United States Patent [19]

Temperilli

[11] **3,879,554**

[45] **Apr. 22, 1975**

[54] **USE OF 1,6-DIMETHYL-8-β-(5-BROMONICOTINOYLOXYMETHYL)-10 α-METHOXYERGOLINE IN TREATING CEREBRAL AND PERIPHERAL METABOLIC VASCULAR DISORDERS**

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[73] Assignee: **Societa' Farmaceutici Italia S.p.A.**, Milan, Italy

[22] Filed: **Apr. 2, 1973**

[21] Appl. No.: **347,342**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 124,448, March 15, 1971, abandoned.

[30] **Foreign Application Priority Data**

Mar. 20, 1970 Italy 22184/70

[52] **U.S. Cl.** **424/259**; 260/285.5

[51] **Int. Cl.** **A61u 27/00**

[58] **Field of Search** 260/285.5; 424/259

[56] **References Cited**

UNITED STATES PATENTS

3,228,943 1/1966 Bernardi et al. 260/285.5

OTHER PUBLICATIONS

Arcari et al., British J. of Pharm., Nov. 1968, Vol. 34, No. 3, p. 700.

Primary Examiner—Stanley J. Friedman

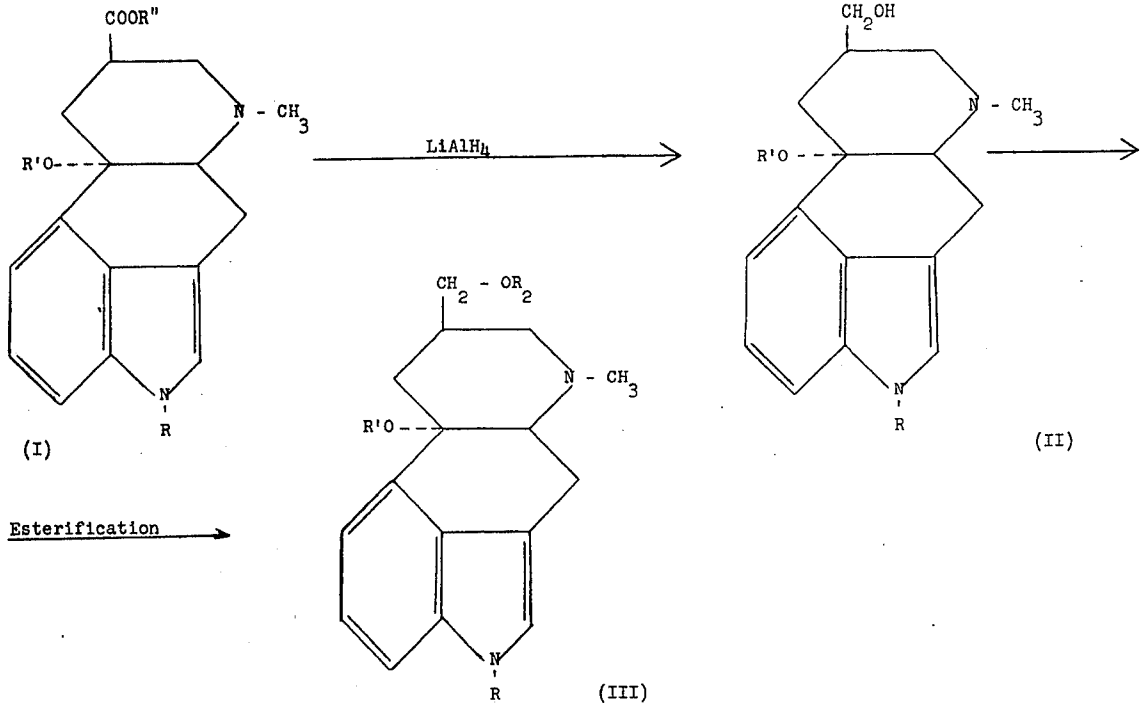
Attorney, Agent, or Firm—Hubbell, Cohen & Stiefel

[57] **ABSTRACT**

1,6-dimethyl-8 beta-(5-bromonicotinoyl-oxymethyl)-10 alpha-methoxy-ergoline, which has been given the name "Nicergoline" and constitutes a new drug active on cerebral and peripheral metabolic-vascular disorders.

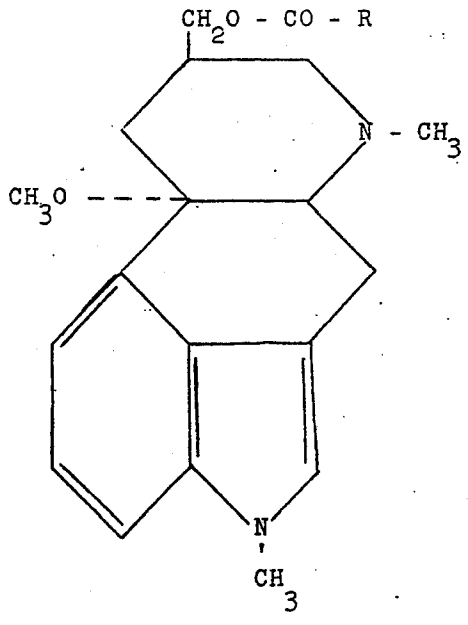
2 Claims, No Drawings

USE OF 1,6-DIMETHYL-8-β-(5-BROMONICOTINOYLOXYMETHYL)-10 α-METHOXYERGOLINE IN TREATING CEREBRAL AND PERIPHERAL METABOLIC VASCULAR DISORDERS



This is a continuation-in-part of application Ser. No. 24,448, filed March 15, 1971, now abandoned.

The present invention has among its objects new processes for using 1-methyl-lumilysergol-10-methylether esters of the formula:



(III)

wherein R is a radical selected from the group consisting of methyl, phenyl, pyridyl-(3)-, 6-methyl-pyridyl-(3)-, and 5-bromopyridyl-(3)-.

Compounds of formula III are described and claimed in U.S. Pat. No. 3,228,943 and have remarkable pharmacological activity as adrenolytic and anti-serotoninic agents. The process described in this patent is:

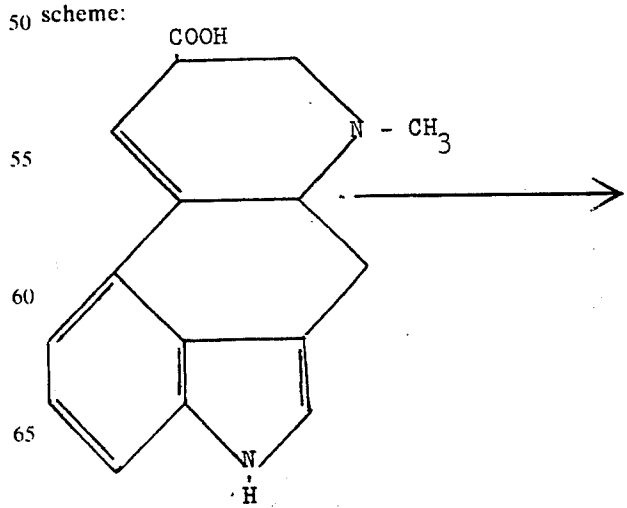
wherein $R = \begin{cases} H \\ CH_3 \end{cases}$

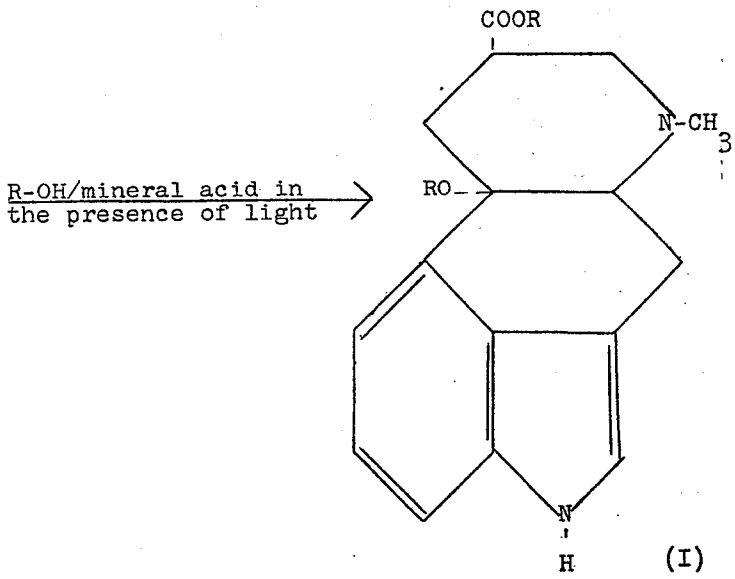
$R' = R'' = \begin{cases} H \\ \text{lower alkyl having from 1 to 4 carbon atoms} \end{cases}$

R_2 is selected from the group consisting of hydrogen and of a radical of:

A) a saturated carboxylic aliphatic acid having from 1 to 4 carbon atoms;
b) diethylcarbamic acid;
c) free benzoic acid which may be substituted by a methoxy and by a chlorine atom;
d) free or substituted nicotinic acid.

Italian Patent Application No. 16762 A/69, filed on May 13, 1969 describes a process for the preparation of lumilysergic acid derivatives according to the scheme:



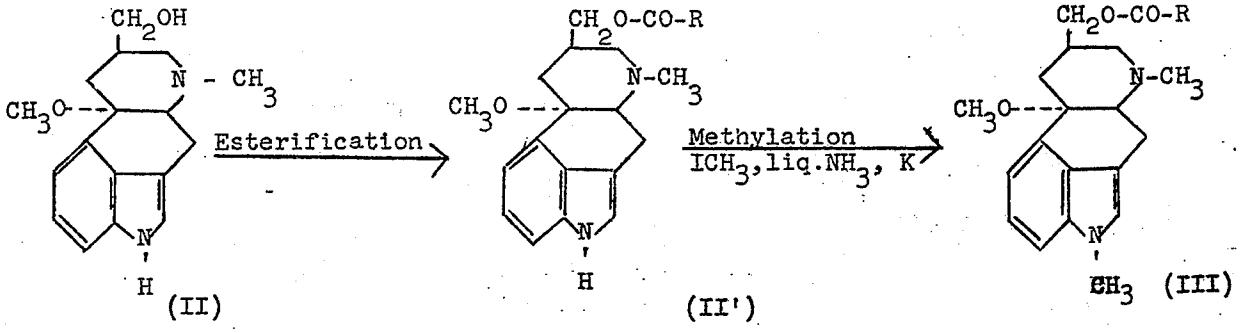


(I)

wherein R is a lower alkyl having from 1 to 4 carbon atoms.

The process allows one to obtain the important intermediate I from commercial monohydrate lysergic acid. This intermediate I, according to the process of the above-mentioned U.S. Pat. No. 3,228,943, is transformed into the useful end products III. According to the above-mentioned U.S. Pat. No. 3,228,943, the methylation step may be performed before or after the irradiation step with U.V. light in order to obtain the useful ergoline end products III having a methyl group attached to the nitrogen atom in position 1. The methylation step may be carried out by reacting the non-methylated ergolines in position 1 with methyl iodide in liquid ammonia in the presence of potassium amide.

It has now been found, and it is one of the objects of the present invention, that it is more advantageous to carry out the methylation at the end of the reaction sequence, according to the scheme:



(II) (II') (III)

wherein R is a radical selected from the group consisting of methyl, phenyl, pyridyl-(3)-, 6-methyl-pyridyl-(3)-, 5-bromopyridyl-(3)-. The esterification is substantially carried out according to the method described in the above-mentioned U.S. patent by reacting the lumilysergol-10-methylether (II) with the anhydride or chloride of an organic acid of the formula R—COOH in the optional presence of a tertiary amine such as pyridine, diethylaniline, triethylamine and the like.

Typical examples of acyl-derivatives, prepared according to the present invention are the acetic, benzoic, nicotinic, 6-methyl-nicotinic and 5-bromonicotinic acid derivatives.

Finally, the lumilysergol-10-methylether esters thus formed are methylated in position 1 of the ergolinic ring. The above-mentioned methylation is performed in a manner known "per se" by reacting the esters dissolved in liquid ammonia with methyl iodide in the presence of potassium amide.

The potassium amide is produced in the same reaction solution by dissolving metallic potassium in liquid ammonia and this solution is oxidized by treatment with ferric nitrate. Afterwards, the lumilysergol-10-methylether ester is added to a liquid ammonia solution which is treated with methyl iodide. The mixture is allowed to react for a period of from 1 to 2 hours and at a temperature of from −60° to −30°C. It is preferable to use a slight excess of potassium amide and methyl iodide.

When the reaction is over, the ammonia is evaporated and the residue is taken up with crushed ice and an organic solvent immiscible with water, such as chloroform. The desired product is contained in the organic layer. The mixture is evaporated in vacuo to dryness and the residue is recrystallized from a suitable solvent selected from the group consisting of esters and lower aliphatic ketones such as ethyl ether and acetone.

It has also been ascertained that 1,6-dimethyl-8 beta-(5-bromonicotinoyl-oxymethyl)-10 alpha-methoxy-ergoline, which is called "Nicergoline," is a new drug which displays valuable activity on cerebral and peripheral metabolic-vascular disorders.

PHARMACOLOGICAL PROPERTIES of Nicergoline

Nicergoline antagonizes the effects of exogenous and endogenous catecholamines on adrenergic receptors because of its alpha-adrenoceptor blocking activity.

The drug possesses a marked myorelaxant action on vessel walls, at the level of musculo-cutaneous vascular districts of the limbs as well as of the exo- and endocranial vessels, which causes an increase in the arterial blood flow. Peripheral vasodilatation takes place at doses which do not significantly affect the splanchnic blood flow or the most important cardiovascular parameters (systemic arterial blood pressure, heart rate, cardiac output).

Unlike hydrogenated ergot alkaloids, Nicergoline does not modify the hypertensive effects due to stimulation of hypothalamic and bulbar centers. Nicergoline clearly differs from the ergot alkaloids in that it does not cause vasoconstriction and does not have any emetic effect, even at high doses.

The drug exerts a specific antagonist action on focal cardiac necroses caused by phenylephrine.

At the brain level, under pathological hypoxic conditions, Nicergoline causes an increase in the uptake of cerebral glucose and of cerebral O_2 as well as a stimulation of brain metabolizing activity. It also acts on the energy state of the brain by favoring the conversion of adenylates into higher energy forms.

Cerebral functions are positively influenced by Nicergoline as shown by a faster recovery of EEG patterns and evoked cortical potantials in ischemic brains of cats treated with the drug. Simultaneously with the effect on the restoration of the cerebral function, a restoration of the ATPase activity of nervous cells occurs as has been revealed by biochemical examinations.

In vitro tests carried out in various animal tissues, Nicergoline causes an accumulation of cyclic AMP in the brain only, probably in connection with its stimulating action on adenylcyclase or with its blocking action of phosphodiesterase in this tissue.

Nicergoline affects the cerebral hemodynamics by decreasing vascular resistance and by increasing blood flow, while it does not interfere with the autoregulation of cerebral vessels. The effects of the drug on metabolism and on cerebral flow in animals are further confirmed by both direct and indirect results of studies carried out in man.

Nicergoline causes an increase of muscular activity, as shown by a higher resistance to muscular fatigue in the mouse.

Nicergoline inhibits in vitro, the aggregation of human platelets, induced by various aggregating agents. In animals, the antiaggregating effect is demonstrated in experimental platelet thrombosis, where the drug inhibits the formation of platelet thrombi.

In man, given at therapeutic doses by oral route, Nicergoline is able to inhibit the induced platelet aggregation.

MECHANISM OF THE ACTION of Nicergoline

Nicergoline possesses a selective blocking activity on alpha-adrenergic receptors.

It causes arteriolar vasodilatation both through a vascular mechanism and through modifications of the tissue metabolism. At the level of the brain it acts, under pathological hypoxic conditions or in the case of decreased efficiency, by activating its metabolism, by restoring the energy balance and by bringing hemodynamics toward normal. It exerts an inhibiting effect on platelet aggregation.

PHARMACOKINETICS

A comparative examination of the results obtained by Nicergoline in rats, in monkeys and in man with radioactive compounds, indicates that Nicergoline is rapidly absorbed both by the subcutaneous and the oral route with large amounts being found in the liver and in the kidney. While it rapidly disappears from the liver, where it is probably metabolized, high concentrations remain in the kidney which is the main excretory route of the metabolites of the drug. Nicergoline is fully metabolized and most of its metabolites have been identified.

CLINICAL ACTIVITY

Studies performed on over 1,000 human patients, including 259 patients checked by means of double blind trials, clearly demonstrated the usefulness of Nicergoline.

In patients suffering from subacute and chronic cerebral vasculopathies, the effects induced by Nicergoline were evaulated with various techniques, and modifications of metabolism and of cerebral hemodynamics toward the normal standard were evidenced.

Both an increase in oxygen and glucose consumption and an increase in the blood flow were observed.

Rheoencephalographic modifications of a "rejuvenation" type as well as the normalization of the radiocirculographic curve were reported.

The electroencephalograms (EEG) showing paroxysmal cuspidal anomalies were often rapidly improved.

A distinctive characteristic of Nicergoline is activity at the level of the brain under pathological conditions of a metabolic-vascular origin, where it acts with a multiple mechanism of action. In these cases, the drug causes stimulation of the metabolism of nervous cells and an increase of cerebral blood flow.

The above effects were confirmed by clinical pharmacology trials as well as by pharmacotherapy studies, in which significant improvements in the neurological, psychic and general symptomatology were reported.

More specifically an improvement of motor defects, sensorial disturbances, aphasic and dysarthric symptoms was demonstrated in subacute stroke patients. A clear improvement in the various disorders examined was also observed with regard to subjective symptomatology (cephalalgia, vertigo, ear buzzing, vision troubles, asthenia, insomnia, increased sensitivity to cold). Finally, unquestionably positive results were obtained with regard to the psycho-affective sphere: characteristic symptoms, such as impairment of concentration and thinking, loss of memory, reduced attention, personality disorders, disorientation, mental confusion, affective lability, emotivity, agitation, either subsided or totally disappeared. Remarkable prophylactic and therapeutic results were also obtained in the case of vascular cephalalgias and migraine.

Obliterative and functional peripheral arteriopathies of various nature (Burger's disease, arteriosclerosis, diabetes, Raynaud's disease) represent another field of clinical employment of Nicergoline. In this field, a clear increase in the peripheral blood flow was evidenced by trials performed with radioisotope clearance, rheography, plethysmography, morpho-oscillography and cutaneous thermometry.

Clinical therapeutic results were represented by an improvement of the muscle-cutaneous blood flow, an improvement of trophic lesions, a decrease in hypersensitivity to cold and the reduction or disappearance of the symptoms of claudicatio intermittens.

Throughout the extensive clinical trials, the drug was perfectly tolerated and proved practical to handle. Unlike other drugs possessing a vasodilating effect, Nicer-

goline does not cause orthostatic hypotension, at therapeutic doses.

Only in hypertensive patients is there a gradual and slight decrease of blood pressure values. The hypotensive effect of drugs administered simultaneously with Nicergoline can be potentiated.

Unlike dihydroergotoxine, Nicergoline has no emetic effects, even at high doses. Trials aimed at evaluating the peripheral blood flow demonstrated that Nicergoline is more active than nicotinic acid and lacks the unwanted side effects which are characteristic of that drug.

INDICATIONS FOR USE

Diffuse cerebral arteriosclerosis

Cerebral arteriosclerosis in hypertension

Cerebral arteriosclerosis in diabetes

Thrombosis and cerebral embolism (stroke) at the subacute stage

Transient cerebral ischemia

Involution syndromes of presenile age, senescence, senility

Prophylaxis of vascular cephalalgia and migraine

Peripheral vasculopathies of various etiologies (functional vasculopathies, Raynaud's disease, arteriosclerosis, diabetes, Burger's disease).

POSOLOGY

Doses of 5–10 mg of "Nicergoline" were administered three times a day orally for periods of several months, either for prophylactic or therapeutic purposes. During the first stage of treatment, that is, for a period of about 10 days, and especially for serious cases, it is advisable to administer Nicergoline by the intramuscular route, at doses of 1–4 mg distributed over a whole day.

In the case of obliterative peripheral arteriopathies, doses as high as 10–15 mg or more/day, distributed over a whole day, can be administered by the intramuscular route.

The intravenous route can be used, especially during the first stage of the treatment or according to the clinical need. Doses ranging between 1–3 mg and 10 mg can be administered by slow infusion in 100–250 ml of saline solution (one or more times a day). In special cases, the intra-arterial route was used, which, however, fails to offer the advantages of a prolonged effect.

The following examples are to illustrate the present invention without limiting it.

EXAMPLE 1

1-methyl-lumilysergol-8-(5'-bromonicotinate)- 10-methylether also known as 1,6-dimethyl-8-beta-(5-bromonicotinoyl-oxymethyl)-10-alpha-methoxy-ergoline.

1.40 g of 5-bromo-nicotinoyl chloride were added, with stirring to a solution of 0.4 g of lumilysergol-10-methylether (prepared according to Example 8 of the U.S. Pat. No. 3,228,943) in 68 ml of pyridine cooled to 0°C. The mixture was allowed to stand for 3 hours with stirring. It was then evaporated in vacuo to dryness, taken up with crushed ice and the pH was adjusted to 11 with sodium hydroxide and extracted with chloroform. The chloroform extract was washed with water and evaporated in vacuo to dryness. The residue was recrystallized from ethyl ether. 2 g of lumilysergol-10-methylether 5'-bromonicotinate melting at 195°–196°C were obtained. 0.242 g of potassium metal was dissolved in 50 ml of liquid ammonia and 0.020 g of ferric nitrate were added to catalyze the formation of potassium amide. Later 2 g of lumilysergol-10-methylether 5'-bromonicotinate, obtained as above-mentioned, were added and after 15 minutes 0.88 g of methyl iodide. After 15 minutes 0.4 g of ammonium chloride was added. The ammonia was evaporated in a nitrogen atmosphere at room temperature, the residue was taken up with crushed ice and chloroform. The chloroform layer, in which the desired product is dissolved, was separated, and then evaporated to dryness. The residue was recrystallized from ethyl ether. 1-methyl-lumilysergol-8-(5'-bromo-nicotinate)-10-methylether, also known as 1,6-dimethyl-8 beta-(5-bromonicotinoyl-oxymethyl)-10-alpha-methoxy-ergoline, was thus obtained, melting at 138°–139°C; $[\alpha]_D^{20} = -20°$ ($c = 1$ in pyridine).

EXAMPLE 2

1-Methyl-lumilysergol-8-acetate-10-methylether

Operating as described in Example 1, but employing acetyl chloride as acylating agent, 1-methyl-lumilysergol-8-acetate-10-methylether was obtained, melting at 115°–117°C; $[\alpha]_D^{20} = -10°$ ($c = 0.2$ in pyridine).

EXAMPLE 3

1-Methyl-lumilysergol-8-benzoate-10-methylether

Operating as described in Example 1, but employing benzoyl chloride as acylating agent, 1-methyl-lumilysergol-8-benzoate-10-methylether was obtained, melting at 167°–169°C; $[\alpha]_D^{20} = -40°$ ($c = 0.3$ in pyridine).

EXAMPLE 4

1-Methyl-lumilysergol-8-nicotinate-10-methylether

Operating as described in Example 1, but employing nicotinoyl as acylating agent, 1-methyl-lumilysergol-8-nicotinate-10-methylether melting at 202°–203°C was obtained; $[\alpha]_D^{20} = -12°$ ($c = 0.2$ in pyridine).

EXAMPLE 5

1-Methyl-lumilysergol-8-(6'-methylnicotinate)-10-methylether

Operating as described in Example 1, but employing 6-methyl-nicotinoyl as acylating agent, 1-methyl-lumilysergol-8-(6'-methylnicotinate)-10-methylether melting at 144°–146°C was obtained.

I claim:

1. A method of inhibiting blood platelet aggregation in the treatment of a cerebral and peripheral metabolic vascular disorder selected from the group consisting of cerebral and peripheral arteriosclerosis, Raynaud's disease, vascular cephalagia and migraine, which comprises administering to a human host an amount of the compound 1,6-dimethyl-8-β-(5-bromonicotinoyloxymethyl)-10-α-methoxyergoline effective to inhibit blood platelet aggregation.

2. A method of inhibiting blood platelet aggregation in the treatment of cerebral thrombosis, which comprises administering to a human host an amount of the compound 1,6-dimethyl-8-β-(5-bromonicotinoyloxymethyl)-10-α-methoxyergoline effective to inhibit blood platelet aggregation.

* * * * *

PO-1050
(5/69)

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,879,554 Dated April 22, 1975

Inventor(s) ALDEMIO TEMPERILLI

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Title page, left side, under "Foreign Application Priority Data": "22184/70" should read -- 22184-A/70 --.

Title page, right side, under "Abstrate" line 3: "'Nicergoline' and constitutes" should read -- "Nicergoline", constitutes --.

Column 1, line 36: "24,448" should read -- 124,448 --.

Column 1, lines 37-38: "proesses" should read -- processes --.

Column 1, line 39: "sters" should read -- esters --.

Column 2, line 40: "A)" should read -- a) --.

Column 5, line 26: "potantials" should read -- potentials --.

Column 5, line 31: "In vitro" should read -- In in vitro --.

Column 6, line 16: "evaulated" should read -- evaluated --.

Column 8, line 1: "were" should read -- was --.

Signed and sealed this 1st day of July 1975.

(SEAL)
Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents
and Trademarks