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VINYL ETHINYL TERTIARY CARBINOLS

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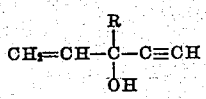
6 Claims. (Cl. 167—52)

This invention is concerned with new and useful organic medicinal agents. In particular, it is concerned with compounds that are effective as hypnotic and/or anticonvulsant agents. This application is a continuation-in-part of our now abandoned but formerly copending applications Serial No. 296,745, filed July 1, 1952, and Serial No. 286,012, filed May 3, 1952.

A number of compounds have been proposed from time to time as hypnotic agents for inducing sleep or sedation and for combatting convulsive reactions. Some of these compounds have undesirable side effects, others are slow to act or act in a very ineffective manner. A compound which may be prepared without great difficulty and which displays a low toxicity and appreciable hypotic and/or anticonvulsant activity is a valuable addition to this class of medicinal agents.

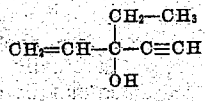
One object of this invention is making available novel compounds which are highly effective in inducing hypnosis and in suppressing excitability in animals and in protecting them against convulsive seizures. Another object of this invention is the preparation of dosage forms of such compounds which may readily be administered by mouth or by injection and which are effective within a short time for the purposes described. Further objects will be apparent from the description of this invention given below.

It has now been found that these objects are accomplished by vinyl ethinyl tertiary carbinols having the following formula:

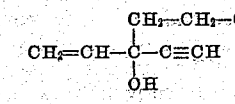


wherein R is an ethyl or propyl group. More specifically, the compounds with which this invention is concerned are 3-ethylpent-1-ene-4-yne-3-ol or ethyl vinyl ethinyl carbinol and 3-n-propylpent-1-ene-4-yne-3-ol or n-propyl vinyl ethinyl carbinol.

Ethyl vinyl ethinyl carbinol is a colorless, mobile liquid having a distinct odor similar to camphor. It is soluble in water to the extent of approximately 0.25 gram/milliliter and it is miscible with most organic solvents such as ethanol, ether, chloroform, acetone and so forth. The product has a boiling point of 84–86° C. at 98 mm. of mercury pressure. Its chemical structure is as follows:



n-Propyl vinyl ethinyl carbinol is a colorless liquid having a distinct but not unpleasant odor. It is soluble in water to the extent of 4% and is miscible with most of the common organic solvents, such as lower aliphatic alcohols, ethers, ketones, halogenated hydrocarbons, aromatic hydrocarbons, glycols, and so forth. This material has a boiling point of 98° to 99° C. at a pressure of 102 mm. of mercury. The product has a density of 0.8733 gram per milliliter at 20° C. Its chemical structure is as follows:



The compounds of this invention are preferably prepared by the condensation of acetylene with the appropriate ketone, i.e. ethyl vinyl ketone or n-propyl vinyl ketone, in the presence of an alkaline condensation agent, such as an alkali or alkaline earth metal or hydroxide. The reaction is preferably conducted in an inert solvent which will dissolve the various reactants, but which does not itself enter into undesirable side reactions. Liquid ammonia has been found to be particularly suitable, but other useful solvents, such as ethers or mixtures of liquid ammonia and ethers, may also be used. The acetylene may be used in the form of a metal acetylide, such as lithium, potassium, or calcium compounds, in which case no metallic catalyst need be used. However, the condensation may be conducted by passing acetylene gas into a solution of the ketone in the presence of a suitable alkaline condensing agent. We have found that lithium dissolved in liquid ammonia is a particularly valuable material for conducting the reaction in question. The proportion of the agent need generally be only about 1 to 1½ moles. However, larger quantities can be used without any serious side reactions. The reaction is conducted under substantially anhydrous conditions and, when liquid ammonia is used as the solvent or as one of the solvents for the reaction, the temperature of the mixture should be lowered so that the ammonia is maintained in the liquified state during the condensation. The temperature may then be elevated to eliminate the solvent. In general, temperatures of from about −40° C. to about +40° C. are suitable. The products which are produced by this condensation have never been prepared before. They may be recovered from the reaction mixture by conventional means, such as distillation. Before recovery of the product it is necessary to remove the condensing agent, for instance by treatment of the reaction mixture with water. The ketones employed in this reaction may in turn be prepared by known methods, such as those described by McMahon et al., Journal of American Chemical Society, vol. 70, p. 2971 (1948).

The following examples are given by way of illustration only and are not to be considered as the sole embodiments of the invention. Resort may be had to such modifications and equivalents as fall within the spirit of the invention and the scope of the appended claims.

EXAMPLE I

Lithium ribbon weighing 4.66 grams was added to 350 milliliters of liquid ammonia over a three-minute period. The flask containing the liquid ammonia was cooled to −40° C. in a suitable low temperature bath and the flask was equipped with an agitator, a dropping funnel, a Dry-Ice condenser and a gas inlet tube. The apparatus was equipped with a drying tube to prevent absorption of moisture from the air. Acetylene gas was bubbled into the solution at the rate of one liter per minute until a clear solution was obtained. This took about 17 minutes. The addition of acetylene was continued at the rate of about 200 milliliters per minute for 90 minutes. Throughout the addition of both the lithium and the acetylene, the mixture was agitated. To the stirred solution was added a solution of 42.5 grams of freshly dis-

tilled ethyl vinyl ketone in 150 milliliters of absolute ether. The addition was made during a period of ten minutes. The stirred mixture was allowed to reflux for two to three hours, then 100 milliliters of absolute ether was added. The mixture was agitated overnight at room temperature with a water-cooled condenser substituted for the Dry-Ice cooled condenser. In the morning, all of the ammonia had evaporated. The mixture in the flask was added to 800 milliliters of ice containing acetic acid. Sufficient acetic acid was added so that the pH was adjusted to 4.0. The aqueous phase was separated and this was extracted twice with 100-milliliter portions of ether. The original ether layer, together with the two extracts, were washed with dilute sodium carbonate solution and then with water. After drying the ether solution over anhydrous magnesium sulfate, the solvent was distilled and the product was fractionated. The material boiled at 80–83° C. under a pressure of 101 mm. of mercury. It weighed 66.8 grams. Part of this material was redistilled through a Vigreaux column, and a fraction boiling at 84–89° C. under 98 mm. of mercury pressure was selected. The colorless liquid was analyzed:

Analysis.—Calcd. for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.19; H, 9.04.

A test with ammoniacal silver solution showed the presence of the acetylenic grouping.

Instead of using lithium metal in the above condensation, calcium was used and the desired ethyl vinyl ethinyl carbinol was again recovered.

EXAMPLE II

A three-neck, two-liter, round-bottom, glass flask was equipped with a stirrer, a Dry Ice condenser, a gas inlet tube, and a plug for the addition of various materials. In the flask was placed 500 milliliters of liquid ammonia and to the liquid was added 6.94 grams of lithium ribbon. Acetone-free acetylene was bubbled through the mixture at a rate of 3.5 liters per minute for 6 minutes. The blue color changed and a gray precipitate, which had formed, dissolved. Acetylene was then bubbled through the mixture at a rate of one liter per minute for 8 minutes. Sufficient liquid ammonia was added to the reaction mixture to replace that which had been lost. A solution of 101.5 grams of n-propyl vinyl ketone in 200 milliliters of ether was added just above the surface of the reaction mixture over a period of 7 minutes. Throughout this addition, a slow stream of acetylene was bubbled through the mixture. The reaction mixture was stirred rapidly throughout these steps and for an additional two hours. In addition, throughout these operations the temperature of the mixture was kept at about that of the boiling point of ammonia. To the mixture was added 250 milliliters of ether. The Dry Ice condenser was removed and replaced with a water-cooled condenser. The mixture was stirred for an hour and a half and then allowed to stand at room temperature overnight. An additional 500 milliliters of ether was added and the mixture was then stirred for one and a half hours. It was poured into 500 milliliters of ice containing 99 milliliters of glacial acetic acid. The mixture had a pH of 4.3. The organic phase was separated and the aqueous phase was extracted twice with 400-milliliter portions of ether. The combined ether phases were extracted with aqueous sodium carbonate solution until a pH of 6.2 in the aqueous phase was reached. The organic phase was then washed with water and dried over anhydrous magnesium sulfate. The product was distilled. 55.5 grams of crude material boiling at 96° to 104° C. at 103 mm. pressure was obtained. This was redistilled and 37.8 grams of a product boiling at 98° to 99° C. at 102 mm. pressure was obtained. This material was analyzed.

Analysis.—Calcd. for $C_8H_{12}O$; C, 77.37; H, 9.74. Found: C, 76.76; H, 9.66.

The compound was also assayed by determining the proportion of acetylenic groups by means of the method of Siggia. It was found to be 95.5% pure.

As indicated above, the compounds of this invention are colorless liquids which are readily adapted to therapeutic use. Marked hypnosis was observed in animals to which they had been administered. Furthermore, the compounds were found to protect such animals effectively against convulsive seizures. The compounds are therefore suitable for use in the treatment of veterinary animals, such as cats, dogs, monkeys, and even mice. They permit certain treatment of animals which would not be possible without the use of a hypnotic agent. For example, the compounds of this invention may be employed to induce hypnosis in mice and thereby facilitate implantation of tumorous tissue which is so vital to the study of cancer. The toxicity of the compounds was found to be quite low when they were administered to mice in amounts sufficient to achieve the desired results, and no harmful pharmacological effects were observed as a result of such administration.

The activity of the tertiary carbinols of this invention is well illustrated by the tests hereinafter described, in which Rockland Farm Swiss mice weighing 18 to 22 grams were used as the experimental animals. The compounds were given subcutaneously in aqueous solution and the onset and duration of sleep in each animal was recorded. "Sleep" is defined as the period during which the animal failed to assume a normal position when placed on its back. "Hypnotic activity" is defined as the dose of the compound in mg. per kg. of body weight which caused sleep in 50% of the animals tested. To determine anticonvulsant activity, each mouse was given subcutaneously a convulsant dose of Metrazol (pentylenetetrazole), i.e. 85 mg./kg., ten minutes after the subcutaneous injection of the compound under test. Anticonvulsant effect was recorded in terms of the amount of the compound which protected 50% of the mice from Metrazol-induced seizure.

The results of these tests are set forth in the following table, which indicates the milligrams of 3-ethylpent-1-ene-4-yne-3-ol and 3-n-propylpent-1-ene-4-yne-3-ol required per kg. of body weight to induce hypnosis and to protect the animals against convulsive seizures.

Table I

Compound	Hypnotic Activity, mg./kg.	Anticonvulsant Activity, mg./kg.
3-ethylpent-1-ene-4-yne-3-ol	180	53
3-n-propylpent-1-ene-4-yne-3-ol	400	400

From the foregoing tests, it is apparent that both of the above compounds possess a significant degree of hypnotic and anticonvulsant activity.

It will be appreciated that the dosage of tertiary carbinol required to induce hypnosis and/or protect against convulsive seizures will vary considerably, depending upon the particular compound selected, the species of animal to be treated, and its individual response to the drug, among other factors. A single effective dosage may range from about 10 to 500 mg. per kilogram of body weight, which is generally sufficient to achieve the desired results. However, for some species and when only a mild sedative or soporific effect is desired, from about 1 to 10 mg. per kilogram of body weight is usually adequate. In exceptional cases, larger doses may be administered without harmful pharmacological effect if the subject is less sensitive to the drug and is of sufficient weight so that the drug is well tolerated at this level. The compounds may be administered in single or divided dosages, using capsules, tablets or other dosage forms providing a unit dosage of the active ingredient in an amount of pref-

erably at least 10 mg., although as high as about 100 to 500 mg. per unit dosage may be employed to advantage. Capsules containing 500 mg. of the active ingredient have been found to be a particularly useful dosage form. When larger doses of the tertiary carbinols are desired, it is preferable to administer two or more capsules or tablets, etc., if necessary, adjusting the content of the tertiary carbinol in the dosage form accordingly.

It should be apparent from the foregoing that the above described compounds may be employed in a variety of medicinal dosage forms, that is, they may be incorporated with various inert pharmaceutical carriers such as solid diluents, oils, etc. or with other biologically active materials, in the form of capsules, elixirs, injectable solutions and the like. Materials for oral administration may be sweetened and flavored with various agents of the type commonly employed for that purpose.

For example, in the preparation of tablets various carriers or diluents, such as lactose, sucrose and calcium carbonate, may be employed, along with distintegrants, such as starch, preferably potato or tapioca starch, alginic acid and certain complex silicates; binding agents, such as gelatin, acacia, and lubricating agents such as magnesium stearate, stearic acid and talc are also useful for tableting purposes. Dry compositions of a similar type may also be employed in gelatin capsules, particularly the hard gelatin type of capsule. In those cases where the tertiary carbinol is normally liquid it has been found especially advantageous to encapsulate the compounds in soft gelatin capsules. For this type of dosage form the active therapeutic agent may first be combined with such agents as polyethylene glycol, propylene glycol or glycerine, which function not only as diluents but also exert a plasticizing action on the gelatin capsule to protect it from becoming denatured by the tertiary carbinol which may result in leakage from the capsule.

When elixirs or suspensions for oral administration are desired, the compounds of this invention may be combined with sugar syrup, flavoring agents and dyes, and if desired, emulsifying and/or suspending agents. In such dosage forms the diluents which may be employed include water, glycerine, propylene glycol, alcohol, various combinations thereof, and the like. Dry powders may also be prepared which are suitable for reconstitution with water prior to use. In like manner, parenteral solutions or suspensions in sterile distilled water may also be emploeyd, containing say 5% of the tertiary carbinol.

When incorporated in such medicinal dosage forms as those previously mentioned, the compounds of this invention may be present in concentrations ranging from about 0.5% by weight to about 90% by weight of the composition, i.e. in an amount sufficient to provide the desired unit dosage as previously described. Lower concentrations are generally not advisable, since the volume of material which must be administered becomes excessive. The invention is further illustrated by the following examples of typical dosage formulations which may be employed for administration of the tertiary carbinols previously described.

EXAMPLE III.—SOFT GELATIN CAPSULES

	Mg.
Ethyl vinyl ethinyl carbinol	500
Polyethylene glycol (average molecular weight 400)	175

EXAMPLE IV.—SOFT GELATIN CAPSULES

n-Propyl vinyl ethinyl carbinol	250
Polyethylene glycol (average molecular weight 400)	87.5

EXAMPLE V.—SOFT GELATIN CAPSULES

n-Propyl vinyl ethinyl carbinol	100
Polyethylene glycol (average molecular weight 400)	153

EXAMPLE VI.—HARD GELATIN CAPSULES

Ethyl vinyl ethinyl carbinol	500
Potato starch	100
Magnesium stearate	10

EXAMPLE VII.—TABLETS

n-Propyl vinyl ethinyl carbinol	250
Sucrose	100
Potato starch	20
Magnesium stearate	5

EXAMPLE VIII.—ORAL SUSPENSION

	Grams
Ethyl vinyl ethinyl carbinol	10
Sucrose	40
Methyl parahydroxybenzoic acid	0.18
Propyl parahydroxybenzoic acid	0.02

Flavoring and color as desired.
Water to make 100 cc.

Each teaspoonful or 5 cc. dosage of the resulting suspension will provide 500 mg. of the tertiary carbinol.

EXAMPLE IX.—ORAL SUSPENSION

	Grams
n-Propyl vinyl ethinyl carbinol	10
Sucrose	40
Methyl parahydroxybenzoic acid	0.18
Propyl parahydroxybenzoic acid	0.02
Ethyl alcohol	10

Flavoring and color as desired.
Water to make 100 cc.

EXAMPLE X.—PARENTERAL SOLUTION

Ethyl vinyl ethinyl carbinol	5

Sterile, distilled water to make 100 cc.

What is claimed is:

1. A therapeutic composition in dosage unit form comprising a significant amount of a pharmaceutical carrier and at least 10 mg. per dosage unit of a compound selected from the group consisting of 3-ethylpent-1-ene-4-yne-3-ol and 3-n-propylpent-1-ene-4-yne-3-ol, said composition being effective for inducing hypnosis in veterinary animals and for protecting the same against convulsive seizures.

2. The composition of claim 1 in which said composition is in tablet dosage unit form.

3. The composition of claim 1 in which said pharmaceutical carrier is a liquid.

4. A therapeutic composition in dosage unit form comprising a significant amount of a pharmaceutical carrier and from about 1 mg. to 500 mg. per dosage unit of a compound selected from the group consisting of 3-ethylpent-1-ene-4-yne-3-ol and 3-n-propylpent-1-ene-4-yne-3-ol, said composition being effective for inducing hypnosis in veterinary animals and for protecting the same against convulsive seizures.

5. A therapeutically effective hypnotic composition in dosage unit form comprising a gelatin capsule containing per capsule at least about 10 mg. of a compound selected from the group consisting of 3-ethylpent-1-ene-4-yne-3-ol and 3-n-propylpent-1-ene-4-yne-3-ol, said composition being effective for inducing hypnosis in veterinary animals and for protecting the same against convulsive seizures.

6. A therapeutically effective hypnotic composition comprising not less than about 0.5% of a compound selected from the group consisting of 3-ethylpent-1-ene-4-yne-3-ol and 3-n-propylpent-1-ene-4-yne-3-ol and a phar-

maceutical carrier therefor, said composition being effective for inducing hypnosis in veterinary animals.

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