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PATENT SPECIFICATION

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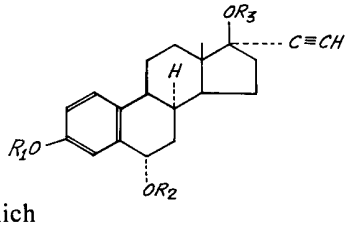
(19)

(54) 6α-HYDROXY-8α-OESTRADIOLS

(71) We, SCHERING AKTIENGESELLSCHAFT a Body Corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, 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 new 6α-hydroxy-8α-oestradiols (including functional derivatives therof) and with their manufacture and use.

The present invention provides compounds of the general formula I



(I)

in which

R_1 represents a hydrogen atom, an acyl group, an unsubstituted or substituted alkyl group or a cycloalkyl group, and R_2 and R_3 each represents a hydrogen atom or an acyl group.

As acyl groups represented by R_1, R_2 and R_3 there come into consideration those of acids capable of forming physiologically tolerable esters. Preferred acids are organic carboxylic acids and sulphonic acids containing 1 to 15, and especially 1 to 8, carbon atoms, which belong to the aliphatic, cycloalipatic, aromatic, aromatic-aliphatic or heterocyclic series. These acids may also be unsaturated and/or polybasic and/or substituted in the usual manner. As examples of substituents there may be mentioned alkyl, hydroxyl, alkoxy, oxo and amimo groups and halogen atoms.

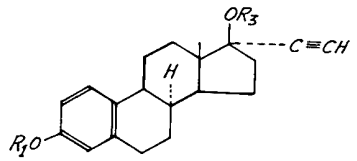
By way of example there may be mentioned the following carboxylic acids, namely formic acid, acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, caproic acid, oenanthic acid, caprylic acid, pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, trimethylacetic acid, diethylacetic acid, tert.-butylacetic acid, cyclopentyl-acetic acid, cyclohexyl-acetic acid, cyclohexane carboxylic acid, phenylacetic acid, phenoxyacetic acid, mono-, di- and trichloracetic acids, aminoacetic acid, diethylaminoacetic acid, piperidinoacetic acid, morpholinoacetic acid, lactic acid, succinic acid, adipic acid, benzoic acid, nicotinic acid, isonicotinic acid and furan-2-carboxylic acid.

As sulphonic acids there come into consideration for example, methane sulphonic acid, ethane sulphonic acid, β-chlorethane sulphonic acid, isopropane sulphonic acid, butane sulphonic acid, cyclopentane sulphonic acid, cyclohexane sulphonic acid, benzene sulphonic acid, para-toluene sulphonic acid, para - chlorobenzene sulphonic acid, N,N-dimethylamino - sulphonic acid, N,N - diethylamino-sulphonic acid, N,N-bis-(β-chlorethyl)-amino-sulphonic acid and pyrrolidino-, piperidino-, piperazino-, N-methylpiperazino- and morpholino-sulphonic acids.

As alkyl groups represented by R_1 there preferably come into consideration lower alkyl groups containing 1 to 5 carbon atoms, which may be branched and/or substituted in the usual manner. As examples of substituents there may be mentioned halogen atoms and lower alkoxy groups. Especially preferred are methyl and ethyl groups.

As cycloalkyl groups represented by R_1 there are to be understood those containing 3 to 8 carbon atoms, of which the cyclopentyl group is preferred.

The present invention also provides a process for the manufacture of the compounds of the general formula I, wherein a compound of the general formula II



(II)

in which R_1 and R_3 have the meanings given above, is fermented with a fungoid culture of a strain selected from the genera *Botryodiplodia, Curvularia, Helminthosporium, Neurospora, Pellicularia, Diplodia, Cladosporium* and *Rhizoctonia*, and, if desired in the resulting compound of the general formula I any free hydroxyl group in the 3-position is etherified or esterified and/or the hydroxyl group in the 6α-position is esterified and/or any free hydroxyl group in the 17β-position is esterified.

The 6α-hydroxylation takes place with fungoid cultures of strains of the genera *Botryodiplodia, Curvularia, Helminthosporium, Neurospora, Pellicularia, Dipolodia, Cladosporium* and *Rhizoctonia*. Suitable strains are, for example, *Botryodiplodia malorum* (CBS 13,450), *Curvularia lunata* (NRRL 2380), *Helminthosporium spec.* (ATCC 20,154), *Neurospora crassa* (ATCC 10,336), *Pellicularia filamentosa* (ATCC 13,289), *Diplodia natalensis* (ATCC 9055), *Cladosporium spec.* (ATCC 13,026) and *Rhizoctonia solani* (ATCC 13,250).

The fermentation may be carried out under the same conditions as those used in the known fermentative conversion of steroids with fungoid cultures.

Thus, there are first determined analytically, especially by thin-layer chromatography, in general usual preliminary tests the most favourable fermentation conditions, for example the choice of the most favourable nutrient medium, the suitable solvent for the substrate, the concentration of the substrate, the technical conditions, for example temperature, aeration and pH-value, and the optimum times for germination, the addition of the substrate and the contact of the substrate with the enzyme of the microorganism.

Thus, it has been found that it is advantageous to use concentrations of about 50 to 1000 mg of substrate per litre of nutrient medium. The pH-value is preferably adjusted to a value within the range of from 5 to 7. The growth temperature is within the range of from 20 to 40°C, and preferably 25 to 35°C. For aeration there is introduced about 1 litre of air per minute per litre of culture liquor. The conversion of the substrate is advantageously followed by thin-layer chromatographic analysis of test extracts. In general, sufficient quantities of the hydroxylated steroid have been formed after 20 to 50 hours.

After the fermentation the products thereof are isolated in a manner known *per se*. The isolation may be carried out, for example, by extracting the fermentation mixture with a polar solvent insoluble in water, for example ethyl acetate, butyl acetate or methyl isobutyl ketone, concentrating the extracts and purifying the resulting crude products, if desired by chromatography and/or crystallization.

In the resulting compounds of the general formula I free hydroxyl groups may then be esterified and/or etherified, depending on the finally desired meanings of R_1, R_2 and R_3.

For esterification there come into consideration the methods customarily used in steroid chemistry. As the hydroxyl groups in the 3-, 6- and 17-positions have different reactivities the hydroxyl groups may be esterified in stages. Depending on the choice of the reaction conditions there are obtained the 3,6- di- or 3,6,17-tri-acyl compounds. Acylation in the 3- and 6-positions is carried out preferably with pyridine/acid anhydride or pyridine/acid halide at room temperature. For acylation of the 17β-hydroxyl group in 3,6-diacylates there are allowed to react with the steroid, for example, an acid anhydride in the presence of a strong acid, for example para-toluene sulphonic acid or perchloric acid, at room temperature or pyridine/acid anhydride with heat. These methods may also be used for converting the free trihydroxy-compound directly into the triacylate.

Etherification with an unsubstituted or substituted alkyl or a cycloalkyl group in the 3-position is preferably carried out with a corresponding halide or sulphate in the presence of a weak base, for example potassium carbonate or sodium carbonate, in an alcoholic solution at the boiling temperature or with a (cyclo-)alkyl halide in the presence of a strong base, for example sodium hydride, at room temperature.

Compounds etherified in the 3-position may then be esterified in the 6-position with a carboxylic or sulphonic acid.

If the trihydroxy-compound is reacted with a sulphonic acid halide in the presence of a teritiary amine at room temperature the 3,6-disulphonic acid ester is obtained. In the case of reaction with methane sulphonic acid chloride it is advantageous to protect the 17-hydroxyl group, for example, by conversion into the 17-tetrahydropyranyl ether, because an unprotected hydroxyl group in the 17-position can easily be split off by the action of methane sulphonic acid chloride.

Furthermore, it is then favourable to operate at temperatures of about −10 to +15°C.

The new 6α-hydroxy-8α-oestradiols (including the functional derivatives thereof) of the general formula I are pharmacologically active substances. They have, for example, a strong oestrogenic activity, which is superior to the activity of the corresponding 6α-hydroxy-oestradiols. The compounds of the present invention have a favourable dissociation between peripheral and central action. Thus, for example, 17α-ethynyl-8α-oestra-1,3,5(10)-triene-3,6α,17β-triol exhibits in the Allen-Doisy test an oestrogenic action of the same magnitude as 17α-ethynl-oestradiol and in the inhibition of ovulation (central inhibition) is only one third as strongly active as 17α-ethynyl-oestradiol. With respect to implantation inhibition, however, the new compounds are more active than 17α-ethynyl-oestradiol.

Owing to their favourable properties the new 6α-hydroxy-8α-oestradiols may be used, for example, in the form of tablets or solutions for the treatment of women in the menopause. Furthermore, the active substances of the present invention can be used in the form of vaginal salves for oestrogen deficiency phenomena, for example atrophic vaginitis. Such a vaginal salve is exemplified in Example 9 below.

Accordingly, the present invention further provides a pharmaceutical preparation which comprises a compound of the general formula I, in admixture or conjuction with a pharmaceutically suitable carrier.

The preparation of the pharmaceutical preparations may be carried out in the usual manner by converting the active substances with, for example, the carrier substances, diluents and taste correctives, customarily used in galenical pharmacy into the desired form of application, for example tablets, dragées, capsules, solutions and salves. The concentration of active substance in the pharmaceutical preparations so formulated depends on the form of application. Thus, a tablet preferably contains 0.01 to 10 mg of active substance, solutions for parenteral administration contain 0.1 to 20 mg of active substance per ml of solution, and vaginal salves contain approximately 0.5 to 20 mg of active substance per 100 ml of salve.

The dosage of the pharmaceutical preparations of the present invention may vary depending on the form of administration and the particular active compound chosen. Moreover, it may vary depending on the particular patient. In general the compounds of the present invention are administered at a concentration that is capable of giving effective results, without causing any disadvantageous or harmful side effects. Thus, they are administered, for example, at a dosage level within the range of approximately 0.02 mg to approximately 20 mg, although in some cases variations can be made, so that a dosage level exceeding 20 mg, for example up to 50 mg, is used. However, a dosage level within the range of from approximately 0.05 mg to approximately 10 mg is preferably used.

In view of their implantation inhibiting action the new oestrogenically-active compounds of the general formula I are suitable for the suppression of female mammal fertility, especially human female fertility by oral administration at a daily dose within the range of from approximately 1 to 10 mg post coitum.

The present invention accordingly further provides a method of contraception, wherein there is administered in a contraceptive dose to a female mammal post coitum a compound of the general formula I; the compound is advantageously administered orally to a female of the human species in a daily dose within the range of from approximately 1 to 10 mg.

The new compounds of the present invention may also be used in combination with gestagens (that is gestagenically-active steroids) as contraceptives, especially for oral administration.

The present invention accordingly further provides a contraceptive preparation which comprises a compound of the general formula I in admixture or conjunction with a gestagen.

The present invention further provides a method of contraception, wherein there is administered in contraception doses to female mammal a compound of the general formula I and a gestagen. Advantageously, there is administered orally to a female of the human species a daily dose of the compound of the general formula I within the range of from approximately 0.015 to 0.050 mg and a daily dose of the gestagen within the range of from approximately 0.05 to 0.50 mg.

The following Examples illustrate the invention:—

Example 1

An Erlenmeyer flask of 2 litres capacity, which contained 500 ml of a nutrient solution sterilized for 30 minutes at 120°C in an autoclave and prepared from 1% of starch-sugar and 1% of soya bean meal. pH-value 6.2, was inoculated with a lyophilic culture of *Botryodiplodia malorum* (CBS 13,450), and agitated for 72 hours at 30°C

on a rotary agitator. With this preculture 10 Erlenmeyer flasks each of 2 litres capacity were inoculated, each of which flasks contained 500 ml of medium of the above mentioned composition. After a growth phase of 6 hours at 30°C on an agitating machine, 1000 mg of 17α-ethynyl-8α-oestra-1,3,5(10)-triene-3,17-diol, dissolved in 20 ml of dimethyl sulphoxide, were distributed among the 10 flasks and further agitated. After a contact time of 44 hours the contents of the flasks were combined, the mycelium was filtered off with suction over filter paper and the culture filtrate was extracted three times with methyl isobutyl ketone. The combined extracts were concentrated to dryness, and the residue was purified by chromatography over a column of silica gel. After crystallization of the main fraction from isopropyl ether 232 mg of pure 17α-ethynyl-8α-oestra-1,3,5(10)-triene-3,6α,17β-triol melting at 210—212°C were obtained.

Example 2

To a solution of 200 mg of 17α-ethynyl-8α-oestra-1,3,5(10)-triene-3,6α,17β-triol in 10 ml of ethyl acetate were added at room temperature in succession 2 ml of acetic anhydride and one drop of perchloric acid (70% strength). After 3 minutes one drop of pyridine was added, and the mixture was washed with a saturated solution of sodium chloride, dried and evaporated. There were obtained 162 mg of 3,6α,17β-triacetoxy-17α-ethynyl-8α-oestra-1,3,5(10)-triene in the form of an amorphous substance.

Example 3

To a solution of 150 mg of 17α-ethynyl-8α-oestra-1,3,5(10)-triene-3,6α,17β-triol in 3ml of pydrine was added 1 ml of acetic anhydride, and the whole was allowed to stand for 16 hours at room temperature. The mixture was then evaporated to dryness with the addition of cyclohexane. The residue was dissolved in methylene chloride, and purified by chromatography over a column of silica gel with methylene chloride/acetone (linear gradient). After crystallization from ether/hexane 95 mg of 3,6α-diacetoxy-17α-ethynyl-8α-oestra-1,3,5(10)-trien-17β-ol melting at 154—156°C were obtained.

By using oenanthic anhydride or caprylic anhydride, instead of acetic anhydride, there were obtained: 3,6α-diheptanoyloxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - trien - 17β-ol and 3,6α dioctanoyloxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - trien - 17β - ol.

Example 4

200 mg of 17α - ethynyl - 8α - oestra - 1,3,5(10) - triene - 3,6α,17β - triol were dissolved by heating in 3 ml of methanol and 1 ml of cyclopentyl bromide, 200 mg of potassium carbonate were then added, and the mixture was heated for 12 hours at the boil under nitrogen. The mixture was then introduced into ice-water rendered acid with acetic acid, and extracted with methylene chloride. The organic phase was washed until neutral, dried and evaporated, The crude product (150 mg) was purified by layer chromatography, and 105 mg of 17α - ethynyl - 3 - cyclopentyloxy - 8α - oestra - 1,3,5(10) - triene - 6α,17β - diol were obtained.

Example 5

To a solution of 350 mg of 17α - ethynyl - 3 - cyclopentyloxy - 8α - oestra - 1,3,5(10) - triene - 6α,17β - diol in 5 ml of ethyl acetate were added 1 ml of acetic anhydride and 1 drop of perchloric acid (70% strength), and the whole was stirred for 3 minutes at room temperature. 0.5 ml of pyridine was then added, and the mixture was washed with a saturated solution of sodium chloride, dried and evaporated. 335 mg of 6α,17β - diacetoxy - 17α - ethynyl - 3 - cyclopentyloxy - 8α - oestra - 1,3,5(10) - triene were obtained in the form of an amorphous substance.

Example 6

500 mg of 17α - ethynyl - 8α - oestra - 1,3,5(10) - triene - 3,6α,17β - triol were dissolved in 5 ml of pydrine, 1.5 ml of butyric anhydride were added, and the whole was stirred for 16 hours at room temperature. The solution was then stirred into 100 ml of cooled sulphuric acid of 8% strength, and the precipitate that separated was washed until neutral. For further purification the product was chromatographed over a column of silica gel and recrystallized from ether/hexane. 310 mg of 3,6α - dibutyryloxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - trien - 17β - ol melting at 101—104°C were obtained.

Example 7

To a solution of 350 mg of 17α - ethynyl - 8α - oestra - 1,3,5(10) - triene - 3,6α,17β - triol in 35 ml of absolute benzene were added 5 ml of triethylamine at room temperature and then, while stirring strongly 2 ml of isopropyl-sulphonic acid chloride. The whole was stirred for 38 hours at room temperature, and then poured on to ice and extracted with ether. The ether phase was washed with water, dried and evaporated. The crude product was purified by gradient chromatography, and 125 mg of 17α - ethynyl - 3,6α - bis - isopropylsulphonyloxy - 8α - oestra - 1,3,5(10) - trien - 17β - ol were obtained.

Example 8

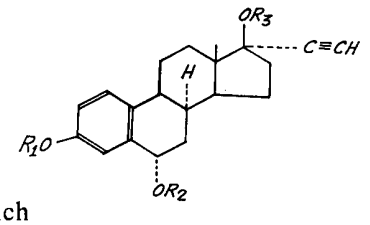
To a boiling solution of 1 gram of potassium carbonate in 20 ml of acetone was slowly added dropwise a solution of 1.2 grams of 17α - ethynyl - 8α - oestra - 1,3,5(10) - triene - 3,6α,17β - triol and 0.6 ml of dimethyl sulphate in 30 ml of acetone, and the whole was then heated at the boil for a further 16 hours. The mixture was then introduced into ice-water, the organic substance was extracted with methylene chloride, and the mixture was washed with water, dried and evaporated. After purification by gradient chromatography 0.6 gram of 17α - ethynyl - 3 - methoxy - 8α - oestra - 1,3,5(10) - triene - 6α,17β - diol was obtained.

Example 9

0.005 gram of 17α - ethynyl - 8α - oestra - 1,3,5(10) - triene - 3,6α,17β - triol
3.000 grams of polyoxyl-40-stearate
7.000 grams of viscous paraffin
7.000 grams of white petroleum jelly
8.000 grams of Eumulsan MD (fatty acid mono- and di-glycerides)
0.070 gram of para-hydroxybenzoic acid methyl ester
0.030 gram of para-hydroxybenzoic acid propyl ester made up to 100 ml with dimineralized water.

WHAT WE CLAIM IS:—

1. A compound of the general formula I



(I)

in which

R_1 represents a hydrogen atom, an acyl group, an unsubstituted or substituted alkyl group or a cycloalkyl group, and R_2 and R_3 each represents a hydrogen atom or an acyl group.

2. A compound as claimed in claim 1, wherein each of the acyl groups represented by R_1, R_2 and R_3 is derived from an organic carboxylic or sulphonic acid containing 1 to 15 carbon atoms.

3. A compound as claimed in claim 2, wherein each of the acyl groups represented by R_1, R_2 and R_3 is derived from an organic carboxylic or sulphonic acid containing 1 to 8 carbon atoms.

4. A compound as claimed in any one of claims 1 to 3, wherein the unsubstituted or substituted alkyl group represented by R_1 is an alkyl group containing 1 to 5 carbon atoms which may be substituted.

5. A compound as claimed in any one of claims 1 to 3, wherein the unsubstituted alkyl group represented by R_1 is a methyl or ethyl group.

6. A compound as claimed in any one of claims 1 to 3, wherein the cycloalkyl group represented by R_1 contains 3 to 8 carbon atoms.

7. A compound as claimed in any one of claims 1 to 3, wherein the cycloalky group represented by R_1 is a cyclopropyl group.

8. 17α - Ethynyl - 8α - oestra - 1,3,5(10) - triene - 3,6α,17β - triol.

9. 3,6α,17β - Triacetoxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - triene.

10. 3,6α - Diacetoxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - trien - 17β - ol.

11. 3,6α - Diheptanoyloxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - trien - 17β - ol.

12. 3,6α - Dioctanoyloxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - trien - 17β - ol.

13. 17α - Ethynyl - 3 - cyclopentyloxy - 8α - oestra - 1,3,5(10) - triene - 6α,17β - diol.

14. 6α,17β - Diacetoxy - 17α - ethynyl - 3 - cyclopentyloxy - 8α - oestra - 1,3,5(10) - triene.

15. 3,6α - Dibutyryloxy - 17α - ethynyl - 8α - oestra - 1,3,5(10) - trien - 17β - ol.

16. 17α - Ethynyl - 3,6α - bis - isopropylsulphonyloxy - 8α - oestra - 1,3,5(10) - trien - 17β - ol.

17. 17α - Ethynyl - 3 - methoxy - 8α - oestra - 1,3,5(10) - triene - 6α,17β - diol.

18. A pharmaceutical preparation which comprises a compound as claimed in claim 1, in admixture or conjunction with a pharamaceutically suitable carrier.

19. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 2 to 7, in admixture or conjunction witha pharmaceutically suitable carrier.

20. A pharmaceutical preparation which comprises the compound claimed in any one of claims 8 to 17, in admixture or conjunction with pharmaceutically suitable carrier.

21. A preparation as claimed in any one of claims 18 to 20, which is in the form of a tablet, dragée, capsule, solution or salve.

22. A preparation as claimed in any one of claims 18 to 20, which is in the form of a tablet containing 0.01 to 10 mg of the active substance.

23, A preparation as claimed in any one of claims 18 to 20, which is in the form of a solution suitable for parenteral administration containing 0.1 to 20 mg of the active substance per ml of solution.

24. A preparation as claimed in any of claims 18 to 20, which is in the form of a

vaginal salve containing approximately 0.5 to 20 mg of the active substance per 100 ml of the salve.

25. A preparation having a composition substantially as described in Example 9 herein.

26. A contraceptive preparation which comprises a compound as claimed in any one of claims 1 to 7, in admixture or conjunction with a gestagen.

27. A contraceptive preparation comprises the compound claimed in any one of claims 8 to 17, in admixture or conjunction with a gestagen.

28. A method of contraception, where there is administered in a contraceptive dose to a female mammal post coitum a compound as claimed in any one of claims 1 to 7.

29. A method of contraception, wherein there is administered in a contraceptive dose to a female mammal post coitum the compound claimed in any one of claims 8 to 17.

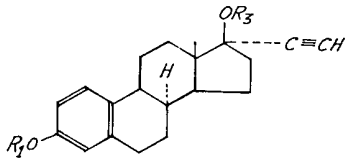
30. A method as claimed in claim 28 or 29, wherein the compound is administered orally to a female of the human species in a daily dose within the range of from approximately 1 to 10 mg.

31. A method of contraception, wherein there is administered in contraceptive doses to a female mammal an oestrogenically-active compound as claimed in any one of claims 1 to 7 and a gestagen.

32. A method of contraception, wherein there is administered in contraceptive doses to a female mammal the oestrogenically-active compound claimed in any one of claims 8 to 17 and a gestagen.

33. A method as claimed in claim 31 or 32, wherein there is administered orally to a female of the human species a daily dose of the oestrogenically-active compound within the range of from approximately 0.015 to 0.050 mg and a daily dose of the gestagen within the range of from approximately 0.05 to 0.50 mg.

34. A process for the manufacture of a compound of the general formula I given in claim 1, in which R_1, R_2 and R_3 have the meanings given in claim 1, wherein a compound of the general formula II



(II)

in which R_1 and R_3 have the meanings given above, is fermented with a fungoid culture of a strain selected from the genera *Botryodiplodia, Curvularia, Helminthosporium, Neurospora, Pellicularia, Diplodia, Cladosporium and Rhizoctonia,* and, if desired in the resulting compound of the general formula I any free hydroxyl group in the 3-position is etherified or esterified and/or the hydroxyl group in the 6α-position is esterified and/or any free hydroxyl group in the 17β-position is esterified.

35. A process as claimed in claim 34, wherein the fermentation is carried out with a culture of
Botryodiplodia malorum (CBS 13,450)
Curvularia lunata (NRRL2380),
Helminithosporium spec. (ATCC 20,154),
Neurospora crassa (ATCC 10,336),
Pellicularia filamentosa (ATCC 13,289),
Diplodia natalensis (ATCC 9055),
Cladosporium spec. (ATCC 13,026) or
Rhizoctonia solani (ATCC 13,250).

36. A process as claimed in claim 34, conducted substantially as described herein.

37. A process for the manufacture of a compound of the general formula I given in claim 1, in which R_1, R_2 and R_3 have the meanings given in claim 1, conducted substantially as described in any one of Examples 1, 2, 4, 5, 7 and 8 herein.

38. A process for the manufacture of a compound of the general formula I given in claim 1, in which R_1, R_2 and R_3 have the meanings given in claim 1, conducted substantially as described in Examples 3 or 6 herein.

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