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MARIHUANA ACTIVE COMPOUNDS

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Serial No. 528,351

9 Claims. (Cl. 260—333)

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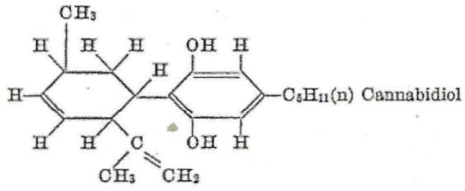
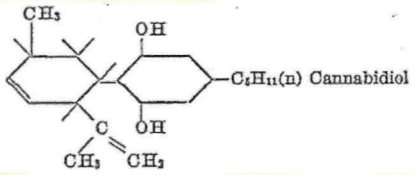
My invention relates to organic chemical compounds for therapeutic uses and includes among its objects and uses the production of such compounds having marihuana activity and greatly improved stability and uniformity in therapeutic strength as compared with crude marihuana from natural sources.

The "red oil," sometimes also called crude ..nnabinol, derived from *Cannabis sativa*, has been shown to contain a number of substances which are therapeutically inactive or toxic, as well as cannabidiol, cannabinol and hydrocannabinols of some sort, either originally present in cannabis or inadvertently generated in varying amounts by the treatment used to produce the red oil.

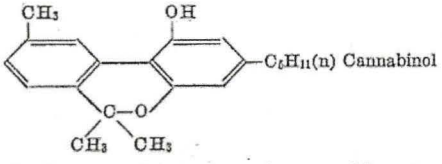
The complete formula for cannabidiol can be written thus:



but it is customary to omit all the hydrogens directly bonded to the rings, and to indicate their presence by drawing the unconnected bonds at the position occupied by each carbon atom having two bonds extending outside the ring. Accordingly, the common structural formula for cannabidiol is as follows:



Cannabinol is represented by the following ..rmula:



Tetrahydrocannabinol may be considered as de-

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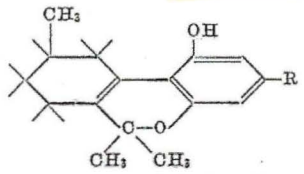
rived from cannabinol by adding four hydrogen atoms and thus eliminating two of the double bonds of the left ring. Thus the formula:

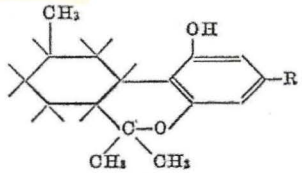


Tetrahydrocannabinol or homologue

represents a tetrahydrocannabinol when R is normal amyl, or a homologue in case R is some other alkyl group.

The double bond in the left ring of cannabidiol and tetrahydrocannabinol has been shown only to make the diagram consistent as to valences. In the synthetic optically inactive tetrahydrocannabinol it occupies the position conjugated to the benzene ring, and it is believed probable that in the natural optically active form derived from cannabidiol it is in the position indicated at the left end of the ring though it may be in the next position upwards from that indicated.

The compounds of the present invention include hexahydrocannabinol and various homologues thereof, which may be represented by the following formula:



Hexahydrocannabinol or homologue

The cannabinol products are disclosed herein, as being derived from three different sources; first, from red oil by the precipitation of cannabidiol and its subsequent isomerization to tetrahydrocannabinol and hydrogenation to the hexahydro compound; second, by a synthesis beginning with a cyclohexanone carboxylate; and third, by a synthesis beginning with pulegone. Various homologues, ethers and esters of hexahydrocannabinol may be prepared, as set forth hereinafter.

Cannabidiol can be produced for the present

purpose by any suitable procedure, such, for instance, as that disclosed in my Patent No. 2,304,669, issued December 8, 1942.

EXAMPLE I

A. *Formation of tetrahydrocannabinols by isomerization of cannabidiol*

A solution of about 0.19 gram of p-toluenesulfonic acid monohydrate and 3.14 grams of crystalline cannabidiol in 100 cc. of dry benzene was refluxed for one and one-half hours. At the end of that time the alkaline Beam test was negative. The benzene solution was extracted twice with about 5% aqueous sodium bicarbonate solution and twice with water. The benzene was then evaporated and the residue distilled under reduced pressure. Four fractions were collected, B. P. 169–172° (0.03 mm.), having essentially the same rotation $[\alpha]_D^{29}$—264° to —270°.

Rotation.—0.0694 grams made up to 5 cc. with 95% ethanol at 29° gave α_D—3.70°; 1, 1; $[\alpha]_D^{29}$—267°.

B. *Hexahydrocannabinol by reduction of tetrahydrocannabinol made from natural cannabidiol*

A solution of 3.14 g. of tetrahydrocannabinol $[\alpha]_D^{27}$—160°, which had been distilled in high vacuo in an all-glass apparatus, in 50 cc. of glacial acetic acid was reduced with hydrogen at room temperature, using 0.1 g. of platinum oxide as catalyst. Hydrogen corresponding to 0.96 mole per mole of tetrahydrocannabinol was absorbed in about four hours, after which hydrogenation continued to proceed but at a very much slower rate. After absorption of one mole equivalent of hydrogen, the solution was filtered and the acetic acid removed in vacuo. The hexahydrocannabinol formed a colorless, highly viscous resin, B. P. 153–155° (0.1 mm.) (bath temp. 180–185°); refractive index n_D^{20} 1.53.48.

Rotation.—0.0252 g. made up to 5 cc. with 95% ethanol at 27° gave α_D—0.71; 1, 2: $[\alpha]_D^{27}$—70°.

Anal.—Calc. for $C_{21}H_{32}O_2$: C, 79.69; H, 1019. Found: C, 79.35; H, 10.43.

It was found that regardless of the initial rotation of the optically active tetrahydrocannabinol used, the hexahydro product always had essentially the same specific rotation, when derived from natural cannabidiol.

EXAMPLE II

A. *1-hydroxy-3-n-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran*

A solution of about 24 grams of 1,3-dihydroxy-5-n-amylbenzene (olivetol), 24 grams of ethyl 5-methylcyclohexanone - 2 - carboxylate and 16 grams of phosphorous oxychloride in 180 cc. of dry benzene is first refluxed for about seven hours. After completion of the refluxing the reaction mixture is first washed with dilute aqueous sodium bicarbonate and is then washed with water. The benzene layer is then separated in the usual manner, the benzene evaporated and the residue (1-hydroxy - 3 - n - amyl - 9 - methyl-7,8,9,10-tetrahydro-6-dibenzopyrone) after purification by recrystallization from ethyl acetate, is obtained as white needles with a melting point of 180°–181° C. If desired, the crude residue after crystallization from methanol may be converted to the pyran as described below.

A suspension of about 9 grams of 1-hydroxy-3-n-amyl-9-methyl-7,8,9,10-tetrahydro-6-dibenzopyrone in 140 cc. of solvent made up of about 3 parts of dry benzene and 1 part of dry di-n-butyl ether is next mixed with a solution of Grignard reagent made up from about 9 grams of magnesium and 22.5 cc. of methyl iodide in 75 cc. of dry ether and the total mixture then refluxed for about eight hours. After refluxing, the reaction mixture is poured onto iced ammonium chloride solution, the organic layer separated, the aqueous layer extracted once with benzene and the combined benzene solutions washed successively with water, dilute aqueous sodium bicarbonate and water. The organic solvent (benzene, etc.) is then evaporated and the residue dissolved or taken up in about 150 cc. of petroleum ether (B. P. 60–100° C.). About 10 drops of 48 per cent aqueous hydrobromic acid is next added to the petroleum ether solution which is then boiled on a hot plate for about thirty minutes while maintaining the volume substantially constant by addition of more solvent as necessary. After separation of the reaction solution, e. g., by decantation, from a small amount of insoluble material, the solvent is evaporated in the usual manner and the residue, 1-hydroxy-3-n-amyl-6,6,9-trimethyl-7,8,9,10-tetrahydro - 6 - dibenzopyran distilled. This product is obtained as a viscous oil, B. P. 175°–180° C. (0.02 mm.), (bath temperature 195°–200° C.); refractive index n_D^{20} 1.5567. On standing it solidifies and may be purified by recrystallization from glacial acetic acid forming white crystals with a melting point of about 72°–73° C.

B. *Hexahydrocannabinol by reduction of 1-hydroxy-3-n-amyl - 6,9 - trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran*

A solution of about 3 grams of the tetrahydro derivative prepared as described above, in 50 cc. of glacial acetic acid is reduced in the usual manner at room temperature in the presence of 0.1 gram of platinum oxide catalyst. After one mole equivalent of hydrogen is absorbed the reaction solution is filtered, the solvent removed and the residue distilled. The hexahydrocannabinol product obtained is an optically inactive colorless, viscous oil, B. P. 212° C. (2 mm.); refractive index n_D^{20} 1.5349.

If, in some cases, the reduction is slow to start or is stopped completely by the presence of small amounts of impurity, warming the product with a little Raney nickel, followed by filtration serves to condition it so that the reduction runs smoothly.

Other derivatives may be prepared in accordance with the procedure set forth above in Example II. This procedure calls for (*a*) condensing an alkyl cyclohexanone-2-carboxylate with a 1,3-dihydroxy-5-alkyl benzene to form the corresponding dibenzopyrone product, (*b*) treating the pyrone product of step (*a*) with a lower alkyl Grignard reagent to form the corresponding tetrahydrodibenzopyran product and (*c*) reducing the pyran product of step (*b*) to form the corresponding hexahydrodibenzopyran.

Example III

A. *Pulegone-orcinol condensation product*

About 3.1 grams of pulegone ($[\alpha]_D^{32}$+24.3°), 2.5 grams of 1.3 dihydroxy-5-methyl-benzene (orcinol), 0.98 gram of phosphorous oxychloride (0.33 mole proportion) and 20 cc. of dry benzene are first mixed together and then refluxed for about four hours. The reaction mixture is then poured into an excess of aqueous sodium bicarbonate and warmed on a steam bath until the phosphorus derivatives are decomposed. After cooling, the benzene layer is separated and the aqueous layer extracted with a mixture of ben-

zene and ether. The organic solvent solutions containing the desired product are then combined, extracted with 2 per cent aqueous sodium hydroxide and the solvent removed in the usual manner. The residue is then vacuum distilled at about 5 mm. (bath 202°–215° C.) at about 170°–180° C. The final product obtained is optically active, the specific rotations in ethanol varying from about $[\alpha]_D^{31}+83.5$ to $+90.4°$ depending on the boiling point of the specific fraction tested.

(*a*) Similar to the above preparation except for the use of an 0.47 mole proportion of $POCl_3$, fractions were obtained having rotations in ethanol of about $[\alpha]_D^{31}+66.0°$ to $+76.9°$.

B. *Pulegone-olivetol condensation product*

About 5 grams of pulegone, 6 grams of 1.3-dihydroxy-5-n-amylbenzene (olivetol), and 1.5 grams of phosphorus oxychloride (0.3 mole proportion) are refluxed in benzene solution for about four hours. The reaction product is then worked up, i. e., treated with sodium bicarbonate solution, etc., as set forth in Example I and vacuum distilled at about 2 mm. (bath 225°–233° C.) at 190°–200° C. The final product obtained is an optically active tetrahydrocannabinol The specific rotations and indices of refraction of the product obtained using the 0.3 mole proportion of $POCl_3$ set forth above vary as follows: fraction (1) boiling point 190°–195° C., specific rotation in ethanol $[\alpha]_D^{32}+72.0$, refractive index n_D^{20} 1.5509; fraction (2) boiling point 195°–197° C., specific rotation in ethanol $[\alpha]_D^{32}+77.0°$, refractive index n_D^{20} 1.5519; fraction (3) boiling point 197°–200° C., specific rotation in ethanol $[\alpha]_D^{32}+73.0°$ refractive index n_D^{20} 1.5529.

Similar to the above preparation except for the use of an 0.53 mole proportion of $POCl_3$, fractions were obtained having specific rotations in ethanol of about $[\alpha]_D^{25}+70.0°$ to $+70.4°$.

Similar to the above preparation except for the use of an 0.76 mole proportion of $POCl_3$ and with six hours of refluxing, fractions were obtained having rotations of about $[\alpha]_D^{25}+48.1°$ to $+53.1°$.

C. *Hexahydrocannabinols by reduction of pulegone condensation products*

The same procedure outline in Example IIB may be employed to produce the hexahydro derivative of either the pulegone-orcinol condensation product of Example IIIA, or the pulegone-olivetol condensation product of Example IIIB.

Other derivatives may be prepared in accordance with the procedure set forth above in Example III. This procedure calls for (*a*) condensing optically active pulegone with a 1,3-dihydroxy-5-alkyl benzene to form the corresponding dibenzopyran product and (*b*) reducing the pyran product of step (*a*) to form the corresponding hexahydrodibenzopyran. The 3-hexyl derivative may be prepared in accordance with Example III by (*a*) condensing optically active pulegone with a 1,3-dihydroxy-5-hexyl benzene to form the corresponding dibenzopyran product and (*b*) reducing the pyran product of step (*a*) to form the corresponding hexahydrodibenzopyran.

EXAMPLE IV

Tetrahydrocannabinol monoacetate

A. A mixture of tetrahydrocannabinol $[\alpha]_D^{34}$ $-164°$ was heated with acetic anhydride and a little fused anhydrous sodium acetate for two hours and worked up in the usual manner. The desired acetate product is a colorless, viscous oil, B. P. 156–158° (0.07 mm.) (bath temperature 175°); refractive index n_D^{20} 1.5232.

Rotation.—0.0281 made up to 5 cc. with 95% ethanol at 34° gave α_D -1.88; 1, 2; $[\alpha]_D^{34}$ $-167°$.

B. Tetrahydrocannabinol $[\alpha]_D^{32}$ $-240°$ was acetylated as described in A above. This product obtained from the higher rotating isomer is a colorless, viscous oil, B. P. 172–174° (0.08 mm.) (bath temp. 195°); refractive index n_D^{20} 1.5242.

Rotation.—0.0373 g. made up to 5 cc. with 95% ethanol at 34° gave α_D 1.72; 1, 2; $[\alpha]_D^{34}$ $-229°$.

The same procedure outlined above may be employed in producing esters from tetrahydrocannabinol derived from any source or from the hexahydro compound disclosed herein.

EXAMPLE V

Tetrahydrocannabinol monomethyl ether

A. Tetrahydrocannabinol $[\alpha]_D^{34}$ $-164°$ was refluxed for 15 hours with anhydrous potassium carbonate and methyl iodide in acetone solution. The ether product was purified from unchanged tetrahydrocannabinol by means of Claisen's potash and yields a colorless, viscous oil, B. P. 168–170° (0.08 mm.) (bath temperature 190–195°); refractive index n_D^{20} 1.5323.

Rotation.—0.0395 g. made up to 5 cc. with 95% ethanol at 32° gave α_D -1.31; 1, 1; $[\alpha]_D^{32}$ $-166°$.

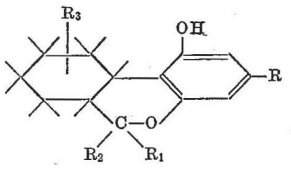
The same procedure outlined above may be employed in producing ethers from tetrahydrocannabinol derived from any source, and any of these ethers may be reduced to the corresponding hexahydro compound by the procedure of Example IIB hereinabove.

This application is a continuation in part of my copending applications: Serial No. 358,306, filed September 25, 1940; Serial No. 401,655, filed July 9, 1941; Serial No. 401,656, filed July 9, 1941; Serial No. 440,971, filed April 29, 1942.

Without further elaboration, the foregoing will so fully explain the invention that others may readily adapt the same for use under various conditions of service.

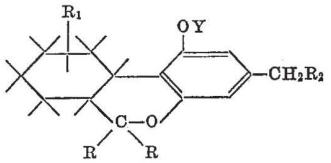
I claim:

1. Hexahydro dibenzopyrans having the formula:



in which R is an alkyl group having from one to eleven carbon atoms, and R_1, R_2 and R_3 are lower alkyl groups.

2. A pyran compound represented by the following formula:

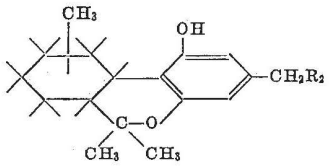


where R represents a lower alkyl group, R_1 is selected from the group consisting of hydrogen and lower alkyl groups, R_2 is selected from the group consisting of hydrogen and alkyl groups containing one to ten carbon atoms and Y is selected from the group consisting of hydrogen and lower alkyl and acyl groups.

3. A pyran compound represented by the formula of claim 2 in which R_2 is an alkyl group containing four carbon atoms.

4. An optically inactive pyran compound represented by the formula of claim 2 in which R_2 is an alkyl group containing five carbon atoms.

5. A pyran compound represented by the following formula:

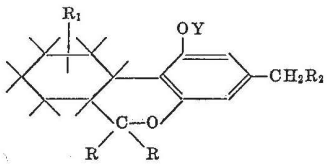


where R_2 is selected from the group consisting of hydrogen and alkyl groups containing one to ten carbon atoms.

6. A pyran compound represented by the formula of claim 5 in which R_2 is an alkyl group containing four carbon atoms.

7. An optically inactive pyran compound represented by the formula of claim 5 in which R_2 is an alkyl group containing five carbon atoms.

8. A pyran compound represented by the following formula:



where R represents a lower alkyl group, R_1 is selected from the group consisting of hydrogen and lower alkyl groups, R_2 is selected from the group consisting of hydrogen and alkyl groups containing one to ten carbon atoms and Y is a lower alkyl group.

9. A pyran compound represented by the formula in claim 8, where R represents a lower alkyl group, R_1 is selected from the group consisting of hydrogen and lower alkyl groups, R_2 is selected from the group consisting of hydrogen and alkyl groups containing one to ten carbon atoms and Y is a lower acyl group.

ROGER ADAMS.

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The following references are of record in the file of this patent:

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Number	Country	Date
547,669	British	Sept. 7, 1942

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PATENT CURRENT ASSIGNEE URL LINK:
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Classifications

- C07D311/80 Dibenzopyrans; Hydrogenated dibenzopyrans

US2419937A

United States

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Inventor: Adams Roger

Worldwide applications

1944 · US

Application US528351A events

1944-03-27 • Application filed by Adams Roger

1944-03-27 • Priority to US528351A

1947-05-06 • Application granted

1947-05-06 • Publication of US2419937A

1964-05-06 • Anticipated expiration

Status • Expired - Lifetime