United States Patent Office

2,917,536

Patented Dec. 15, 1959

2,917,536

AMINOALKYLDICYCLOPROPYLALKYNOLS

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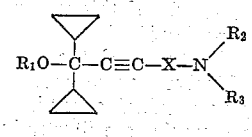
No Drawing. Application September 29, 1958
Serial No. 763,791

3 Claims. (Cl. 260—482)

This invention relates to novel aminoalkynols and derivatives thereof and is more particularly concerned with novel aminoalkyl-1,1-dicyclopropyl-2-alkyn-1-ols and the carbamic acid esters thereof and with novel processes for the preparation of the carbinols.

The novel compounds of the invention can be represented by the following basic formula:



(I)

wherein R_1 represents a radical selected from the group consisting of hydrogen and carbamyl, R_2 and R_3 taken individually represent lower-alkyl radicals containing from one to six carbon atoms such as methyl, ethyl, propyl, butyl, amyl, hexyl and isomeric forms thereof, and R_2 and R_3 taken together with —N< represent a saturated heterocyclic radical containing from five to seven atoms in the ring, one of which, in addition to the amino nitrogen, is selected from the group consisting of carbon, nitrogen oxygen and sulfur, the othe ring atoms being carbon, for example, piperidino, morpholino, thiamorpholino, hexamethyleneimino, pyrrolidino, and the like, and X represents an alkylene radical containing from one to six carbon atoms, which can be straight or branched. They can be used either in the form of the free base or in the form of an acid addition salt thereof.

It is an object of the present invention to provide the compounds of the above general formula and their acid addition salts. It is a further object to provide a process for the preparation of the compounds of formula (I) in which R_1 represents a hydrogen atom. Other objects of the invention will be apparent to those skilled in the art to which this invention pertains.

The compounds of the invention exhibit valuable pharmacodynamic activity as drug potentiators. Surprisingly, the compounds exhibit no significant activity as sedatives and hypnotics although many 1,1-dialkyl-2-propyn-1-ols, and the corresponding carbamic acid esters, closely related to the compounds of the invention exhibit a high degree of such activity. This unexpected lack of hypnotic and sedative activity in the compounds of the invention makes them valuable agents in therapy since they can be employed as drug potentiators without producing sedation and other undesirable side-effects. The drug potentiating activity of the compounds of the invention is illustrated in the following table. The results shown in the table were obtained using the hexobarbital-induced sleep potentiation test in which the test compounds were administered orally or by intraperitoneal injection to mice in doses corresponding to varying proportions of the LD_{50} of the test compound. The increase of sleeping time of the mice after intraperitoneal injection of a standard dose of hexobarbital is noted in the table for each dose of the test compounds and the results obtained using chloropromazine are given for purposes of comparison.

TABLE

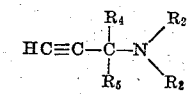
Potentiation of hexobarbital-induced sleep

Compound	LD_{50}, mg./kg.	Method of dosage	Sleep potentiation: Dose (percent of LD_{50})	Sleep potentiation: Percent increase in Sleeping Time
1,1 - dicyclopropyl - 4 - diethylamino-2-butyn-1-ol.	533	oral	40	974
			20	850
		I.P.	20	224
			10	348
Carbamic acid ester of 1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol.	200	I.P.	20	1,221
			10	649
			5	547
			2.5	378
Chloropromazine hydrochloride	165	I.P.	20	1,104
			10	752
			5	447
			2.5	387

The compounds of the invention are also useful, in accordance with U.S. Patents 1,915,334 and 2,075,359, in forming amine fluosilicate mothproofing agents and, in accordance with U.S. Patents 2,425,320 and 2,606,155, in forming amine thiocyanate-formaldehyde condensation products for use as pickling inhibitors.

The acid addition salts of the invention can be prepared, for example, by reacting a compound of Formula I with an equivalent amount of an acid in a solvent such as water, a lower alkanol, for example, methanol, and ethanol, ether, and the like. The required salt can be isolated from the reaction mixture by methods well-known in the art. Thus the salt can be crystallized directly from the solvent used in its preparation, or it can be preicpitated therefrom by the addition of a second solvent, or it can be isolated therefrom by evaporation or by freeze-drying. In certain instances it may be desired to prepare an aqueous solution of a salt of the invention, for example, to obtain a solution for injection purposes, and in such cases the solution can be prepared directly by suspending a compound of Formula I in water and treating the suspension with an equivalent of the appropriate acid, the amount of water present being so chosen that the resulting acid addition salt will be completely soluble. Acids which can be employed in the preparation of the salts of the invention include sulfuric, hydrochloric, hydrobromic, nitric, phosphoric, acetic, lactic, citric, tartaric, benzoic, and toluene-p-sulfonic acids and like pharmaceutically acceptable acids.

The novel process of the invention comprises the preparation of a compound of the Formula I in which the radicals R_2 and R_3 are as hereinbefore defined, R_1 represents a hydrogen atom and X represents a methylene or a substituted methylene radical, by reacting dicyclopropyl ketone with an alkali metal salt of a compound having the formula:



(II)

wherein R_2 and R_3 have the significance hereinbefore defined and R_4 and R_5 are selected from the group consisting of hydrogen atoms and lower-alkyl radicals containing from one to five carbon atoms, the total number of carbon atoms in R_4 and R_5 being not greater than five. The alkali-metal salts which can be employed include the lithium, sodium, and potassium salts, the preferred salt being the lithium salt. The reaction is advantageously conducted in liquid ammonia solution, the alkali metal salt being first formed by dissolving the alkali metal and

the alkylene of Formula II in liquid ammonia. The dicyclopropyl ketone is then added, advantageously in solution in a solvent such as ether, to the solution of the salt so obtained. The desired aminoalkynol can be isolated by allowing the liquid ammonia to evaporate, decomposing the reaction product by the addition of water, separating the free aminoalkynol and purifying the same by standard procedures, for example, by recrystallization, distillation under reduced pressure, etc.

The compounds of Formula II above which are employed as starting materials in the process of the invention can be prepared by methods which are well known in the art. For example, the compounds of Formula II wherein R_4 and R_5 both represent hydrogen atoms can be obtained as the principal product in a Mannich reaction employing acetylene, para-formaldehyde and an amine R_2R_3NH, wherein R_2 and R_3 have the significance hereinbefore described, using essentially the procedure described by Mannich and Chang, Berichte 66, 418 (1933). The compounds of Formula II wherein R_4 represents a hydrogen atom and R_5 represents a methyl group can be prepared by the method described by Gardner, Kerrigan, Rose and Weedon, J.C.S., 1949, 780 in which an amine HNR_2R_3 is reacted with acetylene in the presence of a copper catalyst, the intermediate vinylamine

$$R_2R_3N—CH=CH_2,$$

which is first formed, reacting with a further mole of acetylene to form the desired compound. The compounds of Formula II in which the groups R_4 and R_5 represent hydrogen atoms or lower-alkyl radicals can be prepared by reacting acetylene, an amine R_2R_3NH and an aldehyde or ketone according to the process described in U.S. Patent 2,273,141.

The compounds of Formula I in which the radicals R_1, R_2, R_3, and X have the significance hereinbefore defined can also be prepared by reacting an alkali metal salt of 1,1-dicyclopropyl-2-propyn-1-ol with an aminoalkyl halide of the formula $R_2R_3N—X—Y$ where R_2, R_3, and X have the significance hereinbefore defined and Y represents a halogen atom such as chlorine or bromine. The alkali metals which can be employed include lithium, sodium and potassium, lithium being the preferred metal. The reaction is advantageously performed in liquid ammonia solution. The alkali metal and alkynol are first dissolved in the liquid ammonia and the resulting solution of the alkali metal salt of the alkynol is then treated with the aminoalkyl halide, the latter being used preferably in solution in an inert organic solvent such as ether, and the like. The liquid ammonia is allowed to evaporate and the reaction product is decomposed, for example, by the addition of water. The desired aminoalkynol is separated and purified by standard procedures, for example, recrystallization, distillation under reduced pressure, etc.

The 1,1-dicyclopropyl-2-propyn-1-ol which is employed as starting material in the above process can be prepared by methods which are well-known in the art for the preparation of alkynols. Thus the compound can be obtained by reaction of dicyclopropyl ketone with an alkali metal salt of acetylene in liquid ammonia solution using essentially the procedure described by Campbell, Campbell and Eby, J.A.C.S. 60, 2882 (1938). In addition to its value as an intermediate in the preparation of the compounds of the invention, 1,1-dicyclopropyl-2-propyn-1-ol exhibits pharmacodynamic properties. Thus it shows marked drug potentiating activity and hypnotic and sedative activity.

The compounds of the invention of the Formula I in which the radical R_1 represents a carbamyl radical can be prepared from the corresponding carbinols of Formula I, wherein R_1 represents a hydrogen atom, by methods which are well-known in the art. Thus the carbinols of Formula I wherein R_1 represents hydrogen can be reacted with a chloroformate of the formula $Cl·COOR_6$, wherein

R_6 represents a lower aryl radical such as phenyl, tolyl, and the like, in the presence of a tertiary organic base. The intermediate ester so formed is treated, without isolation, with ammonia, preferably in the form of liquid ammonia. The tertiary organic bases which can be employed in the reaction include pyridine, quinoline, trialkylamines such as trimethylamine, triethylamine, and the like, N-alkylpiperidines such as N-methylpiperidine, N-ethylpiperidine, and the like, and N,N-dialkylanilines such as N,N-dimethyaniline, N,N-diethylaniline, and the like. The reaction is carried out advantageously by treating a solution of a carbinol of the Formula I [R_1=H] in the tertiary organic base, at a temperature below about zero degrees centigrade and preferably about minus fifteen degrees centigrade, with the aryl chloroformate, the addition being made at such a rate that the reaction temperature is maintained in the above range. The reaction product so obtained is added, without further treatment, to an excess of liquid ammonia. After ammonolysis is complete, the excess liquid ammonia is allowed to evaporate and the reaction product is decomposed, for example, by the addition of water. The desired compound is isolated from the reaction mixture and purified by conventional means, for example, by solvent extraction and recrystallization.

The novel compounds of this invention can be combined with solid or liquid pharmaceutical carriers and formulated into the form of tablets, powder packets, or capsules, or dissolved or suspended in suitable solvents, for oral or parenteral administration.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

Example 1

1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol

A total of 3.9 grams (0.56 atom) of lithium ribbon was added in small pieces over a period of two hours to 300 milliliters of liquid ammonia at —78 degrees centigrade. During the same period, a total of 66.7 grams (0.6 mole) of 3-diethylamino-1-propyne (U.S. Patent 2,273,141) was added dropwise to the solution. When the addition of the above reactants was complete, a solution of 55.1 grams (0.50 mole) of discyclopropyl ketone in 600 mililliters of anhydrous ether was added dropwise with stirring. After the addition of the ketone, the ammonia was allowed to boil away and ether was added to keep the volume of the reaction mixture approximately constant during the evaporation. When the ammonia had evaporated, the residual mixture was decomposed carefully with 100 milliliters of water. The ethereal layer was separated and washed with three portions, each of fifty milliliters, of water. The water washes were each extracted with the same portion of fifty milliliters of ether and the latter was added to the original ethereal solution. The combined ethereal solutions were dried over twenty grams of anhydrous sodium sulfate, the solution was filtered and the ether was evaporated. The solid residue was recrystallized from Skellysolve B (mixture of hexanes). There was thus obtained 49.5 grams of 1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol in the form of a crystalline solid which had a melting point of 55 to 56 degrees centigrade.

Analysis.—Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.72; H, 10.33; N, 6.40.

Example 2

The carbamic ester of 1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol

A solution of 22.1 grams (0.1 mole) of 1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol (prepared as described in Example 1) in 30.5 grams (0.31 mole) of triethylamine was cooled to about minus fifteen de-

grees centigrade. To the cold solution was added dropwise, over a period of five hours, 17.2 grams (0.19 mole) of phenyl chloroformate. The resulting mixture was stirred at room temperature for two days and was then poured into 300 milliliters of liquid ammonia. After allowing the solution to reflux for eight hours, the liquid ammonia was evaporated and 200 milliliters of ether was added to the residue. The ethereal solution was washed with small portions of ice-cold sixteen percent aqueous sodium hydroxide solution and with water, dried over anhydrous sodium sulfate and evaporated to dryness. The semi-solid residue was dissolved in a small volume of ether and subjected to chromatographic separation on a column of Florisil (magnesium silicate). The column was eluted with petroleum ether (boiling range thirty to sixty degrees centigrade) containing increasing porportions of ether. The first fractions of the eluate yielded 15.1 grams of unchanged starting material. The later fractions yielded a solid having a melting point of 49 to 73 degrees centigrade which was subjected to a further chromatographic separation. The product so obtained was recrystallized from a mixture of Skellysolve B and acetone to yield the carbamic ester of 1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol in the form of a crystalline solid having a melting point of 88.5 to 89.5 degrees centigrade. The infrared absorption spectrum of the compound (mineral oil mull) exhibited maxima at 1075, 1625, 1710, 3070, 3130, 3260 and 3300 cm.$^{-1}$.

Analysis.—Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.60. Found: C, 69.03; H, 9.13; N, 10.14.

Example 3

1,1-dicyclopropyl-5-diethylamino-2-pentyn-1-ol

A. PREPARATION OF 1,1-DICYCLOPROPYL-2-PROPYN-1-OL

A total of 4.17 grams (0.6 atom) of lithium was added in small pieces over a period of two hours to 450 milliliters of liquid ammonia which was kept saturated with acetylene and cooled at minus seventy degrees centigrade. When all the lithium had dissolved and all the blue color had disappeared, a solution of 55.1 grams (0.5 mole) of dicyclopropyl ketone in 100 milliliters of anhydrous ether was added dropwise with stirring over a period of one hour, the mixture being kept saturated with acetylene throughout this time. The cooling bath was then removed and the ammonia was allowed to evaporate, ether being added at intervals to keep the volume of the reaction mixture approximately constant. When most of the ammonia had evaporated, the flow of acetylene was discontinued and the reaction mixture was allowed to stand overnight at room temperature. The mixture was then carefully hydrolyzed by addition of 75 milliliters of water. The ether layer was separated and washed with four portions, each of fifty milliliters, of water. Each of the water washings was in turn back-extracted with a 50-milliliter portion of ether. The ethereal extract and the original ether layer were combined and dried over anhydrous sodium sulfate. The dried solution was evaporated and the residue was fractionally distilled under reduced pressure. There was thus obtained 59.8 grams (88 percent yield) of 1,1-dicyclopropyl-2-propyn-1-ol in the form of a colorless liquid which had a boiling point of 49 to 53 degrees centigrade at a pressure of 0.35 millimeter of mercury.

Analysis.—Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 80.01; H, 8.70.

B. PREPARATION OF 1,1-DICYCLOPROPYL-5-DIETHYLAMINO-2-PENTYN-1-OL

A total of 2.8 grams (0.4 atom) of lithium ribbon in small pieces and 54.4 grams (0.4 mole) of 1,1-dicyclopropyl-2-propyn-1-ol were added over a period of two

hours to 300 milliliters of liquid ammonia cooled at −70 degrees centigrade. To the resulting mixture was added with stirring a solution of 54.2 grams (0.4 mole) of 2-diethylaminoethyl chloride in 300 milliliters of anhydrous ether over a period of one hour. The cooling bath was then removed and the ammonia was allowed to evaporate, portions of ether being added at intervals to keep the volume of the reaction mixture constant. The mixture was then carefully hydrolyzed by the addition of 100 milliliters of water. The ethereal layer was separated and washed with three portions, each of fifty milliliters, of water. Each of the water washings was in turn back-extracted with a 100-milliliter portion of ether. The ethereal extract and the original ether layer were combined and dried over anhydrous sodium sulfate. The dried solution was evaporated and the residue was recrystallized from Skellysolve B. There was thus obtained 1,1-dicyclopropyl-5-diethylamino - 2 - pentyn-1-ol in the form of a crystalline solid.

Example 4

1,1-dicyclopropyl-4-dimethylamino-2-butyn-1-ol

Using the procedure described in Example 1, but substituting 3-dimethylamino-1-propyne (U.S. Patent 2,273,-141) for 3-diethylamino-1-propyne, there was obtained 1,1-dicyclopropyl-4-dimethylamino-2-butyn-1-ol.

Example 5

1,1-dicyclopropyl-4-di-n-butylamino-2-butyn-1-ol

Using the procedure described in Example 1, but substituting 3-di-n-butylamino-1-propyne (U.S. Patent 2,273,-141) for 3-diethylamino-1-propyne, there was obtained 1,1-dicyclopropyl-4-di-n-butylamino-2-butyn-1-ol.

Example 6

1,1-dicyclopropyl-4-dimethylamino-2-heptyn-1-ol

Using the procedure described in Example 1, but substituting 3-dimethylamino-1-hexyne (U.S. Patent 2,273,-141) for 3-diethylamino-1-propyne, there was obtained 1,1-dicyclopropyl-4-dimethylamino-2-heptyn-1-ol.

Example 7

1,1-dicyclopropyl-4-dimethylamino-2-pentyn-1-ol

Using the procedure described in Example 1, but substituting 3-dimethylamino-1-butyne (U.S. Patent 2,273,-141) for 3-diethylamino-1-propyne, there was obtained 1,1-dicyclopropyl-4-dimethylamino-2-pentyn-1-ol.

Example 8

1,1-dicyclopropyl-4-dimethylamino-4-methyl-2-pentyn-1-ol

Using the procedure described in Example 1, but substituting 3-dimethylamino-3-methyl-1-butyne (U.S. Patent 2,273,141) for 3-diethylamino-1-propyne, there was obtained 1,1-dicyclopropyl-4-dimethylamino - 4 - methyl-2-pentyn-1-ol.

Example 9

1,1-dicyclopropyl-4-morpholino-2-pentyn-1-ol

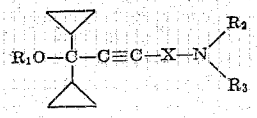
Using the procedure described in Example 1, but substituting 3-morpholino-1-butyne (Gardner et al., supra) for 3-diethylamino-1-propyne, there was obtained 1,1-dicyclopropyl-4-morpholino-2-pentyn-1-ol.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

We claim:

1. A compound selected from the group consisting of (*a*) the free base and (*b*) the pharmaceutically accept-

able acid addition salts of a compound having the general formula:



wherein R_1 represents a radical selected from the group consisting of hydrogen and carbamyl, R_2 and R_3 taken individually represent lower-alkyl radicals and R_2 and R_3 taken together with —N< represent a saturated heterocyclic radical containing from five to seven atoms in the ring, one of which, in addition to the amino nitrogen, is

selected from the group consisting of carbon, nitrogen, oxygen and sulfur, the other ring atoms being carbon, and X represents an alkylene radical containing from one to six carbon atoms, inclusive.

2. 1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol.

3. The carbamic acid ester of 1,1-dicyclopropyl-4-diethylamino-2-butyn-1-ol.

References Cited in the file of this patent

UNITED STATES PATENTS

2,273,141	Reppe	Feb. 17, 1942
2,766,285	Hennion	Oct. 9, 1956
2,798,885	Ensslin	July 9, 1957