Phenylalkane Derivatives in the Treatment of Inflammation

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U.S. Cl. 424—317

16 Claims

ABSTRACT OF THE DISCLOSURE

Compounds of the formula:

which have from 2 to 4 substituents in the B ring wherein R, R3, R4, R5 and R6 represent certain specified substituent groups and p is selected from 0, 1 and 2. The compounds of the invention possess anti-inflammatory activity.

This application is a division of application Ser. No. 132,891, filed Apr. 9, 1971, now issued as U.S. Pat. No. 3,766,263 on Oct. 16, 1973.

This invention relates to phenylalkane derivatives and to processes for their production. The invention also relates to therapeutic compositions comprising as the active ingredient one or more of these phenylalkane derivatives.

Acetyl salicylic acid (aspirin) has been in use for over 50 years for the relief of pain and the alleviation of inflammatory states. In the late 1950's there was much interest in the discovery that stomach ulceration and gastrointestinal bleeding could occur in patients taking aspirin, particularly those patients suffering from various inflammatory states such as rheumatoid arthritis, osteoarthritis, rheumatic fever and ankylosing spondylitis in which the treatment necessitated continued high dosages of the drug. Arylacetic acids have been investigated extensively for anti-inflammatory activity, and thus work has led to the introduction of ibuprofen, for example. This drug in common with other drugs such as Phenylbutazone and aspirin, is strongly ulcerogenic in animals such as rats. We have now prepared novel ary lacetic acid derivatives, in particular ortho phenoxy phenylacetic acid derivatives, which possess anti-inflammatory activity, and certain of which possess to a minimal extent only the ulcerogenic side effects encountered with known anti-inflammatory drugs.

According to the present invention there are provided compounds of the formula:

which are di-, tri- or tetrasubstituted in the B ring, and wherein R is hydrogen or methyl; R3 is hydrogen, methyl or chlorine; R4 is alkyl of from 1 to 4 carbon atoms or chlorine.

R3 is alkyl of from 1 to 6 carbon atoms at position 4, trifluoromethyl at position 5, or hydrogen or chlorine; R4 is hydrogen or chlorine; R5 is alkyl of from 1 to 4 carbon atoms and p is 0 or 1, or p may be 2 when R6 is methyl; and when R3 is alkyl of from 1 to 6 carbon atoms at position 4, R5 may be hydrogen and in this case R6 is chlorine or trifluoromethyl at position 3 and p is 1; provided that the B ring does not have two alkyl groups containing more than one carbon atom in adjacent positions and that in a compound with alkyl substituents at positions 2 and 6 of the B ring at least one of these alkyl substituents is methyl or ethyl; and also provided that the compound does not have more than 3 chlorine substituents.

Additionally, when R3 is alkyl of from 1 to 6 carbon atoms at position 4 or chlorine then R4 may also represent alkyl of from 1 to 4 carbon atoms or hydroxy; R5 may also represent alkyl of from 7 to 18 carbon atoms at position 4 when R6 is chlorine and there are no other substituents in the B ring; R5 may also represent alkyl of from 1 to 4 carbon atoms or hydroxy when R6 is chlorine; and one or more chlorine substituents in the compound may be replaced by bromine. By di-, tri- and tetra-substituted we mean that there are two, three or four substituents in the B ring in addition to the ether linkage.

In a preferred aspect of the invention there are provided compounds of the formula:

wherein R3 is hydrogen or methyl; R7 is chlorine; R8 is chlorine at positions 4 or 5, alkyl of from 1 to 6 carbon atoms at position 4, trifluoromethyl at position 5 or methyl at position 6; and n is 0, 1 or 2.

Additionally when R8 is chlorine at position 4, R7 may also represent a methoxy group; and one or more chlorine substituents in the molecule may be replaced by bromine.

In a particularly preferred aspect the present invention provides 2-chloro-4-alkyl(C1 to C6) phenoxophenylacetic acids which may be optionally substituted by methyl at position 5' of Ring A and 2,4-dichlorosubstituted phenoxophenylacetic acids which may be optionally substituted by one or two methyls in Ring B and methyl at position 5' of Ring A.

The invention also provides therapeutic compositions comprising as active ingredients one or more compounds of Formula I or Formula II in association with a pharmaceutically inactive diluent or carrier.

The compounds and compositions of the present invention have anti-inflammatory and analgesic properties.

The compounds of Formula I in which R is hydrogen may be prepared by reacting together compounds of Formula III and IV.
in which R₁, R₂, R₃ and R⁴ and R⁵ and p are as herein before defined with reference to Formula I, except that neither R² nor R⁵ may represent a hydroxy group, Y is O₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉₉০
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Analysis.—Calcd. for C₉H₇ClNO₅S: C, 63.9; H, 5.9; Cl, 8.4; N, 3.7; S, 8.7.

2-(2-Chloro-4-methylphenyloxy)-5-methylphenylacetic acid (22 g., 0.095 mol) was hydrolysed as in Example 1. The crude product (14 g.) was an oily solid, which was crystallised from carbon tetrachloride to give 10 g. (58%) of material m.p. 88-93°C. A sample recrystallised from light petroleum (b.p. 60-80°C.) gave 2-(2-chloro-4-methylphenyloxy)-5-methylphenylacetic acid as colourless needles (m.p. 95-97°C.);

Analysis.—Calcd. for C₁₉H₁₈ClO: C, 71.3; H, 6.3; Cl, 11.7.

EXEMPLARY 3

2-[2-(2,4-Dichlorophenyl) phenyl] propionic acid

A solution of sodium (2.4 g; 0.088 mole) in ethanol (48 ml.) was added over 3 hours to a solution stirred at 140°C. of ethyl 2-(2,4-dichlorophenyl) phenylacetate (26.0 g; 0.08 mole) in diethyl carbonate (22 ml.).

The ethanol was removed by distillation through a 12 cm. column packed with glass helices. The last traces of ethanol from the reaction were removed by slow distillation for 4 hours at a head temperature of 127°C. After cooling, the solution was poured into conc. hydrochloric acid (400 ml.) and ice (400 g.). Water (400 ml.) was added and the product was extracted with ether.

The ether extracts after washing with water, drying with magnesium sulphate, were evaporated, and the residual oil distilled, diethyl 2-(2,4-dichlorophenyl) phenylmalonate (23 g.) was collected at 177-178°C./0.25 mm.

A solution of sodium (1.15 g; 0.05 mole) in ethanol (100 ml.) was added to a solution of the malonate (19.9 g; 0.05 mole) in ethanol (40 ml.), followed by the addition of methyl iodide (15.6 ml; 0.25 mole). After heating under reflux for 1 hour additional methyl iodide (4 ml.) was added, and heating continued for 1 hour. The solution was evaporated. Water was added, and the product extracted with ether.

The ether extracts after washing with aqueous sodium bisulphite and water, drying with magnesium sulphate, were evaporated to give the methylated malonic ester as an oil (18.6 g.), which was not purified further.

A mixture of the methylated malonic ester (6.6 g.), water (20 ml.), ethanol (24 ml.) and sodium hydroxide (3.0 g.) was heated under reflux for stirring for 3 hours.

The solution was diluted with water, acidified with hydrochloric acid and the product extracted into ether. The ether extracts, after drying with magnesium sulphate, were evaporated to give the methylated malonic acid as an oil (6.4 g.), which was not purified further.

The purified malonic acid (6.4 g.) was decarboxylated by heating at 180° C. for 1 hour and then at 200°C. for 1 hour. The product was crystallised twice from n-hexane to give 2.1 g. of 2-[2-(2,4-dichlorophenyl)phenyl] propionic acid, m.p. 101-103°C.

Analysis.—Calcd. for C₁₇H₁₅ClO₂: C, 75.9; H, 3.9; Cl, 22.8. Found: C, 75.8; H, 4.0; Cl, 22.2.

EXAMPLE 4

2-(2-Chloro-4-n-propyloxy)-5-methylphenylacetic acid

A solution of 2-chloro-4-n-propyloxy) methyl chloride (49.5 g., 0.29 mole) in methanol (200 ml.) was treated with sodium methoxide (6.6 ml. of 24% w/w solution, 0.28 mole). The solution was evaporated in vacuo to give the corresponding phenoxide containing a slight excess of the phenol. This was then allowed to react with the mixture of 2-chloro-5-methylacetoephone and its isomer (145.4 g., 0.56 mole) in the presence of copper as in Example 2. 2-(2-Chloro-4-n-propylphenoxy)-5-methylacetoephone was collected at 155-160°C. at 0.35 mm.

Analysis.—Calcd. for C₁₉H₂₁ClO: C, 71.3; H, 6.3; Cl, 11.7. Found: C, 71.4; H, 6.3; Cl, 11.7.

2-(2-Chloro-4 - n - propyloxy)-5-methylacetoephone (30.3 g., 0.1 mole) was heated with morpholine and sulphur as in Example 1. The yield of 2-(2-chloro-4-n-propyloxy)-5-methylphenylacetoephone was 28.2 g. (70%); m.p. 89-90.5°C. from methanol.

Analysis.—Calcd. for C₁₉H₁₇ClNO: C, 65.4; H, 6.5; Cl, 8.8; N, 3.8; S, 7.9. Found: C, 65.3; H, 6.5; Cl, 8.9; N, 3.5; S, 8.0.

A mixture of 2-(2-Chloro-4 - n - propyloxy)-5-methylphenylacetoephone (25 g., 0.062 mole) and potassium hydroxide (50 g.) in methanol (250 ml.) was heated under reflux for 48 hours. The product was worked up as in Example 1 to give 2-(2-chloro-4-n-propyloxy)-5-methylphenylacetic acid (16.1 g., 82%), m.p. 85-86°C. from light petroleum (b.p. 60-80°C.).

Analysis.—Calcd. for C₁₉H₁₇ClO: C, 67.8; H, 6.0; Cl, 11.1. Found: C, 68.1; H, 6.2; Cl, 11.2.

EXAMPLE 5

2-(2-Chloro-5-trifluoromethoxy)-5-methylphenylacetic acid

A mixture of 2-(2-chloro-5-trifluoromethoxy)-5-methylacetoephone (prepared by the method of Example 4, 15.0 g., 0.045 mole), sulphur (3.8 g., 0.118 mole) and morpholine (14.3 g., 0.165 mole) was heated under reflux for 4 hours. It was then worked up as in Example 1 to give 15.95 g. (83%) of product, m.p. 120-124°C. A portion was crystallised twice from methanol to give 2-(2-chloro-5-trifluoromethoxy)-5-methylphenylacetoephone as pale yellow needles, m.p. 128-129°C.

Analysis.—Calcd. for C₁₉H₁₈ClF₃O₅: C, 55.9; H, 4.4; Cl, 8.2; F, 13.25; N, 3.3; S, 7.5. Found: C, 55.6; H, 4.4; Cl, 8.1; F, 13.6; N, 3.4; S, 7.8.

A mixture of 2-(2-chloro-5-trifluoromethoxy)-5-methylphenylacetoephone (9.0 g., 0.021 mole), acetic acid (60 ml.), concentrated sulphuric acid (9 ml.) and water (13 ml.) was heated under reflux for 24 hours.

The solution was filtered hot from a residue of sulphur. Some of the product crystallised in the cold filtrate and the remainder was isolated by distilling the filtrate with water. The combined solids (6.85 g.) of melting point about 120°C., were crystallised from light petroleum (b.p. 80-100°C.) to give 5.5 g. (76%) of 2-(2-chloro-5-trifluoromethoxy)-5-methylphenylacetic acid as pale pinkish microrystals, m.p. 123-124°C.

Analysis.—Calcd. for C₁₉H₁₇ClF₃O₂: C, 55.7; H, 3.5; Cl, 10.3; F, 16.5. Found: C, 55.8; H, 3.5; Cl, 10.1; F, 16.6%

EXAMPLE 6

2-(2-Chloro-4-n-pentylphenoxy)-5-methylphenylacetic Acid

The crude acid obtained in 52% yield when 2-chloro-5-n-pentylphenol was allowed to react as in Example 4 (footnotes r and u of the table apply) was an oil which could not be crystallised. It was therefore purified via its amide. The oily acid (29.4 g., 0.085 mole) was dissolved in methylene chloride (55 ml.), thiouyl chloride (6.9 ml., 0.095 mole) was added, and the solution was heated under reflux for 2 hours. Volatile material was distilled in vacuo, and two portions of dry benzene were added and similarly removed in vacuo. The crude acid was combined with water (3.8 ml.) and added dropwise with stirring to ammonia (d=0.880, 300 ml.).

The resulting suspension was shaken with ether and filtered from undissolved product. The organic layer was separated from the filtrate, washed with water, dried over magnesium sulphate and evaporated. The solid residue was combined with methanol (100 ml.) and added dropwise several times with ether and then crystallised from methanol to give 11.4 g. of 2-(2-chloro-4-n-pentylphenoxy)-5-methylphenylacetic acid, m.p. 136-137°C. This was heated under reflux with 20% methanolic potassium hydroxide (120 ml.). The solution was
filtered, the filtrate was evaporated to dryness and the residue was taken up in water. The solution was acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried over magnesium sulphate and evaporated to dryness. The residual oil solidified when triturated with light petroleum (b.p. 60–80°C). Crystallization from this solvent afforded 2-(2-chloro-5-hydroxyphenyl)-5-methylphenylacetic acid, m.p. 75–77°; yield 6.7 g. (23% recovery from crude acid 12% overall yield).

**Analysis.**—Calcd. for C$_{12}$H$_{12}$ClO$_4$: C, 69.2; H, 6.7; Cl, 10.2. Found: C, 69.3; H, 6.6; Cl, 10.3%.

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**EXAMPLE 7**

2-(4-Chloro-2-hydroxyphenoxy)-5-methylphenylacetic Acid

A mixture of 2 - (4-chloro-2-hydroxyphenoxy)-5-methylphenylacetic acid (2.3 g, 0.0075 mole), glacial acetic acid (162 ml.) and hydroiodic acid (4.4 ml.) was heated under reflux for 2 hours. Material of b.p. below 100° was removed by distillation and heating under reflux was continued for further 20 hours. The solution was poured into water (200 ml.) and extracted with ether. The extract was washed with aqueous sodium thiosulphate

and then with water, dried over magnesium sulphate, and evaporated to give a yellow oil. This was crystallised from light petroleum (b.p. 60–80° C.) to give 1.9 g. (87%) of 2 - (4-chloro-2-hydroxyphenoxy)-5-methylphenylacetic acid, m.p. 116–117°C.

**Analysis.**—Calcd. for C$_{12}$H$_{12}$ClO$_4$: C, 61.8; H, 4.5; Cl, 12.1. Found: C, 61.8; H, 4.5; Cl, 11.9%.

The table sets out details of further examples of orthophenoxyphenylacetic acid derivatives which may be substituted at position 5' of the A ring and at positions 2, 3, 4, 5 or 6 of the B ring which were prepared by the procedures of the above examples.

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**Analysis.**—Calcd. for C$_{12}$H$_{12}$ClO$_4$: C, 61.8; H, 4.5; Cl, 12.1. Found: C, 61.8; H, 4.5; Cl, 11.9%.
the arthritis has not fully developed are rejected and the remainder divided into groups so that the mean left hind paw volume of each group is approximately the same. The rats are then dosed orally with the drug under test on days 21 to 27 inclusive. The control animals receive the same dose volume (10 mL/kg.) of the drug vehicle, 5% acacia. On day 28 (approximately 24 hours after the final dose) the animals are weighed and the left hind paw volume measured. The results are expressed as the percentage change in paw volume and body weight following drug treatment.

Antipyretic activity has been assessed in yeast-fevered rats using a modification of the method of Winder et al. (J. Pharmacol. exp. therap. 133, 117 (1961)). Screening to determine the extent of gastric ulceration following acute administration of a drug in rats has been carried out by a procedure based on that of Martinmale et al. (Arch. int. Med. 123, 153-158 (1965)). Ulceration was assessed at 4 hours in the case of Phenylbutazone and Ibuprofen, but at 24 hours in the case of the compounds of the invention, for which preliminary studies indicated a greater ulcerogenic effect at 24 hours than at shorter time intervals. Acetylsalicylic acid was used as a positive control for the 24 hour studies.

Table II below sets out results we have obtained on a number of compounds. Calculation of the ratio of the approximate minimum ulcerogenic dose (MUD) to the corresponding approximate daily minimum effective (anti-arthritic) dose (MED) clearly demonstrates the reduced ulcerogenic potential of our compounds relative to their therapeutic activity when compared with established anti-inflammatory agents.

<table>
<thead>
<tr>
<th>Compound</th>
<th>MED (mg/kg. p.o.)</th>
<th>MUD (mg/kg. p.o.)</th>
<th>MUD/MED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid</td>
<td>60</td>
<td>&lt;0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>6</td>
<td>&lt;0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>30</td>
<td>&lt;0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2-(2,4-dichlorophenoxy) phenylacetic acid</td>
<td>20</td>
<td>&lt;0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2-(2,4-dichloro-4'-dimethylphenoxy) phenylacetic acid</td>
<td>20</td>
<td>&lt;0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>2-(3-chloro-4-methylphenoxy) methylphenylacetic acid</td>
<td>40</td>
<td>&gt;500</td>
<td>&gt;12.5</td>
</tr>
<tr>
<td>2-(2-chloro-4'-ethylphenoxy) methylphenylacetic acid</td>
<td>14</td>
<td>&gt;500</td>
<td>&gt;35.7</td>
</tr>
<tr>
<td>2-(3-chloro-4-methylchlorophenoxy) methylphenylacetic acid</td>
<td>20</td>
<td>&gt;500</td>
<td>&gt;25</td>
</tr>
<tr>
<td>2-(2-chloro-4'-n-propylphenoxy) methylphenylacetic acid</td>
<td>30</td>
<td>&gt;500</td>
<td>&gt;16.5</td>
</tr>
</tbody>
</table>

The unsubstituted analogue, o-phenoxyphenylacetic acid, is devoid of anti-inflammatory activity and produces no ulceration after six hours and only slight ulceration 24 hours after administration of 1 g./kg. Moreover, with m-phenoxyphenylacetic acid (no anti-arthritic activity) there was ulceration 4 hours after administration of 100 mg./kg. with p-phenoxyphenylacetic acid ulceration 4 hours after administration of 50 mg./kg. and finally with the analogous p-(2,4-dichlorophenoxy)-phenylacetic acid there was severe ulceration 24 hours after administration of 1 g./kg.

o-Phenoxophenylacetic acid is therefore much less ulcerogenic than the m- and p-isomers. This property is retained in the substituted compounds, which also display anti-inflammatory activity.

Several compounds, e.g. 2-(2,4-dichlorophenoxy) phenylacetic acid and 2-(2,4-dichloro-3,5-dimethylphenox) phenylacetic acid, in addition to anti-inflammatory activity possess anti-ulcer activity. The former compound also has analgesic activity, and exerts an anti-oedematous effect in adrenalecтомized rats.

The pharmaceutically acceptable diluents or carriers which may be admixed with the active compound to form the compositions of this invention are well known. The compositions may be in a form suitable for oral, topical or parenteral use but the preferred method of administration is orally. Such oral compositions may take the form of capsules, tablets, lozenges or granules or liquid preparations such as elixirs, syrups or suspensions. The oral compositions, whether in the form of liquid or solids, may also incorporate disintegrating agents, tabletting aids and other diluents as required.

Tablets or capsules for oral administration contain from 25 to 500 mg. of a compound according to the invention as active ingredient. A preferred tablet or capsule contains from 100 to 500 mg. of 2-(2,4-dichlorophenoxy) phenylacetic acid, 2-(2,4-dichloro-3,5-dimethylphenoxy) phenylacetic acid, 2-(2-chloro-4-ethylphenox)-5-methylphenylacetic acid, 2-(2-methoxy-4-chlorophenoxy)-5-methylphenylacetic acid, or 2-(2-chloro-4-tet-butylphenox)-5-methylphenylacetic acid. A suitable oral daily dose of these preferred compounds for the relief of inflammatory states in human beings, would be from 250 mg. to 5 g. of the active ingredient.

The compounds of the invention may also be incorporated into novel therapeutic compositions with other known therapeutically active compounds such as, for example, codeine. Examples of the formulation and preparation of tablets and capsules for oral administration are set out below:

**Tablet**

An intimate mixture was prepared of equal weights of 2-(2,4-dichlorophenoxy) phenylacetic acid and a tablet base comprising starch with the addition of 1% magnesium stearate as a lubricant. The mixture was compressed into tablets containing 100 mg. of 2-(2,4-dichlorophenoxy) phenylacetic acid.

Similarly tablets containing 50 or 200 mg. of 2-(2,4-dichlorophenoxy) phenylacetic acid were prepared.

**Capsule**

Batches of soft gelatin capsules were prepared, each capsule containing 50, 100 or 200 mg. of 2-(2,4-dichlorophenoxy) phenylacetic acid.

Similar tablets and capsules were prepared containing 50, 100 and 200 mg. of 2-(2,4-Dichloro-3,5-dimethylphenox) phenylacetic acid, 2-(2-Chloro-4-ethylphenox) -5-methylphenylacetic acid, 2-(2-Methoxy-4-chlorophenoxy)-5-methylphenylacetic acid or 2-(2-Chloro-4-tet-butylphenox)-5-methylphenylacetic acid.

I claim:

1. A method for relief of an inflammatory condition which method comprises administering to a subject having such condition a therapeutically effective amount of a compound of the formula:

\[
R^1 \text{CHCOOH} \]

wherein

- R^1 is selected from the group consisting of hydrogen and methyl;
- R^2 is selected from the group consisting of chlorine, bromine and methoxy, provided that R^2 is methoxy only when R^1 is selected from the group consisting of chlorine at position 4 and bromine at position 4;
- R^3 is selected from the group consisting of chlorine at position 4, bromine at position 4, chlorine at position 5, bromine at position 5, 6,7 isoxyl of 1 to 6 carbon atoms at position 4, trifluoromethyl at position 5 and methyl at position 5 and 6,7 is x = 0, 1 or 2.

2. A method for relief of an inflammatory condition which method comprises administering orally to a subject...
having such condition a therapeutically effective amount of a compound of the formula:

\[
\begin{align*}
\text{CH}_2\text{COOH} \\
\text{R}^1 \\
\text{R}^2 \\
\end{align*}
\]

wherein

- \( R^8 \) is selected from the group consisting of hydrogen and methyl;
- \( R^8 \) is chlorine;
- \( R^8 \) is selected from the group consisting of chlorine at position 4, chlorine at position 5, alkyl of from 1 to 6 carbon atoms at position 4, trifluoromethyl at position 5 and methyl at position 6;
- and \( n \) is 0, 1 or 2.

3. A method as claimed in Claim 2 wherein the compound of the formula is administered in the amount of from 250 mg. to 3 g. per day.

4. A method as claimed in Claim 2 wherein the compound of the formula is 2-(2,4-dichlorophenoxy)-phenylactic acid.

5. A method as claimed in Claim 2 wherein the compound of the formula is 2-(2-chloro-4-ethylphenoxy)-5-methylphenylactic acid.

6. A method as claimed in Claim 2 wherein the compound of the formula is 2-(2-chloro-4-ethylphenoxy)-phenylactic acid.

7. A method as claimed in Claim 2 wherein the compound of the formula is 2-(2-chloro-4-sec-butylphenoxy)-5-methylphenylactic acid.

8. A method as claimed in Claim 1 wherein the compound of the formula is 2-(2-methoxy-4-chlorophenoxy)-5-methylphenylactic acid.

9. A pharmaceutical composition for the treatment of inflammatory conditions which comprises an effective anti-inflammatory amount of a compound of the formula:

\[
\begin{align*}
\text{CH}_2\text{COOH} \\
\text{R}^1 \\
\text{R}^2 \\
\end{align*}
\]

wherein

- \( R^8 \) is selected from the group consisting of hydrogen and methyl;
- \( R^8 \) is selected from the group consisting of chlorine, bromine and methoxy, provided that \( R^7 \) is methoxy only when \( R^8 \) is selected from the group consisting of chlorine at position 4 and bromine at position 4;
- \( R^8 \) is selected from the group consisting of chlorine at position 4, chlorine at position 5, alkyl of from 1 to 6 carbon atoms at position 4, trifluoromethyl at position 5 and methyl at position 6;
- and \( n \) is 0, 1 or 2;
- and a pharmaceutically acceptable diluent or carrier.

10. A pharmaceutical composition for oral administration in the treatment of inflammatory conditions which comprises an effective anti-inflammatory amount of a compound of the formula:

\[
\begin{align*}
\text{CH}_2\text{COOH} \\
\text{R}^1 \\
\text{R}^2 \\
\end{align*}
\]

wherein

- \( R^8 \) is selected from the group consisting of hydrogen and methyl;
- \( R^7 \) is chlorine;
- \( R^8 \) is selected from the group consisting of chlorine at position 4, chlorine at position 5, alkyl of from 1 to 6 carbon atoms at position 4, trifluoromethyl at position 5 and methyl at position 6;
- and \( n \) is 0, 1 or 2;
- and a pharmaceutically acceptable, orally ingestible diluent or carrier.

11. A pharmaceutical composition as claimed in Claim 10 in tablet or capsule form wherein each tablet or capsule contains from about 25 to 500 mg. of the compound of the formula.

12. A pharmaceutical composition as claimed in Claim 10 which consists essentially of 2-(2,4-dichlorophenoxy)-phenylactic acid and said diluent or carrier.

13. A pharmaceutical composition as claimed in Claim 10 which consists essentially of 2-(2-chloro-4-ethylphenoxy)-5-methylphenylactic acid and said diluent or carrier.

14. A pharmaceutical composition as claimed in Claim 10 which consists essentially of 2-(2-chloro-4-ethylphenoxy)-phenylactic acid and said diluent or carrier.

15. A pharmaceutical composition as claimed in Claim 10 which consists essentially of 2-(2-chloro-4-sec-butylphenoxy)-5-methylphenylactic acid and said diluent or carrier.

16. A pharmaceutical composition as claimed in Claim 10 which consists essentially of 2-(2-methoxy-4-chlorophenoxy)-5-methylphenylactic acid and said diluent or carrier.

No references cited.

STANLEY J. FRIEDMAN, Primary Examiner
UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION


Inventor(s) KEITH ERNEST GODFREY

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

Column 1, after line 9, insert ---Claims priority, Application Great Britain, April 14, 1970, 17,832/70---;
line 41, change "ulceration" to ---ulceration---;
line 51, change "ulcerogenic" to ---ulcerogenic---;

Column 2, line 51, change the formula to read ---2-(2-chloro-4-alkyl (C₁ to C₆) phenoxy) phenylactic---;
lines 53 and 54, change the formula to read ---2-(2,4-dichlorosubstituted phenoxy) phenylactic---.

Column 3, line 5, change "persence" to ---presence---;
line 32, change the formula to read ---2-(2-chloro-5-trifluoromethylphenoxy)-5-methylphenyl- ---; line 43, change "Co(0Et₂)" to --- CO(0Et₂) ---; line 47, change "ArCHMe(CO₂Et)₂" to ---ArCMe(CO₂Et)₂---; line 51, change "ArCHMe(CO₂H)₂" to ---ArCMe(CO₂H)₂---

Column 6, line 55, change "5-n-pentylphenol" to ---4-n-pentylphenol---.

Column 9, delete lines 47 and 48.

Signed and sealed this 24th day of June 1975.

(SEAL)
Attest:

RUTH C. MASON
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents and Trademarks