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ACETATES OF 3-PIPERIDINOL

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9 Claims. (Cl. 260—294.3)

This invention relates to an ester of cyclic amino-alcohols and particularly to an acetic ester of N-ethyl-3-piperidinol and the salts thereof.

This application is a continuation-in-part of application Serial No. 180,295, filed August 18, 1950, now abandoned, and Serial No. 217,413, filed March 24, 1951, now abandoned.

The reduction of smooth muscle spasm, whether of musculotropic or neurotropic, by atropine, and by various synthetic compounds related in structure to atropine or papaverine, is well known. While many of these compounds will effectively abolish one or the other type of spasm, they are not capable of relieving both types of muscle spasm. Furthermore, the action of the known compounds is usually accompanied by undesirable side effects such as dilatation of the pupil of the eye, dryness of the mouth, large increase in rate of heart beat, hypotension, nausea, and vomiting.

Some esters of N-alkyl-4-piperidinol have been found to be active anti-spasmodics or spasmolytics, but such esters have never been put into use. It is well known that changes in the positions of certain substituents on the piperidine ring may produce profound differences in the physiological activity and effects of such compounds, which differences are not predictable. Thus, N-methyl-4-phenyl-4-propionoxy-piperidine is a potent analgesic, whereas, the corresponding N-methyl-2-phenyl-2-propionoxy-piperidine has only slight analgesic properties, and beta-4-methyl-piperidine-ethyl benzoate has considerable anesthetic action while the 2- and 3-methyl derivatives have no such action. Hence, it will be seen that shifting a group from the 4-position of the piperidine ring may cause complete loss of activity.

I have found that substituted acetic acid esters of N-ethyl-3-piperidinol are effective as an anti-spasmodic in both musculotropic and neurotropic spasms and have longer duration of action with fewer undesirable side effects than various other anti-spasmodics now used.

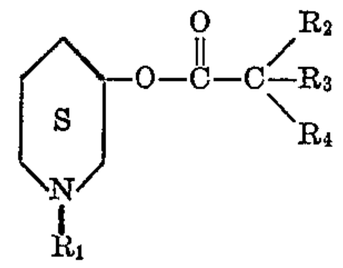
It is, therefore, an object of the present invention to provide a compound for pharmaceutical purposes and having the effect of reducing either involuntary muscle or nervous spasm.

Another object of the invention is to provide a compound having an anti-spasmodic effect in humans, which compound is long lasting in action and which will have only a few undesirable side reactions of minor importance.

A further object of the invention is to provide a series of substituted acetic acid esters of N-ethyl-3-piperidinol having longer activity and side reactions both less in number and of lower intensity than other compounds now in use for reducing spasm of human muscle or nerves.

Generally, the present invention includes the substituted acetic acid esters of N-alkyl-3-piperidinol and the salts thereof and the preparation of such compounds by

the use of simple equipment and procedures. The compounds conform to the type formula:



where:

R_1 is an alkyl radical

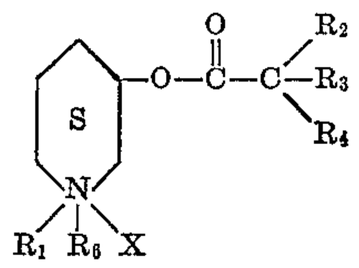
R_2 is H or OH

R_3 is a phenyl, 2-thienyl, cyclohexyl or cyclopentyl radical

R_4 is a phenyl, cyclohexyl, cyclopentyl, or 2-thienyl radical, and

R_3 and R_4 together are a fluorenyl or xanthenyl radical.

The piperidine ring may also have other additives on the N, conforming to the type formula:



where: R_1 and R_6 are lower alkyl radicals and X is an inorganic radical.

N-ethyl-3-piperidyl-diphenylacetate hydrochloride was formed by heating equimolecular amounts of N-ethyl-3-piperidinol and diphenylacetyl chloride in the presence of a solvent for the reactants. The hydrochloride salt was precipitated and is readily purified by recrystallization from a suitable solvent. The free base N-ethyl-3-piperidyl diphenylacetate was obtained as an oily material, by treating the said hydrochloride with sodium hydroxide. N-ethyl-3-piperidyl-diphenylacetate-methiodide was formed by treating free N-ethyl-3-piperidyl-diphenylacetate in an ether solution with methyl iodide.

N-methyl-3-piperidyl-diphenylacetate and its hydrochloride salt differ from the preceding compositions by the substitution of a methyl group on the N of the piperidine ring. The base was made by refluxing N-methyl-3-hydroxy-piperidine with diphenylacetyl chloride and pyridine. The refluxed material is neutralized and extracted with ether. The extract was dried and the ether removed, and the base recovered by vacuum distillation. A solution of the base in ethereal hydrochloric acid precipitated the hydrochloride in crystalline form.

N-ethyl-3-piperidyl-phenylcyclohexylacetate and its hydrochloride and other salts differ from the above compounds by reduction of one of the rings of the diphenylacetic acid moiety to a cyclohexyl ring. Such reduction was carried out in glacial acetic acid with platinum oxide to give phenylcyclohexylacetic acid. The acid was treated with thionyl chloride to obtain the chloride of the acid which was then reacted with pyridine and N-ethyl-3-piperidinol. The resulting compound was neutralized, extracted with ether and dried. After removing the ether, vacuum distillation gave the desired base. The hydrochloride of the above base was formed by dissolving the base in ether and adding ethereal hydrochloric acid. The methobromide of the above base was formed by dissolving the above base in ethyl alcohol and adding methyl-

bromide which is allowed to stand until the reaction is completed. The mixture was then concentrated and the volatiles were removed.

N - ethyl - 3 - piperidyl - benzilate hydrochloride differs from the preceding compounds by the addition of a hydroxy group to the diphenylacetic acid moiety. N-ethyl-3-chloro-piperidine, benzilic acid and isopropanol were refluxed together, filtered and concentrated in vacuo. The concentrate was dissolved acidified and the unreacted acid was removed with ether. After neutralizing the aqueous layer of the mixture, the product was extracted with ether and the solution was dried. The ether was removed and the free base was obtained by vacuum distillation. The hydrochloride was made by treating the free base with ethereal hydrochloric acid.

N-ethyl-3-piperidyl-9-fluorene carboxylate was formed by refluxing 9-fluorene carboxylic acid chloride and N-ethyl-3-hydroxy piperidine in pyridine. A large excess of water was added to the refluxed mixture and the desired product was extracted from the mixture with ether. The mixture was distilled and the distillate was treated with anhydrous ether and hydrochloric acid. The precipitate was crystallized from acetone.

N-ethyl-3-piperidyl-9-xanthene carboxylate was made by refluxing xanthene-9-carboxylic acid and N-ethyl-3-chloro-piperidine in isopropanol. The residue was dissolved in hydrochloric acid and was extracted with ether.

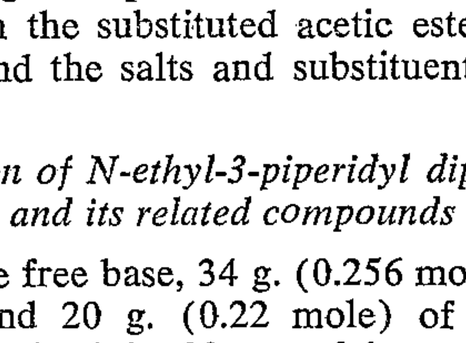
The acid layer is made alkaline and again extracted with ether and ether then removed. The residue was heated, dissolved and acidified to form a precipitate. After removal of solvent, the precipitate was crystallized from isopropanol.

As used in the present application, the word "ester" includes both the esters in the free state and esters combined with, or with various added acids to form salts.

The following examples for illustrative purposes only, show how both the substituted acetic esters of N-ethyl-3-piperidinol and the salts and substituents thereof may be prepared.

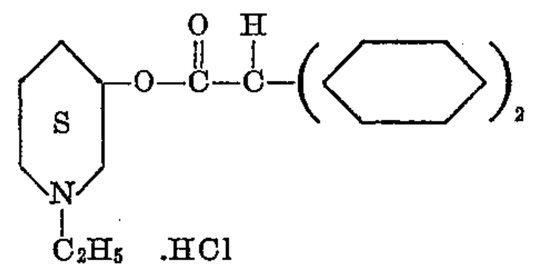
A. *Preparation of N-ethyl-3-piperidyl diphenylacetate, and its related compounds*

To obtain the free base, 34 g. (0.256 mole) of N-ethyl-3-piperidinol and 20 g. (0.22 mole) of diphenylacetyl chloride were mixed in 80 cc. of isopropanol and the solution was refluxed for two hours. The isopropanol was evaporated in vacuo at 30 mm. pressure, the residue was dissolved in 150 cc. of water and the aqueous solution was extracted several times with ether. The aqueous solution was then neutralized with potassium carbonate and extracted with ether. The ethereal solution was dried over anhydrous potassium carbonate and the ether removed by distillation. The product was then distilled at its boiling point 180–181° C. at 0.13 mm. of mercury whereby 14 g. of a clear yellow, viscous liquid was obtained. The nitrogen content for $C_{21}H_{25}NO_2$ was calculated as 4.33% and the nitrogen content found was 4.21%. The structural formula for the free base is:



A mixture of 4.5 g. (0.02 mole) of diphenylacetyl chloride and 2.6 g. (0.02 mole) of N-ethyl-3-piperidinol were dissolved in 50 cc. of acetone and refluxed for three hours. The precipitate was filtered out and washed. The precipitate was then dissolved in isopropyl alcohol and recrystallized, a single recrystallization yielding N-ethyl-3-piperidyl-diphenylacetate hydrochloride melting at 173–174° C. The yield was 4.2 g. (60% of theoretical). The salt is water soluble and ether insoluble and

has a high melting point. The structural formula for the above salt is:

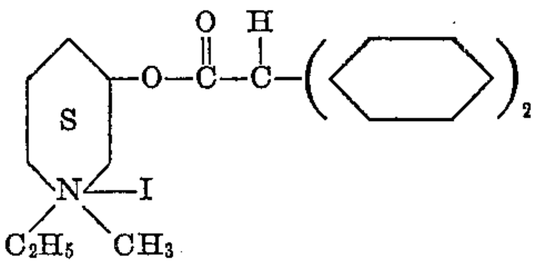


The chlorine content for

$C_{21}H_{26}ClNO$ (or $C_{21}H_{25}NO_2$:HCl)

was calculated as 9.87% and the chlorine content found was 9.79%.

To obtain N-ethyl-3-piperidyl-diphenylacetate-methiodide, 3.23 g. (0.01 mole) of the above free base was dissolved in anhydrous ether and 2.84 g. (0.02 mole) of methyl iodide added. This mixture was allowed to stand whereupon a crystalline precipitate slowly appeared. After one day the product was filtered off to give 4 g. of light yellow material which showed a melting point with decomposition, at 70° C. The compound is soluble in water and in alcohol. The structural formula is:

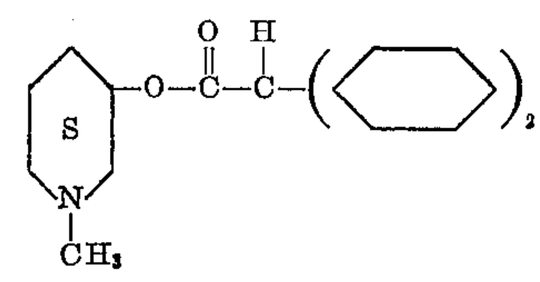


The calculated iodine content of $C_{22}H_{28}NIO_2$ is 27.3% and the content found was 27.7%. The calculated nitrogen content of the above compound is 3.04% and the content found was 2.98%.

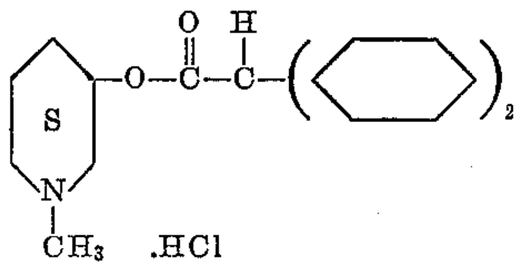
B. *Preparation of N-methyl-3-piperidyl-diphenylacetate hydrochloride, and its related compounds*

3-hydroxy pyridine was catalytically reduced (by the method of Chen-Heng Kao disclosed in Volume 44 of Chemical Abstracts, page 3993) to 3-hydroxy-piperidine with a boiling point of 67–69° C. at 2 mm. of mercury pressure. 9.0 g. (0.09 mole) of 3-hydroxy-piperidine were mixed with 13.1 g. (0.25 mole) of 88% formic acid and 8.9 g. (0.11 mole) of 37% formaldehyde solution and the mixture was refluxed for twenty-four hours. After addition of 5 ml. of concentrated hydrochloric acid, the mixture was distilled at 30 mm. mercury pressure to remove all volatiles. The residue was dissolved in 20 ml. water and the solution was saturated with potassium hydroxide. The solution was then extracted with ether and the ether was removed by distillation. N-methyl-3-hydroxy-piperidine was obtained by distillation and had a boiling point of 81° C. at 15 mm. of mercury. The yield was 7.0 g. (67% of theoretical). The N content for $C_6H_{13}NO$ was calculated as 11.92% and a content of 11.75% was found.

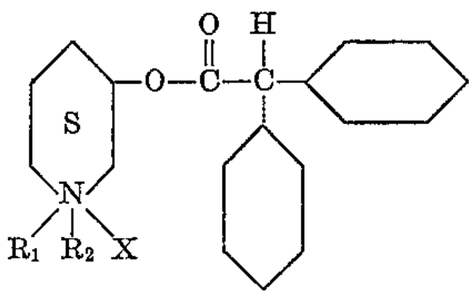
To obtain N-methyl-3-piperidyl-diphenylacetate, 4.5 g. of N-methyl-3-hydroxy-piperidine (0.039 mole) was mixed with 4.0 g. of diphenyl-acetylchloride (0.039 mole) and 50 cc. of dry pyridine which was used as a solvent and was therefore in large molar excess. The mixture was refluxed for four hours and 200 ml. of water containing 30 g. of sodium bicarbonate was added. The solution was extracted with ether and dried with potassium carbonate. The ether was removed by distillation and the desired product was obtained by distilling at 0.06 mm. of mercury. The boiling point of the product was 160–163° C. and 3.0 g. of N-methyl-3-piperidyl-diphenylacetate was obtained. The free base is:



The free base was dissolved in ether and ethereal hydrochloric acid solution was added to obtain 2.7 g. of the crystalline hydrochloride. The product was recrystallized from hot acetone and had a melting point of 193–194° C. For $C_{20}H_{24}ClNO_2$, a Cl content of 10.29% and an N content of 4.06 were calculated. A Cl content of 10.31% and an N content of 4.13% were found. The structural formula is:



From the above examples it will be apparent that various other "onium" compounds can be prepared, such compounds being of the character in which the electronic relations provide one or more so-called "lone electronic pairs" which give a central atom a valence greater than its normal value. Hence, the type compound can be expressed by the structural formula:

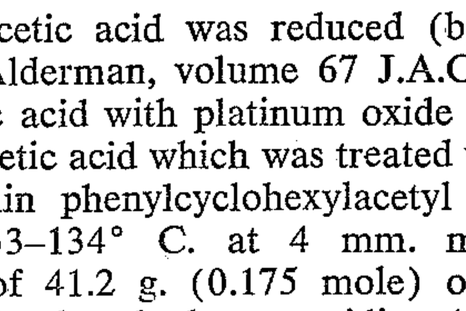


where R_1 and R_2 are lower alkyl radicals and X is an inorganic radical such as a halogen, sulfate or other similar radical.

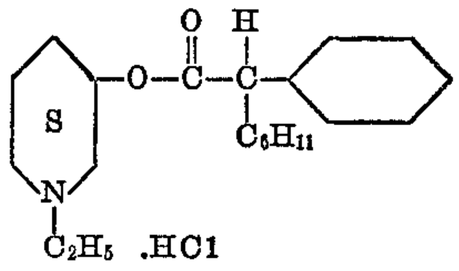
In the above compounds, however, it is preferred that R_1 be an ethyl and that R_2 be a lower alkyl radical, for the uses to which the present compounds are to be put.

C. *Preparation of N-ethyl-3-piperidyl-phenylcyclohexylacetate, and its related compounds*

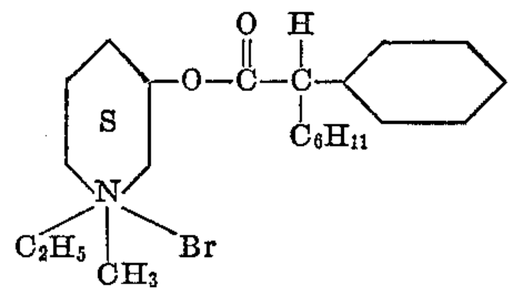
Diphenylacetic acid was reduced (by the method of Smith and Alderman, volume 67 J.A.C.S. page 272) in glacial acetic acid with platinum oxide to obtain phenylcyclohexylacetic acid which was treated with thionyl chloride to obtain phenylcyclohexylacetyl chloride, boiling point of 133–134° C. at 4 mm. mercury pressure. A mixture of 41.2 g. (0.175 mole) of the above acid chloride, 200 ml. anhydrous pyridine (as a solvent having no quantitative relation to the reactants) and 22.6 g. (0.175 mole) of N-ethyl-3-piperidinol was refluxed for six hours. The reaction product was neutralized by addition of 1 liter of 5% of sodium bicarbonate solution. The oily layer was extracted with ether and the extract dried with potassium carbonate. The ether was distilled off and the residue was distilled at 0.55 mm. of mercury. The product boiled at 172–174° C. and a yield of 45.3 g. (78.9% of theoretical) of N-ethyl-3-piperidyl-phenylcyclohexyl-acetate was obtained. The structural formula for the free base is:



10.0 g. of the above intermediate was dissolved in anhydrous ether and treated with an ethereal solution of hydrochloric acid. The oily yellow product was treated with acetone to obtain a white crystalline precipitate melting at 208–215° C. The product was recrystallized from isopropyl alcohol and had a melting point of 214–216° C. A yield of 10.2 g. was obtained which is 93% of theoretical. Based on the formula $C_{21}H_{32}ClNO$, the content of Cl was calculated to be 9.72% and the content of N was calculated to be 3.82%. The Cl content of 9.50% and N content of 3.55% were found. The structural formula of N-ethyl-3-piperidyl-phenylcyclohexylacetate hydrochloride is:



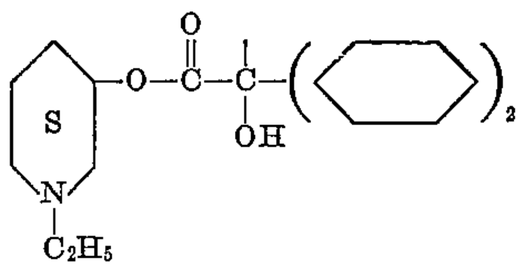
The methobromide derivative of the above base was obtained by dissolving 15.3 g. (0.046 mole) of the above intermediate in 100 cc. of cold ethyl alcohol to which 15.2 g. (0.16 mole) of methyl bromide was added. The mixture was placed in a closed citrate bottle and allowed to stand for one hundred forty-four hours at room temperature. The mixture was then concentrated at 30 mm. of mercury pressure and a yellow oily product was obtained. All of the volatiles were removed from the product in a vacuum desiccator at 2 mm. of mercury. A white powder was obtained which is hygroscopic and the melting point thereof, which was determined in a sealed tube, was found to be 126–127° C. A yield of 14.3 g. (73% of theoretical) was obtained. For the formula $C_{22}H_{34}BrNO_2$, Br content of 18.83% and N content of 3.31% were calculated. Br content of 18.49% and N content of 3.27% were found. The structural formula for N-ethyl-3-piperidyl-phenylcyclohexylacetate methobromide is:



D. *Preparation of N-ethyl-3-piperidyl benzilate, and its related compound*

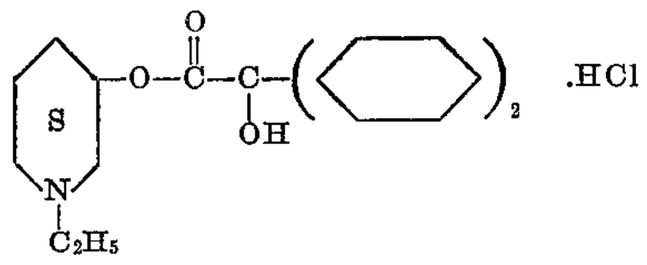
N-ethyl-3-chloropiperidine was prepared according to the method of Fuson and Zirkle described in volume 70, J.A.C.S., page 2760. 12.0 g. (0.081 mole) of N-ethyl-3-chloropiperidine was mixed with 18.6 g. (0.081 mole) of benzilic acid and 80 cc. of anhydrous isopropyl alcohol as a solvent. The mixture was refluxed for seventy-two hours. The solution was then filtered and concentrated at 30 mm. of mercury. The concentrate was dissolved in water, acidified with hydrochloric acid and extracted with ether to remove the unreacted benzilic acid.

The aqueous layer was neutralized with sodium bicarbonate and the product was extracted with ether. The etheral solution of the product was dried with potassium carbonate, the ether was removed by distillation and the residue was distilled at 0.12–0.18 mm. of mercury, the boiling point being 194–198° C. A yield of 16.5 g. (60% of theoretical) of N-ethyl-3-piperidyl-benzilate was obtained. The structural formula is:



6.4 g. of the above free base was dissolved in acetone and ethereal hydrochloric acid added. 6.2 g. of white crystals were obtained, the crystals having a melting point of 186–187° C. The yield was 86% of theoretical. For the formula $C_{21}H_{26}ClNO_3$, a chlorine content of 9.45%

was calculated and the content found was 9.29%. A nitrogen content of 3.72% was calculated and the nitrogen content found was 3.62%. The structural formula for N-ethyl-3-piperidyl-benzilate hydrochloride formula is:

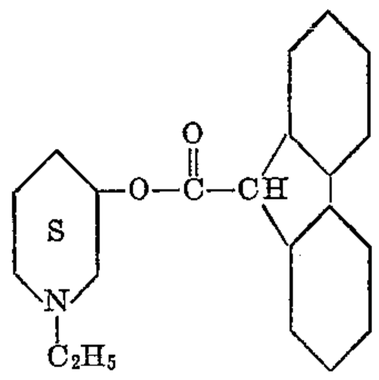


It will be apparent from the various examples given above that other piperidyl esters may be made with different acid moieties.

E. *Preparation of N-ethyl-3-piperidyl-9-fluorene-carboxylate*

A mixture of 14.0 g. (0.064 mole) of 9-fluorene-carboxylic acid chloride and 9.0 g. (0.074 mole) of N-ethyl-3-hydroxy piperidine was dissolved in 60 cc. pyridine and was refluxed for one hour. The product was cooled and mixed with 400 cc. of water. The oily yellow precipitate was extracted with ether and the extract was dried over potassium carbonate. The extract was distilled at 0.3 mm. of mercury at 205–215° C. to obtain 2.0 g. of distillate.

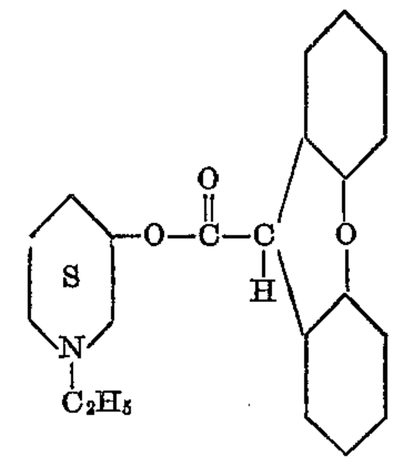
The distillate was dissolved in anhydrous ether and acidified with ethereal hydrochloric acid. A gummy precipitate formed from which the ether was decanted. The precipitate was crystallized from acetone to yield 0.1 g. of the desired product (0.4% of theoretical), melting at 226–227° C. For the formula $C_{21}H_{24}ClNO_2$, a Cl content of 9.94% was calculated and Cl content of 9.97% was found. The structural formula of the above base is:



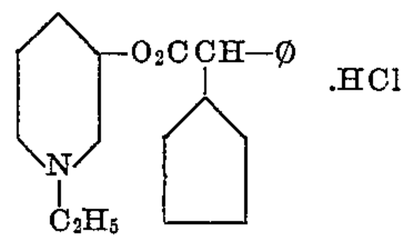
F. *Preparation of N-ethyl-3-piperidyl-9-xanthene carboxylate*

A mixture of 11.0 g. (0.049 mole) of xanthene-9-carboxylic acid and 7.2 g. (0.049 mole) of N-ethyl-3-chloropiperidine was dissolved in 50 cc. of dry isopropyl alcohol and refluxed for seventy-two hours. The mixture was then concentrated at 30 mm. pressure.

The residue was partially dissolved in dilute aqueous hydrochloric acid and extracted twice with ether. The aqueous layer was made alkaline with sodium hydroxide solution and extracted with ether. The extract was dried over potassium carbonate and the ether was removed by distillation. The residue was first heated over a bath water under a vacuum of 2 mm. mercury to remove low boiling point materials and was then dissolved in anhydrous ether and acidified with ethereal hydrochloric acid. A gummy precipitate formed from which the ether was decanted. The precipitate was crystallized in hot isopropyl alcohol to yield 4.1 g. (22% of theoretical) of the desired product. The product had a melting point of 226–227° C. For the formula $C_{21}H_{24}ClNO_3$, a Cl content 9.51% was calculated and Cl content of 9.34% found. An N content 3.75% was calculated and N content 3.74% found. The structural formula of the above free base is:



G. *Preparation of N-ethyl-3-piperidyl phenylcyclopentyl-acetate and hydrochloride thereof*



To 114 g. (0.88 mole) of N-ethyl-3-hydroxypiperidine in 500 cc. of anhydrous benzene was added 196.6 g. (0.88 mole) of phenylcyclopentylacetyl chloride in 500 cc. of benzene in the presence of 107 g. (1.06 moles) of triethylamine. The reaction mixture was stirred at 65–75° C. for 4 hours and the triethylamine hydrochloride removed by filtration. The filtrate was distilled and the basic ester collected at 154–178° C. (0.04 mm.), yield 220 g. (79%).

The hydrochloride salt was formed in acetone by the addition of ethereal hydrochloric acid. The crude salt was recrystallized repeatedly from acetone, M.P. 181–183° C.

Analysis.—Calcd. for $C_{20}H_{30}ClNO_2$: Cl, 10.10; N, 3.98. Found: Cl, 10.13; N, 4.12.

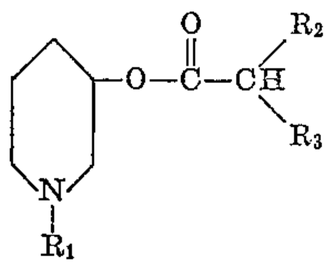
It has been found that the present compositions are nontoxic and alleviate or stop smooth muscle spasm regardless of its origin, and that the compounds are free from the undesirable reactions producing pupil dilation, dryness of mouth and other undesirable side effects.

It is well known that the anti-spasmodic activity of compounds such as the salts disclosed herein, is due to the ester portion of the molecule and not to the acid used to form the salts. Hence, it will be understood that various salts other than those herein disclosed, may be readily made. Such other additional salts include particularly the hydrobromide, maleate, succinate, tartrate, benzoate and phosphate, and are readily prepared from the free base and the corresponding acid in solvents such as acetone, benzene, ether type compounds, ethanol, isopropanol, and other alcohols.

Various changes and modifications of the invention can be made and, to the extent that such variations incorporate the spirit of this invention, they are intended to be included within the scope of the appended claims.

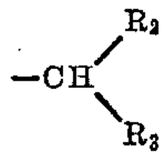
What is claimed is:

1. N-lower alkyl-3-piperidyl-phenyl-cyclohexyl acetate.
2. N-ethyl-3-piperidyl-phenyl-cyclohexyl acetate.
3. N-lower alkyl-3-piperidyl-9-fluorene carboxylate.
4. N-ethyl-3-piperidyl-9-fluorene carboxylate.
5. N-lower alkyl-3-piperidyl-9-xanthene carboxylate.
6. N-ethyl-3-piperidyl-9-xanthene carboxylate.
7. N-lower alkyl-3-piperidyl-phenyl-cyclopentyl acetate.
8. N-ethyl-3-piperidyl-phenyl-cyclopentyl acetate.
9. A member of the group consisting of compounds of the formula



wherein R_1 is lower alkyl, R_2 is a member of the group

consisting of phenyl, cyclopentyl, cyclohexyl and 2-thienyl, R_3 is a member of the group consisting of cyclopentyl, cyclohexyl, 2-thienyl and groups in which



represents a member of the group consisting of fluorenyl and xanthenyl, and nontoxic pharmaceutically acceptable acid addition salts and nontoxic pharmaceutically acceptable lower alkyl halide quaternary ammonium salts thereof.

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UNITED STATES PATENT OFFICE

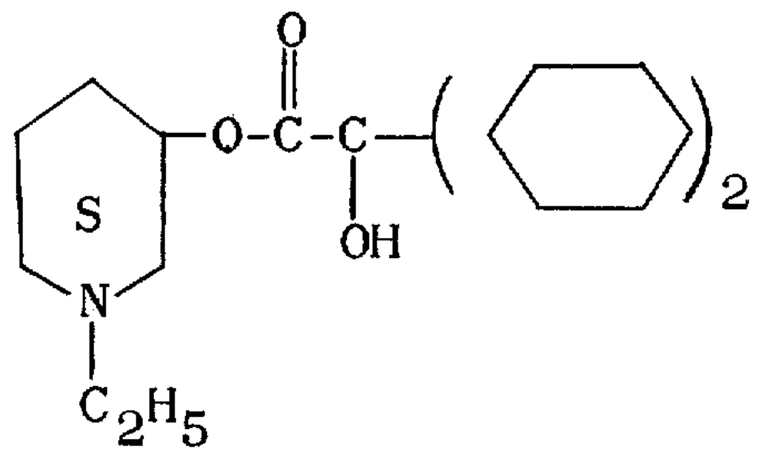
CERTIFICATE OF CORRECTION

Patent No. 2,995,560 August 8, 1961

John H. Biel

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 6, line 55, for "etheral" read -- ethereal --; lines 64 to 68, the formula should appear as shown below instead of as in the patent:



Signed and sealed this 2nd day of January 1962.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

DAVID L. LADD
Commissioner of Patents