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RUDOLF FISCHER

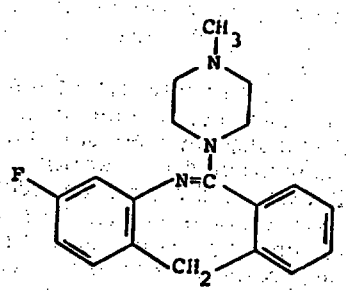
(54) A MORPHANTHRIDINE DERIVATIVE

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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:

A MORPHANTHRIDINE DERIVATIVE

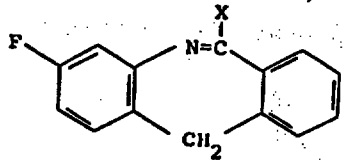
U.K. Patent Specification 1,006,156 and foreign equivalents thereof e.g. Swiss Patent No 436,308 disclose a class of morphanthridine derivatives as being indicated for use as neuroplegics, neuroleptics and analgesics having a cataleptic action. None of the compounds specifically disclosed therein has, however, found value for these indications. The present invention relates to a compound encompassed, but not disclosed nor suggested in the above patent which has surprisingly been found to have a differnt pharmacological profile indicative in particular of a non-cataleptogenic (i.e. non-classical) neuroleptic.

The present invention provides 3-fluoro-6-(4-methyl-1-piperazinyl)-morphanthridine of formula I,



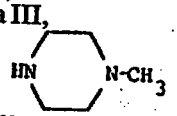
I

The present invention provides a process for the production of the compound of formula I which comprises reacting a compound of formula II,



II

wherein X is a leaving group,
with a compound of formula III,



III

The reaction may be effected in conventional manner for the production of similar compounds. X is preferably chlorine.

The process may be conveniently effected at a temperature of from 50° to 170°C in an inert organic solvent such as xylene or dioxane.

A compound of formula II may be produced in known manner from 3-fluoro-5,6-dihydromorphanthridin-6-one and may be reacted further without purification.

The free base form of the compound of formula I may be converted into acid addition salt forms in conventional manner and vice versa. Suitable acids for salt formation include hydrochloric acid or fumaric acid.

In the following Example all temperatures are in degrees Centigrade and are uncorrected.

EXAMPLE 1: 3-fluoro-6-(4-methyl-1-piperazinyl)-morphanthridine

5g 3-fluoro-5,6-dihydromorphanthridin-6-one, 80 ml phosphorus oxychloride and 2 ml N,N-dimethylaniline are boiled for 4 hours. The excess phosphorus oxychloride is distilled off in a vacuum and the residue is partitioned between ice-water and xylene. The xylene phase is washed with dilute hydrochloric acid and water. The xylene phase is dried over sodium sulphate. The resultant solution containing the imidochloride of the above lactam is concentrated to 50 ml and boiled with 6 ml N-methyl-piperazine for 4 hours.

The cooled reaction mixture is treated with water, made alkaline with concentrated sodium hydroxide solution and extracted with ether. The ether phase is washed with water and extracted with dilute hydrochloric acid. The acid phase is made alkaline and shaken with ether. The ether phase is dried over sodium sulphate, and concentrated, and petroleum ether is added when only a little volume remains whereupon the title compound in free base form of M.Pt.118°-119° crystallizes out.

The compound of formula I exhibits pharmacological activity. In particular the compound exhibits non-cataleptagenic activity as indicated in standard tests. For example in one standard test an inhibition of spontaneous motility is observed in mice on p.o. administration of from about 20 to 50 mg/kg of the compound. On the other hand the compound did not significantly induce catalepsy. Additionally the compound on administration of from 0.1 to 1 mg/kg i.p. to mice inhibits the hypermotility induced by 4,α-dimethyl-m-tyramine. Furthermore, on administration of 2 to 20 mg/kg p.o. of the compound to rats in the sleep/wake cycle test carried out in accordance with the principle of H. Kleinlogel et al European J. Pharmacol. *33*, 159-163 (1975) an increase in sleep phase II characteristic for neuroleptics is observed.

The compound is therefore indicated for use as a neuroleptic. Furthermore, the compound decreases the wake phase in the above-mentioned sleep/wake test and is therefore indicated to have sleep-promoting properties.

Additionally, the compound inhibits the catalepsy induced by tetrabenazine in rats on i.p. administration and is therefore indicated to have anti-depressant properties.

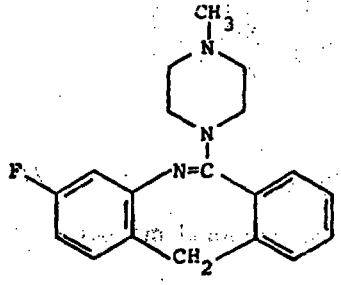
The compound also exhibits a muscle relaxing effect in rabbits on i.v. administration in the method according to Teschendorf et al., Arch.Exp.Pharmacol. *266*, 467-468 (1970) and is therefore indicated to have myotonolytic properties.

As indicated daily dosage for the preferred neuroleptic use is from 25 to 400 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 6 to about 200 mg of the compound, or in sustained release form.

The compound of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base form and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

WHAT WE CLAIM IS:-

1. A process for the production of 3-fluoro-6-(4-methyl-1-piperazinyl)-morphanthridine of formula I,



I

which comprises reacting a compound of formula II,

The process may be conveniently effected at a temperature of from 50° to 170°C in an inert organic solvent such as xylene or dioxane.

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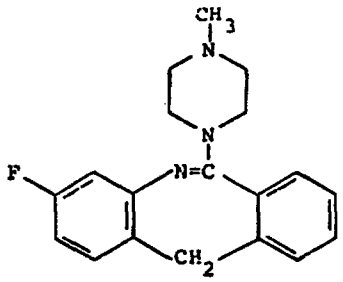
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WHAT WE CLAIM IS:-

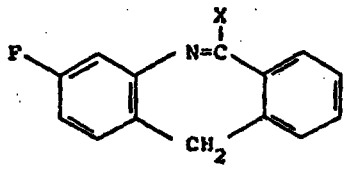
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I

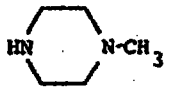
which comprises reacting a compound of formula II,

* C L M S *



II

wherein X is a leaving group,
with a compound of formula III,



III

2. A process for the production of the compound of formula I, as stated in claim 1, substantially as hereinbefore described with reference to the Example.
3. A compound of formula I, whenever produced by a process according to claim 1 or 2.
4. The compound of formula I, as defined in claim 1.
5. The compound of formula I in acid addition salt form.
6. A pharmaceutical composition comprising the compound of claim 3 or 4 in free base form, or in pharmaceutical acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

B.A. YORKE & CO.,

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