingredients are well mixed in a suitable mixer. The mixture is compressed on a tableting machine to slugs of about 2.5 cm diameter and 0.8 cm thickness which are then comminuted to a granulate (about 1.2 mm). The granulate obtained is then compressed to 200 mg tablets.

Example C

Dragées of the following composition:

Core:

3-(5-Nitro-2-thienyl)-1-oxa-2,4-diazaspiro[4,5]dec-2-ene	50 mg
Mannitol	80 mg
Talc	5 mg
Corn starch	15 mg

Core weight: 150 mg

Coating mass:

Sugar	90%	} Coating weight:	150 mg
Rice starch	5%		
Talc	5%		
Core weight			150 mg
Coating weight			150 mg

Total weight: 300 mg

are prepared as follows:

The 1,2,4-oxadiazoline derivative is mixed with the mannitol and passed through a No. 5 sieve (mesh-width about 0.23 mm). The corn starch is boiled with water to give a 10% paste. The powder mixture is homogeneously ground with this paste. The slightly moist mass is granulated by means of a No. 3 sieve (mesh-width about 1.0 mm). The granulate is dried and mixed with the talc. The resulting mixture is compressed to biconvex cores of 150 mg weight. The cores have a diameter of approximately 8.0 mm.

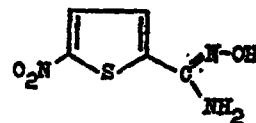
The cores are coated with sugar according to the usual dredging process using sugar syrup up to a final weight of 300 mg.

WHAT WE CLAIM IS:—

1) 3 - (5 - Nitro - 2 - thienyl) - 1 - oxa - 2,4-diazaspiro[4,5]dec-2-ene.

2) A pharmaceutical preparation comprising 3 - (5 - nitro - 2 - thienyl) - 1 - oxa - 2,4 - diazaspiro[4,5]dec - 2 - ene in association with a compatible pharmaceutical carrier material.

3) A process for the manufacture of 3-(5-nitro - 2 - thienyl) - 1 - oxa - 2,4 - diazaspiro[4,5]dec-2-ene, which process comprises reacting the amidoxime of the formula



with cyclohexanone or a ketal thereof. (II)

4) A process according to claim 3, wherein said ketal is the diethyl ketal.

5) A process for the manufacture of 3-(5-nitro - 2 - thienyl) - 1 - oxa - 2,4 - diazaspiro[4,5]dec-2-ene, substantially as hereinbefore described with reference to the foregoing Example.

6) 3 - (5 - Nitro - 2 - thienyl) - 1 - oxa - 2,4 - diazaspiro[4,5]dec - 2 - ene, when manufactured by the process claimed in claim 3, claim 4 or claim 5.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1972.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

