We, JOHANN A. WUELFING, a German Company, of Stresmannallee 6, 404 Neuss, West Germany,

hereby apply for the grant of a Standard Patent for an invention entitled:

"PHARMACEUTICAL COMPOUNDS"

which is described in the accompanying complete specification.

Details of basic application(s):

<table>
<thead>
<tr>
<th>Number</th>
<th>Convention Country</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>7912050</td>
<td>United Kingdom</td>
<td>5th April, 1979</td>
</tr>
</tbody>
</table>

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 9th day of July 1980.

To: THE COMMISSIONER OF PATENTS

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952-1973
DECLARATION IN SUPPORT OF CONVENTION OR
NON-CONVENTION APPLICATION FOR A PATENT
OR PATENT OF ADDITION

In support of the Application made for a patent for an invention entitled:

Johann A. Wuelfing, Stresemannallee 6, 404 Neuss, W. Germany

I do solemnly and sincerely declare as follows:

1. (a) I am the applicant........ for the patent
   for the patent of addition
   or (b) I am authorized by
   Johann A. Wuelfing
   the applicant........ for the patent
   for the patent of addition to make this declaration on its behalf.

   Cross out whichever of paragraphs 1(a) or 1(b) does not apply
   1(b) relates to application made by individual(s)
   1(a) relates to application made by company; insert name of applicant company.

2. (a) 2(a) relates to application made by inventor(s)
   2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventor(s).
   Cross out whichever of paragraphs 2(a) or 2(b) does not apply
   2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of applicant company.

3. The basic application........ as defined by Section 141 of the Act were made
   in ............... on the 5th April, 1979
   by ............... on the
   by ............... on the
   by ............... on the
   by ............... on the
   by ............... on the
   Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

4. The basic application........ referred to in paragraph 3 of this Declaration was
   the first application........ made in a Convention country in respect of the invention the subject
   of the application.

Declared at Neuss this 12th day of June 1980

JOHANN A. WUELFING
PPA. (Wittler) (Dr. Bolte)
Compounds are useful for treating vascular disorders.

Claim

1. A compound of the formula (II):

![Chemical structure](attachment:image.png)

characterised in that

- $R_1$ is a lower alkyl group and $R_2$ is a lower alkyl group; or
- $R_1$ is linked to $R_2$ so that the OR$^1$ and OR$^2$ moieties and the carbon atom to which they are attached form a 1,3-dioxacyclohexa-2,2-diyl, 1,3-dioxacyclopenta-2,2-diyl, or 1,3-dioxacyclohepta-2,2-diyl diradical; and

- $R_3$ and $R_4$ are the same or different and are each a lower alkyl group.
Name of Applicant: JOHANN A. WUELFLNG KG m.b.H.

Address of Applicant: Stresemannallee 6, 404 Neuss, West Germany

Actual Inventor(s): JOACHIM EWALD GORING

Address for Service: DAVIES & COLLISON, Patent Attorneys, 1 Little Collins Street, Melbourne, 3000.

Complete specification for the invention entitled:

"PHARMACEUTICAL COMPOUNDS"

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

- 1 -
British Patent Specification No. 1441562 discloses inter alia that compounds such as those of the formula (I):

![Chemical Structure](image)

wherein $A_1$ and $A_2$ are alkyl groups and $A_3$ is an alkylen moiety, possess blood flow improving properties. It was said in Specification No. 1441562 that the compound of the formula (I) wherein $A_1$ and $A_2$ are n-butyl groups and $A_3$ is a $\text{CH}_2\text{CH}_2$ group was particularly effective. It has now been found that ketals of the compound of the formula (I) wherein $A_1$ and $A_2$ are n-butyl groups and $A_3$ is a $\text{CH}_2\text{CH}_2$ group do not possess potent blood flow enhancing properties. It has been found that certain other ketals do possess good blood flow enhancing properties.

The present invention provides the compounds of the formula (II):

\[
\text{(II)}
\]
wherein

\[ R_1 \] is a lower alkyl group and \( R_2 \) is a lower alkyl group;

or

\[ R^1 \] is linked to \( R^2 \) so that the OR\(^1\) and OR\(^2\) moieties and the carbon atom to which they are attached form a 1,3-dioxacyclohexa-2,2-diyl, 1,3-dioxacyclopenta-2,2-diyl, or 1,3-dioxacyclohepta-2,2-diyl diradical; and

\[ R_3 \] and \( R_4 \) are the same or different end alkyl group;

When used herein the term "lower" means containing 1 to 4 carbon atoms. Such groups may be straight chain or branched. Aptly, lower alkyl groups include methyl, ethyl, n-propyl, iso-propyl and n-butyl groups.

Most suitably \( R^1 \) and \( R^2 \) both represent the same kind of lower alkyl group or alternatively are linked.

Particularly suitable acyclic values for \( R^1 \) and \( R^2 \) are the methyl and ethyl groups, especially ethyl. Particularly suitable cyclic values for C(OR\(^1\)) (OR\(^2\)) are the 1,3-dioxacyclopenta-2,2-diyl and 1,3-dioxacyclopenta-2,2-diyl diradicals especially 1,3-dioxacyclopenta-2,2-diyl.

Particularly suitable values for \( R^3 \) and \( R^4 \) are the ethyl and n-butyl groups, especially n-butyl. \( R^3 \) and \( R^4 \) are often the same.
A preferred group of compounds within those of the formula (II) is those of the formula (III):

$$\text{CH}_3\text{CH}_2\text{C} \equiv \text{OR}^1$$

$$(\text{CH}_2)_5\text{CH}_3$$

$$(\text{III})$$

wherein $R^1$ and $R^2$ are as defined in formula (II).

Particularly suitable $R^1$ and $R^2$ are as so described under formula (II). Especially suitably $R^1$ and $R^2$ are each ethyl, or $\text{C}(\text{OR}^1)(\text{OR}^2)$ is 1,3-dioxacyclopenta-2,2-diyl.

A second preferred group of compounds within those of the formula (II) is those of the formula (IV):

$$(\text{IV})$$

wherein $R^3$ and $R^4$ are as defined in formula (II).
Particularly suitable $R^3$ and $R^4$ are as so described under formula (II). Especially suitably $R^3$ and $R^4$ are each n-butyl.

A third preferred group of compounds within those of the formula (II) is those of the formula (V):

![Chemical Structure](image)

wherein $R^3$ and $R^4$ are as defined in formula (II).

Particularly suitable $R^3$ and $R^4$ are as so described under formula (II). Especially suitably $R^3$ and $R^4$ are each n-butyl or ethyl.

A group of compounds of the present invention is:

- 1,3-dibutylxanthin-7-ylpropan-2-one diethyl ketal,
- 1,3-dibutylxanthin-7-ylpropan-2-one dimethyl ketal,
- 1,3-diethylxanthin-7-ylpropan-2-one diethyl ketal,
- 2-methyl-2-[(1,3-dibutylxanthin-7-yl)methyl]-1,3-dioxalane,
- 2-methyl-2-[(1,3-diethylxanthin-7-yl)methyl]-1,3-dioxalane,
- 2-methyl-2-[(1-butyl-3-ethylxanthin-7-yl)methyl]-1,3-dioxalane, and
- 2-methyl-2-[(1,3-dibutylxanthin-7-yl)methyl]-1,3-dioxacyclohexane
Preferred compounds are:

1,3-dibutylxanthine-7-ylpropan-2-one diethyl ketal and 2-methyl-2-[(1,3-dibutylxanthin-7-yl)methyl]-1,3-dioxalane
1,3-dibutylxanthin-7-ylpropan-2-one dimethyl ketal
1,3-dimethylxanthine-7-ylpropan-2-one diethyl ketal

The compounds of this invention may be used to treat vascular disorders such as intermittent claudication. Thus the present invention also provides a pharmaceutical composition which comprises a compound of the formula (II) and a pharmaceutically acceptable carrier.

Although the compositions of this invention may be in a form suitable for administration by injection, it is preferred that the compositions are adapted for oral administration since this allows for more convenient administration. The compositions of this invention are most suitably provided in unit dose forms, for example as a tablet or capsule. Such dosage forms may, for example, contain 5 to 500 mgs or more usually from 10 to 200 mgs, for example from 15 to 150 mgs. Thus advantageously the unit dose composition of this invention may contain 15, 20, 25, 50, 75, 100 or 150 mgs or the like of the active agent. Such unit dosage forms are normally administered from 1 to 4 times daily in such a way that the daily dose for a 70 kg adult will normally be in the range 40 to 1000 mgs and more usually from 50 to 900 mgs for example 60 to 800 mgs.

Particularly suitable unit dosage forms are tablets and capsules.

The compositions of this invention may be formulated in conventional manner. Thus oral dosage units may contain such conventional agents as fillers (diluents),
lubricants, binders, disintegrants, colourants, flavourings, surface active agents, preservatives, buffering agents and the like. Suitable fillers for use include cellulose, manitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate and the like. Suitable lubricants include stearic acid, magnesium stearate, magnesium lauryl sulphate and the like. Injectable compositions may consist essentially of a sterile, pyrogen free compound of this invention sealed into a vial optionally together with suspending and preserving agents. Such compositions may be made up for administration with sterile water or saline.

The compositions may be prepared by conventional methods of blending, filling, tabletting or the like.

The present invention also provides a process for the preparation of the compounds of this invention which process comprises the reaction of a salt of a 1,3-di-

lower alkylxanthine with a compound of the formula (VI):

\[ \text{ClCH}_2\text{-C-CH}_3 \] (VI)

or the chemical equivalent thereof wherein \( R^1 \) and \( R^2 \) are as defined in relation to formula (II).

Suitable chemical equivalents of the compound of the formula (VI) include the corresponding bromo and iodo compounds and activated esters such as the methanesulphonate or p-toluenesulphonate.

The condensation reaction is generally effected in an organic solvent such as a lower alkanol or acetone. The xanthine salt may be preformed or formed in situ, for example by sodium hydroxide, potassium hydroxide, an alkali metal alkoxide, or the like.

In a further and often more convenient process aspect this invention provides a process for the prepara-
tion of a compound of the formula (VI) which comprises ketalising the corresponding 1,3-di-lower alkyl-7-(2-oxopropyl) xanthine.

Such ketalisation may be carried out under conventional conditions. Thus for the preparation of cyclic ketalts for example a water-free solvent such as benzene or xylene and a catalytic amount of a dehydrating acid such as p-toluenesulphonic acid may be used with a diol at an elevated temperature, for example at reflux temperature. Alternatively, for acyclic ketalts, an orthoester may be used at ambient temperature in the presence of a catalyst such as Amberlyst 15 (see Patwardhan et al., Synthesis, 1974, page 348). In this form of the process a large excess of the orthoester may be used so that the orthoester also acts as solvent.

The desired product may be obtained by evaporating the reaction mixture after washing. The initially obtained product may be purified in conventional manner, for example by recrystallisation from petroleum ether.

The following Examples illustrate the preparation of compounds of the present invention:
**Example 1**

1,3-Dibutylxanthin-7-ylpropan-2-one diethyl ketal (1)

1,3-Dibutyl-7-(2-oxopropyl)-xanthine (32 g), orthoformic acid triethyl ester (150 ml) and Amberlyst 15 (7 g) were stirred over night at room temperature. After addition of a further amount of Amberlyst 15 (72 g), the reaction mixture was stirred for a further 3 hours at room temperature. The Amberlyst 15 was then filtered off and washed with chloroform. The combined solutions were evaporated to dryness in vacuo and the residue purified by column chromatography to yield 1,3-dibutylxanthinyl-7-(propan-2-one) diethyl ketal (15.2 g).

**Elemental Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>60.89</td>
<td>61.10</td>
</tr>
<tr>
<td>H</td>
<td>8.69</td>
<td>8.25</td>
</tr>
<tr>
<td>N</td>
<td>14.20</td>
<td>14.15</td>
</tr>
<tr>
<td>O</td>
<td>16.22</td>
<td>16.41</td>
</tr>
</tbody>
</table>

The structure was confirmed by NMR spectroscopy.

Using analogous procedures the following were prepared:

1,3-dibutylxanthin-7-ylpropan-2-one dimethyl ketal (2)

**Elemental analysis**

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>59.00</td>
<td>58.92</td>
</tr>
<tr>
<td>H</td>
<td>8.25</td>
<td>8.23</td>
</tr>
<tr>
<td>N</td>
<td>15.29</td>
<td>15.26</td>
</tr>
<tr>
<td>O</td>
<td>17.46</td>
<td>17.42</td>
</tr>
</tbody>
</table>
1,3-diethylxanthinyl-7-ylpropan-2-one dimethyl ketal (3)

Elemental analysis

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>56.78</td>
<td>56.72</td>
</tr>
<tr>
<td>H</td>
<td>7.44</td>
<td>7.69</td>
</tr>
<tr>
<td>N</td>
<td>16.55</td>
<td>26.55</td>
</tr>
<tr>
<td>O</td>
<td>18.91</td>
<td>18.85</td>
</tr>
</tbody>
</table>
Example 2

2-Methyl-2-[(1,3-di-n-butylxanthine-7-yl)methyl]-1,3-dioxalane (4)

1,3-Dibutyl-7-(2-oxopropyl)-xanthine (16 g), ethylene glycol (6.8 ml), xylene (80 ml) and p-toluenesulphonic acid (0.0005 g) were treated for several days under reflux. The reaction water was removed by a water separator. After cooling at room temperature the unreacted ethylene glycol was separated from the xylene phase. Petrolether (40/80°) was then added and the resulting precipitate of unreacted 1,3-dibutyl-7-(2-oxopropyl)-xanthine removed by suction. From the remaining xylene solution the xylene was removed under reduced pressure. The oily residue crystallized over a period of several days. This crude 2-methyl-2-[(1,3-di-n-butylxanthin-7-yl)-methyl]-1,3 dioxalane was filtered off by suction and recrystallized from petrolether to yield 4.4 g of solid, m.p. 73°C.

Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>59.32</td>
<td>59.83</td>
</tr>
<tr>
<td>H</td>
<td>7.74</td>
<td>7.54</td>
</tr>
<tr>
<td>N</td>
<td>15.38</td>
<td>15.19</td>
</tr>
<tr>
<td>O</td>
<td>17.56</td>
<td>17.65</td>
</tr>
</tbody>
</table>

The structure was confirmed by NMR spectroscopy.

Using analogous procedures the following were prepared:
2-methyl-2-[(1,3-diethylxanthin-7-yl)methyl]-1,3-dioxalane (5)

Elemental analysis

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>54.53</td>
<td>54.90</td>
</tr>
<tr>
<td>H</td>
<td>6.53</td>
<td>6.47</td>
</tr>
<tr>
<td>N</td>
<td>18.1</td>
<td>17.82</td>
</tr>
<tr>
<td>O</td>
<td>20.75</td>
<td>20.86</td>
</tr>
</tbody>
</table>

2-Methyl-2-[(1-n-butyl-3-ethyl-xanthin-7-yl)-methyl]-1,3-dioxalane (6)

M.pt. 68°C.

Elemental Analysis

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>57.13</td>
<td>56.98</td>
</tr>
<tr>
<td>H</td>
<td>7.19</td>
<td>7.16</td>
</tr>
<tr>
<td>N</td>
<td>16.66</td>
<td>17.14</td>
</tr>
<tr>
<td>O</td>
<td>19.02</td>
<td>18.80</td>
</tr>
</tbody>
</table>

2-methyl-2-[(1,3-dibutylxanthin-7-yl)methyl]-1,3-dioxacyclohexane (7)

Elemental analysis

<table>
<thead>
<tr>
<th></th>
<th>Calculated</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>60.30</td>
<td>60.13</td>
</tr>
<tr>
<td>H</td>
<td>7.99</td>
<td>7.87</td>
</tr>
<tr>
<td>N</td>
<td>14.80</td>
<td>14.94</td>
</tr>
<tr>
<td>O</td>
<td>16.91</td>
<td>16.87</td>
</tr>
</tbody>
</table>
Example 3

Composition

2-Methyl-2-[(1,3-di-n-butylxanthin-7-yl)-methyl]-1,3-dioxalane, magnesium stearate and microcrystalline cellulose may be blended together, passed through a 40 mesh sieve (U.K.) and tabletted on a conventional rotatory machine to produce a batch of 5000 tablets of the following composition:

- Active agent: 50 mg
- Magnesium stearate: 0.2 mg
- Microcrystalline cellulose: 149.8 mg
Illustration of Pharmacological Effectiveness

Methodology

Cats of either sex were anaesthetized by i.p. injection of urethane/chloralose (120/60 mg/kg). The intraduodenal (i.d.) administration of compounds was conducted by means of a plastic catheter which was inserted into the duodenum following midline incision at the abdominal cavity.

i) \( pO_2 \)-measurements

Measurement of muscle surface \( pO_2 \). The skin above the measuring site (3-4 mm in diameter) was removed and one multiwire-surface electrode (Eschweiler, Kiel) was placed on the gastrocnemius muscle of each hindlimb. The femoral artery in one hindlimb was ligated in order to induce ischaemia. Muscle temperature was controlled by means of a thermocouple (Ellab, Copenhagen). The electrode current was measured every 6 to 8 s and collected for periods of 4 min (Hewlett-Packard programmable data logger system 3051 A). After each period, mean value and standard deviation was calculated.

ii) Skeletal muscle contractility

After dissection of the skin of the calf muscles, the sciatic nerve was cut about 3 cm proximal to the knee. The tendon of the calf muscles was cut and connected with an isometric force transducer (SWEMA, SG 3). In order to maintain constant differences and a resting tension of 100 p in cats and 25 p in rats, the hindlimb was fixed at the tibia by means of a clamp. Direct stimulation of the muscles consisted of square wave pulses of 4 msec duration at a frequency of 2 Hz and at a voltage 50 V in cats. In order to keep the muscles
wet and at a normal temperature, the muscles were continuously superfused with 0.9% w/v NaCl solution (38°C). Femoral blood flow was restricted by a graded occlusion of the artery leading to a reduction of contractility by ca. 30%. After having reached a constant level of the contraction force, the appropriate vehicle (NaCl or Methocel) was injected, followed by the test substance.

Results

i) $pO_2$ measurements

<table>
<thead>
<tr>
<th>Compound</th>
<th>dosage (mg/kg)</th>
<th>n</th>
<th>hypoxic tissue</th>
<th>normoxic tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$C_s$</td>
<td>$\Delta pO_2$ (Torr)</td>
</tr>
<tr>
<td>1</td>
<td>0.8</td>
<td>4</td>
<td>1</td>
<td>12.8</td>
</tr>
<tr>
<td>2</td>
<td>32.0</td>
<td>2</td>
<td>1</td>
<td>13.5</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>2</td>
<td>1</td>
<td>7.8</td>
</tr>
<tr>
<td>4</td>
<td>0.8</td>
<td>3</td>
<td>1</td>
<td>6.4</td>
</tr>
<tr>
<td>6</td>
<td>12.5</td>
<td>3</td>
<td>1</td>
<td>13.8</td>
</tr>
</tbody>
</table>

ii) Skeletal muscle contractility under ischaemic conditions

<table>
<thead>
<tr>
<th>substance</th>
<th>dosage (mg/kg)</th>
<th>n</th>
<th>increase of contractility (% of initial values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8</td>
<td>4</td>
<td>+17.2</td>
</tr>
<tr>
<td>2</td>
<td>32.0</td>
<td>2</td>
<td>+35.2, +45.0</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>4</td>
<td>+26.7</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
<td>2</td>
<td>+28.6, +25.0</td>
</tr>
</tbody>
</table>
\[ n = \text{number of animals} \]
\[ C_s = \text{significance coefficient} = \text{number of measuring sites with significant } pO_2 \text{ increase per total number of measuring sites} \]
\[ \Delta pO_2 = \text{mean } pO_2 \text{ increase in experiments with significant } pO_2 \text{ increase (Torr)} \]
\[ E = \text{efficiency-index} = C_s \times \Delta pO_2 \text{ (Torr)} \]

Control values: \( E \) between 0.1 and 1.2 Torr

i.d.* = intraduodenal administration of a suspension in Methoel°

**Toxicity**

No toxic effects were observed at the above test dosages.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS :-

1. A compound of the formula (II):

\[
\begin{array}{c}
\text{R}^3 \quad \text{OR}^1 \\
\text{CH}_3 \quad \text{C-OR}^1 \\
\text{CH}_2-\text{-}\text{OR}^2 \\
\text{N} \quad \text{N} \\
\text{R}^4
\end{array}
\]

(II)

characterised in that

- \( \text{R}^1 \) is a lower alkyl group and \( \text{R}^2 \) is a lower alkyl group;
- or
- \( \text{R}^1 \) is linked to \( \text{R}^2 \) so that the \( \text{OR}^1 \) and \( \text{OR}^2 \) moieties and the carbon atom to which they are attached form a 1,3-dioxacyclohexa-2,2-diyl, 1,3-dioxacyclopenta-2,2-diyl or 1,3-dioxacyclolhepta-2,2-diyl diradical; and
- \( \text{R}_3 \) and \( \text{R}_4 \) are the same or different and are each a lower alkyl group.

2. A compound according to claim 1 of the formula (III):

\[
\begin{array}{c}
\text{CH}_3 \quad \text{C-OR}^1 \\
\text{CH}_2-\text{-}\text{OR}^2 \\
\text{N} \quad \text{N} \\
\text{CH}_3(\text{CH}_2)_3 \quad \text{CH}_3
\end{array}
\]

(III)

characterised in that \( \text{R}^1 \) and \( \text{R}^2 \) are as defined in claim 1.

3. A compound according to claim 1 of the formula (IV):
characterised in that \( R^3 \) and \( R^4 \) are as defined in claim 1.

4. 1,3-dibutylxanthine-7-ylpropan-2-one diethyl ketal.

5. A compound according to claim 1 of the formula (V)

\[
\begin{align*}
\text{(V)}
\end{align*}
\]

characterised in that \( R^3 \) and \( R^4 \) are as defined in claim 1.

6. 2-methyl-2-[1,3-dibutylxanthin-7-yl]methyl]-1,3-dioxalane.

7. A pharmaceutical composition, which composition comprises a compound according to claim 1 together with a pharmaceutically acceptable carrier.

8. A process for the preparation of a compound according to claim 1, characterised by the reaction of a salt of a 1,3-di-lower alkylxanthine with a compound of the formula (VI):

\[
\begin{align*}
\text{(VI)}
\end{align*}
\]
or the chemical equivalent thereof, wherein $R^1$ and $R^2$
are as defined in claim 1.

9. Compounds of the Formulae (II), (III), (IV) and (V),
methods for their manufacture and pharmaceutical compositions
containing them, substantially as hereinbefore described
with reference to the Examples.

10. The steps or features disclosed herein or any
combination thereof.

Dated this 19th day of March, 1980.

JOHANN A. WUELFING M.B.B.S.
By its Patent Attorneys
DAVIES & COLLISON.