968,254

PATENT SPECIFICATION

NO DRAWINGS

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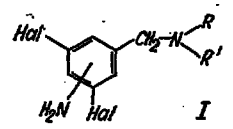
COMPLETE SPECIFICATION

New Dihalogeno-Amine-Benzylamines

We, Dr. KARL THOMAE G.M.B.H., a German Body Corporate of Biberach an der Riss, Germany, 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 compounds having valuable pharmacological properties. In particular, the compounds of the invention have, in general, good secretolytic activity and low toxicity. The compounds of the invention also have in general cough-relieving, monoamine oxidase-inhibiting and anti-pyretic action.

According to the present invention, there are provided new dihalogeno-amino-benzylamines of the general formula



I

in which R^1 represents a lower acyclic aliphatic hydrocarbon group containing from 1 to 5 carbon atoms, or a cycloalkyl, aralkyl or aryl group; and

R represents hydrogen or any of the groups which may be represented by R^1;

or R and R^1, together with the adjacent nitrogen atom, represent a pyrrolidinyl, piperidino or camphidinyl (i.e. $3^1,5^1$-ethylene-$3^1,4^1,4^1$-trimethyl-piperidino) group either unsubstituted or substituted by a lower alkyl group containing from 1 to 5 carbon atoms; and Hal represents chlorine or bromine; and non-toxic acid addition salts thereof. R and R^1 may be the same or different, and where they represent aliphatic hydrocarbon groups, they may represent such groups which are either straight- or branch-chained, saturated or unsaturated.

In one type of preferred compound, R and R^1 represent lower alkyl groups containing 1 to 5 carbon atoms or alkenyl groups containing 3 to 5 carbon atoms, for example methyl, ethyl, isobutyl or allyl groups. Where R and/or R^1 represent cycloalkyl groups, they preferably represent cyclohexyl groups; where they represent aralkyl groups they preferably represent benzyl groups; and where they represent aryl groups, they preferably represent phenyl groups. Preferred non-toxic acid addition salts may be formed from hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, lactic acid, citric acid, tartaric acid or maleic acid.

Particularly preferred compounds by virtue of their valuable pharmacological properties are as follows:—

N - [2 - Amino - 3,5 - dibromo - benzyl] - dibenzylamine,

N - [2 - Amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine,

N - [2 - Amino - 3,5 - dibromo - benzyl] - dicyclohexylamine,

N - [2 - Amino - 3,5 - dibromo - benzyl] - dimethylamine,

N - [2 - Amino - 3,5 - dichloro - benzyl] - N - methyl - cyclohexylamine,

N - [4 - Amino - 3,5 - dibromo - benzyl] - diethylamine,

N - [4 - Amino - 3,5 - dibromo - benzyl] - N - methyl - benzylamine,

N - [4 - Amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine,

N - [4 - Amino - 3,5 - dibromo - benzyl] - N - ethyl - phenylamine,

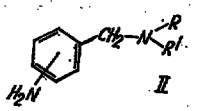
N - [4 - Amino - 3,5 - dibromo - benzyl] - diallylamine,

N - [4 - Amino - 3,5 - dibromo - benzyl] - dicyclopentylamine,

[*Price 4s. 6d.*]

N - [4 - Amino - 3,5 - dibromo - benzyl] - cyclohexylamine,
N - [4 - Amino - 3,5 - dibromo - benzyl] - isobutylamine and
N - [2 - Amino - 3,5 - dibromo - benzyl] - cyclohexylamine.

According to one feature of the invention, there is provided a process for the preparation of the compounds of the invention which comprises reacting an amino-benzylamine of the formula

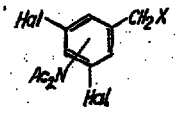


II

in which R and R^1 are as hereinbefore defined and the amino group is in the 2- or 4- position, with at least a molar excess of a chlorinating or brominating agent in an inert organic solvent whereby the 3,5-dihalogeno derivative is produced in the form of its hydrochloride or hydrobromide salt and then, if desired, converting the said hydrochloride or hydrobromide salt to the free base or other non-toxic acid addition salt.

The chlorinating or brominating agent is preferably chlorine or bromine respectively, and the reaction is advantageously carried out at ambient temperature. Preferred solvents are halogeno-hydrocarbons (e.g. chloroform) and glacial acetic acid. In order to obtain the 3,5 dihalogeno derivative, it will be understood that a quantity of chlorinating or brominating agent greatly in excess of a molar excess should not be used as such may give rise to a tri-halogeno derivative.

According to a further feature of the invention, there is provided a process for the preparation of the compounds of the invention which comprises reacting a dihalogeno - diacylamino - benzyl halide of the formula



III

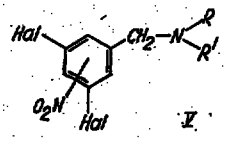
in which Hal is as hereinbefore defined, X represents chlorine or bromine and Ac represents an acyl group, with an amine of the formula

IV

in which R and R^1 are as hereinbefore defined, in the presence of a hydrogen halide-binding agent, de-acylating the compound so formed and, if desired, converting the product to a non-toxic acid addition salt.

The hydrogen halide-binding agent is preferably an inorganic base or a tertiary organic base, and may be provided by using at least a molar excess of the amine of formula IV. The reaction is conveniently carried out in the presence of an organic solvent such as ethanol, benzene or toluene with heating preferably at the reflux temperature of the reaction mixture. Also, if an excess of amine is used in the process, this may serve as a solvent for the reaction. The de-acylation step may be effected by methods known per se e.g. by heating with a dilute mineral acid or a dilute inorganic base.

According to a still further feature of the invention, there is provided a process for the preparation of the compounds of the invention which comprises reducing a dihalogeno-nitro-benzylamine of the formula



V

in which Hal, R and R^1 are as hereinbefore defined, and, if desired, converting the compound so formed to a non-toxic acid addition salt. The reduction may be carried out by one of the well-known methods for reducing nitro groups. One such method comprises catalytic reduction with hydrogen, the catalyst being a noble metal catalyst such as platinum or palladium. This reaction is conveniently carried out in an inert organic solvent such as methanol, ethanol, tetrahydrofuran or dioxan. Alternative reducing agents are hydrazine hydrate/Raney nickel (the reaction preferably being carried out in an inert organic solvent such as methanol) and nascent hydrogen obtained from the reaction of iron, zinc or tin with a mineral acid.

It will be understood that the compounds of the invention in which R represents a lower ~~acylic~~ acyclic aliphatic hydrocarbon group containing from 1 to 5 carbon atoms or a cycloalkyl or aralkyl group can be prepared by a process which comprises first preparing the corresponding compound in which R represents hydrogen in the form of its free base by a process as hereinbefore defined, replacing the hydrogen atom of the free secondary amino group of the compound thus formed to produce a compound in which R represents a lower acyclic aliphatic hydrocarbon group contain-

ing from 1 to 5 carbon atoms, or a cycloalkyl or aralkyl group, and then, if desired, converting the product to a non-toxic acid addition salt. The alkylation, etc. can be effected by methods known per se e.g. by reaction with lower acyclic aliphatic hydrocarbon, cycloalkyl halides or sulphonic acid esters. Where R represents a methyl group, the alkylation can also be carried out using formic acid and formaldehyde.

The starting materials for the processes described above are either known compounds or compounds which can be prepared by known methods. Thus the amino-benzylamines of formula II can be prepared from the known nitro-benzyl halides by reaction with the corresponding secondary amine and subsequent reduction of the nitro-group. The dihalogeno-diacylamino-benzyl bromides of formula III can be prepared from the known 2- or 4-diacylamino-3,5-dihalogeno-~~toluene~~- by reacting these compounds with N-bromo-succinimide. Furthermore, the dihalogeno-nitro-benzylamines of formula V can be prepared by bromination of the known 2- or 4-nitro - 3,5 - dihalogeno - toluenes with N - bromo - succinimide followed by reaction of the compound so formed with the appropriate secondary amine.

The non-toxic acid addition salts are preferably prepared by reacting an alcoholic solution of the appropriate acid with a substantially equimolar proportion of the free base. These salts are in general water-soluble and the salts obtained by the above process i.e. those containing equimolar proportions of the free base and the acid, are the preferred form of salts which are used.

As stated above, the compounds of the invention have a good secretolytic action with low toxicity. These properties are illustrated by the following pharmacological experiments carried out on the substance N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine hydrochloride, hereinafter referred to as substance A.

1. *Expectorant action*

By the term " expectorants " there is understood substances the pharmacological action of which is as secretomotorics and secretolytics. Substances belonging to this group include emetine, potassium iodide, ammonium chloride, guaiacol preparations and the active ingredient of Adhatoda Vasika Nees i.e. vasicine.

The expectorant action of substance A was examined on narcotised rabbits using the method of Perry and Boyd. The results, as given below, are compared with those obtained using emetine:

Substance	Dose mg/kg	Maximum increase of secretion in %	Planimetric evaluation over 5 hours in %
Substance	0.5	69	63
A	1	125	89
	2	88	69
Emetine	0.5	46	34
	1	67	50
	2	35	20
Controls		28	12

After the administration of 0.5 mg/kg or higher doses of substance A, an increased bronchial secretion sets in which is stronger than that obtained using similar doses of emetine.

2. *Atropinised rabbits*

A pre-treatment with 1 mg/kg of Atropin. sulphur i.v. in experiments with 2 mg/kg of substance A and with emetine, had no influence on the increase of the bronchial secretion occurring after administration of these drugs.

3. *Emetic action on awake cats and dogs*

a) *cats*

With three cats having an average weight of 2.5 kg, an intraperitoneal injection of 40 mg/kg of emetine caused, in one case, a vigorous defecation and in the other two cases vomiting, as well as an additional laxation. After the same quantity of substance A had been administered, two out of three animals became restless. Vomiting or diarrhoea never occurred.

b) *dogs*

With dogs having an average weight of 8 kg, the action of 40 mg/kg of substance A administered orally, induced choking and slight vomiting in all the animals.

4. *Gastric juice and HCl-production on rats*

No noticeable influence on the examined criteria existed and no macroscopic changes could be found on the mucous membrane of the abdomen.

5. *Influence on the intestinal motility of mice*

8.32 mg/kg of substance A administered orally using the method of Strickney and coworkers, as modified by Bryant, Felton and Kranz, had no influence upon the speed of motion of the intestine content. Emetine, however, effected an acceleration by 11 and 26% when administered at dosages of 16 mg/kg and 32 mg/kg respectively.

6. *Influence on blood pressure, respiration and heart frequency of cats*

Respiratory inhibition, strong depression of the blood pressure and a decline of frequency with diffuse myocardial damage in the electrocardiogram results from 2.5 mg/kg of emetine administered intraveneously. In contrast, 20 mg of substance A, administered intraveneously causes a stimulation of respiration with a moderate depression of the blood pressure and a small decline of frequency.

7. *Cough-soothing action*

Upon inducing cough reflex according to Domenjer and subsequently intraveneously administering substance A to narcotised cats, the following was observed:

Dose mg/kg	Number of Experiments	Unchanged	Cough reflex markedly weakened	terminated	Duration of action in minutes
1	3	3	—	—	—
2.5	3	1	2	—	60, 50
5	3	—	1	—	50
		—	—	2	76, 53
10	1	—	—	1	63

Thus, with a higher dosage, substance A has a cough-soothing action.

8. *Bronchiolytic action*

The acetyl - choline - bronchiospasm (Konsett-Rössler's method) could not be reduced in guinea pigs by substance A (1-5 mg/kg intraveneously).

9. *Toxicology*

a) *Acute toxicity*

Upon feeding with up to 3 g/kg of substance A, none of the animals under experiment died. This compares with the LD50 for emetine, which is about 242 mg/kg.

b) *Chronic toxicity*

During observations carried out so far, animals treated perorally with 10—20 mg/kg have behaved normally; no toxic consequences which might be associated with the administration of substance A have been observed.

Besides the above pharmacological experimental evidence, the result of clinical testing of substance A provides (a) evidence of a secretomotoric effect (b) evidence of a secretolytic effect and (c) evidence of other effects on the respiration.

On the basis of the pharmacological tests set out above, a suitable dosage of substance A is 1 tablet or 20 drops respectively of the following preparations:—

(a) Tablets containing 4 mg of substance A per tablet with a notch in the centre.

(b) Drop solution containing 4 mg of substance A per 20 drops in a drop bottle.

The invention further provides pharmaceutical compositions comprising as active ingredient one of the compounds of the invention as herein defined in association with a pharmaceutical carrier or excipient. The compositions may be presented in a form suitable for oral, rectal or parenteral administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of capsules, tablets, granules, coated tablets, emulsions, syrups or suspensions, such compositions comprising carriers or excipients conveniently used in the pharmaceutical art. Thus, suitable tabletting excipients include lactose, talc, kaolin, potato and maize starches and magnesium stearate, and a suitable capsule material is gelatine.

For parenteral administration, the carrier or excipient may be a sterile, parenterally acceptable liquid e.g. pyrogen-free water or an aqueous solution of polyvinyl pyrrolidone, or a

parenterally acceptable oil e.g. arachis oil, contained in ampoules.

In compositions for rectal administration, the carrier may comprise a suppository base e.g. cocoa butter or a glyceride.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, and ampoules are examples of preferred dosage unit forms of the compositions of the invention. Each dosage unit may contain 0.5 to 10 mg, preferably 2.0 to 4.0 mg, of the active ingredient.

The following examples illustrate the preparation of dihalogeno-amino-benzylamines according to the invention, and also pharmaceutical compositions containing such compounds as active ingredients:—

EXAMPLE 1

N - [2 - Amino - 3,5 - dibromobenzyl] - diethylamine

A solution of 11.6 g of bromine in 50 cc of chloroform is added dropwise with stirring to a solution of 6.4 g of N - [2 - amino - benzyl] - diethylamine in 50 cc of chloroform. Upon completion of the reaction, the chloroform phase is shaken with 100 cc of 2N caustic soda solution, separated off, dried over sodium sulphate and concentrated to dryness. The hydrochloride of the compound so formed, which is in the form of an oily residue, is prepared by dissolving the compound in 50 cc of ethanol and passing hydrogen chloride into the solution; it has a M.pt. of 214—214.5°C.

EXAMPLE 2

N - [4 - Amino - 3,5 - dibromo - benzyl] - diethylamine

A solution of 39.5 g of bromine in 150 cc of glacial acetic acid is slowly added dropwise with stirring to a solution of 12.6 g of N - [4 - amino - benzyl] - diethylamine in 150 cc of glacial acetic acid. The glacial acetic acid is decanted off from the precipitated hydrobromide, which is then recrystallised from ethanol. M.pt. = 218°C (decomp.).

EXAMPLE 3

N - [2 - Amino - 3,5 - dibromo - benzyl] - diisobutylamine

A solution of 8.5 g of bromine in 30 cc of glacial acetic acid is added dropwise with stirring to a solution of 6.09 g of N - [2 - aminobenzyl] - diisobutyl - amine in 150 cc of glacial acetic acid. The precipitated hydrobromide is separated from the glacial acetic acid by decanting and recrystallised from ethyl acetate. M.pt. = 165—167°C.

EXAMPLE 4

N - [2 - Amino - 3,5 - dibromo - benzyl] - diallylamine

24.7 g of 2 - diacetylamino - 3,5 - dibromo - benzyl bromide are refluxed with 11.8 g of diallylamine in 300 cc of ethanol for 24 hours. After distilling off the alcohol, the residue is dissolved in 1 litre of hot 3N hydrochloric acid and the solution thus obtained is heated for 12 hours under reflux. The reaction product is then made alkaline with 10N caustic soda solution and is extracted three times with 300 cc of chloroform at each extraction. The chloroform phases are combined and dried over sodium sulphate. The chloroform is then evaporated off. The residual base is dissolved in a little ethanol and hydrogen chloride passed through the solution, whereupon the hydrochloride precipitates out. This is separated by filtration with suction and dissolved in about 1 litre of ethyl acetate. Upon concentrating the solution to about 300 cc, the N - [2 - amino - 3,5 - dibromo - benzyl] - diallylamine hydrochloride crystallises out. M.pt. = 109—113°C.

EXAMPLE 5

N - [4 - Amino - 3,5 - dibromo - benzyl] - diallylamine

20.3 g of 4 - diacetylamino - 3,5 - dibromo - benzyl bromide, 6.9 g of diallylamine and 300 cc of anhydrous ethanol are heated for 20 hours under reflux. The ethanol is then removed by distillation and the remaining oily residue is dissolved in 1 litre of hot 3N hydrochloric acid and boiled for 10 hours under reflux. The reaction product is then made alkaline with 10N caustic soda solution and extracted three times with 700 cc of chloroform on each occasion. The chloroform phases are combined, dried over sodium sulphate and concentrated. The partly oily, partly solid residue is dissolved in 100 cc of absolute ethanol and the solution filtered. After concentrating to about 50 cc, hydrogen chloride is passed into the solution. After some time the hydrochloride crystallises out. M.pt. = 191—195°C.

EXAMPLE 6

N - [2 - Amino - 3,5 — dibromo - benzyl] - N - methyl - cyclohexylamine

A solution of 29.3 g of bromine in 50 cc of glacial acetic acid is slowly dropped with stirring into a solution of 15.9 g of N - [2 - amino - benzyl] - N - methyl - cyclohexylamine. The glacial acetic acid is then decanted off and the residual precipitate shaken with 200 cc of 2N caustic soda solution and 600 cc of chloroform until all the solid material is dissolved. The chloroform phase is concentrated to dryness and the residue dissolved in

absolute ethanol. Hydrogen chloride is passed into the solution to precipitate the hydrochloride. M.pt. = 232—235°C (decomp.).

The preparation of further salts of N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl-cyclohexylamine is generally effected by dissolving the free base in absolute alcohol and adding the appropriate acid to the alcoholic solution thus obtained whereupon the corresponding salt crystallises out. With sulphate, however, propanol is preferably used in the place of ethanol, and with nitrate a mixture of butanol and diethyl ether is used.

The following table sets out the melting points of a number of acid addition salts of N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine:—

Salt	Melting Point (°C.)
p-Toluenesulphonate $C_{21}H_{28}Br_2N_2O_3S$	218 — 219° (Decomp.)
Perchlorate $C_{14}H_{21}Br_2ClNO_4$	132.5—134°
Phosphate $C_{14}H_{23}Br_2N_2O_4P$	137 — 138.5°
Bromide $C_{14}H_{21}Br_3N_2$	227.5 — 228° (Decomp.)
Oxalate $C_{16}H_{22}Br_2N_2O_4$	182 — 183°
Chloride $C_{14}H_{21}Br_2ClN_2$	240 — 242° (Decomp.)
Nitrate $C_{14}H_{21}Br_2N_3O_3$	135 — 136°
Sulphate $C_{14}H_{22}Br_2N_2SO_4.C_3H_7OH$	108 — 109°

EXAMPLE 7

N - [4 - Amino - 3,5 - dibromo - benzyl] - N - methyl - benzylamine

A solution of 31.6 g of bromine in 30 cc of glacial acetic acid is added dropwise with stirring to a solution of 18.0 g of N - [4 - amino - benzyl] - N - methyl - benzylamine. The precipitated hydrobromide is separated by decanting from the glacial acetic acid and recrystallised from ethanol. M.pt. = 202—206°C.

EXAMPLE 8

N - [2 - Amino - 3,5 - dibromo - benzyl] - pyrrolidine

17.0 g of N - [2 - aminobenzyl] - pyrrolidine are dissolved in 500 cc of chloroform and at room temperature a solution of 34.0 g bromine, which corresponds to 2.2 mols of bromine per mol of N - [2 - aminobenzyl] - pyrrolidine, in 500 cc of chloroform is added during 90 minutes. The brominated product initially separates off as an oil, and is allowed to stand for about ½ hour with frequent stirring and scratching with a glass rod, whereupon crystallisation gradually takes place. The yellow-coloured crystals are filtered with suction and are washed with a little chloroform. The reaction mixture is then dissolved in hot water, the solution made alkaline to pH 11 with concentrated ammonia and the base extracted four times using 250 cc of chloroform at each extraction. The combined chloroform solutions are dried with soda, filtered, and the chloroform distilled off *in vacuo*. The residue is a brownish oil which, for the preparation

of the hydrochloride, is heated in 40 cc absolute ethanol to 40—50°C; 25 cc of 10% hydrochloric acid are added to the clear solution. After prolonged standing at 0°C, the hydrochloride crystallises out as colourless fine crystals which are filtered with suction and washed with diethyl ether. M.pt. = 219—220°C.

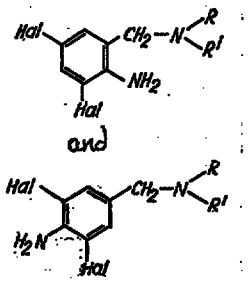
EXAMPLE 9

N - [2 - Amino - 3,5 - dibromo - benzyl] - piperidine

A solution of 16.3 g of bromine in 100 cc of chloroform is added dropwise with stirring to a solution of 9.67 g of N - [2 - amino - benzyl] - piperidine in 150 cc chloroform. The reaction mixture is shaken with 200 cc of 2N caustic soda solution, the chloroform phase is separated off and the aqueous phase again extracted with chloroform. The combined chloroform phases are dried over sodium sulphate and evaporated. The residue is dissolved in about 100 cc of ethanol, 15 cc of concentrated hydrochloric acid are added and the solution allowed to stand whereupon crystallisation takes place.

The N - [2 - amino - 3,5 - dibromo - benzyl] - piperidine hydrochloride crystallises as small leaves, and has a M.pt. = 244—245°C.

By methods similar to those described in the above examples, various 2 - amino- and 4 - amino - dihalogeno - benzylamines, having the general formulae

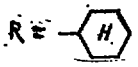
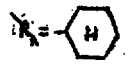


respectively, have been prepared. The following tables set out the melting points of the compounds, and the last column indicates the method used for the preparation of the compounds. Thus, method (a) is that as claimed in claim 23, method (b) is that as claimed in claim 26 and method (c) is that as claimed in claim 33.

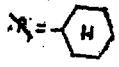
2-AMINO COMPOUNDS

Example No.		Melting point	Process used for preparation
10	Hal = Br R = CH_3 R^1 = CH_3	as Hydrochloride 235 — 237°	a
11	Hal = Br R = $-CH_2-CH_2-CH_3$ R^1 = $-CH_2-CH_2-CH_3$	as Hydrochloride 153 — 156°	a
12	Hal = Br R = $-CH(CH_3)_2$ R^1 = $-CH(CH_3)_2$	as Hydrochloride 159 — 160°	a
13	Hal = Br R = $-C_5H_{11}$ R^1 = $-C_5H_{11}$	as Hydrobromide 111 — 113°	a

2-AMINO COMPOUNDS

Example No.		Melting point	Process used for preparation
14	Hal = Br  	as Hydrobromide 308 — 312° (Decomp.)	b
15	Hal = Br R = —CH_2—CH_2—CH_2 R^1 = —CH_2—CH(—CH_3)—	as Hydrochloride 209 — 215°	a
16	Hal = Br R = —CH_3 R^1 = —CH_2—C_6H_5	as Hydrobromide 218.5 — 219° (Decomp.)	a
17	Hal = Br R = —C_2H_5 R^1 = —CH_2—C_6H_5	as Hydrobromide 179 — 182°	a
18	Hal = Br R = —CH_2—C_6H_5 R^1 = —CH_2—C_6H_5	as Hydrobromide 192 — 196°	a
19	Hal = Br R = —C_2H_5 R^1 = —C_6H_5	as Hydrochloride 123 — 130°	b

4-AMINO COMPOUNDS

Example No.		Melting point	Process used for preparation
20	Hal = Br R = $-CH_3$ R^1 = $-CH_3$	as Hydrochloride 252 — 256°	a
21	Hal = Br R = $-CH_2-CH_2-CH_3$ R^1 = $-CH_2-CH_2-CH_3$	as Hydrobromide 227° (Decomp.)	a
22	Hal = Br R = $-CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{CH}}}}-CH_3$ R^1 = $-CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{CH}}}}-CH_3$	as Hydrochloride 141 — 144°	a
23	Hal = Br R = $-CH_3$ R^1 = 	as Hydrochloride 232 — 235°	a
24	Hal = Br R = $-CH_2-CH_2$ R^1 = $-CH_2-CH_2$	as Hydrochloride 200 — 205°	b
25	Hal = Br R = $-CH_2-CH_2$ R^1 = $-CH_2-CH_2$	as Hydrobromide 224 — 226° (Decomp.)	a
26	Hal = Br R = $-C_2H_5$ R^1 = $-CH_2-C_6H_5$	as Hydrobromide 198 — 203°	a

4-AMINO COMPOUNDS

Example No.		Melting point	Process used for preparation
27	Hal = Br R = $-CH_2-C_6H_5$ R^1 = $-CH_2-C_6H_5$	as Hydrochloride 233 — 235° (Decomp.)	a
28	Hal = Br R = $-C_2H_5$ R^1 = $-C_6H_5$	as Hydrochloride 211 — 215°	b

EXAMPLE 29

N - [2 - Amino - 3,5 - dichloro - benzyl] - piperidine

(a) 3,5 - Dichloro - 2 - diacetylamino - toluene

19 g of 3,5 - dichloro - 2 - acetamino - toluene [Ad. CLAUS, E. STAPELBERG, A. *274*, 285-304 (1893)] are heated with 250 cc of acetic anhydride for 2 hours under reflux. The excess acetic anhydride is then distilled off and the solid residue recrystallised from ethanol. M.pt. = 84—86°.

(b) 3,5 - Dichloro - 2 - diacetylamino - benzyl bromide

15.1 g of 3,5 - dichloro - 2 - diacetylamino - toluene, 11.0 g of N - bromo - succinimide and 0.5 g of dibenzoyl peroxide are heated in 250 cc of carbon tetrachloride under reflux until the undissolved component, which remains at first at the bottom of the flask, rises to the surface (after about 10 hours). After cooling and filtering the solution, the filtrate is concentrated to dryness. The solid residue is recrystallised from ethanol. M.pt. = 122—125°C.

(c) N - [2 - Amino - 3,5 - dichloro - benzyl] - piperidine

9.5 g of 3,5 - dichloro - 2 - diacetlyamino - benzyl bromide and 5 g of piperidine are heated for 18 hours in 250 cc of ethanol under reflux. After distilling off the solvent, the reaction product is dissolved in 1 litre of 3N hydrochloric acid and again heated for 18 hours under reflux. The solution is then made alkaline to pH 10 with 10N caustic soda solution and extracted exhaustively with chloroform. The combined chloroform phases are dried over sodium sulphate and concentrated to dryness. The oily residue is dissolved in 50 cc of absolute ethanol. Hydrogen chloride is then passed into the solution, whereupon the hydrochloride crystallises out. After recrystallising from ethanol, the melting point is 234—235° (decomp.).

EXAMPLE 30

N - [3,5 - Dichloro - 4 - amino - benzyl] - N - methyl - cyclohexylamine

(a) 3,5 - Dichloro - 4 - diacetylamino - toluene

10 g of 3,5 - dichloro - 4 - acetamino - toluene [E. Lellmann, C. Klotz, A. *231*, 308—326 (1886)] are boiled for 2 hours with acetic anhydride under reflux. The excess acetic anhydride is distilled off and the residue recrystallised from petroleum/ether. M.pt. = 59—60°.

(b) 3,5 - Dichloro - 4 - diacetylamino - benzyl bromide

30 g of 3,5 - dichloro - 4 - diacetylamino - toluene, 21 g of N - bromo - succinimide and 3 g of dibenzoyl peroxide are heated in 450 cc of carbon tetrachloride (dried over P_2O_5) under reflux until the undissolved component which at first remains at the bottom of the flask, rises to the surface of the solvent (after about 8 hours). After cooling, the solution is filtered and the filtrate concentrated to dryness. The oily residue is recrystallised from ethanol. M.pt. = 106—123°.

(c) N - [3,5 - Dichloro - 4 - amino - benzyl] - N - methyl - cyclohexylamine

13.5 g of 3,5 - dichloro - 4 - diacetylamino - benzyl bromide and 9 g of N - methyl - cyclohexylamine are heated for 6 hours in 250 cc of absolute ethanol under reflux. The solvent is distilled off and the oily residue boiled with 3N hydrochloric acid for 16 hours. The solution is then made alkaline to pH 10 with about 10N caustic soda solution. The oil thus precipitated crystallises upon standing. The crystallisate is then filtered with suction and recrystallised from ethanol. M.pt. = 62—64°.

The following compounds have also been prepared by methods similar to those described above:—

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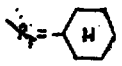
2-Amino compounds

Example 31

Hal = Cl	Melting point as Hydrochloride	Prepared analogously to Example 29
R = CH_3	224—225° (Decomp.)	

R'



Example 32

Hal = Cl	Melting point as Hydrochloride 142—148°	Prepared analogously to Example 29
R = $-CH_2-CH(CH_3)-CH_3$		
R^1 = $-CH_2-CH(CH_3)-CH_3$		

4-Amino compounds

Example 33

Hal = Cl	Melting point as sulphate 132—134°	Prepared analogously to Example 30
R = $-C_2H_5$		
R^1 = $-C_2H_5$		

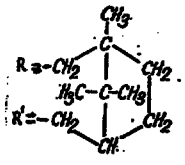
Example 34

Hal = Cl	Melting point as Hydrochloride 237.5—238°	Prepared analogously to Example 30
R = benzyl		
R^1 = benzyl		

Preparation of a compound containing the camphidinyl group

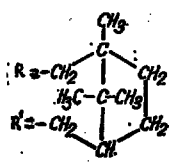
Example 35

2-Amino compound

Hal = Br 	Melting point as 109—111°	Prepared according to the process of claim 23

Example 36

4-Amino compound

Hal = Br 	Melting point as Hydrochloride 238—241° (Decomp.)	Prepared according to the process of claim 23

EXAMPLE 37

N - [2 - Amino - 3,5 - dibromo - benzyl]-isobutylamine

(a) N - [2 - Nitro - benzylidene] - isobutylamine

An ethanolic solution of 1.51 g of 2 - nitro - benzaldehyde and 0.73 g of isobutylamine is heated for 5 hours under reflux. When the reaction is complete, the solvent is distilled off, leaving an oily residue which is used as described in step (b) below without any further purification.

(b) N - [2 - Amino - benzyl] - isobutylamine

2 g of N - [2 - nitro - benzylidene] - isobutylamine (from a) are dissolved in 30 cc of freshly distilled methanol, the solution placed into a shaking flask and catalytically hydrogenated with Pt/H_2. The substance absorbs 4 moles of hydrogen. When the hydrogenation is complete the catalyst is filtered off and the solvent then removed by distillation. 1.7 g of N - [2 - amino - benzyl] - isobutylamine remain as residue.

(c) N - [2 - Amino - 3,5 - dibromo - benzyl] - isobutylamine

1.7 g of N - [2 - amino - benzyl] - isobutylamine are dissolved in 40 cc of glacial acetic acid and 1.64 g of sodium acetate are added to the solution. A solution of 3.2 g of bromine in 10 cc of glacial acetic acid is slowly added dropwise with stirring at room temperature. When the reaction is complete, the glacial acetic acid is distilled off, and the residue is shaken with 60 cc of chloroform and 60 cc of 2N caustic soda solution. The aqueous phase is then separated off and is twice more extracted with chloroform using 60 cc of chloroform at each extraction. The chloroform phases are then combined, dried over sodium sulphate, filtered and the solvent distilled off. 2.56 g of N - [2 - amino - 3,5 - dibromo - benzyl] - isobutylamine remain in the form of a viscous brown oil. In order to prepare the hydrochloride, the product is dissolved in 15 cc of absolute ethanol and the solution is then saturated with hydrogen chloride. The hydrochloride precipitates out and is separated by filtration with suction. After washing with ethyl acetate the hydrochloride is dried and again recrystallised from 25 cc of absolute ethanol. The hydrochloride of N - [2 - amino - 3,5 - dibromo - benzyl] - isobutylamine of m.pt. = 211—213° (decomp.) is thus obtained.

EXAMPLE 38

N - [3,5 - dibromo - 4 - amino - benzyl] - cyclohexylamine

(a) N - [4 - Amino - benzyl] - cyclohexylamine

2.38 g of N - [4 - nitro - benzylidene] - cyclohexylamine (F. G. Baddar, J. Chem.Soc. *1950*, 136—139) are dissolved in 60 cc of freshly dissolved methanol, the solution placed into a shaking flask and catalytically hydrogenated with Pt/H_2. The substance absorbs 4 moles of hydrogen. When the hydrogenation is complete the catalyst is removed by filtration and the solvent by distillation. The residue is an oil which is used in step (b) without further purification.

(b) N - [3,5 - dibromo - 4 - amino - benzyl] - cyclohexylamine

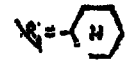
2.19 g of N - [4 - amino - benzyl] - cyclohexylamine are dissolved in 50 cc of glacial acetic acid and 1.85 g of anhydrous sodium acetate is added to the solution. A solution of 3.6 g of bromine in 15 cc of glacial acetic acid is slowly added dropwise with thorough stirring at room temperature. When the reaction is complete, the glacial acetic acid is removed by distillation. 150 cc of chloroform and 150 cc of 2N caustic soda solution are then added to the light-brown residue and the mixture is well shaken. The aqueous phase is separated and is twice more extracted with 150 cc of chloroform at each extraction. The chloroform phases are combined, dried over sodium sulphate, filtered and the solvent distilled off. The residue is 2.92 g of N - [3,5 - dibromo - 4 - amino - benzyl] - cyclohexylamine in the form of a brown oil.

In order to prepare the hydrochloride, the above compound is dissolved in 15 cc of absolute ethanol and the solution is then saturated with hydrogen chloride. The hydrochloride precipitates out from the solution, is separated by filtration with suction, dried and recrystallised from absolute ethanol. M.pt. = 259—262° (decomp.).

The following compounds have also been prepared by processes similar to those described above:—

EXAMPLE 39

2-Amino compound	Melting point as Hydrochloride	Prepared analogously to
Hal = Br R = —H	247—248° (Decomp.)	Example 37



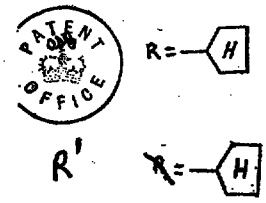
EXAMPLE 40

4-Amino compound		
Hal = Br	Melting point as Hydrochloride 180—183°	Prepared analogously to Example 38
R = H		
$R^1 = CH_2—CH(CH_3)—CH_3$		

Example illustrating the preparation of a compound in which R and R^1 together represent a cyclopentyl group.

EXAMPLE 41

4-Amino compound		
Hal = Br	Melting point as Hydrochloride 189—197° (Decomp.)	Prepared according to the process of claim 23



EXAMPLE 42

N - [2 - Amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine

500 mg of N - [2 - nitro - 3,5 - dibromo - benzyl] - N - methyl - cyclohexyl - ammonium chloride (Melting point = 233—235° Decomp.) are dissolved in 100 cc of methanol and 100 mg PtO_2 are added. Hydrogen is passed into this solution with shaking. When 3 mols of hydrogen have been taken up the catalyst is removed by filtration and the filtrate concentrated to dryness. After recrystallising from ethanol, the melting point of the product is 234—235.5° (decomp.).

EXAMPLE 43

2-Amino compound		
Hal = Br	Melting point as Hydrobromide 244—247°C (Decomp.)	Prepared analogously to Example 37
R = H		
$R^1 = CH_3$		

EXAMPLE 44

N - [2 - Amino - 3,5 - dibromo - benzyl] - N - methyl - benzylamine

4.4 g of N - [2 - amino - 3,5 - dibromo - benzyl] - methylamine are dissolved in 50 cc of ethanol and 1.9 g of benzyl chloride added. After heating for 8 hours, 100 cc of 2N caustic soda are added and the solution is extracted exhaustively with chloroform. The combined chloroform phases are dried over sodium sulphate and concentrated to dryness. The base is dissolved in 25 cc of ethanol and 2 cc of concentrated hydrobromic acid are added, the hydrobromide then crystallising out. After recrystallisation from ethanol, the melting point of the hydrobromide is 218.5—219° (decomp.).

EXAMPLE 45

Preparation of drop solution

100 ml of drop solution is prepared containing the following:

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexyl-amine hydrochloride	0.33 g
Methyl-*p*-hydroxy-benzoate	0.07 g
Propyl-*p*-hydroxy-benzoate	0.03 g
Polyvinyl pyrrolidone	5.00 g
Distilled water	95.57 g
	101.00 g
	= 100 ml.

Preparation

The methyl- and ethyl - *p* - hydroxy benzoates, polyvinyl pyrrolidone and N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine hydrochloride are successively dissolved in the distilled water, which is heated to 80°C. The solution is cooled and filtered free of suspended particles.

20 drops (i.e. about 1.2 ml) contain about 4.0 mg of N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexyl - amine hydrochloride.

EXAMPLE 46

Preparation of Tablets

Tablets are prepared each of which contains the following:

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexyl-amine hydrochloride	2.0 mg
Lactose	60.0 mg
Potato starch (dried)	43.0 mg
Soluble starch	4.0 mg
Magnesium stearate	1.0 mg
	110.0 mg

The N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine hydrochloride and the lactose are triturated together and the triturate is then mixed with the potato starch. The mixture thus obtained is granulated with a 20% aqueous solution of the soluble starch through a 1 mm screen. The moist granulate is dried at 40°C and is then again granulated through the 1 mm screen and mixed with the magnesium stearate. The mixture is then pressed to tablets having a weight of 110 mg using a 7 mm flat die.

EXAMPLE 47

Preparation of Coated Tablets

Coated tablets are prepared, the core of each of which contains the following:

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclo-hexylamine hydrochloride	4.0 mg
Lactose	60.0 mg
Potato starch (dried)	41.0 gm
Soluble starch	4.0 mg
Magnesium stearate	1.0 mg

Preparation

The N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine hydrochloride and the lactose are triturated together and the triturate is then mixed with the potato starch. The mixture thus obtained is granulated with a 20% aqueous solution of the soluble starch through a 1 mm screen. The moist granulate is dried at 40°C and is then again granulated through the 1 mm screen and mixed with the magnesium stearate. The mixture is then pressed to tablet cores having a core weight of 110 mg using a 7 mm convex die.

The tablet cores are then coated by methods known per se with a coating which consists essentially of sugar and talcum. The coated tablets are polished with the aid of beeswax, and have a weight of 170 mg per tablet.

EXAMPLE 48

Preparation of gelatine capsules

Gelatine capsules are prepared each of which contains the following:

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexylamine hydrochloride	4.0	mg
Lactose	96.0	mg
	100.0	mg

The active ingredient is triturated with the lactose and fed into gelatine capsules of suitable size. Each capsule contains 100 mg of lactose plus active ingredient.

EXAMPLE 49

Preparation of Ampoules

Ampoules are prepared each of which contains the following:

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexylamine hydrochloride		2.0	mg
Polyvinyl pyrrolidone		30.0	mg
Distilled water	to	1	ml

Preparation

The N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl cyclohexylamine hydrochloride and polyvinyl pyrrolidone are successively dissolved in distilled water heated to 80°C. The solution is cooled, made up to the required volume and filtered free of suspended particles. The solution is then used to fill white 1 ml ampoules, which are sterilised for 20 minutes at 120°C.

EXAMPLE 50

Preparation of Syrup

A syrup is prepared, 100 ml of which contain the following:

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexylamine hydrochloride	0.04 g
Sodium benzoate	0.20 g
Ammonium chloride	0.70 g
Saccharin-sodium	0.20 g
Sugar	65.0 g
Edible blue No. 2	0.002g
Edible red No. 2	0.007g
Edible yellow No. 2	0.024g
Raspberry flavour	0.40 g
Menthol	0.015g
Ethanol	4.00 g
Distilled water	54.412g
	125.000g

Preparation

The sugar and N - [2 - amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexylamine hydrochloride are dissolved with heating in 45.412 g of water. The solution is cooled (solution A).

The sodium benzoate, ammonium chloride, saccharin-sodium and colouring matter are dissolved in the remaining water (solution B). The menthol is dissolved in the ethanol (solution C).

First solution B and then solution C are stirred into solution A. Finally, the raspberry flavour is added. The syrup is then filtered free of suspended particles.

EXAMPLE 51

Preparation of tablets

Tablets are prepared, each of which contains the following:

PATENT OFFICE

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexylamine hydrochloride	4.0 mg
1-(p-chlorophenyl)-2,3-dimethyl-4-dimethylamino-butanol-(2) hydrochloride	40.0 mg
1-(3,5-Dihydroxyphenyl)-2-isopropylamino-ethanol sulphate	10.0 mg
"Aerosil" pressed	61.0 mg
(The word "Aerosil" is a registered Trade Mark)	
Lactose	50.0 mg
Maize starch (dried)	50.0 mg
Tartaric acid	2.0 mg
"Aerosil" unpressed	2.0 mg
Magnesium stearate	1.0 mg
	220.0 mg

Preparation

The active ingredient, pressed "Aerosil," lactose and maize starch are mixed and granulated with a 1.5% solution of tartaric acid in ethanol through a 1 mm screen. The unpressed "Aerosil" and magnesium stearate are then mixed with the granulate and the mass pressed into tablets weighing 220 mg using a 9 mm flat die.

EXAMPLE 52

Preparation of Syrup

A syrup is prepared, 100 ml of which contain the following:

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexylamine hydrochloride	0.02 g
1-(*p*-chlorophenyl)-2,3-dimethyl-4-dimethylamino-butanol-(2) hydrochloride	0.4 g
1-(3,5-Dihydroxyphenyl)-2-isopropylamino-ethanol sulphate	0.1 g
Sodium benzoate	0.2 g
Ammonium chloride	0.7 g
Saccharin-~~desium~~ sodium	0.2 g
Sugar	65.0 g
Edible blue No. 2	0.002g
Edible red No. 2	0.007g
Edible yellow No. 2	0.024g
Eucalyptus-menthol flavour	0.1 g
Menthol	0.015g
Ethanol	4.0 g
Distilled water	54.232g
	125.000g

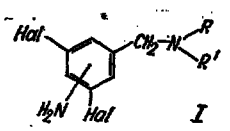
Preparation

The sugar and active ingredient are dissolved in 54.232 g water with heating. The solution is cooled (solution A). The sodium benzoate, ammonium chloride, saccharin-sodium and colouring matter are dissolved in the remaining water (solution B). The menthol and eucalyptus-menthol flavour are dissolved in ethanol solution (solution C).

First, solution B and then solution C are stirred into solution A. The syrup is then filtered free of suspended particles.

WHAT WE CLAIM IS:—

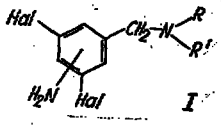
1. Dihalogeno - amino - benzylamines of the general formula



I

in which R and R^1 represent lower acyclic aliphatic hydrocarbon groups containing from 1 to 5 carbon atoms, or cycloalkyl, aralkyl or aryl groups and are the same or different, or R and R^1, together with the adjacent nitrogen atom, represent a pyrrolidinyl, piperidino or camphidinyl group either unsubstituted or substituted by a lower alkyl group containing from 1 to 5 carbon atoms; and Hal represents chlorine or bromine; and non-toxic acid addition salts thereof.

2. Dihalogeno - amino - benzylamines of the general formula



I

in which R^1 represents a lower acyclic aliphatic hydrocarbon group containing from 1 to 5 carbon atoms or a cycloalkyl, aralkyl or aryl group;

R represents hydrogen;

and Hal represent chlorine or bromine; and non-toxic acid addition salts thereof.

3. Compounds according to claim 1 in which both R and R^1 each represents a lower alkyl group containing from 1 to 5 carbon

N-[2-Amino-3,5-dibromo-benzyl]-N-methyl-cyclohexylamine hydrochloride	0.02 g
1-(*p*-chlorophenyl)-2,3-dimethyl-4-dimethylamino-butanol-(2) hydrochloride	0.4 g
1-(3,5-Dihydroxyphenyl)-2-isopropylamino-ethanol sulphate	0.1 g
Sodium benzoate	0.2 g
Ammonium chloride	0.7 g
Saccharin-~~desium~~ sodium	0.2 g
Sugar	65.0 g
Edible blue No. 2	0.002g
Edible red No. 2	0.007g
Edible yellow No. 2	0.024g
Eucalyptus-menthol flavour	0.1 g
Menthol	0.015g
Ethanol	4.0 g
Distilled water	54.232g
	125.000g

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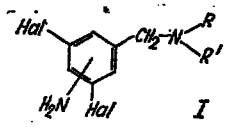
Preparation

The sugar and active ingredient are dissolved in 54.232 g water with heating. The solution is cooled (solution A). The sodium benzoate, ammonium chloride, saccharin-sodium and colouring matter are dissolved in the remaining water (solution B). The menthol and eucalyptus-menthol flavour are dissolved in ethanol solution (solution C).

First, solution B and then solution C are stirred into solution A. The syrup is then filtered free of suspended particles.

WHAT WE CLAIM IS:—

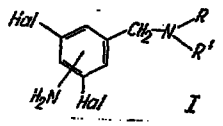
1. Dihalogeno - amino - benzylamines of the general formula



I

in which R and R^1 represent lower acyclic aliphatic hydrocarbon groups containing from 1 to 5 carbon atoms, or cycloalkyl, aralkyl or aryl groups and are the same or different, or R and R^1, together with the adjacent nitrogen atom, represent a pyrrolidinyl, piperidino or camphidinyl group either unsubstituted or substituted by a lower alkyl group containing from 1 to 5 carbon atoms; and Hal represents chlorine or bromine; and non-toxic acid addition salts thereof.

2. Dihalogeno - amino - benzylamines of the general formula



I

in which R^1 represents a lower acyclic aliphatic hydrocarbon group containing from 1 to 5 carbon atoms or a cycloalkyl, aralkyl or aryl group;

R represents hydrogen;

and Hal represent chlorine or bromine; and non-toxic acid addition salts thereof.

3. Compounds according to claim 1 in which both R and R^1 each represents a lower alkyl group containing from 1 to 5 carbon

* C L M S *

atoms or a lower alkenyl group containing from 3 to 5 carbon atoms.

4. Compounds according to claim 3 in which R and R^1 each represents a methyl, ethyl, isobutyl or allyl group.

5. Compounds according to claim 1 or claim 2 in which R^1 represents a cyclohexyl group.

6. Compounds according to claim 1 or claim 2 in which R^1 represents a benzyl group.

7. Compounds according to claim 1 or claim 2 in which R^1 represents a phenyl group.

8. Acid addition salts as claimed in any of claims 1 to 7 in which the acid is hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, lactic acid, citric acid, tartaric acid or maleic acid.

9. N - [2 - Amino - 3,5 - dibromo - benzyl] - dibenzylamine.

10. N - [2 - Amino - 3,5 - dibromo - benzyl] - N - methyl - cyclohexyl - amine.

11. N - [2 - Amino - 3,5 - dibromo - benzyl] - dicyclohexylamine.

12. N - [2 - Amino - 3,5 - dibromo - benzyl] - dimethylamine.

13. N - [2 - Amino - 3,5 - dichloro - benzyl] - N - methyl - cyclohexylamine.

14. N - [4 - Amino - 3,5 - dibromo - benzyl] - diethylamine.

15. N - [4 - Amino - 3,5 - dibromo - benzyl] - N - methyl - benzylamine.

16. N - [4 - Amino - 3,5 - dibromo - benzyl] - N - methyl - cyclo - hexylamine.

17. N - [4 - Amino - 3,5 - dibromo - benzyl] - N - ethyl - phenylamine.

18. N - [4 - Amino - 3,5 - dibromo - benzyl] - diallylamine.

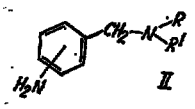
19. N - [4 - Amino - 3,5 - dibromo - benzyl] - dicyclopentylamine.

20. N - [4 - Amino - 3,5 - dibromo - benzyl] - cyclohexylamine.

21. N - [4 - Amino - 3,5 - dibromo - benzyl] - isobutylamine.

22. N - [2 - Amino - 3,5 - dibromo - benzyl] - cyclohexylamine.

23. A process for the preparation of dihalogeno - amino - benzylamines as claimed in claim 1 in which comprises reacting an amino - benzylamine of the formula



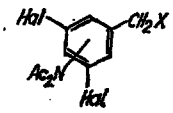
II

in which R and R^1 are as defined in claim 1 and the amino group is in the 2- or 4- position, with at least a molar excess of a chlorinating or brominating agent in an inert organic solvent whereby the 3,5 - dihalogeno derivative is produced in the form of its hydrochloride or hydrobromide salt and then, if desired, converting the said hydrochloride or hydrobromide salt to the free base or other non-toxic acid addition salt.

24. A process according to claim 23 in which the chlorinating or brominating agent is chlorine or bromine.

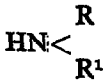
25. A process according to claim 23 or 24 in which the solvent is a halogeno-hydrocarbon or glacial acetic acid.

26. A process for the preparation of dihalogeno-amino-benzylamines as claimed in claim 1 which comprises reacting a dihalogeno-diacylamino-benzyl halide of the formula



III

in which Hal is as defined in claim 1, X represents chlorine or bromine and Ac represents an acyl group, with an amine of the formula



IV

in which R and R^1 are as defined in claim 1, in the presence of a hydrogen halide-binding agent, deacylating the compound so formed and, if desired, converting the product to a non-toxic acid addition salt.

27. A process according to claim 26 in which the hydrogen halide-binding agent is an inorganic base or a tertiary organic base.

28. A process according to claim 27 in which the hydrogen halide-binding agent is provided by using at least a molar excess of the amine of formula IV.

29. A process according to any of claims 26 to 28 in which the reaction is carried out in the presence of an organic solvent.

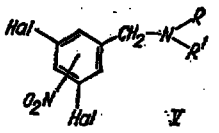
30. A process according to claim 29 in which the organic solvent is ethanol, benzene or toluene.

31. A process according to claim 29 or claim 30 in which the reaction is effected at the reflux temperature of the solvent.

32. A process according to any of claims 26 to 31 in which the de-acylation is effected by heating with dilute mineral acid or a dilute inorganic base.

33. A process for the preparation of dihalogeno-amino-benzylamines as claimed in claim 1 which comprises reducing a dihalogeno - nitro - benzylamine of the formula

* C L M S *



V

in which Hal, R and R^1 are as defined in claim 1 and, if desired, converting the compound so formed to a non-toxic acid addition salt.

34. A modification of a process as claimed in any of claims 23 to 33 for the preparation of a compound as claimed in claim 2 in which, in the compounds of formulae II, IV and V, R represents hydrogen.

35. A process for the preparation of compounds as claimed in claim 1 in which R represents a lower acyclic aliphatic hydrocarbon group containing from 1 to 5 carbon atoms, or a cycloalkyl or aralkyl group which comprises first preparing a compound as claimed in claim 2 in the form of its free base by a process as claimed in claim 34, replacing the hydrogen atom of the free secondary amino group of the compound thus formed by a lower acyclic aliphatic hydrocarbon group containing from 1 to 5 carbon atoms, or a cycloalkyl or aralkyl group and then, if desired, converting the product to a non-toxic acid addition salt.

36. A process according to any of claims 23 to 35 in which the non-toxic acid addition salt is produced by reacting an alcoholic solution of the appropriate acid with a substantially equimolar proportion of the free base.

37. A process according to any of claims 23 to 36 substantially as described in any of Examples 1—44.

38. Dihalogeno - amino - benzylamines when prepared by a process as claimed in any of claims 23 to 37.

39. Dihalogeno - amino - benzylamines as ~~desscribed~~ described in the Examples, other than the compounds claimed in claims 9 to 22.

40. Pharmaceutical compositions comprising as active ingredient a compound as claimed in either of claims 1 and 2 in association with a pharmaceutical carrier or excipient.

41. Compositions according to claim 40 in the form of dosage units.

42. Compositions according to claim 40 or 41 in the form of tablets, coated tablets, capsules, ampoules, drops or syrup.

43. Compositions according to claim 41 or 42 containing 0.5 to 10 mg of active ingredient per dosage unit.

44. Compositions according to claim 43 containing 2.0 to 4.0 mg of active ingredient per dosage unit.

45. Compositions as claimed in any of claims 40 to 44 in which the active ingredient is a compound as claimed in any of claims 9 to 22.

46. Compositions as claimed in claim 40 substantially as described in any of Examples 45—52.

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* C L M S *

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