PATENT SPECIFICATION

NO DRAWINGS

Inventors: PETER OXLEY, NORMAN WILLIAM BRISTOW, JAMES FRASER, JOHN ROSINDALE HOUSLEY, GERALD WOOLFE, ERIC CHARLES WILMSHURST and GEORGE ALFRED HARRISON WILLIAMS

855,556

Date of filing Complete Specification (under Section 3 (3) of the Patents Act 1949): April 14, 1959.

Application Date: May 6, 1958. *No. 14460/58.*

Application Date: June 4, 1958. *No. 17867/58.*

Complete Specification Published: Dec. 7, 1960.

Index at acceptance:—Classes 2(3), C1F1(A1:A2:C2:C4:C6:D2:D3), C1F4(A1:A2:C2:C4:C6:D2:D3:F1:F2:F4), C1J3(B:C2:C3), C3A9; **and 81(1),** B(1S:2S).

International Classification:—A61k. C07c, d.

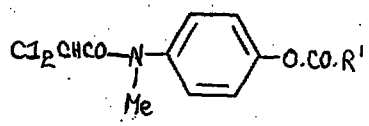
COMPLETE SPECIFICATION

New Acetanilide Derivatives

We, BOOTS PURE DRUG COMPANY LIMITED, a British Company, of Station Street, Nottingham, 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 new derivatives of acetanilide and compositions thereof which are valuable in the treatment of disease.

The invention consists in compounds having the general formula:—



I

wherein R^1 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl, or the group $—R^2COOR^3$ where R^2 is alkylene, arylene, arylenedioxydialkyl, or a divalent heterocyclic radical and R^3 is the 4-(dichloroacet-*N*-methylamido)-phenyl radical, together with simple substituted derivatives of the compounds of the above general formula containing one or more halogen atoms, nitro, amino, alkyl, alkoxy, acyl or methanesulphonyl groups in the radicals other than $—R^2COOR^3$ represented by R^1.

Compounds of the above general formula have been found to have valuable properties as amoebicides.

Dichloroacet-4-hydroxy-*N*-methylanilide — the parent phenol of the esters of the present invention—and the preparation thereof is described and claimed in our British Patent Specification No. 767,148.

The compounds of the invention may be prepared by methods well known in the art for the preparation of esters of phenols. One such method is by the interaction of an alkali metal salt of the parent phenol dichloroacet-4-hydroxy-*N*-methylanilide which is available commercially under the trade name "Entamide" (Registered Trade Mark), with an acid halide of the general formula $R^4CO.X$ in which R^4 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxy alkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl or the group $—R^2—CO.X$ in which R^2 is as hereinbefore defined and X is a halogen atom.

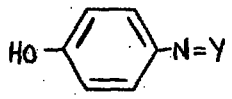
An alternative method of preparation is by the interaction in the presence of an acid binding agent of the parent phenol "Entamide" with an acid halide of the general formula $R^4CO.X$ in which R^4 and X are as hereinbefore defined.

Another alternative method of preparation is by the interaction of the parent phenol "Entamide" with an acid anhydride of the general formula $(R^5CO)_2O$ in which R^5 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl or heterocyclicalkenyl.

Another alternative method of preparation is by the interaction of the parent phenol "Entamide" with an acid of the general formula R^6COOH in which R^6 represents aryl (except unsubstituted phenyl), aralkyl,

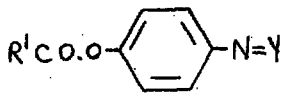
aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl or the group $-R^2COOH$ in which R^2 is as hereinbefore defined in the presence of a condensing agent such as dicyclohexylcarbodiimide, dimethylcyanamide or tetraphosphoric acid.

An alternative method for the preparation of a compound of the general formula I comprises the step of protecting the amino group of *p*-aminophenol to give a compound of the general formula:—



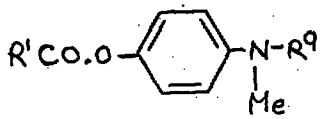
. . . II

wherein —N=Y represents (a) the group $-NHR^7$ wherein R^7 is a formyl, acetyl or dichloroacetyl group or (b) the group $-N=CHR^8$ wherein R^8 represents a phenyl radical or a phenyl radical having a substituent which cannot be esterified or methylated followed by the step of esterification to give a compound of the general formula:—



. . . III

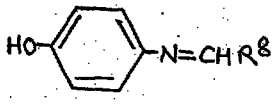
wherein R^1 and the group —N=Y are as hereinbefore defined, followed by the step of methylation and, except in the case where R^7 is a dichloroacetyl group, selectively hydrolysing the methylated product, to yield a compound having the general formula:—



. . . IV

where R^1 is as hereinbefore defined and R^9 is a hydrogen atom or a dichloroacetyl group and then in the case where R^9 is hydrogen, dichloroacetylating. This method of preparation is shown diagrammatically in Figure 1.

A compound having the general formula III wherein the group —N=Y represents the group —NHZ wherein Z is a formyl or acetyl group is prepared by formylating or acetylating *p*-aminophenol and then introducing the group R^1CO. When the group —N=Y represents $-NHCOCHCl_2$ the compounds are prepared by dichloroacetylating *p*-aminophenol and then introducing the group R^1CO—. When the group —N=Y represents the group —N=CHR^8 wherein R^8 represents a phenyl radical or a phenyl radical having a substituent which cannot be esterified or methylated the compounds of the general formula III are prepared by converting *p*-aminophenol to a Schiff's base of the general formula:—



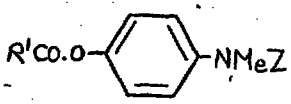
by reaction with an aldehyde of the general formula R^8CHO and then introducing the group R^1CO—.

Compounds of the general formula III in which the group —N=Y represents the group NHR^7 wherein R^7 is a formyl group, an acetyl group or a dichloroacetyl group and R^1 is as above defined are methylated by treatment with a methylating agent in the presence of an alkali. The treatment may be carried out with methyl iodide in the presence of potassium hydroxide or with dimethyl sulphate in the presence of potassium carbonate.

Compounds of the general formula III wherein the group —N=Y represents the group —N=CHR^8 wherein R^8 represents a phenyl radical or a phenyl radical having a substituent which cannot be esterified or methylated by treatment with a suitable methylating agent.

Dichloroacetylation is carried out by treatment with chloral cyanohydrin in the presence of an acid binding agent. The chloral cyanohydrin may be prepared *in situ*.

The resulting methylated product having the general formula:—



in which Z is a formyl or acetyl group and R^1 is as above defined is hydrolysed with dilute mineral acid to remove the group Z.

Compounds having the general formula I may also be prepared by subjecting the corresponding nitro compound to reduction.

Another alternative method of preparation is by treating "Entamide" sulphite with an acid of the general formula R^6COOH in which R^6 is as hereinbefore defined in the presence of an acid binding agent.

The amoebicidal activity of the compounds of the present invention has been demonstrated in animals in the following manner. The technique is substantially that described by Jones (Annals of Tropical Medicine and Parasitology, 1946, *40*, 130) in which newly weaned rats are inoculated intracaecally with trophozoites of E. histolytica. Starting on the

day after inoculation 5 daily doses of the drug under test are administered by stomach tube to each of a group of rats and the animals are killed one day after the final dose. The caecum of each rat is examined both microscopically and macroscopically and the degree of infection of each rate is assessed on an arbitrary scale. The average degree of infection ("A.D.I.") is then calculated for each group. A compound is regarded as showing promising amoebicidal activity when the "A.D.I." of the treated group is less than half that of an undosed control group. With highly effective drugs the rats are completely cleared of amoebae and the "A.D.I." is then nought. The initial screening tests showed that the preferred group of compounds comprised esters of "Entamide" with carboxylic acids containing a heterocyclic nucleus or an aryloxy group e.g. "Entamide" furoate; direct comparison showed it to be approximately 4 times as active as the parent phenol "Entamide" and twice as active as "Entamide" benzoate.

Clinically amoebiasis occurs in both the acute and chronic form and of these only the chronic disease has been controlled by "Entamide" and those esters which are described in B.P. 767,148 and 794,762. We have now discovered that the member of the preferred group of compounds of the present invention which has been selected for clinical trials, viz. "Entamide" 2-fuorate, not only shows increased activity against chronic amoebiasis but also shows activity against the acute form of the disease which may be completely cured by the administration of "Entamide" furoate at a dose rate of 20 mg/kg per day for 10 days. The total dose may vary from 15 mg to 75 mg/kg/day, being preferably 20—40 mg/kg/day, and this dose may be supplied in the form of dosage units which may contain from 100 mg. to 1000 mg. of active material, the dosage units being administered preferably in divided doses throughout the day e.g. 3 or 4 times per day.

The compositions according to the present invention may be adapted for internal or external application although the preferred method of administration is *per os*.

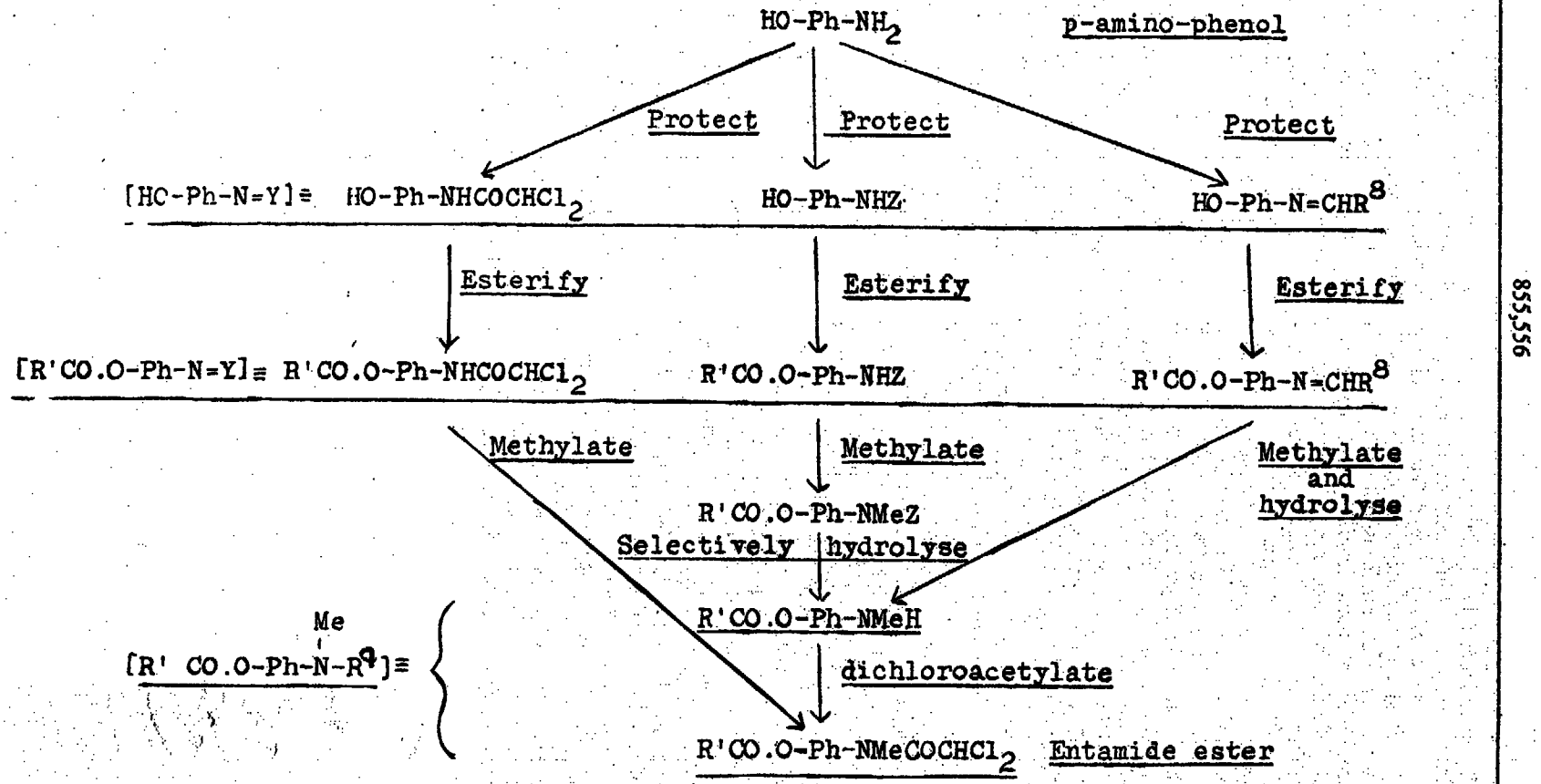
The compositions of the invention which are suitable for oral use may be in the form of solid compositions such as tablets, lozenges, capsules and the like or in the form of liquids, such as suspensions. The diluents which may be employed in the preparation of the compositions of the invention may be any non-toxic substance compatible with the compounds of the invention and include extenders, solvents, suspending agents, binding agents, flavourings and the like. We have found that a convenient method of administering the active compounds of the invention is in the form of a tablet. Such a tablet comprises the active compound in association with any suitable diluent normally employed in the manufacture of tablets and we have found that icing sugar and maize starch give a very satisfactory tablet which is conveniently one of 5 grains or 10 grains total weight. There may also be included in the composition a granulating agent and we prefer to use gum acacia. Small quantities of a lubricant may be included if desired and stearic acid has been found to be highly satisfactory. There may also be included, if desired, colouring and flavouring agents.

Liquid compositions suitable for oral administration of the compounds of the invention include suspensions and syrups comprising the active ingredient in association with compatible suspending agents and the like which are well known in the art.

Figure 1

The symbol -Ph- represents the phenylene radical -  -

The symbol -Z represents the formyl or acetyl radical.



The following non-limitative examples illustrate the invention:—

EXAMPLE 1.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 2-furoate, 13.7 grams of 2-furoyl chloride are added slowly to a stirred solution of 23.4 grams of dichloroacet-4-hydroxy - *N* - methylanilide in 50 ml. of dry pyridine, water cooling being used to keep the temperature below 25° C. The reaction mixture is stirred for a further 40 minutes and then diluted with 400 ml. of ice water containing 100 mg. of sodium hydrosulphite. The product is collected by filtration and recrystallised from 95% alcohol. There is thus obtained 4 - (dichloroacet - *N* - methylamido)phenyl 2-furoate as a crystalline solid which has a melting point of 112.5—114° C. (Found: C, 51.2; H, 3.4. $C_{14}H_{11}Cl_2NO_4$ requires C, 51.2; H, 3.35%).

In a similar manner are prepared the following esters:—

4 - (Dichloroacet - *N* - methylamido)phenyl 4 - methoxy - phenoxyacetate m.p. 93—94.5° C. (Found: C, 54.6; H, 4.4. $C_{18}H_{17}Cl_2NO_5$ requires C, 54.2; H, 4.3%).

4 - (Dichloroacet - *N* - methylamido)phenyl phenoxy - acetate m.p. 108—109° C. (Found: C, 55.3; H, 4.0. $C_{17}H_{15}Cl_2NO_4$ requires C, 55.4; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2-thenoate m.p. 134—135° C. (Found: C, 49.1; H, 3.0. $C_{14}H_{11}Cl_2NO_3S$ requires C, 48.8; H, 3.2%).

4 - (Dichloroacet - *N* - methylamido)phenyl β - naphthoxy - acetate m.p. 121—122° C. (Found: C, 60.4; H, 3.7. $C_{21}H_{17}Cl_2NO_4$ requires C, 60.3; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2 - chloro - phenoxyacetate m.p. 102—104° C. (Found: C, 50.5; H, 3.1. $C_{17}H_{14}Cl_3NO_4$ requires C, 50.7; H, 3.5%).

4 - (Dichloroacet - *N* - methylamido)phenyl 4 - methyl - phenoxyacetate m.p. 69—71° C. (Found: C, 56.6; H, 4.4. $C_{18}H_{17}Cl_2NO_4$ requires C, 56.55; H, 4.45%).

4 - (Dichloroacet - *N* - methylamido)phenyl α - (2 - methyl - phenoxy)propionate m.p. 107—108° C. (Found: C, 57.7; H, 5.2. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8%).

4 - (Dichloroacet - *N* - methylamido)phenyl 5 - bromo - 2 - furoate m.p. 101—103° C. (Found: C, 40.9; H, 2.4. $C_{14}H_{10}BrCl_2NO_4$ requires C, 41.3; H, 2.5%).

EXAMPLE 2.

By the method described in Example 1 but crystallising five times from alcohol, and once from benzene followed by dissolving in acetone and drowning in ice-cold *N* NaOH and a final crystallisation from 95% alcohol, there is obtained 4-(dichloroacet-*N*-methylamido)-phenyl 4 - nitrophenoxyacetate m.p. 133—135° C. (Found: C, 49.5; H, 3.6. $C_{17}H_{14}Cl_2N_2O_6$ requires C, 48.9; H, 3.4%).

EXAMPLE 3.

By the method described in Example 1 but collecting the crude oily product by extraction with chloroform, washing the chloroform solution with half-normal sulphuric acid, aqueous sodium bicarbonate solution and water, drying the solution with anhydrous magnesium sulphate, removing the chloroform by distillation and crystallising the residue from 95% alcohol there are obtained the following as crystalline solids:—

4 - (Dichloroacet - *N* - methylamido)phenyl γ-phenoxy-butyrate m.p. 61—62° C. (Found: C, 57.8; H, 5.0. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8%).

4 - (Dichloroacet - *N* - methylamido)phenyl 3 - chloro - phenoxyacetate m.p. 80—81° C. (Found: C, 50.6; H, 3.8. $C_{17}H_{14}Cl_3NO_4$ requires C, 50.7; H, 3.5%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2-phenoxy-benzoate m.p. 92—93° C. (Found: C, 61.1; H, 4.0. $C_{22}H_{17}Cl_2NO_4$ requires C, 61.4; H, 3.95%).

EXAMPLE 4.

In the preparation of 4 - (dichloroacet-*N*-methylamido)-phenyl nicotinate, 32.5 grams of nicotinyl chloride hydrochloride are added to a stirred solution of 45 grams of dichloroacet-4 - hydroxy - *N* - methylanilide in 140 ml. of dry pyridine. After being stirred for 90 minutes the reaction mixture is quenched with ice water and the product is isolated as in Example 1. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N* - methylamido)phenyl nicotinate which has a melting point of 167—170° C. (Found: C, 53.4; H, 3.5; N, 8.6. $C_{15}H_{12}Cl_2N_2O_3$ requires C, 53.1; H, 3.5; N, 8.3%).

In a similar manner there is prepared 4-(dichloroacet - *N* - methylamido)phenyl picolinate m.p. 130—131° C. (Found: C, 53.1; H, 3.7. $C_{15}H_{12}Cl_2N_2O_3$ requires C, 53.1; H, 3.5%).

EXAMPLE 5.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl isonicotinate 6.4 ml. of benzene sulphonyl chloride are added to a solution of 12.3 grams of isonicotinic acid in 50 ml. of dry pyridine, the temperature rising to 65° C. The solution is stirred at 45° C. for 15 minutes and then heated to 90° C. A solution of 11.7 grams of dichloroacet - 4-hydroxy - *N* - methylanilide in 20 ml. of dry pyridine is added slowly to the stirred solution and stirring at 90° C. is continued for 30 minutes. The solution is cooled, poured into 300 ml. of ice water and the crude product is filtered off and crystallised twice from 95% alcohol. There is thus obtained 4 - (dichloroacet - *N* - methylamido)phenyl isonicotinate which has a melting point of 125—126.5° C. (Found: C, 53.0; H, 3.3. $C_{15}H_{12}Cl_2N_2O_3$ requires C, 53.1; H, 3.5%).

In a similar manner is prepared the following ester:

4 - (Dichloroacet - *N* - methylamido)phenyl 2-furylacrylate m.p. 115—117° C. (Found: C, 54.4; H, 3.6. $C_{16}H_{13}Cl_2NO_4$ requires C, 54.2; H, 3.7%).

EXAMPLE 6.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl α - phenoxyisobutyrate 11.7 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide is slowly added to a solution of 10 grams of α - phenoxyisobutyryl chloride in 50 ml. of dry pyridine and the mixture is maintained at about 20° C. for 20 hours. The reaction mixture is poured into 500 ml. of ice water and the crude product is filtered off, washed with dilute sulphuric acid and water and is crystallised from methanol. There is thus obtained as a crystalline solid 4-(dichloroacet - *N* - methylamido)phenyl α - phenoxyisobutyrate which has a melting point of 85—86° C. (Found: C, 57.5; H, 4.6; N, 3.6. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8; N, 3.5%).

EXAMPLE 7.

By the method described in Example 6 but crystallising the crude product twice from a mixture of chloroform and methanol there is obtained as a crystalline solid 4 - (dichloroacet-*N*-methylamido)phenyl coumarilate which has a melting point of 151—153° C. (Found: C, 57.4; H, 3.4; N, 4.0. $C_{18}H_{13}Cl_2NO_4$ requires C, 57.1; H, 3.4; N, 3.7%).

EXAMPLE 8.

By the method described in Example 6 but extracting the gummy product with ether, washing the ethereal solution with 5*N* sulphuric acid, water, 2*N* sodium hydroxide and water evaporation of the solvent and crystallisation of the gummy product from methanol there is obtained as a crystalline solid 4-dichloroacet - *N* - methylamido)phenyl α - phenoxypropionate which has a melting point of 61—62° C. (Found: C, 56.6; H, 4.45; N, 3.7. $C_{18}H_{17}Cl_2NO_4$ requires C, 56.55; H, 4.45; N, 3.7%).

EXAMPLE 9.

By the method described in Example 8 there is obtained as a gum the following esters.

4 - (Dichloroacet - *N* - methylamido)phenyl α - phenoxy - *n* - butyrate. (Found: C, 57.9; H, 5.2; N, 3.9. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8; N, 3.5%).

4 - (Dichloroacet - *N* - methylamido)phenyl α - phenoxy - *n* - valerate. (Found: C, 58.8; H, 5.2. $C_{20}H_{21}Cl_2NO_4$ requires C, 58.5; H, 5.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl α - phenoxy - *n* - hexanoate. (Found: C, 59.6; H, 5.25. $C_{21}H_{23}Cl_2NO_4$ requires C, 59.4; H, 5.4%).

EXAMPLE 10.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl β - phenoxypropionate, 9.3 grams of thionyl chloride are added to a stirred suspension of 12.9 grams of β-phenoxypropionic acid, in 50 ml. of dry ether and the mixture is maintained at about 20° C. for 16 hours under anhydrous conditions. The solvent is distilled off at 20° C. under reduced pressure and 11.85 grams of the gummy residue are dissolved in 60 ml. of dry pyridine. To the solution is added a solution of 15 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide in dry pyridine. The reaction mixture is drowned in water and the product is collected with ether and crystallised as described in Example 8. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N*-methylamido)phenyl β - phenoxypropionate which has a melting point of 61—62° C. (Found: C, 56.5; H, 4.7. $C_{18}H_{17}Cl_2NO_4$ requires C, 56.55; H, 4.45%).

EXAMPLE 11.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl β - phenoxypropionate, 2.32 ml. of benzoyl chloride dissolved in 10 ml. of dry benzene are added dropwise at room temperature to a stirred suspension of 3.76 grams of finely powdered sodium β-phenoxypropionate in 40 ml. of dry benzene and the stirring is continued for a further 90 minutes. To the stirred solution of the mixed anhydride thus formed there is added a solution of 4.68 grams of dichloroacet-4-hydroxy-*N*-methylanilide in 50 ml. of dry pyridine and the reaction mixture is allowed to stand for about 16 hours and is then poured into 200 ml. of water. The aqueous phase is washed with ether and the ethereal extract is added to the solvent phase. The combined organic phase is washed successively with 5*N* sulphuric acid, water, 2*N* sodium hydroxide and finally water. It is dried with anhydrous sodium sulphate and the solvent is distilled off. The residue is crystallised twice from aqueous methanol and there is thus obtained as a crystalline solid 4-(dichloroacet - *N* - methylamido)phenyl β-phenoxypropionate which has a melting point of 60—61° C. A mixed melting point of this material together with that prepared according to Example 10 is also 60—61° C.

EXAMPLE 12.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl tetrahydro - 2 - furoate 11.2 grams of dicyclohexyl - carbodiimide is added to a warm mixture of 6.27 grams of tetrahydro - 2 - furoic acid, 12.6 grams of dichloroacet - 4 - hydroxy - *N* - methylanilide and 100 ml. of methylene chloride and the mixture is allowed to stand overnight at 20° C. To the mixture is added 1 ml. of glacial acetic acid and after one hour the solution is filtered and the filtrate is washed with aqueous *N* sodium carbonate solution, ice cold 2*N* sodium hydroxide solution and water. It is dried with anhydrous magnesium sulphate and evaporated to an oil which is dissolved in a mixture of equal volumes of benzene and 60—80° C. petroleum ether. The solution is

cooled to 0° C. for three hours, filtered and evaporated to an oil which is distilled *in vacuo*. There is thus obtained as an oil 4-(dichloroacet - *N* - methylamido)phenyl tetrahydro-2-furoate which has a boiling point of 175° C. under a pressure of 0.01 mm. Hg. (Found: C, 50.8; H, 4.5. $C_{14}H_{15}Cl_2NO_4$ requires C, 50.6; H, 4.5%).

EXAMPLE 13.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 3-furoate 6.75 grams of dicyclohexylcarbodiimide is added to a warm mixture of 3.6 grams of 3-furoic acid, 7.7 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide and 75 ml. of methylene chloride and the mixture is allowed to stand overnight at 20° C. To the mixture is added 2 ml. of glacial acetic acid and after standing for 5 hours it is filtered, the filtrate is washed with ice cold 2*N* sodium hydroxide solution, then water, and is dried with anhydrous magesium sulphate. The solvent is evaporated off and the residue is crystallised twice from 95% ethanol. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N* - methylamido)-phenyl 3-furoate which has a melting point of 105.5—107° C. (Found: C, 51.5; H, 3.6. $C_{14}H_{11}Cl_2NO_4$ requires C, 51.2; H, 3.35%).

In a similar manner are prepared the following esters:—

4 - (Dichloroacet - *N* - methylamido)phenyl 4:5 - dibromo - 2 - furoate m.p. 142—144° C. (Found: C, 34.8; H, 1.8. $C_{14}H_9BR_2Cl_2NO_4$ requires C, 34.6; H, 1.85%).

4 - (Dichloroacet - *N* - methylamido)phenyl 5 - methyl - 2 - furoate m.p. 129—131° C. (Found: C, 52.1; H, 3.8. $C_{15}H_{13}Cl_2NO_4$ requires C, 52.6; H, 3.8%).

4 - (Dichloroacet - *N* - methylamido)phenyl γ:γ - bis(fur - 2 - yl) - *n* - valerate. (Found: C, 58.5; H, 5.1. $C_{22}H_{21}Cl_2NO_5$ requires C, 58.6; H, 4.7%).

4 - (Dichloroacet - *N* - methylamido)phenyl α:α - bis - (5 - methylfur - 2 - yl) - propionate m.p. 105—106° C. (Found: C, 58.3; H, 5.0. $C_{22}H_{21}Cl_2NO_5$ requires C, 58.6; H, 4.7%).

EXAMPLE 14.

By the method described in Example 1 save that the acid chloride is dissolved in acetone before addition to the solution of dichloroacet-4 - hydroxy - *N* - methylanilide in pyridine there is obtained as a crystalline solid 4-(dichloroacet - *N* - methylamido)phenyl quinaldate m.p. 143—145° C. (Found: C, 58.3; H, 3.6. $C_{19}H_{14}Cl_2N_2O_5$ requires C, 58.6; H, 3.6%).

EXAMPLE 15.

By the method described in Example 14 but crystallising from acetic acid there is obtained as a crystalline solid 4 - (dichloroacet-*N* - methylamido)phenyl furan - 2:5 - dicarboxylate m.p. 194—194.5° C. (Found: C, 48.6; H, 3.0. $C_{24}H_{18}Cl_4N_2O_7$ requires C, 49.0; H, 3.1%).

EXAMPLE 16.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl pyrazinoate a solution of pyrazinoyl chloride (7.2 grams) in acetone (70 ml.) is slowly added to a stirred solution of dichloroacet - 4 - hydroxy - *N* - methylanilide (11.1 grams) in pyridine (35 ml.). Stirring is continued for half an hour and the reaction mixture is poured into water (400 ml.). The gum which settles out is collected with chloroform and the chloroform solution is washed successively with dilute sulphuric acid, aqueous sodium bicarbonate and water. The solution is dried over anhydrous magnesium sulphate and is evaporated to give a gum which is dissolved in methanol. The methanol solution is evaporated to give a solid which is recrystallised from alcohol. There is thus obtained as a crystalline solid 4-(dichloroacet-*N*-methylamido)phenyl pyrazinoate m.p. 115—117° C. (Found: C, 49.0; H, 3.5; N, 12.0. $C_{14}H_{11}Cl_2N_3O_3$ requires C, 49.4; H, 3.2; N, 12.4%).

EXAMPLE 17.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl *p*-phenylenedioxydiacetate a solution of *p*-phenylenedioxydiacetyl chloride (11.46 grams) in acetone is added to a stirred solution of dichloroacet - 4 - hydroxy - *N*-methylanilide (20 grams) in pyridine (50 ml.). After stirring for two hours at room temperature the reaction mixture is poured into water and the gum which separates is extracted with chloroform. The chloroform solution is washed successively with water, aqueous sodium hydroxide, dilute sulphuric acid and aqueous sodium carbonate solution, dried over anhydrous magnesium sulphate and evaporated to dryness. The solid is crystallised from acetic acid and there is thus obtained as a crystalline solid 4 - (dichloroacet - *N* - methylamido) - phenyl *p* - phenylenedioxydiacetate m.p. 153—154° C. (Found: C, 51.4; H, 3.7. $C_{28}H_{24}Cl_4N_2O_8$ requires C, 51.1; H, 3.65%).

EXAMPLE 18.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 5 - nitro - 2 - furoate, 5 - nitro - 2 - furoic acid (3.95 grams) is refluxed for 24 hours with thionyl chloride (5 ml.), a further 5 ml. of thionyl chloride is added and the refluxing is continued for a further 8 hours. The solution is distilled to dryness, the crude acid chloride is dissolved in acetone and added to a stirred solution of dichloroacet - 4 - hydroxy - *N* - methylanilide (4.7 grams) in pyridine (20 ml.). The product is isolated and purified as described in Example 1 and there is thus obtained 4-(dichloroacet - *N* - methylamido)phenyl 5-nitro-2-furoate m.p. 116—117° C. (Found: C, 45.1; H, 2.9. $C_{14}H_{10}Cl_2N_2O_8$ requires C, 45.0; H, 2.7%).

EXAMPLE 19.

In the preparation of 4 - (dichloroacet-*N*-methylamido)phenyl 5 - methoxycoumarilate,

5 - methoxycoumarilic acid (2 grams) is heated with thionyl chloride (10 ml.) under reflux for one hour and then distilled to dryness. The crude acid chloride is dissolved in 30 ml. of dry pyridine and 2.4 grams of dichloroacet - 4 - hydroxy - *N* - methylanilide is added slowly and the reaction mixture left at room temperature for 20 hours. The product is isolated and purified as described in Example 6 and there is thus obtained as a crystalline solid 4-(dichloroacet - *N* - methylamido)phenyl 5 - methoxycoumarilate m.p. 151—152° C. (Found: C, 55.5; H, 3.6. $C_{19}H_{15}Cl_2NO_5$ requires C, 55.9; H, 3.7%).

In a similar manner there are prepared the following esters.

4 - (Dichloroacet - *N* - methylamido)phenyl 5:7 - dibromo - coumarilate m.p. 171° C. (Found: C, 40.1; H, 2.0. $C_{18}H_{11}Br_2Cl_2NO_4$ requires C, 40.3; H, 2.05%).

4 - (Dichloroacet - *N* - methylamido)phenyl 7 - methoxy - coumarilate m.p. 183—184° C. (Found: C, 55.7; H, 3.8. $C_{19}H_{15}Cl_2NO_5$ requires C, 55.9; H, 3.7%).

EXAMPLE 20.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 2-furoate a mixture of dichloroacet - 4 - hydroxy - *N* - methylanilide (23.4 grams), 2-furoic acid (11.2 grams) and tetraphosphoric acid (55 grams), is stirred and heated on the steam bath for 24 hours. The viscous product is triturated with water and the black solid which results is ground with dilute aqueous sodium hydroxide solution, washed with water and drained. It is extracted with boiling alcohol, filtered and left to crystallise at 0° C. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N* - methylamido)phenyl 2-furoate m.p. 111—112° C. which is undepressed in admixture with material made as described in Example 1.

EXAMPLE 21.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl cinnamate, 17.3 grams of cinnamyl chloride are added slowly to a stirred solution of 23.4 grams of dichloroacet-4-hydroxy - *N* - methylanilide in 50 ml. of dry pyridine, water cooling being used to keep the temperature below 25° C. The reaction mixture is stirred for a further 40 minutes and then diluted with 400 ml. of ice-water containing 100 mg. of sodium hydrosulphite. The product is collected by filtration and recrystallised from 95% alcohol. There is thus obtained 4 - (dichloroacet - *N* - methylamido)phenyl cinnamate as a crystalline solid which has a melting point of 101—102° C. (Found: C, 59.55; H, 4.2. $C_{18}H_{15}Cl_2NO_3$ requires C, 59.35; H, 4.1%).

In a similar manner are prepared the following esters:—

4 - (Dichloroacet - *N* - methylamido)phenyl 4 - methoxybenzoate, m.p. 119—121° C. (Found: C, 55.8; H, 3.9. $C_{17}H_{15}Cl_2NO_4$ requires C, 55.4; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl phthalate, m. p. 137—138° C. (Found: C, 52.5; H, 3.4. $C_{24}H_{20}Cl_4N_2O_6$ requires C, 52.2; H, 3.3%).

4 - (Dichloroacet - *N* - methylamido)phenyl *β* - phenyl - propionate, m.p. 76—77° C. (Found: C, 58.9; H, 4.6. $C_{18}H_{17}Cl_2NO_3$ requires C, 59.0; H, 4.6%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2 - acetylsalicylate, m.p. 175—177° C. (Found: C, 55.1; H, 3.9. $C_{18}H_{15}Cl_2NO_5$ requires C, 54.6; H, 3.8%).

4 - (Dichloroacet - *N* - methylamido)phenyl hexahydrobenzoate, m.p. 76—78.5° C. (Found: C, 56.0; H, 5.7. $C_{16}H_{19}Cl_2NO_3$ requires C, 55.8; H, 5.5%).

4 - (Dichloroacet - *N* - methylamido)phenyl *α*-naphthoate, m.p. 140—141° C. (Found: C, 61.6; H, 4.0 $C_{20}H_{15}Cl_2NO_3$ requires C, 61.8; H, 3.9%).

4 - (Dichloroacet - *N* - methylamido)phenyl *p*-toluate, m.p. 102.5—105° C. (Found: C, 58.0; H, 4.3. $C_{17}H_{15}Cl_2NO_3$ requires C, 58.0; H, 4.3%).

4 - (Dichloroacet - *N* - methylamido)phenyl 4 - nitrobenzoate, m.p. 145—147° C. (Found: C, 49.9; H, 3.1. $C_{16}H_{12}Cl_2N_2O_5$ requires C, 50.2; H, 3.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl 3:4 - dimethoxybenzoate, m.p. 156° C. (Found: 54.3; H, 4.3. $C_{18}H_{17}Cl_2NO_5$ requires C, 54.3; H, 4.3%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2-chlorobenzoate, m.p. 108—110° C. (Found: C, 51.2; H, 3.3. $C_{16}H_{12}Cl_3NO_3$ requires C, 51.6; H, 3.2%).

4 - (Dichloroacet - *N* - methylamido)phenyl 3 - methoxybenzoate, m.p. 113—114° C. (Found: C, 55.6; H, 4.0. $C_{17}H_{15}Cl_2NO_4$ requires C, 55.4; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl hippurate, m.p. 146—148° C. (Found: C, 54.8; H, 4.0. $C_{18}H_{16}Cl_2N_2O_4$ requires C, 54.7; H, 4.05%).

4 - (Dichloroacet - *N* - methylamido)phenyl 3 - bromobenzoate, m.p. 108—109° C. (Found: C, 46.0; H, 3.0. $C_{16}H_{12}BrCl_2NO_3$ requires C, 46.0; H, 2.9%).

EXAMPLE 22.

Following a similar reaction procedure to that described in Example 21, but employing an isolation procedure comprising the steps of dissolving the crude-non-crystalline product in chloroform, washing the chloroform solution with half-normal sulphuric acid, aqueous sodium bicarbonate solution and water, drying the solution with anhydrous magnesium sulphate, removing the chloroform by distillation and crystallising the residue from 95% alcohol, there are obtained the following as crystalline solids:—

4 - (Dichloroacet - *N* - methylamido)phenyl sebacate, m.p. 82—83° C. (Found: C, 53.2; H, 5.0. $C_{28}H_{32}Cl_4N_2O_6$ requires C, 53.0; H, 5.05%).

4 - (Dichloroacet - *N* - methylamido)phenyl diphenylacetate, m.p. 99—101° C. (Found: C, 64.2; H, 4.6. $C_{23}H_{19}Cl_2NO_3$ requires C, 64.5; H, 4.4%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2 - benzoylbenzoate, m.p. 115—116° C. (Found: C, 62.2; H, 4.0. $C_{23}H_{17}Cl_2NO_4$ requires C, 62.4; H, 3.8%).

EXAMPLE 23.

By the method described in Example 21, but additionally crystallising the product from methyl propyl ketone, there is obtained 4-(dichloroacet - *N* - methylamido)phenyl terephthalate as a crystalline solid which has a melting point of 174—177° C. (Found: C, 52.0; H, 3.6. $C_{26}H_{20}Cl_4N_2O_6$ requires C, 52.2; H, 3.3%).

EXAMPLE 24.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 4 - methanesulphonylbenzoate, 22.0 grams of 4-methanesulphonylbenzoyl chloride are added over ten minutes to a stirred solution of 21.5 g. of dichloroacet-4-hydroxy - *N* - methylanilide in 90 ml. of dry pyridine. At the end of this time the mixture is warmed to 40° C. and stirred at this temperature for one hour. The product is then isolated as described in Example 21, giving 4 - (dichloroacet - *N* - methylamido)phenyl 4 - methanesulphonylbenzoate in the form of a solid crystalline solid with a melting point of 166—168° C. when crystallised from benzene. (Found C, 49.4; H, 3.7. $C_{17}H_{15}Cl_2NO_5S$ requires C, 49.0; H, 3.6%).

EXAMPLE 25.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 4 - chlorobenzate a mixture of 5.9 grams of 4 - chlorobenzoic anhydride, 4.7 grams of dichloroacet - 4 - hydroxy-*N* - methylanilide and 20 ml. of dry pyridine is kept at 20° C. for 3 hours and then warmed to 85° C. for 30 minutes, cooled and poured into 200 ml. of ice-water. The product is collected by filtration and recrystallised from alcohol. There is thus obtained 4-(dichloroacet - *N* - methylamido)phenyl 4 - chlorobenzoate as a crystalline solid with a melting point of 98.5—100° C. (Found: C, 51.4; H, 3.3. $C_{16}H_{12}Cl_3NO_3$ requires C, 51.6; H, 3.2%).

EXAMPLE 26.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 4 - chlorobenzoate an intimate mixture of 5.9 grams of 4 - chlorobenzoic anhydride and 4.7 grams of dichloroacet-4-hydroxy - *N* - methylanilide is heated in an oil bath at 130—170° C. for 3 hours. The cooled mixture is then crystallised from alcohol and ground in a mortar with 30 ml. of *N* sodium hydroxide solution and the solid is collected and recrystallised from alcohol to give 4 - (dichloroacet - *N* - methylamido)-phenyl 4 - chlorobenzoate, identical with that prepared as described in Example 25.

EXAMPLE 27.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl α - methoxypropionate, 11.7 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide is added portionwise to a solution of 6.2 grams of α-methoxy-propionyl chloride in 50 ml. of dry pyridine and the mixture is maintained at room temperature for 20 hours. The mixture is quenched by pouring into 500 ml. of water and the product is collected by filtration, washed with dilute sulphuric acid and water and crystallised from methanol. This is thus obtained 4 - (dichloroacet - *N*-methylamide)phenyl α - methoxypropionate as a crystalline solid with a melting point of 110—111° C. (Found: C, 48.9; H, 4.4; $C_{13}H_{15}Cl_2NO_4$ requires C, 48.8; H, 4.7%).

EXAMPLE 28.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl *O* - methylmandelate, 8.1 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide is added portionwise to a solution of 6.4 grams of *O* - methylmandelyl chloride in 32 ml. of dry pyridine and the mixture is maintained at room temperature for 20 hours and is quenched by pouring into 500 ml. of water. The gummy product is extracted with three 100 ml. portions of ether and the combined ethereal extracts are washed successively with 5*N* sulphuric acid, water, 2*N* sodium hydroxide and water. The solution is dried with anhydrous sodium sulphate and evaporated to give a gummy product which is crystallised twice from aqueous methanol. There is thus obtained 4 - (dichloroacet - *N*-methylamido)phenyl *O* - methylmandelate as a crystalline solid with a melting point of 86—88° C. (Found: C, 56.7; H, 4.7; $C_{18}H_{17}Cl_2NO_4$ requires C, 56.55; H, 4.55%).

EXAMPLE 29.

By the method described in Example 28 but washing the ether extract with 50% aqueous methanol, saturated aqueous sodium hydrogen carbonate and water there is obtained 4 - (dichloroacet - *N* - methylamido)phenyl methoxyacetate m.p. 52—54° C. (Found: C, 47.3; H, 4.3. $C_{12}H_{13}Cl_2NO_4$ requires C, 47.1; H, 4.25%).

EXAMPLE 30.

By the method described in Example 28 but extracting with chloroform instead of ether and crystallising from methanol there is obtained 4 - (dichloroacet - *N* - methylamido)-phenyl cyclopropane carboxylate m.p. 114—115° C. (Found: C, 50.5; H, 4.6; N, 4.3. $C_{13}H_{13}Cl_2NO_3$ requires C, 50.1; H, 4.3; N, 4.6%).

EXAMPLE 31.

By the method described in Example 28 but crystallising the product from ether/light petroleum (b.p. 40—60° C.) there are obtained:—

4 - (Dichloroacet - *N* - methylamido)phenyl cyclobutane carboxylate m.p. 68—68.5° C. (Found: C, 53.3; H, 5.0. $C_{14}H_{15}Cl_2NO_3$

requires C, 53.2; H, 4.7%).

4 - (Dichloroacet - *N* - methylamido)phenyl cyclopentanecarboxylate m.p. 57—58° C. (Found: C, 54.0; H, 5.2. $C_{15}H_{17}Cl_2NO_3$ requires C, 54.2; H, 5.1%).

EXAMPLE 32.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 3:4 - dichlorobenzoate, a mixture of 3:4 - dichlorobenzoyl chloride (11.0 grams) dichloroacet - 4 - hydroxy - *N*-methylanilide (11.7 grams) and pyridine (30 ml.) is stirred for one hour and poured into N/4 sodium hydroxide solution (200 ml.). The crude product is collected by filtration and crystallised three times from alcohol and twice from benzene. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N*-methylamido)phenyl 3:4 - dichlorobenzoate m.p. 113—114° C. (Found: C, 47.4; H, 2.7. $C_{16}H_{11}Cl_4NO_3$ requires C, 47.2; H, 2.7%).

EXAMPLE 33.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 4 - aminobenzoate a solution of 4 - (dichloroacet - *N* - methylamido)-phenyl 4 - nitrobenzoate (9.57 grams) in ethyl acetate (180 ml.) is hydrogenated at room temperature and pressure in the presence of a 10% palladium/carbon catalyst (0.1 gram). When the theoretical weight of hydrogen has been absorbed the solution is filtered and concentrated *in vacuo*. The solid residue is crystallised from ethyl acetate and there is thus obtained 4 - (dichloroacet - *N* - methylamido)phenyl 4 - aminobenzoate m.p. 196.5—197° C. (Found: C, 54.2; H, 3.8; N, 8.0. $C_{16}H_4Cl_2N_2O_3$ requires C, 54.4; H, 4.0; N, 7.9%).

EXAMPLE 34.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl phenylglyoxylate a mixture of dichloroacet - 4 - hydroxy - *N*-methylanilide (11.7 grams), phenylglyoxylic acid (7.5 grams), methylene chloride (40 ml.) and pyridine (5 ml.) is cooled to 0° C. and a solution of dicyclohexylcarbodiimide (10.3 grams) in methylene chloride (20 ml.) is slowly added with stirring. The mixture is allowed to stand at 0° C. for 16 hours, and after a further 0.5 grams of phenylglyoxylic acid is added, is filtered. The filtrate is diluted with 2 volumes of ether, washed with dilute acid, water, very rapidly with dilute alkali and finally with water before being dried over anhydrous sodium sulphate and evaporated. The residue is crystallised from methanol and there is thus obtained as a crystalline solid 4-(dichloroacet - *N* - methylamido)phenyl phenylglyoxylate m.p. 87—88.5° C. (Found: C, 56.1; H, 3.5. $C_{17}H_{13}Cl_2NO_4$ requires C, 55.7; H, 3.55%).

EXAMPLE 35.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl α - methoxyisobutyrate, a mixture of dichloroacet - 4 - hydroxy - *N*-methylanilide (11.2 grams), α - methoxyisobutyric acid (5.9 grams), pyridine (5 ml.) and methylene chloride (80 ml.) is stirred at room temperature, a solution of dicyclohexylcarbodiimide (10.3 grams) in methylene chloride (20 ml.) is added and the mixture allowed to stand at room temperature for 16 hours. A further addition of α - methoxyisobutyric acid (0.5 ml.) is made, the mixture is filtered after 1 hour and the filtrate is washed successively with dilute sulphuric acid, water, dilute sodium hydroxide and water. After drying over anhydrous magnesium sulphate the solution is evaporated and the gummy residue is triturated with benzene/light petroleum (60—80° C.). The solution is filtered, evaporated and the gummy residue crystallised from aqueous methanol. There is thus obtained 4-dichloroacet - *N* - methylamido)phenyl α-methoxyisobutyrate m.p. 56—57° C. (Found: C, 50.1; H, 5.2. $C_{14}H_{17}Cl_2NO_4$ requires C, 50.3; H, 5.1%).

EXAMPLE 36.

By a similar method to that described in Example 35 but distilling the oily residue after evaporation of the methylene chloride solution there is obtained 4 - (dichloroacet - *N* - methylamido)phenyl ethoxyacetate as an oil b.p. 167° at 2.5×10^{-3} mm. Hg. (Found: C, 48.9; H, 4.9. $C_{13}H_{15}Cl_2NO_4$ requires C, 48.8; H, 4.7%).

EXAMPLE 37.

In the preparation of 4 - dichloroacet - *N*-methylamido)phenyl β - benzoylpropionate a mixture of β - benzoylpropionic acid (8.9 grams), dichloroacet - 4 - hydroxy - *N*-methylanilide (11.7 grams), methylene chloride (100 ml.) and dicyclohexylcarbodiimide (10.3 grams) is allowed to stand at room temperature for 18 hours, glacial acetic acid (2 ml.) is added and after standing for 1 hour the mixture is filtered. The filtrate is washed with ice-cold aqueous 2*N* sodium hydroxide, then water, dried over anhydrous magnesium sulphate and evaporated to give a gum which crystallises on standing. It is recrystallised from ethyl alcohol and there is thus obtained 4 - (dichloroacet - *N* - methylamido)phenyl β - benzoylpropionate m.p. 94.5—95.5° C. (Found: C, 57.7; H, 4.4. $C_{19}H_{17}Cl_2NO_4$ requires C, 57.9; H, 4.3%).

EXAMPLE 38.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 4 - chlorobenzoate a mixture of dichloroacet - 4 - hydroxy - *N*-methylanilide (11.7 grams), 4 - chlorobenzoic acid (7.82 grams), dimethyl cyanamide (7.0 grams) and carbon tetrachloride (50 ml.) is refluxed for 24 hours, cooled, washed with aqueous sodium hydroxide and sodium bicarbonate and dried over anhydrous magnesium sulphate. The solution is evaporated and the residue is crystallised from alcohol. There is thus obtained as a crystallised solid 4-(dichloroacet - *N* - methylamido)phenyl 4-chlorobenzoate m.p. 97—98° C. and which

had a melting point undepressed in admixture with material prepared by the method described in Example 25.

EXAMPLE 39.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 4 - chlorobenzoate 4-chlorobenzoic acid (2.56 grams) is added to a stirred solution of 4 - (dichloroacet - *N*-methylamido)phenyl sulphite (8.4 grams) in pyridine (15 cc.). After being kept at 20° C. for 18 hours the resulting solution is poured into a mixture of *N* sodium hydroxide (100 cc.), ice (25 grams) and sodium hydrosulphite (0.1 grams). The precipitated solid is collected by filtration, washed with water and dried, giving 4 - (dichloroacet - *N* - methylamido)-phenyl 4 - chlorobenzate in the form of a crystalline solid, m.p. 96—98.5° C., identical with the product prepared in Example 25.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl sulphite a solution of triethylamine (16.6 cc.) in tetrahydrofuran (50 cc.) is added dropwise to an ice-cooled, stirred solution of 4 - (dichloroacet - *N* - methylamido)phenol (23.4 grams) and thionyl chloride (6.00 grams) in tetrahydrofuran (85 cc.) at such a rate that the temperature remains between 6 and 10° C. The mixture is then stirred at 20° C. for 45 minutes and after filtration is evaporated under reduced pressure to give 4 - (dichloroacet - *N* - methylamido)phenyl sulphite in the form of a gum.

EXAMPLE 40.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 2 - furoate a mixture of 4 - dichloroacetamidophenyl 2 - furoate (12.1 grams), anhydrous potassium carbonate (12 grams), acetone (60 cc.) and dimethyl sulphate (4 cc.) is refluxed for 4 hours. The filtered solution is then evaporated under reduced pressure to give an oil, which crystallises on cooling. Two recrystallisations from 95% alcohol give the title compound in the form of a crystalline solid, m.p. 109—111° C., identical with the substance prepared in Example 1.

In the preparation of 4 - dichloroacetamidophenyl 2 furoate, 2-furoyl chloride (10.9 grams) is added over 20 minutes to an ice-cooled, stirred suspension of 4-dichloroacetamidophenol (17.6 grams) in pyridine (60 cc.). After stirring for a further 20 minutes the solution is poured into water (250 cc.) and the precipitated solid is collected by filtration, washed with water, triturated with 95% alcohol (300 cc.) and recrystallised from acetone (150 cc.) with charcoal, giving the title compound in the form of a crystalline solid, m.p. 201—202° C. (Found: C, 49.6; H, 2.9. $C_{13}H_9Cl_2NO_4$ requires C, 49.7; H, 2.9%).

p-Aminophenol is converted to *p*-dichloroacetamidophenol by one of the following methods:—

(a) A mixture of 10.9 grams of *p*-aminophenol 22 grams of chloral cyanohydrin and 75 ml. of anhydrous pyridine is stirred whilst 30 ml. of triethylamine is added slowly with cooling. An exothermic reaction ensues and the rate of addition of triethylamine is adjusted so that the temperature of the reaction mixture is maintained between 10° C. and 15° C. When the addition is complete the cooling bath is removed and the mixture is poured into 200 ml. of a mixture of ice and water. The solid which separates is isolated by filtration, washed with dilute hydrochloric acid until free from pyridine and dried *in vacuo*. The resulting product is recrystallised from a mixture of 35 ml. of alcohol and 50 ml. of water. There is thus obtained *p*-dichloroacetamidophenol in the form of a colourless crystalline solid of melting point 137—139° C.

(b) To a solution of 109 grams of *p*-aminophenol in a mixture of 196 ml. of 5.1 *N* hydrochloric acid and 1.4 litres of water is added with stirring a solution of 295 grams of chloral hydrate in 525 ml. of water, 3 grams of sodium sulphite heptahydrate, and 94 grams of 90% sodium cyanide. To the mixture is then added with stirring 535 ml. of 5.04*N* sodium hydroxide solution. The temperature rises to 49° C. and the mixture is stirred for a further 2 hours during which time the temperature falls to 25° C. Ice is added to the mixture to reduce the temperature to 13° C. and the solid which separates is washed with water then with *N* hydrochloric acid and finally with water before being recrystallised from a mixture of 200 ml. of alcohol and 350 ml. of water. There is thus obtained *p*-dichloroacetamidophenol in the form of a crystalline solid which has a melting point of 137—139° C.

(c) A mixture of 16.5 grams of *p*-aminophenol, 22 grams of sodium acetate trihydrate, 100 ml. of benzene, 200 ml. of water and 0.5 ml. of saturated sodium bisulphite solution is treated with stirring at a temperature of 5—10° C. with a solution of 22.5 grams of dichloroacetyl chloride in 50 ml. of benzene. After the addition has been completed the mixture is stirred for a further hour at room temperature. The solid which has separated is isolated by filtration, washed with water and recrystallised twice from aqueous ethanol. There is thus obtained *p*-dichloroacetamidophenol in the form of a crystalline solid which has a melting point of 137—139° C. [Found C, 43.3; H, 3.2. $C_8H_7O_2NCl_2$ requires C, 43.7; H, 3.2%]

EXAMPLE 41.

Dichloroacet - 4 - hydroxy - *N* - methylanilide (11.7 gm.) was dissolved in water (50 cc.) and caustic soda (5 cc. 50% w/v). Furoyl chloride (7.2 gm.) was added at room temperature and the mixture was shaken vigorously. After several minutes, the product was collected by filtration, washed with a little dilute sodium hydroxide solution and then with water. The solid was recrystallised from alcohol to give 4-dichloroacet-*N*-methylamidophenyl 2-furoate, m.p. 112—114° C, which was undepressed in admixture with authentic material.

EXAMPLE 42.

A mixture of *p*-aminophenol (109 g.) and 95% formic acid (200 ml.) was refluxed gently for 1 hour and then evaporated *in vacuo* on the steam bath until the residue began to crystallise. Water (250 ml.) was added and distillation was continued. The dark residue was collected by filtration, washed with water and dried in the steam oven to give *p*-formamidophenol m.p. 138°—139° C.

A solution of *p*-formamidophenol (27.4 g) in dry pyridine was stirred and cooled to 20° C. 2-Furoyl chloride (28.7 g) was added dropwise at 20° C. and then 200 ml. water was added. An oil separated which crystallised after addition of concentrated hydrochloric acid (100 ml.). The crude product was collected by filtration and recrystallised from 75% ethanol to give *p*-formamidophenyl 2-furoate, m.p. 137—138° C.

(Found: C, 62.3; H, 3.8; N, 6.3. $C_{12}H_9NO_4$ requires C, 62.3; H, 3.9; N, 6.1%).

p-Formamidophenyl 2-furoate (23.1 g) was dissolved in acetone (250 ml) and the solution was refluxed with dry potassium carbonate. Methyl iodide (14.2 g) was added, stirring and refluxing was continued and another addition of methyl iodide (14.2 g) was made. Stirring and refluxing was continued for a total of five hours, the reaction mixture was filtered and the filtrate was evaporated *in vacuo* on the steam bath. The residue was crystallised from 50% aqueous methanol to give 4-(formo-N-methylamido)-phenyl 2-furoate m.p. 118—119° C.

(Found: C, 63.4; H, 4.6; N, 5.8. $C_{13}H_{11}NO_4$ requires C, 63.7; H, 4.5; N, 5.7%).

4 - (Formo - N - methylamido)phenyl furoate (9.8 g) dissolved in warm acetone (40 ml) was refluxed for 1 hour after the addition of concentrated hydrochloric acid (4.5 ml). The colourless needles were filtered off and recrystallised from water to give 4-methylaminophenyl 2-furoate hydrochloride, m.p. 228—229° C.

To a solution of this hydrochloride (8 g) in water (400 ml) was added ammonium hydroxide when the free base crystallised. The colourless crystals were collected by filtration and dried *in vacuo* to give 4-methylaminophenyl 2-furoate, m.p. 91—92° C.

(Found: C, 66.0; H, 5.2; N, 6.8. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 5.1; N, 6.5%).

A solution of 4 - methylaminophenyl 2-furoate (4.34 g) in benzene (50 ml) was stirred with a solution of sodium acetate (10 g) in water (50 ml) and dichloroacetyl chloride (4 g) was added dropwise over 10 minutes. The mixture was stirred for a further 10 minutes and the benzene layer was separated, washed with water, dried over anhydrous sodium sulphate and evaporated to dryness. The residue was crystallised from methanol to give 4 - (dichloroacet - N - methylamido)phenyl 2-furoate m.p. 114—115° C., undepressed in admixture with authentic material.

EXAMPLE 43.

4 - Benzylideneaminophenyl 2 - furoate.

2-Furoyl chloride (16.2 g.) was added slowly to a stirred solution of 4-benzylideneamino-phenol (23.3 g.) in pyridine (75 ml.), external ice cooling keeping the temperature below 15°. The solution was then stirred at room temperature for 0.5 hr. before being poured into ice water (500 ml.). The precipitated ester was filtered off and washed with water and recrystallised from SVM (twice) to give a crystalline solid of m.p. 108—109°.

Found: C, 74.3; H, 4.35; N, 5.2 $C_{18}H_{13}NO_3$ requires C, 74.2; H, 4.5; N, 4.8%.

4 - Methylaminophenyl 2 - furoate.

The above compound (10 g.) was heated for 4 hrs. on the steam bath with dimethyl sulphate (3.5 ml.). Water (50 ml.) was added to the cooled mixture, which was then extracted with chloroform (3 × 30 ml.). The resulting aqueous solution was basified with excess aqueous Na_2CO_3 and the precipitate filtered off, washed with water and recrystallised from SVM (twice) to give a crystalline solid of m.p. 88—90°, undepressed in admixture with a specimen (m.p. 89—90°) prepared by the alternative route.

4 - Dichloroacet - N - methylamidophenyl 2 - furoate.

Triethylamine (8 ml.) was added to an ice-cooled suspension of the above compound (5.07 g.) in pyridine (15 ml.) containing chloral cyanohydrin (4.5 g.). The mixture was kept for 0.5 hr. at 20° and then water (200 ml.) was added. The precipitate was filtered off, washed with water, *N* HCl+water and recrystallised from SVM giving 4-dichloroacet-N-methylamidophenyl 2-furoate, m.p. 112—113.5°, undepressed in admixture with an authentic specimen.

EXAMPLE 44.

A batch of tablets is prepared from the following ingredients:—

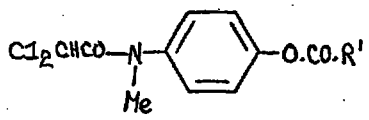
4 - (Dichloroacet - *N* - methylamido)phenyl 2-furoate	30 lbs. 14⁴/₅ oz.
Icing sugar	1 lb. 8 oz.
Maize starch	7lb. 8 oz.
Acacia solution 20%	75 fluid oz.
Stearic acid	3 oz.

The 4 - (dichloroacet - *N* - methylamido) phenyl 2-furoate, icing sugar and 2½ lb. of maize starch are thoroughly mixed together and the mixture is granulated with the addition of the 20% acacia solution.

The granules are dried, sieved and to them is added a further 5 lb. of dried maize starch with mixing followed by the stearic acid. After a final mixing the mixture is tabletted to give a batch of 28,000 10 gr. tablets each containing 0.5 grams of active ingredient.

WHAT WE CLAIM IS:—

1. A compound having the general formula:—



wherein R^1 represents aryl (except unsubstituted phenyl) aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl, or the group $—R^2COOR^3$ where R^2 is alkylene, arylene, arylenedioxydialkyl, or a divalent heterocyclic radical and R^3 is the 4-(dichloroacet - *N* - methylamido)phenyl radical, together with simple substituted derivatives of the compounds of the above general formula containing one or more halogen atoms, nitro, amino, alkyl, alkoxy, acyl or methanesulphonyl groups in the radicals other than $—R^2COOR^3$ represented by R^1.

2. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-furoate.

3. 4 - (Dichloroacet - *N* - methylamido)-phenyl phenoxyacetate.

4. 4 - (Dichloroacet - *N* - methylamido)-phenyl nicotinate.

5. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-thenoate.

6. 4 - (Dichloroacet - *N* - methylamido)-phenyl β-napthoxyacetate.

7. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2 - chlorophenoxyacetate.

8. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4 - methylphenoxyacetate.

9. 4 - (Dichloroacet - *N* - methylamido)-phenyl α - (2 - methylphenoxy)propionate.

10. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-phenoxypropionate.

11. 4 - (Dichloroacet - *N* - methylamido)-phenyl γ - phenoxybutyrate.

12. 4 - (Dichloroacet - *N* - methylamido)-phenyl isonicotinate.

13. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-nitrophenoxyacetate.

14. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3-chlorophenoxyacetate.

15. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-bromo-2-furoate.

16. 4 - (Dichloroacet - *N* - methylamido)-phenyl α - phenoxy - *n* - butyrate.

17. 4 - (Dichloroacet - *N* - methylamido)-phenyl α - phenoxy - *n* - hexanoate.

18. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-phenoxyisobutyrate.

19. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-phenoxy-*n*-valerate.

20. 4 - (Dichloroacet - *N* - methylamido)-phenyl coumarilate.

21. 4 - (Dichloroacet - *N* - methylamido)-phenyl β-phenoxypropionate.

22. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-furylacrylate.

23. 4 - (Dichloroacet - *N* - methylamido)-phenyl tetrahydro-2-furoate.

24. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3-furoate.

25. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-methoxyphenoxyacetate.

26. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-methoxycoumarilate.

27. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4:5 - dibromo - 2 - furoate.

28. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-methyl-2-furoate.

29. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5:7-dibromocoumarilate.

30. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-phenoxybenzoate.

31. 4 - (Dichloroacet - *N* - methylamido)-phenyl picolinate.

32. 4 - (Dichloroacet - *N* - methylamido)-phenyl α:α - bis - (5 - methylfur - 2 - yl)-propionate.

33. 4 - (Dichloroacet - *N* - methylamido)-phenyl quinaldate.

34. 4 - (Dichloroacet - *N* - methylamido)-phenyl γ:γ - bis - (fur - 2 - yl) - *n* - valerate.

35. 4 - (Dichloroacet - *N* - methylamido)-phenyl 7 - methoxycoumarilate.

36. 4 - (Dichloroacet - *N* - methylamido)-phenyl furan-2:5-dicarboxylate.

37. 4 - (Dichloroacet - *N* - methylamido)-phenyl pyrazinoate.

38. 4 - (Dichloroacet - *N* - methylamido)-phenyl *p*-phenylenedioxydiacetate.

39. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-nitro-2-furoate.

40. 4 - (Dichloroacet - *N* - methylamido)-

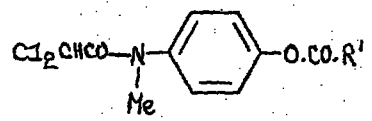
4 - (Dichloroacet - *N* - methylamido)phenyl 2-furoate	30 lbs. 14⁴/₅ oz.
Icing sugar	1 lb. 8 oz.
Maize starch	7lb. 8 oz.
Acacia solution 20%	75 fluid oz.
Stearic acid	3 oz.

The 4 - (dichloroacet - *N* - methylamido) phenyl 2-furoate, icing sugar and 2½ lb. of maize starch are thoroughly mixed together and the mixture is granulated with the addition of the 20% acacia solution.

The granules are dried, sieved and to them is added a further 5 lb. of dried maize starch with mixing followed by the stearic acid. After a final mixing the mixture is tabletted to give a batch of 28,000 10 gr. tablets each containing 0.5 grams of active ingredient.

WHAT WE CLAIM IS:—

1. A compound having the general formula:—



wherein R^1 represents aryl (except unsubstituted phenyl) aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl, or the group $—R^2COOR^3$ where R^2 is alkylene, arylene, arylenedioxydialkyl, or a divalent heterocyclic radical and R^3 is the 4-(dichloroacet - *N* - methylamido)phenyl radical, together with simple substituted derivatives of the compounds of the above general formula containing one or more halogen atoms, nitro, amino, alkyl, alkoxy, acyl or methanesulphonyl groups in the radicals other than $—R^2COOR^3$ represented by R^1.

2. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-furoate.

3. 4 - (Dichloroacet - *N* - methylamido)-phenyl phenoxyacetate.

4. 4 - (Dichloroacet - *N* - methylamido)-phenyl nicotinate.

5. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-thenoate.

6. 4 - (Dichloroacet - *N* - methylamido)-phenyl β-napthoxyacetate.

7. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2 - chlorophenoxyacetate.

8. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4 - methylphenoxyacetate.

9. 4 - (Dichloroacet - *N* - methylamido)-phenyl α - (2 - methylphenoxy)propionate.

10. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-phenoxypropionate.

11. 4 - (Dichloroacet - *N* - methylamido)-phenyl γ - phenoxybutyrate.

12. 4 - (Dichloroacet - *N* - methylamido)-phenyl isonicotinate.

13. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-nitrophenoxyacetate.

14. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3-chlorophenoxyacetate.

15. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-bromo-2-furoate.

16. 4 - (Dichloroacet - *N* - methylamido)-phenyl α - phenoxy - *n* - butyrate.

17. 4 - (Dichloroacet - *N* - methylamido)-phenyl α - phenoxy - *n* - hexanoate.

18. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-phenoxyisobutyrate.

19. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-phenoxy-*n*-valerate.

20. 4 - (Dichloroacet - *N* - methylamido)-phenyl coumarilate.

21. 4 - (Dichloroacet - *N* - methylamido)-phenyl β-phenoxypropionate.

22. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-furylacrylate.

23. 4 - (Dichloroacet - *N* - methylamido)-phenyl tetrahydro-2-furoate.

24. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3-furoate.

25. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-methoxyphenoxyacetate.

26. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-methoxycoumarilate.

27. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4:5 - dibromo - 2 - furoate.

28. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-methyl-2-furoate.

29. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5:7-dibromocoumarilate.

30. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-phenoxybenzoate.

31. 4 - (Dichloroacet - *N* - methylamido)-phenyl picolinate.

32. 4 - (Dichloroacet - *N* - methylamido)-phenyl α:α - bis - (5 - methylfur - 2 - yl)-propionate.

33. 4 - (Dichloroacet - *N* - methylamido)-phenyl quinaldate.

34. 4 - (Dichloroacet - *N* - methylamido)-phenyl γ:γ - bis - (fur - 2 - yl) - *n* - valerate.

35. 4 - (Dichloroacet - *N* - methylamido)-phenyl 7 - methoxycoumarilate.

36. 4 - (Dichloroacet - *N* - methylamido)-phenyl furan-2:5-dicarboxylate.

37. 4 - (Dichloroacet - *N* - methylamido)-phenyl pyrazinoate.

38. 4 - (Dichloroacet - *N* - methylamido)-phenyl *p*-phenylenedioxydiacetate.

39. 4 - (Dichloroacet - *N* - methylamido)-phenyl 5-nitro-2-furoate.

40. 4 - (Dichloroacet - *N* - methylamido)-

* C L M S *

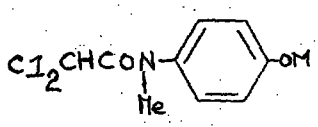
phenyl α-naphthoate.
41. 4 - (Dichloroacet - *N* - methylamido)-phenyl diphenylacetate.
42. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-chlorobenzoate.
43. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-methoxybenzoate.
44. 4 - (Dichloroacet - *N* - methylamido)-phenyl cinnamate.
45. 4 - (Dichloroacet - *N* - methylamido)-phenyl sebacate.
46. 4 - (Dichloroacet - *N* - methylamido)-phenyl phthalate.
47. 4 - (Dichloroacet - *N* - methylamido)-phenyl β-phenylpropionate.
48. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-acetylsalicylate.
49. 4 - (Dichloroacet - *N* - methylamido)-phenyl hexahydrobenzoate.
50. 4 - (Dichloroacet - *N* - methylamido)-phenyl terephthalate.
51. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-nitrobenzoate.
52. 4 - (Dichloroacet - *N* - methylamido)-phenyl *p*-toluate.
53. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-chlorobenzoate.
54. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-methanesulphonylbenzoate.
55. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3:4-dimethoxybenzoate.
56. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-benzoylbenzoate.
57. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3-methoxybenzoate.
58. 4 - (Dichloroacet - *N* - methylamido)-phenyl hippurate.
59. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3:4 - dichlorobenzoate.
60. 4 - (Dichloroacet - *N* - methylamido)-phenyl *O*-methylmandelate.
61. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-methoxypropionate.
62. 4 - (Dichloroacet - *N* - methylamido)-phenyl methoxyacetate.
63. 4 - (Dichloroacet - *N* - methylamido)-phenyl α-methoxyisobutyrate.
64. 4 - (Dichloroacet - *N* - methylamido)-phenyl ethoxyacetate.
65. 4 - (Dichloroacet - *N* - methylamido)-phenyl phenylglyoxylate.
66. 4 - (Dichloroacet - *N* - methylamido)-phenyl cyclopropanecarboxylate.
67. 4 - (Dichloroacet - *N* - methylamido)-phenyl 3-bromobenzoate.
68. 4 - (Dichloroacet - *N* - methylamido)-phenyl cyclopentanecarboxylate.
69. 4 - (Dichloroacet - *N* - methylamido)-phenyl cyclobutanecarboxylate.
70. 4 - (Dichloroacet - *N* - methylamido)-phenyl 4-aminobenzoate.
71. 4 - (Dichloroacet - *N* - methylamido)-phenyl β-benzoylpropionate.

72. A process for the preparation of a compound as claimed in Claim 1 which comprises treating dichloroacet - 4 - hydroxy - *N*-methylanilide or a salt thereof with an esterifying agent.

73. A process as claimed in Claim 72 which comprises reacting dichloroacet - 4 - hydroxy-*N*-methylanilide with an acid halide of the general formula $R^4CO.X$ in which R^4 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyakenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl or the group $—R^2—CO.X$ in which R^2 is alkylene, arylene, cycloalkylene, arylenedioxydialkyl or a divalent heterocyclic radical and X is a halogen atom, in the presence of an acid binding agent.

74. A process as claimed in Claim 72 which comprises reacting dichloroacet-4-hydroxy-*N*-methylanilide with an acid anhydride having the general formula $(R^5CO)_2O$ in which R^5 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl or heterocyclicalkenyl.

75. A process as claimed in Claim 72 which comprises reacting a compound of the general formula:—



wherein M represents an alkali metal or one equivalent of an alkaline earth metal with an acid halide of the general formula $R^4CO.X$ in which R^4 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxy alkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl or the group $—R^2—CO.X$ in which R^2 is alkylene, arylene, cycloalkylene, arylenedioxydialkyl or a divalent heterocyclic radical and X is a halogen atom.

76. A process as claimed in Claim 72 which comprises reacting dichloroacet-4-hydroxy-*N*-methylanilide with an acid of the general formula R^6COOH in which R^6 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl or the group $—R^2COOH$ in which R^2 is alkylene, arylene, arylenedioxydialkyl, or a divalent heterocyclic radical in the presence of a condensing agent.

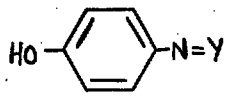
77. A process as claimed in Claim 76 in which the condensing agent is dicyclohexylcarbodiimide.

78. A process as claimed in Claim 76 in which the condensing agent is tetraphosphoric acid.

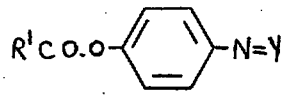
* C L M S *

79. A process as claimed in Claim 76 in which the condensing agent is dimethylcyanamide.

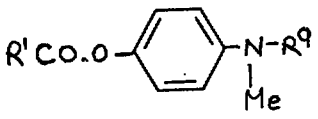
80. A process for the preparation of a compound as claimed in Claim 1 which comprises the step of protecting the amino group of *p*-aminophenol to give a compound of the general formula:—



wherein —N=Y represents (a) the group —NHR^7 wherein R^7 is a formyl, acetyl or dichloroacetyl group or (b) the group —N=CHR^8 wherein R^8 represents a phenyl radical or a phenyl radical having a substituent which cannot be esterified or methylated followed by the step of esterification to give a compound of the general formula:—

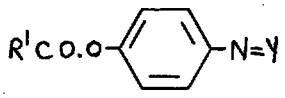


wherein R^1 is as defined in Claim 1 and the group —N=Y is as above defined, followed by the step of methylation and, except in the case where R^7 is a dichloroacetyl group, selectively hydrolysing the methylated product, to yield a compound having the general formula:—



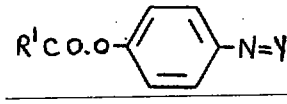
where R^1 is as defined in Claim 1 and R^9 is a hydrogen atom or a dichloroacetyl group and then in the case where R^9 is hydrogen, dichloroacetylating.

81. A process as claimed in Claim 80 wherein a compound of the general formula:—



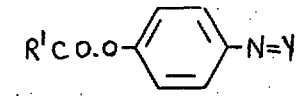
in which the group —N=Y represents the group —NHZ wherein Z is a formyl or acetyl group and the group R^1 is as defined in Claim 1 is prepared by formylating or acetylating *p*-aminophenol and then introducing the group R^{1}CO—.

82. A process as claimed in Claim 80 wherein a compound of the general formula:—

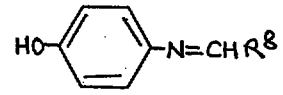


in which the group —N=Y represents —NHCOCHCl$_2$ and the group R^1 is as defined in Claim 1 is prepared by dichloroacetylating *p*-aminophenol and then introducing the group R^{1}CO—.

83. A process as claimed in Claim 80 wherein a compound of the general formula:—

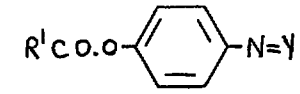


in which —N=Y represents the group —N=CHR^8 wherein R^1 is as defined in Claim 1 and R^8 represents a phenyl radical or a phenyl radical having a substituent which cannot be esterified or methylated is prepared by converting *p*-aminophenol to a Schiff's base of the general formula:—



by reaction with an aldehyde of the general formula R^{8}CHO wherein R^8 is as above defined and then introducing the group R^{1}CO—.

84. A process as claimed in Claim 80 wherein a compound having the general formula:—

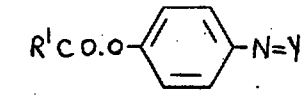


in which the group —N=Y represents the group —NHR^7 wherein R^7 is a formyl group, an acetyl group or a dichloroacetyl group, and R^1 is as defined in Claim 1 is methylated by treatment with a methylating agent in the presence of an alkali.

85. A process as claimed in Claim 84 wherein treatment is carried out with methyl iodide in the presence of potassium hydroxide.

86. A process as claimed in Claim 84 wherein treatment is carried out with dimethyl sulphate in the presence of potassium carbonate.

87. A process as claimed in Claim 80 wherein a compound of the general formula:—



wherein the group —N=Y represents the group —N=CHR^8 wherein R^1 is as defined in Claim 1 and R^8 represents a phenyl radical or a substituted phenyl radical is methylated by treatment with a suitable methylating agent.

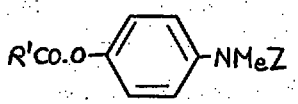
88. A process as claimed in Claim 80 or

* C L M S *

82 wherein the dichloroacetylation is carried out by treatment with chloral cyanohydrin in the presence of an acid binding agent.

89. A process as claimed in Claim 88 wherein the chloral cyanohydrin is prepared *in situ*.

90. A process as claimed in any of claims 84 to 86 wherein the thus produced methylated product having the general formula:—



in which Z is a formyl or acetyl group and R^1 is as defined in Claim 1 is hydrolysed with dilute mineral acid to remove the group Z.

91. A process for the preparation of a compound as claimed in claim 1 which comprises reacting 4 - (dichloroacet - *N* - methylamido)phenyl sulphite with an acid of the general formula R^6COOH in which R^6 represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclicalkyl, heterocyclicalkenyl or the group $—R^2COOH$ in which R^2 is alkylene, arylene, arylenedioxydialkyl, or a divalent heterocyclic radical in the presence of an acid binding agent.

92. A process for the preparation of a compound as claimed in claim 1 which comprises subjecting the corresponding nitro compound to reduction.

93. A process for the preparation of a compound as claimed in any of claims 1 to 71 substantially as herein described with reference to any one of the examples.

94. A compound as claimed in any of claims 1 to 71 when prepared by a process as claimed in any one of claims 72 to 93 or an obvious chemical equivalent thereof.

95. A process for the preparation of 4-(dichloroacet - *N* - methylamido)phenyl 2-furoate substantially as herein described with reference to Examples 1, 20, 41 or 42.

96. 4 - (Dichloroacet - *N* - methylamido)-phenyl 2-furoate whenever prepared by a process as claimed in any one of Claims 72 to 93 or 95 or an obvious chemical equivalent thereof.

97. A therapeutic composition comprising a compound as claimed in any one of Claims 1 to 71, 94 or 96 in association with a pharmaceutically acceptable diluent or carrier.

98. A therapeutic composition as claimed in Claim 97 in which the active compound is 4 - (dichloroacet - *N* - methylamido)phenyl 2-furoate and is present in an amount between 100 mg. and 1000 mg. per dosage unit.

99. A therapeutic composition as claimed in Claim 97 or 98 in which the diluent or carrier comprises icing sugar..

100. A therapeutic composition as claimed in any one of Claims 97 to 99 and comprising also starch.

101. A therapeutic composition as claimed in any one of Claims 97 to 100 and comprising also stearic acid.

102. A therapeutic composition as claimed in any one of Claims 97 to 101 and comprising also gum acacia.

For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52, Chancery Lane, London, W.C.2.

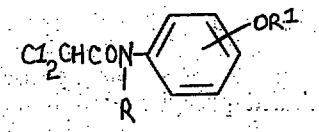
PROVISIONAL SPECIFICATION
No. 14460 A.D. 1958

New Acetanilide Derivatives

We, BOOTS PURE DRUG COMPANY LIMITED, a British Company, of Station Street, Nottingham, do hereby declare this invention to be described in the following statement:—

The present invention relates to an improvement in or modification of that described in our co-pending application Nos. 31482/55 and 7513/56 (Serial No. 794,762).

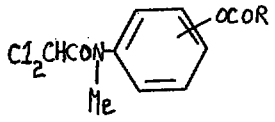
In the said copending application there are described compounds having the general formula:—



wherein R represents a lower alkyl radical containing one to eight carbon atoms inclusive and R^1 represents an $HOSO_2$-group; an $(HO)_2PO$-group; a $—C(=O)R^2$ group wherein R^2 represents alkyl, halogenated alkyl, alkenyl, alkoxy, aralkoxy or phenyl; or a $—C(=X)OR^3$ group wherein X represents oxygen or sulphur and R^3 represents a [dichloroacet-*N*-(lower alkyl)-amido]phenyl radical wherein lower alkyl contains one to eight carbon atoms inclusive which have valuable properties as amoebicides.

It has now been found according to the present invention that compounds having the general formula:—

* C L M S *



wherein R represents aryl (except unsubstituted phenyl), aralkyl, aralkenyl, alkoxyalkyl, a cycloaliphatic group, or the group $-R^1CO.OR^2$ where R^1 represents an alkylene or arylene and R^2 represents the dichloroacet-*N*-methylamidophenyl radical also possess amoebicidal properties comparable to or greater than those of the compounds described in the above co-pending application. The invention also consists in simple substituted products of the compounds of the above general formula containing, for example one or more substituent groups such as halo, nitro, alkyl and alkoxy, in the radical represented by R.

Compounds of the above general formula have been found to have very valuable properties as amoebicides.

The compounds of the invention may be prepared by methods well-known in the art for the preparation of esters of phenols. One such method is by the interaction in the presence of an acid binding agent of the parent phenol such as for example dichloroacet - 4 - hydroxy - *N* - methylanilide which is available commercially under the trade name "Entamide" with an acid halide of the general formula RCOX in which R is as hereinbefore defined with the exception of the group $-R^1CO.OR^2$ and X is a halogen atom. When R represents the group $-R^1CO.OR^2$ the acid halide employed in the reaction is of the general formula $R^1(COX)_2$ in which R^1 and X are as hereinbefore defined.

An alternative method of preparation is by the interaction of an alkali metal salt of the parent phenol such as for example "Entamide" with an acid halide of the general formula RCOX in which R is as hereinbefore defined with the exception of the group $-R^1CO.OR^2$ and X is a halogen. When R represents the group $-R^1CO.OR^2$ the acid halide is of the general formula $R^1(COX)_2$ in which R^1 and X are as hereinbefore defined.

Another alternative method of preparation is by the interaction of the parent phenol such as for example "Entamide" with an acid anhydride of the general formula $(RCO)_2O$ in which R is as hereinbefore defined with the exception of the group $-R^1CO.OR^2$.

The compounds of the invention may also be prepared by methods analogous to those described in our co-pending application No. 34934/57 (Serial No. 850,394) for the preparation of esters of "Entamide" and related compounds.

The invention is illustrated by the following non-limitative examples:—

EXAMPLE 1.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl cinnamate, 17.3 grams of cinnamyl chloride are added slowly to a stirred solution of 23.4 grams of dichloroacet-4-hydroxy-*N*-methylanilide in 50 ml. of dry pyridine, water cooling being used to keep the temperature below 25°C. The reaction mixture is stirred for a further 40 minutes and then diluted with 400 ml. of ice-water containing 100 mg. of sodium hydrosulphite. The product is collected by filtration and recrystallised from 95% alcohol. There is thus obtained 4 - (dichloroacet - *N* - methylamido)-phenyl cinnamate as a crystalline solid which has a melting point of 101—102° C. (Found: C, 59.55, H, 4.2. $C_{18}H_{15}Cl_2NO_3$ requires C, 59.35; H, 4.1%).

In a similar manner are prepared the following esters:—

4 - (Dichloroacet - *N* - methylamido)phenyl 4 - methoxybenzoate, m.p. 119—121° C. (Found: C, 55.8; H, 3.9. $C_{17}H_{15}Cl_2NO_4$ requires C, 55.4; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl phthalate, m.p. 137—138° C. (Found: C, 52.5; H, 3.4. $C_{26}H_{20}Cl_4N_2O_6$ requires C, 52.2; H, 3.3%).

4 - (Dichloroacet - *N* - methylamido)phenyl 3-phenylpropionate, m.p. 76—77° C. (Found: C, 58.9; H, 4.6. $C_{18}H_{17}Cl_2NO_3$ requires C, 59.0; H, 4.6%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2-acetylsalicylate, m.p. 175—177° C. (Found: C, 55.1; H, 3.9. $C_{18}H_{15}Cl_2NO_5$ requires C, 54.6; H, 3.8%).

4 - (Dichloroacet - *N* - methylamido)phenyl hexahydrobenzoate, m.p. 76—78.5° C. (Found: C, 56.0; H, 5.7. $C_{16}H_{19}Cl_2NO_3$ requires C, 55.8; H, 5.5%).

4 - (Dichloroacet - *N* - methylamido)phenyl alpha - naphthoate, m.p. 140—141° C. (Found: C, 61.6; H, 4.0. $C_{20}H_{15}Cl_2NO_3$ requires C, 61.8; H, 3.9%).

4 - (Dichloroacet - *N* - methylamido)phenyl *p*-toluate, m.p. 102.5—105° C. (Found: C, 58.0; H, 4.3. $C_{17}H_{15}Cl_2NO_3$ requires C, 58.0; H, 4.3%).

4 - (Dichloroacet - *N* - methylamido)phenyl 4-nitrobenzoate, m.p. 145—147° C. (Found: C, 49.9; H, 3.1. $C_{16}H_{12}Cl_2N_2O_5$ requires C, 50.2; H, 3.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl 3:4 - dimethoxybenzoate, m.p. 156° C. (Found: C, 54.3; H, 4.3. $C_{18}H_{17}Cl_2NO_5$ requires C, 54.3; H, 4.3%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2 - chlorobenzoate, m.p. 108—110° C. (Found: C, 51.2; H, 3.3. $C_{16}H_{12}Cl_3NO_3$ requires C, 51.6; H, 3.2%).

4 - (Dichloroacet - *N* - methylamido)phenyl 3 - methoxybenzoate, m.p. 113—114° C. (Found: C, 55.6; H, 4.0. $C_{17}H_{15}Cl_2NO_4$ requires C, 55.4; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl hippurate, m.p. 146—148° C. (Found: C, 54.8; H, 4.0. $C_{18}H_{16}Cl_2N_2O_4$ requires C, 54.7; H, 4.05%).

EXAMPLE 2.

Following a similar reaction procedure to that described in Example 1, but employing an isolation procedure comprising the steps of dissolving the crude, non-crystalline product in chloroform, washing the chloroform solution with half-normal sulphuric acid, aqueous sodium bicarbonate solution and water, drying the solution with anhydrous magnesium sulphate, removing the chloroform by distillation and crystallising the residue from 95% alcohol, there are obtained the following as crystalline solids:—

4 - (Dichloroacet - N - methylamido)phenyl sebacate, m.p. 82—83° C. (Found: C, 53.2; H, 5.0. $C_{28}H_{32}Cl_4N_2O_6$ requires C, 53.0; H, 5.05%).

4 - (Dichloroacet - N - methylamido)phenyl diphenylacetate, m.p. 99—101° C. (Found: C, 64.2; H, 4.6. $C_{23}H_{19}Cl_2NO_3$ requires C, 64.5; H, 4.4%).

4 - (Dichloroacet - N - methylamido)phenyl *o* - benzoylbenzoate, m.p. 115—116° C. (Found: C, 62.2; H, 4.0. $C_{23}H_{17}Cl_2NO_4$ requires C, 62.4; H, 3.8%).

EXAMPLE 3.

By the method described in Example 1, but additionally crystallising the product from methyl propyl ketone, there is obtained 4-dichloroacet - N - methylamido)phenyl terephthalate as a crystalline solid which has a melting point of 174—177° C. (Found: C, 52.0; H, 3.6. $C_{26}H_{20}Cl_4N_2O_6$ requires C, 52.2; H, 3.3%).

EXAMPLE 4.

In the preparation of 4 - (dichloroacet - *N*-methylamido)phenyl 4 - methanesulphonyl benzoate, 22.0 grams of 4 - methanesulphonylbenzoyl chloride are added over ten minutes to a stirred solution of 21.5 g. of dichloroacet - 4 - hydroxy - *N* - methylanilide in 90 ml. of dry pyridine. At the end of this time the mixture is warmed to 40° C. and stirred at this temperature for one hour. The product is then isolated as described in Example 1, giving 4 - (dichloroacet - *N* - methylamido)-phenyl 4-methanesulphonylbenzoate in the form of a crystalline solid with a melting point of 166—168° C. when crystallised from benzene. (Found: C, 49.4; H, 3.7. $C_{17}H_{15}Cl_2NO_5S$ requires C, 49.0; H, 3.6%).

EXAMPLE 5.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl 4-chlorobenzoate a mixture of 5.9 grams of 4-chlorobenzoic anhydride, 4.7 grams of dichloroacet-4-hydroxy-*N*-methylanilide and 20 ml. of dry pyridine is kept at 20° C. for 3 hours and then warmed to 85° C. for 30 minutes, cooled and poured into 200 ml. of ice-water. The product is collected by filtration and recrystallised from alcohol. There is thus obtained 4-(dichloroacet - *N* - methylamido)phenyl 4 - chlorobenzoate as a crystalline solid with a melting point of 98.5—100° C. (Found: C, 51.4; H, 3.3. $C_{16}H_{12}Cl_3NO_3$ requires C, 51.6; H, 3.2%).

EXAMPLE 6.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl 4-chlorobenzoate an intimate mixture of 5.9 grams of 4-chlorobenzoic anhydride and 4.7 grams of dichloroacet-4-hydroxy - *N* - methylanilide is heated in an oil bath at 130—170° C. for 3 hours. The cooled mixture is then crystallised from alcohol and ground in a mortar with 30 ml. of *N* sodium hydroxide solution and the solid is collected and recrystallised from alcohol to give 4 - (dichloroacet - N - methylamido)-phenyl 4-chlorobenzoate, identical with that prepared as described in Example 5.

EXAMPLE 7.

In the preparation of 4-dichloroacet-*N*-methylamido)phenyl alpha-methoxypropionate, 11.7 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide are added portionwise to a solution of 6.2 grams of alpha-methoxypropionyl chloride in 50 ml. of dry pyridine and the mixture is maintained at room temperature for 20 hours. The mixture is quenched by pouring into 500 ml. of water and the product is collected by filtration, washed with dilute sulphuric acid and water and crystallised from methanol. There is thus obtained 4-(dichloroacet - *N* - methylamide)phenyl alpha-methoxypropionate as a crystalline solid with a melting point of 110—111° C. (Found: C, 48.9; H, 4.4; $C_{18}H_{15}Cl_2NO_4$ requires C, 48.8; H, 4.7%).

EXAMPLE 8.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl *O*-methylmandelate, 8.1 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide is added portionwise to a solution of 6.4 grams of *O*-methylmandelyl chloride in 32 ml. of dry pyridine and the mixture is maintained at room temperature for 20 hours and is quenched by pouring into 500 ml. of water. The gummy product is extracted with three 100 ml. portions of ether and the combined ethereal extracts are washed successively with 5*N* sulphuric acid, water, 2*N* sodium hydroxide and water. The solution is dried with anhydrous sodium sulphate and evaporated to give a gummy product which is crystallised twice from aqueous methanol. There is thus obtained 4 - (dichloroacet - *N*-methylamido)phenyl *O*-methylmandelate as a crystalline solid with a melting point of 86—88° C. (Found: C, 56.7; H, 4.7; $C_{18}H_{17}Cl_2NO_4$ requires C, 56.55; H, 4.55%).

For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52, Chancery Lane, London, W.C.2.

PROVISIONAL SPECIFICATION

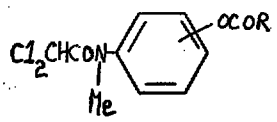
No. 17867 A.D. 1958

New Acetanilide Derivatives

We, BOOTS PURE DRUG COMPANY LIMITED, a British Company, of Station Street, Nottingham, do hereby declare this invention to be described in the following statement:—

This invention relates to new derivatives of acetanilide.

The invention consists in compounds having the general formula:—



wherein R represents aryloxyalkyl, aryloxyalkenyl, aryloxyaryl, a heterocyclic group, heterocyclic alkyl or a heterocyclic alkenyl group together with simple substituted products of the compounds of the above general formula containing, for example, one or more substituent groups such as halo, nitro, alkyl and alkoxy in the radicals represented by R.

The compounds of the above general formula have valuable properties as amoebicides.

The compounds of the invention may be prepared by methods well known in the art for the preparation of esters of phenols including those methods described in our copending application Nos. 34934/57 (Serial No. 850,394), 14460/58 and Serial No. 794,762 for the preparation of esters of Entamide (dichloroacet - 4 - hydroxy - *N*-methylanilide) and related compounds.

Another method of esterification by which the compounds of the invention may be prepared is by the addition of di*cyclo*hexylcarbodiimide to a mixture of the parent phenol and an organic acid in the presence of a solvent. The required ester is isolated by well-known methods.

The following non-limitative examples illustrate the invention.

EXAMPLE 1.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl 2-furoate, 13.7 grams of 2-furoyl chloride are added slowly to a stirred solution of 23.4 grams of dichloroacet-4-hydroxy - *N* - methylanilide in 50 ml. of dry pyridine, water cooling being used to keep the temperature below 25° C. The reaction mixture is stirred for a further 40 minutes and then diluted with 400 ml. of ice water containing 100 mg. of sodium hydrosulphite. The product is collected by filtration and recrystallised from 95% alcohol. There is thus obtained 4 - (dichloroacet - *N* - methylamido)-phenyl 2-furoate as a crystalline solid which has a melting point of 112.5—114° C. (Found: C, 51.2; H, 3.4. $C_{14}H_{11}Cl_2NO_4$ requires C, 51.2; H, 3.35%).

In a similar manner are prepared the following esters:—

4 - (Dichloroacet - *N* - methylamido)phenyl phenoxyacetate m.p. 108—109°C. (Found: C, 55.3; H, 4.0. $C_{17}H_{15}Cl_2NO_4$ requires C, 55.4; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2-thenoate m.p. 134—135°C. (Found: C, 49.1; H, 3.0. $C_{14}H_{11}Cl_2NO_3S$ requires C, 48.8; H, 3.2%).

4 - (Dichloroacet - *N* - methylamido)phenyl β - naphthoxyacetate m.p. 121—122° C. (Found: C, 60.4; H, 3.7. $C_{21}H_{17}Cl_2NO_4$ requires C, 60.3; H, 4.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl 2 - chlorophenoxyacetate m.p. 102—104° C. (Found: C, 50.5; H, 3.1. $C_{17}H_{14}Cl_3NO_4$ requires C, 50.7; H, 3.5%).

4 - (Dichloroacet - *N* - methylamido)phenyl 4 - methylphenoxyacetate m.p. 69—71° C. (Found: C, 56.6; H, 4.4. $C_{18}H_{17}Cl_2NO_4$ requires C, 56.55; H, 4.45%).

4 - (Dichloroacet - *N* - methylamido)phenyl α - (*o* - methylphenoxy) - propionate m.p. 107—108° C. (Found: C, 57.7; H, 5.2. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8%).

4 - (Dichloroacet - *N* - methylamido)phenyl 5 - bromo - 2 - furoate m.p. 101—103° C. (Found: C, 40.9; H, 2.4. $C_{14}H_{10}BrCl_2NO_4$ requires C, 41.3; H, 2.5%).

EXAMPLE 2.

By the method described in Example 1 but crystallised five times from alcohol, and once from benzene followed by dissolving in acetone, and drowning in ice-cold *N* NaOH and a final crystallisation from 95% alcohol there is obtained 4 - (dichloroacet - *N* - methylamido)-phenyl *p*-nitrophenoxyacetate m.p. 133—135° C. (Found: C, 49.5; H, 3.6. $C_{17}H_{14}Cl_2N_2O_6$ requires C, 48.9; H, 3.4%).

EXAMPLE 3.

By the method described in Example 1 but collecting the crude oily product by extraction with chloroform, washing the chloroform solution with half-normal sulphuric acid, aqueous sodium bicarbonate solution and water, drying the solution with anhydrous magnesium sulphate, removing the chloroform by distillation and crystallising the residue from 95% alcohol there are obtained the following as crystalline solids:—

4 - (Dichloroacet - *N* - methylamido)phenyl γ-phenoxybutyrate m.p. 61—62° C. (Found: C, 57.8; H, 5.0. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8%).

4 - (Dichloroacet - *N* - methylamido)phenyl *m* - chlorophenoxyacetate m.p. 80—81° C.

(Found: C, 50.6; H, 3.8. $C_{17}H_{14}Cl_3NO_4$ requires C, 50.7; H, 3.5%).

EXAMPLE 4.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl nicotinate, 32.5 grams of nicotinyl chloride hydrochloride are added to a stirred solution of 45 grams of dichloroacet-4 - hydroxy - *N* - methylanilide in 140 ml. of dry pyridine. After being stirred for 90 minutes the reaction mixture is quenched with ice water and the product is isolated as in Example 1. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N* - methylamido)phenyl nicotinate which has a melting point of 167—170° C. (Found: C, 53.4; H, 3.5; N, 8.6. $C_{15}H_{12}Cl_2N_2O_3$ requires C, 53.1; H, 3.5; N, 8.3%).

EXAMPLE 5.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl *iso*nicotinate 6.4 ml. of benzene sulphonyl chloride are added to a solution of 12.3 grams of *iso*nicotinic acid in 50 ml. of dry pyridine, the temperature rising to 65° C. The solution is stirred at 45° C. for 15 minutes and then heated to 90° C. A solution of 11.7 grams of dichloroacet-4-hydroxy - *N* - methylanilide in 20 ml. of dry pyridine is added slowly to the stirred solution and stirring at 90° C. is continued for 30 minutes. The solution is cooled, poured into 300 ml. of ice water and the crude product is filtered off and crystallised twice from 95% alcohol. There is thus obtained 4-(dichloroacet - *N* - methylamido)phenyl *iso*nicotinate which has a melting point of 125—126.5° C. (Found C, 53.0; H, 3.3. $C_{15}H_{12}Cl_2N_2O_3$ requires C, 53.1; H, 3.5%).

In a similar manner is prepared the following ester:

4 - (Dichloroacet - *N* - methylamido)phenyl 2-furylacrylate m.p. 115—117° C. (Found: C, 54.4; H, 3.6. $C_{16}H_{13}Cl_2NO_4$ requires C, 54.2; H, 3.7%).

EXAMPLE 6.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl α - phenoxy *iso*butyrate 11.7 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide is slowly added to a solution of 10 grams of α - phenoxy - *iso* - butyryl chloride in 50 ml. dry pyridine and the mixture is maintained at about 20° C. for 20 hours. The reaction mixture is poured into 500 ml. of ice water and the crude product is filtered off, washed with dilute sulphuric acid and water and is crystallised from methanol. There is thus obtained as a crystalline solid 4-(dichloroacet - *N* - methylamido)phenyl α - phenoxy *iso*-butyrate which has a melting point of 85—86° C. (Found: C, 57.5; H, 4.6; N, 3.6. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8; N, 3.5%).

EXAMPLE 7.

By the method described in Example 6 but crystallising the crude product twice from a mixture of chloroform and methanol there is obtained as a crystalline solid 4 - (dichloroacet - *N* - methylamido)phenyl coumarilate which has a melting point of 151—153° C. (Found: C, 57.4; H, 3.4; N, 4.0. $C_{18}H_{13}Cl_2NO_4$ requires C, 57.1; H, 3.4; N, 3.7%).

EXAMPLE 8.

By the method described in Example 6 but extracting the gummy product with ether, washing the ethereal solution with 5*N* sulphuric acid, water, 2*N* sodium hydroxide and water, evaporation of the solvent and crystallisation of the gummy product from methanol there is obtained as a crystalline solid 4-(dichloroacet - *N* - methylamido)phenyl α-phenoxypropionate which has a melting point of 61—62° C. (Found: C, 56.6; H, 4.45; N, 3.7. $C_{18}H_{17}Cl_2NO_4$ requires C, 56.55; H, 4.45; N, 3.7%).

EXAMPLE 9.

By the method described in Example 8 there is obtained as a gum the following esters.

4 - (Dichloroacet - *N* - methylamido)phenyl α - phenoxy - *n* - butyrate. (Found: C, 57.9; H, 5.2; N, 3.9. $C_{19}H_{19}Cl_2NO_4$ requires C, 57.6; H, 4.8; N, 3.5%).

4 - (Dichloroacet - *N* - methylamido)phenyl α - phenoxy - *n* - valerate. (Found: C, 58.8; H, 5.2. $C_{20}H_{21}Cl_2NO_4$ requires C, 58.5; H, 5.1%).

4 - (Dichloroacet - *N* - methylamido)phenyl α - phenoxy - *n* - hexanoate. (Found: C, 59.6; H, 5.25. $C_{21}H_{23}Cl_2NO_4$ requires C, 59.4; H, 5.4%).

EXAMPLE 10.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl β-phenoxypropionate, 9.3 grams of thionyl chloride are added to a stirred suspension of 12.9 grams of β-phenoxypropionic acid, in 50 ml. of dry ether and the mixture is maintained at about 20° C. for 16 hours under anhydrous conditions. The solvent is distilled off at 20° C. under reduced pressure and 11.85 grams of the gummy residue are dissolved in 60 ml. of dry pyridine. To the solution is added a solution of 15 grams of dichloroacet - 4 - hydroxy - *N* - methylanilide in dry pyridine. The reaction mixture is drowned in water and the product is collected with ether and crystallised as described in Example 8. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N*-methylamido)phenyl β - phenoxypropionate which has a melting point of 61—62° C. (Found: C, 56.5; H, 4.7. $C_{18}H_{17}Cl_2NO_4$ C, 56.55; H, 4.45%).

EXAMPLE 11.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl β - phenoxypropionate, 2.32 ml. of benzoyl chloride dissolved in 10 ml. of dry benzene are added dropwise at room temperature to a stirred suspension of 3.76 grams of finely powdered sodium β-phenoxypropionate in 40 ml. of dry benzene and the stirring is continued for a further 90 minutes.

To the stirred solution of the mixed anhydride thus formed there is added a solution of 4.68 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide in 50 ml. of dry pyridine and the reaction mixture is allowed to stand for about 16 hours and is then poured into 200 ml. of water. The aqueous phase is washed with ether and the ethereal extract is added to the solvent phase. The combined organic phase is washed successively with 5*N* sulphuric acid, water, 2*N* sodium hydroxide and finally water. It is dried with anhydrous sodium sulphate and the solvent is distilled off. The residue is crystallised twice from aqueous methanol and there is thus obtained as a crystalline solid 4 - (dichloroacet - *N*-methylamido)phenyl β - phenoxypropionate which has a melting point of 60—61° C. A mixed melting point of this material together with that prepared according to Example 10 is also 60—61° C.

EXAMPLE 12.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl tetrahydro-2-furoate 11.2 grams of dicyclohexylcarbodiimide is added to a warm mixture of 6.27 grams of tetrahydro-2-furoic acid, 12.6 grams of dichloroacet-4-hydroxy - N - methylanilide and 100 ml. of methylene chloride and the mixture is allowed to stand overnight at 20° C. To the mixture is added 1 ml. of glacial acetic acid and after one hour the solution is filtered and the filtrate is washed with aqueous *N* sodium carbonate solution, ice cold 2*N* sodium hydroxide solution and water. It is dried with anhydrous magnesium sulphate and evaporated to an oil which is dissolved in a mixture of equal volumes of benzene and 60—80° C. petroleum ether. The solution is cooled to 0° C. for three hours, filtered and evaporated to an oil which is distilled *in vacuo*. There is thus obtained as an oil 4 - (dichloroacet - *N*-methylamido) - phenyl tetrahydro - 2 - furoate which has a boiling point of 175° C. under a pressure of 0.01 mm. Hg. (Found: C, 50.8; H, 4.5. $C_{14}H_{15}Cl_2NO_4$ requires C, 50.6; H, 4.5%).

EXAMPLE 13.

In the preparation of 4-(dichloroacet-*N*-methylamido)phenyl 3-furoate 6.75 grams of dicyclohexylcarbodiimide is added to a warm mixture of 3.6 grams of 3-furoic acid, 7.7 grams of dichloroacet - 4 - hydroxy - *N*-methylanilide and 75 ml. of methylene chloride and the mixture is allowed to stand overnight at 20° C. To the mixture is added 2 ml. of glacial acetic acid and after standing for 5 hours it is filtered, the filtrate is washed with ice cold 2*N* sodium hydroxide solution, then water, and is dried with anhydrous magnesium sulphate. The solvent is evaporated off and the residue is crystallised twice from S.V.M. There is thus obtained as a crystalline solid 4 - (dichloroacet - *N* - methylamido)-phenyl 3-furoate which has a melting point of 105.5—107° C. (Found: C, 51.9; H, 3.4. $C_{14}H_{11}Cl_2NO_4$ requires C, 51.2; H, 3.35%).

For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52, Chancery Lane, London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1960.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.