The hydrogen sulphate salt of the selective phosphodiesterase type IV inhibitor (R)-4-[2-(3-cyclopent oxyloxy-4-methoxyphenyl)-2-phenylethyl]-pyridine hydrogen sulphate salt is described. The salt possesses a number of advantageous chemical and physical characteristics making it particularly suitable for pharmaceutical formulation for use in inter alia the prophylaxis and treatment of asthma.
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(R)-4-(2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl) pyridine hydrogen sulphate salt as PDE type IV inhibitor.

This invention concerns (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt, to processes for its preparation, to pharmaceutical compositions containing it and to its use in medicine.

In our International Patent Specification No. WO 94/14742 we describe a series of tri-substituted phenyl derivatives which are potent inhibitors of the phosphodiesterase (PDE) type IV isoenzyme at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. The compounds are of use in medicine, especially in the prophylaxis and treatment of asthma.

A particularly useful member of the series is (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine, hereinafter also referred to as CT1730. In WO 94/14742 we describe the production of CT1730 as the free base (Example 16 (i)) and generally disclose salts of the compound. The production of the racemate is also described (Example 3a)), together with the production of the corresponding hydrochloride salt.

For the use in medicine of a compound such as CT1730 it is essential that a form is available which has appropriate chemical and physical characteristics which enable the easy preparation of stable pharmaceutical formulations. The free base form of CT1730 is unsuitable for this purpose, but we have now found a particular salt form of the compound which has advantageous chemical and physical characteristics. The salt is particularly suitable for pharmaceutical formulation, especially when compared to other salt forms of CT1730.

Thus according to one aspect of the invention we provide (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt.
The hydrogen sulphate salt of the invention possesses a number of advantageous chemical and physical characteristics. In particular, it is (1) highly crystalline; (2) thermally stable; (3) non-hygroscopic, and (4) soluble in aqueous solutions over a wide range of concentrations. In addition, it is readily prepared free of solvent and other impurities.

All of these properties provide the salt of the invention with easy preparation, handling, purity and stability characteristics which make it a particularly suitable form for pharmaceutical formulation. In contrast, other salt forms of CT1730, particularly the hydrochloride, hydrobromide, hydroiodide, methanesulphonate, p-toluene-sulphonate, besylate, phosphate, sulphate, nitrate, maleate and fumarate, lack one or more of these properties and are unsuitable for formulation.

The salt according to the invention may be prepared from the corresponding CT1730 free base or a salt thereof. Thus, according to a further aspect of the invention, we provide a process for the preparation of (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt which comprises reacting (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine or a salt thereof with sulphuric acid.

The reaction may be performed in any suitable solvent or mixtures of solvents. Particular solvents include alcohols, such as ethanol or isopropyl alcohol, and aromatic hydrocarbons such as benzene and toluene. In general, the reaction may be performed at around ambient temperature or above, for example up to around 50°C.

In this reaction, the starting material is preferably the free base. However another salt may be used, or if desired a mixture of the free base and the other salt.

The free base or salt starting materials for this reaction may be prepared by the methods described in International Patent Specification No. WO 94.14742, or in our International Patent Application No. PCT/GB
94/02799. In these applications the free base is described as above or as
(+)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine.

The salt according to the invention is a selective and potent inhibitor of
PDE IV. The ability of the compound to act in this way may be simply
determined by the tests described in the Examples hereinafter.

The salt according to the invention is thus of particular use in the
prophylaxis and treatment of human diseases where an unwanted
inflammatory response or muscular spasm (for example bladder or
alimentary smooth muscle spasm) is present and where the elevation of
cAMP levels may be expected to prevent or alleviate the inflammation and
relax muscle.

Particular uses to which the salt of the invention may be put include the
prophylaxis and treatment of asthma, especially inflamed lung associated
with asthma, cystic fibrosis, or in the treatment of inflammatory airway
disease, chronic bronchitis, eosinophilic granuloma, psoriasis and other
benign and malignant proliferative skin diseases, endotoxic shock, septic
shock, ulcerative colitis, Crohn's disease, reperfusion injury of the
myocardium and brain, inflammatory arthritis, chronic glomerulonephritis,
atopic dermatitis, urticaria, adult respiratory distress syndrome, diabetes
insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis,
arterial restenosis and atherosclerosis.

The salt of the invention also suppresses neurogenic inflammation through
elevation of cAMP in sensory neurones. It is, therefore, analgesic, anti-
tussive and anti-hyperalgesic in inflammatory diseases associated with
irritation and pain.

The salt according to the invention may also elevate cAMP in lymphocytes
and thereby suppress unwanted lymphocyte activation in immune-based
diseases such as rheumatoid arthritis, ankylosing spondylitis, transplant
rejection and graft versus host disease.
The salt according to the invention have also been found to reduce gastric acid secretion and therefore can be used to treat conditions associated with hypersecretion.

The salt of the invention suppresses cytokine synthesis by inflammatory cells in response to immune or infectious stimulation. It is, therefore, useful in the treatment of bacterial, fungal or viral induced sepsis and septic shock in which cytokines such as tumour necrosis factor (TNF) are key mediators. Also the salt of the invention suppresses inflammation and pyrexia due to cytokines and is, therefore, useful in the treatment of inflammation and cytokine-mediated chronic tissue degeneration which occurs in diseases such as rheumatoid or osteo-arthritis.

Over-production of cytokines such as TNF in bacterial, fungal or viral infections or in diseases such as cancer, leads to cachexia and muscle wasting. The salt of the invention ameliorates these symptoms with a consequent enhancement of quality of life.

The salt of the invention also elevates cAMP in certain areas of the brain and thereby counteract depression and memory impairment.

The salt of the invention suppresses cell proliferation in certain tumour cells and can be used, therefore, to prevent tumour growth and invasion of normal tissues.

For the prophylaxis or treatment of disease the salt according to the invention is particularly suitable for formulation as a pharmaceutical composition. Thus according to a further aspect of the invention we provide a pharmaceutical composition which comprises (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phénylethyl]pyridine hydrogen sulphate salt together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.
Advantageously, the compositions may be prepared using conventional procedures and thus the invention further provides a process for the preparation of a pharmaceutical composition containing (R)-4-[2-(3-cyclopentoxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt together with one or more pharmaceutically acceptable carriers, excipients or diluents which comprises the step or steps of bringing into contact (R)-4-[2-(3-cyclopentoxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt with one or more pharmaceutically acceptable carriers, excipients or diluents

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The salt according to the invention may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations
for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the salt according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the salt according to the present invention is conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of the salt of the invention required for the prophylaxis or treatment of a particular inflammatory condition will vary depending on the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg, e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The following Examples illustrate the invention.
EXAMPLE 1
(R)-4-[2-(3-Cyclopentylxoy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt

(R)-4-[2-(3-Cyclopentylxoy-4-methoxyphenyl)-2-phenylethyl]pyridine

(14.5g, 39mmol; prepared as described in International Patent Application No. PCT/GB94/02799 was dissolved in warm ethanol (150ml) and the clear solution then cooled to room temperature. Concentrated sulphuric acid (3.3ml, 60mmol) was added with swirling over one minute, followed by a few seed crystals. The solution was allowed to stand at room temperature for 1.5 hours during which time needle-like crystals steadily developed. The solution was then left at 40°C overnight to maximise yield. The resulting product was warmed to room temperature and the crystalline product was collected by suction filtration with t-butylmethyl ether washing. Once sufficiently dry, the product was transferred to a vacuum oven and heated in vacuo to dryness (65°C, ~0.05mbar, overnight) to afford the title salt as a white crystalline powder (16.2g); m.p. 144-146°C; Found C, 63.72; H, 6.15; N, 2.97. C_{25}H_{29}NO_{6}S requires C, 63.68; H, 6.20; N, 2.97%.

The title salt (3.3g) was recrystallised (with slow cooling to room temperature, then leaving at room temperature for 2 hours) from absolute ethanol (~40ml). The resulting white needles were filtered, washed with diethyl ether and dried at 75°C at 0.05mbar overnight.

EXAMPLE 2
This example shows the formulation of granules containing (R)-4-[2-(3-cyclopentylxoy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt (referred to in this example as 'Active Ingredient'):

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<td>0.2210g</td>
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<td>Maize Starch BP</td>
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<td>Purified Water</td>
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<td>Colloidal silica (Aerosil 200)</td>
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<td>2.993g</td>
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The granules were used to either fill capsules, or were compressed into tablets.

5 **EXAMPLE 3**
The activity and selectivity of the salt according to the invention was demonstrated in the following tests. In these tests the abbreviation FMLP represents the peptide N-formyl-met-leu-phe.

10 **Isolated Enzyme**
The potency and selectivity of the salt of the invention was determined using distinct PDE isoenzymes as follows:

i. PDE I, rabbit heart

ii. PDE II, rabbit heart

iii. PDE III, rabbit heart, Jurkat cells

iv. PDE IV, HL60 cells, rabbit brain, rabbit kidney and human recombinant PDE IV

v. PDE V, rabbit lung, guinea pig lung

20 A gene encoding human PDE IV has been cloned from human monocytes (Livi, et al., 1990, Molecular and Cellular Biology, 10, 2678). Using similar procedures we have cloned human PDE IV genes from a number of sources including eosinophils, neutrophils, lymphocytes, monocytes, brain and neuronal tissues. These genes have been transfected into yeast using an inducible vector and various recombinant proteins have been expressed which have the biochemical characteristics of PDE IV (Beavo and Reifsnyder, 1990, TIPS, 11, 150). These recombinant enzymes, particularly the human eosinophil recombinant PDE IV, have been used as the basis of a screen for potent, selective PDE IV inhibitors.

30 The enzymes were purified to isoenzyme homogeneity using standard chromatographic techniques.

35 Phosphodiesterase activity was assayed as follows. The reaction was conducted in 150μl of standard mixture containing (final concentrations):
50 mM 2-[(tris(hydroxymethyl)methyl)amino]-1-ethane-sulphonic acid (TES) -NaOH buffer (pH 7.5), 10 mM MgCl₂, 0.1 μM [³H]-cAMP and vehicle or various concentrations of the test compounds. The reaction was initiated by addition of enzyme and conducted at 30°C for between 5 to 30 mins. The reaction was terminated by addition of 50 μl 2% trifluoroacetic acid containing [¹⁴C]-5'AMP for determining recovery of the product. An aliquot of the sample was then applied to a column of neutral alumina and the [³H]-cAMP eluted with 10 ml 0.1 TES-NaOH buffer (pH8). The [³H]-5'-AMP product was eluted with 2 ml 2 M NaOH into a scintillation vial containing 10 ml of scintillation cocktail. Recovery of [³H]-5'AMP was determined using the [¹⁴C]-5'AMP and all assays were conducted in the linear range of the reaction.

The salt according to the invention causes a concentration-dependent inhibition of recombinant PDE IV at 0.1 - 1000 nM with little or no activity against PDE I, II, III or V at concentrations up to 100 μM.

2. **The Elevation of cAMP in Leukocytes**

The effect of the salt of the invention on intracellular cAMP was investigated using human neutrophils or guinea pig eosinophils. Human neutrophils were separated from peripheral blood, incubated with dihydrocytochalasin B and the test compound for 10 min and then stimulated with FMLP. Guinea pig eosinophils were harvested by peritoneal lavage of animals previously treated with intraperitoneal injections of human serum. Eosinophils were separated from the peritoneal exudate and incubated with isoprenaline and test compound. With both cell types, suspensions were centrifuged at the end of the incubation, the cell pellets were resuspended in buffer and boiled for 10 min prior to measurement of cAMP by specific radioimmunoassay (DuPont).

The salt according to the invention induced a concentration-dependent elevation of cAMP in neutrophils and/or eosinophils at a concentration of 0.1 nM.

3. **Suppression of Leukocyte Function**
The salt of the invention were investigated for its effects on superoxide generation, chemotaxis and adhesion of neutrophils and eosinophils. Isolated leukocytes were incubated with dihydrocytochalasin B for superoxide generation only and test compound prior to stimulation with FMLP. The salt according to the invention caused a concentration-dependent inhibition of superoxide generation, chemotaxis and adhesion at a concentration of 0.1nM.

4. **Adverse Effects**

The salt according to the invention is free from adverse effects following repeated overdosage to rats or dogs.
CLAIMS

1. (R)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt.

2. A pharmaceutical composition comprising (R)-4-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt together with one or more pharmaceutically acceptable carriers, excipients or diluents.

3. A process for the preparation of (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine hydrogen sulphate salt which comprises reacting (R)-4-[2-(3-cyclopentyloxy-4-methoxyphenyl)-2-phenylethyl]pyridine and/or a salt thereof with sulphuric acid.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/30 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
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  * O* document referring to an oral disclosure, use, exhibition or other means
  * P* document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search
20 September 1995

Date of mailing of the international search report
2. 10. 95

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