PATENT SPECIFICATION

Inventors: NORMAN WILLIAM BRISTOW, PETER OXLEY, GEORGE ALFRED HARRISON WILLIAMS, ERIC CHARLES WILMSHURST, and GERALD WOOLFE

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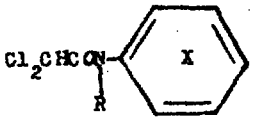
COMPLETE SPECIFICATION

New Acetanilide Derivatives and the Manufacture thereof

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:—

The invention relates to new derivatives of acetanilide which have been found to possess valuable properties as amoebicides.

The invention consists in the compounds of the general formula:

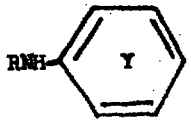


I

in which R represents an alkyl or aralkyl radical and in which the phenyl radical X is substituted by one or more groups which may be the same or different and which are selected from nitro, hydroxy, alkoxy, aralkoxy, aryloxy, carboxyalkoxy, alkenyloxy, alkylendioxy and $-NR^1R^2$ groups wherein R^1 and R^2 may be the same or different and represent hydrogen or an alkyl group.

The compounds of the invention may be prepared in various ways, the most convenient method in each case being dependent on the substituents present in the phenyl radical X.

Thus compounds having the general formula I wherein the phenyl radical X is unsubstituted by the group $-NR^1R^2$ in which R^1 or R^2 or both represent hydrogen may be prepared by the interaction of dichloroacetyl chloride and a substituted aniline of the general formula:



II

in the presence of an acid binding agent wherein R is as above defined and the phenyl radical Y is substituted by one or more groups which may be the same or different and which are selected from nitro, hydroxy, alkoxy, aralkoxy, aryloxy, carboxyalkoxy, alkenyloxy, alkylendioxy and $-NR^1R^2$ groups wherein R^1 and R^2 may be the same or different and represent an alkyl group. The reaction may be conducted between approximately equimolecular quantities of reactants in aqueous suspension or in a mixture of water and an organic solvent, for example benzene, in which the reactants are soluble, in both of which cases the acid-binding agent is preferably sodium acetate. The reaction may also be conducted in an organic solvent, for example benzene, in which the reactants are soluble, in which case it is convenient to employ a molar excess of the substituted aniline as acid-binding agent.

Some of the compounds of the invention represented by formula I which include in the phenyl radical X one or more nitro groups among the substituents as hereinbefore defined may also be made by nitration of the appropriate *N*-dichloracet-*N*-substituted anilide.

Compounds having the general formula I wherein the phenyl radical X is substituted by one or more alkoxy or aralkoxy groups, may be derived from the corresponding hydroxy compounds by methods well known in the art.

Compounds of the invention represented by formula I which include in the phenyl radical X one or more primary amino groups among the substituents as hereinbefore defined may be prepared from the corresponding nitro compounds in known manner by reduction of the latter with, for example, stannous chloride in the presence of hydrochloric acid.

The following non-limitative examples illustrate the invention.

[*Price Brief*] 3s. 6d.

EXAMPLE 1.

In the preparation of dichloroacet-4-hydroxy-*N*-methylanilide, a mixture of 34.5 grams of *p*-methylaminophenol sulphate, 68 grams of sodium acetate trihydrate, 2 grams of sodium bisulphite, 200 c.c. of water and 300 c.c. of benzene is stirred and cooled to approximately 6° C. To the cooled solution is added slowly over a period of 20 minutes a solution of 30 grams of dichloroacetyl chloride in 100 c.c. of benzene, the temperature being maintained within the range of 6°—8° C. throughout. The reaction mixture is then allowed to return to room temperature and after the lapse of 1 hour the solid which has separated is isolated by filtration, washed with water and dried *in vacuo* before being recrystallised from aqueous alcohol and finally from ethyl acetate. There is thus obtained dichloroacet-4-hydroxy-*N*-methylanilide in the form of a crystalline solid which has a melting point of 175° C. (Found N, 6.2. $C_9H_9O_2NCl_2$ requires N, 6.0%).

In a similar manner, from the appropriately substituted aminophenol, the following compounds may be prepared.

Dichloroacet - 2 - hydroxy-*N*-methylanilide m.p. 147—148° C. (Found: N, 6.1. $C_9H_9O_2NCl_2$ requires N, 6.0%).

Dichloroacet-2-hydroxy-*N*-ethylanilide m.p. 112° C. (Found: N, 5.9. $C_{10}H_{11}O_2NCl_2$ requires N, 5.6%).

Dichloroacet - 3 - hydroxy-*N*-methylanilide m.p. 179° C. (Found: C, 46.2; H, 3.8. $C_9H_9O_2NCl_2$ requires C, 46.2; H, 3.9%).

Dichloroacet-4-hydroxy-*N*-ethylanilide m.p. 125° C. (Found: C, 48.9; H, 4.5. $C_{10}H_{11}O_2NCl_2$ requires C, 48.4; H, 4.5%).

EXAMPLE 2.

In the preparation of dichloroacet-4-hydroxy-N-benzylanilide, a solution of 7.4 grams of dichloroacetyl chloride in 25 c.c. of benzene is added slowly over a period of 30 minutes to a stirred solution of 19.9 grams of *p*-benzylaminophenol in 200 c.c. of benzene, the temperature of the mixture remaining at approximately 30° C. during this operation. When the addition is complete the precipitate of *p*-benzylaminophenol hydrochloride is isolated by filtration. The filtrate is washed successively with dilute hydrochloric acid, dilute aqueous sodium carbonate solution and with water before being dried over anhydrous magnesium carbonate and concentrated by distillation to a volume of approximately 30 c.c. The residual solution is allowed to stand at room temperature and the solid which separates is isolated by filtration and dried *in vacuo* at 100° C. There is thus obtained dichloroacet-4-hydroxy-*N*-benzylanilide in the form of a crystalline solid which has a melting point of 149° C. (Found C, 58.5; H, 4.2. $C_{15}H_{13}O_2NCl_2$ requires C, 58.1; H, 4.2).

EXAMPLE 3.

In the preparation of dichloroacet-3:4-dihydroxy-*N*-methylanilide, 4.7 grams of dichloroacetyl chloride in 5 c.c. of methyl propyl ketone is slowly added over a period of 10 minutes to a stirred mixture of 7 grams of 3:4 - dihydroxy - *N* - methylaniline hydrobromide, 7.28 grams of sodium acetate, 8 c.c. of water and 40 c.c. of methyl propyl ketone, the temperature being maintained at 10° C. The reaction is carried out in an atmosphere of nitrogen. After addition is complete, the reaction mixture is stirred for a further 15 minutes and is allowed to stand at room temperature for 2 hours before the organic layer is separated and washed with 20 c.c. of *N* hydrochloric acid and 20 c.c. of *N* sodium carbonate solution. After drying the washed methyl propyl ketone solution over anhydrous sodium sulphate, the solvent is removed by distillation under reduced pressure in an atmosphere of nitrogen. The dark glass-like residue crystallises slowly on standing. The resulting crystals are dissolved in 50 c.c. of ether, the solution so obtained is filtered, and the ether is removed by distillation in an atmosphere of nitrogen. The light brown residue crystallises slowly on standing. There is thus obtained dichloroacet-3:4-dihydroxy-*N*-methylanilide in the form of a crystalline solid which has a melting point of 122—124° C. (Found: C, 44.5; H, 3.75. $C_9H_9O_3NCl_2$ requires C, 43.2; H, 3.6%).

3:4 - Dihydroxy - *N* - methylaniline hydrobromide employed in the above reaction is prepared as follows. 8.4 grams of 3:4-dimethoxy-*N*-methylaniline hydrochloride is heated under reflux with 80 c.c. of 48% aqueous hydrogen bromide for 4 hours. The reaction mixture is cooled and allowed to stand at 0° C. for several days. The resulting buff-coloured crystalline solid is isolated by filtration and washed with acetone and is used in the above reaction without further purification. It has a melting point of 199—200° C.

EXAMPLE 4.

In the preparation of dichloroacet-3:5-dihydroxy-*N*-methylanilide, a mixture of 30 grams of phloroglucinol, 30 c.c. of 25% w/w aqueous methylamine and 30 c.c. of water is shaken in a stoppered flask and allowed to stand overnight with the exclusion of air. The aqueous layer is removed by decanting and the oily residue is dissolved in 50 c.c. of methyl propyl ketone and the resulting solution is mixed with 60 c.c. of 28.5% aqueous sodium acetate. This mixture is stirred at 8—10° C. while 22.2 grams of dichloroacetyl chloride in 25 c.c. of methyl propyl ketone is slowly added over a period of 30 minutes. After stirring for a further 30 minutes, the aqueous layer is separated and discarded, and the methyl propyl ketone layer, after washing with 25 c.c. of *N* hydrochloric acid, 25 c.c. of aqueous sodium acetate and 25 c.c. of water, is evaporated to dryness under reduced pressure. The orange solid residue is recrystallised

from alcohol and from acetone. There is thus obtained dichloroacet-3:5-dihydroxy-*N*-methylanilide in the form of a crystalline solid which has a melting point of 220° C. with decomposition (Found: C, 43.1; H, 3.1. $C_{9}H_{9}O_{3}NCl_{2}$ requires C, 43.2; H, 3.6%).

EXAMPLE 5.

In the preparation of dichloroacet-4-hydroxy-*N*-propylanilide, 8.0 grams of dichloroacetyl chloride in 20 c.c. of benzene is slowly added to a stirred mixture of 4.6 grams of 4-hydroxy-*N*-propylaniline, 5.3 grams of 4-hydroxy-*N*-propylanilinium bromide, 11 grams of sodium acetate, 40 c.c. of water and 40 c.c. of benzene, the temperature being maintained at 5—10° C. The reaction mixture is stirred for a further 45 minutes at 10—15° C. before the precipitated solid is removed by filtration and recrystallised from aqueous alcohol. There is thus obtained dichloroacet-4-hydroxy-*N*-propylanilide in the form of a crystalline solid, which has a melting point of 135—136° C. (Found: C, 50.95; H, 5.15. $C_{11}H_{13}O_{3}NCl_{2}$ requires C, 50.4; H, 5.0%).

EXAMPLE 6.

In the preparation of dichloroacet-3:5-dihydroxy-*N*-ethylanilide. 13.75 grams of dichloroacetyl chloride in 20 c.c. of methyl propyl ketone is slowly added with stirring to a mixture of 13.75 grams of 3:5-dihydroxy-*N*-ethylaniline, 10.5 grams of sodium acetate, 35 c.c. of water and 110 c.c. of methyl propyl ketone. The mixture is stirred for a further 30 minutes before the organic layer is separated, washed with 25 c.c. of *N*-hydrochloric acid, 25 c.c. of *N* sodium carbonate solution and 25 c.c. of water. The solvent is removed by distillation under reduced pressure and the residue is recrystallised from acetone. There is thus obtained dichloroacet-3:5-dihydroxy-*N*-ethylanilide in the form of a crystalline solid which has a melting point of 190° C. (Found: C, 45.7; H, 4.0. $C_{10}H_{11}O_{3}NCl_{2}$ requires C, 45.45; H, 4.2%).

3:5-Dihydroxy-*N*-ethylaniline employed in the above reaction is prepared as follows. A mixture of 20 grams of phloroglucinol, 8.8 c.c. of 63.5% w/v aqueous ethylamine and 80 c.c. of water is allowed to stand for two days. At the end of this time, the precipitated solid is removed by filtration, washed with water, and recrystallised from alcohol. There is thus obtained 3:5-dihydroxy-*N*-ethylaniline in the form of a crystalline solid which has a melting point of 182° C. (Found: N, 9.1%. $C_{8}H_{11}O_{2}N$ requires N, 9.15%).

EXAMPLE 7.

In the preparation of dichloroacet-4-butoxy-*N*-methylanilide a solution of 7.4 grams of dichloracetylchloride in 20 c.c. of benzene is added slowly over a period of 20 minutes to a stirred mixture, maintained at approximately 5° C., of 8.95 grams of 4-butoxy-*N*-methylaniline, 10 grams of sodium acetate trihydrate, 30 c.c. of benzene and 20 c.c. of water. The reaction mixture is allowed to return to room temperature and after the lapse of one hour the benzene layer is isolated, washed successively with dilute hydrochloric acid, dilute sodium carbonate solution and with water, before being dried and evaporated to dryness. The residual oil is fractionally distilled under reduced pressure and that fraction is collected which has a boiling point of 146.5—147° C. at a pressure of 0.15 millimetres of mercury. There is thus obtained dichloroacet-4-butoxy-*N*-methylanilide in the form of an oil, n_{D}^{20} 1.5385 (Found: C, 54.2; H, 5.9. $C_{13}H_{17}O_{2}NCl_{2}$ requires C, 53.8; H, 5.9).

In a similar manner using the appropriately substituted aniline there are prepared the following compounds.

Dichloroacet-4-methoxy-*N*-methylanilide. m.p. 76° C. (Found: C, 48.4; H, 4.45. $C_{10}H_{11}O_{2}NCl_{2}$ requires C, 48.4; H, 4.47).

Dichloroacet-4-methoxy-*N*-ethylanilide. b.p. 142—148° C/6—9 × 10⁻² mm. Found: C, 51.0; H, 5.1. $C_{11}H_{13}O_{2}NCl_{2}$ requires C, 50.4; H, 5.0%.

Dichloroacet-4-ethoxy-*N*-methylanilide. b.p. 130° C./0.1 mm. (Found: C, 51.1; H, 5.1. $C_{11}H_{13}O_{2}NCl_{2}$ requires C, 50.4; H, 5.0%).

Dichloroacet-3-methoxy-*N*-methylanilide. m.p. 125° C. (Found: C, 48.4; H, 4.8. $C_{10}H_{11}O_{2}NCl_{2}$ requires C, 48.4; H, 4.5%).

Dichloroacet-4-methoxy-*N*-propylanilide. b.p. 130° C./0.01 mm. (Found: C, 52.9; H, 5.5. $C_{12}H_{15}O_{2}NCl_{2}$ requires C, 52.2; H, 5.5%).

Dichloroacet-4-*n*-propoxy-*N*-methylanilide. b.p. 130° C./0.03 mm. (Found: C, 52.8; H, 5.5. $C_{12}H_{15}O_{2}NCl_{2}$ requires C, 52.2; H, 5.5%).

Dichloroacet-4-isopropoxy-*N*-methylanilide. b.p. 140° C./0.02 mm. (Found: C, 52.0; H, 5.5. $C_{12}H_{15}O_{2}NCl_{2}$ requires C, 52.2; H, 5.5%).

Dichloroacet-4-allyloxy-*N*-methylanilide. b.p. 130° C./0.01 mm. (Found: C, 52.3; H, 4.7. $C_{12}H_{13}O_{2}NCl_{2}$ requires C, 52.6; H, 4.8%).

Dichloroacet-4-phenoxy-*N*-methylanilide. m.p. 57—58° C. (Found: C, 58.1; H, 4.1. $C_{15}H_{13}O_{2}NCl_{2}$ requires C, 58.1; H, 4.2%).

Dichloroacet-2-methoxy-*N*-methylanilide. m.p. 74° C. (Found: C, 48.8; H, 4.5. $C_{10}H_{11}O_{2}NCl_{2}$ requires C, 48.4; H, 4.4%).

Dichloroacet-3:4-dimethoxy-*N*-methylanilide. m.p. 94° C. (Found: C, 47.2; H, 4.8. $C_{11}H_{13}O_{3}NCl_{2}$ requires C, 47.5; H, 4.7%.

Dichloroacet-2-*n*-butoxy-*N*-methylanilide. b.p. 122—124° C./0.04 mm. (Found: C, 53.75; H, 5.8. $C_{13}H_{17}O_{2}NCl_{2}$ requires C, 53.8; H, 5.9%).

N-methyl-*m*-anisidine which is employed in the preparation of the above-mentioned dichloroacet-3-methoxy-*N*-methylanilide is prepared as follows. A mixture of 20 grams

of form-*m*-anisidine, 30 grams of potassium hydroxide and 100 c.c. of acetone is heated under reflux with stirring for 15 minutes and at the end of this time, 38 grams of methyl iodide in 30 c.c. of acetone is slowly added to the boiling reaction mixture. After heating under reflux for a further 10 minutes, the mixture is allowed to cool, the potassium iodide which is precipitated is removed by filtration and the solvent is removed from the filtrate by distillation. The residual gum is hydrolysed by heating under reflux with 50 c.c. of 6*N* hydrochloric acid for 2 hours, and the resulting solution is evaporated under reduced pressure. The residue is dried by evaporating twice with 15 c.c. of absolute alcohol. The crude hydrochloride so obtained is converted to the free base by treatment with sodium hydroxide solution and the oil so obtained is separated and distilled under reduced pressure. There is thus obtained *N*-methyl-*m*-anisidine in the form of an oil, which has a boiling point of 86—90° C. under a pressure of 1.5—2.5 mm. of mercury. (Found: N, 10.0. $C_8H_{11}ON$ requires N, 10.2%).

In a similar manner, using the formyl derivative of the appropriate amine and the appropriate alkylating agent there are obtained the following compounds which are intermediates for the preparation of some of the above-mentioned dichloroacetanilides. The compounds are described below in the form of their hydrochlorides and may be converted to the free amines by conventional methods before being used to prepare the corresponding dichloroacetanilides by the method described above in which case 2 molecular proportions of sodium acetate are employed in the reaction mixture.

4-methoxy-N-propylaniline hydrochloride, m.p. 125° C. (Found: N, 7.2. $C_{10}H_{15}ONCl$ requires N, 6.9%).

N-methyl-4-*n*-propoxyaniline hydrochloride, m.p. 109° C. (Found: N, 7.2. $C_{10}H_{16}ONCl$ requires N, 6.95%).

4-allyloxy-*N*-methyl aniline hydrochloride, m.p. 92° C. (Found: N, 7.2. $C_{10}H_{14}ONCl$ requires N, 7.0%).

N-methyl-4-phenoxyaniline hydrochloride, m.p. 149—150° C. (Found: N, 6.15. $C_{13}H_{14}ONCl$ requires N, 5.95%).

N-methyl-*o*-methoxyaniline hydrochloride, m.p. 118—120° C. (Found: N, 8.05. $C_8H_{12}ONCl$ requires N, 8.1%).

2-butoxy-*N*-methylaniline hydrochloride, m.p. 124—126° C. (Found: C, 61.25; H, 8.4. $C_{11}H_{18}ONCl$ requires C, 61.3; H, 8.35%).

EXAMPLE 8.

In the preparation of dichloroacet-4-methoxy-N-methylanilide a mixture of 11.7 grams of dichloracet-4-hydroxy-*N*-methylanilide, 7 grams of anhydrous potassium carbonate, 10 grams of methyl iodide and 100 c.c. of acetone is stirred vigorously and heated under reflux for 3 hours when a further 4.5 grams of methyl iodide is added. The reaction mixture is heated under reflux for a further 1.5 hours before being subjected to distillation to reduce the volume to approximately 40 c.c. The cooled residue is poured into a mixture of 150 c.c. of ice water and 10 c.c. of 5*N* sodium hydroxide. The solid which separates is isolated by filtration and is recrystallised from a mixture of benzene and petroleum ether. There is thus obtained dichloroacet-4-methoxy-*N*-methylanilide in the form of a crystalline solid which has a melting point of 74° C. and is identical with the compound described in the latter part of Example 7.

In a similar manner, using dichloracet-3-hydroxy-*N*-methylanilide in place of dichloroacet-4-hydroxy-*N*-methylanilide, there may be prepared dichloroacet-3-butoxy-*N*-methylanilide, m.p. 47—48° C. (Found: C, 54.4; H, 5.7. $C_{13}H_{17}O_2NCl_2$ requires C, 53.8; H, 5.9%).

In a similar manner, using dichloroacet-4-hydroxy-*N*-methylanilide and benzyl chloride, there may be prepared dichloracet-4-benzyloxy-N-methylanilide, m.p. 76° C. (Found: C, 59.0; H, 4.7. $C_{16}H_{15}O_2NCl_2$ requires C, 59.3; H, 4.7%).

EXAMPLE 9.

In the preparation of dichloracet-4-butoxy-*N*-methylanilide, a mixture of 35.1 grams of dichloroacet-4-hydroxy-N-methylanilide, 24 grams of anhydrous potassium carbonate, 200 c.c. of acetone and 30 grams of butyl iodide is heated under reflux with stirring for 5.5 hours. The reaction mixture is concentrated by distillation to approximately 100 c.c. and is poured into a mixture of 400 c.c. of ice water and 30 c.c. of 5*N* sodium hydroxide. The oil which separates is extracted in two portions each of 100 c.c. of benzene and the combined benzene extracts are washed with water, dried over anhydrous sodium sulphate and evaporated. The residue is subjected to distillation under reduced pressure and that fraction is collected which has a boiling point of 140° C. (bath temperature) at a pressure of 0.01 millimetres of mercury. There is thus obtained dichloracet-4-butoxy-N-methylanilide in the form of an oil, n_D^{25} 1.5384, which is identical with the product described in the first half of Example 7.

EXAMPLE 10.

In the preparation of dichloroacet-3-hydroxy-4-methoxy-*N*-methylanilide, a mixture of 5 grams of 4-methylaminoveratrole, 25 c.c. of glacial acetic acid and 15 c.c. of 48% aqueous hydrogen bromide, is heated under reflux for 2 hours in an atmosphere of nitrogen. The solvent is removed by distillation under reduced pressure in an atmosphere of nitrogen to leave a yellow gummy residue. The latter is dissolved in 20 c.c. of water and stirred with 8.4 grams of sodium acetate and

Alternatively the amine hydrochloride may itself be employed in the formation of the dichloroacetanilide according to the method described above

20 c.c. of benzene whilst an atmosphere of nitrogen is maintained. To the suspension so obtained is added with cooling and stirring 3.6 grams of dichloroacetyl chloride in 10 c.c. of benzene and the reaction mixture is left to stand overnight. The solid which separates is isolated by filtration and recrystallised from aqueous alcohol. There is thus obtained dichloroacet - 3 - hydroxy - 4 - methoxy - *N* - methylanilide in the form of a crystalline solid which has a melting point of 162.5—163.5° C. (Found: C, 45.3; H, 4.2. $C_{11}H_{11}O_4Cl_2$ requires C, 45.5; H, 4.2%).

EXAMPLE 11.

In the preparation of 4-(dichloro-*N*-methylacetamido) - phenoxyacetic acid, a mixture of 11.7 grams of dichloroacet-4-hydroxy-*N*-methylanilide, 8.35 grams of ethyl bromoacetate, 6.9 grams of potassium carbonate and 250 c.c. of acetone is heated under reflux with stirring overnight. At the end of this time the reaction mixture is allowed to cool, the insoluble material so obtained is removed by filtration and the acetone is removed by distillation. The residual brown oil is warmed with 50 c.c. of 2*N* sodium hydroxide solution for 30 minutes to give a clear solution. This solution is acidified with 2*N* sulphuric acid and cooled in ice, resulting in a buff-coloured precipitate, which is recrystallised twice from aqueous alcohol and dried in air. There is thus obtained 4 - (dichloro - *N* - methylacetamido)phenoxyacetic acid in the form of a colourless crystalline solid which has a melting point of 104—105.5° C. (Found: C, 43.0; H, 4.4; H_2O, 5.77. $C_{12}H_{11}O_5NCl_2.H_2O$ requires C, 42.6; H, 4.2; H_2O, 5.8%).

EXAMPLE 12.

In the preparation of dichloroacet-3:4-methylenedioxy-*N*-methylanilide, 20 grams of 4-nitromethylenedioxybenzene is hydrogenated at 20° C. and atmospheric pressure in methanol over 0.5 grams of palladised charcoal. Reduction is complete after 4½ hours and the reaction mixture is filtered and the solvent removed from the filtrate by distillation *in vacuo*. The crude 4-aminomethylenedioxybenzene so obtained is formylated by heating under reflux for 1 hour with 50 c.c. formic acid. At the end of this time, excess formic acid is removed by distillation *in vacuo* and the residue is crystallised from 50 c.c. of a mixture of equal volumes of alcohol and water. The 3:4-methylene-dioxyformanilide so obtained has a melting point of 95—96° C. This material is dissolved in 100 c.c. of acetone and the solution so obtained is added to a stirred suspension of 28 grams of powdered potassium hydroxide in 200 c.c. of acetone. After 5 minutes, 28.4 grams of methyl iodide is added and after the exothermic reaction is complete, the suspension is stirred and heated under reflux for 15 minutes. The clear solution is decanted from the sticky precipitate of inorganic salts and evaporated to dryness *in vacuo*. The crude *N* - methyl - 3:4 - methylenedioxyformanilide so obtained is heated on the steam bath for 30 minutes with 100 c.c. of 2*N* hydrochloric acid to give a solution of *N*-methyl-3:4-methylenedioxyaniline hydrochloride. The solution is cooled to room temperature and 100 grams of crystalline sodium acetate and 100 c.c. of water are added. To this solution a solution of 30 grams of dichloroacetyl chloride in 100 c.c. of petroleum ether (boiling range 60—80° C.) is added with vigorous stirring. The product separates out as a gum which rapidly solidifies and is removed by filtration, washed with water and crystallised from a mixture of 50 c.c. of methanol and 20 c.c. of water. There is thus obtained dichloroacet-3:4-methylenedioxy-*N*-methylanilide in the form of a colourless crystalline solid which has a melting point of 98° C. (Found: C, 45.7; H, 3.6. $C_{11}H_9O_3NCl_2$ requires C, 45.8; H, 3.4%).

EXAMPLE 13.

In the preparation of dichloroacet - 4 - hydroxy-N-methyl-3-nitroanilide, a mixture of 18 c.c. of fuming nitric acid and 60 c.c. of glacial acetic acid is slowly added to a stirred suspension of 15 grams of dichloroacet-4-hydroxy-N-methylanilide in 60 c.c. of glacial acetic acid. The reaction temperature is kept below 25° C. by water cooling. When the addition is complete, the resulting clear brown solution is stirred for a further half hour and is poured into a large excess of a mixture of ice and water. The precipitate which separates is collected by filtration, washed with a small quantity of water and crystallised twice from 40 c.c. portions of alcohol. There is thus obtained dichloroacet-4-hydroxy-*N*-methyl-3-nitroanilide in the form of a crystalline solid which has a melting point of 111° C. (Found: N, 10.2. $C_9H_8O_4N_2Cl_2$ requires N, 10.0%).

EXAMPLE 14.

In the preparation of dichloroacet-4-nitro-*N*-methylanilide, a mixture of 40 grams of *N*-methyl-*p*-nitroaniline and 39 grams of dichloroacetyl chloride in 360 c.c. of benzene is heated under reflux for 2 hours. At the end of this time the solution is allowed to cool and is diluted by the addition of 350 c.c. of ether and the precipitate so obtained is collected by filtration. There is thus obtained dichloroacet-4-nitro-*N*-methylanilide in the form of a crystalline solid which has a melting point of 130° C. (Found: N, 10.9. $C_9H_8O_3N_2Cl_2$ requires N, 10.7%).

In a similar manner, using *N*-methyl-*m*-nitroaniline, there is obtained dichloroacet-3-nitro-*N*-methylanilide which has a melting point of 94.5° C. (Found: N, 10.85. $C_9H_8O_3N_2Cl_2$ requires N, 10.7%).

EXAMPLE 15.

In the preparation of dichloroacet-4-dimethylamino-*N*-methylanilide, a solution of

9.0 grams of dichloroacetyl chloride in 20 c.c. of benzene is slowly added to a stirred mixture of 15.1 grams of trimethyl-*p*-phenylenediammonium dichloride, 28 grams of sodium acetate, 50 c.c. of water and 50 c.c. of benzene. The reaction temperature is kept below 10° C. by cooling in an ice-bath. When addition is complete, the stirred solution is allowed to rise to room temperature by removal of the ice-bath and, after 0.75 hours, the ice-bath is replaced and 40 c.c. of 5N sodium hydroxide solution is added slowly to the solution. The benzene layer is separated from the aqueous layer, washed with 50 c.c. of water and, after drying over anhydrous magnesium sulphate, is evaporated to give a crystalline residue. This is recrystallised twice from a mixture of equal parts of benzene and petroleum ether (boiling range 60—80° C.). There is thus obtained dichloroacet - 4 - dimethylamino - *N* - methylanilide in the form of a crystalline solid which has a melting point of 90° C. (Found: N, 11.1. $C_{11}H_{14}ON_2Cl_2$ requires N, 10.7%).

EXAMPLE 16.

In the preparation of dichloroacet-4-hydroxy-3-amino-*N*-methylanilide, 13.9 grams of dichloroacet-4-hydroxy-3-nitro-*N*-methylanilide (prepared as described in Example 13) is slowly added in small portions to a stirred solution of 38 grams of stannous chloride in 35 c.c. of concentrated hydrochloric acid. The reaction temperature is kept below 30° C. by water cooling. When the reaction is complete, the solution is cooled to 0° C. and the precipitate which separates is isolated by filtration and is washed with 20 c.c. of concentrated hydrochloric acid. The washed precipitate is dissolved in 100 c.c. of water containing 5 c.c. of concentrated hydrochloric acid and an excess of hydrogen sulphide is passed into the stirred solution. The precipitate of stannic sulphide so obtained is removed by filtration and excess aqueous ammonia is added to the filtrate producing a small black flocculent precipitate which is removed by filtration. The filtrate is evaporated *in vacuo* to 200 c.c. and is cooled to 0° C. The dark grey precipitate which separates is isolated by filtration and is recrystallised twice from small quantities of aqueous alcohol. There is thus obtained *N*-dichloroacet-4-hydroxy-3-amino-*N*-methylanilide in the form of a crystalline solid which has a melting point of ~~180—189°~~ 108—109° C. (Found: N, 11.2. $C_{11}H_{14}O_2N_2Cl_2$ requires N, 11.2%).

EXAMPLE 17.

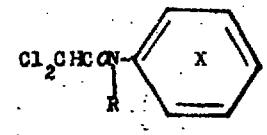
In the preparation of *N*-dichloroacet-4-amino-*N*-methylanilide, 13.2 grams of dichloroacet-*N*-methyl-4-nitroanilide (prepared as described in Example 14) is slowly added to a stirred solution of 45 grams of stannous chloride in 50 c.c. of concentrated hydrochloric acid and 50 c.c. of alcohol at 25° C. The mixture so obtained is stirred at 28° C. for 2 hours and at 40—65° C. for 3 hours, at the end of which time a clear solution is obtained. An excess of 50% sodium hydroxide solution is added with stirring and cooling. The mixture is extracted with 100 c.c. of chloroform and the aqueous layer is separated, subjected to filtration and extracted with two further portions, each of 50 c.c. of chloroform. The combined chloroform extracts are washed with 50 c.c. of water, dried over anhydrous sodium sulphate and evaporated. The solid so obtained is recrystallised from a small amount of alcohol. There is thus obtained *N*-dichloroacet-4-amino-*N*-methylanilide in the form of a colourless crystalline solid which has a melting point of 152—153° C. (Found: C, 46.7; H, 4.3. $C_{10}H_{12}ON_2Cl_2$ requires C, 46.3; H, 4.3%).

EXAMPLE 18.

In the preparation of dichloroacet-4-hydroxy-3:5-dinitro-*N*-methylanilide, 20 grams of dichloroacet-4-hydroxy-3-nitro-*N*-methylanilide (prepared as described in Example 13) is added slowly to 200 c.c. of fuming nitric acid with stirring and cooling to maintain the reaction temperature below 5° C. After addition is complete, the solution so obtained is stirred at 0—5° C. for an hour and is then poured into a large excess of a mixture of ice and water. The precipitate which separates is isolated by filtration and is crystallised from aqueous alcohol to give a yellow crystalline solid which has a melting point of 129—130° C. The crystal structure of this solid changes on keeping at room temperature for a few days to give a stable solid with a higher melting point. There is thus obtained dichloroacet-4-hydroxy-3:5-dinitro-*N*-methylanilide in the form of a crystalline solid which has a melting point of 144—146° C. (Found: N, 13.0 $C_{10}H_9O_6N_4Cl_2$ requires N, 13.0%).

What we claim is:—

1. New derivatives of acetanilide having the formula:



in which R represents an alkyl or aralkyl radical and in which the phenyl radical X is substituted by one or more groups which may be the same or different and which are selected from nitro, hydroxy, alkoxy, aralkoxy, aryloxy, carboxyalkoxy, alkenyloxy, alkylendioxy and —NR¹R² groups wherein R¹ and R² may be the same or different and represent hydrogen or an alkyl group.

2. Dichloroacet-4-hydroxy-*N*-methylanilide.
3. Dichloroacet-2-hydroxy-*N*-methylanilide.
4. Dichloroacet-2-hydroxy-*N*-ethylanilide.
5. Dichloroacet-3-hydroxy-*N*-methylanilide.
6. Dichloroacet-4-hydroxy-*N*-ethylanilide.
7. Dichloroacet-4-hydroxy-*N*-benzylanilide.

9.0 grams of dichloroacetyl chloride in 20 c.c. of benzene is slowly added to a stirred mixture of 15.1 grams of trimethyl-*p*-phenylenediammonium dichloride, 28 grams of sodium acetate, 50 c.c. of water and 50 c.c. of benzene. The reaction temperature is kept below 10° C. by cooling in an ice-bath. When addition is complete, the stirred solution is allowed to rise to room temperature by removal of the ice-bath and, after 0.75 hours, the ice-bath is replaced and 40 c.c. of 5N sodium hydroxide solution is added slowly to the solution. The benzene layer is separated from the aqueous layer, washed with 50 c.c. of water and, after drying over anhydrous magnesium sulphate, is evaporated to give a crystalline residue. This is recrystallised twice from a mixture of equal parts of benzene and petroleum ether (boiling range 60—80° C.). There is thus obtained dichloroacet-4-dimethylamino-*N*-methylanilide in the form of a crystalline solid which has a melting point of 90° C. (Found: N, 11.1. $C_{11}H_{14}ON_2Cl_2$ requires N, 10.7%).

EXAMPLE 16.

In the preparation of dichloroacet-4-hydroxy-3-amino-*N*-methylanilide, 13.9 grams of dichloroacet-4-hydroxy-3-nitro-*N*-methylanilide (prepared as described in Example 13) is slowly added in small portions to a stirred solution of 38 grams of stannous chloride in 35 c.c. of concentrated hydrochloric acid. The reaction temperature is kept below 30° C. by water cooling. When the reaction is complete, the solution is cooled to 0° C. and the precipitate which separates is isolated by filtration and is washed with 20 c.c. of concentrated hydrochloric acid. The washed precipitate is dissolved in 100 c.c. of water containing 5 c.c. of concentrated hydrochloric acid and an excess of hydrogen sulphide is passed into the stirred solution. The precipitate of stannic sulphide so obtained is removed by filtration and excess aqueous ammonia is added to the filtrate producing a small black flocculent precipitate which is removed by filtration. The filtrate is evaporated *in vacuo* to 200 c.c. and is cooled to 0° C. The dark grey precipitate which separates is isolated by filtration and is recrystallised twice from small quantities of aqueous alcohol. There is thus obtained *N*-dichloroacet-4-hydroxy-3-amino-*N*-methylanilide in the form of a crystalline solid which has a melting point of ~~180—139~~ 108—109° C. (Found: N, 11.2. $C_{11}H_{14}O_2N_2Cl_2$ requires N, 11.2%).

EXAMPLE 17.

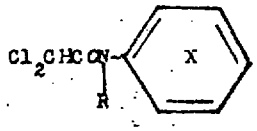
In the preparation of *N*-dichloroacet-4-amino-*N*-methylanilide, 13.2 grams of dichloroacet-*N*-methyl-4-nitroanilide (prepared as described in Example 14) is slowly added to a stirred solution of 45 grams of stannous chloride in 50 c.c. of concentrated hydrochloric acid and 50 c.c. of alcohol at 25° C. The mixture so obtained is stirred at 28° C. for 2 hours and at 40—65° C. for 3 hours, at the end of which time a clear solution is obtained. An excess of 50% sodium hydroxide solution is added with stirring and cooling. The mixture is extracted with 100 c.c. of chloroform and the aqueous layer is separated, subjected to filtration and extracted with two further portions, each of 50 c.c. of chloroform. The combined chloroform extracts are washed with 50 c.c. of water, dried over anhydrous sodium sulphate and evaporated. The solid so obtained is recrystallised from a small amount of alcohol. There is thus obtained *N*-dichloroacet-4-amino-*N*-methylanilide in the form of a colourless crystalline solid which has a melting point of 152—153° C. (Found: C, 46.7; H, 4.3. $C_{11}H_{12}ON_2Cl_2$ requires C, 46.4; H, 4.3%).

EXAMPLE 18.

In the preparation of dichloroacet-4-hydroxy-3:5-dinitro-*N*-methylanilide, 20 grams of dichloroacet-4-hydroxy-3-nitro-*N*-methylanilide (prepared as described in Example 13) is added slowly to 200 c.c. of fuming nitric acid with stirring and cooling to maintain the reaction temperature below 5° C. After addition is complete, the solution so obtained is stirred at 0—5° C. for an hour and is then poured into a large excess of a mixture of ice and water. The precipitate which separates is isolated by filtration and is crystallised from aqueous alcohol to give a yellow crystalline solid which has a melting point of 129—130° C. The crystal structure of this solid changes on keeping at room temperature for a few days to give a stable solid with a higher melting point. There is thus obtained dichloroacet-4-hydroxy-3:5-dinitro-*N*-methylanilide in the form of a crystalline solid which has a melting point of 144—146° C. (Found: N, 13.0. $C_9H_7O_6N_3Cl_2$ requires N, 13.0%).

What we claim is:—

1. New derivatives of acetanilide having the formula:

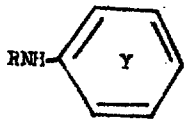


in which R represents an alkyl or aralkyl radical and in which the phenyl radical X is substituted by one or more groups which may be the same or different and which are selected from nitro, hydroxy, alkoxy, aralkoxy, aryloxy, carbexyalkoxy, alkenyloxy, alkylendioxy and —NR R' groups wherein R' and R' may be the same or different and represent hydrogen or an alkyl group.

2. Dichloroacet-4-hydroxy-*N*-methylanilide.
3. Dichloroacet-2-hydroxy-*N*-methylanilide.
4. Dichloroacet-2-hydroxy-*N*-ethylanilide.
5. Dichloroacet-3-hydroxy-*N*-methylanilide.
6. Dichloroacet-4-hydroxy-*N*-ethylanilide.
7. Dichloroacet-4-hydroxy-*N*-benzylanilide.

* C L M S *

8. Dichloroacet - 3 : 4-dihydroxy-*N*-methylanilide.
9. Dichloroacet - 3 : 5-dihydroxy-*N*-methylanilide.
10. Dichloroacet - 4 - hydroxy - *N* - propylanilide.
11. Dichloroacet - 3 : 5 - dihydroxy-*N*-ethylanilide.
12. Dichloroacet-4-butoxy-*N*-methylanilide.
13. Dichloroacet-4-methoxy-*N*-ethylanilide.
14. Dichloroacet-4-ethoxy-*N*-methylanilide.
15. Dichloroacet - 3 - methoxy - *N* - methylanilide.
16. Dichloroacet - 4 - methoxy - *N* - propylanilide.
17. Dichloroacet - 4 - *n*-propoxy-*N*-methylanilide.
18. Dichloroacet - 4-*iso*-propoxy-*N*-methylanilide.
19. Dichloroacet - 4 - allyloxy - *N* - methylanilide.
20. Dichloroacet - 4 - phenoxy - *N* - methylanilide.
21. Dichloroacet - 2 - methoxy - *N*-methylanilide.
22. Dichloroacet-3 : 4-dimethoxy-*N*-methylanilide.
23. Dichloroacet - 2 - *n* - butoxy-*N*-methylanilide.
24. Dichloroacet - 4 - methoxy - *N* - methylanilide.
25. Dichloroacet-3-butoxy-*N*-methylanilide.
26. Dichloroacet - 4 - benzyloxy-*N*-methylanilide.
27. Dichloroacet-3-hydroxy-4-methoxy-*N*-methylanilide.
28. 4-(Dichloro-*N*-methylacetamido)-phenoxyacetic acid.
29. Dichloroacet - 3 : 4 - methylenedioxy-*N*-methylanilide.
30. Dichloroacet - 4 - hydroxy - 3 - nitro-*N*-methylanilide.
31. Dichloroacet-4-nitro-*N*-methylanilide.
32. Dichloroacet-3-nitro-*N*-methylanilide.
33. Dichloroacet - 4 - dimethylamino - *N*-methylanilide.
34. Dichloroacet - 4 - hydroxy - 3-amino-*N*-methylanilide.
35. Dichloroacet-4-amino-*N*-methylanilide.
36. Dichloroacet-4-hydroxy-3 : 5-dinitro-*N*-methylanilide.
37. A process for the production of a compound as claimed in claim 1 wherein the phenyl radical X is unsubstituted by the group —NR^1R^2 in which R^1 or R^2 or both represent hydrogen, wherein dichloroacetyl chloride is reacted with the appropriate substituted aniline of the general formula:



in the presence of an acid-binding agent, wherein R is as above defined and the phenyl radical Y is substituted by one or more groups which may be the same or different and which are selected from nitro, hydroxy, alkoxy, aralkoxy, aryloxy, carboxyalkoxy, alkenyloxy, alkylendioxy and —NR^3R^4 groups wherein R^3 and R^4 may be the same or different and represent an alkyl group, and if desired in the case where the phenyl radical Y contains one or more hydroxy groups, alkylating or aralkylating these groups to form the corresponding alkoxy or aralkoxy derivatives.

38. A process as claimed in claim 37 wherein the acid-binding agent is sodium acetate.

39. A process for the production of a compound as claimed in claim 1 wherein the phenyl radical X as hereinbefore defined is substituted by one or more nitro groups which comprises nitrating the corresponding *N*-dichloracet-*N*-substituted anilide.

40. A process for the production of a compound as claimed in claim 1 wherein the phenyl radical X is substituted by one or more primary amino groups which comprises reducing the corresponding nitro compound.

41. A process as claimed in claim 40 wherein the reduction is carried out with stannous chloride in the presence of hydrochloric acid.

42. A process for the preparation of a compound as claimed in any of claims 1 to 36 substantially as herein described with reference to the Examples.

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

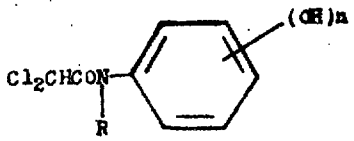
PROVISIONAL SPECIFICATION
No. 21458 A.D. 1954

New Acetanilide Derivatives and the Manufacture thereof

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 which have been found to possess valuable properties.

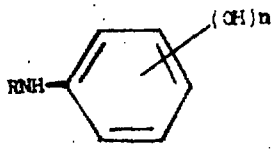
The invention consists in the compounds of the general formula



* C L M S *

where R represents an alkyl or an aralkyl group and where n is an integer which may have a value within the range 1 to 5. Compounds of the general formula have been found to possess properties which render them valuable in the field of food or medicine or in the production of food or medicine. For example, they have been found to possess amoebicidal properties.

The compounds of the invention may be prepared by the interaction of dichloracetyl chloride and a substituted aminophenol of the general formula



where R and n have the meaning hereinbefore defined, in the presence of an acid-binding agent. The reaction may be conducted between approximately equimolecular quantities of reactants in aqueous solution or in a mixture of water and an organic solvent, for example benzene, in which the reactants are soluble, in both of which cases the acid-binding agent is preferably sodium acetate. The reaction may also be conducted in an organic solvent, for example benzene, in which the reactants are soluble, in which case it is convenient to employ a molar excess of aminophenol as acid-binding agent.

The following non-limitative examples illustrate the invention.

EXAMPLE 1.

In the preparation of 4-hydroxy-N-methyldichloracetanilide a mixture of 34.5 grams of *p*-methylaminophenol sulphate, 68 grams of sodium acetate trihydrate, 2 grams of sodium bisulphite, 200 c.c. of water and 300 c.c. of benzene is stirred and cooled to approximately 6° C. To the cooled solution is added slowly over a period of 20 minutes a solution of 30 grams of dichloracetyl chloride in 100 c.c. of benzene, the temperature being maintained within the range of 6–8° C. throughout. The reaction mixture is then allowed to return to room temperature and after the lapse of 1 hour the solid which has separated is isolated by filtration, washed with water and dried *in vacuo* before being recrystallised from aqueous alcohol and finally from ethyl acetate. There is thus obtained 4-hydroxy-N-methyldichloracetanilide in the form of a crystalline solid which has a melting point of 175° C. [Found N, 6.2 : $C_9H_9O_2NCl_2$ requires N, 6.0.]

EXAMPLE 2.

In the preparation of 4-hydroxy-N-benzyldichloracetanilide a solution of 7.4 grams of dichloracetyl chloride in 25 c.c. of benzene is added slowly over a period of 30 minutes to a stirred solution of 19.9 grams of *p*-benzylaminophenol in 200 c.c. of benzene, the temperature of the mixture remaining at approximately 30° C. during this operation. When the addition is complete the precipitate of *p*-benzylaminophenol hydrochloride is isolated by filtration. The filtrate is washed successively with dilute hydrochloric acid, dilute aqueous sodium carbonate solution and with water before being dried over anhydrous magnesium carbonate and concentrated by distillation to a volume of approximately 30 c.c. The residual solution is allowed to stand at room temperature and the solid which separates is isolated by filtration and dried *in vacuo* at 100° C. There is thus obtained 4-hydroxy-N-benzyldichloracetanilide in the form of a crystalline solid which has a melting point of 149° C. [Found C, 58.5 : H, 4.2 : $C_{15}H_{13}O_2NCl_2$ requires C, 58.1 : H, 4.2.]

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

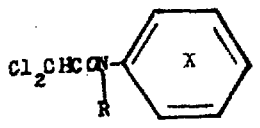
PROVISIONAL SPECIFICATION
No. 27030 A.D. 1954

New Acetanilide Derivatives and the Manufacture thereof

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 invention relates to new derivatives of acetanilide which have been found to possess valuable properties.

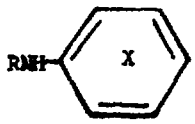
The invention consists in the compounds of the general formula



(I)

where R represents an alkyl or an aralkyl group and where the benzene nucleus X may be substituted by one or more alkoxy, aralkoxy, carboxyalkoxy or alkyleneoxy groups and may additionally be substituted by a hydroxy group. Compounds of the above general formula have been found to possess properties which render them valuable in the field of food or medicine or in the production of food or medicine. For example, they have been found to possess amoebicidal properties.

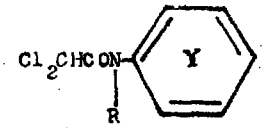
The compounds of the invention may be prepared by the interaction of dichloracetyl chloride and a substituted amiline of the general formula



(II)

where R and X have the significance hereinbefore defined, in the presence of an acid-binding agent. The reaction may be conducted between approximately equimolecular quantities of reactants in aqueous suspension or in a mixture of water and an organic solvent, for example benzene, in which the reactants are soluble, in both of which cases the acid-binding agent is preferably sodium acetate. The reaction may also be conducted in an organic solvent, for example, benzene, in which the reactants are soluble, in which case it is convenient to employ a molar excess of the substituted aniline as acid-binding agent.

Certain of the compounds of the invention may also be obtained from compounds of the general formula



(III)

where the benzene nucleus Y carries one or more hydroxyl groups as substituents [The compounds of the general formula (III) are described in our co-pending application No. 21458/54]. Thus the compounds of general formula (I) in which the nucleus X is substituted by one or more alkoxy groups may be derived from the corresponding compounds of general formula (III) by the use of suitable alkylating agents, for example, the appropriate alkyl iodide.

The following non-limitative examples illustrate the invention:

EXAMPLE 1.

In the preparation of 4-butoxy-N-methyl-N-dichloracetanilide a solution of 7.4 grams of dichloracetylchloride in 20 c.c. of benzene is added slowly over a period of 20 minutes to a stirred mixture, maintained at approximately 5° C., of 8.95 grams of 4-butoxy-N-methylaniline, 10 grams of sodium acetate trihydrate, 30 c.c. of benzene and 20 c.c. of water. The reaction mixture is allowed to return to room temperature and after the lapse of one hour the benzene layer is isolated, washed successively with dilute hydrochloride acid, dilute sodium carbonate solution and with water, before being dried and evaporated to dryness. The residual oil is fractionally distilled under reduced pressure and that fraction is collected which has a boiling point of 146.5—147° C. at a pressure of 0.15 millimetres of mercury. There is thus obtained 4-butoxy-N-methyl-N-dichloracetanilide in the form of an oil, n_D^{20} 1.5385. [Found C, 54.2; H, 5.9 : $C_{13}H_{17}O_2NCl_2$ requires C, 53.8; H, 5.9.]

In similar manner but using 4-methoxy-N-methylaniline in place of 4-butoxy-N-methylaniline there is prepared 4-methoxy-N-methyl-N-dichloracetanilide in the form of a crystalline solid which has a melting point of 76° C. [Found C, 48.4; H, 4.45 : $C_{10}H_{11}O_2NCl_2$ requires C, 48.4; H, 4.47.]

EXAMPLE 2.

In the preparation of 4-methoxy-N-methyl-N-dichloracetanilide a mixture of 11.7 grams of 4-hydroxy-N-methyl-N-dichloracetanilide (prepared as described in co-pending application No. 21458/54) 7 grams of anhydrous potassium carbonate, 10 grams of methyl iodide and 100 c.c. of acetone is stirred vigorously and heated under reflux for 3 hours when a further 4.5 grams of methyl iodide is added. The reaction mixture is heated under reflux for a further 1.5 hours before being subjected to distillation to reduce the volume to approximately 40 c.c. The cooled residue is poured into a mixture of 150 c.c. of ice water and 10 cc. of 5*N* sodium hydroxide. The solid which separates is isolated by filtration and is recrystallised from a mixture of benzene and petroleum ether. There is thus obtained 4-methoxy-N-methyl-N-dichloracetanilide in the form of a crystalline solid which has a melting point of 74° C. and is identical with the compound described in the latter part of Example 1.

EXAMPLE 3.

In the preparation of 4-butoxy-N-methyl-N-dichloracetanilide a mixture of 35.1 grams of 4-hydroxy-N-methyl-N-dichloracetanilide (prepared as described in co-pending application No. 21458/54), 24 grams of anhydrous potassium carbonate, 200 c.c. of acetone and 30 grams of butyl iodide is heated under reflux with stirring for 5.5 hours. The reaction mixture is concentrated by distillation to approximately 100 c.c. and is poured into a mixture of 400 c.c. of ice water and 30 c.c. of 5*N* sodium hydroxide. The oil which separates is extracted in two portions each of 100 c.c. of benzene and the combined benzene extracts are washed with water, dried over anhydrous sodium sulphate and evaporated. The residue is subjected to distillation under reduced pressure and that fraction is collected which has a boiling point of 140° C. (bath temperature) at a pressure of 0.01 millimetres of mercury. There is thus obtained 4-butoxy-N-methyl-N-dichloracetanilide in the form of an oil, n_D^{20} 1.5384, which is identical with the product described in the first half of Example 1.

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

PROVISIONAL SPECIFICATION

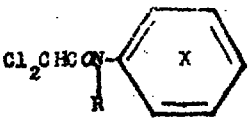
No. 8625 A.D. 1955

New Acetanilide Derivatives and the Manufacture thereof

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 invention relates to new derivatives of acetanilide which have been found to possess valuable properties.

The invention consists in the compounds of the general formula

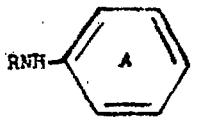


---I

in which R represents an alkyl, aralkyl or aryl group and in which the benzene nucleus X may be substituted by one or more nitro groups and/or one or more groups represented by the formula $-NR_1R_2$ where R_1 and R_2 may be the same or different and may be selected from the class comprising hydrogen atoms, alkyl, aralkyl and aryl radicals, and in which the benzene nucleus X may be additionally substituted by one or more hydroxy, alkoxy, aralkoxy or aryloxy groups. Compounds of the above general formula have been found to possess properties which render them valuable in the field of food or medicine or in the production of food or medicine. For example, they have been found to possess amoebicidal properties.

The compounds of the invention may be prepared in various ways, the most convenient method in each case being dependent on the substituents present in the benzene nucleus X (see formula I).

Thus the majority of compounds represented by formula I may be prepared by the interaction of dichloroacetyl chloride and a substituted aniline of the general formula II



---II

in which R has the significance as hereinbefore defined and in which the benzene nucleus A may be substituted by one or more nitro groups and/or one or more groups represented by the formula $-NR_1R_2$ where R_1 and R_2 may be the same or different and may be selected from the class comprising alkyl, aralkyl and aryl radicals, and in which the benzene nucleus X may be additionally substituted by one or more hydroxy, alkoxy, aralkoxy or aryloxy groups.

Some of the compounds of the invention represented by formula I which include in the benzene ring X one or more nitro groups among the substituents as hereinbefore defined may also be made by nitration of the appropriate *N*-dichloracet-*N*-substituted anilide.

Compounds of the invention represented by formula I which include in the benzene ring X one or more alkoxy or aralkoxy groups among the substituents as hereinbefore defined may also be prepared from the corresponding hydroxy compounds by methods well-known in the art.

Compounds of the invention represented by formula I which include in the benzene ring X one or more amino groups among the substituents as hereinbefore defined may be prepared from the corresponding nitro compounds in known manner by reduction of the latter with, for example, stannous chloride in the presence of hydrochloric acid.

The following non-limitative examples illustrate the invention.

EXAMPLE 1

In the preparation of dichloroacet-4-hydroxy-*N*-methyl-3-nitroanilide, a mixture of 18 cc. of fuming nitric acid and 60 cc. of glacial acetic acid is slowly added to a stirred suspension of 15 grams of dichloroacet-4-hydroxy-*N*-methylanilide (Prepared as described in our co-pending application No. 21458/54) in 60 cc. of glacial acetic acid. The reaction temperature is kept below 25° C. by water cooling. When the addition is complete, the resulting clear brown solution is stirred for a further half hour and is poured into a large excess of a mixture of ice and water. The precipitate which separates is collected by filtration, washed with a small quantity of water and crystallised twice from 40 cc. portions of alcohol. There is thus obtained dichloroacet-4-hydroxy-*N*-methyl-3-nitroanilide in the form of a crystalline solid which has a melting point of 111° C. (Found: N, 10.2. $C_9H_8O_4N_2Cl_2$ requires N, 10.0%).

EXAMPLE 2.

In the preparation of dichloroacet-*N*-methyl-4-nitroanilide, a mixture of 40 grams of *N*-methyl-*p*-nitroaniline and 39 grams of dichloroacetyl chloride in 360 cc. of benzene is heated under reflux for 2 hours. At the end of this time the solution is allowed to cool and is diluted by the addition of 350 cc. of ether and the precipitate so obtained is collected by filtration. There is thus obtained dichloroacet-*N*-methyl-4-nitroanilide in the form of a crystalline solid which has a melting point of 130° C. (Found: N, 10.9. $C_9H_8O_4N_2Cl_2$ requires N, 10.7%).

In a similar manner, using *N*-methyl-*m*-nitroaniline, there is obtained dichloroacet-*N*-methyl-3-nitroaniline which has a melting

point of 94.5° C. (Found: N, 10.85. $C_9H_8O_3N_2Cl_2$ requires N, 10.7%).

EXAMPLE 3.

In the preparation of dichloroacet-4-dimethylamino-N-methylanilide, a solution of 9.0 grams of dichloroacetyl chloride in 20 cc. of benzene is slowly added to a stirred mixture of 13.1 grams of trimethyl-*p*-phenylenediammonium dichloride, 28 grams of sodium acetate, 50 cc. of water and 50 cc. of benzene. The reaction temperature is kept below 10° C. by cooling in an ice-bath. When addition is complete, the stirred solution is allowed to rise to room temperature by removal of the ice-bath and, after 0.75 hours, the ice-bath is replaced and 40 cc. of 5N sodium hydroxide solution is added slowly to the solution. The benzene layer is separated from the aqueous layer, washed with 50 cc. of water and, after drying over anhydrous magnesium sulphate, is evaporated to give a crystalline residue. This is recrystallised twice from a mixture of equal parts of benzene and petroleum ether (boiling range 60—80° C.). There is thus obtained dichloroacet-4-dimethylamino-*N*-methylanilide in the form of a crystalline solid which has a melting point of 90° C. (Found: N, 11.1. $C_{11}H_{14}ON_2Cl_2$ requires N, 10.7%).

In the preparation of 3-amino-*N*-dichloroacet-4-hydroxy-*N*-methylanilide, 13.9 grams of dichloroacet-4-hydroxy-*N*-methyl-3-nitroanilide (prepared as described in Example 1) is slowly added in small portions to a stirred solution of 38 grams of stannous chloride in 35 cc. of concentrated hydrochloric acid. The reaction temperature is kept below 30° C. by water cooling. When the reaction is complete, the solution is cooled to 0° C. and the precipitate which separates is isolated by filtration and is washed with 20 cc. of concentrated hydrochloric acid. The washed precipitate is dissolved in 100 cc. of water containing 5 cc. of concentrated hydrochloric acid and an excess of hydrogen sulphide is passed into the stirred solution. The precipitate of stannic sulphide so obtained is removed by filtration and excess aqueous ammonia is added to the filtrate producing a small black flocculent precipitate which is removed by filtration. The filtrate is evaporated *in vacuo* to 200 cc. and is cooled to 0° C. The dark grey precipitate which separates is isolated by filtration and is recrystallised twice from small quantities of aqueous alcohol. There is thus obtained 3-amino-*N*-dichloroacet-4-hydroxy-*N*-methylanilide in the form of a crystalline solid which has a melting point of 108—109° C. (Found: N, 11.2. $C_9H_{10}O_2N_2Cl_2$ requires N, 11.2%).

EXAMPLE 5.

In the preparation of 4-amino-*N*-dichloroacet-*N*-methylanilide, 13.2 grams of dichloroacet-*N*-methyl-4-nitroanilide (Prepared as described in Example 2) is slowly added to a stirred solution of 45 grams of stannous chloride in 50 cc. of concentrated hydrochloric acid and 50 cc. of alcohol at 25° C. The mixture so obtained is stirred at 28° C. for 2 hours and at 40—65° C. for 3 hours, at the end of which time a clear solution is obtained. An excess of 50% sodium hydroxide solution is added with stirring and cooling. The mixture is extracted with 100 cc. of chloroform and the aqueous layer is separated, subjected to filtration and extracted with two further portions, each of 50 cc., of chloroform. The combined chloroform extracts are washed with 50 cc. of water, dried over anhydrous sodium sulphate and evaporated. The solid so obtained is recrystallised from a small amount of alcohol. There is thus obtained 4-amino-*N*-dichloroacet-*N*-methylanilide in the form of a colourless crystalline solid which has a melting point of 152—153° C. (Found: C, 46.7; H, 4.3. $C_9H_{10}ON_2Cl_2$ requires C, 46.4; H, 4.3%).

EXAMPLE 6.

In the preparation of dichloroacet-4-hydroxy-*N*-methyl-3:5-dinitroanilide, 20 grams of dichloroacet-4-hydroxy-*N*-methyl-3-nitro-anilide (prepared as described in Example 1) is added slowly to 200 cc. of fuming nitric acid with stirring and cooling to maintain the reaction temperature below 5° C. After addition is complete, the solution so obtained is stirred at 0—5° C. for an hour and is then poured into a large excess of a mixture of ice and water. The precipitate which separates is isolated by filtration and is crystallised from aqueous alcohol to give a yellow crystalline solid which has a melting point of 129—130° C. The crystal structure of this solid changes on keeping at room temperature for a few days to give a stable solid with a higher melting point. There is thus obtained dichloroacet-4-hydroxy-*N*-methyl-3:5-dinitroanilide in the form of a crystalline solid which has a melting point of 144-146° C. (Found: N, 13.0. $C_9H_8O_6N_4Cl_2$ requires N, 13.0%).

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

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