Patented May 6, 1947

2,419,937

UNITED STATES PATENT OFFICE

2,419,937

MARIHUANA ACTIVE COMPOUNDS

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No Drawing. Application March 27, 1944,
Serial No. 528,351

9 Claims. (Cl. 260—333)

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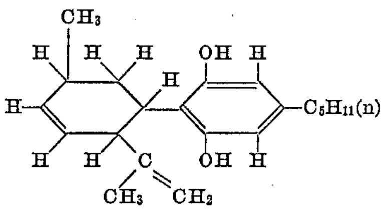
My invention relates to organic chemical compounds for therapeutic uses and includes among its objects and uses the production of such compounds having marihuana activity and greatly improved stability and uniformity in therapeutic strength as compared with crude marihuana from natural sources.

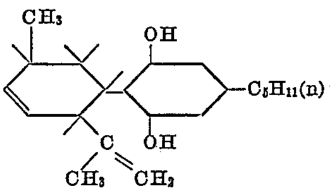
The "red oil," sometimes also called crude cannabinol, derived from *Cannabis sativa,* has been shown to contain a number of substances which are therapeutically inactive or toxic, as well as cannabidiol, cannabinol and hydrocannabinols of some sort, either originally present in cannabis or inadvertently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

The complete formula for cannabidiol can be written thus:



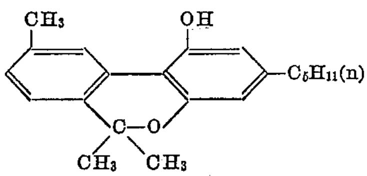
Cannabidiol

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:



Cannabidiol

Cannabinol is represented by the following formula:



Cannabinol

Tetrahydrocannabinol may be considered as de-

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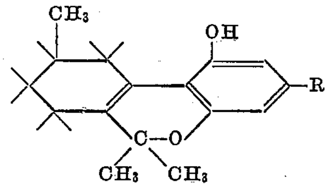
rived from cannabinol by adding four hydrogen atoms and thus eliminating two of the double bonds of the left ring. Thus the formula:

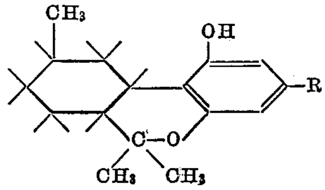


Tetrahydrocannabinol or homologue

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} 1.5348.

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

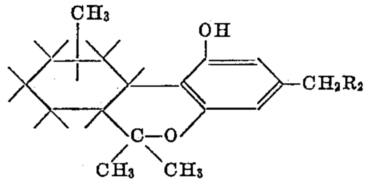
A. Pulegone-orcinol condensation product

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-

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:

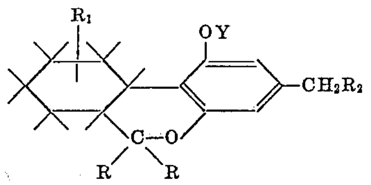


where R_2 is selected from the group consisting of hydrogen and alkyl groups containing one to ten carbon atoms.

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.

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