# United States Patent [19]

**Petrzilka**

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[54] **TETRAHYDRODIBENZOPYRANS**


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[52] **U.S. Cl.** ..... **260/345.3,** 424/283

[51] **Int. Cl.** ..... **C07d 7/20**

[58] **Field of Search** ..... 260/345.3



[56] **References Cited**

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|---|---|---|---|
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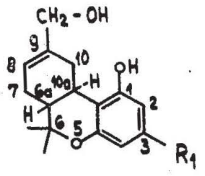
[57] **ABSTRACT**

(-)-1-Hydroxy-3-alkyl-6,6-dimethyl-9-hydroxymethyl-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyrans (Formula 1) are produced in good yields from the corresponding 9-methylene-1,8-di-acyl compounds (Formula 2) by thermal conversion of the latter into the corresponding 1,11-di-acyl compounds (Formula 3) which are converted into the target compound (Formula 1) by removal of the two acyl groups. Formula 1 compounds, where the alkyl group is a straight or branched chain alkyl of from 1–4 and 6–10 C-atoms are novel homologues of the 3-n-pentyl compound, a metabolite of tetrahydrocannabinol known per se. Formula 1 compounds have bactericidic, sedative, analgetic and psychomimetic effect when applied to the human organism. Novel compounds (Formulae 4*a*, 5*b*, 6 and 7) are disclosed as starting materials and/or intermediates, some of them having pharmacological utility similar to the Formula 1 compounds.


**12 Claims, 16 Drawing Figures**



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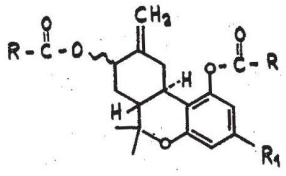

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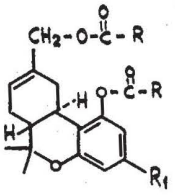

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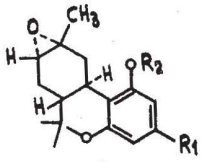

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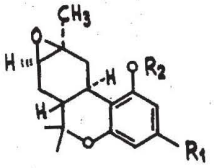

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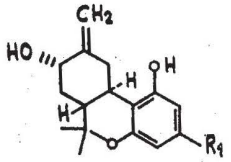

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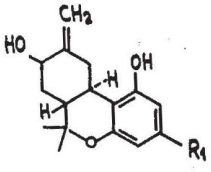

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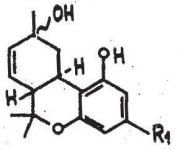

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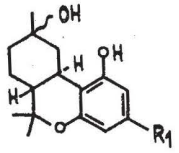

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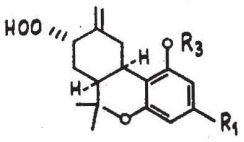

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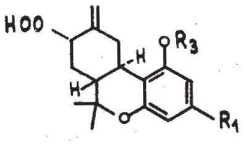

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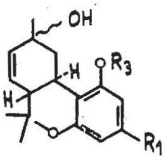

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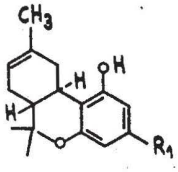

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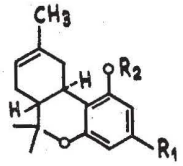

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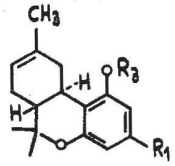

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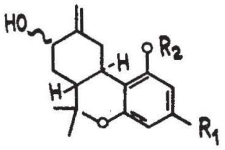

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# TETRAHYDRODIBENZOPYRANS

## BACKGROUND OF THE INVENTION

According to investigations by Monroe E. Wall et al (J.A.C.S. 92:11, pages 3466–3468) and Fang et al (Science, Volume 172, pages 165–167) (-)-trans-tetrahydro-6a,10-dibenzo-(b,d)-pyrans, when administered in vivo to rabbits or contacted in vitro with liver homogenate are converted into derivatives generally called metabolites of THC, i.e. tetrahydrocannabinol. Among the metabolites, the 11-hydroxy metabolite (also referred to herein as the 9-hydroxymethyl metabolite) proved to be several times more active than THC itself. In view of the pharmacological potential of THC and some of its derivatives and the extremely small yields of metabolite production in vivo or in vitro a process of synthesizing such active metabolites in good yields was required. Previous attempts to achieve such synthesis failed, apparently due to the complex and stereo-specific structure of this type of compounds.

It is one of the main objects of this invention to provide a process for producing such metabolites as well as their 3-alkyl homologues.

Another object is to provide for novel starting substances and intermediates for such synthesis.

Other objects will become apparent as the specification proceeds.

## SUMMARY OF INVENTION

In accordance with the above and further objects, I have found that compounds of Formula 1 in which $R_1$ is a straight or branched chain alkyl group including from 1 to about 10 carbon atoms (all compound formulae being given in the attached Formula Sheet) including the 11-hydroxy metabolite of THC known per se, as well as certain 3-alkyl homologues can be obtained in good yields, say in the order of at least 50 % of the theoretical yield, from the corresponding 9-methylene-1,8-di-acyl compound of Formula 2 in which R is hydrogen or a lower alkyl group, preferably methyl, including from 1 through 5 carbon atoms, by thermal conversion of a Formula 2 compound thus yielding the bis-acyl compound of Formula 3, in which R and $R_1$ are as above, which is then converted into the target compound of Formula 1 by removing both acyl groups. The desired Formula 1 compounds including the known 3-n-pentyl compound mentioned above as well as the novel alkyl homologues thereof exhibit pharmacological activity as set forth below more in detail.

Preferably, thermal conversion of compound 2 into compound 3 is achieved by simply heating compound 2, e.g. at temperatures of above 200°C, e.g. from about 250° to about 300°C, a temperature of 290°C ± 10°C being particularly preferred. Inert diluents need not be present during the heating step and, preferably, air is excluded during the thermal conversion of compound 2.

Removal of the two acyl groups from compound 3, i.e. from the conversion product, can be achieved by methods known in the art, e.g. reduction techniques, preferably by heating compound 3 in an enert solvent and in the presence of $LiAlH_4$.

Further, the invention provides, as novel substances, the compounds of Formula 1 in which $R_1$ is straight or branched alkyl of 1–10 C-atoms excluding the compound where $R_1$ is n-pentyl, and the compounds of Formulae 4*a*, 5*b*, 6 and 7 in which $R_1$ is the pentyl group or another $C_1$–$C_{10}$ alkyl group.



## DETAILED DESCRIPTION OF INVENTION

First, with reference to the annexed Formula Sheet and in view of different systems of nomenclature used for tetrahydrodibenzopyrans, Formula 1 shows the target compound and the numbering system used throughout the specification. Before proceeding to the details of the compounds shown it is to be understood that the bonds or lines shown in 6-position of all Formulae do not represent free bonds but methyl groups —$CH_3$, each line representing one such group. By the same token, the free line in 9-position of Formulae 6, 7 and 8*c* also designates a methyl group. On the other hand, the double line in 9-position of Formulae 8*a*, 8*b* and 12 designates a double bond to and including the methylene group =$CH_2$. The two hydrogen atoms in 6*a* and 10*a* are sterically arranged such that the hydrogen at the end of the full line in 6a-position is above the plane of drawing while the hydrogen at the end of the broken line in 10a-position is below the plane of drawing.

The undulated lines shown as bonding signs for specific groups in Formulae 2, 6, 7, 8*c* and 12 indicate that the group thus defined can be in one of two diastereomeric forms, i. e. below or above the plane of drawing. Such Formulae are intended to include either diastereomer or any mixture thereof.

Similarly, the position of the substituents in the 8- or/and 9-positions in Formulae 4*a*, 4*b*, 5*a*, 8*a* and 8*b* are marked to show diastereomers.

Group R in Formulae 2 and 3 is hydrogen or a lower alkye group of from 1 to about 5 C-atoms, R = methyl being a preferred embodiment so that the preferred acyl group in positions 1 and 8 of Formula 2, and 1 and 11 of Formula 3 is the acetyl group.

$R_1$ in Formulae 1–12 is straight or branched chain alkyl, e. g. methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-pentyl, n-heptyl, n-octyl, etc.

$R_2$ in Formulae 4*a*, 4*b* and 12 is a protective group of the type known in the art, preferably the tetrahydropyranyl group.

Also, $R_3$ in Formulae 8*a*, 8*b*, 8*c* and 11 is a protective group and can be the same as $R_2$. A preferred protective group $R_3$ is the acetyl group.

The starting substance, i. e. a Formula 2 compound, for the process of the invention may be obtained in various ways, the following methods A and B being preferred, however. Each method comprises a sequence of steps identified below as A-1 to A-5 and B-1 to B-5:

(A-1) Formula 9 $\xrightarrow{\text{introduction of group } R_2}$ Formula 10
(A-2) Formula 10 $\xrightarrow{\text{Epoxydation}}$ Formulae 4*a*, 4*b*
(A-3) Formulae 4*a*, 4*b* $\xrightarrow{\text{epoxy ring cleavage}}$ Formula 12
(A-4) Formula 12 $\xrightarrow{\text{Removal of } R_2}$ Formulae 5*a*, 5*b*
(A-5) Formulae 5a, 5b $\xrightarrow[\text{both hydroxyls}]{\text{acylation of}}$ Formula 2

(B-1) Formula 9 $\xrightarrow{\text{introduction of } R_3}$ Formula 11
(B-2) Formula 11 $\xrightarrow{\text{Photooxydation}}$ Formulae 8*a*, 8*b*
(B-3) Formulae 8a, 8b $\xrightarrow[\text{perhydroxy groups}]{\text{reduction of}}$ Formulae 5a, 5b, 6
(B-4) Formulae 5*a*, 5*b*, 6 $\xrightarrow{\text{separation from 6}}$ Formulae 5*a*, 5*b v*,
(B-5) Formulae 5a, 5b $\xrightarrow[\text{both hydroxyls}]{\text{acylation of}}$ Formula 2

Accordingly, both preferred methods A and B start from a Formula 9 compound which in turn can be ob-

tained in good yields according to the process disclosed in my U.S. Pat. No. 3,560,528, issued Feb. 7, 1971, incorporated by reference into the present specification.

While specific Examples for both methods A and B will be given below, these are some general remarks regarding the A and B syntheses:

Step A-1: The protective group $R_2$ introduced in this step should be stable under alkaline conditions. Examples of suitable $R_2$ groups are the trimethylsilyl group and the O-tetrahydropyranyl group, the latter being particularly preferred. Suitable procedures are well known per se in the art, as are other suitable groups. Product isolation is neither critical nor required.

Step A-2: Epoxydation of 10 can be effected according to methods known per se, e.g. by means of peracids such as m-chloroperbenzoic acid in inert solvents. The epoxides 4*a*, 4*b* are diastereomers and can be used singly or in mixture for the next step. Product isolation is not required.

Step A-3: Here, the epoxide ring is opened to produce a Formula 12 compound in a manner known per se in the art, e. g. by treatment with a base in an inert solvent using such bases as alkali metal alcoholates, e. g. lithium, sodium or potassium salts of methyl, ethyl, propyl, t-butyl or t-amyl alcohol, butyl lithium being the preferred base.

Step A-4: Now, the protective group will be removed in a manner known per se in the art, e. g. by treatment with a mineral acid, generally a diluted aqueous or alcoholic acid such as hydrochloric, hydrobromic or hydroiodic acid. The preferred acid is hydrochloric acid.

Suitable inert solvents in this and other steps are normally liquid hydrocarbons such as pentane, hexane, benzene, toluene, xylene or ethers, e. g. diethyl ether, benzylmethyl ether, tetrahydrofurane or dimethoxy ethane. The preferred solvent is diethyl ether. The reaction temperature is not critical; in a preferred embodiment of the reaction, the base is added at 0°C, whereupon the temperature is allowed to rise to 35°–80°C.

It is to be noted that steps A-3 and A-4 can be combined into a single treatment, i. e. if group $R_3$ will be removed by the reaction conditions selected to open the epoxide ring. In either case, isolation of product 5*a*, 5*b* is not required, nor is separation of the diastereomers necessary or advantageous.

Step A-5: This is the acylation of both hydroxyls in 8- and 1-position. Depending upon the R group required for compound 2, treatment with the corresponding acid, acid anhydride, acid chloride, etc. under conditions of esterification is quite suitable. Acetylation, e. g. with acetic anhydride in pyridine, is a preferred embodiment.

Preferably, the product of Formula 2 thus obtained is recovered and purified, but a raw product is suitable for subsequent thermal conversion explained more in detail below.

Step B-1: The protective group $R_3$ introduced in this step into compound 9 is not particularly critical and both suitable groups and suitable methods are known per se. However, acyl groups are preferred for $R_3$ and it is even more preferred to use such acyl groups, e. g. the acetyl group, which carry the group R adjacent to the carbonyl group. In other words, if R in Formulae 2 and 3 is to stand for methyl, $R_3$ preferably is acetyl because this will avoid the necessity of exchanging $R_3$ for R in the later stages of this method. Acylation or acetylation can be effected as in step A-5. Purification of product (Formula 11) is not required.

Step B-2: Photooxydation of the Formula 11 compound can be effected by treatment with actinic radiation, preferably UV light, in the presence of oxygen, e. g. gaseous oxygen. As is common in the art of photooxydation, sensitizers can be used in this step, fluorescein and rose bengal being typical examples, and operation in liquid media, e. g. a solvent inert to the irradiation, is preferred. Suitable examples of solvents include normally liquid hydrocarbons such as pentane, hexane, benzene, toluene, xylene and/or alcohols such as methanol, ethanol, propanol, *n* and *t* butanol and *n* and *t* amyl alcohol. A preferred solvent is a 1:1 mixture of benzene/methanol.

The product of this step is a mixture of 8*a*, 8*b* compound with the peroxy-precursor of the compound of Formula 8*c* (i.e. where the hydroxyl in 9-position is a peroxy group). Preferably, this mixture is used directly as the starting material for the subsequent step B-3, and in practice the entire reaction mixture can be used for conducting step B-3.

Step B-3: This involves reduction of the perhydroxy group formed in step B-2 which is another technique well known per se.

Numerous reduction techniques will also cause removal of the protective group $R_3$ in this step. This, in fact, is preferred. If the reduction method used will not remove group $R_3$, an additional step to effect this will be required, unless this group does already constitute the desired substituent for the 1-position of compound 2, e.g. if R is to be methyl and $R_3$ is acetyl.

In either case, the result of this step is a mixture of diastereometric compound 5*a*, 5*b* (with either free hydroxyl in 1-position or still carrying group $R_3$ on the oxygen in 1-position) together with compound of Formula 6 which is a side product of this method but also an interesting new chemical species as explained below.

A preferred reduction technique for step B-3 is treatment with sodium borohydride, e.g. in methanol. Reductions of this type yield the free 1-phenols of Formulae 5*a*, 5*b* and 6 directly.

Step B-4: This involves separation of the combined diastereomers 5*a*, 5*b* from compound 6, both for the purposes of improving the yields in the subsequent use of 5*a*, 5*b* toward production of compound 1 as well as for recovering the valuable "side-product" of Formula 6. Simple distillation and/or chromatography techniques are suitable for this purpose.

Step B-5: The diastereomers recovered in step B-4 (i.e. Formulae 5*a*, 5*b* compounds) are acylated to produce the desired Formula 2 compound. This step is the same as A-5.

As noted above, compounds of Formula 6 are a novel species. They are obtained according to step 1-3 of the above method B and isolated as a product from step B-4. In general, they exhibit valuable pharmacological properties of the type disclosed herein for Formula 1 compounds. In addition, they can be converted into another novel species, i.e. compounds of Formula 7, by conventional catalytic hydrogenation methods. The novel Formula 7 compounds exhibit pharmacological utility of the type disclosed for Formula 1 compounds.

Turning now to the conversion of Formula 2 compounds into Formula 3 compounds (the latter being then converted into the subject target compound of

Formula 1), it has been mentioned above that this conversion can be simply achieved by heating of compound 2. The mechanism of the rearrangement involved has not been fully established but it is surprising indeed that conversion of compound 2 into compound 3 can be achieved by mere heating in good yields, considering the complexity and steric specifity of the molecular structures involved.

Presence of a liquid inert phase is not necessary for the thermal conversion and is not even preferred. If a liquid inert phase or diluent is to be used, common inert solvents such as benzene, toluene, xylene, biphenyl ether, etc. are suitable. When such liquids are used for the thermal conversion of compound 2, apparatus means suitable for withstanding the autogenic pressure of the mixture at conversion temperatures of above 200°C will have to be used.

According to a preferred way of effecting thermal conversion, the Formula 2 compound is heated without additives to a temperature of from about 200° to about 300°C, preferably 250°–300°C, and most preferred to about 290°C (± 10°C). Heating under vacuum, e.g. 0.001 torr, is preferred, for example by introducing Formula 2 compound into a suitable recipient, evacuation of air therefrom, and sealing the recipient, e. g. a heavy glass tube.

The reaction time can be varied between about 1–60 minutes with higher temperatures requiring shorter reaction times, and vice-versa. At about 290°C a reaction time of about 15 minutes is preferred and renders yields of Formula 3 compound in the order of about 60 % by weight.

Removal of the acyl groups in 1- and 11-position of Formula 3 yields the target compound of Formula 1. Suitable techniques for removing acyl groups such as to leave the hydroxyl group instead of the acyl are well known per se, e.g. reduction or hydrolysis. The reduction technique in an inert liquid medium is preferred here for practical reasons (product purity), e.g. using lithium aluminium hydride ($LiAlH_4$) as reduction agent and an inert solvent, e.g. tetrahydrofuran, dimethoxyethane, diethyl ether, etc. the last named solvent being preferred for ease of subsequent removal and product recovery.

The product thus obtained can be purified in a manner known per se, e.g. chromatography.

As mentioned above, compounds of formula 1 are useful as psychomimetic agents, sedatives and analgesics. They can be formulated as novel pharmaceutical preparations together with conventional pharmaceutical organic or inorganic carrier materials suitable for internal administration. Pharmaceutical Formula compositions containing the compounds of Formula 1 can be administered parenterally or orally, the dosages to be adjusted according to individual requirements. For example, these compounds can be adminstered in dosages of from about 0.1 mg/kg to about 5 mg/kg per day, either in a single or in a repeated divided dosage. The novel pharamceutical compositions can contain such conventional organic or inorganic inert carrier materials as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene glycols, vaseline or the like. The pharmaceutical preparations can be in the conventional solid forms such as tablets, dragees, suppositories, capsules or in conventional liquid form such as solutions, suspensions of emulsions. The pharmaceutical compositions can be submitted to conventional pharmaceutical expedients such as sterilization and/or can contain conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting agents, emulsifying agents, salts for adjusting the osmotic pressure, buffers or the like. They also can contain other therapeutically useful materials.

The following Examples are illustrative but not limitative of the invention. Percentages are by weight unless indicated otherwise.

## EXAMPLE I

### Preparation of (-)-1-O-tetrahydropyraryl-3-n-pentyl-6,6,9-trimethyl-6a,10-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formula 10):

3.14 of Formula 9 compound ($R_1$ = n-pentyl) are added dropwise to a solution of 4.20 g 3,4-dihydro-2H-pyran (commercial grade) in 20 ml of methylene chloride containing 20 mg of p-toluene sulfonic acid. The mixture is stirred for 1 hour at room temperature. After addition of ethyl ether, the resulting solution is extracted with 2 n sodium hydroxide solution. After drying the ether solution over sodium sulfate the ether is evaporated leaving 5.0 g of an oily residue which is purified by chromatography over 100 g of aluminium oxide (trade product from M. Woelm Corp., Eschwege, Germany). Elution with petroleum ether yields 2.86 g of the desired Formula 10 compound ($R_1 = C_5H_{11}$, $R_2$ =tetrahydropyranyl).

The Rf value of this compound in chloroform is 0.60, the boiling point at 0.01 torr is 195°–205°C. $\alpha_D^{20}$ = −221°C (0.36 in chloroform). Analytical data and IR, NMR and MS spectra confirm the structure given.

## EXAMPLE II

### Preparation of (-)-8,9-epoxy-1-0-tetrahydropyranyl-3-n-pentyl-6,6,9-trimethyl-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formulae 4*a*, 4*b*):

2.86 g of the compound obtained in Example I are dissolved in 20 ml of methylene chloride. Then 1.6 g of m-chloro-perbenzoic acid (commercial grade) dissolved in 30 ml of methylene chloride are added dropwise to the solution at room temperature. The resulting mixture is kept at room temperature for 15 hours. Thereafter, the excess of m-chloro-perbenzoic acid is destroyed by addition of aqueous 10 % sodium sulfite solution. The organic layer obtained is washed with aqueous sodium bicarbonate solution and dried over sodium sulfate. The crude residue is chromatographed on 60 g of "Florisil," a commercial magnesium silicate absorbent. Elution with benzene yields 1.9 g of pure compound according to Formulae 4*a*, 4*b*, in which $R_1$ is $C_5H_{11}$ and $R_2$ is tetrahydropyranyl. Analytical data as well as IR, NMR and MS spectra confirm the structure given.

The Rf value in chloroform is 0.19. The boiling point is 165°–170°C/0.01 mmHg.

## EXAMPLE III

### Preparation of (-)-1-0-tetrahydropyranyl-3-n-pentyl-8-hydroxy-6,6,9-trimethyl-9-methylidene-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formula 12)

6 ml of a 2.5 molar solution of butyllithium in hexane are added dropwise to a solution of 1.491 g of the com-

pound obtained according to Example II in 30 ml of dry ethyl ether at a temperature of 0°C. When addition is complete, the temperature of the solution is allowed to rise to ambient temperature. Then, the reaction mixture is refluxed for 4 hours. After addition of ice, the organic layer obtained is washed with water and dried over sodium sulfate. After evaporation of the ether 1.436 g of a yellow oil are obtained. Chromatography over aluminium oxide (neutral grade, Woelm Corp.) and elution with methylene chloride yields 850 mg of the compound of Formula 12 ($R_1$ = n-pentyl, $R_2$ = tetrahydropyranyl).

Analytical data as well as IR, NMR and MS spectra confirm the structure given.

The Rf value in chloroform is 0.10. The boiling point is 210–220°C/0.001 mmHg.

## EXAMPLE IV

### Preparation of (-)-1,8-dihydroxy-3-n-pentyl-6,6-dimethyl-9-methylidene-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formulae 5*a*, 5*b*)

**393** mg of the compound obtained according to Example III are dissolved in 20 ml of dioxane. 4 ml of 2 n sulfuric acid are added to this solution. The resulting mixture is stirred over night at room temperature. Extraction with ether yields 411 mg of viscous yellow oil which is then chromatographed over 10 g of "Florisil" (magnesium silicate). Elution with methylene chloride yields 250 mg of the compound of Formulae 5*a*, 5*b* ($R_1$ = n-pentyl).

Analytical data as well as IR, NMR and MS spectra confirm the structure given.

The Rf value in chloroform/methanol 9:1 is 0.50. The boiling point is 215°C/0.001 mmHg.

## EXAMPLE V

### Preparation of (-)-1,8-bisacetoxy-3-n-pentyl-6,6-diemthyl-9-methylidene-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formula 2)

300 mg of the compound obtained according to Example IV are dissolved in 3 ml acetic anhydride and 3 ml of anhydrous pyridine. The resulting solution is kept under argon in a dry atmosphere for 12 hours at room temperature. After evaporation of the solvents under reduced pressure the residue is dissolved in ether and extracted with aqueous sodium bicarbonate solution. After evaporation of the dried ether extract the residue is distilled at 180°C/0.01 mmHg.

357 of pure Formula 2 compound (R = methyl, $R_1$ = n-pentyl) are obtained.

Analytical data as well as IR, NMR and MS spectra confirm the structure given.

The Rf value in chloroform is 0.40.

## EXAMPLE VI

### Preparation of (-)-1-acetoxy-3-pentyl-6,6-dimethyl-9-acetoxymethyl-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formula 3)

185 mg of the compound obtained in Example V are heated in a tube sealed under high vacuum to 290°C and kept at this temperature for 15 minutes. Distillation of the reaction product at 200°C/0.001 mmHg yields 160 mg of a reaction mixture from which the Formula 3 compound (R = methyl, $R_1$ = n-pentyl) is obtained by chromatography on 5 g of "Florisil" and elution in a yield of 105 mg.

The Rf value of this compound in chloroform is 0.25. Analytical data as well as IR, MMR and MS spectra confirm the structure given.

## EXAMPLE VII

### Preparation of (-)-1-hydroxy-3-n-pentyl-6,6-dimethyl-9-hydroxymethyl-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formula 1)

185 mg of the compound obtained according to Example VI are dissolved in 5 ml of dry ether and the solution is added dropwise to a solution of 35 mg of lithium aluminum hydride in 5 ml of ether. The mixture is refluxed for 2 hours. The excess reagent is decomposed by addition of aqueous sodium sulfate solution. After drying over anhydrous sulfate the ether solution is filtered and the ether evaporated. Chromatography over 6 g of "Florisil" with benzene/chloroform yields the compound of Formula 1 ($R_1$ = n-pentyl).

Analytical data as well as IR, NMR and MS spectra confirm the structure given in Formula 1.

The Rf value in chloroform/methanol 97:3 is 0.30. The boiling point is 220°C/0.001 mm torr. $(\alpha)_D^{20}$ = −231°C (0.21 in chloroform).

## EXAMPLE VIII

### Preparation of (-)-1-acetoxy-3-n-pentyl-6,6,9-trimethyl-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formula 11)

6.2 g of the compound of Formula 9, in which $R_1$ is n-pentyl, are dissolved in 20 ml of acetic anhydride and 20 ml of pyridine. The solution is kept at room temperature for 12 hours. After evaporation of the solvents the residue is dissolved in ether and the solution extracted with aqueous sodium bicarbonate solution. The ether is evaporated and the residue dried under high vacuum at 80°C. 6.98 g of the compound of Formula 11 ($R_1$ = n-pentyl, $R_3$ = acetyl) are obtained.

Analytical data as well as IR, NMR and MS spectra confirm the structure given.

The Rf value in chloroform/methanol 97:3 is 0.70. The boiling point is 145°C/0.001 torr.

## EXAMPLE IX

### Preparation of (-)-1,8-dihydroxy-3-n-pentyl-6,6-dimethyl-9-methylidene-6a,10a-trans-6a,7,10,10a-tetrahydrodibenzo-(b,d)-pyran (Formulae 5*a*, 5*b*)

6.88 g of the compound obtained in Example VII and 200 mg of rose bengal are dissolved in 130 ml of equal parts by weight of benzene/methanol 1:1. Gaseous oxygen is bubbled through the solution and the solution is irradiated by means of a conventional high-pressure mercury lamp of the type used for photochemical reactions during 8 hours at room temperature (20°–25°C). The reaction mixture (containing compounds 8*a*, 8*b*) is cooled in ice and treated with a total of 15 g of sodium borohydride added portionwise. After completion of the addition stirring is continued for 12 hours at room temperature. Then, 1 n hydrochloride acid is added until the pH of the solution is 7–8. Extraction

with ether, drying the ether extract with sodium sulfate and evaporation of the solvent yields 7.36 g of a product which is purified by chromatography on 150 g of "Florisil." Elution with benzene/hexane 1:1 and pure benzene yields a mixture of the enantiomeric secondary alcohols of Formulae 5*a*, 5*b* ($R_1$ = n-pentyl). Pure product yield is 44 %. The product is the same as that of Example IV and can be used as described in Examples V, VI and VII.

## EXAMPLE X

Preparation of
(-)-1,9-dihydroxy-3-n-pentyl-6,6,9-trimethyl-6a-10a-trans-6a,10,10a-tetrahydrodibenzo-(b,d)-pyran
(Formula 6)

When the absorbent "Florisil" remaining in Example IX after elution of the Formula 5*a*, 5*b* compound is further eluted with 3:1 benzene/ether, 2.65 g of tertiary alcohol of Formula 6 compound ($R_1$ = n-pentyl) are obtained.

Analytical data as well as IR, NMR and MS spectra confirmed the structure given.

The Rf value is 0.16 in chloroform/methanol 97:3. ($\alpha$) = −76.5 (0.5 in chloroform).

## EXAMPLE XI

Preparation of
(-)-1,9dihydroxy-3-n-pentyl-6,6,9-trimethyl-6a,10a-trans-6a,7,8.10,10a-hexahydrodibenzo-(b,d)-pyran
(Formula 7).

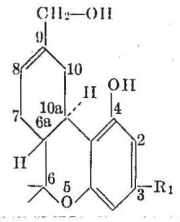
237 mg of the product of Example X are dissolved in 20 ml of ethanol. After addition of 50 mg of "Adams"-catalyst, the mixture is treated with hydrogen to effect hydrogenation of the double bond between positions 7 and 8. After filtration and evaporation of the solvent 192 mg of Formula 7 compound ($R_1$ = n-pentyl) are obtained.

The Rf value in chloroform/methanol 95:5 is 0.33.

Analytical data as well as IR, NMR and MS spectra confirm the structure given.

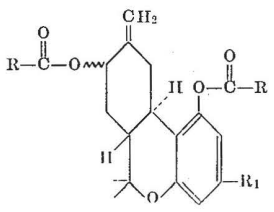
What is claimed is:

**1.** A process for preparing a compound of the formula



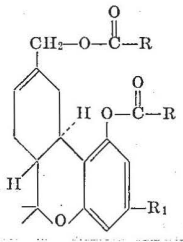
(1)

where $R_1$ is selected from the group consisting of straight and branched chain alkyl radicals containing from about 10 C-atoms, comprising the steps of (a) heating a compound of the formula



(2)

where R is selected from the group consisting of hydrogen and alkyl radicals of from 1 to about 5 C-atoms to form a compound of the formula



(3)

(b) reacting said formula (3) with a deacylation agent, and (c) recovering the formula (1) compound thus obtained.

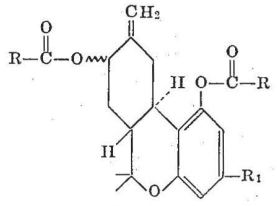
**2.** The process as claimed in claim **1**, wherein said compound of formula (2) is heated to a temperature in the range of from about 200°C to about 300°C.

**3.** The process as claimed in claim **2**, wherein said compound of formula (2) is heated to about 290°C.

**4.** The process as claimed in claim **1**, wherein $R_1$ is the n-pentyl radical.

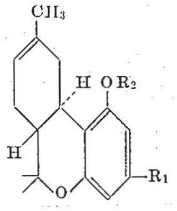
**5.** The process as claimed in claim **1**, wherein R is the methyl group.

**6.** A process for preparing a compound of the formula



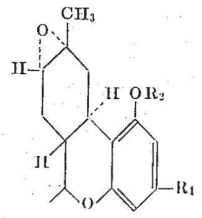
(2)

where R is selected from the group consisting of hydrogen and alkyl groups having from 1 to about 5 C-atoms, and $R_1$ is selected from the group consisting of straight and branched chaim alkyl radicals having from 1 to about 10 C-atoms, comprising the steps of reacting a compound of the formula

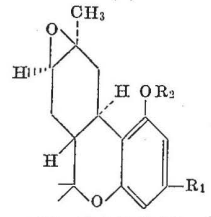


(10)

where $R_2$ is a protective group, with a peracid to obtain a compound of the formulae

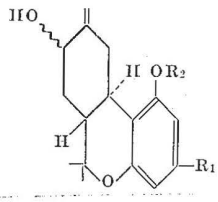


(4a)



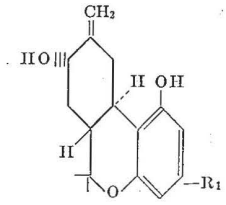
(4b)

reacting the compound (4b) with a base to produce a compound of the formula

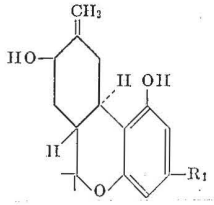


(12)

reacting the compound (12) with an agent capable of removing said $R_2$ group and forming compounds of the formulae



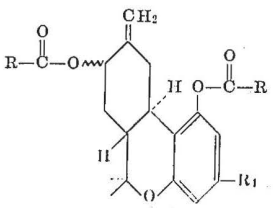
(5a)



(5b)

reacting compound (5*a*), (5*b*) with an acylating agent to yield compound (2).

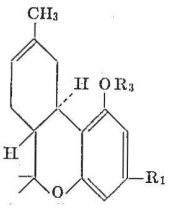
**7.** A process for preparing a compound of the formula



(2)

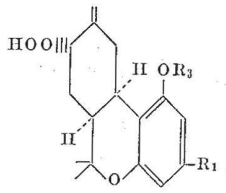
where R is selected from the group consisting of hydrogen and alkyl groups having from 1 to about 5 C-atoms, and $R_1$ is selected from the group consisting of straight and branched chain alkyl radicals having from 1 to about 10 C-atoms, comprising the steps of oxidizing a compound of the formula



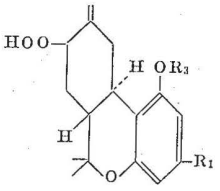


(11)

where $R_3$ is a protective group, by treatment with actinic radiation in the presence of oxygen to obtain compounds of the formulae

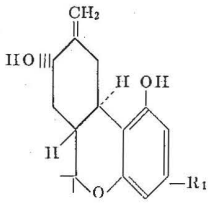


(8a)

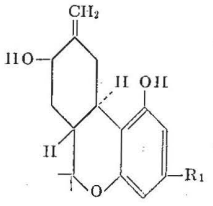


(8b)

reacting compounds (8*b*) with a reducing agent to obtain compounds of the formulae



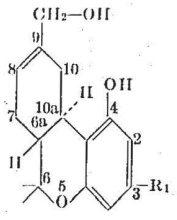
(5a)



(5b)

reacting compounds (5*a*), (5*b*) with an acylating agent to yield compound (2).

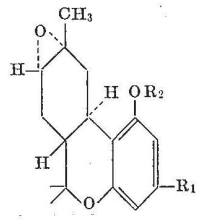
**8.** A compound of the formula



(1)

where $R_1$ is selected from the group consisting of straight and branched chain alkyl radicals containing from 1 to about 10 C-atoms, with the proviso that $R_1$ is not the n-pentyl group.

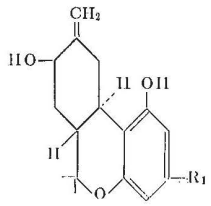
**9.** A compound of the formula



(4a)

where $R_1$ is selected from the group consisting of straight and branched chain alkyl radicals containing from 1 to about 10 C-atoms and $R_2$ is hydrogen.

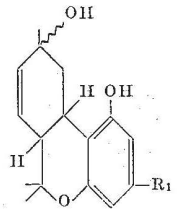
**10.** A compound of the formula



(5b)

where $R_1$ is selected from the group consisting of straight and branched chain alkyl radicals containing from 1 to about 10 C-atoms.

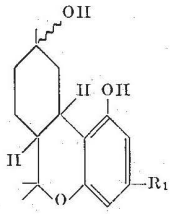
**11.** A compound of the formula



(6)

where $R_1$ is selected from the group consisting of straight and branched chain alkyl radicals containing from 1 to about 10 C-atoms.

**12.** A compound of the formula



(7)

where $R_1$ is selected from the group consisting of straight and branched chain alkyl radicals containing from 1 to about 10 C-atoms.

* * * * *

**ACTUAL PATENT URL LINK:**
**https://patentimages.storage.googleapis.com/81/5d/a0/be14f73c480ec4/US3873576.pdf**

**PATENT CURRENT ASSIGNEE URL LINK:**
**https://patents.google.com/patent/US3873576A/en?oq=us++3873576**

## Abstract

(-)-1-Hydroxy-3-alkyl-6,6-dimethyl-9-hydroxymethyl-6a,10a-trans6a,7,10,10a -tetrahydrodibenzo-(b,d)-pyrans (Formula 1) are produced in good yields from the corresponding 9-methylene-1,8di-acyl compounds (Formula 2) by thermal conversion of the latter into the corresponding 1,11-di-acyl compounds (Formula 3) which are converted into the target compound (Formula 1) by removal of the two acyl groups. Formula 1 compounds, where the alkyl group is a straight or branched chain alkyl of from 1-4 and 6-10 Catoms are novel homologues of the 3-n-pentyl compound, a metabolite of tetrahydrocannabinol known per se. Formula 1 compounds have bactericidic, sedative, analgetic and psychomimetic effect when applied to the human organism. Novel compounds (Formulae 4a, 5b, 6 and 7) are disclosed as starting materials and/or intermediates, some of them having pharmacological utility similar to the Formula 1 compounds.

## Images (2)


## Classifications

US3873576A
United States



**Inventor:** Theodor Petrzilka

**Worldwide applications**

1971 ~~CH~~ 1972 ~~US~~ DE JP ~~FR~~ ~~GB~~

**Application US295262A events**

**1971-10-14** • Priority to CH1496671A

**1972-10-05** • Application filed by Theodor Petrzilka

**1975-03-25** • Application granted

**1975-03-25** • Publication of US3873576A

**1992-03-25** • Anticipated expiration

**Status** • Expired - Lifetime