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NOVEL DERIVATIVES OF TETRAHYDRO-CANNABINOL

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7 Claims

ABSTRACT OF THE DISCLOSURE

Novel 1-[2-(dilower-alkylamino)alkoxy]-3-alkyl (and cycloalkyl-lower-alkyl) 6a,7,8,10a-(and 6a,7,9,10a- and 7,8,9,10-) tetrahydro - 6,6,9-trilower-alkyl-6H-dibenzo[b,d]pyrans, and acid salts thereof. These compounds possess biological activity and are useful as therapeutic agents.

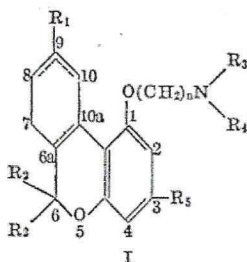
This invention relates to novel derivatives of Δ^6 , Δ^8 , Δ^9 tetrahydrocannabinols and the preparation of the same.

The invention sought to be patented, in its composition aspects, resides in the concept of a class of chemical compounds which is designated as 1-[2-(dilower-alkylamino)alkoxy] - 3 - alkyl (and cycloalkyl-lower-alkyl) 6a,7,8,10a-(and 6a,7,9,10a- and 7,8,9,10-) tetrahydro-6,6,9-trilower-alkyl - 6H - dibenzo[b,d]pyrans and acid and quaternary salts thereof, some of the acid salts of which are water soluble. The tangible embodiments of this composition aspect of the invention possess the inherent use characteristics of having biological activity as determined by standard pharmacological test procedures for potential therapeutic drugs.

It is therefore a primary object of this invention to provide novel chemical compositions of matter and a method of forming them. It is another object to provide chemical compositions which exhibit CNS properties. Other objects of the invention will in part be obvious and will in part be apparent hereinafter.

The invention accordingly comprises the several steps and the relation of one or more of such steps with respect to each of the others, and the composition of matter possessing the characteristics, properties and relation of components which will be exemplified in the compositions hereinafter described, and the scope of the invention will be indicated in the claims.

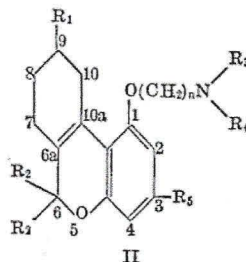
Without limiting the generality of the foregoing, illustrative and preferred embodiments of our 1-[2-(dilower-alkylamino)alkoxy]-3-alkyl (and cycloalkyl-lower-alkyl) 6a,7,8,10a-(and 6a,7,9,10a- and 7,8,9,10-) tetrahydro-6,6,9-trilower-alkyl-6H-dibenzo[b,d]pyrans are those of the Formula I



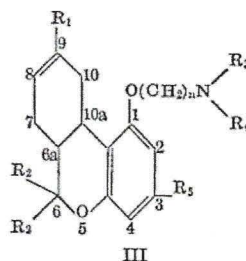
wherein n is a whole number ranging from 1 to 7, R_1 , R_2 , R_3 and R_4 are lower alkyl and R_5 is alkyl or cycloalkyl-lower-alkyl.

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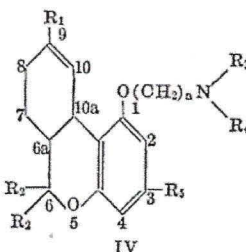
The compounds of the class of Formula I may be either the Δ^6 , Δ^8 or Δ^9 structure. Those of the Δ^6 structure, or the 1 - [2-(dilower-alkylamino)alkoxy]-3-alkyl (and cycloalkyl-lower-alkyl) - 7,8,9,10-tetrahydro-6,6,9-trilower-alkyl-6H-dibenzo[b,d]pyrans, have the Formula II



Those compounds of the Δ^8 structure, or the 1-[2-(dilower-alkylamino)alkoxy]-3-alkyl (and cycloalkyl-lower-alkyl) - 6a,7,9,10a-tetrahydro-6,6,9-trilower-alkyl-6H-dibenzo[b,d]pyrans, have the Formula III



Those compounds of the Δ^9 structure, or the 1-[2-(dilower-alkylamino)alkoxy]-3-alkyl (and cycloalkyl-lower-alkyl) - 6a,7,8,10a-tetrahydro-6,6,9-trilower-alkyl-6H-dibenzo[b,d]pyrans, have the Formula IV



In Formulas II-IV n and R_1 - R_5 have the same meanings as in Formula I.

As used herein, the term "lower-alkyl" means saturated, monovalent aliphatic-radicals including straight and branched-chain radicals of from one to six carbon atoms, as illustrated by, but not limited to methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, amyl, hexyl, and the like.

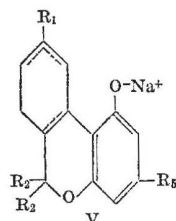
As used herein, the term "alkyl" means saturated monovalent aliphatic-radicals, including straight and branched-chain radicals of from one to twenty carbon atoms, as illustrated by, but not limited to methyl, n-amyl, n-hexyl, 2-heptyl, n-heptyl, 3-methyl-2-octyl, n-octyl, 2-nonyl, 2-tetradecyl, n-hexadecyl, 2-eicosanyl, and the like.

As used herein, the term "cycloalkyl" means cyclic saturated aliphatic-radicals of from three to eight carbon atoms, as illustrated by, but not limited to cyclopropyl, cyclobutyl, 2-methylcyclobutyl, cyclohexyl, 4-methylcyclohexyl, cyclooctyl, and the like.

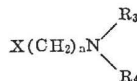
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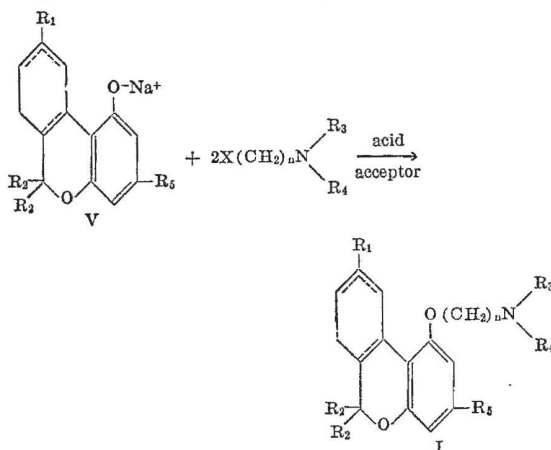
The invention in its process aspect is described in residing in the process of reacting a compound of Formula V



with a compound of the formula



where X is a halogen, n is a whole number from 1 to 7 and R_3 and R_4 are lower alkyl. The reaction is carried out in an organic solvent inert under the conditions of the reaction, for example methanol, ethanol, isopropanol, or dimethylformamide, and in the presence of an acid acceptor. This reaction may be represented as



The compounds of Formula V may be prepared by the procedure disclosed by D. Petrzilka, W. Haefliger and C. Sikemeier in *Helvetica Chimica Acta*, 52: 1102 (1969).

Due to the presence of a basic tertiary amino grouping, the compounds of this invention form acid-addition salts, some of which are water-soluble, as well as quaternary ammonium salts. The compounds of Formulas I, II, III and IV in free base form, are converted to the acid-addition salt form by interaction of the base with an acid. In like manner, the free bases can be regenerated from the acid-addition salt form in the conventional manner, that is by treating the salts with strong aqueous bases, for example alkali metal hydroxides, alkali metal carbonates, and alkali metal bicarbonates. The bases thus regenerated can then be interacted with the same or a different acid to give back the same or different acid-addition salt. Thus the novel bases and all of their acid-addition salts are readily interconvertible.

The quaternary ammonium salts of the compounds of Formulas I-IV are obtained by the addition of esters of strong acids to the free base form of the compounds, said esters having a molecular weight less than about 300. A preferred class of esters comprises alkyl, alkenyl, and phenyl-lower-alkyl esters of strong inorganic acids or organic sulfonic acids, including such compounds as methyl chloride, methyl bromide, methyl iodide, ethyl bromide, propyl chloride, allyl chloride, allyl bromide, methyl sulfate, methyl benzene-sulfonate, methyl p-toluenesulfonate, benzyl chloride, benzyl bromide, and substituted benzyl

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halides, for example p-chlorobenzyl chloride, 3,4-dichlorobenzyl chloride, pentachlorobenzyl chloride, p-nitrobenzyl chloride, p-methoxybenzyl chloride, and the like.

It will thus be appreciated that each of Formulas I-IV not only represents the structural configuration of the bases of our invention but each is also representative of the respective structural entity which is common to all of our respective compounds of Formulas I-IV whether in the form of the free bases or in the form of the salts of the bases. We have found that by virtue of this common structural entity, the bases and their acid-addition salts as well as the quaternary ammonium salts have inherent pharmacodynamic activity of a type to be more fully described hereinbelow. This inherent pharmacodynamic activity can be enjoyed in useful form for pharmaceutical purposes by employing the free bases themselves or the acid-addition salts formed from pharmaceutically-acceptable acids or esters of strong acids, that is, acids or esters of strong acids, that is, acids or esters whose anions are innocuous to the animal organism in effective doses of the salts so that beneficial properties inherent in the common structural entity represented by the free bases are not vitiated by side-effects ascribable to the anions.

In utilizing this pharmacodynamic activity of the salts of the invention, we prefer of course to use pharmaceutically-acceptable salts. Although water-insolubility, high toxicity, or lack of crystalline character may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical-application, the water-insoluble or toxic salts can be converted to the corresponding pharmaceutically-acceptable bases by decomposition of the acid-addition salt with aqueous base as explained above, or alternatively, the acid-addition salt can be converted to any desired pharmaceutically-acceptable acid-addition salt by double decomposition reactions involving the anion, for example, by ion-exchange procedures.

As in the base of the acid-addition salts, water-insolubility, high toxicity, or lack of crystalline character may make some quaternary ammonium salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water-insoluble or toxic salts can be converted to the corresponding pharmaceutically-acceptable salts by double decomposition reactions involving the anion, for example, by ion-exchange procedures. Alternatively, if the anion of the original quaternary salt forms a water-insoluble silver salt, the quaternary salt will react with silver oxide in aqueous medium to form the corresponding quaternary ammonium hydroxide, the original anion being removed as a precipitate. The quaternary ammonium hydroxide solution can then be neutralized with any desired acid, weak or strong, to produce a new quaternary ammonium salt in which the anion is different from that of the original salt. In this way quaternary ammonium salts in which the anion is derived from a weak acid are formed.

Moreover, apart from their usefulness in pharmaceutical applications, our salts are useful as characterizing or identifying derivatives of the free bases or in isolation or purification procedures. Such characterizing or purification acid addition salt derivatives, like all of the acid-addition salts, can, if desired, be used to regenerate the pharmaceutically-acceptable free bases by reaction of the salts with aqueous base, or alternatively the acid-addition or quaternary ammonium salt can be converted to a pharmaceutically-acceptable salt by, for example, ion-exchange procedures.

It will be appreciated from the foregoing that all of the acid-addition and quaternary ammonium salts of our new bases are useful and valuable compounds regardless of considerations of solubility, toxicity, physical form, and the like, and accordingly are within the purview of the instant invention.

The novel features of the compounds of the invention, then, resides in the concept of the bases and the cationic forms of the new compounds of Formulas I-IV and not in any particular acid or ester moiety or anion associated with the salt forms of the compounds; rather, the acid or ester moieties or anions which can be associated in the salt forms are in themselves neither novel nor critical and therefore can be any anion or acid-like substance capable of salt formation with bases. In fact, in aqueous solutions, the base form or water-soluble acid-addition salt form of the compounds of the invention both possess a common protonated cation or ammonium ion.

Thus appropriate acid-addition salts are those derived from such diverse acids as formic acid, acetic acid, isobutyric acid, alpha-mercaptopropionic acid, malic acid, fumaric acid, succinic acid, succinamic acid, tartaric acid, citric acid, lactic acid, benzoic acid, 4-methoxybenzoic acid, phthalic acid, anthranilic acid, 1-naphthalenecarboxylic acid, cinnamic acid, cyclohexanecarboxylic acid, mandelic acid, tropic acid, crotonic acid, acetylenedicarboxylic acid, sorbic acid, 2-furancarboxylic acid, cholic acid, pyrenecarboxylic acid, 2-pyridinecarboxylic acid, 3-indoleacetic acid, quinic acid, sulfamic acid, methane-sulfonic acid, isethionic acid, benzenesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, butylarsonic acid, diethylphosphinic acid, p-aminophenylarsinic acid, phenylstibinic acid, phenylphosphinous acid, methylphosphinic acid, phenylphosphonic acid, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid, perchloric acid, nitric acid, sulfuric acid, phosphoric acid, hydrocyanic acid, phosphotungstic acid, molybdic acid, phosphomolybdic acid, pyrophosphoric acid, arsenic acid, picric acid, picrolonic acid, barbituric acid, boron trifluoride, and the like.

The acid-addition salts are prepared either by dissolving the free base in an aqueous solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The quaternary ammonium salts are prepared by mixing the free base and an appropriate alkyl halide in an inert solvent. Heating may be used to facilitate the reaction, although salt formation usually takes place readily at room temperature. The quaternary ammonium salt separates directly or can be obtained by concentration of the solution.

The compounds of Formula I-IV have been shown to possess central nervous system activity as evidenced by gross overt changes induced by parenteral administration in mice in standard tests involving observations of psychomotor activity, reactivity to stimuli, and ability to perform normal, non-conditioned motor tasks. (See Irwin, Animal and Clinical Pharmacologic Techniques in Drug Evaluation, Year Book Medical Publishers, Inc., Chicago, Ill., pp. 36-54 (1964)). Exemplary of this activity is the fact that the compound of Example 1 is a depressant of spontaneous motor activity of doses of the order of 10 to 20 mg./kg. As an example of reactivity to stimuli, an ED₅₀ value of between about 20 and 25 mg./kg. was determined in the Eddy hot plate test when administered parenterally. (For a complete description of the test used see N. B. Eddy and D. Leimbach, Journal of Pharmacology and Experimental Therapeutics, 160:217 (1968)). These activities indicate the compounds' usefulness as psychotherapeutic agents.

The compounds can be prepared for use by dissolving under sterile conditions a salt form of the compounds in water (or an equivalent amount of a non-toxic acid if the free base is used) or in a physiologically compatible aqueous medium such as saline, and stored in ampoules for intramuscular injection. Alternatively, they can be incorporated in unit dosage form as tablets or capsules for oral administration either alone or in combination with suitable adjuvants such as calcium carbonate, starch, 75

lactose, talc, magnesium stearate, gum acacia, and the like. Still further the compounds can be formulated for oral administration in aqueous alcohol, glycol or oil solutions or oil-water emulsions in the same manner as conventional medicinal substances are prepared.

The molecular structures of the compounds of our invention were assigned on the basis of study of their infrared, ultraviolet and NMR spectra and their transformation products, and confirmed by the correspondence of calculated and found values for the elementary analyses for representative examples.

The following example will further illustrate the invention without, however, limiting it thereto.

1-[2-(diethylamino)ethoxy]-3-pentyl-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran

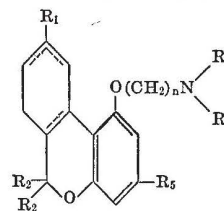
3.14 grams of Δ⁹ tetrahydrocannabinol (1-hydroxy-3-pentyl - 6a,7,8,10a - tetrahydro - 6,6,9 - trimethyl-6H-dibenzo[b,d]pyran), prepared according to Petrzilka, Haefliger and Sikemeier, Helvetica Chimica Acta, 52:1102 (1969), was dissolved in 50 ml. of absolute ethanol and added to one equivalent of a freshly prepared solution of KOC₂H₅ in ethanol. The mixture was refluxed for one-half hour and the ethanol was then removed under vacuum. The semi-solid thus obtained was further dried overnight under vacuum. The dried powder was dissolved in 50 ml. of dry benzene and to the clear solution was added 2.15 grams of diethylaminoethyl chloride (freshly prepared from its hydrochloride). This mixture was refluxed for four hours. After cooling, the organic layer was washed with water until neutral and the solvent was evaporated to give a mobile oily residue. This material was chromatographed on 100 grams of a standard chromatographic absorbent (e.g., Florisil) and eluted with a 40% ether/petroleum ether (boiling range 30-40° C.) mixture to give the desired product (α_D²² = -163 (ethyl alcohol)) which was soluble in 0.1 N HCl solution.

Analysis.—Calculated for C₂₇H₄₃O₂N (percent): C, 78.37; H, 10.48; N, 3.38. Found (percent): C, 78.05; H, 10.38; N, 3.18.

It will thus be seen that the objects set forth above, among those made apparent from the preceding description, are efficiently attained, and, since certain changes may be made in carrying out the above method and in the composition set forth without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

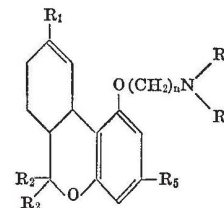
We claim:

1. A compound having the formula



wherein *n* is a whole number ranging from 1 to 7, R₁, R₂, R₃ and R₄ are lower alkyl of from one to six carbon atoms and R₅ is alkyl of from one to twenty carbon atoms or cycloalkyl-lower-alkyl wherein the cycloalkyl moiety contains from three to eight ring carbon atoms.

2. A compound in accordance with claim 1 having the formula

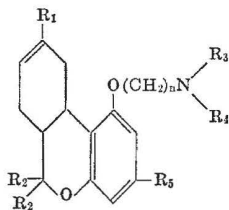


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wherein n is a whole number ranging from 1 to 7, R_1 , R_2 , R_3 and R_4 are lower alkyl of from one to six carbon atoms and R_5 is alkyl of from one to twenty carbon atoms or cycloalkyl-lower-alkyl wherein the cycloalkyl moiety contains from three to eight ring carbon atoms.

3. A compound in accordance with claim 2 wherein n is two, R_1 and R_2 are methyl, R_3 and R_4 are ethyl and R_5 is pentyl and said compound is 1-[2-(diethylamino)ethoxy] - 3 - pentyl-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran.

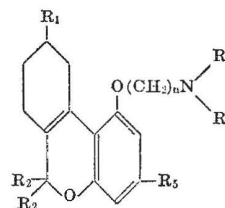
4. A compound in accordance with claim 1 having the formula



wherein n is a whole number ranging from 1 to 7, R_1 , R_2 , R_3 and R_4 are lower alkyl of from one to six carbon atoms and R_5 is alkyl of from one to twenty carbon atoms or cycloalkyl-lower-alkyl wherein the cycloalkyl moiety contains from three to eight ring carbon atoms.

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5. A compound in accordance with claim 1 having the formula



wherein n is a whole number ranging from 1 to 7, R_1 , R_2 , R_3 and R_4 are lower alkyl of from one to six carbon atoms and R_5 is alkyl of from one to twenty carbon atoms or cycloalkyl-lower-alkyl wherein the cycloalkyl moiety contains from three to eight ring carbon atoms.

6. The acid addition salt of the compounds of claim 1.

7. The quaternary ammonium salt of the compounds of claim 1.

References Cited

UNITED STATES PATENTS

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3,454,601	7/1969	Fried	260—345.9

JOHN M. FORD, Primary Examiner

U.S. Cl. X.R.

424—283

ACTUAL PATENT URL LINK:

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Abstract

NOVEL 1-(1-(DILOWER-ALKYLAMINO)ALKYLOXY)-3 ALKYL (AND CYCLOALKYL-LOWER-ALKYL) 6A,7,8,10A- AND 7,8,9,10-) TETRAHYDRO - 6,6,9-TRILOWER-ALKYL-6H-DIBENZO(B,D)PYRANS, AND ACID SALTS THEREOF. THESE COMPOUNDS POSSES BIOLOGICAL ACTIVITY AND ARE USEFUL AS THERAPEUTIC AGENTS.

Classifications

C07D311/80 Dibenzopyrans; Hydrogenated dibenzopyrans

US3649650A

United States

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Inventor: Raj K Razdan, Harry G Pars

Current Assignee : Arthur D Little Inc

Worldwide applications

1970 • [US](#)

Application events ⓘ

- 1970-02-13 • Application filed by Arthur D Little Inc
- 1970-02-13 • Priority to US1132370A
- 1972-03-14 • Application granted
- 1972-03-14 • Publication of US3649650A
- 1989-03-14 • Anticipated expiration

Status • Expired - Lifetime