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PROCESS FOR THE PRODUCTION OF ALKAMINE ESTERS

Schmul Hersch Horenstein, Berlin-Halensee, and Hermann Pählicke, Berlin-Reinickendorf, Germany; vested in the Alien Property Custodian

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This invention relates to a process for the production of alkamine esters.

Three main methods are available for the production of esters viz. the action of acids on alcohols in the presence of a condensing medium, the reaction of acid halides with the alcohols, and the treatment of alkyl halides with the salt of the acid to be esterified. When applying these methods to the production of alkamine esters, various difficulties are encountered. The first two methods frequently fail when it is desired to esterify sensitive amino-alcohols or acids of more complicated structure; while the third method is not suitable for the esterification of the amino-alcohols for the reason that it presupposes the use of the free aminoalkyl halides, which readily tend to decompose or to form inner ring compounds at the high temperatures and protracted periods of treatment required for the reaction. The so-called interchange of ester radicals, i. e. the displacement of simple alcohol residues from the ester bond by aminoalcohols, also only leads to the desired end in certain particularly favorable cases. A special possibility for the production of aminoalkyl esters is finally provided by the reaction of alkyl halide esters with amines. However, this reaction does not proceed smoothly except in simple cases. It generally requires the application of pressure, and saponification frequently re-occurs, in the case of sensitive esters, in consequence of the excess of base required.

The foregoing difficulties are encountered in a particularly high degree in the esterification of alkamines with quaternarily combined nitrogen of the choline type. When starting from the cholines or their salts, mixtures of salts of the cholines and their esters are always obtained, which, in consequence of the ready liability of the ester bases to decompose, cannot be purified. For the same reason the use of alkyl halide bases is out of the question. Hitherto it was thus substantially only possible to produce esters of choline when alkyl halide esters were treated with trimethylamine. By this means, however, only the esters of the simple aliphatic acids with choline could be isolated in the form of their pure salts, while most of the other choline esters mentioned in prior publications have either not been separated at all or only in the form of their platinum double salts.

The present invention relates to a method capable of quite universal application to the production of esters of the aminoalcohols with the most diverse acids. The method is based on the discovery that, if the hydrogen halide acid esters of alkamines are converted into the amine salts of the acids to be esterified, compounds are produced which tend towards a rearrangement in which the anion changes places with the halogen forming the ester group. This thus produces the hydrogen halide acid salts of the esters of the aminoalcohols with those acids which were originally combined on a salt-forming basis with the nitrogen of the aminoalcohol. The reaction may be represented diagrammatically as follows:

$$\equiv N.(CH_2)_n \ldots\ldots \text{Hal.} \longrightarrow \equiv N.(CH_2)_n \ldots\ldots X$$
$$\downarrow X \qquad\qquad \longrightarrow \downarrow \text{Hal.}$$

where X indicates the acid residue. The amine salt of the hydrogen halide acid ester of the aminoalcohol with the acid to be esterified may be produced by known methods, for example by simply bringing together the calculated amounts of the substances in question in the presence or absence of a solvent, or by double decomposition between a suitable acid salt and a salt of the aminoalkyl halide. In both cases the hydrogen halide acid ester is neutralized immediately and thereby rendered immune from the danger of decomposition or internal ring formation.

In order to bring about the rearrangement, the amine salts produced in this manner or their solutions are heated for a few hours to temperatures over 50° C. When double decomposition between two salts is employed, it is possible to isolate the conversion product, in order to be able to accomplish the subsequent rearrangement with a purified substance. During the heat treatment, the progress of the rearrangement can be observed in simple fashion by quantitative examination of the formation of ionised halogen. The process represents the mildest universally applicable method of esterification of aminoalcohols. The esterification takes place, with a neutral reaction, within the molecule itself, without needing any auxiliary substances or producing any by-products. On the completion of the reaction, the resulting salts may be purified in the usual manner by recrystallisation from a suitable solvent or by liberation of the aminoesters and fresh conversion into a salt.

The process is particularly suitable for the production of compounds which are used as medicaments, or as intermediate products for the production of medicaments.

The process will now be illustrated with reference to the following examples:

Example 1

Bromide of choline lactate

147 parts of trimethylbromethyl ammonium bromide are dissolved in about 800 parts of water and mixed with 124 parts of silver lactate by shaking. After a short time no more ionised bromine can be detected in the solution. The

solution is then filtered off from the silver bromide and the filtrate concentrated in vacuo, when a little more silver bromide separates and is removed. Evaporation to dryness follows, a crystal pulp being then first obtained, which on further heating gives a syrupy residue. The latter is left for six hours at a temperature of about 90° C. during which time the gradually increasing appearance of ionised halogen can be observed by taking samples. On completion of the rearrangement, the substance is recrystallised from butyl alcohol and the resulting crystals are washed with ether. The yield amounts to 120 parts (79% of theory). Hygroscopic crystals. 0.7444 grm.=29.05 ccms. $n/10$ $AgNO_3$=31.24% bromide (calculated 31.22% of Br.).

EXAMPLE 2

Acetyl choline bromide

12.4 parts of trimethylbromethyl ammonium bromide are dissolved in water and mixed as above with 9.2 parts of silver acetate. The filtrate is evaporated in vacuo, freed from silver bromide still separating, and the residue is left in a boiling water bath. The crystals at first present then disappear and after some time the whole of the contents of the flask then recrystallises spontaneously. The substance is then recrystallised from butyl alcohol, suction-filtered and dried in vacuo. Yield 7.75 parts (68.5% of theory). M. P. 142–143° C. 0.3754 gram of substance=16.6 ccms. $n/10$ $AgNO_3$=35.4% of Br. (calculated 35.4% of Br.). The determination of the saponification number at room temperature proves that the substance is not contaminated with choline bromide. 0.2756 grm. consumes 12.22 ccms. $n/10$ NaOH (calculated 12.19 ccms.).

EXAMPLE 3

Bromide of choline mandelate

24.7 parts of trimethylbromethyl ammonium bromide are treated with 25.9 parts of silver mandelate in aqueous solution and separated from the silver bromide. On evaporation of the solution, already ionised bromine is formed. The residue is left for three hours at 90°, during which time it melts completely. After recrystallisation from ispropyl alcohol, 25.8 parts (81.2% of theory) of the salt are obtained in readily water-soluble crystals having a M. P. of 152–154° C. 0.6004 grm.=18.85 ccms. $n/10$ $AgNO_3$=25.1% of bromine (calculated 25.16%).

EXAMPLE 4

Bromide of choline phenyl quinoline carboxylate

A solution produced, from a solution of 24.7 parts of trimethylbromethyl ammonium bromide in water, by shaking with 39 parts of silver phenylquinoline carboxylate is evaporated to dryness in vacuo, the residue is dissolved in hot methyl alcohol and separated from the silver bromide still present, and the filtrate is evaporated again in vacuo. The residue then first solidifies into a transparent resin, which melts after some time and recrystallises after further heating. After a reaction time of eight hours, the substance is recrystallised twice from isopropyl alcohol, whereupon 23.9 grms. (57.4% of theory) of the new compound are obtained. Faintly yellowish, readily water-soluble crystals, M. P. 210–212° C. 0.6902 grm.=16.55 ccms. $n/10$ $AgNO_3$=19.18% of bromine (calculated 19.2% of Br.).

EXAMPLE 5

Bromide of choline deoxycholic acid ester

22 grms. of deoxycholic acid are dissolved in the calculated amount of ammonia and precipitated with silver nitrate in the presence of methyl alcohol. The resulting silver salt is washed with methyl alcohol and ether and dried in vacuo, when however it obstinately retains water and solvent. 13 grms. of trimethylbromethyl ammonium bromide are then dissolved in water, and this solution is mixed with the aforesaid silver salt. The reaction proceeds rapidly in the cold, and the whole contents of the vessel thickens considerably, and it is therefore mixed with the same amount of methyl alcohol whereupon it can easily be filtered off from the silver bromide separated. The filtrate is then evaporated in vacuo and the residue is left for six hours at 60–65° C. After recrystallisation twice from butyl alcohol 21.9 grms. (75% of theory) of the new compound are obtained in the form of a readily water soluble well crystallised salt having a M. P. of 232–234° (with decomposition). 0.6498 grm.=11.6 ccms. of $n/10$ $AgNO_3$=14.3% of bromine calculated 14.34%. Saponification number 0.3706 grm.=6.7 ccms. $n/10$ NaOH=100.8%.

EXAMPLE 6

Bromide of choline cholic acid ester

16.8 grms. of trimethylbromethyl ammonium bromide are treated with 35 grms. of silver cholate (obtained by dissolving cholic acid in the calculated amount of ammonia and precipitation with silver nitrate in aqueous methyl alcoholic solution) filtered off from the silver bromide, and the filtrate is evaporated to dryness in vacuo. The residue forms hard fragments, which are finely pulverised and heated for eight hours to 100° C. The substance is extracted hot with alcohol, the filtrate is re-evaporated and recrystallised from butyl alcohol. The new compound represents the well crystallised water-soluble salt having a M. P. of 236–238° C. (accompanied by decomposition). 0.5879 grm.=10.1 ccms. $n/10$ $AgNO_3$=13.75% of bromine. Saponification number 0.7880 grm.=13.8 ccms. $n/10$ NaOH=100.2%.

EXAMPLE 7

Diethylaminoethyl p-nitrobenzoate

16.7 grms. of p-nitrobenzoic acid are distributed in 80 ccms. of isopropylalcohol and mixed with 13.5 grms. of diethylchlorethylamine, whereupon a clear solution is produced which is boiled for 2½ hours under reflux. On cooling, the whole solidifies into a crystal pulp which is suction filtered and again recrystallised from isopropylalcohol. 23.5 grms. (78% of theory) of the hydrochloride are obtained with a M. P. of 175–176° C. 0.5024 grm.=16.6 ccms. $n/10$ $AgNO_3$=11.73% chlorine (calculated: 11.79% chlorine).

EXAMPLE 8

Hydrochloride of diethylaminoethyl theobromine-1-acetate

17.2 grms. of diethylchloroethylamine hydrochloride are dissolved in 50 ccms. of water and mixed and shaken with 38 grms. of silver theobromine-1-acetate suspended in 150 ccms. of water. After a short time no more ionised chlorine can be detected. The reaction mixture is freed from silver chloride, the filtrate is evaporated in vacuo, and the residue is left for 7 hours in all in the boiling water bath. The contents of

the flask are at first syrupy and then gradually solidify into a brittle mass. The substance is twice recrystallised from isopropyl alcohol and forms a well crystallised salt readily soluble in water with a neutral reaction, with a M. P. of 206–208° C. 0.5680 grm.=15.05 $n/10$ $AgNO_3$= 9.42% of chlorine (calculated 9.5%).

EXAMPLE 9

Hydrochloride of diethylaminoethyl benzilate

11.4 grms. of benzilic acid are dissolved in 40 ccms. of isopropyl alcohol and neutralised with 7 grms. of diethylchloroethylamine. The solution is heated to boiling point for two hours under reflux and then cooled, whereupon the compound crystallises out. After recrystallisation from isopropyl alcohol, 15 grms. (82.7% of theory) of the hydrochloride are produced, with a M. P. of 173–174.5°. 0.4014 grm.=11.15 ccms. $n/10$ $AgNO_3$=9.85% of chlorine (calculated 9.78%). The salt is fairly difficultly soluble in water. On mixing the aqueous solution with potash, the free base with a M. P. of 50–51° C. is obtained. In order to produce the substance, the benzilic acid may also be neutralised with the chlorine base in methyl alcohol, the solution may be evaporated and the residue heated at 60° for two hours, whereupon the new salt crystallises directly from the melt.

EXAMPLE 10

Hydrochloride of diethylaminoethyl diphenyl acetate

21.2 grms. of diphenyl acetic acid are dissolved in acetone together with 13.5 grms. of diethylchloroethylamine, and this solution is evaporated in vacuo. The residue is thereupon heated for six hours to a temperature of 65–70°. The reaction product is dissolved in water, mixed with hydrochloric acid until an acid reaction to Congo red is obtained, and freed from any unreacted diphenyl acetic acid by shaking out with ether. The acid solution is rendered alkaline with sodium carbonate, and the base precipitated is taken up in ether. By treatment with alcoholic hydrochloric acid and recrystallisation of the resulting salt from acetic acid, the hydrochloride of diethylaminoethyl diphenylacetate, with a M. P. of 112–113.5° C. is obtained from the ethereal solution. 0.4326 grm.=12.65 ccms. $n/10$ silver nitrate=10.35% of chlorine (calculated 10.22%).

EXAMPLE 11

Hydrochloride of (β-piperidinoethyl) benzoate

15 grams of β-piperidinoethyl chloride and 12.2 grams of benzoic acid are dissolved in 70 ccms. of alcohol, and the solution is evaporated at about 45° C. in vacuo. The residue is left for two more hours at about 55°, during which it gradually solidifies. The product is comminuted and heated again for six hours at 85° C. The reaction product is then dissolved in butyl alcohol, filtered off from small undissolved impurities and mixed with a little ether. After a short time the hydrochloride with a M. P. of 174–176° C. crystallises out. 0.3034 grm.=11.25 ccms. $n/10$ $AgNO_3$= 13.18% of chlorine (calculated 13.18%).

EXAMPLE 12

Hydrochloride of diethylaminoethyl salicylate

A solution of 15.75 parts of salicylic acid in alcohol is neutralised with 15.5 parts of diethylchloroethylamine and the resulting solution is evaporated under reduced pressure at 40–45° C. The residue is then heated for two more hours to 70° C. and heated for ten more hours at 90–100°, and the reaction product is recrystallised from acetone. The hydrochloride with a M. P. of 144–145° C. is obtained with a yield of about 70% of theory. The compound dissolves readily in water with an acid reaction, and gives a powerful phenol reaction with iron chloride. 0.3169 grm.= 11.65 ccms. $n/10$ $AgNO_3$=13.05% of chlorine (calculated 12.96%).

EXAMPLE 13

Hydrochloride of diethylaminopropyl cinnamate

14.8 grms. of cinnamic acid in 100 ccms. of alcohol are neutralised with 14.9 grms. of diethylchloropropylamine, and the alcohol is driven off in vacuo. The residue is heated for 8 hours to 85–90° C. whereupon the melt begins to crystallize. On scraping the sides of the vessel, the whole contents of the vessel then crystallise, and after recrystallisation from isopropyl alcohol, the salt having a M. P. of 131–133° C. is obtained in the form of a readily water-soluble product. 0.4972 grm.=16.45 ccms. $n/10$ $AgNO_3$=11.77% of chlorine (calculated 11.94% of chlorine).

EXAMPLE 14

Diethylaminoethyl mandelate

15.2 grms. of mandelic acid and 13.5 grms. of diethylchloro-ethylamine are dissolved in isopropyl alcohol, and the solution is heated for four hours under reflux. On evaporation of the solution, the hydrochloride of the new compound is left in the form of a viscous oil, which is readily soluble in alcohols, and is insoluble in ether and benzene. If the hydrochloride is dissolved in water, the base can be precipitated with sodium carbonate and then taken up in ether. The ether is washed out with cold water and the ester base is produced, on evaporation of the ether, in the form of an oil which is insoluble in water. 0.2560 grm.=10.3 ccms. $n/10$ HCl (calculated 10.2 ccms).

EXAMPLE 15

Hydrochloride of the diethylaminoethyl ester of trichlorobutyl adipic ester

30.5 grms. of the acid of trichlorobutyladipic ester (German Patent 583,852) are dissolved in xylene, and neutralised with 13.5 grms. of diethylchlorethylamine. The solution is heated for six hours under reflux, then cooled and separated from a light crystallisation. The clear filtrate is somewhat concentrated in vacuo and the new product is precipitated with dry ether. The substance thereby separates in a flaky viscous form. If it is allowed to stand under ether, the precipitate changes into a finely crystalline state. The resulting hydrochloride dissolves in water, alcohols and in aromatic hydrocarbons. It is almost insoluble in ether and petroleum ether. 0.5942 grm.=13.7 ccms. $n/10$ $AgNO_3$=8.2% of chlorine in ionised form (calculated 8.05). 0.2380 grm., after previous saponification with soda lye, consume 21.3 ccms. $n/10$ $AgNO_3$=31.8% of total chlorine (32.2%).

EXAMPLE 16

Bromide of choline pyroracemate

24.7 parts of trimethyl bromethyl ammonium bromide are dissolved in methyl alcohol and stirred up with 19.5% of silver pyroracemate. The solution, freed from precipitated silver bromide, is evaporated in vacuo at a low temperature and the residue is heated for four hours at 85 to 90°

C. The contents of the flask are then dissolved in alcohol and the substance precipitated with ether. The precipitate is at first oily but after having been triturated several times with dry ether and having then been allowed to stand in the vacuum desiccator it becomes solid. The yield amounts to about 80% of theory. 0.3572 grm.=14.05 ccms. $n/10$ $AgNo_3$=31.5 bromine (calculated 31.5).

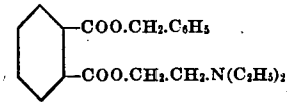
EXAMPLE 17

(2.2-dimethyl-3-diethylamino-propyl) dl-tropate

4.1 grms. of dl-tropic acid are mixed with 4.5 grms. of 2.2-dimethyl-3-diethylaminopropyl-1-chloride, and slowly heated in the oil bath. The contents of the flask are at first in the form of a melt consisting of two layers, which becomes homogeneous when the temperature is gradually raised to 160–170° C. After a reaction period of one hour the flask is cooled, and the contents are dissolved in water and the resulting ester is precipitated with soda lye and taken up with ether. After evaporation of the ether, the base remains in the form of an oil of thick consistency which, when treated with phosphoric acid in alcoholic solution gives a phosphate having the melting point of 139–141° C. The yield amounts to about 80% of theory.

EXAMPLE 18

Diethylaminoethyl benzyl phthalate



25.6 grms. of mono-benzyl phthalic acid are dissolved in isopropyl alcohol and the solution is mixed with 13.5 parts of diethylchloroethylamine and then heated for 3 hours under reflux, whereupon the solvent is evaporated off in vacuo and the residue is dissolved in water. On mixture with sodium carbonate solution, the base is precipitated. It is then taken up in ether, and on evaporation of the solvent the base is then obtained in the form of oil giving no crystallised salts. 0.5528 grm.=15.7 ccms. $n/10$ HCl (calculated 15.6 ccms.).

EXAMPLE 19

Choline mandelate

12.3 parts of trimethylbromethyl ammoniumbromide are thoroughly triturated with 8.7 parts of sodium mandelate and this mixture is heated in the oil bath. As soon as the mixture begins to sinter, heating stops and the mixture is left to cool, with stirring. After recrystallisation from butyl alcohol the salt is obtained with a yield of about 75% of theory. Analysis: 0.2164 grm. consume 6.8 ccms. $n/10$ $AgNO_3$=25.16% bromine (calculated 25.16%).

EXAMPLE 20

Diethylaminoethyl benzilate

10 parts of sodium benzilate are mixed with seven parts of diethylaminoethyl chloride hydrochloride, and heated in the oil bath. The mixture is left for a short time at 140° and the contents of the flask are recrystallised from isopropyl alcohol. The hydrochloride of the benzil acid ester is obtained with a M. P. of 174–175° C.

What we claim and desire to secure by Letters Patent of the United States is:

1. A process for the production of alkamine esters comprising converting the hydrogen halide ester of an alkamine into the amine salt of the carboxylic acid to be esterified and subjecting said amine salt to a rearrangement in which the acid radical changes place with the halogen.

2. A process for the production of alkamine esters comprising converting the hydrogen halide ester of an alkamine into the amine salt of the carboxylic acid to be esterified and subjecting said amine salt to a rearrangement in which the acid radical changes place with the halogen by heating the amine salt to a temperature above 50° C.

3. A process for the production of alkamine esters comprising reacting the hydrogen halide ester of an alkamine with the carboxylic acid to be combined, and subjecting the amine salt thus formed to a rearrangement in which the acid radical changes place with the halogen.

4. A process for the production of alkamine esters comprising reacting the hydrogen halide ester of an alkamine with the carboxylic acid to be combined, isolating the amine salt thus formed, and subjecting said amine salt to a rearrangement in which the acid radical changes place with the halogen.

5. A process for the production of alkamine esters comprising reacting the ammonium halide of a hydrogen halide ester of an alkamine with a salt of the carboxylic acid to be combined, and subjecting the amine salt thus formed by double decomposition to a rearrangement in which the acid radical changes place with the halogen.

6. A process for the production of alkamine esters comprising reacting an ammonium halide of a hydrogen halide ester of an alkamine with a salt of the carboxylic acid to be combined, isolating the amine salt thus formed by double decomposition, and subjecting said amine salt to a rearrangement in which the acid radical changes place with the halogen.

7. A process for the production of choline esters, comprising converting trimethyl haloethylammonium halide by double decomposition into an amine salt of the carboxylic acid to be esterified, and subjecting said amine salt to a rearrangement in which the acid radical changes place with the halogen.

8. A process for the production of choline esters comprising converting trimethyl-haloethyl ammonium halide by double decomposition into an amine salt of the carboxylic acid to be esterified, isolating said amine salt, and subjecting said amine salt to a rearangement in which the acid radical changes place with the halogen.

HERMANN PÄHLICKE.
SCHMUL HERSCH HORENSTEIN.