

## PATENT SPECIFICATION

(11) 1308327

## NO DRAWINGS

- (21) Application No. 17832/70 (22) Filed 14 April 1970  
 (23) Complete Specification filed 19 April 1971  
 (44) Complete Specification published 28 Feb. 1973  
 (51) International Classification C07C 65/14, A61K 27/00  
 (52) Index at acceptance  
 C2C 17X—186—272 1E7B2 1E7E1 1E7H2 1E7N3  
 1Q11J 1Q4 1Q6B1 1Q7A 1Q8C 1Q9D2 1Q9F1  
 215 220 227 22Y 255 25Y 30Y 311 313 31Y  
 338 342 34Y 351 355 35Y 364 36Y 372 379  
 388 500 50Y 573 624 625 62X 662 665 694  
 699 KQ QZ UR  
 A5B 294 29X 381 38Y 392 420 421 42Y 480 482 48Y  
 586 58Y 642 64Y 77Y  
 (72) Inventor KEITH ERNEST GODFREY



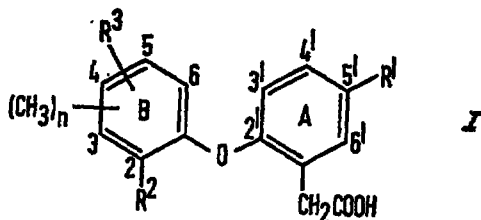
(54) PHENYLALKANE DERIVATIVES AND PROCESSES  
 FOR THE PREPARATION THEREOF

(71) We, RECKITT & COLMAN PRODUCTS LIMITED, a British Company, of Dansom Lane, Hull, Yorkshire, 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:—

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 1950s 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 this 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 arylacetic acid derivatives, in particular *ortho*-phenoxyphenylacetic 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:—



wherein R<sup>1</sup> is hydrogen or methyl;

R<sup>2</sup> is chlorine;

R<sup>3</sup> 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.

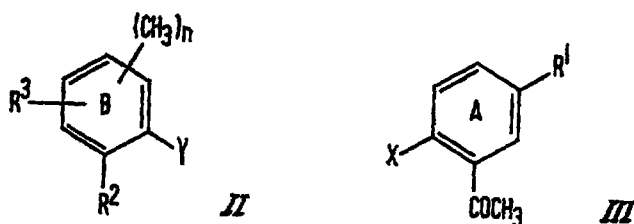
Additionally when R<sup>3</sup> is chlorine at position 4, R<sup>2</sup> may also represent a methoxy group; and one or more chlorine substituents in the molecule may be replaced by bromine.

In a particularly preferred aspect the present invention provides 2-(2-chloro-4-alkyl(C<sub>1</sub> to 6)phenoxy)phenylacetic acids which may be optionally substituted by methyl at positions 5' of Ring A and 2-(2,4-dichloro-phenoxy)phenylacetic acid which may be optionally substituted by one or two methyl groups in Ring B and methyl at position 5' of Ring A.

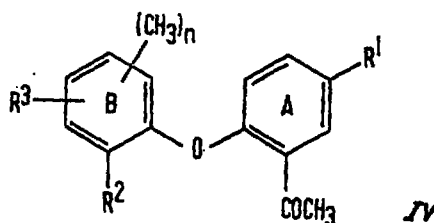
The invention also provides therapeutic compositions comprising as active ingredient one or more compounds of Formula I in association with a pharmaceutically inactive diluent or carrier.

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

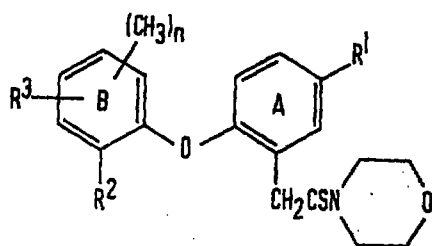
The compounds of Formula I may be prepared by reacting together compounds of Formulae II and III.



in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and n are as hereinbefore defined with reference to Formula I, Y is Ona or OK and X is chlorine, bromine or iodine, at a temperature of at least 120°C in the presence of a copper catalyst to produce a compound of Formula IV



which is thereafter transformed into a compound of Formula I by treatment with sulphur and morpholine to form a thioacetmorpholide of Formula V



which is then hydrolysed.

The copper catalyst used in the above reaction is preferably copper in finely divided form.

The hydrolysis of the thioacetmorpholide is conveniently carried out under basic conditions, but where there is a trifluoromethyl substituent in the molecule acidic conditions may be necessary, for example it has been found that 2-(2-chloro-5-trifluoromethylphenoxy)-5-methyl-phenylacetic acid must be hydrolysed under acidic conditions.

The compounds of Formulae II and III, when not commercially available, may be prepared by standard techniques.

Of the following Examples, Example 1 illustrates a standard procedure employed in the rest of the Examples which illustrate the invention: —

#### Example 1

2-(2,4-Dichloro-5-Methylphenoxy)-5-Chlorophenylacetic Acid.

A mixture of 2,5-dichloroacetophenone (37.8g, 0.2 mole), sodium 2,4-dichloro-

5-methylphenoxide (79.6g, 0.4 mole), 2,4-dichloro-5-methylphenol (35.4g, 0.2 mole) and a copper catalyst (1.0g, prepared according to R. Q. Brewster and T. Groening "Organic Syntheses", John Wiley & Sons, Inc., New York, 1943, Coll. Vol 11, p 446) was stirred under an atmosphere of nitrogen at an internal temperature of 120—125°C for about 24 hours. The mixture was cooled, diluted with water and extracted three times with ether. The combined extracts were washed free of 2,4-dichloro-5-methylphenol with dilute sodium hydroxide solution, and then washed with water and dried. The ether was evaporated and the residue was distilled. The product (30g, 45%) was collected at 168—174°C/0.25 mm and solidified on being cooled. A sample was crystallised from methanol to give 2-(2,4-dichloro-5-methylphenoxy)-5-chloroacetophenone, m.p. 73—74.5°C

*Anal.* Calcd. for  $C_{15}H_{11}Cl_3O_2$ : C, 54.7; H, 3.4; Cl, 32.3  
Found: C, 54.55; H, 3.35; Cl, 32.6%

2-(2,4-Dichloro-5-methylphenoxy)-5-chloroacetophenone (18.0g, 0.055 mole), morpholine (17.1g, 0.197 mole) and sulphur (4.6g, 0.143 mole) were heated under gentle reflux for 24 hours. The warm mixture was poured into methanol (85 ml) and left to cool in an ice bath. The yellow crystals which formed (17.5g, 75%) were filtered off. A portion was crystallised from methanol, giving 2-(2,4-dichloro-5-methylphenoxy)-5-chlorophenylthioacetmorpholide as pale yellow needles, m.p. 135.5—137°C.

*Anal.* Calcd. for  $C_{19}H_{18}Cl_3NO_2S$ :  
C, 53.0; H, 4.2; Cl, 24.7; N, 3.25; S, 7.4  
Found: C, 53.0; H, 4.3; Cl, 24.5; N, 3.2; S 7.2%

2 - (2,4 - Dichloro - 5 - methylphenoxy) - 5 - chlorophenylthioacetmorpholide (14.0g, 0.032 mole), potassium hydroxide (14.0g) and methanol (140 ml) were heated under reflux for 72 hours. (In the other Examples employing this reaction step, a reflux time of at least 48 hours was used.) The mixture was evaporated, water was added and the mixture was extracted with ether. The aqueous layer was then acidified with concentrated hydrochloric acid and the product was extracted into ether. The ether extracts were washed with water, dried and evaporated. The solid residue (10.5g, 93%) was crystallised from light petroleum (B.p. 80—100°) to give 2-(2,4-dichloro-5-methylphenoxy)-5-chlorophenylacetic acid as colourless needles, m.p. 145—148°C.

*Anal.* Calcd. for  $C_{17}H_{11}Cl_3O_3$ : C, 52.1; H, 3.2; Cl, 30.8  
Found: C, 52.1; H, 3.25; Cl, 30.2%

The overall yield of acid from 2,5-dichloroacetophenone is 32%.

#### Example 2

##### 2-(2-Chloro-4-methylphenoxy)-5-methylphenylacetic Acid.

*p*-Chlorotoluene was acetylated with acetyl chloride in the presence of aluminium chloride by the method of A. F. Dokukina, et al., Zhur. obshchei Khim, 1956, 26, 1651 (Chem. Abs 1957, 51 1886a). The product was a mixture containing about 70% of the desired 2-chloro-5-methylacetophenone and 30% of the isomeric 5-chloro-2-methylacetophenone, and was used without separation of the isomers. This is satisfactory, since the minor component contains an unactivated chlorine atom (in contrast to the major component, the chlorine atom of which is activated by the *ortho*-acetyl group) and is recovered unchanged after reaction of the mixture with a phenoxide.

The chloromethylacetophenone mixture described above (33.7g, 0.2 mole), sodium 2-chloro-4-methylphenoxide (66.0g; 0.4 mole), 2-chloro-4-methylphenol (14.25g, 0.1 mole) and a copper catalyst (1.0g, prepared as in Example 1 above) were stirred in a nitrogen atmosphere for about 24 hours at an internal temperature of 120—125°. The reaction mixture was worked up as in Example 1. Distillation of the crude product in vacuo afforded 11.2g of forerun, B.p. 60—137°C/0.3 mm (consisting largely of 5-chloro-2-methylacetophenone), followed by the desired 2-(2-chloro-4-methylphenoxy)-5-methylacetophenone (27.3g, 71% yield based on amount of 2-chloro-5-methylacetophenone present in the original mixture) B.p. 137—143°C/0.3 mm.

*Anal.* Calcd. for  $C_{16}H_{13}ClO_2$ : C, 70.0; H, 5.5; Cl, 12.9  
 Found: C, 69.9; H, 5.8; Cl, 12.7%

2-(2-Chloro-4-methylphenoxy)-5-methylacetophenone (146g, 0.53 mole) was heated with sulphur and morpholine as in Example 1. On pouring the reaction mixture into methanol there was obtained 170g (85%) of yellow solid.

Crystallisation from methanol afforded 2-(2-chloro-4-methylphenoxy)-5-methylphenylthioacetmorpholide m.p. 99—102°C.

*Anal.* Calcd. for  $C_{20}H_{23}ClNO_2S$ :

C, 63.9; H, 5.9; Cl, 9.4; N, 3.7; S, 8.5  
 Found: C, 63.9; H, 5.8; Cl, 9.7; N, 3.9; S, 8.7%

2-(2-chloro-4-methylphenoxy)-5-methylphenylthioacetmorpholide (22g, 0.059 mole) was hydrolysed as in Example 1. The crude product (14 g) was an oily solid, which was crystallised from carbon tetrachloride to give 10g (58%) of material of m.p. 88—93°C. A sample recrystallised from light petroleum (B.p. 60—80°C) gave 2-(2-chloro-4-methylphenoxy)-5-methylphenylacetic acid as colourless needles, m.p. 95—97°C.

*Anal.* Calcd. for  $C_{16}H_{13}ClO_2$ : C, 66.1; H, 5.2; Cl, 12.2  
 Found: C, 66.25; H, 5.25; Cl, 12.4%

#### Example 3

2-(2-chloro-4-*n*-propylphenoxy)-5-methylphenylacetic acid.

A solution of 2-chloro-4-*n*-propylphenol (49.5g, 0.29 mole) in methanol (200 ml) was treated with sodium methoxide in methanol (62.6 ml of 24% w/v 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 a mixture of 2-chloro-5-methylacetophenone and its isomer (94.5g, 0.56 mole) in the presence of copper as in Example 2. 2-(2-Chloro-4-*n*-propylphenoxy)-5-methylacetophenone was collected at 155—160°C at 0.35 mm (66.1g, 75%).

*Anal.* Calcd. for  $C_{18}H_{19}ClO_2$ : C, 71.3; H, 6.3; Cl, 11.7.  
 Found: C, 71.4; H, 6.3; Cl, 11.7%

2-(2-Chloro-4-*n*-propylphenoxy)-5-methylacetophenone (30.3g, 0.1 mole) was heated with morpholine and sulphur as in Example 1. The yield of 2-(2-chloro-4-*n*-propylphenoxy)-5-methylphenylthioacetmorpholide was 28.2g (70%); m.p. 89—89.5°C from methanol.

*Anal.* Calcd. for  $C_{22}H_{26}ClNO_2S$ :

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*-propylphenoxy)-5-methylphenylthioacetmorpholide (25g, 0.062 mole) and potassium hydroxide (50g) 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*-propylphenoxy)-5-methylphenylacetic acid (16.1 g, 82%), m.p. 85—86°C from light petroleum (B.p. 60—80°C).

*Anal.* Calcd. for  $C_{18}H_{19}ClO_2$ : C, 67.8; H, 6.0; Cl, 11.1  
 Found: C, 68.1; H, 6.2; Cl, 11.2%.

#### Example 4

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

A mixture of 2-(2-chloro-5-trifluoromethylphenoxy)-5-methylacetophenone (prepared by the method of Example 3, 15.0g, 0.045 mole), sulphur (3.8g, 0.118 mole) and morpholine (14.3g, 0.165 mole) was heated under reflux for 4 hours. It was then worked up as in Example 1 to give 15.95g (83%) of product, m.p. 120—124°C. A portion was crystallised twice from methanol to give 2-(2-chloro-5-trifluoromethylphenoxy)-5-methylphenylthioacetmorpholide as pale yellow needles, m.p. 128—129°C.

*Anal.* Calcd. for  $C_{20}H_{19}ClF_3NO_2S$ :

C, 55.9; H, 4.45; 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%.

5 A mixture of 2-(2-chloro-5-trifluoromethylphenoxy)-5-methylphenylthioacet- 5  
morpholide (9.0g, 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 product crystallised in the cold filtrate and the  
remainder was isolated by diluting the filtrate with water. The combined solids (6.85g)  
10 of melting point about 120°C, were crystallised from light petroleum (b.p. 80—100°C)  
to give 5.5g (76%) of 2-(2-chloro-5-trifluoromethylphenoxy)-5-methylphenylacetic 10  
acid as pale pinkish microcrystals, m.p. 123—124°C.

*Anal.* Calcd. for  $C_{16}H_{12}ClF_3O_3$ : 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 5

15 2-(2-Chloro-4-n-pentylphenoxy)-5-methylphenylacetic Acid 15  
The crude acid obtained in 52% yield when 2-chloro-4-n-pentylphenol was  
allowed to react as in Example 3 (footnote r of the Table applies) was an oil which  
could not be crystallised. It was therefore purified via its amide. The oily acid (29.4g,  
0.085 mole) was dissolved in methylene chloride (50 ml.), thionyl chloride (6.9 ml,  
20 0.095 mole) was added, and the solution was heated under reflux for 2 hours. Volatile 20  
material was distilled in vacuo, and two portions of dry benzene were added and  
similarly removed in vacuo. The crude acid chloride was taken up in dry benzene (100  
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  
25 layer was separated from the filtrate, washed with water, dried over magnesium 25  
sulphate and evaporated. The solid residue was combined with the material obtained  
by filtration and triturated several times with ether and then crystallised from methanol  
to give 11.4g of 2-(2-chloro-4-n-pentylphenoxy)-5-methylphenylacetamide, m.p.  
30 136—137.5°C. This was heated under reflux with 20% methanolic potassium 30  
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  
35 triturated with light petroleum (b.p. 60—80°C). Crystallisation from this solvent 35  
afforded 2-(2-chloro-4-n-pentylphenoxy)-5-methylphenylacetic acid, m.p. 75—77°;  
yield 6.7g (23% recovery from crude acid, 12% overall yield)

*Anal.* Calcd. for  $C_{20}H_{23}ClO_3$ : C, 69.2; H, 6.7; Cl, 10.2

Found: C, 69.3; H, 6.6; Cl, 10.3%

40 The table sets out details of further examples of *ortho*-phenoxyphenylacetic acid 40  
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 Examples 1, 2 or 3.

TABLE I

| Ex-<br>ample | Ring<br>A | Substituent on |    |    |    |    | Yield<br>% | m.p.<br>°C. | Crystn.<br>Solvent            | Formula                                                        | % Calc. |     |              | % Found |      |              |
|--------------|-----------|----------------|----|----|----|----|------------|-------------|-------------------------------|----------------------------------------------------------------|---------|-----|--------------|---------|------|--------------|
|              |           | Ring B         |    |    |    |    |            |             |                               |                                                                | C       | H   | Cl           | C       | H    | Cl           |
|              |           | 2              | 3  | 4  | 5  | 6  |            |             |                               |                                                                |         |     |              |         |      |              |
| 6            |           | Cl             |    | Cl |    |    | 37         | 134—136°    | CCl <sub>4</sub>              | C <sub>14</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>3</sub> | 56.6    | 3.4 | 23.9         | 56.6    | 3.1  | 23.6         |
| 7            |           | Cl             |    |    | Cl |    | 19         | 119—121     | CCl <sub>4</sub>              | C <sub>14</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>3</sub> | 56.6    | 3.4 | 23.9         | 56.6    | 3.2  | 23.8         |
| 8            |           | Cl             |    | Me |    |    | 19         | 149—150     | CCl <sub>4</sub>              | C <sub>15</sub> H <sub>13</sub> ClO <sub>3</sub>               | 65.1    | 4.7 | 12.8         | 64.9    | 4.7  | 13.1         |
| 9            |           | Cl             |    | Cl | Me |    | 29         | 131—133     | CCl <sub>4</sub>              | C <sub>15</sub> H <sub>13</sub> Cl <sub>2</sub> O <sub>3</sub> | 57.9    | 3.9 | 22.8         | 57.7    | 3.7  | 22.9         |
| 10           |           | Cl             | Mc | Cl | Me |    | 22         | 159—162     | CCl <sub>4</sub>              | C <sub>16</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>3</sub> | 59.1    | 4.3 | 21.8         | 59.3    | 4.1  | 21.5         |
| 11           | Mc        | Cl             |    |    | Cl |    | 33         | 153.5—155   | C <sub>6</sub> H <sub>6</sub> | C <sub>15</sub> H <sub>12</sub> Cl <sub>1</sub> O <sub>3</sub> | 57.9    | 3.9 | 22.8         | 57.9    | 3.9  | 23.1         |
| 12           | Me        | Cl             |    | Cl | Mc | —  | 27         | 147—149     | EtOH/H <sub>2</sub> O         | C <sub>16</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>3</sub> | 59.1    | 4.3 | 21.8         | 59.2    | 4.5  | 21.6         |
| 13           | Me        | Cl             |    | Cl |    | Me | 18         | 133—134     | L.P.40—60°                    | C <sub>16</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>3</sub> | 59.1    | 4.3 | 21.8         | 59.5    | 4.6  | 21.9         |
| 14           | Me        | Cl             |    | Me |    |    | 24         | 97.5—100    | L.P.60—80°                    | C <sub>17</sub> H <sub>17</sub> ClO <sub>3</sub>               | 67.0    | 5.6 | 11.6         | 66.7    | 5.65 | 11.5         |
| 15           | Me        | Cl             | Me | Cl | Me |    | 30         | 153—154     | L.P.60—80°                    | C <sub>17</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>3</sub> | 60.2    | 4.8 | 20.9         | 60.2    | 4.8  | 21.0         |
| 16           | Mc        | Cl             |    | Cl |    |    | 30         | 127—128     | CCl <sub>4</sub>              | C <sub>15</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>3</sub> | 57.9    | 3.9 | 22.8         | 57.8    | 4.1  | 22.8         |
| 17           | Me        | Cl             |    |    |    | Mc | 17         | 135—136     | CCl <sub>4</sub>              | C <sub>16</sub> H <sub>15</sub> ClO <sub>3</sub>               | 66.1    | 5.2 | 12.2         | 66.0    | 5.15 | 12.5         |
| 18           |           | Br             |    | Br |    |    | 22         | 146—148     | MeOH/H <sub>2</sub> O         | C <sub>14</sub> H <sub>10</sub> Br <sub>2</sub> O <sub>3</sub> | 43.55   | 2.6 | 41.4<br>(Br) | 43.7    | 2.6  | 41.5<br>(Br) |

TABLE I (Continued)

| Ex-<br>ample | Ring<br>A | Substituent on |   |                                     |   |   |        | Yield<br>% | m.p.<br>°C. | Crystn.<br>Solvent | Formula                                          | % Calc |     |       | % Found |     |      |
|--------------|-----------|----------------|---|-------------------------------------|---|---|--------|------------|-------------|--------------------|--------------------------------------------------|--------|-----|-------|---------|-----|------|
|              |           | Ring B         |   |                                     |   |   |        |            |             |                    |                                                  | C      | H   | Cl    | C       | H   | Cl   |
|              |           | 2              | 3 | 4                                   | 5 | 6 | Method |            |             |                    |                                                  |        |     |       |         |     |      |
| 19           |           | Cl             |   | Et                                  |   |   | 1(d,u) | 15         | 117—119     | L.P.60—80°         | C <sub>16</sub> H <sub>15</sub> ClO <sub>3</sub> | 66.1   | 5.2 | 12.2  | 66.1    | 5.2 | 12.1 |
| 20           | Me        | Cl             |   | Et                                  |   |   | 2(f,u) | 34         | 106—107.5   | L.P.60—80°         | C <sub>17</sub> H <sub>17</sub> ClO <sub>3</sub> | 67.0   | 5.6 | 11.6  | 67.3    | 5.9 | 11.3 |
| 21           | Me        | Cl             |   | i-Pr                                |   |   | 3(j,r) | 31         | 100—101     | Hexane             | C <sub>18</sub> H <sub>19</sub> ClO <sub>3</sub> | 67.8   | 6.0 | 11.1  | 67.5    | 5.9 | 11.3 |
| 22           | Me        | Cl             |   | n-Bu                                |   |   | 3      | 23         | 70—71.5     | L.P.60—80°         | C <sub>19</sub> H <sub>21</sub> ClO <sub>3</sub> | 68.6   | 6.4 | 10.65 | 68.1    | 6.4 | 10.8 |
| 23           | Me        | Cl             |   | i-Bu                                |   |   | 3(r)   | 20         | 85—86       | L.P.80—100°        | C <sub>19</sub> H <sub>21</sub> ClO <sub>3</sub> | 68.6   | 6.4 | 10.65 | 68.5    | 6.4 | 10.5 |
| 24           | Me        | Cl             |   | s-Bu                                |   |   | 3(w)   | 15         | 53—54       | Hexane             | C <sub>19</sub> H <sub>21</sub> ClO <sub>3</sub> | 68.6   | 6.4 | 10.65 | 68.35   | 6.3 | 10.9 |
| 25           | Me        | Cl             |   | t-Bu                                |   |   | 2(f,u) | 25         | 133—134     | L.P.80—100°        | C <sub>19</sub> H <sub>21</sub> ClO <sub>3</sub> | 68.6   | 6.4 | 10.65 | 68.7    | 6.0 | 10.9 |
| 26           | Me        | Cl             |   | n-C <sub>6</sub><br>H <sub>13</sub> |   |   | 3(r)   | 40         | 71—73       | L.P.60—80°         | C <sub>21</sub> H <sub>25</sub> ClO <sub>3</sub> | 69.9   | 7.0 | 9.8   | 69.8    | 7.1 | 9.9  |
| 27           | Me        | MeO            |   | Cl                                  |   |   | 2(c,u) | 12         | 104—105.5   | CCl <sub>4</sub>   | C <sub>16</sub> H <sub>15</sub> ClO <sub>4</sub> | 62.7   | 4.9 | 11.6  | 62.7    | 5.0 | 11.8 |

## Footnotes to Table I

- a — Ketone: phenoxide: phenol in molar ratio 2: 4: 1  
 b — Ketone: phenoxide: phenol in molar ratio 1: 1: 1  
 c — Ketone: phenoxide: phenol in molar ratio 1: 2: 1  
 5 d — Ketone: phenoxide: phenol in molar ratio 2: 2: 1 5  
 e — Ketone: phenoxide: phenol in molar ratio 4: 6: 3  
 f — Ketone: phenoxide: phenol in molar ratio 4: 2: 1  
 h — The phenoxide-phenol mixture was prepared using the proportions and method of  
 Example 3. The subsequent procedure was that of Example 1, using 2 molar  
 10 proportions of *o*-chloroacetophenone to 1 molar proportion of phenoxide. 10  
 j — Ketone: phenoxide: phenol in molar ratio 3: 1: 0  
 m — large excess of the phenol required to solubilise the reaction mixture  
 r — The thioacetmorpholide was not obtained as a solid when the hot reaction mixture  
 was poured into methanol. The methanol was evaporated and the residue was  
 15 dissolved in ether. The solution was washed with dilute hydrochloric acid to  
 remove morpholine, and then with water, dried over magnesium sulphate and  
 evaporated. The residual oil was then hydrolysed by the procedure used for solid  
 thioacetmorpholides. 15  
 t — Thioacetmorpholide hydrolysed in a mixture of 30g. potassium hydroxide and  
 20 20 ml of 2-ethoxyethanol. 20  
 u — 20% potassium hydroxide in methanol was used for the hydrolysis stage.  
 w — The crude acid was purified via its amide as in Example 5.
- L.P. refers to light petroleum of the given b.p. range.
- 25 Screening for anti-inflammatory activity has been carried out employing the  
 established adjuvant arthritis test, based on a procedure described by Newbould  
 (Brit. J. Pharmacol. 35, 487 (1969)). The following is a brief description of the method  
 which we use: — 25
- On day 0 of the test 0.05ml of liquid paraffin containing 5 mg/ml of dead  
 30 *Mycobacterium tuberculosis* is injected into the plantar surface of the left hind paw of  
 male rats. On day 21 the animals are weighed and the arthritis assessed by measurement  
 of the volume of the left hind (injected) paw. Those animals in which 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  
 35 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  
 40 of the method of Winder et al (J. Pharmac. exp. therap. 133, 117 (1961)). 40
- Screening to determine the extent of gastric ulceration following acute administra-  
 tion of a drug in rats has been carried out by a procedure based on that of Martindale  
 et al. (J. Pharm. Pharmacol, 12, 153T—158T (1960)). Ulceration was assessed at 4  
 hours in the case of Phenylbutazone and Ibuprofen, but at 24 hours in the case of the  
 45 compounds of the invention, for which preliminary studies indicated a greater ulcero-  
 genic effect at 24 hours than at shorter time intervals. Acetylsalicylic acid was used as  
 a positive control for the 24 hour studies. 45
- 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  
 50 corresponding approximate daily minimum effective (anti-arthritis) dose (MED) clearly  
 demonstrates the reduced ulcerogenic potential of our compounds relative to their  
 therapeutic activity when compared with established anti-inflammatory agents. 50

TABLE II

| Compound                                                    | MED<br>(mg/kg p.o.) | MUD<br>(mg./kg p.o.) | MUD/MED     |
|-------------------------------------------------------------|---------------------|----------------------|-------------|
| Acetylsalicylic acid                                        | 60                  | < 60 > 30            | < 1.0 > 0.5 |
| Phenylbutazone                                              | 6                   | <100 > 30            | <16.7 > 5.0 |
| Ibuprofen                                                   | 50                  | < 17 > 10            | < 0.3 > 0.2 |
| 2-(2,4-dichlorophenoxy)<br>phenylacetic acid                | 20                  | <800 > 500           | <40 > 25    |
| 2-(2,4-dichloro-3,5-dimethyl-<br>phenoxy)phenylacetic acid  | 20                  | <800 > 500           | <40 > 25    |
| 2-(2-chloro-6-methylphenoxy)<br>5-methylphenylacetic acid   | 40                  | > 500                | > 12.5      |
| 2-(2-chloro-4-ethylphenoxy)<br>5-methylphenylacetic acid    | 14                  | > 500                | > 35.7      |
| 2-(2-methoxy-4-chlorophenoxy)<br>5-methylphenylacetic acid  | 29                  | > 500                | > 17.2      |
| 2-(2-chloro-4-n-propylphenoxy)<br>5-methylphenylacetic acid | 33                  | > 500                | > 15.0      |

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 1g/kg. Moreover, with *m*-phenoxyphenylacetic acid (no anti-arthritic activity) there was ulceration 4 hours after administration of 100mg/kg, and with *p*-phenoxyphenylacetic acid ulceration 4 hours after administration of 50mg/kg, and finally with the analogous *p*-(2,4-dichlorophenoxy)phenylacetic acid there was severe ulceration 24 hours after administration of 1g/kg.

*o*-Phenoxyphenylacetic 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-dimethylphenoxy)phenylacetic acid, possess, in addition to anti-inflammatory activity, antipyretic activity. The former compound also has analgesic activity, and exerts an anti-oedematous effect in adrenalectomized 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 oral. 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

5

10

15

20

also incorporate flavouring agents, colouring matter, disintegrating agents, tableting 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-ethylphenoxy)-5-methylphenylacetic acid, 2-(2-methoxy-4-chlorophenoxy)-5-methylphenylacetic acid, or 2-(2-chloro-4-tert-butylphenoxy)-5-methylphenylacetic acid. A suitable oral daily dose of these preferred compounds for the relief of inflammatory states in human beings, would be from 250mg to 3 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.

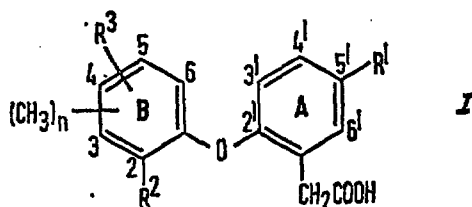
#### Capsule

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-dimethylphenoxy) phenylacetic acid, 2-(2-chloro-4-ethylphenoxy)-5-methylphenylacetic acid, 2-(2-methoxy-4-chlorophenoxy)-5-methylphenylacetic acid or 2-(2-chloro-4-tert-butylphenoxy)-5-methylphenylacetic acid.

#### WHAT WE CLAIM IS:—

1. Compounds of the formula:—



wherein  $R^1$  is hydrogen or methyl;

$R^2$  is chlorine;

$R^3$  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.

2. A modification of the compounds of Formula I as claimed in claim 1 wherein  $R^2$  may also represent methoxy when  $R^3$  is chlorine at position 4.

3. A modification of the compounds as claimed in claim 1 or claim 2 wherein one or more chlorine substituents in the compound is/are replaced by bromine.

4. Compounds of Formula I as claimed in claim 1 which are 2-(2-Chloro-4-alkyl( $C_1$  to  $C_6$ )phenoxy)phenylacetic acids which may be optionally substituted by methyl at position 5' of Ring A.

5. Compounds of Formula I as claimed in claim 1 which are 2-(2,4-Dichlorophenoxy)phenylacetic acid which may be optionally substituted by one or two methyl groups in Ring B and methyl at position 5' of Ring A.

6. 2-(2-Chloro-4-methylphenoxy)-5-methylphenylacetic acid.

7. 2-(2-Chloro-4-*n*-propylphenoxy)-5-methylphenylacetic acid.

8. 2-(2-Chloro-5-trifluoromethylphenoxy)-5-methylphenylacetic acid.

9. 2-(2-Chloro-4-*n*-pentylphenoxy)-5-methylphenylacetic acid.

10. 2-(2,4-Dichlorophenoxy)phenylacetic acid.

11. 2-(2,5-Dichlorophenoxy)phenylacetic acid.

12. 2-(2-Chloro-4-methylphenoxy)phenylacetic acid.

13. 2-(2,4-Dichloro-5-methylphenoxy)phenylacetic acid.

also incorporate flavouring agents, colouring matter, disintegrating agents, tableting 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-ethylphenoxy)-5-methylphenylacetic acid, 2-(2-methoxy-4-chlorophenoxy)-5-methylphenylacetic acid, or 2-(2-chloro-4-tert-butylphenoxy)-5-methylphenylacetic acid. A suitable oral daily dose of these preferred compounds for the relief of inflammatory states in human beings, would be from 250mg to 3 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.

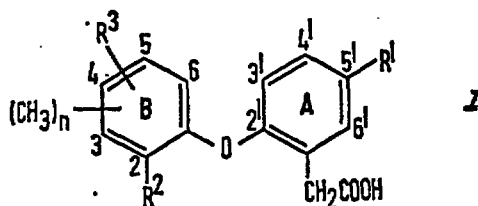
#### Capsule

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-dimethylphenoxy) phenylacetic acid, 2-(2-chloro-4-ethylphenoxy)-5-methylphenylacetic acid, 2-(2-methoxy-4-chlorophenoxy)-5-methylphenylacetic acid or 2-(2-chloro-4-tert-butylphenoxy)-5-methylphenylacetic acid.

#### WHAT WE CLAIM IS:—

1. Compounds of the formula:—



wherein R<sup>1</sup> is hydrogen or methyl;

R<sup>2</sup> is chlorine;

R<sup>3</sup> 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.

2. A modification of the compounds of Formula I as claimed in claim 1 wherein R<sup>2</sup> may also represent methoxy when R<sup>3</sup> is chlorine at position 4.

3. A modification of the compounds as claimed in claim 1 or claim 2 wherein one or more chlorine substituents in the compound is/are replaced by bromine.

4. Compounds of Formula I as claimed in claim 1 which are 2-(2-Chloro-4-alkyl(C<sub>1</sub> to 6)phenoxy)phenylacetic acids which may be optionally substituted by methyl at position 5' of Ring A.

5. Compounds of Formula I as claimed in claim 1 which are 2-(2,4-Dichlorophenoxy)phenylacetic acid which may be optionally substituted by one or two methyl groups in Ring B and methyl at position 5' of Ring A.

6. 2-(2-Chloro-4-methylphenoxy)-5-methylphenylacetic acid.

7. 2-(2-Chloro-4-n-propylphenoxy)-5-methylphenylacetic acid.

8. 2-(2-Chloro-5-trifluoromethylphenoxy)-5-methylphenylacetic acid.

9. 2-(2-Chloro-4-n-pentylphenoxy)-5-methylphenylacetic acid.

10. 2-(2,4-Dichlorophenoxy)phenylacetic acid.

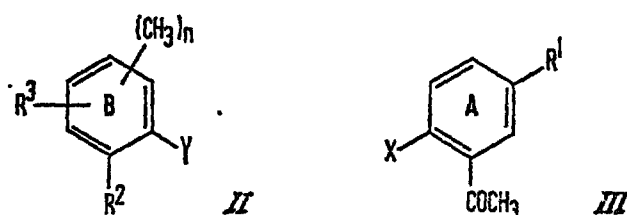
11. 2-(2,5-Dichlorophenoxy)phenylacetic acid.

12. 2-(2-Chloro-4-methylphenoxy)phenylacetic acid.

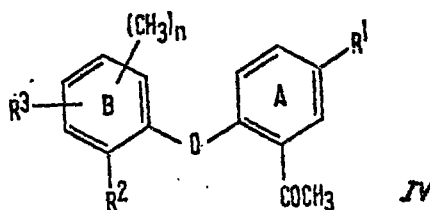
13. 2-(2,4-Dichloro-5-methylphenoxy)phenylacetic acid.



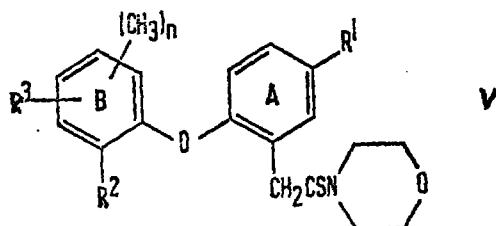
14. 2-(2,4-Dichloro-3,5-dimethylphenoxy)phenylacetic acid.  
 15. 2-(2,5-Dichlorophenoxy)-5-methylphenylacetic acid.  
 16. 2-(2,4-Dichloro-5-methylphenoxy)-5-methylphenylacetic acid.  
 17. 2-(2-Chloro-4,5-dimethylphenoxy)-5-methylphenylacetic acid.  
 18. 2-(2,4-Dichloro-3,5-dimethylphenoxy)-5-methylphenylacetic acid.  
 19. 2-(2,4-Dichlorophenoxy)-5-methylphenylacetic acid.  
 20. 2-(2-Chloro-6-methylphenoxy)-5-methylphenylacetic acid.  
 21. 2-(2,4-Dibromophenoxy)phenylacetic acid.  
 22. 2-(2-Chloro-4-ethylphenoxy)phenylacetic acid.  
 23. 2-(2-Chloro-4-ethylphenoxy)-5-methylphenylacetic acid.  
 24. 2-(2-Chloro-4-*i*-propylphenoxy)-5-methylphenylacetic acid.  
 25. 2-(2-Chloro-4-*n*-butylphenoxy)-5-methylphenylacetic acid.  
 26. 2-(2-Chloro-4-*i*-butylphenoxy)-5-methylphenylacetic acid.  
 27. 2-(2-Chloro-4-*s*-butylphenoxy)-5-methylphenylacetic acid.  
 28. 2-(2-Chloro-4-*t*-butylphenoxy)-5-methylphenylacetic acid.  
 29. 2-(2-Chloro-4-*n*-hexylphenoxy)-5-methylphenylacetic acid.  
 30. 2-(2-Methoxy-4-chlorophenoxy)-5-methylphenylacetic acid.  
 31. Compounds of Formula I as hereinbefore described with reference to any one of the Examples.  
 32. A pharmaceutical composition which comprises as active ingredient a compound as claimed in any one of claims 1 to 31 in admixture with a pharmaceutically inactive diluent or carrier.  
 33. A pharmaceutical composition as claimed in claim 32 in tablet or capsule form for oral administration which contains from 25 to 500 mg of the active ingredient.  
 34. A process for the preparation of compounds of Formula I as claimed in claims 1 to 3, which process comprises reacting together compounds of Formula II and III



in which  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ , and  $n$  are as hereinbefore defined in claims 1 to 3,  $\text{Y}$  is  $\text{ONa}$  or  $\text{OK}$  and  $\text{X}$  is chlorine, bromine or iodine, at a temperature of at least  $120^\circ\text{C}$  in the presence of a copper catalyst to produce a compound of Formula V



which is thereafter transformed into a compound of Formula I by treatment with sulphur and morpholine to form a thioacetmorpholide of Formula V



which is then hydrolysed.



35. A process for the preparation of compounds of Formula I as hereinbefore defined in claims 1 to 3 substantially as hereinbefore described with reference to any one of the Examples.

BOULT, WADE & TENNANT,  
Chartered Patent Agents,  
112 Hatton Garden, London EC1N 8NA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1973  
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from  
which copies may be obtained.

