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3,264,309

N'[N-(MONOCARBOCYCLIC ARYL) CARBAMYL-LOWER-ALKYL] - 1,5 - IMINOCYCLOALKANES, -IMINOCYCLOALKENES AND RELATED COMPOUNDS

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This application is a continuation-in-part of my prior copending application Serial No. 697,531, filed November 20, 1957, now abandoned.

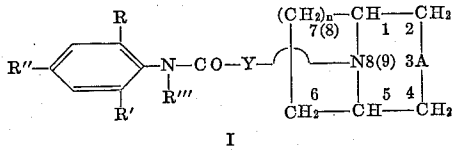
This invention relates to new monocarbocyclic arylcarbamyl-lower-alkylamines, to salts thereof, and to methods for the preparation thereof.

N' - [N-(monocarbocyclic aryl)carbamyl-lower-alkyl] amines and N'-[N-lower-alkyl-N-(monocarbocyclic aryl) carbamyl-lower-alkyl]amines wherein the amino moiety is dialkylamino or piperidino are known. The invention resides in the concept of the compounds obtained when the known types of N-(monocarbocyclic aryl)carbamyl-lower-alkyl and N-lower-alkyl-N-(monocarbocyclic aryl) carbamyl-lower-alkyl radicals are attached to the nitrogen atoms of a 1,5-iminocycloalkane or 1,5-iminocycloalkene radical, whereby new and useful compounds are produced.

In the compounds of my invention the monocarbocyclic aryl radicals can be unsubstituted phenyl or phenyl substituted by substituents known in compounds of the lidocaine type having local anesthetic activity, such as lower-alkyl, lower-alkoxy or halogen.

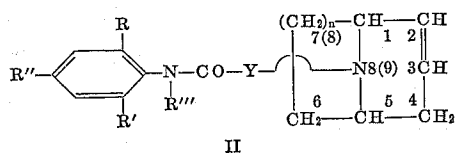
In the compounds of my invention the 1,5-iminocycloaliphatic ring has at least seven ring members, preferably seven or eight, and can be unsubstituted or substituted in the 3-position by such known types of radicals as hydroxy, acyloxy, halogen, oxo, carboalkoxy, and the like. In the case where a 1,5-iminocycloalkene radical is present, the ring preferably has the double bond at the 2,3-position of the ring.

A preferred aspect of the invention relates to compounds having the formulas:



I

or



II

wherein R, R' and R'' represent hydrogen, lower-alkyl, lower-alkoxy or halogen radicals, R''' represents hydrogen

or a lower-alkyl radical, Y represents a lower-alkylene radical, *n* represents an integer from 1 to 2, and A represents CH_2, CH(OH), C=O, CHCl, CHBr, CH(O-Acyl), C(OH)(COO-lower-alkyl) or C(OH)(lower-alkyl). The invention also relates to salts of the foregoing.

In the above general Formulas I and II, R, R' and R'' each represents hydrogen, lower-alkyl, lower-alkoxy or halogen radicals and can be the same or different. When R, R' and R'' represent lower-alkyl or lower-alkoxy radicals, they can have from one to about four carbon atoms and can be straight or branched, and thus stand for such groups as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, methoxy, ethoxy, propoxy, butoxy, and the like. When R, R' and R'' represent halogen atoms, they stand for any of the four halogens, fluorine, chlorine, bromine or iodine. A particularly preferred class of compounds are those in which R and R' represent lower-alkyl radicals and R'' represents hydrogen.

In the above general Formulas I and II, R''' represents hydrogen or a lower-alkyl radical. When R''' represents a lower-alkyl radical, it can have from one to four carbon atoms and can be straight or branched, and thus stands for such groups as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, 2-methylpropyl, and the like.

In the above general Formulas I and II, Y represents a lower-alkylene bridge having from one to about five carbon atoms which can be straight or branched, and thus includes such groups as methylene, ethylene, propylene, 1-methylethylene, 2-methylethylene, butylene, pentylene, and the like. A particularly preferred group of compounds are those in which Y has one or two carbon atoms, i.e., when Y is methylene or ethylene.

In the above general Formula I, *n* is 1 or 2. When *n* is 1, the 1,5-iminocycloalkane moiety is a cycloheptane ring, and the whole molecule is a derivative of nortropane. When *n* is 2, the 1,5-iminocycloalkane moiety is a cyclooctane ring, and the whole molecule is a derivative of granatanine. The numbering systems are in accordance with the standard nomenclature used in The Ring Index (Patterson and Capell, Reinhold Publishing Corp., 1940), and in Chemical Abstracts. In the 1,5-iminocycloalkane or -alkene moiety the parenthetical numbers 8 and 9 are used in the case where *n* is 2.

In the above general Formula I, A represents, inter alia, a CH(O-Acyl) group. The exact nature of the acyl group is not critical, provided it is a carboxylic acyl group of relatively low molecular weight, less than about 250. A preferred group of acyl radicals includes lower-alkanoyl, such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, caproyl, and the like; carboxy-lower-alkanoyl, such as hemi-succinyl, hemi-glutaryl, hemi-adipyl, and the like; monocarbocyclic aroyl, such as benzoyl, p-toluyl, p-nitrobenzoyl, 3,4-dinitrobenzoyl, p-methoxybenzoyl, 3,4,5-trimethoxybenzoyl, and the like; monocarbocyclic aryl-lower-alkanoyl, such as phenylacetyl, 2-phenylpropionyl, 1-phenylpropionyl, p-nitrophenylacetyl, and the like; lower-alkanoyl, such as acryloyl, crotonoyl, and the like; monocarbocyclic aryl-lower-alkenoyl, such as cinnamoyl, p-nitrocinnamoyl, phenylcrotonoyl, and the like; and carbamyl, CONR'R'', wherein R' and R'' are hydrogen or lower-alkyl groups, such as carbamyl, N-methylcarbamyl, N,N-dimethylcarbamyl, and the like.

The compounds of my invention have pharmacody-

namic properties, in particular, local anesthetic activity. For example, 8-[N-(1,6-dimethylphenyl)carbamylmethyl]nortropane as its hydrochloride salt was found to be about 7.5 times as active as procaine hydrochloride and 2.3 times as active as lidocaine hydrochloride when tested by the intracutaneous wheal test in guinea pigs [Bulbring and Wajda, J. Pharmacol. & Exptl. Therap. 85, 78 (1945)]. When tested by the corneal anesthesia method by topical application on the rabbit eye, this compound was found to be about 1.6 times as active as cocaine hydrochloride.

The compounds of the invention are prepared by reacting an N-(monocarbocyclic aryl)carbamyl-lower-alkyl halide or an N-lower-alkyl-N-(monocarbocyclic aryl)-carbamyl-lower-alkyl halide with a 1,5-iminocycloalkane or 1,5-iminocycloalkane. A preferred method comprises heating the reactants at a temperature between about 50° C. and 150° C. in the presence of an acid-acceptor. The reaction is preferably carried out in an organic solvent, inert under the conditions of the reaction, such as anhydrous lower-alkanols, benzene, xylene, and the like. The acid-acceptor neutralizes the hydrogen halide which is split out during the course of the reaction, and is a basic substance which forms water-soluble by-products easily separable from the main product of the reaction, including such substances as alkali metal salts of weak acids, e.g., sodium carbonate, potassium carbonate, sodium acetate, sodium alkoxides, sodium amide, and the like. The acid-acceptor can also be in the form of an excess quantity of 1,5-iminocycloalkane or -alkene, which can be recovered in the form of the hydrohalide salt and used again.

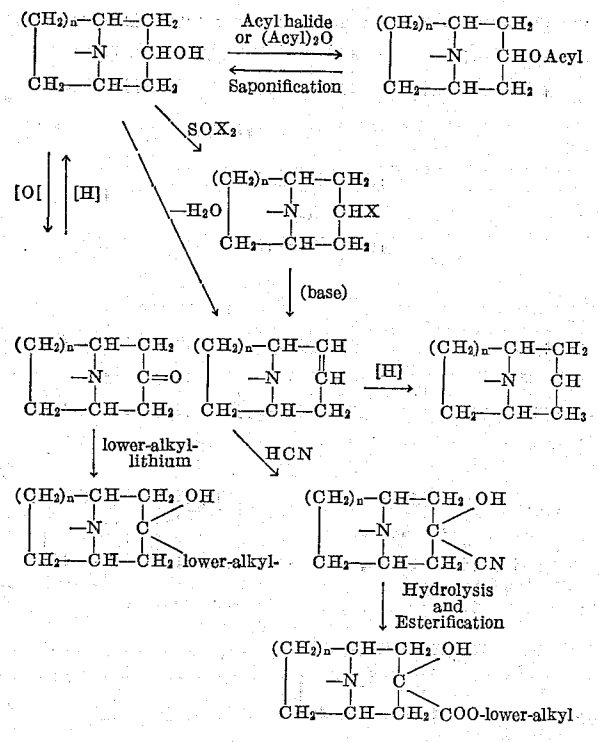
The various groups represented by A in the above general Formula I are readily interconvertible. Compounds bearing a hydroxy group in the 3-position of the 1,5-iminocycloalkane ring can be esterified by conventional methods, as by heating with the appropriate acid halide or acid anhydride, to give the corresponding acyloxy compounds. 3-hydroxy compounds can also be oxidized to the corresponding 3-oxo compounds, e.g., with chromic oxide, and conversely, the oxo compounds reduced to the hydroxy compounds, e.g., by catalytic hydrogenation. The hydroxy compounds can be dehydrated to introduce a double bond between the 1- and 2-positions of the 1,5-iminocycloalkane ring, e.g., by heating with mineral acid, potassium bisulfate, or the like, and the double bond reduced to give compounds unsubstituted in the 3-position ($A=CH_2$). Alternatively the hydroxy group in the 3-position can be replaced by chlorine or bromine by treating with the thionyl chloride or thionyl bromide, and the resulting 3-chloro or 3-bromo compound can then be dehydrohalogenated by heating with a base, such as alkali metal hydroxides or alkoxides or amino compounds, to give the same unsaturated compound obtained by dehydration of the 3-hydroxy compound.

The compounds and intermediates wherein A is C=O are converted to compounds where A is C(OH)(lower-alkyl) by a Grignard reaction with a lower-alkyl-lithium. Compounds wherein A is C=O also serves as intermediates for the compounds where A is C(OH)(COO-lower-alkyl); reaction with hydrogen cyanide gives the cyanhydrin [A=C(OH)(CN)] which can then be hydrolyzed to the corresponding carboxylic acid

[A=C(OH)(COOH)]

and esterified with a lower alkanol.

These changes in the group A are preferably effected before the 1,5-iminocycloalkane and N-(monocarbocyclic aryl)carbamyl-lower-alkyl or N-lower-alkyl-N-(monocarbocyclic aryl)-carbamyl-lower-alkyl moieties are combined in order to avoid side reactions with the amide linkage. The foregoing is summarized in the following flow-sheet (X is Cl or Br):



My N'-[N-(monocarbocyclic aryl)carbamyl-lower-alkyl]-amines and N'-[N-lower-alkyl-N-(monocarbocyclic aryl)carbamyl-lower-alkyl]amines are useful in the free base form or in the form of acid-addition or quaternary ammonium salts, and both forms are within the purview of the invention, and, in fact, are considered to be one and the same invention. The acid-addition and quaternary ammonium salts are simply a more convenient form for use, and in practice, use of the salt form inherently amounts to use of the base form. As used in the appended claims, unless specifically designated otherwise, the terms "N'-[N-(monocarbocyclic aryl)carbamyl-lower-alkyl]-1,5-iminocycloalkane" and "-iminocycloalkene" and "N'-[N-lower-alkyl-N-(monocarbocyclic aryl)carbamyl-lower-alkyl]-1,5-iminocycloalkane" and "-iminocycloalkene" mean both the free base form and the acid-addition and lower-alkyl, lower-alkenyl and monocarbocyclic aryl-lower-alkyl quaternary ammonium salt form of the molecular structure recited. Pharmacologically acceptable salts are salts whose anions are innocuous to the animal organism in pharmacological doses of the salts, so that beneficial physiological properties inherent in the free bases are not vitiated by side-effects ascribable to the anions; in other words, the latter do not substantially affect the pharmacological properties inherent in the cations. Appropriate acid-addition salts are those derived from mineral acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, nitric acid, sulfuric acid, and phosphoric acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, sulfamic acid and quinic acid and naphthalenesulfonic acid. The quaternary ammonium salts are obtained by the addition of alkyl, alkenyl or aralkyl esters of inorganic acids or organic sulfonic acids to the free base form of the compounds. The alkyl, alkenyl or aralkyl esters so used include such compounds as methyl chloride, methyl bromide, methyl iodide, ethyl bromide, propyl chloride, 2-hydroxyethyl bromide, allyl chloride, allyl bromide, methyl sulfate, methyl benzenesulfonate, methyl p-toluenesulfonate, benzyl chloride, benzyl bromide, and substituted benzyl halides, such as p-chlorobenzyl chloride,

p-nitrobenzyl chloride, o-chlorobenzyl chloride, p-methoxy benzyl chloride, and the like.

The acid-addition salts are prepared either by dissolving the free base in an aqueous solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The quaternary ammonium salts are prepared by mixing the free base and the alkyl, alkenyl or aralkyl ester in an organic solvent. Heating can be used to facilitate the reaction, although salt formation usually takes place readily at room temperature. The quaternary ammonium salt separates directly or can be obtained by concentration of the solution.

An alternative method of preparation of the quaternary ammonium salts comprises direct reaction of an N-(monocarbocyclic aryl)carbamyl-lower-alkyl halide or an N-lower - alkyl-N-(monocarbocyclic aryl)carbamyl-lower-alkyl halide with an N'-hydrocarbon substituted 1,5-iminocycloalkane or -alkene.

Although pharmacologically acceptable salts are preferred, those having toxic anions are also useful. All acid-addition salts are useful as intermediates in purification of the free bases, and toxic acid-addition and quaternary ammonium salts are useful as intermediates in preparing pharmacologically acceptable salts by ion exchange procedures. All crystalline salts are also useful as characterizing derivatives of the free bases.

The structures of the compounds of the invention have been established by chemical analysis and by the processes for their preparation, which can only lead to compounds of the assigned structures.

The following examples will further illustrate the invention, without the latter being limited thereto.

EXAMPLE 1

8 -[N - (2,6 - dimethylphenyl)carbamylmethyl]-3-hydroxynortropane [I; R and R' are CH_3, R'' and R''' are H, Y is CH_2, *n* is 1, A is CH(OH)].—A mixture of 9.9 g. (0.05 mole) of N - (2,6 - dimethylphenyl)carbamylmethyl chloride, 7.0 g. (0.055 mole) of nortropine and 5.3 g. (0.05 mole) of powdered anhydrous sodium carbonate in 150 ml. of absolute ethanol was refluxed with stirring for twenty-four hours. Another 2.7 g. of sodium carbonate was then added and the mixture refluxed for twenty-four hours longer. The reaction mixture was filtered, the solid material washed with ethanol, and the combined filtrate and washings were concentrated in vacuo. The residue was dissolved in 400 ml. of hot benzene, and the benzene solution was washed several times with water and then extracted with dilute hydrochloric acid. The acid extracts were made basic with concentrated ammonium hydroxide and the precipitated product was collected by filtration. The product was purified by dissolving it in 250 ml. of hot benzene, concentrating the volume to 125 ml. and allowing the product to crystallize. There was thus obtained 11.9 g. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - hydroxynortropane, M.P. 177–178.5° C. (corr.) after drying over phosphorus pentoxide at 100° C. and 0.1 mm. for four hours.

Analysis.—Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.79; H, 8.39; N, 9.72. Found: C, 70.78; H, 8.20; N, 9.67.

The hydrochloride salt of 8-[N-(2,6-dimethylphenyl)-carbamylmethyl]-3-hydroxynortropane was prepared from a solution of 84 g. of the free base in isopropyl alcohol solution by addition of an excess of concentrated hydrochloric acid. The salt separated upon cooling the solution, and there was obtained 89 g., M.P. 235–237° C. (corr.).

Analysis.—Calcd. for $C_{17}H_{24}N_2O_2.HCl$: N, 8.63; Cl, 10.92. Found: N, 8.47; Cl, 10.68.

The methiodide salt of 8-[N-(2,6-dimethylphenyl)-carbamylmethyl]-3-hydroxynortropane was prepared from a solution of 2 g. of the free base and 4 g. of methyl iodide in 75 ml. of acetone. The solution was kept at room temperature for three days, and the product which separated was collected by filtration and washed with acetone, giving 2.4 g. of methiodide. A sample of the methiodide when recrystallized from ethanol and dried over phosphorus pentoxide at 80° C. and 0.2 mm. for four hours had the M.P. 234–237° C. (corr.).

Analysis.—Calcd. for $C_{18}H_{27}N_2O_2I$: N, 6.51; I, 29.50. Found: N, 6.50; I, 29.59.

Pharmacological evaluation of 8-[N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - hydroxynortropane hydrochloride in aqueous solution administered intradermally in guinea pigs according to the method of Bulbring and Wajda [J. Pharmacol. & Exptl. Therap. 85, 78 (1945)] has shown that this compound in terms of its free base is approximately 2.4 times as active a local anesthetic as procaine. 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-hydroxynortropane hydrochloride was found to have an acute intravenous toxicity (LD_{50}) in mice of 24±0.5 mg./kg.

By replacement in the preceding preparation of the N-(2,6-dimethylphenyl)carbamylmethyl chloride by a molar equivalent amount of N-phenylcarbamylmethyl chloride, N-(2-methyl - 6 - chlorophenyl)carbamylmethyl chloride, N-(2,4,6-trimethylphenyl)carbamylmethyl chloride, N-(2,4,6-triisopropylphenyl)carbamylmethyl chloride, or N-(2,6-dimethyl-4-n-butoxyphenyl)carbamylmethyl chloride (prepared from 2,6 dimethyl-4-n-butoxyaniline and chloroacetyl chloride), there can be obtained, respectively, 8-(N-phenylcarbamylmethyl) - 3 - hydroxynortropane [I; R, R', R'' and R''' are H, Y is CH_2, *n* is 1, A is CH(OH)]; 8-[N-(2-methyl-6-chlorophenyl)carbamylmethyl]-3-hydroxynortropane [I; R is CH_3, R' is Cl, R'' and R''' are H, Y is CH_2, *n* is 1, A is CH(OH)]; 8-[N-(2,4,6-trimethylphenyl)carbamylmethyl] - 3 - hydroxynortropane [I; R, R' and R'' are CH_3, R''' is H, Y is CH_2, *n* is 1, A is CH(OH)]; 8-[N-(2,4,6-triisopropylphenyl)carbamylmethyl] - 3 - hydroxynortropane [I; R, R' and R'' are $CH(CH_3)_2$, R''' is H, Y is CH_2, *n* is 1, A is CH(OH)]; or 8-[N-(2,6-dimethyl-4-n-butoxyphenyl)carbamylmethyl]-3-hydroxynortropane [I; R and R' are CH_3, R'' is $O(CH_2)_3CH_3$, R''' is H, Y is CH_2, *n* is 1, A is CH(OH)].

By replacement in the preceding preparation of the N-(2,6-dimethylphenyl)carbamylmethyl chloride by a molar equivalent amount of 1-methyl-2-[N-(2,6-dimethylphenyl)carbamyl]ethyl chloride (prepared from 2,6-dimethylaniline and β-chlorobutyryl chloride) or 5-[N-(2,6-dimethylphenyl)carbamyl]pentyl chloride (prepared from 2,6-dimethylaniline and ε-chlorocaproyl chloride), there can be obtained, respectively 8-{1-methyl-2-[N-(2,6-dimethylphenyl)carbamyl]ethyl} - 3 - hydroxynortropane [I; R and R' are CH_3, R'' and R''' are H, Y is $CH_2CH(CH_3)$, *n* is 1, A is CH(OH)]; or 8-{5-[N-(2,6-dimethylphenyl)carbamyl]pentyl} - 3 - hydroxynortropane [I; R and R' are CH_3, R'' and R''' are H, Y is $(CH_2)_5$, *n* is 1, A is CH(OH)].

By replacement in the preceding preparation of the nortropine by a molar equivalent amount of 3-granataninol there can be obtained 9-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-hydroxygranatanine [I; R and R' are CH_3, R'' and R''' are H, Y is CH_2, *n* is 2, A is CH(OH)].

By replacement in the preceding preparation of the nortropine by a molar equivalent amount of 3-nortropanone, 3-chloronortropane (from nortropine and thionyl chloride), 3-bromonortropane (from nortropine and thionyl bromide), 3-benzoyloxynortropane (from nortropine and benzoyl chloride), or 3-hydroxy-3-methylnortropane (from 3-nortropanone and methyllithium), there can be obtained, respectively, 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-oxonortropane [I; R and R' are CH_3, R'' and R''' are H, Y is CH_2, *n* is 1, A is C=O]; 8-[N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - chloronortropane [I; R and R' are CH_3, R'' and R''' are H, Y is

CH_2, *n* is 1, A is CHCl]; 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-bromonortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is CHBr]; 8-[N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - benzoyloxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $CH(OCOC_6H_5)$]; or 8-[N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - hydroxy-3-methylnortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $C(OH)(CH_3)$].

8-[N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - hydroxynortropane can be reacted with hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, acetic acid, quinic acid, 2-naphthalenesulfonic acid, phosphoric acid, methyl iodide, methyl bromide, ethyl bromide, allyl bromide, benzyl chloride, o-chlorobenzyl chloride, methyl p-toluenesulfonate, or methyl sulfate, to give, respectively, the hydrochloride, hydrobromide, hydriodide, sulfate or bisulfate, acetate, quinate, 2-naphthalenesulfonate, phosphate or acid phosphate, methiodide, methobromide, ethobromide, allobromide, benzochloride, o-chlorobenzochloride, metho-p-toluenesulfonate, or methosulfate salt.

EXAMPLE 2

8 - [N - (2,6 - dimethylphenyl)carbamylmethyl]nortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is CH_2].—A mixture of 5.9 g. (0.030 mole) of N-(2,6-dimethylphenyl)carbamylmethyl chloride and 7.0 g. (0.063 mole) of nortropane in 150 ml. of dry benzene was refluxed for eight hours. After the reaction mixture had been allowed to stand overnight, the white precipitate of nortropane hydrochloride was removed by filtration and washed with benzene. The combined benzene filtrate and washings were washed with two 50 ml. portions of water and extracted with dilute hydrochloric acid (4 ml. of concentrated hydrochloric acid in 50 ml. of water), and washed with water until neutral. The acid extracts were combined, filtered, and made basic with ammonium hydroxide. The product was collected by filtration, dissolved in 700 ml. of hot hexane and the solution was filtered and concentrated to a volume of 300 ml. There was thus obtained 7.2 g. of 8-[N-(2,6 - dimethylphenyl)carbamylmethyl]nortropane which was recrystallized from 350 ml. of hexane and dried over phosphorus pentoxide at 80° C. and 0.2 mm. for six hours, giving a sample having the M.P. 154–155° C. (corr.).

Analysis.—Calcd. for $C_{17}H_{24}N_2O$: N (total), 10.29; N (basic), 5.14. Found: N (total), 10.25; N (basic), 5.11.

The hydrochloride salt of 8-[N-(2,6-dimethylphenyl)-carbamylmethyl]nortropane was prepared from a solution of 39 g. of the free base in 200 ml. of isopropyl alcohol and 12.2 ml. of concentrated hydrochloric acid. The solution was filtered while hot and then cooled to 5° C. whereupon the product separated. The salt was collected by filtration, washed with cold isopropyl alcohol and dry ether, and dried at 70° C. for twenty hours, giving 40.5 g., M.P. 233–236° C. (corr.).

Analysis.—Calcd. for $C_{17}H_{24}N_2O.HCl$: Cl, 11.47; N, 9.07. Found: Cl, 11.44; N, 8.95.

Pharmacological evaluation of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropane hydrochloride in aqueous solution administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately 7.5 times as active a local anesthetic as procaine, and 2.3 times as active as lidocaine. 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropane hydrochloride was found to have an acute intravenous toxicity (LD_{50}) in mice of 10.5±0.9 mg./kg.

EXAMPLE 3

8 - [N - (2,6-dimethylphenyl)carbamylmethyl]nortropidine [II; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1] was prepared from 5.9 g. (0.030 mole) of N-(2,6-dimethylphenyl)carbamylmethyl chloride and 6.9 g. (0.063 mole) of nortropidine in 150 ml. of dry benzene according to the manipulative procedure described above in Example 2. There was thus obtained 4.6 g. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropidine, M.P. 161.5–164° C. (corr.) when recrystallized from a benzene-hexane mixture.

Analysis.—Calcd. for $C_{17}H_{22}N_2O$: N (total), 10.36; N (basic), 5.18. Found: N (total), 10.31; N (basic), 5.13.

Pharmacological evaluation of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropidine in the form of an aqueous solution of its acid-addition salt administered intradermally to guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately 2.7 times as active a local anesthetic as procaine. 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropidine was found to have an acute intravenous toxicity (LD_{50}) in mice of 13±1.2 mg./kg.

EXAMPLE 4

8 - [N - (2,6-dimethylphenyl)carbamylmethyl]pseudo-3-hydroxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is CH(OH)].—A mixture of 5.9 g. (0.030 mole) of N-(2,6-dimethylphenyl)carbamylmethyl chloride, 8.0 g. (0.063 mole) of pseudo-nortropine in 100 ml. of absolute ethanol was refluxed for eight hours. The reaction mixture was allowed to stand overnight and then was concentrated in vacuo. The residue was refluxed for several minutes with 100 ml. of chloroform, cooled, and the insoluble pseudo-nortropine hydrochloride was removed by filtration and washed with chloroform. The combined chloroform filtrate and washings were washed with three 25 ml. portions of water, extracted with dilute hydrochloric acid (5 ml. of concentrated hydrochloric acid in 50 ml. of water), and finally washed with four 10 ml. portions of water. The combined acid extracts and washings were filtered and made basic with concentrated ammonium hydroxide. The product which separated was collected and dissolved in 200 ml. of benzene, and the solution was filtered, concentrated to 75 ml. and diluted with 30 ml. of hexane. There was thus obtained 7.1 g. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]pseudo - 3 - hydroxynortropane which was further purified by recrystallization successively from benzene-hexane, ethyl acetate-hexane and ethyl acetate, and dried over phosphorus pentoxide at room temperature and 0.1 mm. for twenty-four hours to give a sample with the M.P. 176.5–178.5° C. (corr.). A mixed melting point with the 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-hydroxynortropane obtained in Example 1 showed a depression to 149–160° C.

Analysis.—Calcd. for $C_{17}H_{24}N_2O_2$: N (total), 9.72; N, (basic), 4.86. Found: N (total), 9.52; N (basic), 4.82.

Pharmacological evaluation of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]pseudo-3-hydroxynortropane in an aqueous solution of its acid-addition salt administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately 0.9 times as active a local anesthetic as procaine. 8-[N-(2,6-dimethylphenyl)carbamylmethyl]pseudo - 3 - hydroxynortropane was found to have an acute intravenous toxicity (LD_{50}) in mice of 58±4.8 mg./kg.

EXAMPLE 5

8 - {2-[N - (2,6-dimethylphenyl)carbamyl]ethyl}-3-hydroxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2CH_2, *n* is 1, A is CH(OH)].—A mixture of 12.7 g. (0.060 mole) of 2-[N-(2,6-dimethylphenyl)carbamyl]ethyl chloride, 8.0 g. (0.063 mole) of nortropine and 6.4 g. (0.06 mole) of anhydrous sodium carbonate in 200 ml. of absolute ethanol was refluxed for twenty hours. The inorganic solids were removed by filtration,

washed with ethanol, and the combined ethanol filtrate and washings were concentrated in vacuo. The residue was dissolved in 200 ml. of dilute acetic acid, the solution filtered through filter cel, and then made basic with solid potassium carbonate. The mother liquors were decanted from the resulting gum which was then washed with water and dissolved in chloroform. The chloroform solution was washed with 50 ml. of water, filtered, and concentrated in vacuo. The resulting pale yellow oil was dissolved in 150 ml. of boiling benzene, and the solution was filtered and concentrated to 75 ml. and diluted with 35 ml. of hexane, giving 10.6 g. of crystalline product, M.P. 117–119° C. The latter was recrystallized twice from a benzene-hexane mixture and then twice from ethyl acetate and dried over phosphorus pentoxide at 100° C. and 0.05 mm. for five hours giving 8-{2-[N-(2,6-dimethylphenyl)carbamyl]ethyl}-3-hydroxynortropane, M.P. 151–153° C. (corr.).

Analysis.—Calcd. for $C_{18}H_{26}N_2O_2$: N (total), 9.27; N (basic), 4.63. Found: N (total), 9.06; N (basic), 4.62.

Pharmacological evaluation of 8-{2-[N-(2,6-dimethylphenyl)carbamyl]ethyl}-3-hydroxynortropane in an aqueous solution of its acid-addition salt administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately 1.2 times as active a local anesthetic as procaine. 8-{2-[N-(2,6 - dimethylphenyl)carbamyl]ethyl}-3-hydroxynortropane was found to have an acute intravenous toxicity (LD_{50}) in mice of 6.8±0.4 mg./kg.

EXAMPLE 6

8 - {2-[N-(2,6-dimethylphenyl)carbamyl]ethyl}nortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2CH_2, *n* is 1, A is CH_2] was prepared from 8.5 g. (0.040 mole of N-(2,6-dimethylphenyl)carbamylethyl chloride, 4.7 g. (0.042 mole) of nortropane and 4.2 g. (0.04 mole) of sodium carbonate in 200 ml. of absolute ethanol according to the manipulative procedure described above in Example 5. There was thus obtained 9.9 g. of 8 - {2 - [N-(2,6-dimethylphenyl)carbamyl]ethyl}nortropane, M.P. 119–122° C. (corr.) when recrystallized from hexane.

Analysis.—Calcd. for $C_{18}H_{26}N_2O$: N (total), 9.78; N (basic), 4.89. Found: N (total), 9.73; N (basic), 4.85.

Pharmacological evaluation of 8-{2-[N-(2,6-dimethylphenyl)carbamyl]ethyl}nortropane in an aqueous solution of its acid-addition salt administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately 4 times as active a local anesthetic as procaine. 8-{2-[N-(2,6-dimethylphenyl)carbamyl]ethyl}nortropane was found to have an acute intravenous toxicity (LD_{50}) in mice of 8.6±0.6 mg.kg.

EXAMPLE 7

8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-acetoxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $CHOCOCH_3$].—A mixture of 4 g. of 8 - [N - (2,6-dimethylphenyl)carbamylmethyl]-3-hydroxynortropane (prepared as described above in Example 1) and 4 ml. of acetic anhydride in 20 ml. of pyridine was allowed to stand at room temperature overnight. The reaction mixture was then heated on a steam bath for two hours and concentrated in vacuo. The residue was dissolved in 25 ml. of absolute ethanol and the solution again concentrated in vacuo. The residue was dissolved in 200 ml. of dilute acetic acid, and the solution filtered through filter cel and then made basic with potassium carbonate. The mixture was cooled and the product collected by filtration and recrystallized from hexane, giving 4.1 g., M.P. 129–131° C. The latter was recrystallized from a mixture of 25 ml. of benzene and 50 ml. of hexane, and dried over phosphorus pentoxide at 100° C. and 0.3 mm. for eight hours, giving 3.9 g. of 8-[N-(2-6-dimethylphenyl)carbamylmethyl]-3-acetoxynortropane, M.P. 142.5–144.5° C. (corr.).

Analysis.—Calcd. for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.90; H, 8.07; N, 8.32.

Pharmacological evaluation of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-acetoxynortropane in an aqueous solution of its acid-addition salt administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately equally as active a local anesthetic as procaine. 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-acetoxynortropane was found to have an acute intravenous toxicity (LD_{50}) in mice of 30±1.6 mg./kg.

By replacement in the preceding preparation of the acetic anhydride by a molar equivalent amount of cinnamoyl chloride, 3,4,5-trimethoxybenzoyl chloride, N,N-dimethylcarbamyl chloride, hexanoyl chloride, succinic anhydride, or phenylacetyl chloride, there can be obtained, respectively, 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-cinnamoyloxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is

$$CHOCOCH{=}CHC_6H_5]$$

8 - [N - (2,6 - dimethylphenyl)carbamylmethyl]-3-trimethoxybenzoylnortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $CHOCOC_6H_2(OCH_3)_3$]; 8 - [N-(2,6-dimethylphenyl)carbamylmethyl]-3-dimethylcarbamyloxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $CHOCON(CH_3)_2$]; 8 - [N-(2,6-dimethylphenyl)carbamylmethyl]-3-hexanoyloxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $CHOCO(CH_2)_4CH_3$]; 8-[N-(2,6 - dimethylphenyl)carbamylmethyl]-3-(β-carboxypropionyloxy)nortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $CHOCOCH_2CH_2COOH$]; 8 - [N - (2,6-dimethylphenyl)carbamylmethyl]-3-phenylacetoxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is $CHOCOCH_2C_6H_5$].

EXAMPLE 8

8 - [N-(2,6-dimethylphenyl)carbamylmethyl]-3-propionyloxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2 *n* is 1, A is $CHOCOC_2H_5$] was prepared from 5 g. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-hydroxynortropane and 5 g. of propionic anhydride in 25 ml. of pyridine according to the manipulative procedure described above in Example 7. This compound had the M.P. 143–144° C. (corr.) when recrystallized from a benzene-hexane mixture.

Analysis.—Calcd. for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.14. Found: C, 69.84; H, 8.02; N, 7.91.

EXAMPLE 9

8 - {2 - [N - (2,6 - dimethylphenyl)carbamyl]ethyl}-3-acetoxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2CH_2, *n* is 1, A is $CHOCOCH_3$] was prepared from 4 g. of 8-{2-[N-(2,6-dimethylphenyl)carbamyl]ethyl}-3-hydroxynortropane and 4 ml. of acetic anhydride in 20 ml. of pyridine according to the manipulative procedure described above in Example 7. This compound had the M.P. 119–123° C. (corr.) when recrystallized from a benzene-hexane mixture.

Analysis.—Calcd. for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.14. Found: C, 69.43; H, 8.46; N, 7.91.

Pharmacological evaluation of 8-{2-[N-(2,6-dimethylphenyl) - carbamyl]ethyl} - 3 - acetoxynortropane in an aqueous solution of its acid-addition salt administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately 1.3 times as active a local anesthetic as procaine.

EXAMPLE 10

8 - [N-(2,6-dimethylphenyl)carbamylmethyl]-3-propionyloxynortropane [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2CH_2, *n* is 1, A is $CHOCOC_2H_5$] was prepared from 5 g. of 8-[N-(2,6-dimethylphenyl)-carbamylmethyl] 3-hydroxynortropane and 5 g. of propionic anhydride in 20 ml. of pyridine according to the manipulative procedure described above in Example 7. There was thus obtained 5.5 g. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-propionyloxynortropane, M.P. 109–111° C. (corr.) when recrystallized from hexane.

Analysis.—Calcd. for $C_{21}H_{30}N_2O_3$: C, 70.35; H, 8.44; N, 7.82; O, 13.39. Found: C, 70.58; H, 8.39; N, 7.63; O, 13.45.

EXAMPLE 11

(*a*) *Nor-α-ecgonine methyl ester.*—Northropinone hydrochloride (48.5 g., 0.30 mole) was added portionwise over a period of fifteen minutes to a solution of 21.5 g. (0.33 mole) of potassium cyanide in 75 ml. of water. The solid cyanhydrin which had separated was collected by filtration, washed with pyridine and dried over phosphorus pentoxide. The cyanhydrin (56 g.) was added portionwise with stirring to 500 ml. of concentrated hydrochloric acid at 10–15° C. The mixture was stirred for several hours, allowed to stand overnight at room temperature and then concentrated in vacuo. The residue was dried by adding benzene and distilling off the benzene in vacuo. The residue was washed with acetone and the solid product was collected and then refluxed in 400 ml. of methanol on a steam bath for four hours while hydrogen chloride gas was bubbled through. The solution was allowed to stand at room temperature for sixty-six hours and then concentrated in vacuo. The residue was dissolved in about 100 ml. of water, decolorized with activated charcoal, and the solution was treated with solid potassium carbonate until a white solid separated. The mixture was extracted with three 100 ml. portions of chloroform, and the chloroform solution was dried over anhydrous calcium sulfate and concentrated, giving 22.8 g. of solid product. The aqueous layer was further saturated with potassium carbonate, and the solid which separated was collected and washed with three 150 ml. portions of chloroform. The chloroform washes were used to extract the aqueous filtrate, then dried and concentrated, giving an additional 5.5 g. of solid product. The combined solid product was recrystallized from 200 ml. of ethyl acetate, giving 15.6 g. of nor-α-ecgonine methyl ester, M.P. 143-145° C.

(*b*) *8 - [N - (2,6-dimethylphenyl)carbamylmethyl]-3-hydroxy-3-carbomethoxynortropane* [I; R and *R′* are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is

$C(OH)(COOCH_3)$]

A mixture of 5.7 g. (0.030 mole) of N-(2,6-dimethylphenyl)carbamylmethyl chloride, 5.6 g. (0.030 mole) of nor-α-ecgonine methyl ester and 3.5 g. (0.033 mole) of anhydrous sodium carbonate in 250 ml. of ethanol was refluxed for five hours. The reaction mixture was worked up according to the procedure described above in Example 5. There was thus obtained 5.9 g. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - hydroxy-3-carbomethoxynortropane, M.P. 197–199° C. (corr.) when recrystallized from ethyl acetate.

Analysis.—Calcd. for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.57; N, 8.09. Found: C, 65.55; H, 7.24; N, 8.07.

EXAMPLE 12

(*a*) *Nortropinone ethylene glycol ketal.*—A mixture of 48.5 g. (0.30 mole) of nortropinone hydrochloride, 90 ml. (1.5 moles) of ethylene glycol and 1 g. of p-toluenesulfonic acid monohydrate in 500 ml. of dry benzene was refluxed for nineteen hours under a water separator. The excess benzene and ethylene glycol were then removed in vacuo on a steam bath. The residue was stirred with about 400 ml. of dry acetone and filtered, giving 41.9 g. of solid product. The filtrate was concentrated in vacuo to remove the acetone and additional ethylene glycol, and the residue was again treated with acetone to give an additional 11.9 g. of solid product. The two crops of solid product were combined and stirred with 75 ml. of saturated potassium carbonate solution. Chloroform was added, the mixture was stirred and the chloroform solution separated. The aqueous mixture was filtered to remove inorganic salts which were washed with chloroform, and the combined chloroform extracts and washings were filtered through anhydrous calcium sulfate and concentrated in vacuo. The residue was distilled through a Vigreux column, and the fraction boiling at 68–69° C. (0.7–0.8 mm.) was collected and redistilled, giving 34.2 g. of nortropinone ethylene glycol ketal, B.P. 70° C. (0.8 mm.).

(*b*) *8 - [N - (2,6-dimethylphenyl)carbamylmethyl] nortropinone ethylene glycol ketal* was prepared from 7.9 g. (0.040 mole) of N-(2,6-dimethylphenyl)carbamylmethyl chloride, 7.4 g. (0.044 mole) of nortropinone ethylene glycol ketal and 6.4 g. of anhydrous sodium carbonate in 200 ml. of absolute ethanol according to the manipulative procedure described above in Example 1. The product was isolated in the form of the free base and recrystallized successively from benzene-hexane, ethyl acetate-hexane and ethyl acetate, giving 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropinone ethylene glycol ketal, M.P. 126–129° C.

Analysis.—Calcd. for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.94; N, 8.48. Found: C, 69.33; H, 8.08; N, 8.46.

(*c*) *8 - [N-(2,6-dimethylphenyl)carbamylmethyl] nortropinone* [I; R and R′ are CH_3, R″ and R‴ are H, Y is CH_2, *n* is 1, A is C=O].—A mixture of 2.4 g. of 8-[N-(2,6 - dimethylphenyl) - carbamylmethyl]nortropinone ethylene glycol ketal, 2 ml. of concentrated hydrochloric acid and 15 ml. of water was kept at room temperature for about seventy hours. The reaction mixture was made basic with saturated potassium carbonate, and the solid material which separated was collected by filtration and dissolved in chloroform. The chloroform solution was filtered through anhydrous calcium sulfate and concentrated in vacuo. The residue was dissolved in 50 ml. of boiling benzene, and the solution was filtered, concentrated to 25 ml. and diluted with 75 ml. of hexane. The solution was cooled, and the resulting product which separated was collected by filtration, recrystallized from 25 ml. of benzene and 75 ml. of hexane and dried over phosphorus pentoxide at 100° C. and 0.2 mm. for six hours, giving 1.6 g. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl[nortropinone, M.P. 204–205° C. (corr.).

Analysis.—Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.29; H, 7.74; N, 9.78. Found: C, 71.22; H, 8.05; N, 9.72.

The oxime of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropinone was prepared by heating 4.3 g. of the ketone, 4 g. of hydroxylamine hydrochloride, 12 ml. of pyridine and 100 ml. of absolute ethanol at 100° C. until a clear solution resulted. The reaction mixture was kept overnight at room temperature, refluxed one hour, and then concentrated in vacuo. The residue was crystallized from water, giving 3.8 g. of the oxime which had the M.P. 198.5–201° C. (corr.) when recrystallized from acetone.

Analysis.—Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.74; H, 7.69; N, 13.94. Found: C, 67.50; H, 7.56; N, 13.87.

EXAMPLE 13

8-[N-ethyl-N - (2,6-dimethylphenyl)carbamylmethyl]-3α-hydroxy-nortropane [I; R and R′ are CH_3, R″ is H, R‴ is C_2H_5, Y is CH_2, *n* is 1, A is CH(OH)].—A solution of 14 g. of chloroacetyl chloride in 50 ml. of dry benzene was added dropwise over a one hour period to a stirred solution of N-ethyl-2,6-dimethylaniline (14.9 g., 0.1 mole) in 100 ml. of dry benzene while maintaining

the temperature at 18 to 28° C. The mixture was then warmed on a steam bath for about two and a half hours, cooled and diluted to 300 ml. with benzene. The solution was extracted once with dilute hydrochloric acid, three times with water and twice with saturated sodium bicarbonate solution. The organic layer was dried, filtered, and taken to dryness in vacuo. The residual oil was taken into hot hexane, charcoaled and filtered. On cooling, the product separated as large crystals which were collected and dried giving N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl chloride, M.P. 41–43° C. (uncorr.).

Analysis.—Calcd. for $C_{12}H_{16}NClO$: N, 6.22. Found: N, 6.22.

The N-ethyl-N - (2,6-dimethylphenyl)carbamylmethyl chloride (6.76 g., 0.03 mole) and nortropine (8.01 g., 0.063 mole) in 250 ml. of acetonitrile were refluxed for about 18 hours. The reaction mixture was worked up according to the procedure described above in Example 2. There was thus obtained 3.76 g. of 8-[N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl] - 3α - hydroxynortropane, M.P. 95.2–98.4° C. (corr.).

Ananlysis.—Calcd. for $C_{19}H_{28}N_2O_2$: N (basic), 4.43; N (total), 8.86. Found: N (basic), 4.41; N (total), 8.87.

By replacement in the preceding preparation of the N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl chloride by a molar equivalent amount of 2-[N-ethyl-N-(2,6-dimethyl-4-isopropylphenyl)-carbamyl]ethyl chloride, N-butyl-N-(2-chloro-6-methylphenyl)carbamylmethyl chloride, or N-isopropyl - N - (2,6-dimethylphenyl)carbamylmethyl chloride, there can be obtained, respectively, 8-{2-[N-ethyl-N-(2,6-dimethyl - 4 - isopropylphenyl)carbamyl]ethyl}-3-hydroxynortropane [I; R and R' are CH_3, R'' is $CH(CH_3)_2$, R''' is C_2H_5, Y is CH_2CH_2, *n* is 1, A is CH(OH); 8-[N-butyl - N - (2-chloro-6-methylphenyl)-carbamylmethyl]-3-hydroxynortropane [I; R is CH_3, R' is Cl, R'' is H, R''' is C_4H_9, Y is CH_2, *n* is 1, A is CH(OH)]; or 8-[N-isopropyl-N-(2,6-dimethylphenyl)carbamylmethyl]-3-hydroxynortropane [I; R and R' are CH_3, R'' is H, R''' is $CH(CH_3)_2$, Y is CH_2, *n* is 1, A is CH(OH)].

By replacement in the preceding preparation of the nortropane by a molar equivalent amount of 3-nortropanone, 3-chloronortropane (from nortropine and thionyl chloride), 3-bromonortropane (from nortropine and thionyl bromide), 3-benzoyloxynortropane (from nortropane and benzoyl chloride), 3-hydroxy-3-methylnortropane, nortropane, nortropidine or 3-granataninol, there can be obtained, respectively, 8-[N-ethyl-N-(2,6-dimethylphenyl)-carbamylmethyl]-3-oxonortropane [I; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 1, A is C=O]; 8-[N-ethyl - N - (2,6-dimethylphenyl)carbamylmethyl]-3-chloronortropane [I; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 1, A is CHCl]; 8-[N-ethyl-N-(2,6 - dimethylphenyl)carbamylmethyl]-3-bromonortropane [I; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 1, A is CHBr]; 8-[N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl] - 3-benzoyloxynortropane [I; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 1, A is $CH(OCOC_6H_5)$]; 8-[N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl]-3-hydroxy - 3-methylnortropane [I; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 1, A is $C(CH_3)(OH)$]; 8-[N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl]nortropane [I; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 1, A is CH_2]; 8 - [N - ethyl-N-(2,6-dimethylphenyl)carbamylmethyl]nortropidine [II; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 1]; 9-[N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl] - 3 - hydroxygranatanine [I; R and R' are CH_3, R'' is H, R''' is C_2H_5, Y is CH_2, *n* is 2, A is CH(OH)].

EXAMPLE 14

8-[N-propyl - N - (2,6 - dimethylphenyl)carbamylmethyl]-3-hydroxynortropane [I; R and R' are CH_3, R'' is H, R''' is $(CH_2)_2CH_3$, Y is CH_2, *n* is 1, A is CHOH].—N-propyl-2,6-dimethylaniline (16.3 g., 0.1 mole) in 150 ml. of dry benzene was treated with a solution of 15.0 g. (0.13 mole) of chloroacetyl chloride in 600 ml. of dry benzene according to the manipulative procedure described above in Example 13. The product was recrystallized from hexane giving 20.1 g. of N-propyl-N-(2,6-dimethylphenyl)carbamylmethyl chloride, M.P. 59–60° C. (uncorr.).

Analysis.—Calcd. for $C_{13}H_{18}NClO$: N, 5.84; Cl, 14.80. Found: N, 5.92; Cl, 15.00.

N-propyl - N - (2,6-dimethylphenyl)carbamylmethyl chloride (7.19 g., 0.03 mole) and 8.01 g. (0.063 mole) of nortropine in 250 ml. of acetonitrile were reacted according to the manipulative procedure described above in Example 2. The product was isolated in the form of the free base and recrystallized from dry benzene giving 4.56 g. of 8-[N-propyl-N-(2,6-dimethylphenyl)carbamylmethyl]-3-hydroxynortropane, M.P. 119.6–121.0° C. (corr.).

Analysis.—Calcd. for $C_{20}H_{30}N_2O_2$: N (total), 8.49; N (basic), 4.25. Found: N (total), 8.39; N (basic), 4.17.

EXAMPLE 15

1-{8-[N - methyl - N-(2,6-dimethylphenyl)carbamyl]ethyl}-3-hydroxynortropane hydrochloride [I; R, R' and R''' are CH_3, R'' is H, Y is $CHCH_3$, *n* is 1, A is CHOH].—A solution of 26.0 g. (0.12 mole) of α-bromopropionyl bromide in 60 ml. of dry benzene was added dropwise with stirring and cooling to a solution of 13.5 g. (0.10 mole) of N-methyl-2,6-dimethylaniline in 120 ml. of dry benzene according to the manipulative procedure described above in Example 13. The product was recrystallized from hexane giving 17.1 g. of 1-[N-methyl-N - (2,6-dimethylphenyl)carbamylethyl]bromide, M.P. 80–80.5° C. (uncorr.).

Analysis.—Calcd. for $C_{12}H_{16}BrNO$: C, 53.34; H, 5.97; Br, 29.6. Found: C, 53.29; H, 5.77; Br, 29.4.

The 1-[N-methyl-N-(2,6 - dimethylphenyl)carbamylethyl]-bromide (8.1 g., 0.03 mole), nortropine (4.2 g., 0.033 mole) and sodium bicarbonate (7.5 g., 0.09 mole) in 100 ml. of acetonitrile were refluxed for 72 hours. The reaction mixture was worked up according to the procedure described above in Example 1. The product was isolated in the form of the hydrochloride salt and recrystallized from an isopropanol-acetone mixture giving 1.3 g. of 1-{8-[N-methyl - N-(2,6-dimethylphenyl)carbamyl]ethyl} - 3 - hydroxynortropane hydrochloride, M. P. 250.0–251.2° C. (dec.) (corr.).

Analysis.—Calcd. for $C_{19}H_{28}N_2O_2 \cdot HCl$: C, 64.66; H, 8.28; N, 7.94. Found: C, 64.88; H, 8.54; N, 7.91.

EXAMPLE 16

8-[N-methyl - N-(2,6-dimethylphenyl)carbamylmethyl]nortropane [I; R, R' and R''' are CH_3, R'' is H, Y is CH_2, *n* is 1, A is CH_2].—N-methyl-2,6-dimethylaniline (9.6 g., 0.064 mole) was treated with 15 ml. of chloroacetyl chloride in dry toluene according to the manipulative procedure described above in Example 13. The product was recrystallized from pentane giving 10.8 g. of N-methyl-N-(2,6 - dimethylphenyl)carbamylmethyl chloride, M.P. 41–43° C. (uncorr.).

N-methyl-N-(2,6-dimethylphenyl)carbamylmethyl chloride (6.35 g., 0.03 mole) was treated with 7.01 g. (0.063 mole) of nortropane in 250 ml. of acetonitrile according to the manipulative procedure described above in Example 2. The product was isolated as the free base and recrystallized from hexane giving 4.08 g. of 8-[N-methyl-N-(2,6-dimethylphenyl)carbamylmethyl]nortropane, M.P. 82.6–86.6° C. (corr.).

Analysis.—Calcd. for $C_{18}H_{26}N_2O$: C, 75.50; H, 9.15; N, 9.78. Found: C, 76.46; H, 9.25; N, 9.85.

Pharmacological evaluation of 8-[N-methyl-N-(2,6-dimethylphenyl)carbamylmethyl]nortropane in an aqueous solution of its acid addition salt administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms

of its free base is approximately as active as a local anesthetic as procaine.

EXAMPLE 17

8 - [N - ethyl - N - (2,6 - dimethylphenyl)carbamylmethyl]nortropane [I; R and R′ are CH_3, R″ is H, R‴ is C_2H_5, Y is CH_2, *n* is 1, A is CH_2].—N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl chloride (6.76 g., 0.03 mole) was reacted with 7.01 g. (0.063 mole) of nortropane in 250 ml. of acetonitrile according to the manipulative procedure described above in Example 2. The product was isolated in the form of the free base and recrystallized from hexane giving 5.10 g. of 8-[N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl]nortropane, M.P. 81.6–83.4° C. (corr.).

Analysis.—Calcd. for $C_{19}H_{28}N_2O$: N (total), 9.48; N (basic), 4.66. Found: N (total), 9.48; N (basic), 4.60.

Pharmacological evaluation of 8-[N-ethyl-N-(2,6-dimethylphenyl)carbamylmethyl]nortropane in an aqueous solution of its acid addition salt administered intradermally in guinea pigs according to the method of Bulbring and Wajda, loc. cit., has shown that this compound in terms of its free base is approximately 2.3 times as active a local anesthetic as procaine.

EXAMPLE 18

8 - [N - propyl - N - (2,6 - dimethylphenyl)carbamylmethyl]nortropane hydrochloride [I; R and R′ are CH_3, R″ is H, R‴ is $(CH_2)_2CH_3$, Y is CH_2, *n* is 1, A is CH_2].—N-propyl - N - (2,6-dimethylphenyl)carbamylmethyl chloride (7.19 g., 0.03 mole) was reacted with 7.01 g. (0.063 mole) of nortropane in 260 ml. of acetonitrile according to the manipulative procedure described above in Example 2. The product was isolated in the form of its hydrochloride salt and recrystallized from an ethanol-ether mixture giving 4.57 g. of 8-[N-propyl-N-(2,6-dimethylphenyl) carbamylmethyl]nortropane hydrochloride, M.P. 142.6–143.6° C. (corr.).

Analysis.—Calcd. for $C_{20}H_{30}N_2O.HCl$: N, 7.98; Cl, 10.10. Found: N, 8.04; Cl, 10.28.

The intermediate N-lower-alkyl-substituted-anilines used in the preparation of the N-lower-alkyl-N-(monocarbocyclic aryl)carbamyl-lower-alkyl halides are prepared by reducing the corresponding N-lower-alkanoyl-substituted-anilines with an alkali metal aluminum hydride, for example, lithium aluminum hydride, in an organic solvent inert under the conditions of the reaction, for example, ether or tetrahydrofuran. The products are isolated from an alkaline medium. The following intermediate N-lower-alkyl-substituted-anilines were thus prepared:

N-methyl-2,6-dimethylaniline, B.P. 89–90° C./14.7 mm., n_D^{25}, 1.5356, prepared from N-formyl-2,6-dimethylaniline.

Analysis.—Calcd. for $C_9H_{13}N$: N, 10.35. Found: N, 10.22.

N-ethyl-2,6-dimethylaniline, B.P. 93–95° C./15 mm., n_D^{25}, 1.5225, prepared from N-acetyl-2,6-dimethylaniline.

Analysis.—Calcd. for $C_{10}H_{15}N$: N, 9.38. Found: N, 9.29.

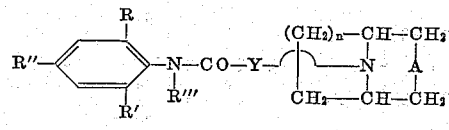
N-propyl-2,6-dimethylaniline, B.P. 115.5–118.5° C./24 mm., n_D^{25}, 1.5177, prepared from N-propionyl-2,6-dimethylaniline.

Analysis.—Calcd. for $C_{11}H_{17}N$: N, 8.57. Found: N, 8.72.

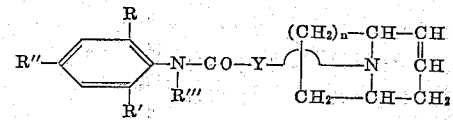
Local anesthetic compositions can be formulated using the novel N′-[N-(monocarbocyclic aryl)carbamyl-lower-alkyl]-1,5-iminocyclo-alkanes and -alkenes and their salts disclosed herein together with excipients. By an excipient I mean any inert substance used to give the compositions a suitable form or consistency. In the case of liquid compositions for topical or injectable administration, the excipient is sterile water, optionally containing additional compatible ingredients for stabilizing and the like purposes such as methyl para-hydroxybenzoate, chlorobutanol, sodium bisulfite, sodium chloride, dextrose, inositol, etc., or containing other pharmacodynamically active ingredients such as a vasoconstrictor agent, e.g., epinephrine, phenylephrine. In the case of ointment or cream compositions for topical application, the excipient is preferably petrolatum, optionally containing additional compatible ingredients such as lanolin, mineral oil, white wax, wool fat, etc. Illustrative of such local anesthetic compositions of my invention are the following: an injectable aqueous preparation comprising in each cubic centimeter 10 mg. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl] nortropane hydrochloride, 7 mg. of sodium chloride and 1 mg. of methyl para-hydroxybenzoate; an injectable aqueous preparation comprising in each cubic centimeter 20 mg. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropane hydrochloride, 0.01 mg. of epinephrine hydrochloride, 6 mg. of sodium chloride and 1 mg. of methyl para-hydroxybenzoate; a topical aqueous composition comprising 10 mg. of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropane hydrochloride, 4 mg. of chlorobutanol and enough distilled water to make 1 ml. of solution; an ointment comprising 1% of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropane dissolved in white petrolatum.

I claim:

1. A member of the group consisting of (A) compounds having the formula

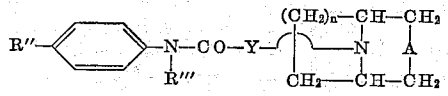


and compounds having the formula

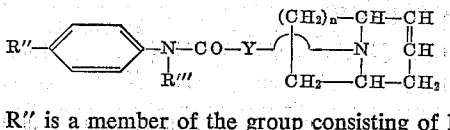


where R and R′ each are a member of the group consisting of lower-alkyl, lower-alkoxy, and halogen; R″ is a member of the group consisting of hydrogen, lower-alkyl, lower-alkoxy, and halogen; R‴ is a member of the group consisting of hydrogen and lower-alkyl, Y is lower-alkylene, *n* is an integer from 1 to 2, and A is a member of the group consisting of CH_2, CH(OH), C=O, CHCl, CHBr, CH(OAcyl) wherein Acyl is a carboxylic acyl group conventionally used in the tropine alkaloid art and having a molecular weight less than about 250, C(OH)(COO-lower-alkyl), and C(OH)(lower-alkyl); (B) pharmacologically acceptable acid-addition salts thereof; and (C) pharmacologically acceptable lower-alkyl, lower-alkenyl and monocarbocyclic aryl-lower-alkyl quaternary ammonium salts thereof.

2. A member of the group consisting of (A) compounds having the formula:



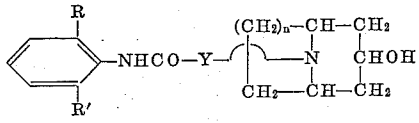
and compounds having the formula



where R″ is a member of the group consisting of hydrogen, lower-alkyl, lower-alkoxy, and halogen; R‴ is a member of the group consisting of hydrogen and lower-alkyl, Y is lower-alkylene, *n* is an integer from 1 to 2, and A is a member of the group consisting of CH_2, C=O, CHCl, CHBr, CH(OAcyl) wherein Acyl is a carboxylic acyl group conventionally used in the tropine alkaloid art and having a molecular weight less than about 250, C(OH)(COO-lower-alkyl), and C(OH)(lower-alkyl);

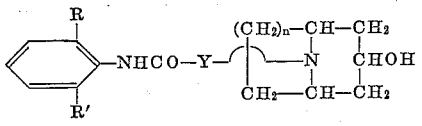
and (B) pharmacologically acceptable acid-addition salts thereof.

3. A pharmacologically acceptable acid-addition salt of a compound having the formula



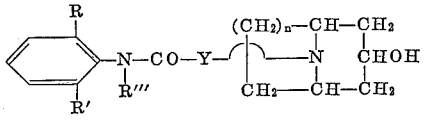
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 1.

4. A pharmacologically acceptable acid-addition salt of a compound having the formula



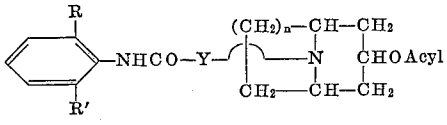
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 2.

5. A pharmacologically acceptable acid-addition salt of a compound having the formula



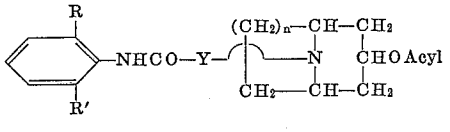
wherein R, R′ and R‴ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 1.

6. A pharmacologically acceptable acid-addition salt of a compound having the formula



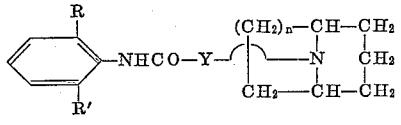
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, *n* represents the integer 1, and Acyl represents a carboxylic acyl group conventionally used in the tropine alkaloid art and having a molecular weight less than about 250.

7. A pharmacologically acceptable acid-addition salt of a compound having the formula



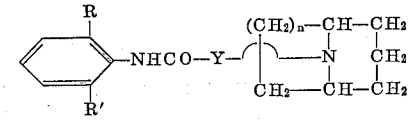
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, *n* represents the integer 2, and Acyl represents a carboxylic acyl group conventionally used in the tropine alkaloid art and having a molecular weight less than about 250.

8. A pharmacologically acceptable acid-addition salt of a compound having the formula



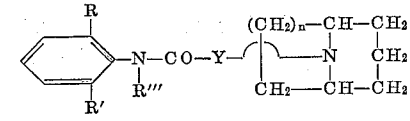
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 1.

9. A pharmacologically acceptable acid-addition salt of a compound having the formula



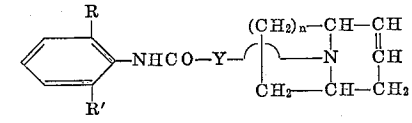
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 2.

10. A pharmacologically acceptable acid-addition salt of a compound having the formula



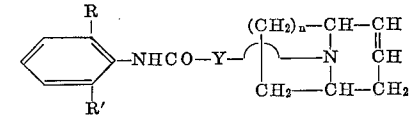
wherein R, R′ and R‴ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 1.

11. A pharmacologically acceptable acid-addition salt of a compound having the formula



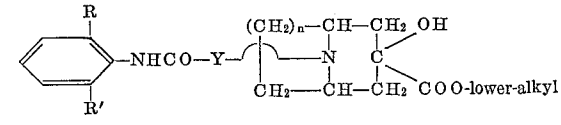
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 1.

12. A pharmacologically acceptable acid-addition salt of a compound having the formula



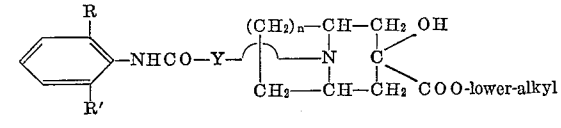
wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 2.

13. A pharmacologically acceptable acid-addition salt of a compound having the formula



wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 1.

14. A pharmacologically acceptable acid-addition salt of a compound having the formula



wherein R and R′ represent lower-alkyl radicals, Y represents a lower-alkylene radical, and *n* represents the integer 2.

15. A pharmacologically acceptable acid-addition salt of 8-[N - (2,6 - dimethylphenyl)carbamylmethyl] - 3 - hydroxynortropane.

16. 8-[N-(2,6 - dimethylphenyl)carbamylmethyl]-3-hydroxynortropane hydrochloride.

17. A pharmacologically acceptable acid-addition salt of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-(lower-alkanoyloxy)-nortropane.

18. A pharmacologically acceptable acid-addition salt of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-3-acetoxynortropane.

19. A pharmacologically acceptable acid-addition salt of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropane.

20. 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropane hydrochloride.

21. A pharmacologically acceptable acid-addition salt of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]nortropidine.

22. A pharmacologically acceptable acid-addition salt of 8-[N-(2,6-dimethylphenyl)carbamylmethyl]-nor-α-ecgonine methyl ester.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,264,309 August 2, 1966

Bernard L. Zenitz

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 3, line 2, for "(1,6-" read -- (2,6- --; line 16, for "1,5-iminocycloalkane" read -- 1,5-iminocycloalkene --; column 9, line 37, for "mole" read -- mole) --; column 10, line 46, for "CH_2 n" read -- CH_2, n --; column 11, line 17, for "Northropinone" read -- Nortropinone --; column 13, line 23, for "Ananlysis" read -- Analysis --.

Signed and sealed this 22nd day of August 1967.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents