

1

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XANTHENE DERIVATIVES AND PROCESS OF MAKING SAME

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The present invention relates to xanthene derivatives and more particularly to xanthene derivatives having a basic side chain in 9-position, and to a process of making same.

Introduction of a basic side chain in 9-position into the xanthene molecule yields compounds which possess valuable pharmacological properties. A number of 9-dialkylamino alkyl xanthenes, for instance, have been described, heretofore, as effective spasmolytic agents. Said compounds are produced by reacting xanthene lithium with dialkyl amino alkyl halogenides. Only lithium xanthene starting material because other metal-organic xanthene compounds could not be produced or were available only with great difficulty. Direct production of a metal-organic xanthene compound by means of a potassium-sodium alloy has also been described. However, the yield of said known metal-organic compound, as determined by conversion into xanthene carboxylic acid, is very low and their method of production, therefore, is only of theoretical interest.

The high price of lithium metal renders the process using xanthene lithium too expensive for large scale production. Attempts to directly react xanthene with sodium metal were unsuccessful because the hydrogen atom in 9-position is not reactive enough. Xanthene differs in this respect fundamentally from fluorene of similar structure. In fluorene, substitution by sodium takes place very readily. Even when mixing xanthene with an organic sodium compound capable of acting as sodium transferring carrier, for instance, with phenyl sodium, no reaction takes place. Thereby it does not make any difference in what respect the reaction conditions, the solvent, and the reaction temperature are varied.

It is one object of this invention to overcome the difficulties encountered heretofore in producing xanthene sodium and to provide a simple and inexpensive process of making such xanthene sodium in an excellent yield.

Another object of this invention is to provide a process of converting said xanthene sodium into xanthene compounds having a basic side chain in 9-position, said process permitting the production of said xanthene compounds of a high degree of purity.

Still another object of this invention is to provide a process of converting xanthene compounds having a basic side chain in 9-position into quaternary ammonium compounds of surprising pharmacological activity.

A further object of this invention is to provide new and valuable xanthene compounds having a basic side chain in 9-position, said compounds combining excellent spasmolytic properties with high antihistaminic activity.

Another object of this invention is to provide new and valuable quaternary ammonium compounds derived from such xanthene compounds with a basic side chain in 9-position, said quaternary ammonium compounds having considerably increased spasmolytic activity without showing any substantial decrease in antihistaminic activity.

Other objects of this invention and advantageous fea-

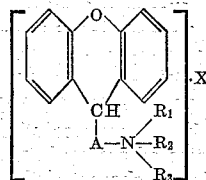
2

tures thereof will become apparent as the description proceeds.

According to the present invention xanthene can be readily converted into xanthene sodium by allowing a carrier capable of transferring sodium metal, to act in statu nascendi in a suitable solvent upon xanthene. The reaction takes place under slightly exothermic conditions. The carrier capable of transferring sodium metal in situ is preferably produced by means of finely divided sodium metal. It was found that the yield of xanthene sodium is considerably increased when using an amount of sodium metal in excess to the equimolecular amount. This is very surprising; for, it could be expected that an excess of sodium metal would have an unfavorable effect since, in general, reaction of the Wurtz-Fittig type are favored by an excess of said metal. However, in contrast thereto, an excess of sodium metal of about 3 to 4 times the theoretical amount is preferably used in this reaction.

Furthermore it was found that the presence of such an excess of sodium metal, even in finely divided form, does not impede or disturb subsequent reaction of the resulting xanthene sodium with basic alkyl halogenides. This is very surprising and it could not be expected that, apparently, xanthene sodium is considerably more reactive and, therefore, reacts much more rapidly with said alkyl halogenides than said excess of sodium metal being present in the reaction mixture. The reaction proceeds almost instantaneously even at low temperatures. Therefore, it is not necessary to keep the heat sensitive basic alkyl halogenides at elevated temperature for a longer period of time. Consequently the alkyl halogenides do not polymerize nor are they destroyed as this is the case on prolonged heating of said halogenides. The resulting reaction product contains only a small amount of impurities and is obtained in a very pure state. The great technical advantage is achieved by the process according to this invention that the reaction can be carried out with inexpensive sodium metal whereby the yield is at least equal to that obtained when working with xanthene lithium. A number of the many basic xanthene compounds obtained according to the new process of this invention exhibit especially favorable properties inasmuch as they combine intensive spasmolytic properties with high antihistaminic activity. Among such compounds there may be mentioned 9-(β -piperidino ethyl) xanthene, 9-(β -pyrrolidino ethyl) xanthene, 9-(β -diisopropyl amino ethyl) xanthene and others.

According to the present invention it is possible to substantially increase the spasmolytic activity of said compounds by converting them into their quaternary ammonium compounds and especially into their methobromides. Such quaternary ammonium compounds correspond to the general formula



wherein A is an alkyl residue and preferably a lower alkyl residue and R₁ and R₂ are alkyl residue and preferably lower alkyl residues and R₁ and R₂ together with the nitrogen atom to which they are attached, a residue which forms a heterocyclic residue, preferably a five to six membered heterocyclic residue, while R₃ is an alkyl residue, preferably a lower alkyl residue and X is an anionic residue, preferably the anionic residue of a hydrogen halide.

It is quite surprising that such quaternization does not impair or reduce their antihistaminic activity; for, it is a

3

well known fact that all known antihistaminic agents lose their antihistaminic activity or at least are considerably reduced in such activity by conversion into quaternary ammonium compounds.

The methobromides of many of such xanthene derivatives have a neurotropic activity which is equal up to about two thirds of the neurotropic activity of atropine. They have about the same musculotropic activity as papaverine, and they are, at the same time, excellent antihistaminic agents. Thus, they represent a very favorable combination of valuable pharmacological properties.

In addition thereto, said methobromides have the further advantage that inhibition of saliva secretion caused by their administration and measured on the narcotized rabbit is only about one hundredth of that caused by administration of atropine. While atropine, even when administered in small doses, produces, as a side-reaction, the well known feeling of dryness in the mouth, the methobromide of 9-(piperidino ethyl)xanthene, for instance, is substantially free of said side-effect. It is evident that the absence of such side-effects is of considerable advantage in clinical administration of said compound.

The following examples serve to illustrate the present invention without, however, limiting the same thereto.

Example 1

200 g. of sodium metal are placed in a flask and are very finely pulverized in 1300 cc. of anisole by vigorous shaking in a nitrogen atmosphere and at a temperature of about 105° C.

The mixture is cooled to about 50° C. 182 g. of xanthene, dissolved in a small amount of warmed anisole are added at said temperature to said mixture. As soon as the reaction mixture has cooled to a temperature of about 35° C., chlorobenzene is added. Thereby the mixture is vigorously stirred and 105 cc. of chlorobenzene are added so slowly that the reaction temperature does not exceed 40° C. After a very short period of time the mixture starts to assume a red color and finally becomes intensely dark red colored. After the addition of chlorobenzene the mixture is cooled to room temperature while stirring vigorously and continuously.

147 g. of β -piperidino ethyl chloride dissolved in 200 cc. of anisole are gradually added to said dark red mixture thereby maintaining the temperature between 40° C. and 45° C. Thereafter stirring is continued for half an hour and 2 liters of methanol are slowly and gradually added to destroy excess sodium metal. The reaction mixture is evaporated to dryness in a vacuum and the residue is extracted with 4 liters of diisopropyl ether. The ethereal solution is filtered and gaseous hydrogen chloride is passed into the filtrate in an amount just sufficient to precipitate the chlorohydrate of the resulting base in crystalline form. After allowing the mixture to stand for some time, the chlorohydrate is filtered off and washed with some diisopropyl ether. Recrystallization from a mixture of isopropanol-di-isopropyl ether (1:1) yields the chlorohydrate of 9-(β -piperidino ethyl) xanthene in substantially pure condition in the form of colorless crystals melting at 200–202° C.

Precipitation of the aqueous solution of said chlorohydrate with an excess of ammonia yields the free base in colorless crystals of characteristic odor. The base melts at 56° C. Yield: About 240 g.

Example 2

130 g. of β -pyrrolidino ethyl chloride dissolved in 200 cc. of anisole are gradually added to xanthene sodium prepared from 182 g. of xanthene in the manner described in Example 1. Care must be taken that the temperature of the reaction mixture does not exceed 45° C. during the addition of said chloride. Thereafter, the reaction mixture is kept at 40° C. for 30 minutes and excess sodium metal is then decomposed by the addition

4

of methanol. 300 cc. of water are added and the solvents are distilled off. 2 liters of di-isopropyl ether are added to the residue and the resulting solution, after filtration, is extracted with 1 liter of dilute hydrochloric acid. Decolorizing carbon is added to the hydrochloric acid solution which is then filtered. Sufficient amounts of dilute sodium hydroxide are added to render the filtrate alkaline. 9-(β -pyrrolidino ethyl) xanthene base precipitates first as an oil which subsequently solidifies. Said base is filtered off, washed with water, and dried. Melting point: 81–82° C.

On dissolving said base in di-isopropyl ether and precipitation with gaseous hydrogen chloride, the chlorohydrate of said 9-(β -pyrrolidino ethyl) xanthene, melting at 210° C. is obtained. It is readily soluble in water and ethanol.

Example 3

20 g. of sodium metal are finely pulverized by shaking in 130 cc. of anisole in a nitrogen atmosphere at 115° C. The suspension is allowed to cool to 40–50° C. 18.2 g. of xanthene, dissolved in anisole, are added to said suspension and are thoroughly mixed therewith. As soon as the temperature has decreased to about 35° C., 10.5 cc. of chlorobenzene are added, drop by drop, to said mixture. Care must be taken that the temperature during such addition of chlorobenzene does not exceed 40° C. About 1 hour after said addition has been completed, a solution of 16 g. of di-isopropyl amino ethyl chloride in 60 cc. of anisole is slowly added, thereby maintaining the temperature between 45° C. and 50° C. The light red color disappears and the reaction mixture assumes a brown color. Excess sodium is destroyed with 200 cc. of methanol whereafter the reaction mixture is evaporated to dryness, at the end in a vacuum. The residue is extracted by means of di-isopropyl ether and the ethereal solution is precipitated by introducing gaseous hydrogen chloride. The precipitated crude chlorohydrate of 9-(β -di-isopropyl amino ethyl) xanthene is recrystallized from acetone or a mixture of isopropanol and di-isopropyl ether (1:1). Colorless fine needles are obtained which melt at 180° C. and which are readily soluble in water and ethanol.

The base obtained from said chlorohydrate in the manner described in Example 1, is solide.

Example 4

200 g. of 9-(β -piperidino ethyl) xanthene are dissolved in 900 cc. of methyl ethyl ketone and an excess of methyl bromide is introduced into said solution. The temperature of the reaction mixture increases considerably. Crystallization sets in after a certain period of time. As seen as crystals stop to precipitate, the precipitate is filtered off, washed with ether, and dried. The resulting methobromide of 9-(piperidino ethyl) xanthene forms colorless crystals which are very readily soluble in water and melt at 218° C.

In place of anisole there may be used, while otherwise proceeding as described in the above given examples, other inert non-polar organic solvents, such as ether, dibutylether, methylcellosolve, although anisole is the preferred solvent.

Likewise, in place of chloro benzene, there may be employed bromo benzene, iodo benzene.

Other halogenides of organic bases than those employed in the preceding examples may also be used, such as di-lower alkyl amino lower alkyl halogenides, for instance, dimethyl amino methyl halogenides, di-n-propyl amino propyl halogenides, di-n-butyl amino ethyl halogenides, methyl butyl amino ethyl halogenides, diallylaminethyl halogenides or 2-methyl pyrrolidino ethyl halogenides, morpholino ethyl halogenides, 2-methylpiperidino ethyl halogenides, 2,6-dimethylpiperidino ethyl halogenides.

Quaternization may be effected by other alkyl halogenides than methyl bromide, for instance, by methyl

5

iodide, methyl chloride, benzyl chloride, or by dimethyl sulfate, diethyl sulfate.

In place of methyl ethyl ketone there may be used as inert organic solvent other ketones such as acetone, diethyl ketone, methylisobutyl ketone or other inert solvents, such as alcohol, isopropanol or the quaternizing agent itself.

The temperature during formation of xanthene sodium and reaction with the organic base preferably does not exceed 45° C. since at lower temperature better yields and purer products are obtained.

Many other changes and variations in the reaction conditions, the concentrations of solutions of the reactants, the reaction temperature and duration, the methods of working up the reaction mixtures and of isolating and purifying the reaction products, and the like may be made by those skilled in the art in accordance with the principles set forth herein and in the claims annexed thereto.

The 9-dialkyl amino alkyl xanthene compounds as produced according to the present invention and their quaternary ammonium derivatives are preferably administered perorally in the form of liquid or solid preparations.

Such preparations are obtained, for instance, by diluting the active compounds with a solid pulverulent extending agent or pharmaceutical carrier to form an intimate mixture thereof. The components of said mixture are, for instance, intimately mixed in a ball mill or the like device to the desired degree of fineness, or the finely powdered solid carrier is impregnated with a solution of said compounds in water or another suitable solvent whereafter the water or solvent is removed by evaporation, preferably while milling.

Said 9-dialkyl amino alkyl xanthene compounds and their quaternary ammonium derivatives may also be converted into tablets, pills, and the like compressed preparations whereby the commonly used diluting agents, binders, and the like additives are employed, such as sugar, lactose, talcum, starch, bolus alba, pectine, and, as binders, gelatine, gum arabic, methyl cellulose, yeast extract, agar, tragacanth, and others. When using water soluble diluents and binders, tablets etc. are obtained which are water soluble and may be used for preparing dilute aqueous solutions of said active compounds.

The content of active compound in said preparations may be varied. It is necessary that the active compound is present in said preparations in such an amount that a suitable dosage will be ensured. Ordinarily the preparation should not contain less than 0.1% of the active compound. The preferred amounts to be employed are between 5% and 25% of the preparation. To use greater amounts is also possible although administration of suitable doses becomes more difficult. Tablets containing, for instance, between about 25 mg. and 125 mg. and preferably about 50 mg. of the active compound per tablet have proved to be especially suitable.

The following examples illustrate in what manner suitable preparations for therapeutical use are prepared without, however, being limited thereto.

Example 5

9-(β -pyrrolidino ethyl) xanthene chlorohydrate	250.0	G.
Potato starch	34.0	
Pectine	8.0	

are intimately mixed with each other and successively granulated first with a solution of

Stearic acid	5.0	G.
in isopropyl alcohol	25.0	

and then with a solution of

Gelatine	3.0	g--
in water	25.0	cc--

The granulated mass is passed through a suitable sieve,

6

superficially dried, again passed through the sieve, and completely dried. Tablets weighing about 120 mg. and containing about 100 mg. of the xanthene compound, are pressed from said granulated mass.

Example 6

Vanillin	0.4	G.
Potato starch	6.6	

are finely ground and intimately mixed with each other. To said mixture there is added an intimate mixture of

9-(β -di-isopropyl amino ethyl) xanthene metho-		G.
bromide	30.0	
Potato starch and	122.5	
lactose	122.5	

The resulting mixture is successively granulated first with a solution of

Gelatine	6.0	g--
in water	60.0	cc--

and then with a solution of

Stearic acid	6.0	g--
in isopropyl alcohol	20.0	cc--

The well mixed mass is passed through a suitable sieve, dried superficially, and mixed with

Talcum	6.0	G.
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The mixture is again passed through the sieve and is completely dried. Tablets weighing about 0.5 g. which contain about 50 mg. of the xanthene compound are pressed from said mass. The tablets may be sugar coated.

Other preparations for therapeutical use may be produced in a similar manner.

Such preparations are successfully administered as effective, non-narcotic spasmolytic agents causing relaxation of smooth muscle by direct papaverine-like action and by indirect atropine-like action through the autonomic nervous system. They possess also a marked antihistaminic activity. They have been found of value in the treatment of gastro-intestinal irritability responsible for cariospasm, and, generally, in relaxing spasms of the gastrointestinal, biliary, and genito-urinary tracts. Administration of 50 mg. to 150 mg. initially to determine tolerance and effect and of the thus determined dosage every 6 hours has given satisfactory results.

I claim:

1. In a process of producing xanthene derivatives having a basic side chain in 9-position, the steps comprising contacting xanthene in a non-polar organic solvent with a sodium-transferring agent in statu nascendi and adding to the resulting xanthene sodium a halogen substituted organic base.

2. In a process of producing xanthene derivatives having a basic side chain in 9-position, the steps comprising shaking sodium metal in a non-polar organic solvent at elevated temperature to convert said sodium metal into the finely divided state, adding to said finely divided sodium metal an organic carrier having a halogen atom replaceable by sodium in its molecule, contacting xanthene with the resulting solution of the sodium-transferring agent in statu nascendi and adding to the resulting xanthene sodium a halogen substituted organic base.

3. In a process of producing xanthene derivatives according to claim 2, wherein an excess of sodium metal over the equimolecular amount is used.

4. In a process of producing xanthene derivatives according to claim 3, wherein the excess of sodium metal is an excess of three to four times the equimolecular amount.

5. In a process of producing xanthene derivatives according to claim 1, wherein the temperature during for-

mation of xanthene sodium and reaction with the organic base does not exceed 45° C.

6. In a process of producing xanthene derivatives having a basic side chain in 9-position, the steps comprising contacting xanthene in a non-polar organic solvent with a sodium-transferring agent in statu nascendi, adding to the resulting xanthene sodium a halogen substituted organic base, and reacting the resulting xanthene derivative substituted in 9-position by a basic side chain, with a quaternizing reagent.

7. In a process of producing xanthene derivatives according to claim 6, wherein the quaternizing agent is an alkyl halogenide.

8. In a process of producing xanthene derivatives according to claim 7, wherein the quaternizing agent is methyl bromide.

9. In a process of producing xanthene derivatives according to claim 7, wherein the quaternizing agent is reacted with the xanthene derivative in the presence of an inert organic solvent.

10. In a process of producing xanthene derivatives according to claim 9, wherein the inert organic solvent is methyl ethyl ketone.

11. In a process of producing xanthene derivatives having a basic side chain in 9-position, the steps comprising adding xanthene to a suspension of finely divided sodium metal in anisole, gradually adding a halogeno benzene at elevated temperature to said mixture at such a rate that the temperature of the reaction mixture does not substantially exceed about 40° C., and adding to the resulting xanthene sodium solution a halogen substituted organic base.

12. In a process of producing 9-(β -piperidino ethyl) xanthene, the steps comprising adding xanthene to a suspension of finely divided sodium metal in anisole, gradually adding chlorobenzene at elevated temperature to said mixture at such a rate that the temperature of the reaction mixture does not substantially exceed about 40° C. while stirring vigorously, gradually adding a solution of β -piperidino ethyl chloride in anisole to the resulting xanthene sodium solution, thereby maintaining the temperature of the reaction mixture between about 40° C. and about 45° C., and continuing stirring until the reaction between xanthene sodium and β -piperidino ethyl chloride is substantially completed.

13. In a process of producing 9-(β -piperidino ethyl)

xanthene methobromide, the steps comprising adding xanthene to a suspension of finely divided sodium metal in anisole, gradually adding chlorobenzene at elevated temperature to said mixture at such a rate that the temperature of the reaction mixture does not substantially exceed about 40° C. while stirring vigorously, gradually adding a solution of β -piperidino ethyl chloride in anisole to the resulting xanthene sodium solution, thereby maintaining the temperature of the reaction mixture between about 40° C. and about 45° C., continuing stirring until the reaction between xanthene sodium and β -piperidino ethyl chloride is substantially completed, and reacting the resulting 9-(β -piperidino ethyl) xanthene with methyl bromide to form the methobromide thereof.

14. In a process of producing 9-(β -pyrrolidino ethyl) xanthene, the steps comprising adding xanthene to a suspension of finely divided sodium metal in anisole, gradually adding chlorobenzene at elevated temperature to said mixture at such a rate that the temperature of the reaction mixture does not substantially exceed about 40° C. while stirring vigorously, gradually adding a solution of β -pyrrolidino ethyl chloride in anisole to the resulting xanthene sodium solution, thereby maintaining the temperature of the reaction mixture between about 40° C. and about 45° C., and continuing stirring until the reaction between xanthene sodium and β -pyrrolidino ethyl chloride is substantially completed.

15. In a process of producing 9-(β -di-isopropylamino ethyl) xanthene, the steps comprising adding xanthene to a suspension of finely divided sodium metal in anisole, gradually adding chlorobenzene at elevated temperature to said mixture at such a rate that the temperature of the reaction mixture does not substantially exceed about 40° C. while stirring vigorously, gradually adding a solution of β -di-isopropylamino ethyl chloride in anisole to the resulting xanthene sodium solution, thereby maintaining the temperature of the reaction mixture between about 45° C. and about 50° C., and continuing stirring until the reaction between said xanthene sodium and β -di-isopropylamino ethyl chloride is substantially completed.

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