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ESTERS OF AJMALINE AND RELATED COMPOUNDS

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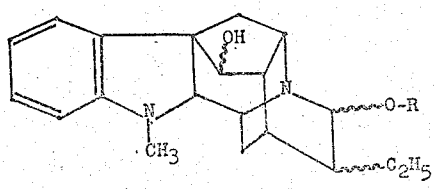
This invention relates to and has for its object the provision of new 21-O-acyl ajmaline compounds. More particularly it concerns compounds of the Formula I



(I)

in which R represents the acyl radical of a carboxylic acid of aliphatic character, the quaternary ammonium derivatives and the salts of these compounds as well as process for manufacturing them.

The acyl radical R represents primarily that of an aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, araliphatic or heterocyclyl-aliphatic carboxylic acid containing up to 15 carbon atoms, such, for example, as the acyl radical of a lower aliphatic monocarboxylic acid, particularly a lower alkane monocarboxylic acid, e.g. formic, acetic, propionic, butyric, pivalic, caproic, 2,2-dimethyl-butyric acid and the like, a lower alkene monocarboxylic acid, e.g. acrylic, methacrylic, crotonic, 3-butene carboxylic acid and the like, a hydroxy-lower alkane monocarboxylic acid, e.g. glycolic, lactic acid and the like, a lower alkoxy-lower alkane monocarboxylic acid, e.g. methoxy-acetic, ethoxy-acetic, β-methoxy-propionic, tri-(methoxymethyl)-acetic acid and the like, a lower alkanoyl-lower alkane monocarboxylic acid, e.g. acetoacetic, pyruvic acid and the like, a lower aliphatic dicarboxylic acid, for example, a lower alkane dicarboxylic acid, e.g. oxalic, malonic, succinic, dimethylsuccinic, glutaric, α,α-dimethyl glutaric, β-methylglutaric acid and the like, a lower alkane dicarboxylic acid half ester with a lower alkanol, e.g. succinic acid monomethyl ester, glutaric acid monoethylester and the like, a lower alkene dicarboxylic acid, e.g. itaconic, maleic, citraconic, pyrocinchonic, xeronic, fumaric acid and the like, a lower alkene dicarboxylic acid half ester with a lower alkanol, e.g. maleic acid monoethyl ester and the like, a hydroxy-lower alkane dicarboxylic acid, e.g. malic, tartaric acid and the like, as well as the optically active forms thereof, a lower alkoxy-lower alkane dicarboxylic acid, e.g. α,β-dimethoxy-succinic acid and the like, a lower alkoxy-lower alkene dicarboxylic acid, e.g. ethoxy-maleic acid and the like, a lower aliphatic tricarboxylic acid, for example, a lower alkane tricarboxylic acid, e.g. tricarballylic acid and the like, a lower alkene tricarboxylic acid, e.g. aconitic acid and the like, a hydroxy-lower alkane tricarboxylic acid, e.g. citric acid and the like, a cycloaliphatic monocarboxylic acid, such as a cycloalkane monocarboxylic acid, in which cycloalkane has from five to seven carbon atoms as ring members, e.g. cyclohexane carboxylic acid and the like, a cycloaliphatic-aliphatic monocarboxylic acid, such as cycloalkyl-lower alkane monocarboxylic acid, in which cycloalkyl has from five to seven carbon atoms as ring members, e.g. β-cyclopentyl-propionic, cyclohexylacetic acid and the like, a monocyclic or bicyclic carbocyclic aryl-aliphatic carboxylic acid, e.g. phenylacetic, β-phenylpropionic, (3,4,5-trimethoxy-phenyl)-acetic, cinnamic, mandelic, 4-methoxy-cinnamic, ferulic, o-ethoxycarbonyl-ferulic acid and the like, a monocyclic or bicyclic heterocyclic aryl-aliphatic carboxylic acid, e.g. 3-pyridyl-acetic, 4-pyridyl-acetic, 2-thienyl-acetic acid and the like, or any other suitable carboxylic acid, such as an amino carboxylic acid, e.g. methionine, tryptophane, lysine, arginine, aspartic, glutamic, hydroxy-glutamic acid and the like.

Quaternary ammonium derivatives of the compounds of this invention are particularly those with a lower alkyl halide, e.g. methyl, ethyl, propyl or isopropyl chloride, bromide or iodide and the like, with a di-lower alkyl sulfate, e.g. dimethyl sulfate, diethyl sulfate and the like, with a lower alkyl lower alkane sulfonate, e.g. methyl or ethyl methane sulfonate or ethane sulfonate and the like, a lower alkyl carbocyclic aryl sulfonate, e.g. methyl p-toluene sulfonate and the like, or any other suitable reactive ester of an alcohol with a strong acid.

Salts of the new compounds of this invention are particularly pharmaceutically acceptable, non-toxic acid addition salts, especially those with inorganic acids or organic carboxylic or sulfonic acids having from one to fifteen carbon atoms, such as with those described hereinafter. Also included are the corresponding quaternary ammonium salts, in which the anion is derived from an inorganic acid other than hydrohalic or sulfuric acids, or an organic carboxylic acid, such as one of those furnishing the acyl radical previously mentioned.

The new compounds of this invention have antifibrillatory properties and are virtually free from toxic and unwarranted side effects at the pharmacologically effective doses. They can, therefore, be used for the treatment of cardiac irregularities, such as auricular or ventricular arrhythmias or fibrillation.

Particularly outstanding antifibrillatory properties are exhibited by 21-O-R_1-ajmaline, 21-O-R_1-isoajmaline and 21-O-R_1-sandwicine (i.e. 21-O-R_1-17-epi-ajmaline), in which R_1 stands for lower alkanoyl, preferably for acetyl, but also for formyl, propionyl, butyryl, pivaloyl, caproyl, 2,2-dimethyl-butyryl and the like, or for lower alkanoyl substituted by lower alkoxy groups, preferably for tri-(methoxymethyl)-acetyl, but also for methoxy-acetyl, ethoxy-acetyl, β-methoxy-propionyl and the like, and their pharmaceutically acceptable, non-toxic acid addition salts and quaternary lower alkylammonium salts.

The new compounds of this invention may be prepared by esterifying ajmaline compounds containing a free 17- and 21-hydroxyl group with a carboxylic acid of aliphatic character or a reactive functional derivative thereof and isolating the 21-O-acyl compounds formed or converting in 21-O-R-ajmaline compounds in which R represents the acyl radical of a carboxylic acid of aliphatic character, and containing in the 17-position a group convertible into a hydroxyl group, this group into a free 17-hydroxyl group and/or, if desired, converting a resulting salt into the free compound or into another salt, and/or, if desired, converting a resulting free compound into a salt or quaternary ammonium compound thereof, and/or, if desired, converting a resulting quaternary ammonium compound into another quaternary ammonium compound.

The esterification procedure may be carried out in an acidic, a neutral or, surprisingly, even in an alkaline medium according to the Schotten-Baumann procedure for esterifying alcohols. The latter modification of the esterification procedure can successfully be applied, though it is well known in the art that the complex ring structure of ajmaline compounds is destroyed by the action of alkaline agents.

The reaction may be performed, for example, by treating the ajmaline compound with a carboxylic acid of aliphatic character or a reactive functional derivative thereof, for example with a halide, e.g. the chloride or

bromide, an anhydride, e.g. the normal or mixed anhydride or ketene, or an ester, such as a lower alkyl or aralkyl ester, e.g. the methyl, ethyl, propyl, butyl, benzyl, p-nitro-benzyl ester and the like. The esterification may be carried out in the presence of an inert diluent, for example a hydrocarbon, such as an alkane, e.g. hexane and the like, a monocyclic carbocyclic aromatic hydrocarbon, e.g. benzene, toluene, xylene and the like, a halogenated hydrocarbon, such as a halogenated aliphatic hydrocarbon, e.g. methylene chloride, chloroform, ethylene chloride and the like, an ether, such as diethylether, tetrahydrofurane, dioxane and the like, or mixtures thereof or any other suitable diluent, or in the absence of a solvent or diluent, for example by treating the ajmaline compound with a corresponding acid anhydride. Depending on the method used for the esterification procedure, several reaction accelerators may be applied. Esterification with the free acid is preferably performed in the presence of a strong mineral acid, such as sulfuric acid and the like, that with an acid halide preferably in the presence of an alkaline agent, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate, such as sodium, potassium or barium hydroxide, potassium or calcium carbonate, sodium bicarbonate and the like, or an organic base, for example a tri-lower alkylamine, e.g. trimethylamine, triethylamine and the like, or a heterocyclic base, e.g. pyridine, collidine and the like. Using an ester as the reactive functional derivative of the acid, several transesterification catalysts may be applied, such for example as alkali metal alcoholates, e.g. sodium methylate and the like, alkali metal cyanides, e.g. potassium cyanide and the like, quaternary ammonium bases, e.g. benzyl-trimethylammonium hydroxide and the like. The above reactions may be carried out under cooling, at normal or elevated temperature, in an open or closed vessel and/or if necessary in the atmosphere of an inert gas, e.g. nitrogen.

In order to obtain the desired new compounds in optimum yields, mild esterification conditions should be applied. Reacting the ajmaline compounds for example with an acid anhydride, it is sufficient to heat the reaction mixture on the steam bath for few minutes only. Using acid halides in the presence of alkaline agents for the esterification, the latter should be carried out below or at room temperature. The new compounds formed, may be isolated in known manner, for example by crystallization, precipitation or chromatography.

The starting materials used are preferably compounds of the Formula I in which R represents hydrogen, such as ajmaline or isoajmaline. Starting materials containing in the 17- and/or 21-position a hydroxyl group opposite to the configuration in ajmaline as is the case, for example, in sandwicine, can be prepared from 17-O-R_2 and/or 21-O-R_2-ajmaline or -isoajmaline, in which R_2 stands for the acyl radical of an organic sulfonic acid, such as an aliphatic or aromatic sulfonic acid, containing up to 15 carbon atoms, e.g. methane sulfonic, ethane sulfonic, p-toluene sulfonic, 4-bromo-benzene sudfonic, 3- or 4-nitro-benzene sulfonic acid and the like, by hydrolysis, if necessary in the presence of a tertiary amine, such as a tri-lower alkylamine, e.g. triethylamine and the like. The 17,21-di-O-R_2-ajmaline or -isoajmaline may be prepared according to the procedure of Anet et al., J. Chem. Soc., 1954, p. 1242, whereas the corresponding monoacylates are obtainable according to the method described above and hereinbelow. Sandwicine and 17-epi-isoajmaline may also be prepared by reduction of ajmalidine or isoajmalidine, for example with catalytically activated hydrogen or with sodium borohydride. Both methods, the hydrolysis and reduction, may be applied in order to obtain the appropriate starting material.

In case the new compounds are prepared by conversion of a group present in the 17-position of 21-O-acyl ajmaline compounds into a free 17-hydroxyl group, those compounds preferably used as starting material, in which the

17-hydroxyl group can be formed without affecting the 21-O-acyl group. Preferred groups convertible into a free 17-hydroxyl group are, for example, the oxo group, acyloxy radicals of carbonic acid half esters, such as the benzyloxycarbonyloxy, tertiary butyloxycarbonyloxy group and the like, or benzyloxy radicals, such as the benzyloxy or α-phenylethoxy radical. These groups can be converted into a hydroxyl group in known manner, for example by treatment with hydrogenating agents, such, for example, as catalytically activated hydrogen. A 17-oxo group present, for example, in 21-O-acyl ajmalidine or isoajmalidine compounds, may also be converted into a 17-hydroxyl group, whose configuration is opposite to that in ajmaline or isoajmaline, by treatment with a complex light metal hydride, such as an alkali metal borohydride, e.g. sodium borohydride. The above reactions are preferably carried out in the presence of inert diluents, for example in those described hereinbefore.

The starting material used in the above procedure can be obtained, for example, by esterifying ajmalidine compounds with a reactive functional derivative of a carboxylic acid of aliphatic character or by protecting both, the 17- and 21-hydroxyl group of ajmaline compounds, for example by esterification with the halide of a carbonic acid half ester, such as carbobenzoxy-chloride and the like or by etherification with benzyl halides, such as benzylchloride and the like. The obtained di-esters can be easily hydrolysed into the 17-O-monoacylates, for example by heating an acid addition salt, such as the monohydrochloride, of the di-esters in water on a steam bath for a short time, for example about 5 to 45 minutes. The aforementioned dibenzylethers may be partially hydrogenolyzed, for example with the stoichiometric amount of catalytically activated hydrogen. In the so obtained compounds containing a protected 17-hydroxyl group, the free 21-hydroxyl group may be esterified with a reactive functional derivative of a carboxylic acid of aliphatic character by methods in themselves known.

Depending on the procedure used, the new compounds are obtained in the free form or in the form of their salts. The salts of the new compounds may be converted into the free bases in a manner known per se, for example by reaction with a basic agent, for example aqueous ammonia, an alkali metal hydroxide, moist silver oxide and the like, or an ion exchange resin.

A resulting salt may be converted into another salt, for example, by treatment with a metal salt of an acid, preferably with such a metal salt of which the metal forms with the anion of the ajmaline compound an insoluble salt, or with an ion exchange resin.

The free bases may be converted into acid addition salts of inorganic or organic, pharmaceutically acceptable, non-toxic acids, if desired in the presence of a suitable solvent or diluent. Acids of the aforementioned kind are for example mineral acids, such as hydrochloric, hydrobromic, sulfuric, phosphoric, nitric or perchloric acid or organic carboxylic or sulfonic acids, such as formic, acetic, propionic, oxalic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, dihydroxymaleic or pyruvic acid; phenylacetic, benzoic, para-aminobenzoic, anthranilic, para-hydroxybenzoic, salicylic or para-aminosalicylic acid; methane sulfonic, ethane sulfonic, hydroxyethane sulfonic or ethylene sulfonic acid; toluene sulfonic, naphthalene sulfonic or sulfanilic acid; methionine, tryptophan, lysine or arginine.

Quaternary ammonium derivatives of the compounds of this invention may be obtained by reacting a resulting free compound with a quaternating agent, preferably a lower alkyl halide, sulfate or sulfonate, such for example as, methyl or ethyl-chloride, -bromide or -iodide, dimethyl or diethyl sulfate, methyl or ethyl-methane sulfonate, -ethane sulfonate or -p-toluene sulfonate and the like.

A resulting quaternary ammonium compound may be converted into another quaternary ammonium compound, such as a quaternary ammonium hydroxide, for example,

by reacting a quaternary ammonium halide with silver oxide, by treating a quaternary ammonium sulfate with barium hydroxide, or a quaternary ammonium salt with an anion exchange preparation, or by electrodialysis. From a resulting quaternary ammonium hydroxide, there may be formed a quaternary ammonium salt by treating it with an acid. Quaternary ammonium salts may be converted directly into other quaternary ammonium salts, for example, a quaternary ammonium iodide, when reacted with silver chloride or with hydrogen chloride in methanol, yields a quaternary ammonium chloride; a corresponding conversion may also be achieved by treating a quaternary ammonium salt with a suitable anion exchange preparation, for example, with those outlined hereinbefore as being useful for the preparation of acid addition salts. The above reactions, for example the salification or quaternization, may be preformed in the presence of a solvent or diluent, if necessary at an elevated temperature and/or in a closed vessel and/or in the atmosphere of an inert gas, e.g. nitrogen.

The invention also comprises any modification of the general process, wherein a compound obtainable as an intermediate at any stage of the process is used as the starting material and the remaining step(s) of the process is (are) carried out; or the process is discontinued at any stage, or in which the starting materials are formed in the course of the reaction or used in the form of their salts. Also included within the scope of the invention are any new intermediates, such, for example, as compounds of the Formula I, in which R represents the acyl radical of an organic sulfonic acid or 21-O-R_3-ajmalidine and 21-O-R_3-isoajmalidine, in which R_3 represents the acyl radical of a carboxylic acid of aliphatic character or of an organic sulfonic acid. Examples for these acyl radicals are given hereinbefore.

In the process of this invention such starting materials are preferably used which lead to final products mentioned in the specification as preferred embodiments of the invention.

The compounds of this invention may be used in the form of pharmaceutical preparations for enteral or parenteral use, which contain the new compounds, particularly the salts thereof in admixture with a pharmaceutical organic or inorganic, solid or liquid carrier. For making up the preparations there can be employed substances which do not react with the new compounds, such as water, gelatine, lactose, starches, stearic acid, magnesium stearate, stearyl alcohol, talc, vegetable oils, benzyl alcohol, gums, propylene glycol, polyalkylene glycols, cholesterol or any other known carrier for pharmaceutical preparations. The latter may be in solid form, for example, as tablets, dragees, capsules and the like, or in liquid form, for example, as solutions, suspensions, emulsions and the like. If desired, they may contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying agents and the like, salts for varying the osmotic pressure, buffers, etc. They also may contain, in combination, other useful substances.

The following examples illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade.

Example 1

To a mixture of 2.00 g. of ajmaline and 20 ml. of tetrahydrofuran, rapidly stirred in a flask cooled in an ice bath, is added dropwise and simultaneously 10 ml. of a 10-n-solution of aqueous sodium hydroxide and a solution of 4 ml. of acetyl chloride in 15 ml. of tetrahydrofuran over a period of 1½ hours at such a rate that the solution is always alkaline. Stirring is continued 30 minutes and then the reaction mixture is extracted with benzene, the extract is washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue (2.40 g.) yields after recrystallization from benzene-hexane 1.04 g. of 21-O-acetyl ajmaline, which melts first at 117°, resolidifies and remelts at 187–188°; $[\alpha]_D$=+100° (in methanol), pk_a=5.4 (80% methyl-Cellosolve).

Example 2

1.389 g. of isoajmaline are acetylated with acetylchloride in tetrahydrofuran and in the presence of sodium hydroxide using the same procedure as described in Example 1. There are obtained 500 mg. of 21-O-acetyl-isoajmaline melting at 210–211°; $[\alpha]_D^{24}$=+36.5° (in methanol), pk_a=4.9 (80% methyl-Cellosolve).

Example 3

The mixture of 933 mg. of 21-O-acetyl-ajmaline, 15 ml. methylene chloride and 3 ml. methyliodide is allowed to stand overnight at room temperature. An oil, representing the 21-O-acetyl-ajmaline methiodide, settles out, which does not crystallize from a number of solvents.

Example 4

The mixture of 244 mg. of 21-O-acetyl-isoajmaline, 10 ml. methylene chloride and 2 ml. of methyliodide is allowed to stand at room temperature overnight. The oil separated crystallizes on scratching. There are obtained 285 mg. of 21-O-acetyl-isoajmaline methiodide which melts at 254–256° and after recrystallization from methanol at 259–261°.

Example 5

The mixture of 22 g. of ajmaline and 100 ml. of acetic acid anhydride is heated on the steam bath for 10 minutes. Thereupon, the acetic acid anhydride is removed under reduced pressure and the residue crystallized from diethyl ether. There are obtained 9 g. of 21-O-acetyl-ajmaline melting at 190–191°.

Example 6

The mixture of 1.00 g. of isoajmaline and 5 ml. acetic acid anhydride is heated on the steam bath for 5 minutes and then evaporated under reduced pressure. The residue crystallizes on addition of diethyl ether and yields 184 mg. of 21-O-acetyl-isoajmaline melting at 210–212°.

Example 7

The mixture of 1.5 g. of ajmaline and 5 ml. of pyridine is added to 2.25 ml. of tri-(methyoxymethyl)-acetyl chloride and the solution is allowed to stand at room temperature for 5 days. Thereupon, the reaction mixture is extracted with methylene chloride and water, the methylene chloride-extract is dried over anhydrous sodium sulfate and evaporated. The residue (2.62 g.) is dissolved in benzene and chromatographed on alumina (neutral), activity III). The material is eluted with benzene, benzene-methylene chloride and finally with methylene chloride, which latter eluate yields the pure 21-O-[tri-(methoxymethyl)-acetyl]-ajmaline, melting at 150–152°.

Example 8

139 mg. of 21-O-[tri-(methoxymethyl)-acetyl]-ajmaline dissolved in 1 ml. of methanol is treated with a diethylether-solution of hydrogen chloride. The solvents are partly removed and the residue again treated with ethereal hydrogen chloride. The precipitated 21-O-[tri-(methoxymethyl)-acetyl]-ajmaline monohydrochloride is filtered off and recrystallized from methanol-diethylether; M.P. 278–280° $[\alpha]_D^{24}$=+87.4° (in methanol).

Example 9

The mixture of 300 mg. of 21-O-acetyl-ajmalidine and 10 ml. of methanol is shaken in an atmosphere of hydrogen in the presence of 50 mg. of pre-reduced platinum oxide. When the uptake of hydrogen has ceased, the catalyst is filtered off and the solution concentrated to dryness. The so obtained 21-O-acetyl sandwicine (21-O-acetyl-17-epi-ajmaline) is an amorphous substance, ν_{OO}=1742 $cm.^{-1}$. Its hydrochloride, prepared according to the method given in Example 8 melts at 250–251° with decomposition.

The starting material can be prepared in the following manner:

The mixture of 375 mg. ajmalidine, 4 ml. of benzene and 0.4 ml. of acetic anhydride is briefly heated on the steam bath. The cooled solution is washed with dilute aqueous ammonia, dried over anhydrous sodiumsulfate and evaporated to dryness. The 21-O-acetyl-ajmalidine formed (400 mg.) is recrystallized from ethanol and melts at 180–182°; ν_{CO}=1745 cm.$^{-1}$ (broad band).

Example 10

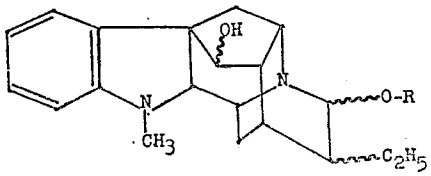
250 mg. of sandwicine in 4 ml. of benzene are heated briefly on the steam bath with 250 mg. of acetyl chloride. The 21-O-acetyl-sandwicine hydrochloride crystallizes out and is filtered off; M.P. 250–251° (dec.). The free base generated from th salt is amorphous but showes the carbonyl band in the infra-red spectrum at 1738 cm.$^{-1}$.

The starting material may be prepared as follows:

300 mg. of ajmalidine dissolved in 10 ml. of methanol are catalytically reduced as in shown in Example 9. The obtained amorphous sandwicine (300 mg.) has the expected properties, for example $[\alpha]_D$=175° (in chloroform), the infra-red spectrum shows no absorption in the carbonyl region.

What is claimed is:

1. A member selected from the group consisting of a compound of the Formula I



(I)

in which R is lower alkanoyl substituted by lower alkoxy, a lower alkyl quaternary ammonium compound thereof, and a non-toxic acid addition salt of such compound.

2. 21-O-R_1-ajmaline, in which R_1 is lower alkanoyl substituted by lower alkoxy.

3. 21-O-R_1-isaojmaline, in which R_1 is lower alkanoyl substituted by lower alkoxy.

4. 21-O-R_1-sandwicine, in which R_1 is lower alkanoyl substituted by lower alkoxy.

5. 21-O-[tri-(methoxymethyl)-acetyl]-ajmaline.

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