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ALKAMINE ESTERS OF Δ^2-CYCLOPENTENYL-Δ^2-CYCLOHEXENYLACETIC ACID

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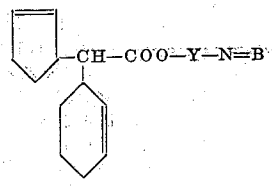
8 Claims. (Cl. 260—294.3)

1

This invention relates to aminoalkyl esters of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acids and to therapeutically acceptable salts thereof which are useful as antispasmodic agents. This is a continuation-in-part of our co-pending application, S. N. 639,405, filed January 5, 1946, now abandoned.

These esters have the formula



where Y is an alkylene bridge having at least two carbon atoms separating the oxygen and nitrogen atoms, and —N=B is a tertiary-amino group wherein B represents two alkyl groups or the atoms necessary to complete a heterocyclic ring. More specifically Y may be a divalent hydrocarbon radical such as ethylene, propylene, butylene, 1-methylethylene, 2-methylethylene or 1-methylbutylene; and —N=B includes such structures as dimethylamino, ethylmethylamino, diethylamino, dipropylamino, dibutylamino, butylpropylamino, piperidyl, 2-methylpiperidyl, morpholinyl, thiomorpholinyl, beta-hydroxyethylethylamino, etc. These may be classed together as aliphatic tertiary-amino groups, the heterocyclic rings are distinctly non-aromatic in character and can be thought of as two alkyl groups joined together by a divalent bridge such as —CH_2—, —O— or —S—.

These compounds are generally used in the form of water-soluble acid-addition salts or quaternary ammonium derivatives. The acids which may be used to prepare the salts are those which produce, when combined with the basic esters, salts whose anions are relatively innocuous to the animal organism in therapeutic doses of the salts, so that the beneficial physiological properties inherent in the basic esters are not vitiated by side-effects ascribable to the anions. Appropriate acid addition salts are those derived from mineral acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, and sulfuric acid; and organic acids such as acetic acid, citric acid and tartaric acid. The quaternary ammonium derivatives are obtained by the addition of alkyl or aralkyl esters of inorganic acids or organic sulfonic acids, such as methyl chloride, methyl bromide, methyl iodide, ethyl bromide, propyl chloride, benzyl chloride, benzyl bromide,

2

methyl sulfate, methyl benzenesulfonate, methyl p-toluenesulfonate, etc.

Synthetic antispasmodics usually have both a musculotropic (papaverine-like) action and neurotropic (athropine-like) action. It is desirable that new compounds be introduced which have high neurotropic activity but which lack the characteristic undesirable physiological side-effects of atropine.

Our compounds are distinguished by high neurotropic activity, and, in addition, several members of the series show antihistaminic action.

Our compounds are conveniently prepared by esterification of Δ^2-cyclopentenyl-Δ^2-cyclohexenyl acetic acid with an amino alcohol. The acid itself may be prepared by successive alkylations of diethyl malonate or ethyl cyanoacetate with a Δ^2-cyclopentenyl halide and a Δ^2-cyclohexenyl halide, followed by hydrolysis and decarboxylation of the disubstituted malonic or cyanoacetic esters to Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid. The preferred method involves alkylation of diethyl Δ^2-cyclopentenylmalonate with 1,2-dibromocyclohexane to give directly diethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylmalonate. The expected simple alkylation product of this reaction, diethyl Δ^2-cyclopentenyl-2-bromocyclohexylmalonate, is not isolated, hydrogen bromide being split out under the reaction conditions used to give the desired 2–3 double bond in the cyclohexane ring. The substituted malonic ester is hydrolyzed to the manolic acid by heating under pressure with a potassium hydroxide solution. Further heating under normal pressure causes elimination of one carboxyl group from the malonic acid to give Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid.

The compounds of our invention, basic esters of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid, and their acid addition salts are prepared by one of the following methods.

(1) An acid halide or anhydride of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid is reacted with a tertiary-aminoalkanol of the formula

HO—Y—N=B

where Y is an alkylene bridge of at least 2 carbon atoms and —N=B is a tertiary-amino group. The reaction is effected by simple admixture of the two components although heating is generally used to accelerate the reaction. The free basic ester is obtained by addition of alkali to the reaction mixture. The basic ester may be converted to an acid addition salt by the addition, preferably in non-aqueous medium, of a thera-

peutically acceptable acid, such as hydrogen chloride in alcoholic solution.

(2) The Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid is reacted with a tertiary-aminoalkanol using a mineral acid, such as sulfuric acid, as a catalyst, present in an amount greater than that necessary to neutralize the amino alcohol. The free basic ester and its acid addition salts are obtained as in method (1).

(3) The Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid is heated with a tertiary-aminoalkyl halide of the formula Z—Y—N=B, where Z is halogen (preferably chlorine or bromine) and Y and B have the same meaning as before. The free basic ester and its acid addition salts are obtained as in method (1).

(4) A metallic salt of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid is heated or simply mixed with a tertiary-aminoalkyl halide. In this case the free basic ester is formed directly.

Quaternary ammonium salts are prepared by mixing the free basic ester with a lower alkyl or aralykyl ester of a strong inorganic acid or organic sulfonic acid, preferably in an inert organic solvent such as benzene or ether, with or without gentle heating. The salt either crystallizes immediately or can be obtained by concentration of the solvent.

Example 1

(*a*) *Diethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylmalonate.*—To a solution of 74 g. of sodium in 1.2 liters in absolute ethanol is added 271.2 g. of diethyl Δ^2-cyclopentenylmalonate. Most of the alcohol is distilled off and toluene is added and distilled off until the boiling point reached is about 110° C. Enough more dry toluene is added to bring the volume to about 800 cc. and then 387.2 g. of 1,2-dibromocyclohexane is added slowly. After refluxing for two hours the mixture is cooled, 600 cc. of water is added and the layers are separated. The solvent is removed and the product is distilled through an efficient column giving about 202 g. (53.2%) of diethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylmalonate, B. P. 124° C. (0.15 mm.).

(*b*) *Δ^2 - cyclopentenyl - Δ^2 - cyclohexenylacetic acid.*—To a solution of 40 g. of potassium hydroxide in a 100 cc. of ethanol is added 40 g. of diethyl Δ^2- cyclopentenyl-Δ^2- cyclohexenylmalonate. The mixture is placed in a bomb and heated to a 140–160° C. for 3 hours. After cooling, the product is dissolved in one liter in water and extracted with ether. Acidification of the aqueous layer gives an oil which is taken up in ether, washed with water and dried over anhydrous sodium sulfate. The ether is removed and the residue is heated to 180° C. until no more carbon dioxide is evolved. The residue is distilled in vacuo and the fraction that distills at 101° C. under 0.01 mm. pressure is collected, giving Δ^2 - cyclopentenyl - Δ^2 - cyclohexenylacetic acid, $n_D^{25}=1.5120$; $d_4^{25}=1.0600$.

(*c*) *Beta-diethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate and its hydrochloride.*—Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid (22 g.) is neutralized with an alcoholic solution of sodium methoxide and 14.5 g. of beta-diethylaminoethyl chloride in isopropyl alcohol is added. The mixture is refluxed from three to four hours, the solution is cooled and ether added to precipitate the salts. After filtration, the solvent is removed by vacuum disillation, and the residue is distilled at 116° C. under 0.02 mm. pressure. The distillate is taken up in dry ether and the ester hydrochloride is precipitated by the addition of anhydrous hydrogen chloride gas. The precipitated hydrochloride of beta-diethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate is filtered and dried; M. P. 108–110.5° C.

Example 2

(*a*) *Δ^2 - cyclopentenyl - Δ^2 - cyclohexenylacetyl chloride.*—A solution of 41.2 g. (0.2 m.) of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid and 35.7 g. (0.3 m.) of thionyl chloride in 100 cc. of dry benzene is refluxed for two and one-half hours. The solvent is removed by distillation, more benzene added and again concentrated to insure complete removal of excess thionyl chloride. The residue is distilled at reduced pressure giving about 41 g. (85%) of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetyl chloride, B. P. 110° C. (0.3 mm.); $n_D^{25°}=1.5180$; $d_4^{25°}=1.0974$.

(*b*) *Beta-(N-piperidyl)-ethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate and its hydrochloride.*—A solution of 30 g. (0.134 m.) of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetyl chloride and 17.3 g. (0.134 m.) of beta-N-piperidylethanol in 100 cc. of dry benzene is refluxed for four hours. Some of the product crystallizes at this point as the hydrochloride and is filtered off after cooling. This hydrochloride is neutralized with sodium carbonate solution. The benzene filtrate is diluted with ether and extracted with water and dilute hydrochloric acid; the aqueous extracts are neutralized with sodium carbonate and combined with the other sodium carbonate solution obtained above. The free basic ester is extracted with ether which is then dried over anhydrous sodium sulfate and concentrated. The product distills at 139° C. (0.07 mm.), giving about 25.1 g. (59%) of beta-(N-piperidyl)-ethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate; $n_D^{25°}=1.5070$; $d_4^{25°}=1.0222$.

The hydrochloride is made in the usual manner. It precipitates from ether as fine crystals in about 94% yield, M. P. 133–142° C.

Example 3

Beta-dimethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate and its hydrochloride are prepared by methods previously described starting with Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid and beta-dimethylaminoethanol. The free basic ester boils at 110° C. (0.05 mm.), $n_D^{25}=1.4948$; $d_4^{25}=1.0012$, and its hydrochloride has the M. P. 129–133.5° C.

Example 4

1-diethylamino-2-propyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate and its hydrochloride are prepared by methods previously described starting with Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid and 1-diethylamino-2-propanol. The free basic ester boils at 116° C. (0.03 mm.), $n_D^{25}=1.4882$; $d_4^{25}=0.9786$, and its hydrochloride has the M. P. 118–120° C.

Example 5

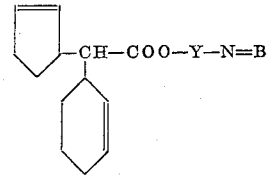
Beta-(N-morpholinyl)-ethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate and its hydrochloride are prepared by methods previously described starting with Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid and beta-(N-morpholinyl)-ethanol. The free basic ester boils at 130° C. (0.02 mm.), $n_D^{25}=1.5083$; $d_4^{25}=1.0655$, and its hydrochloride has the M. P. 144–145° C.

Example 6

Gamma-diethylaminopropyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate and its hydrochloride are prepared by methods previously described starting with Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid and gamma-diethylaminopropanol. The free basic ester boils at 131° C. (0.07 mm.), $n_D^{25}=1.4900$; $d_4^{25}=0.9761$, and its hydrochloride has the M. P. 115–118° C.

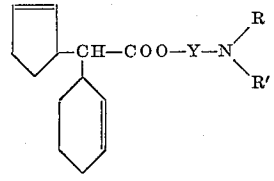
We claim:

1. A substance of the group consisting of basic esters of the formula



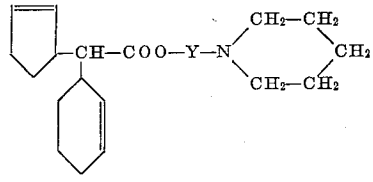
wherein Y is an alkylene bridge of 2–5 carbon atoms and —N=B is a tertiary-amino group of the class consisting of di-lower-alkylamino, piperidyl and morpholinyl radicals; and acid addition and quaternary ammonium salts thereof.

2. A substance of the group consisting of basic esters of the formula



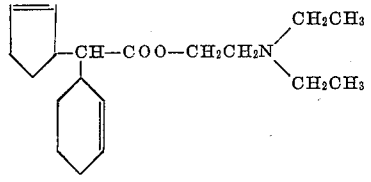
wherein Y is an alkylene bridge of 2–5 carbon atoms and R and R′ are lower alkyl groups; and acid addition and quaternary ammonium salts thereof.

3. A substance of the group consisting of basic esters of the formula



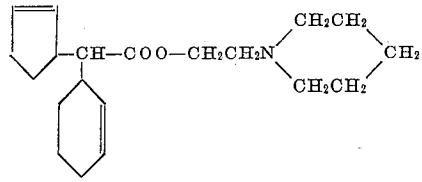
where Y is an alkylene bridge of 2–5 carbon atoms; and acid addition and quaternary ammonium salts thereof.

4. A substance of the group consisting of beta-diethylaminoethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate having the formula



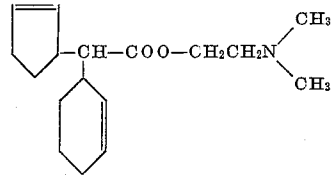
and acid addition and quaternary ammonium salts thereof.

5. A substance of the group consisting of beta-(N-piperidyl)-ethyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate having the formula



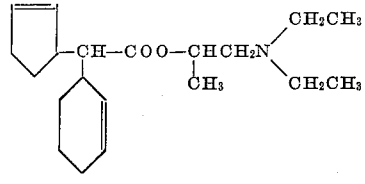
and acid addition and quaternary ammonium salts thereof.

6. A substance of the group consisting of beta-dimethylaminoalkyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate having the formula



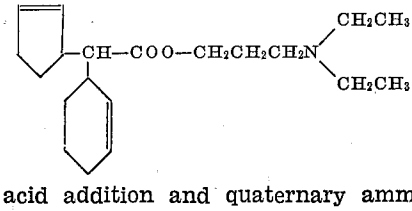
and acid addition and quaternary ammonium salts thereof.

7. A substance of the group consisting of 1-diethylamino-2 propyl Δ^2-cyclopentenyl-Δ^3-cyclohexenylacetate having the formula



and acid addition and quaternary ammonium salts thereof.

8. A substance of the group consisting of gamma-diethylaminopropyl Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetate having the formula



and acid addition and quaternary ammonium salts thereof.

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CHARLOTTE ANNE HART.

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Certificate of Correction

Patent No. 2,538,795 January 23, 1951

ROBERT BRUCE MOFFETT ET AL.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows:

Column 2, line 32, for "manolic" read *malonic*; column 6, line 27, for "-2 propyl" read *-2-propyl*;

and that the said Letters Patent should be read as corrected above, so that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 3rd day of April, A. D. 1951.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.