PATENT SPECIFICATION

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Complete Specification entitled (54) 6α-METHYL-PREDNISOLONE DERIVATIVES, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

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The following statement is a full description of this invention, including the best method of performing it known to us:

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This invention relates to 6α-prednisolone derivatives and is more especially concerned with sulpho derivatives of 6α-prednisolone as well as processes for their preparation and pharmaceutical compositions containing these derivatives as active ingredients.

The present invention provides 6α-methylprednisolone derivatives, characterized in that they correspond to formula I in which M represents a hydrogen atom or an alkali-metal atom. Examples of suitable compounds according to formula I are 6α-methylprednisolone-21-sulphoesters such as 6α-methylprednisolone-lithium-21-metasulphobenzoate.

The present invention also provides a process for preparing the derivatives defined by formula I, process which comprises reacting a functional derivative of methanesulphonic acid with 6α-methylprednisolone, to obtain the product of formula II and then reacting the product of formula II so obtained with an m-sulphobenzoic acid dialkaline salt in the presence of an alkylamide and either (a) isolating the product of formula I thus obtained in which M represents an alkali-metal atom, or (b) passing the said product of formula I over an ion exchange resin, used in acid form so as to obtain the product of formula I in which M represents a hydrogen atom and then, if desired, reacting the latter product with an alkali-metal hydroxide or an alkaline carbonate so as to obtain the product of formula I in which M represents an alkali-metal atom.
One example of a preferred process for preparing the derivatives of formula I described above, is as follows:

a) 6α-methylprednisolone is dissolved in pyridine, and cooled to a temperature of about -10°C and methanesulphonyl chloride is added. This solution is refluxed for a few minutes and 6α-methylprednisolone 21-methysulphonate is collected.

b) The 6α-methylprednisolone 21-methysulphonate obtained from step (a) is heated with metasulphobenzoic acid disodium salt in the presence of a dialkylamide such as dimethylformamide and 6α-methylprednisolone-sodium-21-metasulphobenzoate is then collected.

c) The 6α-methylprednisolone-sodium-21-metasulphobenzoate obtained from step (b) is suspended in water, an acid ion exchange resin is added and the suspension is filtered. The filtrate is collected and contains the product of formula I in which M represents a hydrogen atom, this latter product is isolated if desired, or the filtrate is made alkaline using an alkali-metal hydroxide and the product is collected and has the formula I in which M represents an alkali-metal atom.

The derivatives of formula I possess very valuable pharmacological and more specifically anti-inflammatory, properties. Because of these remarkable properties the derivatives of formula I are very useful in human therapeutics, more specifically in the treatment of inflammatory manifestations of rheumatic or arthritic origin.
The usual dose, variable according to the product used, the subject treated and the infirmity concerned, can be for example from 2 to 100 mg. per day, by injectable route in a man.

The invention according to a further aspect includes pharmaceutical compositions containing as active principle at least one of the products of formula I and more specifically includes injectable aqueous solutions of these products.

These pharmaceutical compositions of this invention are formulated in such a way that they can be administered by digestive, parenteral or local routes. They can be solids or liquids and may be prepared in currently used pharmaceutical acceptable forms such as for example plan or sugar-coated compressed tablets, lozenges, granules, suppositories, injectable preparations, ointments, creams, gels; they are prepared according to the usual methods.

The active principle or principles can be incorporated with excipients normally used in these pharmaceutical compositions, such as talc, gum acacia, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, diverse wetting, dispersing or emulsifying agents, conservatives.

The new 6α-methylprednisolone derivatives of formula I present important advantages. On the one hand they are easily
soluble in water, but above all, whilst retaining pharmacological
activity of known water soluble 6α-methylprednisolone derivatives
possess imposed stability in aqueous solution over known
compounds. We have thus established that in 1.5% aqueous
solutions of 6α-methylprednisolone-lithium-21-metasulphobenzoate,
heated to 100°C for 6 hours, the concentration of free 6α-
methylprednisolone shows no notable increase, whilst for
example in 1.5% aqueous solutions of 6α-methylprednisolone
hemisuccinate sodium salt, heated in the same conditions, the
concentrations of free 6α-methylprednisolone showed an increase
of about 50%. (Additionally we will show further on in the
description that the two aforesaid 6α-methylprednisolone
derivatives present an activity of the same kind).

Preferred pharmaceutical compositions in accordance
with this invention are aqueous solutions and more specifically
aqueous injectable solutions containing 6α-methylprednisolone-
lithium-21-metasulphobenzoate. One example of a suitable
aqueous solution is one which contains 6α-methylprednisolone-
lithium-21-metasulphobenzoate, propyleneglycol, lithium benzoate
and water.

The invention will now be more fully described in the
following non-limitative example.

Example I : 6α-methylprednisolone- and lithium-21-metasulpho-
benzoate :

Stage A : 6α-methylprednisolone-sodium 21-metasulphobenzoate
A mixture of 6 g. of monosodium metasulphobenzoate and 6 ml. of water is heated to 90°C - 95°C while agitating and 2.45 g. of sodium bicarbonate added, then 160 ml. of dimethylformamide are added and the mixture distilled while agitating until the boiling point remains constant at 150°C - 151°C, the suspension is cooled to 95°C, under an atmosphere of nitrogen 10 g. of 6α-methylprednisolone-21-methylsulphonate are added the mixture agitated for 5 hours at 95°C - 100°C, and evaporated to dryness under vacuum, the residue is taken up with 30 ml. of ethanol and evaporated to dryness under vacuum.

The residue is made into a paste in a heated state in 60 ml. of ethyl acetate and refluxed for 10 minutes. The residue is vacuum filtered and washed with ethyl acetate and dried under vacuum; the sodium salt is once again recrystallized from water. After drying under vacuum at 50°C, then at ambient temperature, one obtains 10.04 g. of 6α-methylprednisolone-sodium-21-metasulphobenzoate, in the form of colourless crystals, soluble in methanol, slightly soluble in water, melting at a temperature higher than 260°C; its rotatory power is : (α)° = +149° (c = 1% methanol).

**Analysis** : \( C_{29}H_{34}O_9Na \) = 580.63

**Calculated** : C% 60.0  H% 5.73  S% 5.52

**Found** : 60.4  5.4  5.5

**U.V. Spectrum - Methanol** :

Max. at 235 nm \( \varepsilon 1\%_{1cm} = 405 \)
Flame spectrum:
Na% = 4.10 - 4.14 (theory: 3.95)

Stage B: 6α-methylprednisolone-lithium-21-metasulphobenzoate

5 g. of 6α-methylprednisolone-sodium-21-metasulphobenzoate is suspended in 125 ml. of water, agitated for a few minutes, 25 c.c. of activated Dowex 50 resin acid form is added and agitated for 40 minutes; the solution is poured on to a column containing 65 ml. of activated Dowex 50 resin acid form, the (pH = 1 to pH = 3) liquid is collected and cooled, 15.3 ml. of N/2 aqueous solution of lithium hydroxide is added to the acid phase obtained, while agitating and it is evaporated to dryness; the residue is suspended in 10 ml. of n-butanol admixed with 0.25 ml. of water and heated under agitation; the temperature is brought back to 30°C, filtered, the limpid filtrate is brought to +10°C and crystallization started. The mixture is left to stand for one night at +5°C then for one hour at 0°C and vacuum-filtered; the precipitate is washed with ice-cooled n-butanol, dried under vacuum then in an oven at 85°C and finally under vacuum; there is obtained 2.35 g. of 6α-methylprednisolone-lithium-21-metasulphobenzoate in the form of colourless crystals, soluble in water and methanol, melting at a temperature higher than 260°C, its rotatory power is:

(α) 20° = 153° (c = 1%, methanol).

Analysis: C29H30O9SLi = 564.58
Calculated: S% 5.68 Li% 1.23
Found: 5.6-5.8 1.16-1.16
U. V. Spectrum - Methanol:

Max. at 235 nm

$E_{1\%}^{1cm} = 428$

The 6α-methylprednisolone-21-methylsulphonate can be prepared as follows:

There is dissolved 10 g. of 6α-methylsulphonate (3,20-dioxo 6α-methyl 11β,17α,21-trihydroxypregna 1,4-diene) in 40 ml. of pyridine, under agitation, which is cooled to -10°C and 4.96 g. of methanesulphonyl chloride is added while agitating for one hour 45 minutes at -10°C, this is poured into a mixture of 75 g. of ice and 250 ml. of a 280 g/litre aqueous solution of sodium acid sulphate and agitated for 30 minutes; precipitate is vacuum filtered and washed with water till absence of sulphate and dried under vacuum.

There is refluxed for 5 minutes 11.3 g. of residue with 56 ml. of 80% ethanol under agitation; this is brought back to ambient temperature and the mixture is kept at this temperature for 30 minutes, vacuum-filtered, the precipitate is washed with ethanol containing 80% water, and dried under vacuum; there is obtained 10.44 g. of 6α-methylprednisolone-21-methylsulphonate.

The product is in the form of colourless crystals, soluble in acetone, insoluble in water, melting at 248°C - 249°C; its rotatory power is: $(\alpha)_D^{20} = +83.5^\circ$ (c = 1%, acetone).

Analysis: $C_{23}H_{32}O_7S = 452.57$

Calculated: C% 61.04  H% 7.13  S% 7.05

Found: 60.8  7.0  6.9
Example of injectable solution containing 2% 6α-methyl prednisolone
6α-methylprednisolone- and lithium-21-meta-
sulphobenzoate quantity corresponding to:
6α-methylprednisolone .................................. 20 g.
lithium benzoate ...................................... 200 mg.
propyleneglycol ......................................... 300 ml.
water .................................................. q.s. 1000 ml.

The 6α-methylprednisolone-lithium-metasulphobenzoate
and the lithium benzoate are dissolved in the water/propylene-
glycol mixture, which is filtered with Sartorius membrane of
porousness about 0.250 μ and divided into ampoules of 3 ml. and
sterilised for one hour at 120°C.
Example of compressed tablets
Compressed tablets are prepared in accordance with
the following formula:
6α-methylprednisolone- and lithium-21-meta-
sulphobenzoate ........................................ 50 mg.
excipient q.s. for 1 compressed tablet made up to .... 200 mg.
(detail of excipient: lactose, starch, talc, magnesium
stearate).
The claims defining the invention are as follows:

1. 6α-methylprednisolone derivatives of formula I in which M represents a hydrogen atom or an alkali metal atom.
2. 6α-methylprednisolone-lithium-21-metasulphobenzoate.
3. Process for preparing the derivatives defined by formula I of claim 1, which comprises reacting a functional derivative of methanesulphonic acid with 6α-methylprednisolone so as to obtain the product of formula II, reacting the product of formula II thus obtained with an m-sulphobenzoic acid dialkaline salt in the presence of a dialkylamide and either (a) isolating the product of formula I thus obtained in which M represents an alkali metal atom, or (b) passing the said product of formula I over an ion exchange resin, used in acid form, so as to obtain the product of formula I in which M represents a hydrogen atom, and also if desired, reacting this latter product with an alkali metal hydroxide or an alkaline carbonate so as to obtain the product of formula I in which M represents an alkali metal atom.
4. Process according to claim 3, wherein the m-sulphobenzoic acid dialkaline salt is a disodium salt, that the dialkylamide is dimethylformamide and that the alkali-metal hydroxide is lithium hydroxide.
5. Pharmaceutical compositions, characterized in that they contain as active principle one at least of the derivatives of formula I of claim 1.
5. Pharmaceutical compositions according to claim 5, containing as active ingredient 6α-methylprednisolone-lithium-21-metasulphobenzoate, a pharmaceutically acceptable carrier or a propellant.

7. Aqueous injectable solution, comprising 6α-methylprednisolone-lithium-21-metasulphobenzoate.

8. Aqueous injectable solution, characterized in that it contains 6α-methylprednisolone-lithium-21-metasulphobenzoate, propylene glycol and lithium benzoate.

D A T E D  this 16th day of May, 1973.

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