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3-METHOXY-4-CARBAMIDOMETHOXY-PHENYLACETIC ACID ESTERS

Rudolf Hiltman, Hartmund Wollweber, Friedrich Hoffmeister, and Wolfgang Wirth, all of Wuppertal Elberfeld, Germany, assignors to Farbenfabriken Bayer Aktiengesellschaft, Leverkusen, Germany, a corporation of Germany

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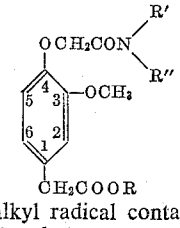
8 Claims. (Cl. 260—326.3)

This invention relates to N-alkyl-substituted 3-methoxy-4-carbamidomethoxy-phenylacetic acid esters. More particularly, the present invention relates to novel pharmacologically valuable N-alkyl-substituted 3-methoxy-4-carbamidomethoxy-phenylacetic acid alkyl and alkenyl esters and to methods for the preparation thereof.

The compounds of the invention are embraced by the general formula:



wherein R is an alkyl radical containing 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, butyl, or an alkenyl radical containing normally 3 to 4 carbon atoms, e.g. allyl, butenyl; and each of R′ and R″ is also an alkyl radical containing 1 to 4 carbon atoms; or hydrogen, provided, however, that when one of the moieties represented by R′ and R″ is hydrogen, the other is an alkyl radical. Alternatively, R′ and R″ may be joined to provide a single alkylene radical containing from 4 to 10 carbon atoms, and preferably 4 to 6 carbon atoms, the terminal carbons of which are thus attached to the single nitrogen atom to constitute a heterocyclic nitrogen-containing moiety, e.g. piperidino, pyrrolidino; or R′ and R″ may each be an alkylene radical connected at their terminal carbons positioned remote from the nitrogen atom through a hetero component, such as a chalcogen, for example, oxygen, to constitute a heterocyclic radical such as a morpholino group.

Illustrative of these compounds are 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid ethyl ester, 3 - methoxy - 4 - N - tert. - butylcarbamidomethoxy-phenylacetic acid ethyl ester, 3-methoxy-4-pyrrolidino-carbamidomethoxy-phenylacetic acid ethyl ester, 3-methoxy - 4-N,N-diethylcarbamidomethoxy-phenylacetic acid-n-propyl ester, 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid methyl ester, and 3-methoxy-4 - N,N - diethylcarbamidomethoxy - phenylacetic acid-n-butyl ester.

The procedure for preparing the compounds of the invention are standard, and include, for example, the reaction of homovanillic acid alkyl or alkenyl esters with N-mono- or N,N-dialkylated haloacetamides or with other reactive esters of N-alkylated glycollic acid amides in the presence of alkaline condensation agents. As starting substances, lower esters of homovanillic acid are preferably used, such as the methyl, ethyl, propyl, butyl, or allyl ester, with chloracetamides to the nitrogen atom of which is attached one or two alkyl radicals, each containing 1 to 4 carbon atoms, or a single alkylene radical, the terminal carbons of which are attached to the nitrogen atom to provide a heterocyclic amino moiety; or a ring structure wherein a plurality of carbon atoms are interrupted by, for example, a chalcogen atom to provide, by way of illustration, a morpholino group. Thus, the preferred and corresponding nitrogen substituents of the reactant chloracetamides are suitably characterized by the values R′ and R″ of the general formula above defining the products of the invention. Illustrative of these amides are N-tert.-butyl-chloracetamide, N-propyl-chloracetamide, N,N-diethyl-chloracetamide, chloracetyl-pyrrolidine, chloracetyl-piperidine and chloracetyl-morpholine. In order to prevent a transesterification, the alcohol corresponding to the ester is expediently used as a solvent. As a condensation agent, sodium alcoholate is especially suitable. However, hydroxyl group-free solvents such as toluene may likewise be used. In this case, the sodium compound of the ester used as a starting material is initially prepared by procedures well-known to those skilled in the art. A solvent which is particularly preferred for the conversion of these sodium phenolates is dimethylformamide in which sodium compounds are readily soluble.

Another method of preparation consists in esterifying appropriate N-alkyl-substituted 3 - methoxy - 4 - carbamidomethoxy-phenylacetic acids with saturated or unsaturated aliphatic alcohols according to known methods. Lower N - alkyl - substituted 3-methoxy-4-carbamidomethoxy-phenylacetic acid alkyl esters such as the methyl ester may also be converted into the corresponding higher esters by transesterification with higher alcohols.

The N-alkyl-substituted 3-methoxy-4-carbamidomethoxy-phenylacetic acid alkyl and alkenyl esters encompassed by the general formula and obtained as described above are, as indicated, valuable agents for inducing narcosis. When administered to a subject intravenously, these compounds are capable of inducing a relatively brief narcotizing effect, as well as one of a depth and duration sufficient and efficacious for performance of surgery on the treated subject, while effecting a rapid inception and withdrawal of the desired and operative degree of narcosis, thus providing a significantly more rapid return to street capacity in treated subjects than is available with narcotic agents employed for like purposes heretofore. This characteristic of the compounds of the invention is, of course, of decisive importance in instances of minor surgery where brief but relatively profound narcosis and, indeed, attainment of the complete tolerance stage, is required together with a rapid return to normal awareness and function on the part of the treated subject.

By way of illustrating the aforesaid advantages inherent in the esters described herein, 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid-n-propyl ester, obtained by the practice of the invention, has been compared with the known narcotizing agent, 5-methyl-5-cyclohexenyl-N-methyl-barbituric acid sodium salt. The results obtained by intravenous administration to dogs is indicated in the following table:

TABLE

	Product of Invention [1]	Control Product [2]
(a) Dose ..... mg./kg.	40	40
(b) Stage of Narcosis Attained [3]	VI	VI
(c) Total Time of Narcosis ..... minutes	17	166
(d) Narcosis Period From VI to IV in percent of Total Time of Narcosis [3]	47	17

[1] 3-methoxy-4-N, N-diethylcarbamidomethoxy-phenylacetic acid-n-propyl ester.
[2] 5-methyl-5-cyclohexenyl-N-methyl-barbituric acid.
[3] Stage of narcosis VI corresponds, according to Magnus-Girndt, to deep narcosis with complete absence of reflexes; stage of narcosis IV corresponds to lateral position, the corneal and pinching reflexes being maintained. The period between the stages of narcosis VI and IV is an approximate measure of the time available for operation.

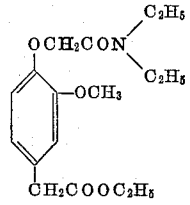
Similar results have been attained in tests undertaken with rabbits.

It has thus been determined that at equivalent dosages, the compounds of the invention effect the attainment in mammalian subjects of a like depth of narcosis to that achieved by compositions widely known and employed heretofore, but differing from these latter compositions in the reduced total time of narcosis attained thereby; that is the period of time elapsed from the onset of the narcotized state to the disappearance of all narcotic symptoms, and hence a return to normal functioning of the subject, e.g. the street capacity of the individual.

The following examples are further illustrative of the invention.

Example 1

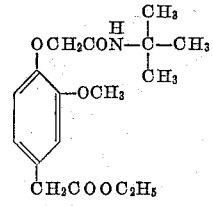
PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID ETHYL ESTER, OF THE FORMULA



To 21 g. of homovanillic acid ethyl ester is added a solution of 2.3 g. of sodium in 100 ml. of alcohol. After driving off the alcohol under vacuum, the residue in the flask is dissolved in 100 ml. of dimethylformamide. After the addition of 0.5 g. of sodium iodide, 15 g. of chloracetic acid-N,N-diethylamide are added dropwise while stirring to the solution heated to 130° C., and the mixture is further heated, until the alkaline reaction has disappeared; a period of about three hours. From the cooled reaction mixture the precipitated salts are removed by filtering off with suction. After driving off the dimethylformamide under vacuum, the product is fractionated under vacuum, and 22.5 g. of 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid ethyl ester of B.P. 204° C.–207° C./0.6 mm. Hg is thus obtained as a water-insoluble yellowish oil.

Example 2

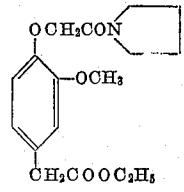
PREPARATION OF THE COMPOUND, 3-METHOXY-4-N-TERT. BUTYLCARBAMIDOMETHOXY-PHENYLACETIC ACID ETHYL ESTER, OF THE FORMULA



In the manner described in Example 1, wherein an equivalent amount of chloracetic acid-N-tert. butyl amide is substituted for the amide employed as a reactant therein, the product compound, 3-methoxy-4-N-tert.-butylcarbamidomethoxy-phenylacetic acid ethyl ester of B.P. 191° C. to 193° C./0.4 mm. Hg is produced.

Example 3

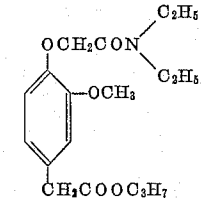
PREPARATION OF THE COMPOUND, 3-METHOXY-4-PYRROLIDINOCARBAMIDOMETHOXY-PHENYLACETIC ACID ETHYL ESTER, OF THE FORMULA



In accordance with the procedure described in Example 1, but substituting chloracetic acid-pyrrolidinoamide for the amide employed as a reactant therein, the product compound, 3-methoxy-4-pyrrolidinocarbamidomethoxy-phenylacetic acid ethyl ester having a B.P. of 201° C.–204° C./1 mm. Hg is obtained.

Example 4

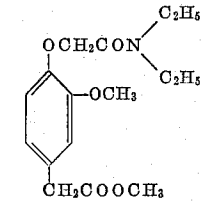
PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID-n-PROPYL ESTER, OF THE FORMULA



To a solution of 4 g. of sodium in 200 ml. of n-propanol is added 39 g. of homovanillic acid-n-propyl ester (B.P. 160° C.–162° C./4 mm. Hg) and the mixture is concentrated by evaporation under vacuum. After dissolving the residue in 200 ml. of dimethylformamide and the addition of 0.5 g. of sodium iodide, 26.2 g. of chloracetic acid-N,N-diethylamide are added dropwise with stirring at an internal temperature of 130° C., an the mixture is further heated at 130° C. for three hours. Working up of the reaction mixture according to Example 1 yields 44.3 g. of 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid-n-propyl ester as a yellowish oil of B.P. 210° C.–212° C./0.7 mm. Hg.

Example 5

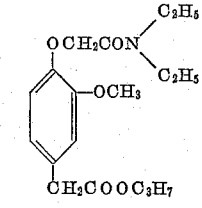
PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID METHYL ESTER, OF THE FORMULA



To a solution of 3.2 g. of sodium in 200 ml. of methanol are added 26 g. of homovanillic acid methyl ester (B.P. 149° C./6 mm. Hg), the mixture is concentrated by evaporation under vacuum and the residue dissolved in 200 ml. of dimethylformamide. After the addition of 0.5 g. of sodium iodide, 19.7 g. of chloracetic acid-N,N-diethylamide are added dropwise at 130° C. and the process is continued as described in Example 1. 18 g. of 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid methyl ester of B.P. 199° C.–201° C./0.6 mm. Hg are thus obtained as a pale yellow oil.

Example 6

PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID-n-PROPYL ESTER, OF THE FORMULA

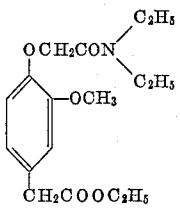


Fifty grams of the 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid methyl ester prepared by the method described in Example 5 are dissolved in 300 ml. of n-propanol and, after the addition of 0.1 g. of sodium-n-propylate, heated in an effective column, until methanol no longer goes over. After driving off the excess propyl alcohol, the product is distilled under vacuum and 46 g. of the 3-methoxy-4-N,N-diethylcarbamidomethoxy-phen-

ylacetic acid-n-propyl ester of B.P. 210° C.–212° C./0.7 mm. Hg described in Example 4 are thus obtained.

Example 7

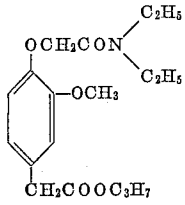
PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID ETHYL ESTER, OF THE FORMULA



To a solution of 2.3 g. of sodium in 100 ml. of alcohol are added 21 g. of homovanillic acid ethyl ester and 0.5 g. of sodium iodide. The mixture is heated under a reflux condenser while stirring and 15 g. of chloracetic acid-N, N-diethylamide are added dropwise. After boiling for a further eight hours, the alcohol is driven off under vacuum and the residue taken up with water and benzene. The separated benzene layer is washed with dilute sodium hydroxide solution and water and then dried over sodium sulphate. After driving off the solvent, the product is distilled under vacuum and 21 g. of the 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid ethyl ester of B.P. 204° C.–207° C./0.6 mm. Hg described in Example 1 are thus obtained.

Example 8

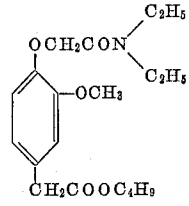
PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID-n-PROPYL ESTER, OF THE FORMULA



Twenty grams of 3-methoxy-4-N,N-carbamidomethoxy-phenylacetic acid (M.P. 119° C.–120° C.) obtainable from the methyl ester (the preparation of which is described in Example 5) by saponification with alkali, are heated under a reflux condenser with 200 ml. of n-propyl alcohol containing 3% hydrogen chloride for eight hours. After driving off the solvent, the product is taken up with benzene, washed with a sodium carbonate solution and water, and dried over sodium sulphate. After driving off the benzene, the residue is distilled under vacuum, and 19.8 g. of 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid-n-propyl ester of B.P. 210° C.–212° C./0.7 mm. Hg are thus obtained.

Example 9

PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID-n-BUTYL ESTER, OF THE FORMULA

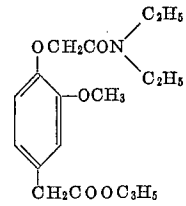


To a solution of 5.2 grams of sodium in 200 milliliters

(cc.) of n-butanol are added 54.4 grams of the n-butyl ester of homovanillic acid (B.P. 145° C.–146° C./0.5 mm. Hg) and 0.5 gram of sodium iodide. The whole is heated under a reflux condenser, and 33.8 grams of the N,N-diethylamide of chloracetic acid is added dropwise thereto. After boiling the reaction product another eight hours, it is allowed to cool, subjected to a suction filtration, and washed with n-butanol. The n-butanol is driven off in a vacuum, the residue taken up in benzene, and the benzene solution washed with a caustic soda solution and water. After drying with sodium sulfate and driving off the solvent, the residue is distilled in a vacuum. There are thus obtained 52 grams of the n-butyl ester of 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid, with a boiling point of 194° C./0.7 mm. Hg.

Example 10

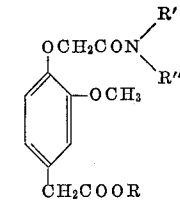
PREPARATION OF THE COMPOUND, 3-METHOXY-4-N,N-DIETHYLCARBAMIDOMETHOXY-PHENYLACETIC ACID ALLYL ESTER OF THE FORMULA



Fifty grams of the 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid methyl ester prepared by the method described in Example 5 are dissolved in 300 ml. of allyl alcohol and, after addition of 0.1 g. of sodium, heated in an effective column, until methanol no longer goes over. After driving off the excess allyl alcohol, the product is distilled under vacuum and 43 g. of the 3-methoxy-4-N,N-diethylacarbamidomethoxy-phenylacetic acid allyl ester of B.P. 208–210° C./0.8 mm. Hg are thus obtained.

What is claimed is:

1. A 3-methoxy-4-carbamidomethoxy-phenylacetic acid ester of the formula:



wherein R is a member selected from the group consisting of an alkyl of from 1 to 4 carbon atoms and an alkenyl of from 3 to 4 carbon atoms; and R′ and R″ are joined to provide members selected from the group consisting of piperidino, pyrrolidino, and morpholino.

2. 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid ethyl ester.

3. 3-methoxy-4-N-tert.-butylcarbamidomethoxy-phenylacetic acid ethyl ester.

4. 3-methoxy-4-pyrrolidinocarbamidomethoxy-phenylacetic acid ethyl ester.

5. 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid-n-propyl ester.

6. 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid methyl ester.

7. 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid-n-butyl ester.

8. 3-methoxy-4-N,N-diethylcarbamidomethoxy-phenylacetic acid allyl ester.

No references cited.