United States Patent Office 2,823,209 Patented Feb. 11, 1958



2,823,209

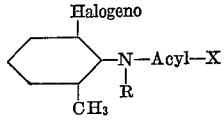
# AMINOALKANOYL-HALO-TOLUIDIDES

Henry Martin, Zurich, Switzerland, assignor to Cilag Limited, Schaffhausen, Switzerland, a Swiss company

No Drawing. Application February 24, 1953
Serial No. 338,601
Claims priority, application Switzerland
February 25, 1952
4 Claims. (Cl. 260—326.3)

This invention relates to new halogen-containing amino fatty acid anilides, their acid addition and quaternary ammonium salts and their production.

The invention provides new chemical compounds being amino fatty acid 2-halogeno-6-methyl anilides of the formula

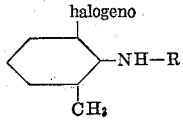



wherein "halogeno" signifies a chlorine or bromine atom, R is a hydrogen atom or a lower alkyl radical, "Acyl" is the radical of a lower straight or branched fatty acid and X is the radical of a secondary amine and acid addition salts and quaternary salts of said amino fatty acid 2-halogeno-6-methyl anilides.

It has been found that the new compounds of the above general formula have a powerful local anaesthetic effect. Various halogen-containing amino fatty acid anilides have previously been described. United States specification No. 2,343,071, for example, described the production of N,N-dimethyl amino acetic acid-3,4-dichloro-anilide-N-3',4'-dichloro benzylate as a white powder giving a clear solution in water which is suitable as a moth proofing agent. This quaternary compound has not the slightest local anaesthetic effect; nor has the intermediate product N,N-dimethyl-amino acetic acid-3,4-dichloro-anilide. The o-, m- and p-iodo anilides of diethylamino acetic acid also have no anaesthetic effect (Arkiv för Kemi, Mineralogi o. Geologi, vol. 22A, No. 18, page 19). It was therefore surprising to find that, unlike the above-mentioned halogen-containing dialkyl amino acetic acid anilides, the 2-halogeno-6-methyl-anilides of N-substituted amino fatty acids show very remarkable local anaesthetic properties. Although it is known that certain amino fatty acid xylidides and mesidides have an anaesthetic effect, the o-toluidides of aliphatic amino fatty acids, for example dimethyl amino acetic acid N-methyl-o-toluidide and N-morpholino acetic acid o-toluidide have no, or at least no perceptible effect.

The new compounds of the invention are distinguished by their excellent properties. They have a low toxicity and an outstanding anaesthetic effect. They can, if desired, be mixed with vasoconstrictor agents such as adrenaline. Their aqueous acid solutions are stable and may be applied without affecting the tissues. Unlike the difficultly accessible xylidides of the amine fatty acids, the new 2-halogeno-6-methyl anilides may easily be produced synthetically in any desired quantity and may be obtained without a time-consuming purification of the starting material.

The new compound can be produced as follows: A compound of the formula






wherein R has the above-defined meaning, or a salt thereof, for example, 2-chloro-6-methylaniline or one of its N-alkyl derivatives or a hydrochloride of such a compound, is treated with a compound yielding the amino fatty acid radical.

In some cases it is easier to proceed step by step and to employ in the first instance a compound yielding the halogeno fatty acid radical. In this case the halogeno fatty acid halogeno-methylanilide first obtained is reacted with an amine to obtain the desired amino fatty acid toluidide.

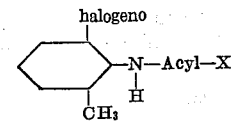
Other methods are also available for producing the new halogen-containing N-substituted amino fatty acid toluidides: Amino fatty acid halogeno-methyl-anilides unsubstituted at the aliphatic nitrogen may be alkylated or aralkylated in known manner to form N,N-substituted amino fatty acid halogeno-methylanilides. Or the corresponding reactive, unsaturated fatty acid halogeno-methyl-anilides, for example the corresponding amide of acrylic acid, are reacted with secondary amines in the presence of catalysts to form β-N,N-dialkyl-amino fatty acid 2-halogeno-6-methyl-anilides. 2-halogeno-6-methyl anilines suitable for the reaction include 2-chloro-6-methyl aniline, 2-bromo-6-methyl-aniline, their N-alkyl derivatives and their salts, for example the hydrochlorides.

Compounds yielding the fatty acid radical X-Acyl- of the general formula include: dialkylamino acetic acids and their reactive derivatives, for example N-allyl-amino acetic acids, β-(N,N-diethylamino)-propionic acid, lower alkyl esters of N,N-dibenzyl amino acetic acid, dibenzyl-amino acetic acid amide, and also reactive halogeno fatty acid derivatives such as chloro-acetic acid, chloro-acetic acid anhydride, chloro-acetyl chloride, α-chloro-propionic acid chloride, α-bromo-propionic acid bromide, β-bromo-propionic acid bromide, α,β-dibromo-propionyl chloride, α-bromo-butyric acid bromide and reactive unsaturated acids such as acrylic acid and methacrylic acid and their reactive derivatives such as methacrylic acid chloride.

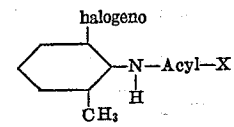
In general the reaction with the aromatic base occurs in a solvent such as aqueous acetone, ethyl acetate, dioxane or chloroform. Depending on the circumstances and the reactants, the reaction may also be carried out in the molten state without a solvent, as for example may the reaction of 3-chloro-2-toluidide hydrochloride with chloro-acetic acid amide.

Bases which are suitable for the reaction with the halogeno fatty acid toluidides include: ammonia, primary or secondary amines, for example mono-n-butyl-amine, allyl amine, dimethyl amine, diethyl amine, morpholine, piperidine, α-methyl piperidine, pyrrolidine, cyclohexyl amine and benzyl methyl amine.

Derivatives alkylated at the aromatic nitrogen may furthermore be prepared by alkylating an amino fatty acid halogeno-methyl-anilide of the formula




which is preferably caused to react in form of an N-alkali metal salt




Preferred alkylating agents are the esters of alkanols with strong inorganic acids, for example hydrohalide, sulphuric acid, alkyl- and aryl-sulphonic acid esters.

The new compounds of the invention may be used as local anaesthetics in the form of their salts with inorganic

and organic acids, for example as hydrochlorides, tartrates and citrates.

The following examples illustrate the production of the new compounds:

*Example 1*

141 parts by weight of 2-chloro-6-methylaniline are dissolved in 250 parts of acetone, a solution of 205 parts of crystallised sodium acetate in 300 parts of water is added and then 142 parts of chloro acetyl chloride at a temperature of 38–55° C. are added drop by drop with stirring in the course of 3 hours. After some time the chloro-acetic acid-2-chloro-6-methylanilide starts separating. After stirring for one hour 200 parts of water are added and the mixture cooled with continued stirring. The condensation product is filtered off with suction, washed with water and dried in vacuo. Yield 189 parts. The crude product sinters at 123° C. and melts at 139.5–140.5° C. When recrystallised from diluted alcohol the melting point is 140–141° C.

109 parts of chloro-acetic acid 2-chloro-6-methyl-anilide thus obtained are suspended in 180 parts of ethanol and 110 parts of diethylamine are added. The temperature rises to 34° C. and a great part of the reaction mixture dissolves. After half an hour the whole is dissolved. First it is stirred for 4 hours at room temperature, then for three hours at 45–50° C. and finally for 4 hours at 65–75° C. A sample tested with dilute hydrochloric acid gives a clear solution. Afterwards the alcohol and the excess diethylamine are distilled off with steam, and after cooling the remaining oil is taken up in ether. After drying the etheral solution and separating the solvent, an oil remains in a yield of 117 parts. The reaction with diethylamine may also take place in benzene.

The N,N-diethylamino-acetic acid 2-chloro-6-methylanilide thus obtained boils under 0.1 mm. Hg at 129–130° C.

The hydrochloride of the base, when recrystallised from acetonitrile, melts at 154–155° C.

In a similar manner the N,N-dimethylamino-acetic acid 2-chloro-6-methylanilide may be produced; the free base distils under 0.2 mm. Hg at 128–132° C. and melts at 71–73° C. The hydrochloride melts at 231–234° C.

N-morpholino-acetic acid 2-chloro-6-methylanilide obtained in an analogous manner melts at 119.5–120.5° C. when recrystallised from methyl isobutyl ketone; the corresponding hydrochloride melts at 210.5–213.5° C.

N-piperidino-acetic acid 2-chloro-6-methylanilide melts at 107–108° C.; the hydrochloride melts at 172–173° C.

N-β-methylpiperidino-acetic acid 2-chloro-6-methylanilide melts at 97–99° C.; the hydrochloride melts at 177–180° C.

Instead of 2-chloro-methylaniline, 2-bromo-6-methylaniline may be used; by using α- or β-chloro-propionyl chloride instead of chloro-acetyl chloride and reacting the obtained α- or β-chloro-propionic acid 2-chloro-6-methylanilide which is respectively obtained with the aforementioned amines, the analogous α- or β-amino propionic acid 2-chloro-6-methylanilide is obtained respectively.

*Example 2*

Chloro-acetic acid 2-chloro-6-methylanilide obtained as described in Example 1 is treated for 24 hours in the autoclave with methanol containing an excess of ammonia at 60–70° C. The solution is evaporated and dried in vacuo. The residue is boiled up in water made acid to Congo red paper, the small amount of resin and undissolved matter remaining is filtered off and the solution is concentrated on the water bath. On cooling a thick crystalline mass is obtained; it is filtered and the filtrate is treated with solid sodium chloride. Thereupon the hydrochloride of amino-acetic acid 2-chloro-6-methylanilide precipitates in beautiful crystals. It is recovered, dried and recrystallised from alcohol. It melts at 290° C. with decomposition.

The amino-acetic acid 2-chloro-6-methylanilide is then methylated with aqueous formaldehyde solution and formic acid or with dimethyl sulphate in a benzene solution, yielding N,N-dimethylamino-acetic acid 2-chloro-6-methylanilide, B. P. 129–130° C./0.1 mm. Hg.

*Example 3*

141 parts of 2-chloro-6-methylaniline are dissolved in absolute ether and reacted with stirring at 10–20° C. with 52 parts of methacrylic acid chloride for 10 minutes. The temperature slowly rises to 38° C. and a thick mass is slowly formed. After standing over night the reaction mixture is filtered with suction, the residue is washed with ether and the ether is washed in turn with dilute hydrochloric acid and 2 N sodium hydroxide. After drying and separating the solvent, an oil is obtained which becomes solid at about 95° C. The resultant methacrylic acid-2-chloro-6-methylanilide is recrystallised from tetrachloro methane and petroleum ether in beautiful leaflets of melting point 100–102° C.

20 parts of this acetic acid amide are heated for 16 hours under reflux with an excess of diethylamine in the presence of a few drops of trimethyl benzyl ammonium hydroxide on the water bath and then treated with dilute hydrochloric acid. The liquid is filtered from a little undissolved material and made slightly alkaline, and the excess diethylamine is distilled off with steam. The resultant β-N,N-diethylamino-isobutyric acid 2-chloro-6-methylanilide is filtered, dried and distilled. B. P. 135–139° C./0.1 mm. Hg.

Acrylic acid 2-chloro-6-methylanilide on reaction with diethylamine gives γ-N,N-diethylamino-propionic acid 2-chloro-6-methylanilide and on reaction with dimethylamine gives γ-N,N-dimethylamino-propionic acid 2-chloro-6-methylanilide, the hydrochloride of which melts at 78.5–79.5° C.

*Example 4*

1 mol. of 2-chloro-6-methylaniline hydrochloride is thoroughly mixed with 1 mol of chloro-acetamide and heated on an oil bath up to 125–130° C. The reaction mixture becomes solid after first beginning to melt. After one hour it is taken up in xylene and treated with a little charcoal. From the filtered solution, chloro-acetic acid 2-chloro-6-methylanilide of melting point 140–141° C. crystallises. It is reacted with pyrrolidine as described in Example 1, forming N-pyrrolidino-acetic acid 2-chloro-6-methylanilide melting at 84–85° C., its hydrochloride melting at 194–196° C.

*Example 5*

By reacting chloro-acetic acid 2-chloro-6-methylanilide with 2-methyl-piperidine in excess, 2-methylpiperidino-acetic acid 2-chloro-6-methylanilide is obtained melting at 97–98° C., its hydrochloride melting at 177–178° C.

*Example 6*

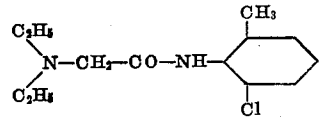
23 gms. of chloro-acetic acid N-methyl-2-chloro-6-methylanilide (obtained from 2-chloro-6-methyl-N-methylaniline and chloro-acetic acid chloride by the above described process) are heated under reflux for 15 hours with stirring with 20 gms. of pyrrolidine in 40 cc. of absolute ethanol. Afterwards the alcohol and surplus pyrrolidine are distilled off with steam, the remaining aqueous solution is saturated with sodium chloride and the oil which separates is taken up in ether. The ether is dried with sodium sulphate and evaporated, and the residue is distilled in vacuo. In this way 17 gms. of pyrrolidino-acetic acid N'-methyl-2-chloro-6-methylanilide are obtained, boiling under 0.05 mm. Hg at 123–125° C. The new compound is easily soluble in dilute mineral acid. An aqueous solution of the hydrochloride shows a pH of 6.6.

*Example 7*

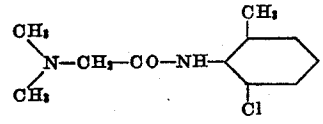
In an analogous manner to that described in Example 1, 23 gms. of chloro-acetic acid N-methyl-2-chloro-6-methylanilide are reacted with 20 gms. of diethylamine to give 22 gms. of N,N-diethylamino-acetic acid N'-methyl-2-chloro-6-methylanilide boiling under 0.35 mm. Hg. at 127–130° C. An aqueous solution of the hydrochloride shows a pH of 6.6. The following are obtained in an analogous manner to that described in the foregoing examples: N,N-diethylamino-acetic acid N'-ethyl-2-chloro-6-methylanilide, N,N-diethylamino-acetic acid N'-propyl-2-chloro-6-methylanilide, piperidino-acetic acid N'-methyl-2-chloro-6-methylanilide, α-methylpiperidino-acetic acid N'-methyl-2-chloro-6-methylanilide, morpholino-acetic acid N'-methyl-2-chloro-6-methylanilide, as well as the corresponding 2-bromo compounds.

What I claim is:

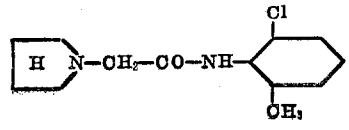
1. The new chemical compound of the formula



2. The new chemical compound of the formula

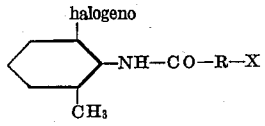


3. The new chemical compound of the formula





4. New chemical compound selected from the group consisting of amino fatty acid-2-halogeno-6-methyl-anilides and hydrochloric acid addition salts thereof, said amino fatty acid-2-halogeno-6-methyl anilides having the formula



wherein halogeno is an atom selected from the group consisting of chlorine and bromine, R is a member selected from the group consisting of —$CH_2$—, —$CH_2$—$CH_2$— and

and X is a member selected from the group consisting of a (di-lower alkyl)-amino group and a pyrrolidino group.


**References Cited** in the file of this patent

UNITED STATES PATENTS

| | | |
|---|---|---|
| 2,139,190 | Iselin et al. | Dec. 6, 1938 |
| 2,343,071 | Martin et al. | Feb. 29, 1944 |
| 2,441,498 | Loefgren et al. | May 11, 1948 |

OTHER REFERENCES

Loefgren: "Ar Foer Kemi, Mineralogi och Geologic," vol. 22A, No. 18, pp. 1–30 (1946).

Loefgren et al.: "Svensk Kern Tid," vol. 58, pp. 206–231 (1946).