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2,862,967

N - ALKYL - N - (ALKYLATED - BENZYL)DIHALO- ACETAMIDES AND PREPARATION THEREOF

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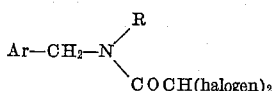
No Drawing. Application December 9, 1955
Serial No. 551,999

9 Claims. (Cl. 260—562)

This invention relates to novel N-alkyl-N-(alkylated-benzyl)dihaloacetamides, to their preparation, and to amebicidal compositions containing these compounds as active ingredients thereof.

During and since World War II, it has become increasingly apparent that amebiasis is even more serious a problem than had been previously assumed. This realization has stimulated the search for new drugs effective in treating this debilitating disease. The search has been directed toward finding highly effective, non-toxic, non-metallic and relatively inexpensive remedies to improve on the presently available and only limitedly useful drugs such as carbasone, chiniofon, diiodohydroxyquinoline and emetine bismuth iodine. Other workers recently have found the relatively new chlortetracycline and oxytetracycline to be highly effective; however, these antibiotics suffer the disadvantages of being relatively expensive and, when tested in hamsters, of producing marked bloating of the cecum and altering the cecal flora. It is well known that these antibiotics also often adversely disturb and alter the intestinal flora in human patients because of their broad antibacterial spectrum. In contrast, my new compounds have very slight if any antibacterial activity and can be expected therefore to have little if any effect on the normal intestinal flora.

My search has resulted in the compounds of the instant invention, these compounds having the general formula



where Ar is a phenyl radical substituted by from one to three lower alkyl radicals, and R is a lower alkyl radical.

These compounds not only have markedly high amebicidal activities as evidenced by cure of hamsters infected with amebiasis, but also surprisingly low toxicities. Moreover, they have a novel and relatively simple chemical structure that does not resemble and is not suggested by any amebicidal agent known prior to my work in this field. My new compounds of course vary among themselves in magnitude of amebicidal activity, but even the less active embodiments are from three to four times more active than the commercial amebicidal agents, chiniofon and diiodohydroxyquinoline, while the more active embodiments are from about 10 to 20 times more active than these two commercial quinoline amebicides; and from about 2 to 3 times more active than carbasone (the commercial arsenical preparation). Coupled with this high activity, my compounds have remarkably low toxicities.

In my search for new amebicidal agents, I have prepared N-benzyl-N-methyldichloroacetamide, a compound which had been reported by Mannich and Kuphal at the University of Berlin over forty years ago [Archiv. der Pharmazie, pp. 539-547 (1912)]. These German chemists of long ago, in attempting to prepare isoquinolines, had prepared this compound as a possible intermediate;

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however, they failed in all attempts to convert it into an isoquinoline derivative. Thus, they found no utility for this compound and it was completely neglected until, in the course of my search for new amebicidal compositions, and stimulated by my discovery of the amebicidal value of analogs, I recently prepared it and had tested it for amebicidal activity. I found this old and until now useless compound to possess amebicidal activity, being less active than the most active embodiments of the instant application but, at the same time, being considerably more active than chiniofon and diiodohydroxyquinoline and more active than carbasone.

In the above formula for my new compounds, the alkyl substituents of the phenyl radical designated by Ar can be in any of the available positions of the phenyl nucleus, and have from one to six carbon atoms, including such substituents as: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 2-butyl, n-pentyl, n-hexyl, and the like. Preferred embodiments of the compounds of my invention are those with at least one alkyl substituent having from three to six carbon atoms.

The lower alkyl radical of the above general formula, designated as R, has preferably from one to six carbon atoms and includes such examples as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-methylpentyl, and the like.

The halogen atoms of the dihaloacetyl radicals of my compounds, designated in the above formula as —COCH(halogen)₂, can be chloro, bromo, iodo or fluoro, such dihaloacetyl radicals including dichloroacetyl, dibromoacetyl, diiodoacetyl, difluoroacetyl, bromochloroacetyl, bromiodoacetyl, and the like.

The compounds of my invention were prepared by treating an N-(lower alkyl)-alkylated-benzylamine of the formula, Ar-CH₂NH-R, with a dihaloacetyl halide, where Ar and R have the meanings given above. The halo radical attached to the carbonyl function, was preferably chloro; however, other halo radicals, i. e., bromo, iodo, fluoro, also can be used. Illustrations of the process of my invention are: the preparation of N-isopropyl-N-(2,4,6-trimethylbenzyl)dichloroacetamide by treating N-isopropyl-2,4,6-trimethylbenzylamine with dichloroacetyl chloride; the preparation of N-isobutyl-N-(3,4-diethylbenzyl)dibromoacetamide by treating N-isobutyl-3,4-diethylbenzylamine with dibromoacetyl bromide; N-n-hexyl-N-(4-n-butylbenzyl)diiodoacetamide by treating N-n-hexyl-4-n-butylbenzylamine with diiodoacetyl iodine; the preparation of N-isopropyl-N-(2,4-dimethylbenzyl)bromochloroacetamide by treating N-isopropyl-2,4-dimethylbenzylamine with bromochloroacetyl chloride. The reaction was carried out preferably below room temperature, with chilling as necessary.

The compounds where the lower alkyl radical R is methyl were prepared also by reacting an N-methyl-alkylated-benzylamine, Ar-CH₂NHCH₃, with a lower alkyl dihaloacetate, e. g., methyl dichloroacetate, where the lower alkyl portion of this intermediate ester has from one to six carbon atoms. Illustrations of this modification of my process are: the preparation of N-methyl-N-(2,4-diisopropylbenzyl)dichloroacetamide by reacting N-methyl-2,4-diisopropylbenzylamine with methyl dichloroacetate; and the preparation of N-methyl-N-(4-n-butylbenzyl)dibromoacetamide by reacting N-methyl-4-n-butylbenzylamine with ethyl dibromoacetate. The reaction was run by mixing the reactants and allowing them to stand from about one to four days at room temperature or by heating the reaction mixture for shorter periods (such as about 12 to 18 hours) at an elevated temperature (such as 45 to 60° C.). I found that N-(lower alkyl)-alkylated-benzylamines where the lower alkyl radical is larger than methyl would not undergo the reaction with the lower

alkyl dihaloacetates to form the corresponding disubstituted dihaloacetamides.

The intermediate N-(lower alkyl)-alkylated-benzylamines were prepared either by treating an alkylated-benzaldehyde of the formula ArCHO with an alkylamine of the formula RNH_2 followed by catalytic reduction of the anil, $\text{ArCH}=\text{N}-\text{R}$, or by treating an alkylated-benzyl halide, $\text{ArCH}_2\text{-halogen}$, with an alkylamine, RNH_2 . Illustrations of these two procedures for preparing the intermediate N-(lower alkyl)-alkylated-benzylamines are given, respectively, as follows: the preparation of N-isopropyl-2,4,6-trimethylbenzylamine by treating 2,4,6-trimethylbenzaldehyde with isopropylamine to form the anil which is then catalytically reduced; the formation of N-isopropyl-4-n-butylbenzylamine by treating 4-n-butylbenzyl chloride with isopropylamine.

My invention is further illustrated by the following examples without however being limited thereto.

EXAMPLE 1

A. N-(lower alkyl)-alkylated-benzylamines from alkylated-benzaldehydes

This method of preparing the intermediate N-(lower alkyl)-alkylated-benzylamines is illustrated by the following preparation of N-isopropyl-4-isopropylbenzylamine: A mixture of 22.2 g. of 4-isopropylbenzaldehyde and 9 g. of isopropylamine was warmed on a steam bath for thirty minutes and then dissolved in 125 ml. of ethanol and reduced catalytically with palladium-on-charcoal catalyst. After the catalyst had been filtered off, the filtrate was fractionally distilled, yielding 16.5 g. of N-isopropyl-4-isopropylbenzylamine, B. P. $82-85^\circ\text{C}$. at 0.65 mm., n_D^{25} 1.4968.

Analysis.—Calcd. for $\text{C}_{13}\text{H}_{21}\text{N}$: N, 7.34. Found: N, 6.96.

Other N-(lower alkyl)-alkylbenzylamines prepared by the above procedure, using the appropriate alkylbenzaldehyde and lower alkylamine, are given in the following paragraphs:

N-isopropyl-4-methylbenzylamine (19 g.), B. P. $55-57^\circ\text{C}$. at 0.5 mm., n_D^{25} 1.4990, prepared from 24 g. of 4-methylbenzaldehyde and 12 g. of isopropylamine. *Analysis*.—Calcd. for $\text{C}_{11}\text{H}_{17}\text{N}$: N, 8.59. Found: N, 8.52.

N-methyl-4-methylbenzylamine (9.2 g.), B. P. $92-94^\circ\text{C}$. at 15 mm., n_D^{25} 1.5162, prepared from 18 g. of 4-methylbenzaldehyde and 125 ml. of 20% methanolic methylamine (0.7 mole). *Analysis*.—Calcd. for $\text{C}_9\text{H}_{13}\text{N}$: N, 10.36. Found: N, 10.21.

N-methyl-3-methylbenzylamine (14.8 g.), B. P. $90-92^\circ\text{C}$. at 15 mm., n_D^{25} 1.5170, prepared from 18 g. of 3-methylbenzaldehyde and 125 ml. of 20% methanolic methylamine (0.7 mole). *Analysis*.—Calcd. for $\text{C}_9\text{H}_{13}\text{N}$: N, 10.36. Found: N, 10.22.

N-methyl-4-isopropylbenzylamine (35 g.) B. P. $102-107^\circ\text{C}$. at 15 mm., prepared from 65 g. of 4-isopropylbenzaldehyde and 155 ml. of 26.8% methanolic methylamine. *Analysis*.—Calcd. for $\text{C}_{11}\text{H}_{17}\text{N}$: N, 8.60. Found: N, 8.42.

Other N-(lower alkyl)-alkylated-benzylamines can be prepared according to the procedure given above using the appropriate alkylated-benzaldehyde and lower alkylamine; such compounds include N-isopropyl-3,4-diisopropylbenzylamine, N-methyl-4-n-hexylbenzylamine, N-isobutyl-4-isobutylbenzylamine, N-(2-methylbutyl)-2,4,6-trimethylbenzylamine, N-n-hexyl-3,4-diethylbenzylamine, and the like.

B. N-(lower alkyl)-N-(alkylated-benzyl) dihaloacetamides

The preparation of these compounds using a dihaloacetyl halide is illustrated by the following preparation of N-isopropyl - N - (4-isopropylbenzyl)dichloroacetamide: 12.5 g. of dichloroacetyl chloride was added dropwise with stirring at 0°C . to a mixture of 16 g. of N-isopropyl-4-isopropylbenzylamine, 150 ml. of ethylene dichloride and 84 ml. of 1 N sodium hydroxide solution.

The mixture was allowed to warm up to room temperature and stirring was continued for one hour. The organic layer was separated, washed with 1 N hydrochloric acid, then water, and dried. The ethylene dichloride was removed by distillation and the product, N-isopropyl-N-(4-isopropylbenzyl)dichloroacetamide, was obtained by distillation in vacuo, B. P. $125-130^\circ\text{C}$. at 0.05 mm.

Analysis.—Calcd. for $\text{C}_{15}\text{H}_{21}\text{Cl}_2\text{NO}$: C, 59.61; H, 7.00; Cl, 23.50.

Found: C, 59.70; H, 7.12; Cl, 23.53.

When the above procedure is followed by using diiodoacetyl iodide, dibromoacetyl bromide, difluoroacetyl fluoride or bromochloroacetyl chloride in place of dichloroacetyl chloride, the following respective compounds result: N-isopropyl-N-(4-isopropylbenzyl)diiodoacetamide, N-isopropyl-N-(4-isopropylbenzyl)dibromoacetamide, N-isopropyl-N-(4-isopropylbenzyl)difluoroacetamide or N-isopropyl-N-(4-isopropylbenzyl)bromochloroacetamide.

Other N-(lower alkyl) - N - (alkylbenzyl)dichloroacetamides can be prepared according to the procedure given above using the appropriate reactants; such compounds include N-isopropyl-N-(3,4-diisopropylbenzyl)dichloroacetamide, N-methyl - N - (4-n-hexylbenzyl)dichloroacetamide, N-isobutyl - N - (4-isobutylbenzyl)dichloroacetamide, N-(2-methylbutyl)-N-(2,4,6-trimethylbenzyl)dichloroacetamide, N-(n-hexyl)-N-(3,4-diethylbenzyl)dichloroacetamide, and the like.

EXAMPLE 2

N-methyl-N-(4-isopropylbenzyl)dichloroacetamide

This compound was prepared by reacting N-methyl-4-isopropylbenzylamine with either (A) dichloroacetyl chloride or (B) methyl dichloroacetate.

A. This preparation was carried out following the procedure described in Example 1B using 16.3 g. of N-methyl-4-isopropylbenzylamine, 100 ml. of ethylene dichloride, 100 ml. of 1N sodium hydroxide solution and 16.2 g. of dichloroacetyl chloride. The resulting product, N-methyl-N-(4-isopropylbenzyl)dichloroacetamide, melted at $49.1-50.8^\circ\text{C}$. (corr.) when recrystallized from n-hexane.

Analysis.—Calcd. for $\text{C}_{13}\text{H}_{17}\text{Cl}_2\text{NO}$: C, 56.94; H, 6.25; Cl, 25.86. Found: C, 57.13; H, 5.68; Cl, 25.30.

B. A mixture of 8.15 g. of N-methyl-4-isopropylbenzylamine and 7.3 g. of methyl dichloroacetate was allowed to stand at room temperature for twenty-four hours. The reaction mixture was then dissolved in benzene and washed several times with 1N hydrochloric acid, water, 2.5% aqueous sodium hydroxide solution and, finally, water. The benzene solution was dried over anhydrous calcium sulfate and the benzene was removed by distillation to give 9.5 g. of N-methyl-N-(4-isopropylbenzyl)dichloroacetamide. This product is identical with the compound obtained following the procedure of Example 2A, as determined by a mixed melting point.

EXAMPLE 3

N-methyl-N-(4-methylbenzyl)dichloroacetamide

This preparation was carried out following the procedure described in Example 2B using 8.5 g. of N-methyl-4-methylbenzylamine and 9 g. of methyl dichloroacetate and using a reaction period of three days. The product, N-methyl-N-(4-methylbenzyl)dichloroacetamide, melted at $84.1-85.5^\circ\text{C}$. (corr.) when recrystallized from n-hexane.

Analysis.—Calcd. for $\text{C}_{11}\text{H}_{13}\text{Cl}_2\text{NO}$: C, 53.69; H, 5.32; Cl, 28.21. Found: C, 53.68; H, 5.25; Cl, 29.26.

EXAMPLE 4

N-methyl-N-(3-methylbenzyl)dichloroacetamide

This preparation was carried out following the procedure described in Example 2B using 12 g. of N-methyl-3-methylbenzylamine and 13 g. of methyl dichloroacetate allowing the reactants to stand at room temperature for

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three days. The product, N-methyl-N-(3-methylbenzyl)-dichloroacetamide, was obtained by distillation *in vacuo*, B. P. 128° C. at 0.4 mm., n_D^{25} 1.5514. On standing this product solidified, M. P. 37.0–40.2° C. (corr.) when recrystallized from n-hexane.

Analysis.—Calcd. for $C_{11}H_{13}Cl_2NO$: C, 53.69; H, 5.32; Cl, 28.81. Found: C, 53.38; H, 5.56; Cl, 29.18.

EXAMPLE 5

N-isopropyl-n-(4-methylbenzyl)dichloroacetamide

This preparation was carried out following the procedure described in Example 1B using 8.1 g. of N-isopropyl-4-methylbenzylamine, 100 ml. of ethylene dichloride, 50 ml. of 1N sodium hydroxide solution and 7.3 g. of dichloroacetyl chloride in 20 ml. of ethylene dichloride. There was thus obtained the product, N-isopropyl-N-(4-methylbenzyl)dichloroacetamide, B. P. 120° C. at 0.05 mm.

Analysis.—Calcd. for $C_{13}H_{17}Cl_2NO$: C, 56.90; H, 6.26; Cl, 25.90. Found: C, 57.35; H, 6.26; Cl, 25.99.

The N-(lower alkyl)-N-(alkylated-benzyl)dihaloacetamides of the foregoing examples when administered orally in aqueous suspension to hamsters infected with *Endamoeba criceti* were found to completely clear the animals of the infection at drug levels below 100 mg. per kg. of body weight. Some of the compounds, for instance, N-methyl-N-(4-isopropylbenzyl)dichloroacetamide and N-isopropyl-N-(4-isopropylbenzyl)dichloroacetamide have ED_{50} values in the range between 16 and 20 mg. per kg. of body weight, ED_{50} meaning the effective dose necessary to clear 50% of the hamsters of the amebic infection. Coupled with this high activity, my compounds have very low toxicities. For example, N-methyl-N-(4-isopropylbenzyl)dichloroacetamide has an acute oral ALD_{50} (mice; 7-day) of 5335 mg. per kg.

For purposes of comparison, the amebicidal activities (in terms of ED_{50} values determined as outlined above) of available drugs of commerce are given as follows: chiniofon, 286 mg. per kg.; diiodohydroxyquinoline, 235 mg. per kg.; carbasone, 45 mg. per kg.; chlortetracycline, 22.9 mg. per kg.; and oxytetracycline, 8.75 mg. per kg.

For practical medication, my new N-alkyl-N-(alkylated-benzyl)dihaloacetamides are best administered orally in solid form with the aid of a carrier. Thus, the compounds can be formulated in unit dosage form as tablets in combination with an adjuvant such as one or more of the following: calcium carbonate, starch, gelatin, talc, magnesium stearate, acacia, and the like, or alternatively, they can be employed in capsule form either alone or admixed with an adjuvant. My compounds can also be advantageously combined with other amebicides such as chloroquine when desired. Illustrative of a tablet formulation of my compounds is one weighing 660 mg. and containing 500 mg. of N-isopropyl-N-(4-isopropylbenzyl)dichloroacetamide, 25 mg. of calcium carbonate as a diluent, 90 mg. of starch as a disintegrator, 30 mg. of gelatin as a binder and 15 mg. of talcum as a lubricant. Illustrative of a capsule formulation is one containing 500 mg. of N-methyl-N-(4-isopropylbenzyl)dichloroacetamide, 40 mg. of starch and 10 mg. of talcum. Other tablet and capsule formations can be made varying the quanti-

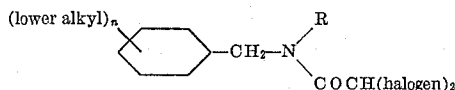
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ties of adjuvants or using other N-(lower alkyl)-N-(substituted-benzyl)dihaloacetamides as active amebicidal ingredients.

This application is a continuation-in-part of my co-pending application Serial No. 352,058, filed April 29, 1953, now abandoned.

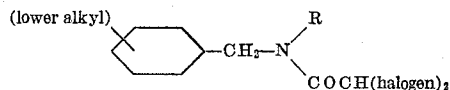
I claim:

1. An N-alkyl-N-(alkylbenzyl)dihaloacetamide having the formula



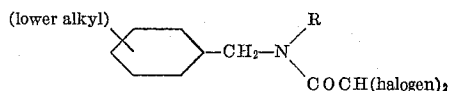
where n is an integer from 1 to 3 and R is a lower alkyl radical.

2. An N-alkyl-N-(monoalkylbenzyl)dihaloacetamide having the formula



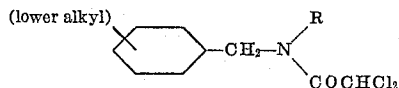
where R is a lower alkyl radical.

3. An N-alkyl-N-(monoalkylbenzyl)dihaloacetamide having the formula



where the lower alkyl substituent of the phenyl nucleus has from three to six carbon atoms, and R is a lower alkyl radical.

4. An N-alkyl-N-(monoalkylbenzyl)dichloroacetamide having the formula



where the lower alkyl substituent of the phenyl nucleus has from three to six carbon atoms, and R is a lower alkyl radical.

5. N-methyl-N-(4-isopropylbenzyl)dichloroacetamide.

6. N-isopropyl-N-(4-isopropylbenzyl)dichloroacetamide.

7. N-methyl-N-(4-methylbenzyl)dichloroacetamide.

8. N-methyl-N-(3-methylbenzyl)dichloroacetamide.

9. N-isopropyl-N-(4-methylbenzyl)dichloroacetamide.

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60	Rebstock et al.; "J. Am. Chem. Soc.," vol. 73 (1951), page 3670.

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 2,862,967

December 2, 1958

Alexander R. Surrey

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 1, line 28, and column 2, line 48, for "iodine", in each occurrence, read -- iodide --; column 2, line 25, for "l-butyl" read -- 2-butyl --; column 4, line 11, for "followed by" read -- followed but --; line 15, for "diidoacetamide" read -- diiodoacetamide --; line 67, for "Cl,28.21" read -- Cl,28.81 --; column 5, line 42, for "8.75 mg. per kg." read -- 18.75 mg. per kg.--; line 62, for "formations" read -- formulations --.

Signed and sealed this 21st day of April 1959.

(SEAL)

Attest:

KARL H. AXLINE
Attesting Officer

ROBERT C. WATSON
Commissioner of Patents