Patented Jan. 23, 1951 2,538,793

UNITED STATES PATENT OFFICE

2,538,793

ALKAMINE ESTERS OF CYCLOPENTYL-ALKYLACETIC ACIDS

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No Drawing. Application August 10, 1948, Serial No. 43,542

9 Claims. (Cl. 260—294.3)

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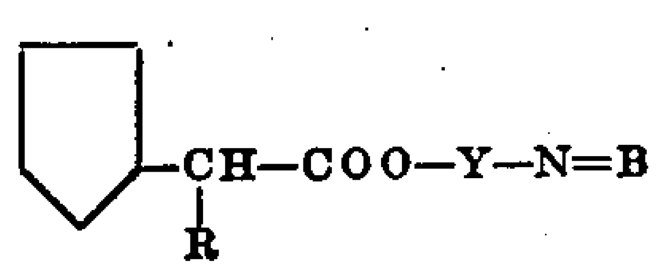
This invention relates to aminoalkyl esters of cyclopentylalkylacetic acids and to thereapeutically acceptable salts thereof which are useful as antispasmodic agents. This is a continuation-in-part of our copending application, S. N. 643,480, filed January 25, 1946, now abandoned. These esters have the formula



where R is an alkyl group of 4–6 carbon atoms, 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

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

Synthetic antispasmodics usually have both a musculotropic (papaverine-like) action and neurotropic (atropine-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 the corresponding substituted acetic acid, $(C_5H_9)—CHR—COOH$. The acids themselves are prepared in the following general manner. The sodio derivative of diethyl cyclopentylmalonate, $(C_5H_9)—CH—(COOC_2H_5)_2$, is alkylated with RX, where R is an alkyl group of 4–6 carbons and X is a halogen atom; i. e. chlorine, bromine or iodine. The resulting cyclopentylalkylmalonic ester,

$$(C_5H_9)—CR—(COOC_2H_5)_2$$

is hydrolyzed by heating with 30% alcoholic potassium hydroxide in a bomb at 140–150° C., and decarboxylated at 180° C. at atmospheric pressure, giving the desired cyclopentylalkylacetic acid. In many instances we prefer to prepare these acids by a slightly more indirect method which involves preparation of the corresponding Δ^2-cyclopentenylalkylmalonic ester,

$$C_5H_7—CR—(COOC_2H_5)_2$$

by alkylation of diethyl Δ^2-cyclopentenylmalonate, followed by reduction of the double bond. This method is desirable because it provides intermediates for the basic esters of Δ^2-cyclopentenylalkylacetic acids which are also valuable compounds.

In some cases where the malonic esters are difficult to prepare because of the steric hindrance of the groups involved, an alternative procedure can be used. This is based on the method of Alexander and Cope [J. Am. Chem. Soc. 66, 886 (1944)], which involves condensation of an aldehyde or ketone with ethyl cyanoacetate and reduction of the resulting ethylenic double bond, all carried out in one step. In preparing the compounds of the present invention the carbonyl compound used has a structure such that the group R in the resulting substituted cyanoacetic ester, R—CH(CN)—$COOC_2H_5$, has 4–6 carbon atoms. For example, condensation of ethyl cyanoacetate and methyl isopropyl ketone in the presence of ammonium acetate, acetic acid and palladium-on-charcoal in an atmosphere of hydrogen gives ethyl (1,2-dimethylpropyl)-cyanoacetate. The sodio-derivative of the mono-substituted cyanoacetic ester is then alkylated with a cyclopentylhalide to give an ethyl cyclopentylalkylcyanoacetate, (C_5H_9)—CR(CN)—$COOC_2H_5$. This is hydrolyzed and decarboxylated to the corresponding cyclopentylalkylacetic acid,

$$(C_5H_9)—CHR—COOH$$

although in lower yield than the hydrolysis and decarboxylation of the corresponding malonic ester. Substituted acetamides appear as byproducts and more drastic conditions of hydrolysis lead to decomposition. Again, in many instances we prefer to prepare first a Δ^2-cyclopentenylalkylcyanoacetate

$$(C_5H_7)—CR(CN)—COOC_2H_5$$

by alkylation of a mono-substituted cyanoacetic ester with a Δ^2-cyclopentenylhalide, followed by reduction of the ring double bond to a cyclopentylalkylcyanoacetate. Although one step longer, this process provides intermediates for the preparation of valuable basic esters of Δ^2-cyclopentenylalkylacetic acids as well as those of the present invention.

The preferred method, the malonic ester or cyanoacetic ester synthesis, in a given case depends upon the nature of the alkyl group to be introduced. If the alkyl group to be introduced is of the straight chain type or is branched at the end, the malonic ester synthesis is preferred. If the alkyl group is branched, particularly near its point of juncture with the rest of the molecule, the cyanoacetic ester method is preferred.

The esters of our invention, having the general formula C_5H_9—CH(R)—COO—Y—N=B as described above, and their acid addition salts, are prepared from the free acid by one of the following methods:

(1) An acid halide or anhydride of a cyclopentylalkylacetic 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 therapeutically acceptable acid, such as hydrogen chloride in alcoholic solution.

(2) The cyclopentylalkylacetic 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 cyclopentylalkylacetic 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 a cyclopentylalkylacetic 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 aralkyl 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-isobutlymalonate.*—To a stirred suspension of 27.6 g. (1.2 m.) of powered sodium in 240 cc. of dry toluene is slowly added 271.6 g. (1.2 m.) of diethyl Δ^2-cyclopentenylmalonate. [Noller and Adams, J. Am. Chem. Soc. 48, 2444 (1926).] After nearly all of the sodium has reacted at reflux temperature, 210 g. (1.5 m.) of isobutyl bromide is added dropwise and the mixture refluxed for sixteen hours. After cooling, the mixture is neutralized with dilute acetic acid, and the toluene layer is washed with water, dried over anhydrous sodium sulfate and concentrated. The residue is distilled at reduced pressure, first through a Claisen head and then redistilled through an efficient fractionating column. After discarding considerable low boiling material, the product distils at 73° C. (0.02 mm.) giving about 145 g. (46%) of diethyl Δ^2-cyclopentenyl-isobutylmalonate,

$$n_D^{25}=1.4580,\ d_4^{25}=1.0157$$

(b) *Diethyl cyclopentyl-isobutylmalonate.*—A solution of 77.7 g. (0.275 m.) of diethyl Δ^2-cyclopentenyl-isobutylmalonate in 30 cc. of alcohol is hydrogenated in the presence of 0.2 g. of Adams platinum oxide catalyst at about 50 pounds pressure. Reduction is complete in about one hour. The product is recovered and distilled at reduced pressure through a Claisen head, giving about 76 g. (98%) of diethyl cyclopentyl-isobutylmalonate, B. P. 96° C. (0.04 mm.); $n_D^{25}=1.4532$; $d_4^{25}=1.0023$.

(c) *Cyclopentyl-isobutylacetic acid.*—A mixture of 1160 g. of diethyl cyclopentyl-isobutylmalonate with a solution of 1000 g. of potassium hydroxide in 2500 cc. of ethanol is heated in a bomb at 140–150° C. for three hours. After cooling, most of the alcohol is distilled off, water is added to the residue and the whole neutralized with hydrochloric acid. The substituted acetic acid is extracted with ether, and the ether extracts are washed with water and with saturated sodium chloride solution containing a little sodium bicarbonate, and finally dried over anhydrous sodium sulfate. The ether is then distilled off and the residue heated to 170° C. until carbon dioxide ceases to be evolved. Distillation at reduced pressure gives about 810 g. (97%) of cyclopentyl-isobutylacetic acid, B. P. 79–82° C. (0.08 mm.); $n_D^{25}=1.4549$; $d_4^{25}=0.9525$.

(d) *Beta-diethylaminoethyl cyclopentyl-isobutylacetate and its hydrochloride.*—Cyclopentyl-isobutylacetic acid (19 g., 0.103 m.) is neutralized to phenolphthalein with alcoholic sodium ethoxide, and 13.9 g. (0.103 m.) of beta-diethylaminoethyl chloride in 40 cc. of isopropyl alcohol is then added. After standing for several days (or refluxing for several hours), the sodium chloride is removed by filtration, and the volatile solvents are distilled off. The basic ester is dissolved in ether, washed with water and extracted with cold dilute hydrochloric acid. The acid solution is washed with ether and made basic with sodium carbonate. The liberated basic ester is extracted with ether and the ether solution dried over anhydrous sodium sulfate. Distillation of the product at reduced pressure after removal of the ether gives about 20 g. (68%) of beta-diethylaminoethyl cyclopentyl - isobutylacetate, B. P. 113° C. (0.03 mm.); $n_D^{25}=1.4527$; $d_4^{25}=0.9119$.

The hydrochloride of beta-diethylaminoethyl cyclopentyl-isobutylacetate is prepared by passing hydrogen chloride gas into a solution of 18 g. of the free basic ester in absolute ether. A colloidal precipitate forms which crystallizes upon stirring. After filtering, washing with ether and drying, the hydrochloride is obtained, 19.2 g. (94%), M. P. 118.5–119.5° C.

EXAMPLE 2

(a) *Cyclopentyl - isobutylacetyl chloride.*—A mixture of 814 g. (4.42 m.) of cyclopentyl-isobutylacetic acid (see Example 1 for preparation of this acid) and 726 cc. of technical grade thionyl chloride is heated on a steam bath until gas ceases to be evolved. The excess thionyl chloride is removed by distillation and the product is distilled from a Claisen flask giving about 866 g. (96.5%) of cyclopentyl-isobutylacetyl chloride, B. P. 99° C. (6 mm.), $n_D^{25}=1.4608$; $d_4^{25}=0.9913$.

(b) *Beta-(N-piperidyl)-ethyl cyclopentyl-isobutylacetate and its hydrochloride.*—Beta-(N-piperidyl)-ethyl alcohol (19.2 g., 0.148 m.) is dissolved in 100 cc. of dry pyridine and 30 g. (0.148 m.) of cyclopentyl-isobutylacetyl chloride is added, and the mixture is allowed to stand for a few minutes and finally heated on a steam bath for four hours. After cooling the mixture, it is shaken with a solution of 12 g. of sodium carbonate monohydrate in 250 cc. of water and the water layer is separated and extracted with ether. The combined organic layers are concentrated using a water aspirator and the residue distilled at reduced pressure, giving about 37 g. (85%) of beta-(N-piperidyl)-ethyl cyclopentyl-isobutylacetate, B. P. 106–108° C. (0.02 mm.); $n_D^{25}=1.4717$; $d_4^{25}=0.9600$.

The hydrochloride is prepared by passing dry hydrogen chloride gas into a solution of 34 g. (0.115 m.) of the free basic-ester in 500 cc. of anhydrous ether. A white, crystalline precipitate forms which is filtered and dried giving about 31 g. (82%) of the hydrochloride of beta-(N-piperidyl)-ethyl cyclopentyl-isobutylacetate, M. P. 177.5–180° C.

EXAMPLE 3

Beta - (N-beta-hydroxyethyl-N-ethylamino)-ethyl cyclopentyl-isobutylacetate and its hydrochloride.—To a solution of 13.3 g. (0.1 m.) of N-ethyl-diethanolamine in 50 cc. of triethylamine is slowly added 22.3 g. (0.11 m.) of cyclopentyl-isobutylacetyl chloride. Upon warming, a crystalline precipitate separates. After several hours on a steam bath, the solvent is removed, the residue dissolved in dilute hydrochloric acid, and the solution is extracted twice with ether and made basic with sodium hydroxide. The product is extracted with ether, washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the ether, the product is distilled at reduced pressure from a 50 cc. Claisen flask containing a 6'' fractionating column packed with 1/8'' helices. The main fraction boils at 106° C. (0.012 mm.) giving about 14.2 g. (43%) of beta-(N-beta-hydroxyethyl-N-ethylamino)-ethyl cyclopentyl-isobutylacetate; $n_D^{25}=1.4653$; $d_4^{25}=0.9706$.

The hydrochloride is prepared in the usual manner by passing dry hydrogen chloride gas through a solution of the basic-ester in anhydrous ether. The dry, crystalline, hygroscopic product has the M. P. 59–62° C.

EXAMPLE 4

(a) *Ethyl (1,2 - dimethylpropyl) - cyanoacetate.*—A mixture of 56.6 g. (0.55 m.) of methyl isopropyl ketone, 6 cc. of glacial acetic acid, 3.9 g. of ammonium acetate, 75 cc. of 95% ethanol and 2 g. of palladium-on-charcoal catalyst is shaken in an atmosphere of hydrogen at room temperature and 50 pounds pressure. Reduction is complete in about one hour. Five such runs are combined, filtered, and the solvent is removed in vacuo on a steam bath. The residue is taken up in ether, washed with water, sodium bicarbonate solution and saturated salt solution, and dried over anhydrous sodium sulfate. After removing the solvent, the product is distilled twice at reduced pressure from a Claisen flask and then through an efficient fractionating column, giving about 143 g. (31%) of nearly colorless ethyl (1,2-dimethylpropyl)-cyanoacetate, B. P. 60° C. (0.12 mm.); $n_D^{25°}=1.4322$; $d_4^{25°}=0.9552$.

(b) *Ethyl Δ^2 - cyclopentenyl - (1,2-dimethylpropyl)-cyanoacetate.*—To 11.5 g. (0.5 m.) of sodium melted under 100 cc. of dry toluene in a 1 liter flask, is slowly added (with vigorous stirring) 91.5 g. (0.5 m.) of ethyl (1,2-dimethylpropyl)-cyanoacetate. When practically all of the sodium has reacted, 77 g. (0.75 m.) of Δ^2-cyclopentenyl chloride is added. Sodium chloride separates and the reaction mixture tests acidic almost immediately. Water is added, the layers separated, and the aqueous layer is extracted with ether. The combined organic layers are washed with saturated sodium chloride solution, and the solvent is removed in vacuo. The residue is distilled at reduced pressure, first from a Claisen flask and then through an efficient fractionating column, giving about 84 g. (67%) of yellow ethyl Δ^2-cyclopentenyl-(1,2-dimethylpropyl)-cyanoacetate, B. P. 84° C. (0.07 mm.); $n_D^{25°}=1.4709$; $d_4^{25°}=0.9974$.

(c) *Ethyl cyclopentyl - (1,2-dimethylpropyl)-cyanoacetate.*—A solution of 44.8 g. (0.18 m.) of ethyl Δ^2 - cyclopentenyl - (1,2-dimethylpropyl)-cyanoacetate in 100 cc. of ethanol is hydrogenated at 50 pounds pressure and 30° C. with 0.2 g. of platinum oxide catalyst. The theoretical amount of hydrogen is absorbed in one hour, and, after filtering, the solvent is removed and the product is distilled at reduced pressure, giving about 40 g. (88.5%) of ethyl cyclopentyl-(1,2-dimethylpropyl)-cyanoacetate, B. P. 76° C. (0.01 mm.); $n_D^{25}=1.4637$; $d_4^{25}=0.9850$.

(*d*) *Cyclopentyl - (1,2-dimethylpropyl)-acetic acid.*—A mixture of 38.7 g. (0.154 m.) of ethyl cyclopentyl - (1,2-dimethylpropyl)-cyanoacetate with a solution of 75 g. of potassium hydroxide in 125 cc. of 90% ethanol is heated in a bomb in an oil bath at 160–180° C. for 42 hours. After cooling, the contents of the bomb are diluted with water and a crystalline neutral fraction [cyclopentyl-(1,2-dimethylpropyl)-acetamide] is filtered off. The filtrate is acidified and the acidic oil is extracted with ether, washed three times with water and once with saturated sodium chloride solution containing a little sodium bicarbonate, and finally dried over anhydrous sodium sulfate. After removal of the solvent, the product is distilled at reduced pressure from a Claisen flask giving about 9.7 g. (32%) of cyclopentyl-(1,2-dimethylpropyl)-acetic acid, B. P. 96° C. (0.06 mm.); $n_D^{25}=1.4651$; $d_4^{25}=0.9668$.

(*e*) *Beta-diethylaminoethyl cyclopentyl-(1,2-dimethylpropyl)-acetate and its hydrochloride.*—This is prepared from the substituted acetic acid using sodium ethoxide and beta-diethylaminoethyl chloride according to the method shown in Example 1, part (*d*). Eight and three-tenths grams of the acid results in about 8.4 g. (67%) of beta-diethylaminoethyl cyclopentyl-(1,2-dimethylpropyl)-acetate, B. P. 108° C. (0.06 mm.); $n_D^{25}=1.4601$; $d_4^{25}=0.9272$.

The hydrochloride is prepared in the usual manner from the basic-ester and dry hydrogen chloride gas in either solution. The crude product is recrystallized from methyl isobutyl ketone giving about a 69% yield of hydrochloride, M. P. 141–146° C.

EXAMPLE 5

(*a*) *Ethyl Δ²-cyclopentenyl-(1-methylbutyl)-cyanoacetate.*—To 18.4 g. (0.8 m.) of sodium melted under 180 cc. of dry toluene in a 1 liter flask, is slowly added (with vigorous stirring) 124 g. (0.8 m.) of ethyl (1-methylbutyl)-cyanoacetate [Alexander and Cope, J. Am. Chem. Soc. 66, 886 (1944)]. When practically all of the sodium has reacted, 123 g. (1.2 m.) of Δ^2-cyclopentenyl chloride is added. Sodium chloride separates and the reaction mixture tests acidic almost immediately. Water is added, the layers are separated and the aqueous layer is extracted with ether. The organic layer is washed with saturated sodium chloride solution and the solvent is removed at reduced pressure. The product is distilled at reduced pressure, first from a Claisen flask and then through an efficient column, giving about 125 g. (63%) of ethyl Δ^2-cyclopentenyl-(1-methylbutyl)-cyanoacetate, B. P. 95° C. (0.2 mm.); $n_D^{25}=1.4678$; $d_4^{25}=0.9893$.

(*b*) *Ethyl cyclopentyl-(1-methylbutyl)-cyanoacetate.*—A solution of 62.4 g. (0.25 m.) of ethyl Δ^2-cyclopentenyl-(1-methylbutyl) - cyanoacetate in 100 cc. of ethanol is hydrogenated at room temperature and 50 pounds pressure using 0.2 g. of platinum oxide catalyst. In about one hour reduction is complete. The catalyst is removed by filtration and the solvent removed. The product is distilled at reduced pressure from a Claisen flask, giving about 62 g. (98%) of ethyl cyclopentyl-(1-methylbutyl)-cyanoacetate, B. P. 95° C. (0.27 mm.); $n_D^{25}=1.4606$; $d_4^{25}=0.9762$.

(*c*) *Cyclopentyl-(1-methylbutyl)-acetic acid.*—A mixture of 40 g. of ethyl cyclopentyl-(1-methylbutyl)-cyanoacetate with a solution of

70 g. of potassium hydroxide in 115 cc. of 90% ethanol is heated in a bomb immersed in an oil bath at 170–180° C. for 46 hours. On diluting the contents of the bomb with water, a crystalline precipitate separates which is collected, washed with water and dried; weight, 11 g. (35%). This proves to be cyclopentyl-(1-methylbutyl)-acetamide, and a sample when recrystallized from hexane melts at 94–109° C. The basic aqueous filtrate from above is extracted with ether and then acidified with hydrochloric acid. The product is recovered and purified as in Example 1, part *c* giving about 11 g. (35%) of cyclopentyl-(1-methylbutyl)-acetic acid, B. P. 96° C. (0.07 mm.); $n_D^{25}=1.4623$; $d_4^{25}=0.9591$.

(*d*) *Beta - diethylaminoethyl cyclopentyl-(1-methylbutyl)-acetate and its hydrochloride.*—Cyclopentyl-isobutylacetic acid (11 g., 0.055 m.) is neutralized to phenolphthalein with alcoholic sodium ethoxide, and 7.5 g. (0.055 m.) of beta-diethylaminoethyl chloride in 25 cc. of isopropyl alcohol is then added. After standing for several days (or refluxing for several hours), the sodium chloride is removed by filtration, and the volatile solvents are distilled off. The basic ester is dissolved in ether, washed with water and extracted with cold dilute hydrochloric acid. The acid solution is washed with ether and made basic with sodium carbonate. The liberated basic ester is extracted with ether and the ether solution dried over anhydrous sodium sulfate. Distillation of the product at reduced pressure after removal of the ether gives about 11 g. (66%) of beta-diethylaminoethyl cyclopentyl - (1-methylbutyl)-acetate, B. P. 124° C. (0.35 mm.); $n_D^{25}=1.4594$; $d_4^{25}=0.9161$.

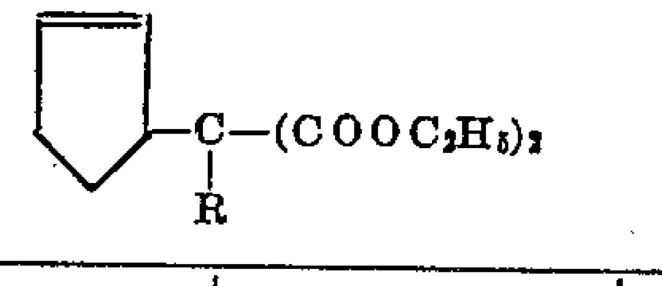
The hydrochloride of beta-diethylaminoethyl cyclopentyl-(1-methylbutyl)-acetate is prepared by passing hydrogen chloride gas into a solution of 9.5 g. of the basic ester in absolute ether. A crystalline precipitate forms which is filtered, washed with ether and dried, giving about 6.9 g. (65%) of the hydrochloride. When recrystallized from methyl isobutyl ketone it melts at 99–103° C.

Additional compounds have been made by the methods outlined in the preceding examples and are disclosed in the following tables:

TABLE I

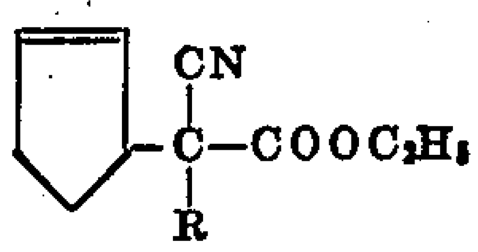
CYCLOPENTENYL DERIVATIVES

A. *Malonates*



R	B. P. ° C. (□ mm.)	n_D^{25}	d_4^{25}
CH_3CHCH_2— CH_3 (branch)	73 (0.02)	1.4580	1.0157
$CH_3(CH_2)_3$—	94 (0.04)	1.4576	--------
$CH_3(CH_2)_4$—	84–90 (0.02–0.03)	1.4584	1.0010
$CH_3CHCH_2CH_2$— CH_3 (branch)	99 (0.038)	1.4580	1.0007
$CH_3CH_2CHCH_2$— CH_3 (branch)	83 (0.03)	1.4581	0.9970
$CH_3CH_2CHCH_2$— CH_2CH_3 (branch)	90 (0.01)	1.4616	0.9966

B. *Cyanoacetates*

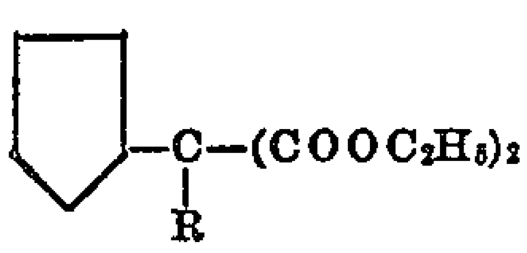


R	B. P. ° C. (□ mm.)	n_D^{25}	d_4^{25}
$CH_3CH_2CH(CH_3)$—	93 (0.26)	1.4680	1.0004
$CH_3CH_2CH_2CH(CH_3)$—	95 (0.21)	1.4678	0.9893
$CH_3CH(CH_3)CH(CH_3)$—	84 (0.07)	1.4709	0.9974

TABLE II

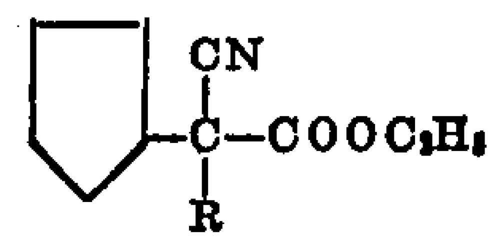
Cyclopentyl Derivatives

A. *Malonates*



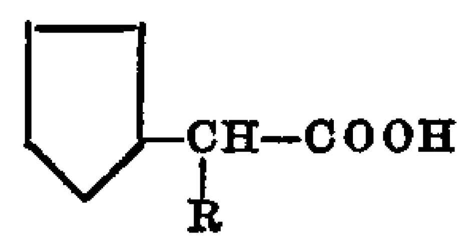
R	B. P. ° C. (□ mm.)	n_D^{25}	d_4^{25}
$CH_3CH(CH_3)CH_2$—	96 (0.04)	1.4536	1.0023
$CH_3(CH_2)_3$—	81 (0.02)	1.4494	0.9937
$CH_3(CH_2)_4$—	98 (0.04)	1.4525	0.9887
$CH_3CH(CH_3)CH_2CH_2$—	101 (0.04)	1.4524	0.9914
$CH_3CH_2CH(CH_3)CH_2$—	109 (0.25)	1.4527	0.9874
$CH_3CH_2CH(CH_2—CH_3)CH_2$—	95 (0.005)	1.4571	0.9884

B. *Cyanoacetates*



R	B. P. ° C. (□ mm.)	n_D^{25}	d_4^{25}
$CH_3CH_2CH(CH_3)$—	96 (0.25)	1.4603	0.9865
$CH_3CH_2CH_2CH(CH_3)$—	95 (0.27)	1.4606	0.9762
$CH_3CH(CH_3)—CH(CH_3)$—	76 (0.01)	1.4637	0.9850

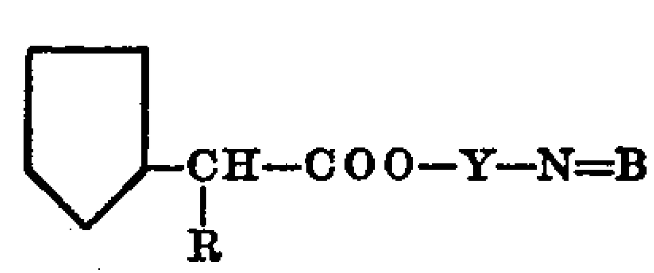
C. *Acetic acids*



R	B. P. ° C. (□ mm.)	n_D^{25}	d_4^{25}
$CH_3CH(CH_3)CH_2$—	79 (0.08)	1.4549	0.9525
$CH_3(CH_2)_3$—	88 (0.09)	1.4555	0.9549
$CH_3(CH_2)_4$—	96 (0.02)	1.4569	0.9481
$CH_3CH(CH_3)CH_2CH_2$—	94 (0.055)	1.4559	0.9438
$CH_3CH_2CH(CH_3)CH_2$—	114 (0.35)	1.4570	0.9483
$CH_3CH_2CH(CH_2—CH_3)CH_2$—	103 (0.028)	1.4600	0.9436
$CH_3CH_2CH(CH_3)$—	89 (0.08)	1.4618	0.9693
$CH_3CH_2CH_2CH(CH_3)$—	96 (0.07)	1.4623	0.9591
$CH_3CH(CH_3)—CH(CH_3)$—	96 (0.062)	1.4651	0.9668

TABLE III

Basic Esters



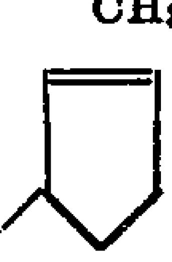
Compound	R	Y—N=B	B. P. ° C. (□ mm.)
1	$CH_3CH(CH_3)CH_2$—	$—CH_2CH_2N(CH_2CH_3)_2$	113 (0.03)
2	$CH_3CH(CH_3)CH_2$—	$—CH_2CH_2N(CH_3)_2$	90 (0.03)
3	$CH_3CH(CH_3)CH_2$—	$—CH_2CH_2N$()(CH_2CH_3)	114 (0.008)
4	$CH_3CH(CH_3)CH_2$—	$—CH_2CH_2N<(CH_2CH_2)_2>CH_2$	106-108 (0.02)

TABLE III—Continued

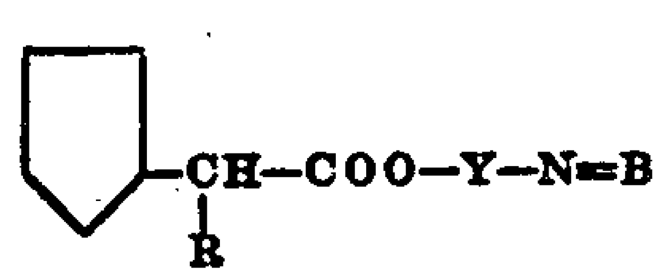
BASIC ESTERS—Continued

Com-pound	R	Y—N=B	B. P. ° C. (□ mm.)
5	$CH_3CH(CH_3)CH_2$—	$-CH_2CH_2N(CH_2CH_2CH_3)(CH_2CH_3)$	106 (0.012)
6	$CH_3(CH_2)_3$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	101 (0.02)
7	$CH_3CH_2CH(CH_3)$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	110 (0.14)
8	$CH_3CH_2CH(CH_3)$—	$-CH_2CH_2N(CH_3)(CH_3)$	76 (0.02)
9	$CH_3(CH_2)_4$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	106 (0.02)
10	$CH_3CH(CH_3)-CH(CH_3)$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	108 (0.06)
11	$CH_3CH_2CH_2CH(CH_3)$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	124 (0.35)
12	$CH_3CH(CH_3)CH_2CH_2$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	83 (0.025)
13	$CH_3CH_2CH(CH_3)CH_2$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	97 (0.02)
14	$CH_3CH_2CH(CH_2CH_3)CH_2$—	$-CH_2CH_2N(CH_2CH_3)(CH_2CH_3)$	95 (0.005)

Compound	n_D^{25}	d_4^{25}	Hydrochloride, M. P. °C.
1	1.4527	0.9119	118.5–119.5
2	1.4519	0.9204	111 –114.5
3	1.4760	0.9548	----------
4	1.4717	0.9600	177.5–180
5	1.4653	0.9706	59 –62
6	1.4548	0.9166	107 –108
7	1.4591	0.9198	115 –116
8	1.4565	0.9402	105 –109
9	1.4561	0.9118	103.5–105
10	1.4601	0.9272	141 –146
11	1.4594	0.9161	99 –103
12	1.4550	0.9100	117 –118.5
13	1.4552	0.9110	116 –177
14	1.4568	0.9176	111.5–113

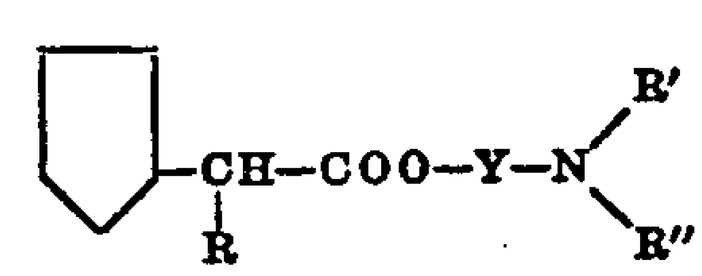
We claim:

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



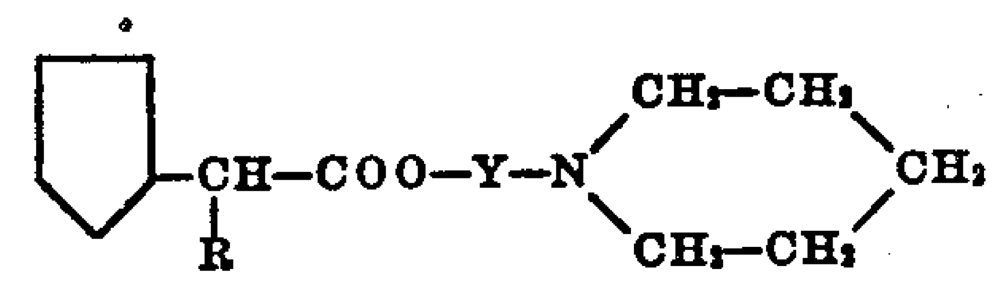
wherein R is an alkyl group of 4–6 carbon atoms, Y is an alkylene bridge of 2–5 carbon atoms and —N═B is a tertiary-amino group of the class consisting of di-lower-alkylamino, piperidyl and morpholinyl radicals; and acid addition and quaternary ammonium salts thereof.

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



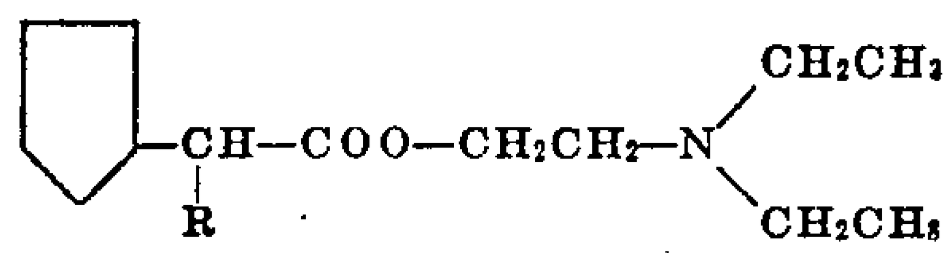
wherein R is an alkyl group of 4–6 carbon atoms, Y is an alkylene bridge of 2–5 carbon atoms and R′ and R″ are lower alkyl groups; and acid addition and quaternary ammonium salts thereof.

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



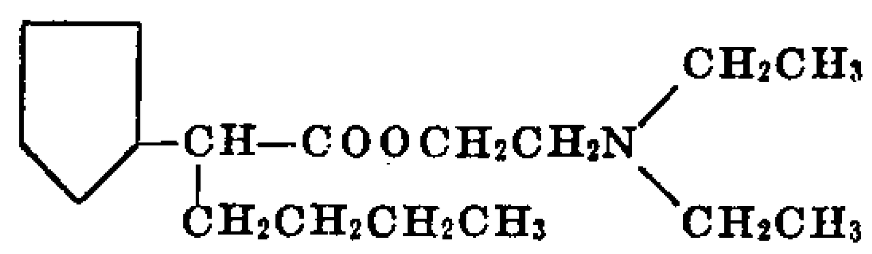
wherein R is an alkyl group of 4–6 carbon atoms and Y is an alkylene bridge of 2–5 carbon atoms; and acid addition and quaternary ammonium salts thereof.

4. A substance of the group consisting of the formula



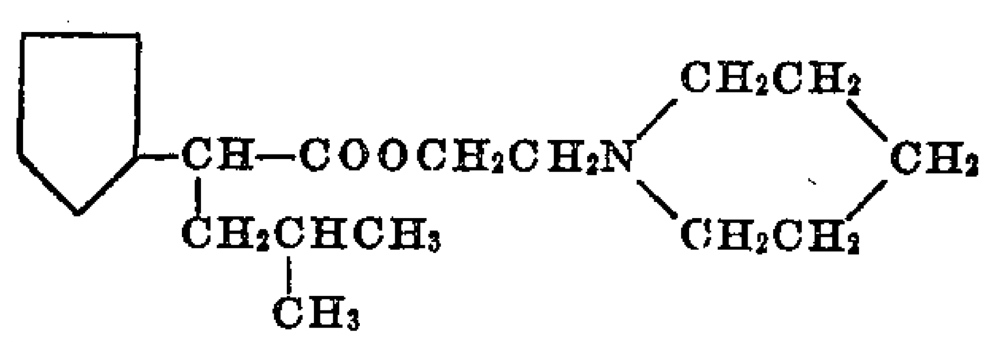
wherein R is an alkyl group of 4–6 carbon atoms, and acid addition and quaternary ammonium salts thereof.

5. A substance of the group consisting of beta-diethylaminoethyl cyclopentyl - n - butylacetate of the formula



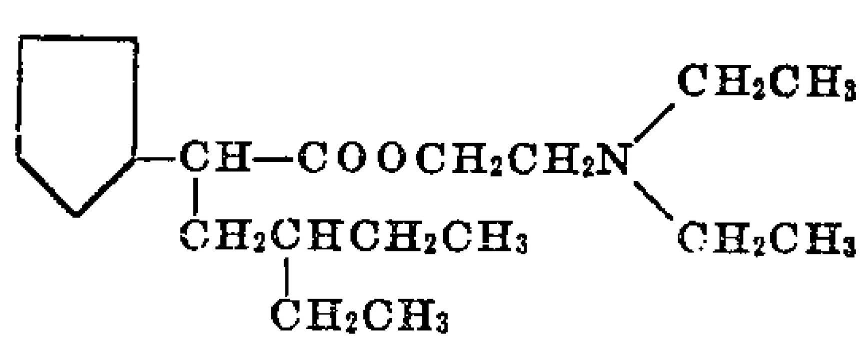
and acid addition and quaternary ammonium salts thereof.

6. A substance of the group consisting of beta-(N-piperidyl)-ethyl cyclopentyl - isobutylacetate of the formula



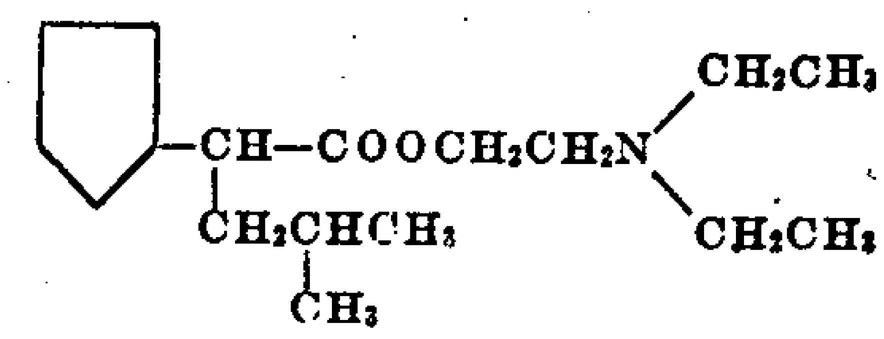
and acid addition and quaternary ammonium salts thereof.

7. A substance of the group consisting of beta-diethylaminoethyl cyclopentyl - (2 - ethylbutyl) - acetate of the formula



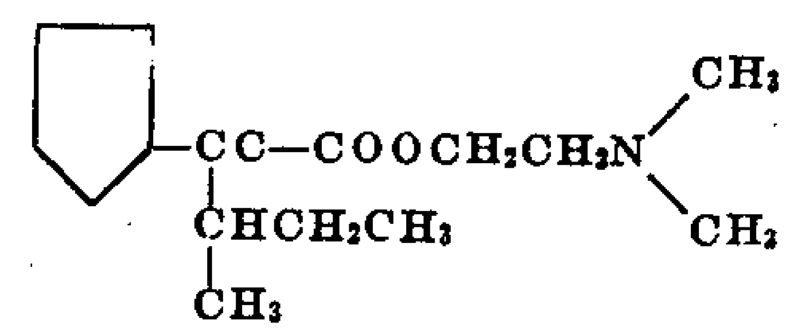
and acid addition and quaternary ammonium salts thereof.

8. A substance of the group consisting of beta-diethylaminoethyl cyclopentyl-isobutylacetate of the formula



and acid addition and quaternary ammonium salts thereof.

9. A substance of the group consisting of beta-dimethylaminoethyl cyclopentyl - sec.-butylacetate of the formula



and acid addition and quaternary ammonium salts thereof.

ROBERT BRUCE MOFFETT.
CHARLOTTE ANNE HART.

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Certificate of Correction

Patent No. 2,538,793 — 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 4, line 35, for "-isobutlymalonate" read *-isobutylmalonate*; column 7, line 36, for the word "either" read *ether*; columns 11 and 12, Table III, under the heading "Y—N=B", opposite compound "5", for

$$-CH_2CH_2N\begin{matrix} \diagup CH_2CH_2CH \\ \diagdown CH_2CH_3 \end{matrix} \quad \text{read} \quad -CH_2CH_2N\begin{matrix} \diagup CH_2CH_2OH \\ \diagdown CH_2CH_3 \end{matrix}$$

line 61, opposite compound "13", for "116–177" read *116–117*; column 13, line 1, after "of", second occurrence, insert *a compound of*; column 14, line 14, for that portion of the formula reading "$—CC—COOCH_2CH_2N$" read *$—CH—COOCH_2CH_2N$*;

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 10th day of April, A. D. 1951.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.