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## PATENT SPECIFICATION

NO DRAWINGS

1.139.332

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Date of Application and filing Complete Specification: 7 April, 1966.  
No. 15497/66.

Application made in Switzerland (No. 4961) on 8 April, 1965.  
Complete Specification Published: 8 Jan., 1969.

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Index at acceptance:—C2 C(1E6K4, 1E6K7, 1E7D1, 1E7E1, 1E7F1, 1E7N5, 1F1B, 1F1C4, 1F1D2, 1F2A1, 1F2C2, 1F2C4, 1F2D2, 1F4C4, 1F4D2, 1F4F2, 1F4F3, 1H1A2, 1H1C2, 1H2A2, 1H2A7, 1H2C2, 1Q2, 1Q6B1, 1Q7A, 1Q8C, 1Q9A, 1Q9D2, 1Q9F2, 1Q9E, 1Q11J, 2A2, 2A14, 2B6A2, 2B6B, 2B6G2, 2B6G11, 2B49C1, 2B49G3, 2R16, 1E32Y, 1E36Y, 1E50Y, 1E220, 1E322, 1E360, 1E361, 1E503, 1E660, 1G32Y, 1G36Y, 1G50Y, 1G220, 1G322, 1G360, 1G361, 1G503, 1G610, 1G652, 1G680); A5 B(1S, 2S, 31)

Int. Cl.:—C 07 c 101/64

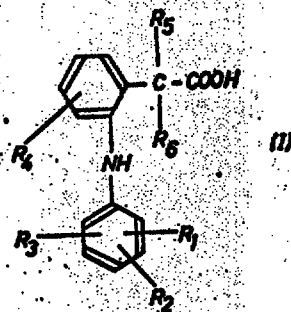
## COMPLETE SPECIFICATION

## Substituted Phenylacetic Acids and Processes for Their Production

5 We, J. R. GEIGY A.G. a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, 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:—

10 The present invention concerns a process for the production of new substituted phenylacetic acids and their salts, these new compounds themselves and medicaments containing them as well as the use of such medicaments.

15 Substituted phenylacetic acids of the general formula I



wherein

20  $R_1$  represents a low alkyl or alkoxy radical, a halogen atom up to the atomic number 35 or the trifluoromethyl group, and  $R_2$  and

[Price 4s. 6d.]

$R_3$  each represent hydrogen, a low alkyl or alkoxy radical or a halogen atom up to the atomic number 35, 25

$R_4$  represents hydrogen, a low alkyl or alkoxy radical, a halogen atom up to the atomic number 35 or the trifluoromethyl group, 30

$R_5$  and  $R_6$  each represent hydrogen, a low alkyl radical or a benzyl radical, 35

and their salts with inorganic and organic bases, have not been known hitherto. It has now been found that the compounds of general formula I and their salts have valuable pharmacological properties, in particular antiphlogistic (anti-inflammatory), analgetic and antipyretic activity with, at the same time, a favourable therapeutic index. They can be administered orally, rectally or, particularly in the form of aqueous solutions of their salts, also parenterally, in particular intramuscularly, for the treatment of rheumatic, arthritic and other inflammatory diseases. The antiphlogistic action can be proved in pharmacological trials, for example on the UV erythema in the guinea pig and bolous alba oedema in the rat. 40

In addition, these substances are capable of absorbing UV rays at 290–300 m $\mu$ , which are responsible for sun burn, and they are therefore suitable as UV absorbers for cosmetic purposes, e.g. in sun tan lotions, because they allow the desired tanning rays over 315 m $\mu$  to come through. 45

Throughout the specification, including the claims, "low" as used to qualify "alkyl" and

P.113 25p SPECIFICATION AMENDED - SEE ATTACHED SLIP

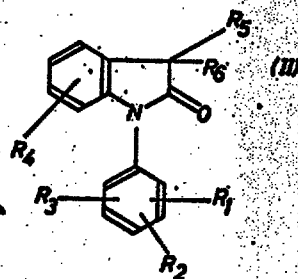
"alkoxy" radicals is intended to mean a maximum of 4 carbon atoms.

In the compounds of general formula I and in the corresponding starting materials mentioned below,  $R_1$  to  $R_6$ , independently of each other represent, as low alkyl radicals, e.g. methyl or ethyl radicals. Some of the symbols mentioned can also represent, e.g. n-propyl, isopropyl, n-butyl, sec. butyl or tert. butyl radicals. Low alkoxy radicals or halogen atoms  $R_1$  to  $R_6$  are, e.g. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy or isobutoxy radicals or chlorine, fluorine or bromine atoms.

As low alkyl radicals,  $R_5$  and  $R_6$ , preferably represent methyl or ethyl radicals.

One group of compounds of the general formula I, which may be mentioned specifically are those in which  $R_1$ ,  $R_2$  and  $R_3$  have the meanings defined beneath formula I above and  $R_4$ ,  $R_5$  and  $R_6$  each represent hydrogen, and their salts with inorganic and organic bases.

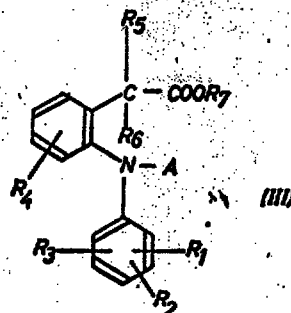
To produce an acid of the general formula I and its salts with inorganic or organic bases, a compound of the general formula II



wherein  $R_1$ — $R_6$  have the meanings given above, is reacted with an alkali metal hydroxide, alkali metal carbonate or alkaline earth metal hydroxide while heating and, if desired, the acid is liberated from the alkali or alkaline earth salt obtained. This can be converted into another salt with an organic or inorganic base if desired.

Suitable solvents are, in particular, aqueous low alkanols such as ethanol, methanol or n-butanol; ethylene glycol or dimethyl formamide can also be used. The hydrolysis is performed, e.g. at or at a little under the boiling temperature of the solvent; at least one equivalent of an alkali metal hydroxide or carbonate or alkaline earth metal hydroxide, particularly sodium or potassium hydroxide, is used therefor.

The compounds of general formula I are produced by a second process by reacting, while heating, a compound of the general formula III



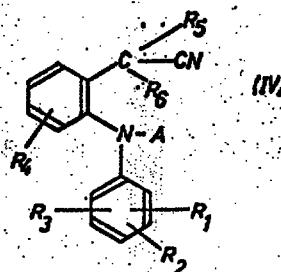
wherein

A represents hydrogen or carboxylic acyl radical of at most 4 carbon atoms, particularly the acetyl radical, and

$R_7$  represents a low alkyl or an aralkyl radical, particularly the benzyl radical, and

$R_1$ — $R_6$  have the meanings given above, with an alkali metal hydroxide, carbonate or bicarbonate, an alkaline earth metal hydroxide or a basic ion exchanger, or if  $R_7$  is the benzyl radical, splitting this off by hydrogenolysis with catalytically activated hydrogen. Suitable solvents for the hydrolysis are, in particular, aqueous low alkanols such as methanol, ethanol, n-butanol, and also ethylene glycol or dimethyl formamide. The hydrolysis is performed, e.g. at or at just below the boiling point of the solvent using at least one equivalent of the base. More advantageously, the hydrogenolysis is performed under normal pressure and at room temperature to 50°C in the presence of palladium charcoal in alcohol.

Compounds of the general formula I are obtained by a third process by reacting, while heating, a compound of general formula IV



wherein  $R_1$ — $R_6$  and A have the meanings given above, with an alkali metal hydroxide in an aqueous solvent. Suitable solvents are, in particular, aqueous low alkanols such as ethanol, methanol, or n-butanol, and also ethylene glycol or dimethyl formamide. The hydrolysis is performed, e.g. at or at a little under the boiling temperature of the solvent using at least two equivalents of an alkali

metal hydroxide, in particular sodium or potassium hydroxide.

- The starting materials of general formula II, which can be termed 1-aryl-2-indolinones, 1-aryl-oxindoles or lactams of 2-arylamino-phenylacetic acids, are in their turn, new compounds. To introduce the radicals  $R_1$  and  $R_2$ , such 1-aryl-2-indolinones are alkylated with an alkyl halide or dialkyl sulfate in the presence of sodium hydride or sodium amide in dimethyl formamide, or they are treated with an aralkyl halide, preferably with benzyl chloride. A benzyl radical can also be introduced into such 1-aryl-2-indolinones by first reacting them with benzaldehyde and then reducing the 1-aryl-3-benzal-2-indolinone formed, e.g. with activated hydrogen. The compounds of general formula II are produced, e.g. analogously to the known 1-phenyl-2-indolinone from corresponding, unsymmetrically substituted diphenylamines by chloroacetylating them to form substituted 2-chloro-N-phenyl-acetanilides and heating the latter with aluminium chloride at temperatures about 160°C or by heating them with aluminium chloride in suitable solvents such as tetrachloroethane or nitrobenzene at 100–150°C. Some diphenylamines substituted corresponding to the definition of  $R_1$ — $R_2$  are known and others can be produced analogously, e.g. according to A. W. Chapman, J. Chem. Soc. 1929, 569–572, by heating N,O-diaryl-iminoesters and hydrolysing the N,N-diarylamides formed by rearrangement, or according to the method used by R. B. Moffett et al, J. Am. Chem. Soc. 82, 1605 (1960), starting from optionally substituted *o*-chloro- or *o*-bromo-benzoic acids and substituted anilines and decarboxylating the  $\alpha$ -anilino-benzoic acids formed.

- A particularly suitable method for the production of diphenylamines substituted corresponding to the definition of  $R_1$ — $R_2$  is that of Goldberg, Ber. 40, 4541 (1907) by which an optionally substituted acetanilide is reacted with a bromo-benzene substituted corresponding to the definition of  $R_2$ .

- Compounds of general formula II containing a low alkyl group as  $R_1$  and hydrogen as  $R_2$  can be obtained by reacting  $\alpha$ -halogen alkanolic acid halides with diphenylamines substituted corresponding to the definitions of  $R_1$  to  $R_2$  and then closing the ring. If thereby a mixture of isomers is formed, they are separated from each other by known techniques, e.g. chromatography.

- Another method for the production of compounds of general formula II consists in acid saponification of compounds of general formulae III and IV whereby ring closure occurs.

The starting materials of general formula III having a low alkyl group as  $R_1$  and an

acyl group as A can be obtained, e.g. by converting the corresponding cyano compounds in imino-ether hydrochlorides and decomposing the latter with water.

These starting materials can also be obtained, however, starting from the acids of general formula I by treating the latter in the known way with alkylating agents such as diazo alkanes or dialkyl sulphates.

The low alkyl and aralkyl esters of general formula III can also be obtained by other known esterification processes, e.g. by the N,N - dimethyl formamide - dincopentyl acetal process of H. Büchi, K. Steen and A. Eschenmoser (Ang. Chemie 75, (1963) 1176) or with thionyl chloride at -10°C in abs. alkyl or aralkyl alcohol according to Brenner (Helv. Chim. Acta 34, (1953) 1114).

The starting materials of general formula IV are obtained, for example, by reacting  $\alpha$  - halogen - N - aryl - *o* - toluidines with sodium or potassium cyanide. Surprisingly,  $\alpha$  - chloro - *o* - toluidines or  $\alpha$  - chloro - *o* - toluidines are formed in a one-step reaction from *o*-arylamino-benzyl alcohols, i.e. on boiling the latter with acetyl chloride. Some of the *o*-aryl-amino-benzyl alcohols substituted corresponding to the definition of  $R_1$ — $R_2$  are known and others can be obtained, e.g. by reduction of N-aryl-anthranilic acid alkyl esters with lithium aluminium hydride in ether or tetrahydrofuran, sodium borohydride in methanol, or sodium borohydride and lithium bromide in diglyme (diethylene glycol dimethyl ether). The N-aryl-anthranilic acids can be reduced, e.g. with lithium aluminium hydride.

Low alkyl groups  $R_1$  and  $R_2$  can also be introduced by alkylation of compounds of general formulae III and IV which are unsubstituted in the  $\alpha$ -position.

The substituted phenylacetic acids of general formula I and their salts with inorganic and organic bases can be administered orally, rectally or parenterally, in particular intramuscularly. They can also be applied externally in foundations for sun-tan oils and ointments.

Salts suitable for therapeutic administration are those with pharmacologically acceptable inorganic and organic bases, i.e. with bases which themselves do not have a physiological action in the usual dosages or which have a desired action, e.g. in forms for parenteral administration, those which have, in particular, a local anaesthetic action. Suitable salts are, e.g. sodium, potassium, lithium, magnesium, calcium and ammonium salts as well as salts with ethylamine, triethylamine, ethanolamine, diethanolamine, diethylaminoethanol, ethylenediamine, benzylamine, procain, pyrrolidine, piperidine, morpholine, 1 - ethyl piperidine or 2-piperidino ethanol.

The daily dosages to be taken internally

- of free acids of general formula I or of pharmacologically acceptable salts thereof for the treatment of rheumatic, arthritic and other inflammatory diseases vary between 100 and 1500 mg for adult patients. Suitable dosage units such as dragées (sugar coated tablets), tablets, suppositories or ampoules, preferably contain 25—300 mg of a free acid or a pharmacologically acceptable salt thereof.
- Dosage units for oral administration preferably contain between 1% and 90% of an acid of general formula I or of a pharmacologically acceptable salt thereof as active substance. They are produced by combining the active substances, e.g. with solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch or amylopectin; also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants such as magnesium or calcium stearate or polyethylene glycols (Carbowaxes—"Carbowax" is a registered Trade Mark) of suitable molecular weights, to form tablets or dragée cores. The latter are coated, e.g. with concentrated sugar solutions which can also contain, e.g. gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between varying dosages of active substance.
- The following prescriptions further illustrate the production of tablets and dragées:
- a) 100.0 g of active substance, e.g. [ $\sigma$ -(2, 6 - dichloro - m - toluidino) - phenyl]-acetic acid or its calcium or lithium salt are mixed with 550.0 g of lactose and 292.0 g of potato starch, the mixture is moistened with an alcoholic solution of 8.0 g of gelatine and granulated through a sieve. After drying, 60.0 g of potato starch, 60.0 g of talcum, 10.0 g of magnesium stearate and 20.0 g of colloidal silicium dioxide are mixed in and the mixture is pressed into 10,000 tablets each weighing 200 mg and containing 100 mg of active substance. The tablets can be grooved for better adaptation of the dosage.
- b) 200.0 g of active substance, e.g. [ $\sigma$ -(2, 6 - dichloro - m - toluidino) - phenyl]-acetic acid are well mixed with 16 g of maize starch and 6.0 g of colloidal silicium dioxide. The mixture is moistened with a solution of 2.0 g of stearic acid, 6.0 g of ethyl cellulose and 6.0 g of stearin in about 70 ml of isopropyl alcohol and granulated through a sieve III (Ph. Helv. V). The granulate is dried for about 14 hours and then passed through sieve III—IIIa. It is then mixed with 16.0 g of maize starch, 16.0 g of talcum and 2.0 g of magnesium stearate and pressed into 1000 dragée cores. These are coated with a concentrated syrup from 2.000 g of shellac, 7.500 g of gum arabic, 0.150 g of dyestuff, 2.000 g of highly dispersed silicium dioxide, 25.000 g of talcum and 53.350 g of sugar and dried. The dragées obtained each weigh 360 mg and contain 200 mg of active substance.
- Dosage units for rectal administration are, for example, suppositories which consist of a combination of an acid of general formula I or a suitable salt thereof with a neutral fatty foundation, or also gelatine rectal capsules which contain a combination of an active substance or a suitable salt thereof with polyethylene glycols (Carbowaxes) of suitable molecular weight.
- Ampoules for parenteral, particularly intramuscular, administration preferably contain a water-soluble salt, e.g. the sodium salt, of a substituted phenylacetic acid of general formula I, in a concentration of, preferably, 0.5—5%, in aqueous solution, optionally together with suitable stabilising agents and buffer substances.
- One of the following prescriptions can be used for the production of sun-tan creams:
- |    |                                                               |            |     |
|----|---------------------------------------------------------------|------------|-----|
| c) | [ $\sigma$ - (2, 6 - dichlor - anilino)-phenyl] - acetic acid | 1.0 g      |     |
|    | paraffin oil, thinly liquid                                   | 1.0 g      | 95  |
|    | polyoxyethylene sorbitan mono-stearate                        | 2.0 g      |     |
|    | polyoxyethylene sorbitol lanoline derivative                  | 1.5 g      |     |
|    | sorbitol solution 70%                                         | 3.0 g      | 100 |
|    | stearic acid                                                  | 15.0 g     |     |
|    | preservative + perfume                                        | q.s.       |     |
|    | water                                                         | ad 100.0 g |     |
| d) | [ $\sigma$ - (2, 6 - dichlor - anilino)-phenyl] - acetic acid | 1.0 g      | 105 |
|    | propylene glycol                                              | 28.0 g     |     |
|    | glycerine monostearate                                        | 18.0 g     |     |
|    | polyoxyethylene - sorbitan mono-laurate                       | 8.0 g      | 110 |
|    | thimicrosal (solution 1:1000)                                 | 1.0 g      |     |
|    | perfume                                                       | q.s.       |     |
|    | water                                                         | ad 100.0g  |     |
- The following examples further illustrate the performance of the processes according to the invention but they in no way limit the scope of the invention. The temperatures are given in degrees Centigrade and percentages are by weight unless expressly stated otherwise.
- EXAMPLE 1
- [ $\sigma$  - (2, 6 - dichloro - m - toluidino)-phenyl] - acetic acid
- A solution of 40 g of 1 - (2, 6 - dichloro-

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tolyl) - 2 - indolinone in 280 ml of 1N-sodium hydroxide solution and 420 ml of ethanol is refluxed for 2 hours. The clear solution is cooled and the ethanol is distilled off at a bath temperature of 40° under 11 Torr. The aqueous residue is extracted with 100 ml of ether and cooled to 5° by the addition of ice (about 50 g) and external cooling. 2N hydrochloric acid is then added while stirring until the pH of the solution is about 6. The precipitated acid is taken up in 400 ml of ether, the ether solution is separated and the aqueous solution is again extracted with 200 ml of ether. The ether solutions are washed with 50 ml of water, combined, dried over sodium sulphate and concentrated under 11 Torr without heating. After adding petroleum ether to the concentrated ethereal solution, [o - (2, 6 - dichloro - m - toluidino) - phenyl] - acetic acid crystallises out. After recrystallisation from ether/petroleum ether, it melts at 146—149°.

#### EXAMPLE 2

- The following compounds are produced in an analogous manner to Example 1.
- [2 - (2', 6' - dichloranilino) - 5 - chlorophenyl] - acetic acid, M.P. 181—183° from methanol;
  - [2 - (2', 6' - dichloranilino) - phenyl] - acetic acid, M.P. 256—158°;
  - [2 - (2', 6' - dichloro - m - toluidino) - 5 - chlorophenyl] - acetic acid, M.P. 152—156° from ether/petroleum ether;
  - [2 - (2', 6' - dichloro - m - toluidino) - 5 - methoxyphenyl] - acetic acid, M.P. 120—122° from ether/petroleum ether;
  - [2 - (2', 6' - dichloranilino) - 5 - bromophenyl] - acetic acid, recrystallised from ether/petroleum, decomposes at 161°.

#### Preparation of starting materials

The necessary starting materials for Examples 1 and 2 may be produced, for example, as follows:

- 45  
50  
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60
- a) 2,6 - dichloro - N - phenyl - m - toluidine
- 7 g of N - (2, 6 - dichloro - m - tolyl) - anthranilic acid are heated for 2 hours at 280°. The cooled melt is dissolved in 30 ml of benzene and the benzene solution is extracted with 5 ml of 2N sodium carbonate and 5 ml of water. The solution is dried with sodium sulphate and concentrated. The residue is distilled whereupon 2, 6 - dichloro - N - phenyl - m - toluidine is obtained as a yellow oil, B.P. 115—120°/0.001 Torr.
- The following compounds are obtained analogously:
- N - phenyl - 2, 6 - xylydene, B.P. 123—125°/0.01 Torr;
  - N - (p - chlorophenyl) - 2, 6 - xylydene; B.P. 126—127°/0.01 Torr;

- N - phenyl - 2, 3 - xylydene, B.P. 100—102°/0.005 Torr;
  - 2, 6 - dichloro - diphenylamine, B.P. 109—111°/0.003 Torr;
  - 2, 6, 4' - trichlorodiphenylamine, B.P. 123—125°/0.001 Torr;
- 2,6-Dichloro-diphenylamine can also be produced as follows:

#### 2,6-dichloro-diphenylamine

15 g of 2, 6 - dichloro - acetanilide are dissolved in 150 ml of bromobenzene. 5.5 g of calcinated potassium carbonate and 0.5 g of copper powder are added. The mixture is then refluxed for 4 days the water formed being removed by a water separator. The mixture is then cooled and subjected to steam distillation. The residue is extracted with 200 ml of ether. The ether solution is filtered through Hyflo ("Hyflo" is a registered Trade Mark) and the residue is concentrated to dryness under 11 Torr. The residue is dissolved in 60 ml of 10% ethanolic potassium hydroxide solution and the solution is refluxed for 3 hours. The solution is then concentrated to dryness at 40° under 11 Torr. 10 ml of water are added to the residue which is then extracted with 100 ml of ether. The ether solution is removed and extracted with 20 ml of water. The ether solution is then dried with sodium sulphate and concentrated to dryness under 11 Torr. The residue is distilled under high vacuum. The 2,6-dichloro-diphenylamine boils, as a yellow oil, at 115°/0.01 Torr. The yield is 43% of the theoretical.

The following compounds are produced analogously:

- 2, 6 - dichloro - N - phenyl - m - toluidine, B.P. 117—120°/0.001 Torr;
  - N - phenyl - 2, 3 - xylydene, B.P. 100—102°/0.005 Torr;
  - N - phenyl - 2, 6 - xylydene, B.P. 125°/0.01 Torr;
  - N - (4' - chlorophenyl) - 2, 6 - xylydene, B.P. 124°/0.01 Torr;
  - 2, 6 - dichloro - 4' - chlorodiphenylamine, B.P. 121°/0.01 Torr;
  - 2, 6 - dichloro - N - p - tolyl - m - toluidine, B.P. 131—135°/0.005 Torr;
  - 2, 6, 4' - trichloro - N - phenyl - m - toluidine, B.P. 135—145°/0.005 Torr;
  - 2, 6 - dichloro - N - p - methoxyphenyl - m - toluidine, B.P. 115—130°/0.001 Torr;
- 2, 6 - Dichloroacetanilide is produced as follows:

#### 2,6-dichloroacetanilide

40 ml of acetyl chloride are slowly added dropwise to a solution of 81 g of 2,6-dichloraniline in 30 ml of glacial acetic acid. The solution is then heated in a water bath until the development of hydrogen chloride has been completed. It is then cooled to

room temperature and the mixture is poured onto ice. The crystals which separate are filtered off and recrystallised from glacial acetic acid. The 2,6-dichloroacetanilide melts at 180—181°. The yield is 70% of the theoretical.

The following compounds are produced analogously:

2', 6' - dichloro - aceto - *m* - toluidide, M.P. 179—181° from glacial acetic acid/water;

aceto - 2', 3' - xylidide, M.P. 175—177° from glacial acetic acid/water;

aceto - 2', 6' - xylidide, M.P. 181° from glacial acetic acid/water;

Some of these compounds are known.

b) N - phenyl - 2, 2', 6' - trichloro - aceto - *m* - toluidide

4 g of 2, 6 - dichloro - N - phenyl - *m* - toluidide and 40 ml of freshly distilled chloroacetyl chloride are refluxed for 1 hour. The dark solution is then concentrated at a bath temperature of 50° under 11 Torr. The residue is dissolved in 70 ml of ethyl acetate/ether 1:1. This solution is extracted with 10 ml of 2N potassium bicarbonate solution and 10 ml of water, dried over sodium sulphate and concentrated under 11 Torr. The N - phenyl - 2, 2', 6' - trichloro - aceto - *m* - toluidide crystallises from cyclohexane, M.P. 117—118°.

The following compounds are produced analogously:

2 - chloro - N - (*p* - chlorophenyl) - N - (2, 6 - dichlorophenyl) - acetamide, M.P. 130—131° from ethanol/water;

2 - chloro - N - phenyl - aceto - 2', 3' - xylidide, M.P. 124—126° from cyclohexane;

2 - chloro - N - (2, 6 - dichlorophenyl) - N - phenyl - acetamide, M.P. 143—144° from methanol;

2 - chloro - aceto - 2', 6' - xylidide, M.P. 94—96° from ethanol;

2 - chloro - N - (*p* - chlorophenyl - 2', 6' - xylidide, M.P. 104—106° from ethanol; N - (*p* - tolyl) - 2, 2', 6' - trichloro - aceto - *m* - toluidide, M.P. 67—69° from ether/petroleum ether;

N - (*p* - chlorophenyl - 2, 2', 6' - trichloro - aceto - *m* - toluidide, M.P. 106—107° from ethyl acetate/petroleum ether;

N - *p* - methoxyphenyl - 2, 2', 6' - trichloro - aceto - *m* - toluidide, as a yellow oil.

c) 1-(2,6-dichloro-*m*-tolyl)-2-indolinone

4 g of N - phenyl - 2, 2', 6' - trichloro - aceto - *m* - toluidide and 4 g of aluminium chloride are well mixed together and heated for 2 hours at 160°. The melt is cooled and poured onto about 50 g of ice whilst it is still warm. The oil which separates is dissolved in 50 ml of chloroform, the chloroform solution is washed with 10 ml of

water, dried over sodium sulphate and concentrated under 11 Torr. The residue is distilled. The 1 - (2, 6 - dichloro - *m* - tolyl - 2 - indolinone boils at 128—130°/0.001 Torr. The oil obtained which crystallises on standing, melts at 129—132°.

The following compounds are produced analogously:

1 - (2, 6 - dichlorophenyl) - 5 - chloro - 2 - indolinone, M.P. 130—131° from ethanol/water;

1 - (2, 6 - dichlorophenyl) - 2 - indolinone, M.P. 126—127° from methanol;

1 - (2, 6 - dichloro - *m* - tolyl) - 5 - chloro - 2 - indolinone, M.P. 152—154° from ethyl acetate/petroleum ether.

1 - (2, 6 - dichloro - *m* - tolyl) - 5 - hydroxy - 2 - indolinone

10 g of N - *p* - methoxyphenyl - 2, 2', 6' - trichloro - aceto - *m* - toluidide and 20 g of finely pulverised aluminium chloride are mixed and the mixture is heated for 1 hour at 280° under an atmosphere of nitrogen. It is cooled and a large quantity of ice and water are added to the melt which has solidified. A black precipitate is formed which is filtered off and dried at 80° under 11 Torr. The 1 - (2, 6 - dichloro - *m* - tolyl) - 5 - hydroxy - 2 - indolinone, when purified by chromatography on a neutral aluminium oxide column, melts at 184—187°; yield 60% of the theoretical.

1 - (2, 6 - dichloro - *m* - tolyl) - 5 - methoxy - 2 - indolinone

8.1 g of crude 1 - (2, 6 - dichloro - *m* - tolyl) - 5 - hydroxy - 2 - indolinone are dissolved in 26.3 ml of 1N sodium hydroxide solution. 3.7 g of dimethyl sulphate are then added to the solution and the whole is refluxed for half an hour. After cooling, the reaction solution is extracted with 400 ml of ethyl acetate. The organic phase is filtered, the filtrate is washed once with water and once with saturated sodium chloride solution, dried over sodium sulphate and concentrated, under 11 Torr, to dryness. The residue is purified by chromatography on an aluminium oxide column and, after recrystallisation from ether/petroleum ether, it melts at 135—136°; yield 20% of the theoretical.

1 - (2, 6 - dichlorophenyl) - 5 - bromo - indolinone

A solution of 11.2 g of 1 - (2, 6 - dichlorophenyl) - 2 - indolinone in 700 ml of ethanol is added to a solution of 8 g of potassium bromide and 2.08 g of bromine in 160 ml of water. The mixture is vigorously shaken and then left to stand for 3 hours at 0°. The alcohol is then evaporated off and the insoluble precipitate is filtered off from the remaining aqueous solution. The latter

is then taken up in methylene chloride. The methylene chloride solution is dried over sodium sulphate and concentrated to dryness under 11 Torr. The residue consists of a mixture, 60% of which is 1 - (2, 6 - dichlorophenyl) - 5 - bromo - 2 - indolinone. This is purified by repeatedly chromatographing on a silica gel column and, after having been crystallised several times from ether or ether/petroleum ether, it melts at 188—190°.

## EXAMPLE 3

[*o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - Trifluoro - *m* - toluidino)-phenyl] - acetic acid

9.5 g of  $\alpha$  - cyano - N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - aceto - *o* - toluidide are dissolved in 100 ml of ethanol and 90 ml of 1N sodium hydroxide solution. The solution is refluxed overnight. It is cooled and concentrated to about 70 ml at 40° under 11 Torr. The aqueous alkaline solution is extracted with 50 ml of ether, this ether solution is separated and the aqueous phase is acidified with 2N hydrochloric acid. The acid solution is extracted with 50 ml of ether, the ether extract is washed with water, the ether solution is dried over sodium sulphate and concentrated under 11 Torr without heating. The residue crystallises from ether/petroleum ether. After recrystallisation from ether/petroleum ether, [*o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - toluidino)-phenyl] - acetic acid melts at 112—114°. The yield is 35% of the theoretical.

## EXAMPLE 4

The compound produced in Example 3 may also be produced as follows:

A solution of 16.4 g of *o* - [ $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - acetamido] - phenyl-acetic acid ethyl ester in 225 ml of 95% ethanol and 67 ml of 2N sodium hydroxide solution is refluxed for 16 hours. The ethanol is then distilled off at 40° under 11 Torr and the aqueous solution which remains is extracted with 40 ml of ether. The ethereal phase is separated, the aqueous phase is cooled to 0—5° by the addition of ice and acidified to pH 6 with 2N hydrochloric acid. The oil which separates out is dissolved in 200 ml of ether, the ethereal solution is washed with 20 ml of water and dried over sodium sulphate. It is then concentrated under 11 Torr without warming. On adding petroleum ether, [*o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - toluidine) - phenyl] - acetic acid crystallises out, M.P. 112—114°.

## EXAMPLE 5

The following compound may be produced in an analogous manner to Example 4:

[*o* - (6 - methoxy - *m* - toluidino)-phenyl] - acetic acid M.P. 105—107° (from ether).

## Preparation of starting materials

The starting materials for Examples 3, 4 and 5 can be produced, for example, as follows:

a) *o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - toluidino)-benzyl alcohol

8.7 g of lithium bromide are added to a solution of 3.8 g of sodium borohydride in 160 ml of anhydrous diglyme.

The mixture is stirred for half an hour at room temperature. A solution of 14.8 g of N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl)-anthranilic acid methyl ester in 40 ml of anhydrous diglyme is added dropwise. The whole is then heated for 3 hours at 100°, cooled and poured onto a mixture of 300 g of ice and 30 ml of concentrated hydrochloric acid. After stirring for a short time, the oil which separates is extracted with 300 ml of ethyl acetate. The ethyl acetate solution is washed with 2N potassium bicarbonate solution and water, dried over sodium sulphate and concentrated at 40° under 11 Torr. The residue is distilled on a short Vigreux column. The *o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - toluidino) - benzyl alcohol boils at 127—129°/0.001 Torr. The yield is 75% of the theoretical.

a') 9.97 g of lithium aluminium hydride are suspended in 100 ml of abs. ether and the suspension is cooled to 5° while stirring. A solution of 36.8 g of N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - anthranilic acid methyl ester in 140 ml of abs. ether is added slowly dropwise, the addition being made under an atmosphere of nitrogen with external cooling. The mixture is then stirred for 18 hours at room temperature. 10 ml of water, 10 ml of 15% sodium hydroxide solution and another 30 ml of water are added dropwise to the stirred mixture which has been cooled to 0°. The whole is stirred for 1 hour at room temperature and then filtered. The filtrate is concentrated at 40° under 11 Torr. The residue is fractionated by means of a short Vigreux column. In this way, *o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - toluidino) - benzyl alcohol is obtained as a yellow oil, B.P. 130—131°/0.001 Torr. The following compounds are obtained analogously:

*o* - (2, 3 - xylidino) - benzyl alcohol, B.P. 136—141°/0.005 Torr;

*o* - (6 - methoxy - *m* - toluidino) - benzyl alcohol, M.P. 138—139° from methanol;

*o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - 6 - chloro - *m* - toluidino) - benzyl alcohol, M.P. 100—101° from petroleum ether;

4 - chloro - 2 - (2', 6' - xylidino) - benzyl alcohol, M.P. 141—142°;

5 - methoxy - 2 - (2', 6' - dichloranilino)-benzyl alcohol, M.P. 112—113° from cyclohexane.

5 a<sup>11</sup>) A solution of 7 g of N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$ -trifluoro - *m* - tolyl) - anthranilic acid methyl ester in 60 ml of methanol is added dropwise to 9 g of sodium borohydride. The suspension is then stirred for 2 hours at room temperature and then refluxed for 3 hours. It is cooled, diluted with 80 ml of water and extracted with 300 ml of ethyl acetate. The ethyl acetate solution is separated, dried over sodium sulphate and concentrated under 11 Torr. The residue is fractionally distilled. The *o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - benzyl alcohol boils at 128—131°/0.001 Torr. The yield is 55% of the theoretical.

15 a<sup>111</sup>) 4 - Chloro - 2 - (2', 6' - dichloro-anilino) - benzyl alcohol

20 A suspension of 50 g of 4 - chloro - 2 - (2', 6' - dichloroanilino) - benzoic acid in 250 ml of abs. tetrahydrofuran is added dropwise at 5—15° to 8 g of lithium aluminium hydride in 50 ml of abs. tetrahydrofuran. The reaction mixture is stirred for half an hour at 5°, for 1 hour at 25° and for 3 hours under reflux whereupon, at 0—5°, 30 ml of 2N sodium hydroxide solution are carefully added dropwise. After adding 200 ml of tetrahydrofuran, the organic solution is removed from the crystalline precipitate by filtration under suction and the latter is well washed with tetrahydrofuran.

30 The combined solutions are concentrated, taken up in ethyl acetate and washed with 2N sodium carbonate solution and saturated sodium chloride solution. Concentration of the organic phase yields 44.4 g of a dark brown oil which is distilled. B.P. 195—200°/0.003 Torr. M.P. (recrystallised from ether/petroleum ether) 151—152°. Yield 31.5 g (66%).

40 b)  $\alpha$  - Chloro - N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro-*m* - tolyl) - aceto - toluidide

45 A solution of 23 g of *o* - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro-*m* - tolyl) - benzyl alcohol in 70 ml of acetyl chloride is refluxed for 1 hour under an atmosphere of nitrogen. The orange coloured solution is then concentrated at a bath temperature of 40° under 11 Torr. The residue is dissolved in 150 ml of ethyl acetate/ether 1:1. The organic phase is washed with

50 20 ml of 2N potassium bicarbonate solution and 20 ml of water, dried over sodium sulphate and concentrated in vacuo. A pale oil remains which crystallises from ether/petroleum ether. The  $\alpha$  - chloro - N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - aceto - *o* - toluidide obtained melts at 83—85°. Analogously was obtained  $\alpha$  - chloro - N - (6-methoxy - *m* - tolyl) - aceto - *o* - toluidide, M.P. 121—123° (from petroleum ether).

55 c)  $\alpha$  - Cyano - N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro-*m* - tolyl) - aceto - *m* - toluidide

60 A solution of 11.6 of  $\alpha$  - chloro - N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - aceto - *o* - toluidide in 60 ml of dimethyl sulphoxide is added within 10 minutes to a suspension of 2.2 g of sodium cyanide in 20 ml of dimethyl sulphoxide, the addition being made at 40° while stirring. The temperature should not exceed 40° during the addition. The mixture is then stirred for 3 hours at 40°, cooled to 10° and diluted with 200 ml of water. The solution is extracted four times with 150 ml of ethyl acetate. The ethyl acetate solutions are then shaken with 200 ml of 6N hydrochloric acid and then with 30 ml of water, dried over sodium sulphate and concentrated at 40° under 11 Torr. The  $\alpha$  - cyano - N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - aceto - *o* - toluidide which remains as a yellow oil can be used directly. Analogously was obtained  $\alpha$  - cyano - N - (6 - methoxy - *m* - tolyl) - aceto - *o* - toluidide. M.P. 108—109° from cyclohexane.

d) *o* - [N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - acetamido] - phenylacetic acid ethyl ester

85 A solution of 50 g of  $\alpha$  - cyano - N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro - *m* - tolyl) - aceto - *o* - toluidide in 550 ml of abs. ether and 375 ml of abs. ethanol is cooled to 0—5° while stirring and excluding moisture. Dry hydrogen chloride is introduced into the solution for 4 hours, during which the temperature should not exceed 5°. Hydrogen chloride is then introduced for another 5 hours at room temperature. The solution is then left to stand overnight at room temperature after which it is evaporated to dryness at a bath temperature of 40° under 11 Torr. The residue is dissolved in 140 ml of water, the solution is covered with 150 ml of ether and the whole is refluxed for 2 hours on a steam bath. It is then cooled, the ether phase is removed and the aqueous solution is again extracted with 200 ml of ether. The combined ether solutions are dried over sodium sulphate and evaporated at 40° under water jet vacuum. The residue is fractionated by means of a Vigreux column under high vacuum. The *o* - [N - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - trifluoro-*m* - tolyl) - acetamido] - phenylacetic acid ethyl ester boils at 110—115°/0.001 Torr. Analogously was obtained [*o* - N - (6 - methoxy - *m* - tolyl) - acetamido] - phenylacetic acid ethyl ester B.P. 130—135°/0.001 Torr.

#### EXAMPLE 6

[*o* - (3 - trifluoromethyl - 6 - chloro-anilino) - phenyl] - acetic acid

120 A solution of 18.4 g of  $\alpha$  - cyano - N - (3-trifluoromethyl - 6 - chlorophenyl) - *o* - toluidine in 120 ml of 1N sodium hydroxide solution and 120 ml of ethanol is refluxed for 10 hours. The volume of the reaction solution is then reduced at 40° under reduced pressure to about 80 ml and the

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- aqueous solution is extracted with 100 ml of ether. The aqueous-alkaline phase is then acidified at 5° with 2N hydrochloric acid and the oil which separates is taken up in ether. The ether solution is removed, washed with water, dried over sodium sulphate and, without heating, is concentrated under reduced pressure. On adding petroleum ether, the  $\alpha$  - (3 - trifluoromethyl - 6 - chloro - phenyl) -  $\sigma$  - toluidine crystallises out, M.P. 94—96°; yield 55% of the theoretical.
- 5 The following compounds are obtained analogously:
- 10  $\alpha$  - cyano - 4 - chloro - N - (2, 6 - dichlorophenyl) -  $\sigma$  - toluidine, M.P. 113—115°;
- $\alpha$  - cyano - 4 - chloro - N - (2, 6 - xylyl) -  $\sigma$  - toluidine, M.P. 131—132°;
- $\alpha$  - cyano - 5 - methoxy - N - (2, 6 - dichlorophenyl) -  $\sigma$  - toluidine, M.P. 169—171°.

Preparation of Starting Material

15  $\alpha$  - Cyano - N - (3 - trifluoromethyl - 6 - chlorophenyl) -  $\sigma$  - toluidine used as starting material in Example 6 may be produced as follows:

- a)  $\alpha$  - Chloro - N - (3 - trifluoromethyl - 6 - chlorophenyl) -  $\sigma$  - toluidine
- 20 A solution of 20 g of  $\alpha$  - (3 - trifluoromethyl - 6 - chloroanilino) - benzyl alcohol in 70 ml of acetyl chloride is refluxed for 16 hours under an atmosphere of nitrogen. The solution is then concentrated at about 40° under reduced pressure. The residue is taken up in 40 ml of benzene and again concentrated. The residue is then taken up in 200 ml of ether, the ethereal solution is washed with 2N sodium carbonate solution and water, dried over sodium sulphate and the solvent is evaporated off under reduced pressure. The oil which remains is distilled under high vacuum, B.P. 120°/0.001 Torr. The  $\alpha$  - chloro - N - (3 - trifluoromethyl - 6 - chlorophenyl) -  $\sigma$  - toluidine can be crystallised from petroleum ether, M.P. 50—51°. The yield is 32% of the theoretical.
- 30 The following compounds are obtained analogously:
- 4 - chloro - 2 - (2', 6' - dichloroanilino) - benzyl chloride
- 4 - chloro - 2 - (2', 6' - dimethylanilino) - benzyl chloride, M.P. 113—117°
- 45 5 - methoxy - 2 - (2', 6' - dichloroanilino) - benzyl chloride, M.P. 82—84° from petroleum ether.
- b)  $\alpha$  - Cyano - N - (3 - trifluoromethyl - 6 - chlorophenyl) -  $\sigma$  - toluidine
- 50 A suspension of 6 g of sodium cyanide in 120 ml of dimethyl sulphoxide is heated to 40°. Then a solution of 33 g of  $\alpha$  - chloro - N - (3 - trifluoromethyl - 6 - chlorophenyl) -  $\sigma$  - toluidine in 150 ml of dimethyl sulphoxide is added while stirring, during which addition the temperature should not rise above 40°. The mixture is stirred for 3 hours at 40° and then diluted with 600 ml of water. The solution is then extracted three times with 1000 ml of ethyl acetate each time. The combined extracts are washed with 100 ml of 6N hydrochloric acid and
- c) 4 - chloro - 2 - (2', 6' - dichloroanilino) - benzyl bromide
- Hydrogen bromide is introduced for 15 minutes into a solution of 3.3 g of 4 - chloro - 2 - (2', 6' - dichloroanilino) - benzyl alcohol, and 50 ml of benzene which is then stirred for half an hour while bubbling nitrogen through. The benzene solution is washed with 2N sodium carbonate solution and concentrated. The crystals formed are used without further purification. Yield 92%.
- The following compounds are produced analogously:
- $\alpha$  - bromo - N - (2, 6 - xylyl) -  $\sigma$  - toluidine, M.P. 107—109°;
- $\alpha$  - bromo - N - (2, 6 - dichlorophenyl) -  $\sigma$  - toluidine, M.P. 102—104°.

## EXAMPLE 7

- $\alpha$  - (2, 6 - dichloro -  $m$  - toluidino) - hydratropic acid
- (2 - [ $\sigma$  - 2, 6 - dichloro -  $m$  - toluidino) - phenyl] - propionic acid)
- 105 A solution of 3.1 g of 1 - (2, 6 - dichloro -  $m$  - tolyl) - 3 - methyl - 2-indolinone in 35 ml of ethanol and 20 ml of 1N sodium hydroxide solution is refluxed for 1 hour. The solution is then concentrated at 50° under 11 Torr, the residue is dissolved in 200 ml of water and the aqueous solution is extracted with 50 ml of ether. The aqueous solution is separated and acidified at 5° with 2N hydrochloric acid. The oil which separates is dissolved in 100 ml of ether, the ether solution is washed with a little water, dried over sodium sulphate and concentrated under 11 Torr. The residue is crystallised from ether/petroleum ether. After recrystallisation from ether/petroleum ether, the  $\alpha$  - (2, 6 - dichloro -  $m$  - toluidino) - hydratropic acid melts at 143—145°. The yield is 30% of the theoretical.
- 120

## EXAMPLE 8

The following compounds are produced in an analogous manner to Example 7:

- 5  $\alpha$  - (2, 6 - dichloranilino) - hydratropic acid, M.P. 154—156° from ether/petroleum ether;  
 2 - [ $\sigma$  - (2, 6 - dichloro - *m* - toluidino)-phenyl] - butyric acid;  
 10 [ $\sigma$  - (2, 6 - dichloranilino) - phenyl] - benzyl acetic acid, M.P. 132—133° from ether/petroleum ether;

## Preparation of Starting Materials

The indolinones used as starting material in Examples 7 and 8 are produced as follows:

- a) N - phenyl - 2,2', 6' - trichloropropiono - *m* - toluidide  
 A solution of 5 g of 2, 6 - dichloro-N - phenyl - *m* - toluidide (obtained according to example 1 a) in 20 ml of  $\alpha$  - chloropropionyl chloride is refluxed for 1 hour while introducing nitrogen. It is then evaporated to dryness in vacuo at 40° and the residue is dissolved in ethyl acetate/chloroform 1:1. The solution is extracted with 2N potassium bicarbonate solution and water, dried over sodium sulphate and concentrated at 40° under 11 Torr. The residue is distilled in a bulb tube. The N - phenyl-2, 2', 6' - trichloropropiono - *m* - toluidide boils at 155—160°/0.001 Torr. Crystallised from ether/petroleum ether, the compound melts at 105—107°. The yield is 59% of the theoretical.  
 35 The following compounds are produced analogously:  
 2 - chloro - N - phenyl - N - (2, 6 - dichlorophenyl) - propionamide M.P. 123—125° from methanol, and  
 40 2 - chloro - N - phenyl - propiono - 2' 6'-xylidide, M.P. 126—128° from methanol.

- b) 1 - (2, 6 - dichloro - *m* - tolyl) - 3-methyl - 2 - indolinone  
 45 A mixture of 31.2 g of 2, 2', 6' - trichloro - N - phenyl - propiono - *m* - toluidide and 31.2 g of aluminium chloride is heated for 2 hours at 160°. The melt is cooled and poured onto 500 g of ice. The oil which separates is dissolved in 100 ml of ether. The ether solution is washed with 50 ml of 2N potassium bicarbonate solution and with 100 ml of water, dried over sodium sulphate and concentrated in vacuo at 40°. The residue is chromatographed on 500 g of neutral aluminium oxide.  
 55 The fractions 3—7, eluted with benzene, contain 1 - (2, 6 - dichloro - *m* - tolyl) - 3-methyl - 2 - indolinone. They are combined and crystallised from ether, M.P. 110—130°. The yield is 44% of the theoretical.

60 The following compound is produced analogously:  
 1 - (2, 6 - dichlorophenyl) - 3 - methyl - 2 - indolinone, M.P. 98—99° from ethyl acetate/petroleum ether.

The following compound is produced analogously:

- 1 - (2, 6 - dichlorophenyl) - 3 - methyl - 2 - indolinone, M.P. 98—99° from ethyl acetate/petroleum ether.

- c) 3 - Ethyl - 1 - (2, 6 - dichlorophenyl) - 2 - indolinone

A solution of 5.6 g of 1 - (2, 6 - dichlorophenyl) - 2 - indolinone in 10 ml of abs. dimethyl formamide is added to a suspension of 1 g of sodium hydride in mineral oil, suspended in 30 ml of abs. dimethyl formamide, the addition being made dropwise at 0—5°. The mixture is then stirred for 40 minutes at 10° after which 3.2 g of ethyl iodide are added dropwise. The mixture is then stirred for 15 hours at room temperature. It is poured onto ice and extracted with 200 ml of ether. The ether solution is separated, washed with water, dried over sodium sulphate and evaporated to dryness under 11 Torr. The residue is chromatographed on 200 g of neutral aluminium oxide. The fractions 2—3, eluted with ether/petroleum ether 1:1, contain the pure 3 - ethyl - 1 - (2, 6 - dichlorophenyl) - 2-indolinone. After crystallising twice, from methanol, the compound melts at 100—101°. The yield is 15% of the theoretical.

- d) 1 - (2, 6 - dichlorophenyl) - 3-benzal - 2 - indolinone

2.78 g of 1 - (2, 6 - dichlorophenyl) - 2-indolinone are dissolved in 50 ml of abs. ethanol, 1.06 g of benzaldehyde and 2 drops of piperidine are then added and the whole is heated for 5 hours at 50°. The reaction mixture is then concentrated in vacuo and the residue is purified by chromatography on an aluminium oxide column. Crystallised from ether, the 1 - (2, 6 - dichlorophenyl) - 3 - benzal - 2 - indolinone melts at 135—136°. The yield is 80% of the theoretical.

- e) 1 - (2, 6 - dichlorophenyl) - 3-benzyl - 2 - indolinone

3 g of the 1 - (2, 6 - dichlorophenyl) - 3-benzal - 2 - indolinone obtained above are dissolved in 100 ml of dioxan. 0.2 g of 5% platinum charcoal are then added and it is hydrogenated at room temperature under normal pressure. 1 - (2, 6 - dichlorophenyl) - 3 - benzyl - 2 - indolinone is formed. The yield is 60%.

## EXAMPLE 9

- $\alpha$  - (2, 6 - dichloro - *m* - toluidino) -  $\alpha$ -methyl - hydratropic acid

- (2 - [ $\sigma$  - (2, 6 - dichloro - *m* - toluidino)-phenyl] - 2 - methyl - propionic acid)

A solution of 1.5 g of 1 - (2, 6 - dichlorophenyl) - 3,3 - dimethyl - 2 - indolinone in 15 ml of ethanol and 10 ml of 2N sodium hydroxide solution is refluxed for 48 hours.

- It is then cooled to room temperature and 50 ml of water are added. The crystals which precipitate are filtered off. The filtrate is extracted with 30 ml of ether. The ether solution is separated and the aqueous phase is acidified with 2N hydrochloric acid. The precipitated crystals are dissolved in chloroform/ether 1:1, the organic phase is washed with water, dried over sodium sulphate and concentrated at 40° under 11 Torr. The residue crystallises from ether. The *o* - (2, 6-dichloro - *m* - toluidino) -  $\alpha$  - methyl hydropic acid melts, after recrystallisation from ether, at 187—192°. The yield is 20% of the theoretical.

#### Preparation of starting material

The starting material used in Example 9 is produced as follows:

- a) 1 - (2, 6 - dichlorophenyl) - 3,3 - dimethyl - 2 - indolinone  
A solution of 5.6 g of 1 - (2, 6 - dichlorophenyl) - 2 - indolinone (M.P. 126—127°) in 10 ml of abs. dimethyl formamide is added to a suspension of 2.1 g of sodium hydride-mineral oil (1:1) in 30 ml of abs. dimethyl formamide, the addition being made dropwise at 0—5° under an atmosphere of nitrogen. The whole is stirred for 40 minutes at 10° whereupon 7 g of methyl iodide are added dropwise. The mixture is then stirred for 15 hours at room temperature after which it is poured onto crushed ice. It is extracted with 200 ml of ether 5 times. The ether extracts are combined and washed with 100 ml of water, dried over sodium sulphate and concentrated under 11 Torr. The residue is crystallised from ether. The 1 - (2, 6 - dichlorophenyl) - 3,3 - dimethyl - 2 - indolinone melts at 128—130°. The yield is 67% of the theoretical.

#### EXAMPLE 10

[*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid

- A solution of 1 g of [*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid methyl ester in 20 ml of methanol and 5 ml of 2N potassium bicarbonate solution is refluxed for 15 hours. It is concentrated to dryness in vacuo, diluted with 70 ml of water and the aqueous solution is extracted with 20 ml of ether. The aqueous solution is acidified with 2N hydrochloric acid, the oil which separates is extracted with ether and the ether solution is washed with water, dried over sodium sulphate and concentrated, without heating, under 11 Torr. The [*o* - (2, 6-dichloroanilino) - phenyl] - acetic acid crystallises from ether/petroleum ether, M.P. 156—158°. The yield is 75% of the theoretical.

#### EXAMPLE 11

[*o* - (2, 6 - dichloroanilino) - phenyl] - acetic

acid ethyl ester, M.P. 50—52°, can be saponified in an analogous manner to Example 10.

#### Preparation of starting materials

The esters used as starting materials in Examples 10 and 11 are obtained as follows:

- a) [*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid methyl ester

100 ml of 2% ethereal diazomethane solution are slowly added dropwise to a solution of 10 g of [*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid (M.P. 156—158°) in 150 ml of abs. ether. The solution is left to stand overnight at room temperature whereupon it is concentrated to dryness at 40° under 11 Torr. The residue is dissolved in 100 ml of ether. The ether solution is extracted with 50 ml of 1N potassium bicarbonate solution and water, dried over sodium sulphate and concentrated at 40° under 11 Torr. The residue crystallises from ether/petroleum ether. The [*o* - (2, 6-dichloroanilino) - phenyl] - acetic acid methyl ester melts at 101—102°. The yield is 72% of the theoretical.

- b) [*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid ethyl ester

A solution of 16 g of [*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid in 1600 ml of water and 40 ml of 2N sodium hydroxide solution is cooled to 5°. 10 ml of diethyl sulphate are added while stirring, the solution being cooled in an ice bath. It is stirred for 2 hours at 5—10° and then another 20 ml of 2N sodium hydroxide solution and 10 ml of diethyl sulphate are added. The reaction mixture is then stirred for 15 hours at room temperature. The crystals which precipitate are filtered off, well washed with water and dissolved in 100 ml of ether. The ether solution is extracted with 30 ml of water, dried over sodium sulphate and concentrated at 40° under reduced pressure. The [*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid ethyl ester crystallises from ether/petroleum ether, M.P. 50—52°. The yield is 15% of the theoretical.

#### EXAMPLE 12

[*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid

1.2 g of [*o* - (2, 6 - dichloroanilino) - phenyl] - acetic acid benzyl ester are dissolved in 50 ml of ethanol and, after the addition of 0.2 g of 5% palladium charcoal, the solution is hydrogenated at room temperature and low pressure. The hydrogenation is complete after 1-1/4 hours. The catalyst is filtered off and the filtrate is concentrated to dryness at room temperature under 11 Torr. The residue is recrystallised from ether/petroleum ether, M.P. 156—

158°. The yield is 67% of the theoretical.

#### Preparation of starting material

The benzyl ester used as starting material in Example 12 is produced as follows:

- 5 [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester

A solution of 2.96 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid, 1.2 g of abs. benzyl alcohol and 3 g of dimethyl formamide dincopentyl acetal in 40 ml of methylene chloride is stirred for 55 hours under an atmosphere of nitrogen. The methylene chloride is then distilled off under 12 Torr. The residue is diluted with 50

15 ml of ethyl acetate, the solution is extracted with water and dried over sodium sulphate. The solution is concentrated to dryness at 40° under 11 Torr. The residue is chromatographed on 60 g of neutral aluminium oxide.

20 Eluted with ether/petroleum ether 7:3, fractions 2 and 3 contain pure [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester. The yield is 30% of the theoretical.

It can also be obtained, however, as follows:

25 6 ml of thionyl chloride are added dropwise to 40 ml of abs. benzyl alcohol, the addition being made dropwise at -10° while stirring well and introducing nitrogen. After 5 minutes at -10°, a solution of 2.96 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid in 10 ml of abs. benzyl alcohol is added dropwise. The reaction mixture is then stirred for 15 hours at room temperature whereupon it is poured onto ice. The oil which separates is extracted with 100 ml of ether. The ether extract is washed with 10 ml of 2N potassium bicarbonate solution and water, dried over sodium sulphate and the ether solution is evaporated to dryness at 40° under 11 Torr. The residue is chromatographed on 90 g of neutral aluminium oxide. Eluted with ether/petroleum ether 1:1, the fractions 1 and 2 contain the pure [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester. The yield is 48% of the theoretical.

30 of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid in 10 ml of abs. benzyl alcohol is added dropwise. The reaction mixture is then stirred for 15 hours at room temperature whereupon it is poured onto ice. The oil which separates is extracted with 100 ml of ether. The ether extract is washed with 10 ml of 2N potassium bicarbonate solution and water, dried over sodium sulphate and the ether solution is evaporated to dryness at 40° under 11 Torr. The residue is chromatographed on 90 g of neutral aluminium oxide. Eluted with ether/petroleum ether 1:1, the fractions 1 and 2 contain the pure [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester. The yield is 48% of the theoretical.

35 The oil which separates is extracted with 100 ml of ether. The ether extract is washed with 10 ml of 2N potassium bicarbonate solution and water, dried over sodium sulphate and the ether solution is evaporated to dryness at 40° under 11 Torr. The residue is chromatographed on 90 g of neutral aluminium oxide. Eluted with ether/petroleum ether 1:1, the fractions 1 and 2 contain the pure [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester. The yield is 48% of the theoretical.

40 of the theoretical.

#### EXAMPLE 13

- 50 [o - (2, 6 - dichloranilino) - phenyl] - acetic acid

A solution of 0.5 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid methyl ester (M.P. 101-102°) in 40 ml of 75% ethanol and 12 g of Dowex ("Dowex" is a registered Trade Mark), 1 ion exchanger (OH form, 20-50 mesh) are stirred for 15 hours in a round flask at 50° and then filtered. The residue is suspended in 20 ml of water and the suspension is acidified at 5° with 1N hydrochloric acid. 30 ml of ether are added, the whole is shaken and the ether solution is separated. The ether solution is washed with

10 ml of water, dried over sodium sulphate and, when cold, is concentrated to dryness under 11 Torr. The [o - (2, 6 - dichloranilino) - phenyl] - acetic acid crystallises from ether/petroleum ether, M.P. 156-158°. The yield is 45% of the theoretical.

#### EXAMPLE 14

- [o - (2, 6 - dichloranilino) - phenyl] - acetic acid, sodium salt.

A solution of 186 g of 1 - (2, 6 - dichlorophenyl) - 2 - indolinone in 660 ml of ethanol and 660 ml of 2N sodium hydroxide solution is refluxed for 4 hours. The solution is then cooled and left to stand for 4 hours at 0-5°. The crystals which form are filtered off and recrystallised from water. The sodium salt of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid melts at 283-285°. The yield is 97% of the theoretical.

#### EXAMPLE 15

The sodium salt of [5 - chloro - 2 - (2, 6 - dichloranilino) - phenyl] - acetic acid is produced analogously to Example 14. It melts at 296° on recrystallisation from water.

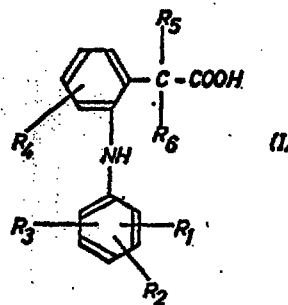
#### EXAMPLE 16

- [o - (2, 6 - dichloranilino) - phenyl] - acetic acid, potassium salt.

20 ml of 8% ethanolic potassium hydroxide solution are added to a solution of 8.9 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid in 50 ml of ethanol. The solution is boiled for 10 minutes with active charcoal, filtered and concentrated under 11 Torr. On adding ether, the potassium salt of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid crystallises out, M.P. 300-330° with decomposition.

#### WHAT WE CLAIM IS:—

1. Substituted phenylacetic acids of the general formula I



wherein

- R<sub>1</sub> represents a low alkyl or alkoxy radical, a halogen atom up to the atomic number 35 or the trifluoromethyl group,

R<sub>2</sub> and

R<sub>3</sub> each represent hydrogen, a low alkyl



158°. The yield is 67% of the theoretical.

#### Preparation of starting material

The benzyl ester used as starting material in Example 12 is produced as follows:

#### 5 [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester

A solution of 2.96 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid, 1.2 g of abs. benzyl alcohol and 3 g of dimethyl formamide dioneopentyl acetal in 40 ml of methylene chloride is stirred for 55 hours under an atmosphere of nitrogen. The methylene chloride is then distilled off under 12 Torr. The residue is diluted with 50 ml of ethyl acetate, the solution is extracted with water and dried over sodium sulphate. The solution is concentrated to dryness at 40° under 11 Torr. The residue is chromatographed on 60 g of neutral aluminium oxide. Eluted with ether/petroleum ether 7:3, fractions 2 and 3 contain pure [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester. The yield is 30% of the theoretical.

It can also be obtained, however, as follows:

6 ml of thionyl chloride are added dropwise to 40 ml of abs. benzyl alcohol, the addition being made dropwise at -10° while stirring well and introducing nitrogen. After 5 minutes at -10°, a solution of 2.96 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid in 10 ml of abs. benzyl alcohol is added dropwise. The reaction mixture is then stirred for 15 hours at room temperature whereupon it is poured onto ice. The oil which separates is extracted with 100 ml of ether. The ether extract is washed with 10 ml of 2N potassium bicarbonate solution and water, dried over sodium sulphate and the ether solution is evaporated to dryness at 40° under 11 Torr. The residue is chromatographed on 90 g of neutral aluminium oxide. Eluted with ether/petroleum ether 1:1, the fractions 1 and 2 contain the pure [o - (2, 6 - dichloranilino) - phenyl] - acetic acid benzyl ester. The yield is 48% of the theoretical.

#### EXAMPLE 13

#### 50 [o - (2, 6 - dichloranilino) - phenyl] - acetic acid

A solution of 0.5 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid methyl ester (M.P. 101—102°) in 40 ml of 75% ethanol and 12 g of Dowex ("Dowex" is a registered Trade Mark), 1 ion exchanger (OH form, 20—50 mesh) are stirred for 15 hours in a round flask at 50° and then filtered. The residue is suspended in 20 ml of water and the suspension is acidified at 5° with 1N hydrochloric acid. 30 ml of ether are added, the whole is shaken and the ether solution is separated. The ether solution is washed with

10 ml of water, dried over sodium sulphate and, when cold, is concentrated to dryness under 11 Torr. The [o - (2, 6 - dichloranilino) - phenyl] - acetic acid crystallises from ether/petroleum ether, M.P. 156—158°. The yield is 45% of the theoretical.

#### EXAMPLE 14

#### [o - (2, 6 - dichloranilino) - phenyl] - acetic acid, sodium salt.

A solution of 186 g of 1 - (2, 6 - dichlorophenyl) - 2 - indolinone in 660 ml of ethanol and 660 ml of 2N sodium hydroxide solution is refluxed for 4 hours. The solution is then cooled and left to stand for 4 hours at 0—5°. The crystals which form are filtered off and recrystallised from water. The sodium salt of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid melts at 283—285°. The yield is 97% of the theoretical.

#### EXAMPLE 15

The sodium salt of [5 - chloro - 2 - (2, 6 - dichloranilino) - phenyl] - acetic acid is produced analogously to Example 14. It melts at 296° on recrystallisation from water.

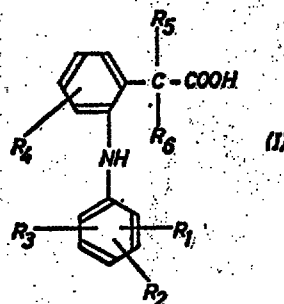
#### EXAMPLE 16

#### [o - (2, 6 - dichloranilino) - phenyl] - acetic acid, potassium salt.

20 ml of 8% ethanolic potassium hydroxide solution are added to a solution of 8.9 g of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid in 50 ml of ethanol. The solution is boiled for 10 minutes with active charcoal, filtered and concentrated under 11 Torr. On adding ether, the potassium salt of [o - (2, 6 - dichloranilino) - phenyl] - acetic acid crystallises out, M.P. 300—330° with decomposition.

#### WHAT WE CLAIM IS:—

1. Substituted phenylacetic acids of the general formula I



wherein

R<sub>1</sub> represents a low alkyl or alkoxy radical, a halogen atom up to the atomic number 35 or the trifluoromethyl group,

R<sub>2</sub> and

R<sub>3</sub> each represent hydrogen, a low alkyl

R<sub>4</sub>

5

R<sub>5</sub>  
R<sub>6</sub>

10

and  
bases

2.

pheny

3.

15 chlor

4.

5 - c

5. |

5 - n

20 6.

pheny

7.

bromo

25 8. [

pheny

9. |

anilin

10.

30 toluidi

11.

pheny

12.

toluidi

13.

35 α - ben

14.

toluidi

acid.

95 15. |

acetic

40 16.

general

in R<sub>5</sub>

radical.

45 17. :

general

R<sub>1</sub>, F

cla

50 R<sub>4</sub>, |

and the

bases.

18. F

stituted

formula

55 with inc

or alkoxy radical or a halogen atom up to the atomic number 35,

$R_4$  represents hydrogen, a low alkyl or alkoxy radical, a halogen atom up to the atomic number 35 of the trifluoromethyl group,

$R_5$  and

$R_6$  each represent hydrogen, a low alkyl radical or a benzyl radical,

and their salts with inorganic and organic bases.

2. [o - (2, 6 - Dichloro - *m* - toluidino)-phenyl] - acetic acid.

3. [2 - (2', 6' - Dichloroanilino) - 5-chlorophenyl] - acetic acid.

4. [2 - (2', 6' - Dichloro - *m* - toluidino)-5-chlorophenyl] - acetic acid.

5. [2 - (2', 6' - Dichloro - *m* - toluidino)-5-methoxyphenyl] - acetic acid.

6. [o - (6 - Methoxy - *m* - toluidino)-phenyl] - acetic acid.

7. [2 - (2', 6' - Dichloroanilino - 5-bromophenyl] - acetic acid.

8. [o - ( $\alpha$ ,  $\alpha$ ,  $\alpha$  - Trifluoro - *m* - toluidino)-phenyl] - acetic acid.

9. [o - (3 - trifluoromethyl - 6 - chloroanilino) - phenyl] - acetic acid.

10. 2 - [o - (2, 6 - Dichloro - *m* - toluidino) - phenyl] - propionic acid.

11. 2 - [o - (2, 6 - Dichloroanilino)-phenyl] - propionic acid.

12. 2 - [o - (2, 6 - Dichloro - *m* - toluidino) - phenyl] - butyric acid.

13. [o - (2, 6 - Dichloroanilino) - phenyl]- $\alpha$  - benzyl - acetic acid.

14. 2 - [o - (2, 6 - Dichloro - *m* - toluidino) - phenyl] - 2 - methyl - propionic acid.

15. [o - (2, 6 - Dichloroanilino) - phenyl]-acetic acid.

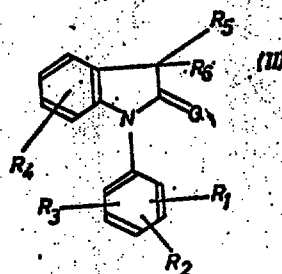
16. Substituted phenylacetic acids of the general formula I claimed in claim 1, wherein  $R_4$  and  $R_6$  represents a methyl or ethyl radical.

17. Substituted phenylacetic acids of the general formula I given in claim 1, wherein  $R_1$ ,  $R_2$  and  $R_3$  have the meanings given in claim 1, and

$R_4$ ,  $R_5$  and  $R_6$  each represent hydrogen, and their salts with inorganic and organic bases.

18. Process for the production of a substituted phenylacetic acid of the general formula I, defined in claim 1, and their salts with inorganic and organic bases, which com-

prises reacting while heating, a compound of the general formula II



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  have the meanings given in claim 1, with an alkali metal hydroxide or an alkaline earth metal hydroxide or an alkali metal carbonate and, if desired, liberating the acid from the alkaline earth or alkali metal salt obtained.

19. Process as claimed in claim 18, in which the reaction is performed in aqueous ethanol, aqueous methanol, aqueous *n*-butanol, ethylene glycol or dimethyl formamide as solvents.

20. Process as claimed in claim 18 or 19, in which the reaction is performed at a temperature at or just below the boiling temperature of the solvent.

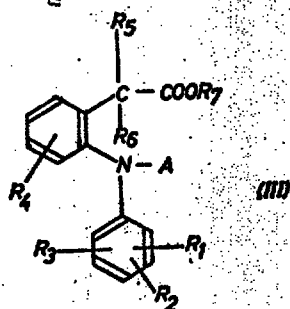
21. Process for the production of a substituted phenylacetic acid of the general formula I, as defined in claim 17, and their salts with inorganic and organic bases, which comprises reacting, while heating, a compound of the general formula II, given in claim 18 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$  and  $R_6$  have the meanings given in claim 17, within an alkali metal hydroxide or an alkaline earth metal hydroxide, and, if desired, liberating the acid from the alkaline earth or alkali metal salt obtained.

22. Process as claimed in claim 21, in which the reaction is performed in aqueous ethanol, aqueous methanol or aqueous *n*-butanol as solvent.

23. Process as claimed in claim 21 or 22, in which the reaction is performed at a temperature at or just below the boiling temperature of the solvent.

24. Process for the production of a phenylacetic acid of the general formula I, defined in claim 1 and the salts thereof, which comprises reacting, while heating, a compound of the general formula III





wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  have the meanings given in claim 1, and  $R_7$  represents a low alkyl or aralkyl radical, particularly the benzyl radical, and  $A$  represents hydrogen or a carboxylic acyl radical of at most 4 carbon atoms, with an alkali metal hydroxide, an alkaline earth metal hydroxide, an alkali metal carbonate or bicarbonate or with a basic ion exchanger, or, if  $R_7$  is an aralkyl radical, splitting it off by hydrogenolysis with catalytically activated hydrogen and, if desired, liberating the acid from the alkaline earth or alkali metal salt obtained.

25. Process as claimed in claim 24, in which  $A$  represents an acetyl radical.

26. Process as claimed in claim 24 or 25, in which the reaction is performed in the presence of aqueous methanol, aqueous ethanol, aqueous n-butanol, ethylene glycol or dimethyl formamide.

27. Process as claimed in any one of claims 24 to 26, in which the hydrolysis is performed at or just below the boiling point of the solvent.

28. Process as claimed in claim 24, in which the hydrogenolysis is performed under normal pressure, at room temperature to 50°C in the presence of palladium charcoal in alcohol.

29. Process as claimed in any one of claims 24 to 28, in which  $R_7$  is the benzyl radical.

30. Process for the production of a substituted phenylacetic acid of the general formula I as defined in claim 17, and the salts thereof, which comprises reacting, while heating, a compound of the general formula III given in claim 24, wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  have the meanings given in claim 17,  $R_7$  represents a low alkyl radical and  $A$  represents a carboxylic acyl radical of at most 4 carbon atoms, with an alkali metal hydroxide, or an alkaline earth metal hydroxide and, if desired, liberating the acid from the alkaline earth or alkali metal salt obtained.

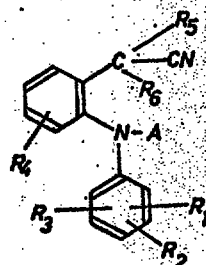
31. Process as claimed in claim 30, in which the reaction is performed in aqueous ethanol, aqueous methanol or aqueous n-butanol as solvent.

32. Process as claimed in claim 30 or

31, in which the reaction is performed at or just below the boiling temperature of the solvent.

33. Process as claimed in any one of claims 30 to 32 in which  $A$  represents an acetyl radical.

34. Process for the production of a substituted phenylacetic acid of the general formula I defined in claim 1, and the salts thereof, which comprises reacting, while heating, a compound of the general formula IV



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  have the meanings given in claim 1, and  $A$  has the meaning given in claim 24, with an alkali metal hydroxide in an aqueous solvent and, if desired, liberating the acid from the alkali metal salt obtained.

35. Process as claimed in claim 24, in which the solvent comprises ethanol, methanol, n-butanol, ethylene glycol or dimethyl formamide.

36. Process as claimed in claim 34 or 35, in which the reaction is performed at or just below the boiling temperature of the solvent.

37. Process as claimed in any one of claims 34 to 36, in which the alkali metal hydroxide comprises sodium hydroxide or potassium hydroxide.

38. Process for the production of a substituted phenylacetic acid of the general formula I, defined in claim 17, and the salts thereof, which comprises reacting, while heating, a compound of the general formula IV, given in claim 34, wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  have the meanings given in claim 17 and  $A$  represents a carboxylic acyl radical of at most 4 carbon atoms, with an alkali metal hydroxide in an aqueous low alkanol as solvent and, if desired, liberating the acid from the alkali metal salt obtained.

39. Process as claimed in claim 38, in which the low alkanol is ethanol, methanol or n-butanol.

40. Process as claimed in claim 38 or 39, in which the reaction is performed at or just below the boiling temperature of the solvent.

41. Process for the production of a salt of a substituted phenylacetic acid of the general formula I, defined in claim 1, and which comprises converting a free acid of

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the general formula I, defined in claim 1 into a salt with an inorganic or organic base.

42. Process for the production of a salt of a substituted phenylacetic acid of the general formula I defined in claim 17, which comprises converting a free acid of the general formula I, defined in claim 17, into a salt with an inorganic or organic acid.

43. Process for the production of new substituted phenyl-acetic acids of the general formula I, defined in claim 1, and salts thereof, substantially as hereinbefore described with reference to and as illustrated in Example 1 or 4.

44. Process for the production of new substituted phenylacetic acids of the general formula I, defined in claim 1, and salts thereof, substantially as hereinbefore described with reference to and as illustrated in any one of Examples 2, 3, and 5 to 16.

45. Compounds of the general formula I, defined in claim 1 and salts thereof, substantially as hereinbefore described with reference to and as illustrated in Example 1 or 4.

46. Compounds of the general formula I, defined in claim 1 and salts thereof, substantially as hereinbefore described with reference to and as illustrated in Examples 2, 3 and 5 to 16.

47. Medicament containing at least one compound of the general formula I, defined in claim 1 or an addition salt with an organic or inorganic base together with a pharmaceutically acceptable, inert carrier.

48. Medicament containing at least one compound of the general formula I, defined in claim 17 or an addition salt with an organic or inorganic base together with a pharmaceutically acceptable, inert carrier.

49. Sun-tan cream or lotion containing at least one compound of the general formula I, defined in claim 1, or an addition salt with an organic or inorganic base.

50. Sun-tan cream or lotion containing at least one compound of the general formula I, defined in claim 17 or an additional salt with an organic or inorganic base.

51. Medicaments substantially as hereinbefore described with reference to and as illustrated in the foregoing prescriptions a) and b).

52. Sun tan cream substantially as hereinbefore described with reference to and as illustrated in the foregoing prescriptions c) and d).

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Liverpool, 1.  
Chartered Patent Agents.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.  
Published by the Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

## ERRATA

### SPECIFICATION No. 1,139,332

Page 1, line 49, for "bolous" read "bolus"

Page 3, line 85, for "of" read "or"

Page 5, line 31, for "256" read "156"

Page 5, lines 61, 63, 104, 106, for "xylidene" read "xylidine"

Page 5, line 117, for "Dichloroacetanilide" read "Dichloracetanilide"

Page 5, line 119, for "dichloroacetanilide" read "dichloracetanilide"

Page 6, line 40, after "-N-" insert "(" (first occurrence)

Page 7, line 38, after "-[" insert "N-("

Page 9, line 15, for "chlorophenyl" read "chlorophenyl"

Page 10, line 89, for "indoline" read "indol-  
inone"

Page 11, line 42, for "dichloroanilino" read "dichloranilino"

Page 11, lines 44 and 45, for "dichloroanilino" read "dichloranilino"

Page 13, line 5, for "of" read "or"

Page 13, line 35, for "benyl" read "benzyl"

Page 14, line 72, for "24" read "34"

THE PATENT OFFICE  
3rd February 1969

