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Bindra

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[54] **9-HYDROXYDIBENZO[B,D]PYRANS AND INTERMEDIATES**

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[21] Appl. No.: **819,471**

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Related U.S. Application Data

[63] Continuation of Ser. No. 730,672, Oct. 7, 1976, abandoned, which is a continuation-in-part of Ser. No. 628,210, Nov. 3, 1975, abandoned.

[51] **Int. Cl.**[2] **A61K 31/35**; C07D 493/12

[52] **U.S. Cl.** ..... **424/248.55**; 424/250; 424/263; 424/274; 424/284; 544/150; 260/326.5 CA; 260/326.34; 546/196; 546/269; 546/187; 260/345.3; 546/194; 544/364; 544/375

[58] **Field of Search** ..... 260/296 T, 345.3, 268 H; 424/248, 250, 284; 544/150

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,901,926	8/1975	Winn et al.	260/297 R X
3,929,835	12/1975	Winn et al.	260/345.3
3,968,125	7/1976	Archer	260/345.3

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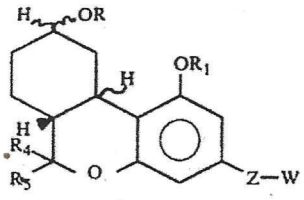
Attorney, Agent, or Firm—Connolly and Hutz

[57] **ABSTRACT**

9-Hydroxydibenzo[b,d]pyrans useful as analgesics, hypotensives, immunosuppressants, tranquilizers; as anti-secretory and anti-anxiety drugs; intermediates therefor and derivatives thereof having the formulae



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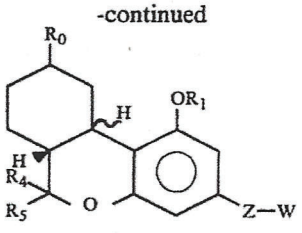
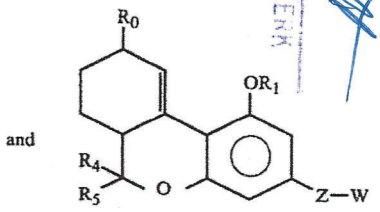


II

and



III

wherein R is hydrogen or alkanoyl having from one to five carbon atoms;

R_1 is hydrogen, alkanoyl having from one to five carbon atoms or —CO—$(CH_2)_p$—NR_2R_3 wherein p is 0 or an integer from 1 to 4; each of R_2 and R_3 when taken individually is hydrogen or alkyl having from one to four carbon atoms; R_2 and R_3 when taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring selected from piperidino, pyrrolo, pyrrolidino, morpholino and N-alkylpiperazino having from one to four carbon atoms in the alkyl group;

each of R_4 and R_5 is hydrogen, methyl or ethyl;

R_0 is oxo or alkylenedioxy having from two to four carbon atoms;

Z is

(a) alkylene having from one to nine carbon atoms;

(b) —$(alk_1)_m$—X—$(alk_2)_n$—wherein each of (alk_1) and (alk_2) has from 1 to 9 carbon atoms, with the proviso that the summation of carbon atoms in (alk_1) plus (alk_2) is not greater than 9;

each of m and n is 0 or 1;

X is O, S, SO or SO_2; and

W is methyl, phenyl, p-chlorophenyl, p-fluorophenyl, pyridyl, piperidyl, cycloalkyl having from 3 to 7 carbon atoms, or monosubstituted cycloalkyl wherein the substituent is phenyl, p-chlorophenyl or p-fluorophenyl;

with the proviso that when W is methyl, Z is

—$(alk_1)_m$—X—$(alk_2)_n$—.

21 Claims, No Drawings

EXAMPLE 7

dl-5-Hydroxy-3-Hydroxymethylene-2,2-Dimethyl-7-(2-Heptyloxy)-4-Chromanone

To the sodium hydride obtained by washing 9.23 g. (192 mM) of 50% sodium hydride in mineral oil dispersion with pentane is added dropwise, over a 30 minute period, a solution of dl-5-hydroxy-2,2-dimethyl-7-(2-heptyloxy)-4-chromanone (5.90 g., 19.2 mM) and ethyl formate (34.9 ml., 432 mM). After the addition is complete, ether (475 ml.) is added and the resulting mixture refluxed. After 18 hours, the reaction mixture is cooled to room temperature and acidified with 1N hydrochloric acid. The organic layer is separated and the aqueous layer is further extracted with ether (3 × 125 ml.). The combined ether extracts are dried over sodium sulfate and concentrated under vacuum to yield 6.41 g. (>100%) of dl-5-hydroxy-3-hydroxymethylene-2,2-dimethyl-7-(2-heptyloxy)-4-chromanone as an oil.

NMR $\delta_{CDCl_3}^{TMS}$ 13.4 (one broad singlet proton, hydroxylic), 11.8 (one proton singlet, phenolic hydroxylic, 7.4 (one broad proton singlet, vinyl), 6.1 6.0 (2 one proton doublets, J = 3Hz, aromatic), 4.8–4.2 (one proton multiplet, methine), 2.1–0.7 (20 proton multiplet for the remaining protons).

In like manner, appropriate reactants of Example 6 are converted to: dl-5-hydroxy-3-methylene-2,2-dimethyl-7-[2-(5-phenyl)pentyloxy]-4-chromanone, an oil.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.3 (D,3,α-methyl, J = 7 Hz), 1.3–2.0 (M,4, ethylene), 1.4 (S,6,gem dimethyl), 2.3–2.8 (bd., T,2-benzylic methylene), 4.1–4.7 (M,1,methine), 5.8–6.0 (M,2,aromatic), 7.0–7.4 (M,6,aromatic and vinylic), 10.0 (S,1,phenolic), 13.3 (bd,S,1,hydroxylic);

dl-5-hydroxy-3-hydroxymethylene-2,2-dimethyl-7-[2-(4-phenyl)butyloxy]-4-chromanone, an oil;

dl-5-hydroxy-3-hydroxymethylene-2,2-dimethyl-7-cyclohexyloxy-4-chromanone;

IR (Kbr) C=O 1620 cm^{-1}; OH 3420 cm^{-1}

MS: (mol.ion) 318

NMR: $\delta_{CDCl_3}^{TMS}$ 1.1–2.3 (M,10,C_5H_{10}-cyclohexyl), 1.55 (S,6,gem dimethyl), 4.1–4.5 (M,1-cyclohexylmethinyl), 3.9–6.1 (M,2,aromatic), 7.1–7.5(d,l,methinyl), 11.6 (S,1,hydroxyl, D_2O overlay).

dl-5-hydroxy-3-hydroxymethylene-2,2-dimethyl-7-(1-methyl-3-phenoxypropyl)-4-chromanone, an oil (from reactant of Example 1):

R_f = 0.42 (silica gel, 18-benzene:1-ethyl acetate)

MS: (mol.ion) 368

EXAMPLE 8

dl-6a,7-Dihydro-1-Hydroxy-6,6-Dimethyl-3-(2-Heptyloxy)-6H-Dibenzo-[b,d]pyran-9(8H)-One

To a solution of dl-5-hydroxy-3-hydroxymethylene-2,2-dimethyl-7-(2-heptyloxy)-4-chromanone (5.17 g., 15.4 mM) and methylvinyl ketone (2.27 ml., 27.9 mM) in methanol (23 ml.) is added triethylamine (0.54 ml.). The reaction is stirred for 16 hours at room temperature and then diluted with ether (250 ml.). The resulting ether solution is extracted with 10% sodium carbonate (6 × 30 ml.), dried over sodium sulfate, and concentrated under vacuum to yield 6.11 g. of an oil. The residue is refluxed with ethanol (45 ml.) and 2N potassium hydroxide (45 ml.) for 16 hours. Thereafter, the reaction solution is cooled, acidified with 6N hydrochloric acid and extracted with dichloromethane (3 × 100 ml.). The organic phase is dried over sodium sulfate and evaporated to yield 6.3 g. of a dark solid. The solid is triturated in hot ether to yield 1.00 g. of the title compound, m.p. 185°–189° C.; 1.26 g. of further material is obtained via silica gel chromatography of the mother liquor. The total yield is 42.3%.

NMR ($CDCl_3$) δ 11.2 (one broad proton singlet, phenolic OH), 7.9 (one broad proton singlet, vinyl), 6.2, 5.9 (two one proton doublets, J ≅ 3Hz, aromatic protons), 4.6–4.0 (one proton multiplet, methine ether), 3.0–0.6 (25 proton multiplet, remaining protons).

IR (KBr) C = O 1600 cm^{-1}.

Analysis: Calc'd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44%. Found: C, 73.41; H, 8.37%.

UV $\lambda_{max}^{CH_3CH_2OH}$ = 342 mμ(ε = 26,800).

The following compounds are similarly prepared from appropriate reactants of Example 7:

dl-6a,7-dihydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6H-dibenzo[b,d]pyran-9(8H)-one;

m.p. 140°–168° C;

NMR: $\delta_{CDCl_3}^{TMS}$ 1.3 (D,2,α-methyl, J = 7 Hz), 1.1–2.3 (M,15,remaining protons), 2.3–3.0 (bd,T,2,benzylic-methylene), 4.1–4.7 (M,1,methine), 5.95 (D,1,aromatic, J = 2 Hz), 6.3 (D,1,aromatic, J = 2 Hz), 7.2–7.4 (M,5,aromatic), 8.0 (D,1,vinylic, J = 2 Hz).

IR: (KBr) C = O 1563 cm^{-1}

Analysis: Calc'd for $C_{26}H_{30}O_4O$: C, 76.82; H, 7.44%. Found: C, 76.74; H, 7.48%.

MS: (mol.ion) 406

dl-6a,7-dihydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenylbutoxy)-6H-dibenzo[b,d]pyran-9(8H)-one;

M.P. 163° C.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.2, 1.3 (d,3,methyl), 1.45 (S,6,gem dimethyl), 1.65–2.2 (M,2,methylene), 2.3–2.95 (M,4,methylene,benzylic methylene), 4.1–4.6 (M,1, methinyl), 5.9, 6.15 (2d,2,aromatic), 7.15 (S,6,aromatic, hydroxyl-D_2O overlay), 7.95 (6S,1,olefinic proton).

MS: (mol.ion) 392

dl-6a,7-dihydro-1-hydroxy-6,6-dimethyl-3-cyclohexyloxy-6H-dibenzo[b,d]pyran-9(8H)-one;

M.P. 259°–254° C.

IR (KBr) C=O 1590 cm^{-1}; OH 3390 cm^{-1}

NMR: δ_{DMSO} 1.05–3.0 (M,15,C_5H_{10}-cyclohexyl, 6a-methinyl, 7-methylene, 8-α-methylene), 1.45 (S,6,gem, dimethyl), 4.0–4.4 (M,1,methinyl), 5.8–6.1 (2d,2,aromatic), 7.1–7.25 (d,l,olefinic proton), 7.3 (S,1,hydroxyl-D_2O overlay).

dl-6a,7-dihydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenoxypropyl)-6H-dibenzo[b,d]pyran-9(8H)-one, a light yellow solid:

M.P. 203°–206° C.

MS: (mol.ion) 392

Analysis: Calc'd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19%. Found: C, 76.33; H, 7.12%.

EXAMPLE 9

dl-6aβ,7,10,10aα-Tetrahydro-1-Hydroxy6,6-Dimethyl-3-(2-Heptyloxy)-6H-Dibenzo[b,d]pyran-9(8H)-One

A solution of dl-6aβ,7-dihydro-1-hydroxy-6,6-dimethyl-3-(2-heptyloxy)-6H-dibenzo[b,d]pyran-9(8H)-one (1.2 g., 3.3 mM) in tetrahydrofuran (9 ml.) is added dropwise to a rapidly stirred solution of lithium (25 mg.) in liquid ammonia (45 ml.) at −78° C. During the addition an additional 75 mg. of lithium is added to insure the blue color. After an additional 15 minutes of stirring solid ammonium chloride is added to discharge the blue color. The excess ammonia is allowed to evaporate and the residue was diluted with water (45 ml.) and acidified with 10% hydrochloric acid. The aqueous

solution is extracted with dichloromethane (3 × 50 ml.) and the dichloromethane extracts dried over sodium sulfate and evaporated to yield 1.30 g. of a crude semi-solid which is purified via silica gel column chromatography to yield 0.614 g. (50.9%) of product, m.p. 155°–158° C. after recrystallization from chloroform-/hexane.

NMR ($CDCl_3$) δ - 8.2 (one proton singlet, phenolic OH), 5.8–6.3 (2 proton multiplet, aromatic), 3.9–4.6 (2 proton multiplet, methine ether and C-10 equatorial), 0.3–3.2 (26 proton multiplet, remaining protons).

IR (KBr) C = O 1737 cm^{-1}.

MS (m/e) 360 (M+), 261 (M-99).

Analysis: Calc'd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95%. Found: C, 73.05; H, 8.82%.

and the corresponding cis-isomer:

dl-6aβ,7,10,10aβ-tetrahydro-1-hydroxy-6,6-dimethyl-3-(2-heptyloxy)-6H-dibenzo[b,d]pyran-9(8H)-one, m.p. 141°–146° C. (from ether/hexane).

IR: (KBr) C=O 1718 cm^{-1}.

MS (m/e) 360 (M^+), 261 (M-99)

Similarly, the following compounds are prepared from products of Example 8:

dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6H-dibenzo[b,d]pyran-9(8H)-one; m.p. 122°–125° C.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.3 (D,3α-methyl,J=7Hz), 1.1–3.0 (M,16, remaining protons), 2.3–3.0 (bd.T,2,benzylic methylene), 4.1 (bd.D,1,C-10 equatorial,J=14Hz), 4.1–4.7 (M,1,methine), 5.95 (D,1,aromatic,J=2Hz), 6.1 (D,1,aromatic,J=2Hz), 7.2–7.4 (M,5,aromatic), 7.9 (S,1,phenolic).

IR: (KBr) C=O 1709 cm^{-1}

Analysis: Calc'd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90%. Found: C, 76.22; H, 7.79%.

and the corresponding cis-isomer:

dl-6aβ,7,10,10aβ-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6H-dibenzo[b,d]pyran-9(8H)-one, m.p. 141°–142° C.

IR: (KBr) C=O 1707 cm^{-1}

MS: (mol.ion) 408

Analysis: Calc'd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.90%. Found: C, 76.58; H, 7.92%.

dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenylpropoxy)-6H-dibenzo[b,d]pyran-9(8H)-one, m.p. 160° C.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.2, 1.3 (d,2, -methyl), 1,4 (S,6,gem dimethyl), 1.65–2.9 (M,11,remaining protons), 3.9–4.5 (M,2,10aα-proton, methinyl), 5.9–6.1 (2d,2, aromatic), 7.2 (S,5,aromatic), 7.9 (S,1,hydroxyl-D_2O overlay)

MS: (mol.ion) 394

dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-cyclohexyloxy-6H-dibenzo[b,d]pyran-9(8H)-one, m.p. 215°–218° C.

IR (KBr) C=O 1695 cm^{-1}; OH 3225 cm^{-1}

MS: (mol.ion) 344

NMR: $\delta_{CDCl_3}^{TMS}$ 1.0–3.2 (M,18,C_5H_{10} -cyclohexyl, 6aβ,7,8,10,10aβ-protons), 1.5 (S,6,gem dimethyl), 3.9–4.3 (M,1,cyclohexyl-methinyl), 5.9, 6.05 (2d,2, aromatic), 8.9 (bs,1,hydroxyl-D_2O overlay).

dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenoxypropyl)-6H-dibenzo[b,d]pyran-9(8H)-one:

M.P. 167°–170° C.

MS: (mol.ion) 394

Analysis: Calc'd for $C_{25}H_{30}O_4$: C, 76.11 H, 7.66%. Found: C, 75.93; H, 7.63; %.

NMR $\delta_{CDCl_3}^{TMS}$ 7.87 (S,1,phenolic proton), 7.42–6.67 (M,5, C_6H_5), 6.33 (S,2,aromatic H_2 + H_5), 4.42–1.00 (M,22,non-aromatics—including triplet centered at 3.90 for —CH_2—O—, singlet at 1.48 for CH_3, doublet centered at 1.27 for CH_3, singlet at 1.13 for CH_3 and 11 other methylene, methine protons).

EXAMPLE 10

dl-6aβ,7,8,9,10,10aα-Hexahydro-1-6,6-Dimethyl-3-(2-Heptyloxy)-6H-Dibenzo[b,d]pyran-9β-ol

To a solution dl-β6aβ,7,10,10aα-tetrahydr-1-hydroxy-6,6-dimethyl-3-(2-heptyloxy)-6-H-dibenzo[b,d]pyran-9(8H)-one (0.60 g., 1.66 mM) in ethanol (18 ml.), stirred at room temperature under nitrogen is added sodium borohydride (275 mg.). The reaction is stirred for 30 minutes and poured onto a mixture of ice (35 ml.), 10% hydrochloric acid (35 ml.) and ether (200 ml.). The ether layer is separated and the aqueous layer extracted with additional ether (2 × 100 ml.). The combined ether extracts are dried over sodium sulfate and evaporated to an oil. Crystallization from hexane yielded 305 mg. (50.3%) of product, m.p. 102°–104° C.

NMR $\delta_{CDCl_3}^{TMS}$ - 7.9–6.7 (one broad proton singlet, hydroxylic), 6.1–5.8 (two broad proton singlet, aromatic), 4.5–0.5 (31 proton multiplet, remaining protons).

IR (KBr) OH 3390 cm^{-1}.

Analysis: Calc'd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45%. Found: C, 72.52; H, 9.18%.

Similarly, the following are prepared from appropriate tetrahydro compounds:

dl-6aβ,7,8,9,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6H-dibenzo[b,d]pyran-9β-ol, an amorphous solid.

IR: (KBr) OH 3390 cm^{-1}

MS: (mol.ion) 410

(NMR: $\delta_{CDCl_3}^{TMS}$ 1.3 (P,3,α-methyl), 1.0–4.5 (M,24,remaining protons), 5.8–6.0 (M,2,aromatic), 6.8–7.3 (M,5,aromatic).

dl-6aβ,7,8,9,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenylpropyloxy)-6H-dibenzo[b,d]pyran-9β-ol, an amorphous solid.

MS: (mol.ion) 396

dl-6aβ,7,8,9,10,10aα-1-hydroxy-6,6-dimethyl-3-cyclohexyloxy-6H-dibenzo[b,d]pyran-9β-ol:

M.P. 214°–216° C.

IR (KBr) OH 3365 cm^{-1}; 3125 cm^{-1}

MS: (mol.ion) 346

NMR: $\delta_{CDCl_3}^{TMS}$ [1.0–3.0 (M,23,C_5H_{10}-cyclohexyl,-gem dimethyl, 7,8,9α,10 protons), 3.5–4.15 (M,2,6aβ,-10aα protons), 4.35–4.7 (M,1,cyclohexyl-methinyl), 4.85–5.05 (bd,1,hydroxyl-D_2O overlay), 6.1–6.45 (M,2,aromatic), 9.7 (S,1,hydroxyl-D_2O overlay).

dl-6aβ,7,8,9,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenoxypropyl)-6H-dibenzo[b,d]pyran-9β-ol:

M.P. 151°–152° C.

R_f = 0.25 (silica gel, 9-ether:1hexane)

MS: (mol.ion) 396

Analysis: Calc'd for $C_{25}H_{32}O_4$: C, 75.72; H, 8.14%. Found: C, 75.79; H, 8.39%.

dl-6aβ,7,8,9,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenoxypropyl)-6H-dibenzo[b,d]pyran-9α-ol; an oil.

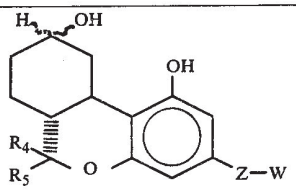
R_f = 0.35 (silica gel, 9-ether:1-hexane)

MS: (mol.ion) 396

EXAMPLE 11

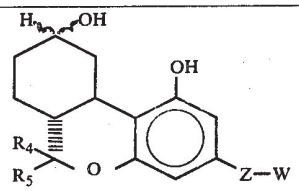
The following compounds are prepared according to the procedures of Examples 1–5 from appropriate (3,5-dihydroxy)phenyl compounds of the formula 3,5-

$(HO)_2C_6H_3$—Z—W and the appropriate acid of formula R_4R_5C=CH—COOH.



R_4	R_5	Z	W
CH_3	CH_3	$-(CH_2)_6-$	C_6H_5
H	H	$-(CH_2)_7-$	C_6H_5
CH_3	CH_3	$-(CH_2)_8-$	C_6H_5
CH_3	H	$-CH(CH_3)(CH_2)_5-$	C_6H_5
C_2H_5	C_2H_5	$-CH(CH_3)(CH_2)_6-$	C_6H_5
CH_3	CH_3	$-CH(CH_3)(CH_2)_7-$	C_6H_5
H	H	$-CH(CH_3)(CH_2)_3-$	$4\text{-}FC_6H_4$
CH_3	C_2H_5	$-C(CH_3)_2(CH_2)_3-$	C_6H_5
CH_3	CH_3	$-(CH_2)_3-CH(CH_3)-$	C_6H_5
CH_3	H	$-CH(CH_3)(CH_2)_2CH(CH_3)-$	C_6H_5
C_2H_5	H	$-CH(CH_3)(CH_2)_3-$	$4\text{-}ClC_6H_4$
C_2H_5	C_2H_5	$-CH(CH_3)(CH_2)_4-$	$4\text{-}ClC_6H_4$
CH_3	CH_3	$-CH(CH_3)(CH_2)_2-$	$4\text{-}ClC_6H_4$
H	H	$-CH(CH_3)(CH_2)-$	$4\text{-}ClC_6H_4$
CH_3	CH_3	$-CH(CH_3)(CH_2)-$	$4\text{-}FC_6H_4$
CH_3	CH_3	$-CH(CH_3)(CH_2)_2-$	4-pyridyl
H	H	$-(CH_2)_3$	2-pyridyl
C_2H_5	H	$-(CH_2)_3$	3-pyridyl
CH_3	CH_3	$-(CH_2)_3$	4-pyridyl
H	C_2H_5	$-(CH_2)_3$	2-piperidyl
H	H	$-(CH_2)_3$	4-piperidyl
CH_3	H	$-(CH_2)_4$	2-pyridyl
C_2H_5	H	$-(CH_2)_4$	4-pyridyl
C_2H_5	C_2H_5	$-(CH_2)_4$	3-piperidyl
CH_3	CH_3	$-(CH_2)_4$	4-piperidyl
H	H	$-(CH_2)_2$	C_6H_5
H	H	$-CH(CH_3)(CH_2)_2-$	$4\text{-}FC_6H_4$
CH_3	H	$-CH(CH_3)(CH_2)_2-$	$4\text{-}ClC_6H_4$
C_2H_5	C_2H_5	$-CH(CH_3)(CH_2)_2-$	C_6H_5
H	H	$-CH(CH_3)(CH_2)_3-$	C_6H_5
CH_3	CH_3	$-CH_2CH(CH_3)CH_2-$	2-pyridyl
H	H	$-CH_2CH(CH_3)CH_2-$	4-piperidyl
C_2H_5	H	$-CH(CH_3)CH(CH_3)CH_2-$	3-pyridyl
C_2H_5	C_2H_5	$-CH(CH_3)CH(CH_3)CH_2-$	4-pyridyl
H	H	$-CH(CH_3)CH(CH_3)CH_2-$	3-piperidyl
CH_3	C_2H_5	$-CH(CH_3)(CH_2)_2-$	2-pyridyl
CH_3	C_2H_5	$-CH(CH_3)(CH_2)_2-$	3-pyridyl
CH_3	CH_3	$-CH(CH_3)(CH_2)_2-$	4-piperidyl
H	H	$-CH(CH_3)(CH_2)_3-$	3-pyridyl
CH_3	CH_3	$-CH(CH_3)(CH_2)_3-$	4-piperidyl
CH_3	CH_3	$-CH(CH_3)CH(C_2H_5)CH_2-$	4-pyridyl
C_2H_5	CH_3	$-CH(C_2H_5)(CH_2)_2-$	4-pyridyl
C_2H_5	H	$-CH(C_2H_5)(CH_2)_2-$	2-piperidyl
H	H	$-CH(C_2H_5)(CH_2)_2-$	4-piperidyl
CH_3	H	$-CH_2CH(C_2H_5)CH_2-$	3-pyridyl
CH_3	CH_3	$-CH(C_2H_5)(CH_2)_3-$	3-pyridyl
CH_3	CH_3	$-CH(C_2H_5)(CH_2)_3-$	4-pyridyl
C_2H_5	C_2H_5	$-CH(C_2H_5)CH(CH_3)CH_2-$	2-pyridyl
H	H	$-CH(C_2H_5)CH(C_2H_5)CH_2-$	4-pyridyl
H	H	$-CH(C_2H_5)CH(C_2H_5)CH_2-$	2-piperidyl
CH_3	CH_3	$-(CH_2)_3CH(CH_3)-$	C_6H_5
CH_3	CH_3	$-(CH_2)_3CH(CH_3)-$	$4\text{-}FC_6H_4$
CH_3	CH_3	$-(CH_2)_3CH(CH_3)-$	4-pyridyl
H	H	$-(CH_2)_3CH(CH_3)-$	C_6H_{11}
CH_3	CH_3	$-(CH_2)_3CH(CH_3)-$	C_6H_{11}
CH_3	CH_3	$-CH(CH_3)(CH_2)_2CH(CH_3)-$	C_6H_5
CH_3	H	$-CH(CH_3)(CH_2)_2CH(CH_3)-$	C_6H_{11}
C_2H_5	C_2H_5	$-CH(CH_3)(CH_2)_2CH(CH_3)-$	4-piperidyl
CH_3	CH_3	$-CH(CH_3)(CH_2)_3-$	C_6H_{11}
H	H	$-CH(CH_3)(CH_2)_2CH(CH_3)-$	C_6H_{11}
C_2H_5	C_2H_5	$-(CH_2)_3-$	C_6H_{11}
CH_3	H	$-(CH_2)_4-$	C_6H_{11}
CH_3	C_2H_5	$-(CH_2)_8-$	C_6H_{11}
CH_3	CH_3	$-(CH_2)_2-$	C_4H_7
CH_3	CH_3	$-CH_2CH(CH_3)CH_2-$	C_5H_9
H	CH_3	$-CH_2CH(CH_3)CH_2-$	C_5H_9
CH_3	CH_3	$-CH(CH_3)(CH_2)_2-$	C_7H_{13}
H	H	$-CH(CH_3)CH(CH_3)CH_2-$	C_6H_{11}
CH_3	CH_3	$-CH(CH_3)(CH_2)_3-$	C_5H_9
CH_3	CH_3	$-(CH_2)_4-$	C_6H_5
CH_3	CH_3	$-(CH_2)_2CH(C_2H_5)-$	C_6H_5
CH_3	CH_3	$-C(CH_3)_2-$	C_6H_5
H	CH_3	$-CH(CH_3)CH_2CH(C_2H_5)-$	C_6H_5
H	CH_3	$-CH(CH_3)CH_2-$	C_5H_9
H	CH_3	$-CH(CH_3)CH_2-$	C_3H_5
C_2H_5	H	$-CH(CH_3)CH(CH_3)-$	C_6H_{11}
CH_3	CH_3	$-CH(CH_3)(CH_2)_4-$	C_5H_9

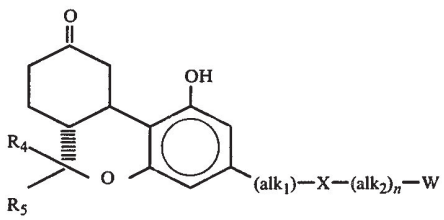
-continued



R_4	R_5	Z	W
CH_3	CH_3	$-CH(C_2H_5)(CH_2)_2-$	C_6H_5

EXAMPLE 12

Compounds of the following formula are obtained from appropriate reactants of Preparations K and Y and appropriate acids of formula R_4R_5C=CH—COOH by the procedures of Examples 1–4 (R_4 and R_5 = H, CH_3 or C_2H_5):



Reduction of the keto compounds with sodium borohydride according to the procedure of Example 5 affords the corresponding 9-hydroxy compounds (both isomers formed; the β-form predominates). The sulfoxide and sulfone compounds of Examples 15 and 16 are reduced in like manner to the corresponding 9-hydroxy compounds.

EXAMPLE 13

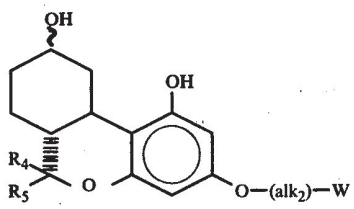
dl-5-Hydroxy-2,2-dimethy-7-(1-methyl-4-phenylbutoxy)-4-chromanone

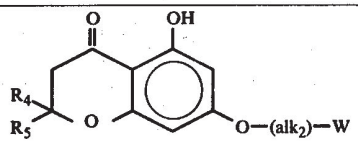
A mixture of 5-phenyl-2-pentanol (16.4 g., 100 mM), triethylamine (28 ml., 200 mM) and dry tetrahydrofuran (80 ml.) under a nitrogen atmosphere is cooled in an ice/water bath. Methanesulfonyl chloride (8.5 ml., 110 mM) in dry tetrahydrofuran (20 ml.) is added dropwise at such a rate that the temperature holds essentially constant. The mixture is allowed to warm to room temperature and is then filtered to remove triethylamine hydrochloride. The filter cake is washed with dry tetrahydrofuran and the combined wash and filtrate evaporated under reduced pressure to give the product as an oil. The oil is dissolved in chloroform (100 ml.) and the solution washed with water (2 × 100 ml.) and then with saturated brine (1 × 20 ml.). Evaporation of the solvent affords 21.7 g. (89.7%) yield of 5-phenyl-2-pentanol mesylate which is used in the next step without further purification.

A mixture of 2,2-dimethyl-5,7-dihydroxy-4-chromanone (2.08 g., 10 mM), potassium carbonate (2.76 g., 20 mM), N,N-dimethylformamide (10 ml.) and 5-phenyl-2-pentanol mesylate (2.64 g., 11 mM), under a nitrogen atmosphere, is heated to 80°–82° C. in an oil bath for 1.75 hours. The mixture is cooled to room temperature and then poured into ice/water (100 ml.). The aqueous solution is extracted with ethyl acetate (2 × 25 ml.) and the combined extracts washed successively with water

(3 × 25 ml.) and saturated brine (1 × 25 ml.). The extract is then dried ($MgSO_4$), decolorized with charcoal and evaporated to give the product as an oil which crystallizes upon seeding with pure product; m.p. 83°–84° C. Yield = quantitative.

In like manner, the following compounds are prepared from appropriate 2,2-R_4R_5-5,7-dihydroxy-4-chromanones and appropriate alkanols. The necessary alkanol reactants not previously described in the literature are prepared from appropriate aldehydes or ketones via the Wittig reaction of Preparation G.





R_4	R_5	alk_2	W	alk_2	W	R_4	R_5
CH_3	CH_3	$CH_2C(CH_3)_2(CH_2)_4$	CH_3	$(CH_2)_3$	3-pyridyl	CH_3	CH_3
CH_3	CH_3	$CH_2CH(CH_3)(CH_2)_2CH(CH_3)CH_2$	CH_3	$(CH_2)_3$	4-pyridyl	CH_3	H
CH_3	H	$CH(CH_3)CH_2CH(CH_3)CH_2CH(CH_3)$	CH_3	$(CH_2)_4$	2-pyridyl	CH_3	C_2H_5
CH_3	H	$(CH_2)_2CH(CH_3)CH_2CH(CH_3)$	CH_3	$(CH_2)_3$	2-piperidyl	H	H
H	H	$CH(CH_3)(CH_2)_2C(CH_3)_2$	CH_3	$(CH_2)_3$	4-piperidyl	CH_3	H
C_2H_5	C_2H_5	$CH_2CH(C_2H_5)$	C_6H_5	$(CH_2)_3$	4-FC_6H_4	CH_3	CH_3
CH_3	C_2H_5	$CH_2CH_2CH(CH_3)$	C_6H_5	$(CH_2)_3$	4-ClC_6H_4	H	H
CH_3	CH_3	$(CH_2)_4$	C_6H_5	$(CH_2)_4$	C_6H_5	C_2H_5	H
H	H	$(CH_2)_4CH(C_2H_5)$	C_6H_5	$(CH_2)_4$	4-FC_6H_4	C_2H_5	H
H	CH_3	$(CH_2)_7$	C_6H_5	$CH(CH_3)(CH_2)_2$	2-pyridyl	H	H
H	H	$CH(CH_3)(CH_2)_5$	C_6H_5	$CH(CH_3)(CH_2)_2$	3-pyridyl	C_2H_5	C_2H_5
C_2H_5	H	$(CH_2)_9$	C_6H_5	$CH(CH_3)(CH_2)_3$	4-pyridyl	CH_3	CH_3
CH_3	CH_3	$(CH_2)_9$	CH_3	$CH(CH_3)(CH_2)_2$	4-piperidyl	CH_3	CH_3
H	CH_3	$CH(CH_3)CH_2$	2-pyridyl	$CH(C_2H_5)(CH_2)_2$	2-pyridyl	H	CH_3
H	C_2H_5	$CH_2C(CH_3)_2$	2-pyridyl	$CH(C_2H_5)(CH_2)_2$	4-pyridyl	CH_3	CH_3
H	CH_3	$(CH_2)_3$	2-pyridyl	$CH(C_2H_5)(CH_2)_2$	4-piperidyl	C_2H_5	CH_3
C_2H_5	CH_3	$(CH_2)_2$	2-pyridyl	$CH(CH_3)(CH_2)_2$	4-FC_6H_4	H	C_2H_5
H	H	$(CH_2)_2$	4-pyridyl	$CH(CH_3)(CH_2)_2$	4-ClC_6H_4	CH_3	H

R_4	R_5	alk_2	W	R_4	R_5	alk_2	W
CH_3	CH_3	CH_2	C_6H_5	CH_3	CH_3	—	4-pyridyl
H	H	CH_2	C_6H_5	CH_3	CH_3	—	4-piperidyl
CH_3	CH_3	CH_2	4-FC_6H_4	CH_3	H	—	2-$(C_6H_5)C_6H_{10}$
CH_3	CH_3	—	C_6H_5	H	H	—	4-$(C_6H_5)C_6H_{10}$
CH_3	CH_3	—	4-FC_6H_4	CH_3	CH_3	—	3-$(C_6H_5)C_7H_{12}$
C_2H_5	H	—	4-ClC_6H_4	CH_3	CH_3	$—CH_2—$	CH_3
C_2H_5	C_2H_5	—	C_6H_5	CH_3	CH_3	$—(CH_2)_3—$	CH_3
H	H	—	4-FC_6H_4	CH_3	CH_3	$—(CH_2)_6—$	CH_3
CH_3	CH_3	—	C_3H_5	CH_3	CH_3	$—(CH_2)_9—$	CH_3
H	H	—	C_3H_5	CH_3	H	$—(CH_2)_6—$	CH_3
CH_3	CH_3	—	C_4H_7	C_2H_5	C_2H_5	$—(CH_2)_3—$	CH_3
CH_3	H	—	C_4H_7	CH_3	CH_3	$—C(CH_3)_2(CH_2)_5—$	CH_3
C_2H_5	C_2H_5	—	C_5H_9	CH_3	H	$—C(CH_3)_2(CH_2)_5—$	CH_3
CH_3	CH_3	—	C_5H_9	CH_3	CH_3	$—CH(CH_3)CH(CH_3)—(CH_2)_4—$	CH_3
CH_3	H	—	C_6H_{11}				
CH_3	H	—	C_7H_{13}				
CH_3	CH_3	—	2-$(C_6H_5)C_3H_4$				
CH_3	CH_3	—	1-$(C_6H_5)C_4H_6$				
CH_3	CH_3	—	2-$(C_6H_5)C_5H_8$				
CH_3	H	—	2-$(C_6H_5)C_5H_8$				
CH_3	CH_3	—	4-$(C_6H_5)C_6H_{10}$				
C_2H_5	C_2H_5	—	3-$(C_6H_5)C_6H_{10}$				

EXAMPLE 14

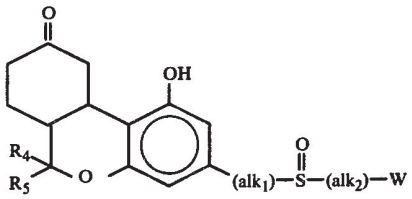
The products of Example 13 are converted to compounds having the formula below by the procedures of Examples 1–5.

EXAMPLE 15

dl-6aβ,7,10,10aα-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenylsulfinylpropyl)-6H-dibenzo[b,d]-pyran-9(8H)-one

Equimolar amounts of m-chloroperbenzoic acid and dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenylthiopropyl)-6H-dibenzo[b,d]pyran-9(8H)-one are reacted together in a mixture of chloroform and acetic acid (2:1) at room temperature for 1 hour. The organic phase is washed with water, dried ($MgSO_4$) and evaporated to dryness to give the product.

In like manner the thio others of Example 12 are oxidized to the corresponding sulfoxides of formula

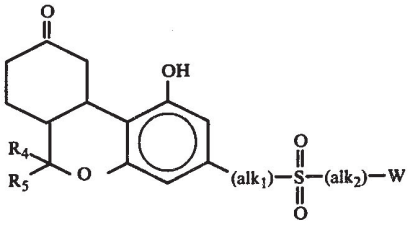


EXAMPLE 16

dl-6aβ,7,10,10aα-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-3-phenylsulfonylpropyl)-6H-dibenzo[b,d]-pyran-9(8H)-one

The procedure of Example 15 is repeated but using two equivalents of m-chloroperbenzoic acid as oxidizing agent per mole of thio ether reactant.

Similarly, the thio ethers of Example 12 are converted to their corresponding sulfonyl derivatives to give compounds of the formula:



EXAMPLE 17

(−)-Trans 3-(1-methyl-4-phenylbutyl)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran-1-β-ol

To a stirred solution of (+) p-mentha-2,8-dien-1-ol (4.9 g., 0.0322 mole) and 5-(1-methyl-4-phenylbutyl)-resorcinol (8.2 g., 0.032 mole) in dry methylene chloride (200 ml.) is added anhydrous magnesium sulfate (4 g., 0.332 mole). The mixture is stirred under a nitrogen atmosphere and cooled to 0° C. Freshly distilled boron trifluoride etherate (2 ml., 0.016 mole) is then added dropwise over a 5 minute period. The reaction mixture is stirred for 1.5 hours at 0° C. and anhydrous sodium bicarbonate (10 g., 0.119 mole) is added. Stirring is continued until the dark color fades. The reaction mixture is filtered and evaporated to give 11.7 g. (93.6%) of a resinous product. The product is purified via column chromatography on an activated magnesium silicate, available from M C & B Manufacturing Chemists, 2909 Highland Avenue, Cincinnati, Oh., under the trademark "Florisil", to give 3.4 g. (27%) of the desired product as a mixture of optically active diasteriomers.*

*$[\alpha]_d^{25}$ (C = 1.0, $CHCl_3$) = −100.8°.

NMR $\delta_{CDCl_3}^{TMS}$ 1.1 (S,3,C_1-methyl), 1.3, 1.45 (2S,6,gem dimethyls), 1.75 (S,3,C_9-methyl), 0.7–3.0 (M,12,remaining protons), 3.0–3.6 (M,1,C_{10a}-proton), 5.05 (S,1,hydroxyl,D_2O overlay), 6.1 (S,1,C_4-proton, aromatic), 6.4 (M,2,C_2-proton,aromatic,C_{10}-proton), 7.1–7.5 (M,5,aromatic protons).

MS: (mol.ion) 390

It is converted to the optically active 6aβ,7,10,10aα-tetrahydro-1-hydroxy-3-(1-methyl-4-phenylbutyl)-6,6-dimethyl-6H-dibenzo[b,d]pyran-9(8H)-one diasteriomers according to the procedure of Wildes et al., *J. Org. Chem.*, 36, 721–3 (1971)

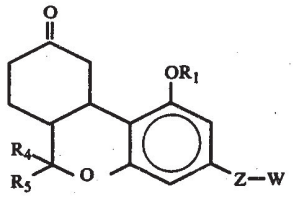
EXAMPLE 18

dl-6aβ,7,10,10aα-tetrahydro-1-(4-morpholinobutyryloxy)-6,6-dimethyl-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]pyran-9(8H)-one hydrochloride

To a stirred solution of dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]pyran-9(8H)-one (0.52 g., 1.28 mM) in dry methylene chloride (25 ml.) is added 4-morpholinobutyric acid hydrochloride (0.268 g., 1.28 mM). The mixture is stirred at room temperature under a nitrogen atmosphere. A 0.1 M solution of dicyclohexylcarbodiimide in methylene chloride (12.8 ml., 1.28 mM) is added dropwise and the mixture stirred for 24 hours. It is filtered and evaporated to give the title product, which is purified by column chromatography on silica gel.

EXAMPLE 19

The procedure of Example 18 is repeated but using the appropriate dl-6aβ,7,10,10aα-tetrahydro-6,6-R_4R_5-3-(Z-W)-6H-dibenzo[b,d]pyran-9(8H)-ones of Examples 4, 9 and those produced as penultimate products in the procedures of Examples 11, 12 and 14; and the appropriate alkanoic acid or acid of formula HOO-C—$(CH_2)_p$—NR_2R_3.HCl to produce esters of the formula



wherein R_4, R_5, Z and W are as defined in Examples 4, 9, 11, 12 and 14 and R_1 is

R_1*	R_1*
—$COCH_3$	—$CO(CH_2)_3NHC_4H_9$
—$COCH_2CH_3$	—$CO(CH_2)_2N(C_4H_9)_2$
—$CO(CH_2)_3CH_3$	—$COCH_2$-piperidino
—$COCH_2NH_2$	—$COCH_2$-pyrrolo
—$CO(CH_2)_2NH_2$	—$COCH_2$-(N-methyl)piperidino
—$CO(CH_2)_4NH_2$	—$CO(CH_2)_2$-morpholino
—$COCH_2N(CH_3)_2$	—$CO(CH_2)_2$-N-butyl)piperidino
—$CO(CH_2)_2N(C_2H_5)_2$	—$CO(CH_2)_3$-pyrrolidino
—$CO(CH_2)_4NHCH_3$	—$CO(C_2H_4)$-(N-ethyl)piperidino
—$CONH_2$	—CO-piperidino
—$CON(CH_3)_2$	—CO-(N-methyl)piperidino
—$CON(C_4H_9)_2$	—CO-morpholino
—$CON(C_2H_5)_2$	—CO-pyrrolo

*Basic esters are obtained as their hydrochloride salts. Careful neutralization with sodium hydroxide affords the free ester.

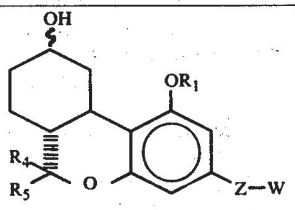
EXAMPLE 20

dl-6aβ,7,8,9,10,10aα-Hexahydro-1-(4-morpholinobutyryloxy)-6,6-dimethyl-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]pyran-9β-ol hydrochloride

The title product of Example 5 is esterified according to the procedure of Example 18 to produce the above-named ester salt.

In like manner, the remaining products of Example 5 and those of Examples 10–12 and 14 are converted to esters having the formula shown below wherein R_4, R_5,

Z and W are as defined in said Examples and R_1 has the values given below:



R_1	R_1
$-COCH_3$	$-COCH_2$-pyrrolo
$-CO(CH_2)_2CH_3$	$-COCH_2$-pyrrolidino
$-CO(CH_2)_3CH_3$	$-COCH_2$-morpholino
$-COCH_2NH_2$	$-COCH_2$-(N-methyl)piperazino
$-COCH_2N(CH_3)_2$	$-COCH_2$-(N-butyl)piperazino
$-CO(CH_2)_2NHCH_3$	$-CO(CH_2)_2$-piperidino
$-CO(CH_2)_2N(i\text{-}C_3H_7)_2$	$-CO(CH_2)_2$-(N-isopropyl)piperazino
$-COCH_2N(C_4H_9)_2$	$-CO(CH_2)_3$-pyrrolidino
$-CO(CH_2)_4N(C_2H_5)_2$	$-CO(CH_2)_4$-(N-ethyl)piperazino
$-CONH_2$	-CO-piperidino
$-CON(CH_3)_2$	-CO-(N-methyl)piperazino
$-CONHC_2H_5$	-CO-morpholino
$-CON(C_4H_9)_2$	-CO-pyrrolo

EXAMPLE 21

dl-6a,7-Dihydro-1-hydroxy-6,6-diemthyl-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]pyran-9(8H)-one

(A) dl-Ethyl 5-Hydroxy-4-methyl-7-(1-methyl-4-phenylbutyl)-coumarin-3-propionate

A mixture of 2-(3,5-dihydroxphenyl)-5-phenylpentane (33 g., 0.13 M), (Preparation C) diethyl α-acetoglutarate (32.2 g., 0.14 M) and phosphorous oxychloride (20 g., 0.13 M), protected from atmospheric moisture, is stirred at room temperature. After 10 days, the mixture is dissolved in chloroform, washed three times with water, dried (Na_2SO_4), and evaporated. The residue is subjected to silica gel chromatography (eluents - 9 benzene:1 ether) to yield 22 g. of the desired ester, m.p. 58°–70° C. from hexane. Further recrystallization from ethyl acetate/hexane affords an analytical sample: m.p. 78°–85° C.

Analysis: Calc'd for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16%. Found: C, 73.82; H, 7.13%.

MS: (mol.ion) 422

(B)

dl-7,10-Dihydro-1-hydroxy-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]pyran-6,9(8H)-dione

To the sodium hydride powder obtained by washing 10.0 g. (0.21 mole) of 50% sodium hydride in mineral oil dispersion with dry hexane is added 20.6 g. (0.049 mole) of the ester of part A of this example and the two powders are mixed thoroughly. The reaction flask is cooled to 15°–17° C. and dimethyl sulfoxide (200 ml.) is added directly into the reaction flask. After stirring for an additional hour at 15°–17° C., the reaction is kept overnight in the refrigerator. After warming to room temperature the reaction mixture is poured into a rapidly stirred mixture of 600 ml. of ice and water and 40 ml. of concentrated hydrochloric acid, more ice being added as needed to keep the mixture cold. The slurry thus produced is stirred for an additional hour and is then decanted. The residual gum is heated on the steam bath with excess concentrated sodium bicarbonate solution and, while still warm, the resultant solid is filtered. The filter cake is washed with bicarbonate solution and water and recrystallized from ethyl acetate/hexane to give 4.5 g. of cyclized product, m.p. 163°–164° C. Further purification is achieved by recrystallization from methanol; m.p. 166°–167° C.

Analysis: Calc'd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43%. Found: C, 76.50; H, 6.56%.

MS: (mol.ion) 376

(C)

dl-7,8,9,10-Tetrahydro-1-hydroxy-3-(1-methyl-4-phenylbutyl)spiro[6H-dibenzo[b,d]pyran-9,2′-[1′,3′]dioxolan]-6-one

A solution of 0.031 mole of the cyclized product of part B of this example in benzene (500 ml.) containing ethylene glycol (10 ml.) and p-toluenesulfonic acid (10 mg.) is heated overnight under reflux (Dean-Stark trap). The solution is cooled, poured into water containing excess sodium bicarbonate and the organic phase separated, dried (Na_2SO_4) and evaporated to yield the desired ketal.

(D)

dl-6a,7-Dihydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]pyran-9(8H)-one

A slurry of 0.175 mole of the above produced ketal in ether (1.5 liters) is added over 90 minutes to the Grignard reagent prepared from magnesium (44.6 g., 1.84 g-atoms) and methyl iodide (110 ml., 251 g., 1.77 moles) in ether (1.8 liters). After refluxing for 2 days the reaction is treated carefully with 1N hydrochloric acid (200 ml.), and then with 6N hydrochloric acid (740 ml.). The mixture is stirred vigorously for 1 hour and then the ether layer washed once with water and once with 5% sodium bicarbonate. The ether layer is dried (Na_2SO_4) and concentrated to yield the desired unsaturated ketone. If desired, it is purified by crystallization and/or column chromatography (see Examples 3 and 8).

In like manner, the remaining 1-(Z-W-substituted)-3,5-dihydroxybenzenes of Preparation C and those of Preparations D, E, K, M, Q, R and T are converted to the corresponding dl-6a,7-dihydro-1-hydroxy-6,6-dimethyl-3-(Z-W)-6H-dibenzo[b,d]-pyran-9(8H)-ones.

EXAMPLE 22

dl-6aβ,7,10,10aα-Tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutyloxy)-6H-dibenzo[b,d]pyran-9(8H)-one, Ethylene Ketal

A solution of dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutyloxy)-6H-dibenzo[b,d]pyran-9(8H)-one (60 mg., 0.145 mM), ethylene glycol (0.5 ml.), benzene (10 ml.) and a crystal of p-toluenesulfonic acid is heated at reflux for three hours. The reaction mixture is then cooled and concentrated. The concentrate is shaken up in chloroform and the chloroform phase washed first with sodium bicarbonate and then with water. It is then dried ($MgSO_4$) and concentrated to give the ketal as a light brown oil (63 mg.).

Repetition of this procedure but using propylene glycol, trimethylene glycol and tetramethylene glycol, in place of ethylene glycol, affords the corresponding ketals.

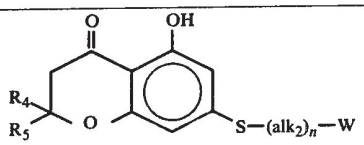
By means of this procedure the ketone products of Examples 3, 4, 8, 9, 11, 12, 14–16, 18, 19 and 21 are converted to the corresponding ethylene, trimethylene and tetramethylene ketals.

EXAMPLE 23

dl-5-Hydroxy-2,2-dimethyl-7-(2-heptylmercapto)-4-chromanone

To a solution of 5-hydroxy-7-mercapto-2,2-dimethyl-4-chromanone (19.7 g., 87.1 mM) and potassium hydroxide (2.44 g., 43.5 mM) in N,N-dimethylformamide (58 ml.) is added with stirring 2-bromoheptane (15.77 g., 88.0 mM). The mixture is heated for four days at 100° C., cooled to room temperature and then added to a mixture of aqueous sodium hydroxide (110 ml. of 1N), water (45 ml.) and chloroform (150 ml.). The mixture is agitated, the phases separated and the aqueous layer extracted with more chloroform (150 ml.). The combined chloroform layers are washed with 1N sodium hydroxide (2 × 100 ml.) dried over sodium sulfate and concentrated to an oil. The unreacted 2-bromoheptane is removed by distillation and the residue purified by silica gel chromatography to give the title product.

The following compounds are similarly prepared from appropriate reactants of the formula Br-$(alk_2)_n$-W from the appropriate 5-hydroxy-7-mercapto-2,2-R_4R_5-substituted-4-chromanone:



R_4	R_5	n	(alk_2)	W
H	CH_3	1	$-CH(CH_3)(CH_2)_4-$	CH_3
C_2H_5	C_2H_5	1	$-CH(CH_3)(CH_2)_4-$	CH_3
CH_3	CH_3	1	$-CH(CH_3)(CH_2)_3-$	C_6H_5
H	CH_3	1	$-CH(CH_3)(CH_2)_3-$	C_6H_5
CH_3	CH_3	1	$-CH(CH_3)(CH_2)_2-$	C_6H_5
CH_3	CH_3	1	$-CH(CH_3)(CH_2)_3-$	4-pyridyl
H	H	1	$-CH(CH_3)(CH_2)_3-$	4-pyridyl
CH_3	CH_3	1	$-CH_2-$	C_6H_5
CH_3	CH_3	1	$-(CH_2)_4-$	C_6H_5
CH_3	C_2H_5	1	$-(CH_2)_7-$	C_6H_5
CH_3	CH_3	1	$-C(CH_3)_2(CH_2)_5-$	CH_3
CH_3	H	1	$-C(CH_3)_2(CH_2)_5-$	CH_3
CH_3	CH_3	1	$-CH(CH_3)CH(CH_3)(CH_2)_4-$	CH_3
H	CH_3	1	$-CH(CH_3)CH(CH_3)(CH_2)_4-$	CH_3
CH_3	CH_3	1	$-(CH_2)_3-$	3-pyridyl
CH_3	H	1	$-(CH_2)_3-$	4-pyridyl
H	CH_3	1	$-CH(CH_3)CH_2-$	2-pyridyl
H	H	1	$-(CH_2)_2-$	4-pyridyl
C_2H_5	CH_3	1	$-CH(CH_3)(CH_2)_2-$	4-piperidyl
CH_3	CH_3	0	—	C_6H_5
CH_3	CH_3	0	—	C_6H_{11}
H	CH_3	0	—	$4\text{-}FC_6H_4$
C_2H_5	H	0	—	$4\text{-}ClC_6H_4$
C_2H_5	C_2H_5	0	—	C_6H_5
CH_3	CH_3	0	—	C_3H_5
H	H	0	—	C_3H_5
CH_3	H	0	—	C_4H_7
CH_3	CH_3	0	—	C_5H_9
CH_3	H	0	—	C_7H_{13}
CH_3	CH_3	0	—	$2\text{-}(C_6H_5)C_3H_4$
CH_3	CH_3	0	—	$2\text{-}(C_6H_5)C_5H_8$
CH_3	CH_3	0	—	$4\text{-}(C_6H_5)C_6H_{10}$
CH_3	CH_3	0	—	$3\text{-}(C_6H_5)C_7H_{12}$
H	H	0	—	$4\text{-}(C_6H_5)C_6H_{10}$
CH_3	CH_3	0	—	4-pyridyl
CH_3	CH_3	0	—	4-piperidyl

EXAMPLE 24

dl-6aβ,7,10,10aα-Tetrahydro-1-acetoxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6H-dibenzo[b,d]pyran-9(8H)-one

Pyridine (15 ml.), acetic anhydride (15 ml.) and dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutoxy)-6H-dibenzo[b,d]pyran-9(8H)-one (4.06 g.) are combined at 0° C. and the mixture stirred for ½ hour at 0° C. The reaction mixture is poured onto ice/water and acidified with dilute hydrochloric acid. The acidified mixture is extracted with ethyl acetate (2 × 100 ml.), the extracts combined and washed with brine. The extract is then dried ($MgSO_4$) and evaporated to give a colorless oil which is crystallized from ether-pentane. Yield = 1.69 g.; m.p. 95°–96° C.

Analysis: Calc'd for $C_{28}H_{34}O_5$: C, 74.64; H, 7.61%. Found: C, 74.55; H, 7.59%.

Evaporation of the mother liquor gives a second crystalline fraction which is digested in hexane. Yield = 1.74 g.; m.p. 94°–96° C.

By means of this procedure but using the appropriate alkanoic acid anhydride and the appropriate dl-6aβ,7,10,10aα-tetrahydro-6,6-R_4,R_5-3-(Z-W)-6H-dibenzo[b,d]pyran-9(8H)-ones of Examples 4, 9, 11, 12 and 14 as reactants, affords the propionyloxy, butyryloxy and valeryloxy esters thereof.

Reduction of the 9-keto group of the thus-produced mono esters according to the procedure of Example 5 affords the corresponding 9-hydroxy derivatives. A mixture of the 9α- and 9β-isomers is produced.

EXAMPLE 25

dl-6aβ,7,8,9,10,10aα-Hexahydro-1,9-diacetoxy-6,6-dimethyl-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]-pyran

A solution of dl-6aβ,7,8,9,10,10aα-hexahydro-1-hydroxy-6,6-dimethyl-3-(1-methyl-4-phenylbutyl)-6H-dibenzo[b,d]pyran-9β-ol (2.0 g.) in pyridine (20 ml.) is treated at 10° C. with acetic anhydride (20 ml.) and the

mixture stirred for 18 hours under nitrogen. The reaction mixture is worked up according to the procedure of Example 24.

In like manner, the 1,9-dihydroxy compounds of Examples 5, 10–12, 14 and 15 are converted to their diacetoxy, dipropionyloxy, dibutyryloxy and divaleryloxy esters.

EXAMPLE 26

dl-6aβ,7,10,10aα-Tetrahydro-1-(4-N-piperidyl-butyroxy)6,6-dimethyl-3-[2-(5-phenyl)pentyloxy]-6H-dibenzo[b,d]pyran-9(8H)-one hydrochloride

A mixture of dl-6aβ,7,10,10aα-tetrahydro-1-hydroxy-6,6-dimethyl-3-[2-(5-phenyl)pentyloxy]-6H-dibenzo[b,d]pyran-9(8H)-one (1.26 g., 3.08 mmoles), 4-N-piperidyl butyric acid hydrochloride (0.639 g., 3.08 mmoles) and dicyclohexylcarbodiimide (0.698 g., 3.39 mmoles) in dry dichloromethane (3.5 ml.) is stirred at 20° C. for 18 hours. The reaction is cooled to 0° C., stirred for ½ hour and filtered. The filtrate is evaporated to an oil which is washed with ether (3 ×) and evaporated to yield 1.78 g. (97%) of dl-6aβ,7,10,10aα-tetrahydro-1-(4-N-piperidyl-butyroxy)-6,6-dimethyl-3-[2-(5-phenyl)pentyloxy]-6H-dibenzo[b,d]pyran-9(8H)-one hydrochloride as a solid, white foam.

IR; (KBr) NH ⊕ 2667, 2564, C = O 1779 and 1730 cm^{-1}.

MS (mol.ion): (M β -HCl), 407, 262, 247, 154, 98 and 91.

PREPARATION A

2-Bromo-5phenylpentane

To phosphorus pentabromide, prepared by addition of bromine (9.0 g.) in methylene chloride (10 ml.) to phosphorous tribromide (15.0 g.) in methylene chloride (15 ml.) at 0° C., is added 5-phenyl-2-pentanol (8.2 g.) in metnhylene chloride at 0° C. The mixture is stirred for 2.5 hours at 0° C. and is then allowed to warm to room temperature. Water (50 ml.) is added, the mixture stirred for 1 hour and the methylene chloride layer separated. The extraction is repeated and the combined extracts washed with water, saturated sodium bicarbonate solution, brine and then dried over magnesium sulfate. Concentration of the dried extracts gives 12.4 g. of title product as a light yellow oil.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.6 (D, 3, methyl, J = 7Hz), 1.6–2.0 (M, 4, ethylene), 2.3–3.0 (bd, T, 2, benzylic-methylene), 3.7–4.2 (M, 1, methine), 6.9–7.4 (M, 5, aromatic).

PREPARATION B

2-(3,5-Dimethoxyphenyl)-5-phenylpentane

A solution of 1-bromopropylbenzene (51.7 g.) in ether (234 ml.) is added dropwise over a 2-hour period to a refluxing mixture of magnesium (7.32 g.) in ether (78 ml.). The reaction mixture is refluxed for 30 minutes longer and then a solution of 3,5-dimethoxy-acetophenone (50 g.) in ether (78 ml.) is added dropwise and heated to reflux for 1.5 hours. The reaction is quenched by addition of saturated ammonium chloride (234 ml.), the ether layer is separated and the aqueous phase extracted with ether (3 × 200 ml.). The combined ether extracts are dried over magnesium sulfate and concentrated under vacuum to yield 81 g. of an oil. Forty grams of the oil is hydrogenated in a mixture containing ethanol (300 ml.), concentrated hydrochloric acid (2 ml.) and 5% palladium-on-carbon (5 g.). The catalyst is filtered off and the ethanol removed under vacuum. The residue is distilled under vacuum yielding 28 g. of 2-(3,5-dimethoxyphenyl)-5-phenylpentane (b.p. 0.125 mm., 154°–159° C.).

NMR: $\delta_{CDCl_3}^{TMS}$ 1.25 (d,3,α-CH_3), 1.3–2.1 (M,4,ethylene), 2.2–2.9 (M, 3,benzylic-methylene, methinyl), 3.45 (S,6,methoxyl), 6.2–6.7 (M,3,aromatic), 7.2 (S,5,aromatic).

PREPARATION C

2-(3,5-Dihydroxyphenyl)-5-phenylpentane

A mixture of 2-(3,5-dimethoxyphenyl)-5-phenylpentane (22 g.) and pyridine hydrochloride (94 g.) under nitrogen is heated to 190° C. for 2 hours with vigourous stirring. The reaction mixture is cooled, dissolved in 6N hydrochloric acid (200 ml.) and diluted with water to 600 ml. The aqueous solution is extracted with ethyl acetate (4 × 100 ml.), the ethyl acetate extracts dried over sodium sulfate and concentrated under vacuum to yield 24 g. of crude product. The product is purified by silica gel chromatography to yield 19.2 g. of 2-(3,5-dihydroxyphenyl)-5-phenylpentane as an oil.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.1 (d,3,α-methyl), 1.35–1.65 (M,4,ethylene), 2.2–2.8 (M,3,benzylic-methylene, methinyl), 6.1–6.5 (M,3,aromatic), 6.65 (bd.S.,2, hydroxyl), 7–7.4 (M,5,aromatic).

Following the procedures of Preparations B and C, the compounds listed below are prepared by substituting the appropriate 1-bromoalkylbenzene for 1-bromopropylbenzene:

2-(3,5-(dihydroxyphenyl)-6-phenylhexane

NMR: $\delta_{CDCl_3}^{TMS}$ 1.1 (D,3,α-methyl, J-7 cps), 1.0–1.9 [M,6,ΦCH$_2$CH$_2$)$_3$—CH(CH$_3$)—Ar], 2.2–2.8 (M,3,benzylic methylene, methinyl), 6.0 (bd.S.,2,phenolic OH), 6.2–6.4(M,3,aromatic), 7.1–7.4(M,5,aromatic).

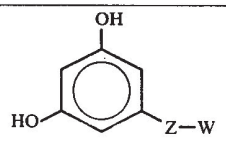
1-(3,5-dihydroxyphenyl)-2-phenylethane

m.p.: 76°–77° C.

2-(3,5-dihydroxyphenyl-4-phenylbutane (an oil)

NMR: $\delta_{CDCl_3}^{TMS}$ 1.1, 1.25 (d,2,methyl), 1.45–2.0 (M,2,methylene), 2.15–2.7 (M,3,benzylic-methylene, methinyl), 6.3 (S,3,aromatic), 6.85 (S,2,hydroxyl-D_2O overlay), 7.1 (S,5, aromatic).

The following compounds are prepared in like manner from the appropriate alcohol and 3,5-dimethoxybenzaldehyde or 3,5-dimethoxyacetophenone by the methods of Preparations A, B and C:



Z	W
CH(CH$_3$)CH$_2$	C$_5$H$_9$
CH(CH$_3$)(CH$_2$)$_2$	C$_5$H$_9$
CH(CH$_3$)CH$_2$	C$_3$H$_5$
CH(CH$_3$)CH(CH$_3$)	C$_6$H$_{11}$
CH(CH$_3$)(CH$_2$)$_3$	C$_6$H$_{11}$
CH(CH$_3$)(CH$_2$)$_4$	C$_5$H$_9$
CH(CH$_3$)(CH$_2$)$_5$	C$_6$H$_{11}$
CH(C$_2$H$_5$)(CH$_2$)$_2$	C$_6$H$_{11}$
(CH$_2$)$_3$	C$_5$H$_9$
CH(C$_2$H$_5$)(CH$_2$)$_3$	C$_6$H$_5$
C(CH$_3$)$_2$	C$_6$H$_5$
(CH$_2$)$_4$	C$_6$H$_5$
(CH$_2$)$_2$CH(C$_2$H$_5$)	C$_6$H$_5$
CH(CH$_3$)CH$_2$CH(C$_2$H$_5$)	C$_6$H$_5$

PREPARATION D

1-(3,5-Dihydroxyphenyl)-2-methyl-4-phenylbutane

A solution of n-butyl lithium (29 ml. of 2.2M) is added dropwise to 3,5-dimethoxybenzyl triphenylphosphonium bromide (31.5 g.) in tetrahydrofuran (200 ml.) with stirring and the resulting deep red solution is stirred for one-half hour. Benzyl acetone (9.4 g.) is added dropwise and the reaction mixture stirred for 12 hours. It is then adjusted to pH 7 by addition of acetic acid and concentrated under reduced pressure. The residue is extracted with methylene chloride and the extract evaporated to give crude 1-(3,5-dimethoxyphenyl)-2-methyl-4-phenyl-1-butene as an oil. It is purified by chromatography on silica gel (400 g.) and elution with benzene. Yield: 10 g. as an oil.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.95 (S,3), 2.3–3.1 (M,4), 3.8 (S,6), 6.15–6.6 (M,3), 7.1–7.5 δ(M,6).

The 1-(3,5-dimethoxyphenyl)-2-methyl-4-phenyl-1-butene (9.4 g.) thus prepared is dissolved in ethanol (250 ml.) and catalytically hydrogenated at 45 p.s.i. in the presence of palladium-on-charcoal (1 g. of 10%) and concentrated hydrochloric acid (1 ml.). Yield: 9.4 g. of 1-(3,5-dimethoxyphenyl)-2-methyl-4-phenylbutane as an oil.

NMR: $\delta_{CDCl_3}^{TMS}$ 0.9 (d,3), 1.35–1.95 (M,3), 2.2–2.9 (M,4), 3.75 (S,6), 6.35 (S,3), 7.25 δ(S,5).

It is demethylated according to the procedure of Preparation C to give 1-(3,5-dihydroxyphenyl)-2-methyl-4-phenylbutane.

The 3,5-dimethoxybenzyl triphenylphosphonium bromide is prepared by refluxing a mixture of 3,5-dimethoxybenzyl bromide (12 g.) and triphenylphosphine (14.2 g.) in acetonitrile (200 ml.) for 1 hour. The reaction mixture is then cooled and the crystalline product recovered by filtration, washed with ether and dried (20 g.); m.p. 269°–270° C.

PREPARATION E

2-Methyl-2-(3,5-dihydroxyphenyl)-5-phenylpentane

To a solution of the Grignard reagent prepared from 2-phenylbromoethane (5.5 g.), magnesium (0.8 g.) and dry ether (60 ml.) is added a solution of 2-methyl-2-(3,5-dimethoxyphenyl)propionitrile (2.75 g.) in dry ether (20 ml.). The ether is distilled off and replaced by dry benzene (50 ml.) and the mixture refluxed for 48 hours. It is then decomposed by careful treatment with dilute sulfuric acid and heated on a steam bath for 1 hour. The mixture is then extracted with ether, the extract dried ($MgSO_4$) and concentrated to an oil. Distillation of the oil in vacuo affords 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenyl-3-pentanone; b.p. 168° C./0.2 mm. (Yield: 2.32 g., 60%)

The thus-produced pentanone (58 g.) is dissolved in ethanol (400 ml.) and treated with sodium borohydride (10 g.) at room temperature. The reaction mixture is stirred for 12 hours and is then cooled and neutralized with 6N hydrochloric acid. The ethanol is removed under reduced pressure and the residue extracted with ether. The extract is dried ($MgSO_4$) and concentrated to give 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenyl-3-pentanol as an oil (52 g., 88% yield).

The pentanol (16 g.) is taken up in ether (100 ml.) and reacted with powdered potassium (2.5 g.) in ether (200 ml.). Carbon disulfide (equimolar to the potassium) is added and the mixture stirred for a half hour. Methyl iodide (9.0 g.) is then added and the reaction mixture stirred for 6 hours. The resulting suspension is filtered and the filtrate concentrated under reduced pressure. The residue is taken up in ethanol (150 ml.), Raney nickel added (25 g.) and the mixture refluxed for 18 hours. Evaporation of the alcohol and distillation of the residue gives 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenyl-3-pentene.

The pentene derivative is catalytically hydrogenated according to the procedure of Preparation D and the resulting 2-methyl-2-(3,5-dimethoxyphenyl)-5-phenyl-3-pentane dimethylated via the procedure of Preparation C to give the product.

PREPARATION F

3,5-Dibenzyloxyacetophenone

Over a period of 1.5 hours, methyl lithium (531 ml. of a 2 molar solution, 1.06 M) is added under a nitrogen atmosphere to a rapidly stirring solution of 3,5-dibenzyloxybenzoic acid (175 g., 0.532 M) in ether (250 ml.) - tetrahydrofuran (1400 ml.) maintained at 15°–20° C. After stirring an additional 0.75 hour at 10°–15° C., water (600 ml.) is slowly added keeping the reaction temperature below 20° C. The aqueous layer is separated and extracted with ether (3 × 250 ml.). The organic phases are combined, washed with saturated sodium chloride solution (4 × 300 ml.), dried over sodium sulfate, and concentrated under vacuum to give an oil which slowly crystallized from isopropylether. The crude product is recrystallized from ether-hexane to yield 104.7 g. (59%) of product; m.p. 59°–61° C.

PREPARATION G

Ethyl 3-(3,5-Dibenzyloxyphenyl)crotonate (Wittig Reaction)

A mixture of 3,5-dibenzyloxyacetophenone (43.2 g., 0.13 mole) and carbethoxymethylenetriphenylphosphorane (90.5 g., 0.26 mole) is heated under a nitrogen atmosphere at 170° C. for 4 hours. The clear melt is cooled to room temperature, triturated with ether and the precipitate of triphenyl phosphine oxide removed by filtration. The filtrate is concentrated under vacuum to an oily residue which is chromatographed over silica gel (1500 g.) and eluted with benzene:hexane solutions of increasing benzene concentration beginning with 40:60 and ending with 100% benzene. Concentration of appropriate fractions gives an oily residue which is crystallized from hexane. Yield: 40.2 g. (77%); m.p. 73°–75° C.

Analysis: Calc'd for $C_{26}H_{26}O_4$: C, 77.58; H, 6.51%. Found: C, 77.72; H, 6.60%.

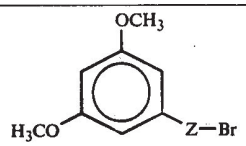
In like manner, ethyl 3-(3,5-dimethoxyphenyl)crotonate is prepared from 3,5-dimethoxyacetophenone (51.7 g.) and carbethoxymethylene triphenylphosphorane (200 g.). Yield = 61.8 g., 86%, b.p. 146°–162° C. at 0.3 mm.

PREPARATION H

3-(3,5-Dibenzyloxyphenyl)-1-butanol

A solution of ethyl 3-(3,5-dibenzyloxyphenyl)crotonate (24.1 g., 60 mM) in ether (250 ml.) is added to a mixture of lithium aluminum hydride (3.42 g., 90 mM) and ether (250 ml.). Aluminum chloride (0.18 g., 1.35 mM) is added and the mixture refluxed for 12 hours and then cooled. Water (3.4 ml.), sodium hydroxide (3.4 ml. of 6N) and water (10 ml.) are then added successively to the reaction mixture. The inorganic salts which precipitate are filtered off and the filtrate is then concentrated

-continued



Z
$C(C_2H_5)CH_2$

PREPARATION M

4-(3,5-Dihydroxypenyl)-1-(4-pyridyl)pentane

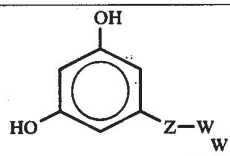
A mixture of 3-(3,5-dimethoxyphenyl)butyl triphenylphosphonium bromide (19.0 g., 35.4 mmoles) in dimethylsulfoxide (50 ml.) is added to 4-pyridinecarboxaldehyde (3.79 g., 35.4 mmoles) in tetrahydrofuran (40 ml.). The resulting mixture is then added dropwise to a slurry of 50% sodium hydride (1.87 g., 39 mmoles) in tetrahydrofuran (20 ml.) under a nitrogen atmosphere at 0°–5° C. Following completion of addition, the mixture is stirred for one hour at 0°–5° and then concentrated under reduced pressure. The concentrate is diluted with water (200 ml.) and then acidified with 6N HCl. The aqueous acid solution is extracted with benzene (4 × 50 ml.). It is then made basic and extracted with ethyl acetate (3 × 50 ml.). Evaporation of the combined extracts after drying ($MgSO_4$) affords 4-(3,5-dimethoxyphenyl)-1-(4-pyridyl)-1-pentene (7.1 g., 70%) as an oil.

Catalytic hydrogenation of the thus-produced pentene derivative according to the procedure given in Preparation D gives 4-(3,5-dimethoxyphenyl)-1-(4-pyridyl)pentane in quantitative yield; m.p. 131°–133° C.

The pentane derivative thus obtained is demethylated by heating a mixture of the compound (7.15 g., 25 mmoles) and pyridine hydrochloride (35 g.) under a nitrogen atmosphere at 210° C. for 8 hours. The hot mixture is poured into water (40 ml.) and the resulting solution made basic with 6N sodium hydroxide. Water and pyridine are removed by distillation in vacuo. Ethanol (50 ml.) is added to the residue and the inorganic salts which precipitate are filtered off. The filtrate is concentrated in vacuo and the residue chromatographed on silica gel (150 g.) using as eluting agents 5% ethanol/benzene (4 liters), 10% ethanol/benzene (1 liter), 13% ethanol/benzene (1 liter) and 16% ethanol/benzene (5 liters). The product is isolated as a glassy solid by concentration of appropriate fractions of the eluate. Yield = 5.0 g. (78%).

The 3-(3,5-dimethoxyphenyl)butyltriphenylphosphonium bromide is prepared by refluxing a mixture of 1-bromo-3-(3,5-dimethoxyphenyl)butane (21.5 g., 78.5 mmoles) and triphenyl phosphine (20.5 g., 78.5 mmoles) in xylene (60 ml.) for 18 hours. The reaction mixture is then cooled to room temperature and filtered. The filter cake is washed with ether and dried in a vacuum desicator to give 36.4 g. (86%) yield of product; m.p. 190°–200° C.

Repetition of this procedure but using the appropriate bromo-(3,5-dimethoxyphenyl)alkane and the appropriate aldehyde or ketone affords the following compounds.



Z	W
$(CH_2)_3$	2-pyridyl
$(CH_2)_3$	3-pyridyl
$(CH_2)_3$	4-pyridyl
$(CH_2)_3$	2-piperidyl
$(CH_2)_3$	4-piperidyl
$(CH_2)_4$	2-pyridyl
$(CH_2)_4$	4-pyridyl
$(CH_2)_4$	3-piperidyl
$(CH_2)_4$	4-piperidyl
$CH_2CH(CH_3)CH_2$	2-pyridyl
$CH_2CH(CH_3)CH_2$	4-piperidyl
$CH(CH_3)CH(CH_3)CH_2$	3-pyridyl
$CH(CH_3)CH(CH_3)CH_2$	4-pyridyl
$CH(CH_3)CH(CH_3)CH_2$	3-piperidyl
$CH(CH_3)(CH_2)_2$	2-pyridyl
$CH(CH_3)(CH_2)_2$	3-pyridyl
$CH(CH_3)(CH_2)_2$	4-piperidyl
$CH(CH_3)(CH_2)_3$	3-pyridyl
$CH(CH_3)(CH_2)_3$	4-piperidyl
$CH(CH_3)CH(C_2H_5)CH_2$	4-pyridyl
$CH(C_2H_5)(CH_2)_2$	4-pyridyl
$CH(C_2H_5)(CH_2)_2$	2-piperidyl
$CH(C_2H_5)(CH_2)_2$	4-piperidyl
$CH_2CH(C_2H_5)CH_2$	3-pyridyl
$CH(C_2H_5)(CH_2)_3$	3-pyridyl
$CH(C_2H_5)(CH_2)_3$	4-piperidyl
$CH(C_2H_5)CH(CH_3)CH_2$	2-pyridyl
$CH(C_2H_5)CH(C_2H_5)CH_2$	4-pyridyl
$CH(C_2H_5)CH(C_2H_5)CH_2$	2-piperidyl
$(CH_2)_3$	C_6H_{11}
$CH(CH_3)(CH_2)_3$	C_6H_{11}
$(CH_2)_4$	C_3H_5
$(CH_2)_2$	C_4H_7
$CH_2CH(CH_3)CH_2$	C_5H_9
$CH(CH_3)(CH_2)_2$	C_7H_{13}
$CH(CH_3)CH(CH_3)CH_2$	C_6H_{11}
$(CH_2)_6$	C_6H_5
$(CH_2)_7$	C_6H_5
$(CH_2)_8$	C_6H_5
$CH(CH_3(CH_2)_6$	C_6H_5
$CH(CH_3)(CH_2)_7$	C_6H_5
$CH(CH_3)(CH_2)_3$	$4\text{-}FC_6H_4$
$C(CH_3)_2(CH_2)_3$	C_6H_5
$CH(CH_3)(CH_2)_3$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)_4$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)$	$4\text{-}FC_6H_4$
$CH(CH_3)(CH_2)_2$	$4\text{-}FC_6H_4$
$CH(CH_3)(CH_2)_2$	$4\text{-}ClC_6H_4$
$(CH_2)_3CH(CH_3)$	C_6H_{11}
$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_5
$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_{11}
$CH(CH_3)(CH_2)_2CH(CH_3)$	4-piperidyl
$CH(CH_3)(CH_2)_3$	C_6H_{11}
$CH(CH_3)(CH_2CH(CH_3)$	C_6H_{11}
$(CH_2)_3$	C_6H_{11}
$(CH_2)_4$	C_6H_{11}
$(CH_2)_8$	C_6H_{11}

PREPARATION N

3,5-Dimethoxy-α-methylstyrene Oxide

To a solution of dimethylsulfoxonium methylide (69.4 mM) in dimethyl sulfoxide (65 ml.) at room temperature is added solid 3,5-dimethoxyacetophenone (10 g., 55.5 mM). The reaction mixture is stirred for 1 hour at 25° C., for ½ hour at 50° C. and is then cooled. The mixture is diluted with water (50 ml.) and added to a mixture of ice water (200 ml.) — ether (250 ml.) — low boiling petroleum ether (25 ml.) The organic extract is washed twice with water (250 ml.), dried ($MgSO_4$) and evaporated to an oil. Fractional distillation of the oil yields 8.0 g. (75%) of 3,5-dimethoxy-α-methylstyrene oxide, b.p. 93°–97° C., 0.2 mm.

IR (CCL_4): 2780, 1595, 1196, 1151, 1058 cm^{-1}.

UV (95% ethanol): λ_{max} = 279 nm (ϵ = 2068)

MS (mol.ion): 194

PMR ($CDCl_3$) (60 MHz): δ (1.70 (S, CH_3—), 2.76 (d, J = 6 Hz,

2.95 (d, J = 6 Hz,

3.81 (S, CH_3O—), 6.41 (t, J = 2 Hz, ArH) and 6.58 (d, J = 2 Hz, ArH).

Analysis: Calc'd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%. Found: C, 67.96; H, 7.28%.

PREPARATION O

2-(3,5-Dimethoxyphenyl)-2-hydroxypropyl-2-phenylethyl Ether

A mixture of dry 2-phenylethanol (30 ml. 251 mM) and sodium metal (690 mg., 30 mM) is heated at 110° C. for 30 minutes. The resulting 1M solution of sodium 2-phenylethoxide is cooled to 60° C., 3,5-dimethoxy-α-methylstyrene oxide (2 g., 10.3 mM) added and the reaction heated 15 hours at 60° C. The reaction mixture is cooled and added to a mixture of ether and water. The ether extract is dried over magnesium sulfate and evaporated. Excess 2-phenylethanol is removed by vacuum distillation (b.p. ~65° C., 0.1 mm.) leaving a 3.5 g. residue. The residue is purified via column chromatography on Merck silica gel 60 (300 g.) and eluted in 15 ml. fractions with 60% ether-pentane. Fractions 52–88 yielded 2.9 g. (89%) of 2-(3,5-dimethoxyphenyl)-2-hydroxypropyl 2-phenylethyl ether.

IR (CCl_4): 3534, 1595, 1202, 1153 cm^{-1}.

UV (95% ethanol): λ_{max} = 278 (ε = 1830), 273 (ε + 1860).

MS: (mol.ion) 316

PMR ($CDCl_3$, 60 MHz): δ 1.46 (S, CH_3—), 2.86 (S, OH), 2.86 (t, J = 7 Hz, —CH_2—Ph), 3.53 (S, —CH_2O), 3.71 (t, J = 7 Hz, —CH_2O), 3.80 (S, OCH_3), 6.38 (t, J = 2 Hz, Arh), 6.61 (d, J = 2 Hz, ArH) and 7.23 (S, PhH).

Analysis: Calc'd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65%. Found: C, 71.92; H, 7.63%.

PREPARATION P

2-(3,5-Dimethoxyphenyl)propyl 2-Phenylethyl Ether

To a 0° C. solution of 2-(3,5-dimethoxyphenyl)-2-hydroxypropyl 2-phenylethyl ether (550 mg., 1.74 mM) in pyridine (2 ml.) is added dropwise phosphorous oxychloride (4.77 ml., 5.22 mM). The reaction is allowed to warm to 20° C. over a 1.5 hour period. It is then stirred for 1.5 hours at 20° C. and then added to ether (150 ml.) and 15% sodium carbonate (100 ml.). The organic phase is separated and washed with 15% sodium carbonate (3 × 50 ml.), dried over magnesium sulfate and evaporated to an oil. The oil is dissolved in absolute ethanol (15 ml.), 10% palladium-on-carbon (100 mg.) added and the mixture stirred under one atmosphere of hydrogen gas. When hydrogen uptake ceases (26.5 ml., 20 min.), the reaction is filtered through diatomaceous earth and the filtrate evaporated to an oil. The oil is purified via preparative layer chromatography on silica gel plates, eluted twice with 6:1 pentane:ether to yield 211 mg. 840%) of 2-(3,5-dimethoxyphenyl)propyl 2-phenylethyl ether.

IR (CCl_4): 1600, 1205, 1155, 1109 cm^{-1}.

MS: (mol.ion) 300

PMR ($CDCl_3$, 60 MHz) δ 1.22 (d, J = 7 Hz, CH_3—), 2.82 (t, J = 7 Hz, CH_2Ph), ~2.8 (H—C—Me), ~3.6 (—CH_2—O—CH_2—), 3.75 (S, OCH_3), 6.35 (m, ArH) and 7.18 (S, PhH).

PREPARATION Q

2-(3,5-Dihydroxyphenyl)propyl 2-Phenylethyl Ether

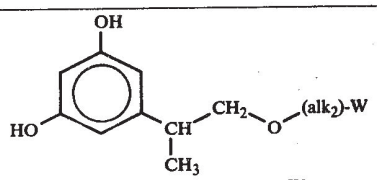
A mixture of 2-(3,5-dimethoxyphenyl)propyl 2-phenylethyl ether (195 mg., 0.65 mM), pyridine (0.4 ml., 4.96 mM) and dry pyridine hydrochloride (4 g., 34.6 mM) is heated at 190° C. for 6 hours. The reaction mixture is cooled and added to a mixture of water (100 ml.) and ether (150 ml.). The ether extract is washed once with water (50 ml.) and, along with a second ether extract (50 ml.) of the aqueous phase, is dried over magnesium sulfate and evaporated to an oil. The oil is purified via preparative layer chromatography on silica gel plates, eluted six times with 30% ether-pentane to yield 65.8 mg. (37%) of 2-(3,5-dihydroxyphenyl)propyl 2-phenylethyl ether.

IR ($CHCl_3$): 3559, 3279, 1605, 1147, 1105 cm^{-1}.

MS: (mol.ion) 272

PMR ($CDCl_3$, 60 MHz) δ 1.18 (d, J = 7 Hz, CH_3—), 2.80 (t, J = 7 Hz, —CH_2Ph), 2.80 (H—C—Me), 3.4–3.8 (—CH_2OCH_2—), 6.08 (t, J = 2 Hz, ArH), 6.21 (d, J = 2 Hz, ArH) and 7.16 (S, PhH).

The following compounds are prepared from appropriate alkanols by the methods of Procedures O and P.



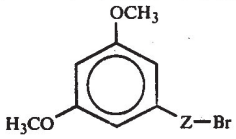
(alk$_2$)	W
—$(CH_2)_6$—	CH_3
—$(CH_2)_6$	C_6H_5
—$(CH_2)_4$	CH_3
—$CH(CH_3)CH_2$	CH_3
—$CH(CH_3)(CH_2)_4$	CH_3
—(CH_2)—	4-FC_6H_4
—$(CH_2)_2$—	4-pyridyl
—$(CH_2)_2$—	2-piperidyl
—$CH(CH_3)CH_2$—	4-piperidyl
—$(CH_2)_2CH(CH_3)(CH_2)_2$—	CH_3
—$CH(CH_3)$—	CH_3
—$C(CH_3)_2$—	CH_3

PREPARATION R

4-(3,5-Dihydroxyphenyl)-1-phenoxypentane

Under a nitrogen atmosphere a mixture of 3,5-dibenzyloxyacetophenone (50.0 g., 0.15 M) in tetrahydrofuran (175 ml.) and 3-phenoxypropyltriphenylphosphonium bromide (7.18 g., 0.15 M) in dimethylsulfoxide (450 ml.) is added dropwise over 1.75 hours to a suspension of 50% sodium hydride (7.89 g., 0.165 M) (previously washed with pentane) in tetrahydrofuran (75 ml.) maintained at 0°–5° C. After stirring for 4 hours at 0°–5° C. the reaction is allowed to warm to room temperature and is then carefully stirred into ice water (2000 ml.), acidified with concentrated hydrochloric acid, and extracted with ethyl acetate (5 × 400 ml.). The combined organic phases are washed with saturated sodium chloride solution (3 × 300 ml.), dried over sodium sulfate

-continued



Z
$C(C_2H_5)CH_2$

PREPARATION M

4-(3,5-Dihydroxypenyl)-1-(4-pyridyl)pentane

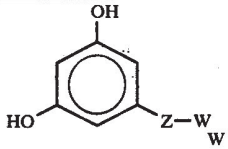
A mixture of 3-(3,5-dimethoxyphenyl)butyl triphenylphosphonium bromide (19.0 g., 35.4 mmoles) in dimethylsulfoxide (50 ml.) is added to 4-pyridinecarboxaldehyde (3.79 g., 35.4 mmoles) in tetrahydrofuran (40 ml.). The resulting mixture is then added dropwise to a slurry of 50% sodium hydride (1.87 g., 39 mmoles) in tetrahydrofuran (20 ml.) under a nitrogen atmosphere at 0°–5° C. Following completion of addition, the mixture is stirred for one hour at 0°–5° and then concentrated under reduced pressure. The concentrate is diluted with water (200 ml.) and then acidified with 6N HCl. The aqueous acid solution is extracted with benzene (4 × 50 ml.). It is then made basic and extracted with ethyl acetate (3 × 50 ml.). Evaporation of the combined extracts after drying ($MgSO_4$) affords 4-(3,5-dimethoxyphenyl)-1-(4-pyridyl)-1-pentene (7.1 g., 70%) as an oil.

Catalytic hydrogenation of the thus-produced pentene derivative according to the procedure given in Preparation D gives 4-(3,5-dimethoxyphenyl)-1-(4-pyridyl)pentane in quantitative yield; m.p. 131°–133° C.

The pentane derivative thus obtained is demethylated by heating a mixture of the compound (7.15 g., 25 mmoles) and pyridine hydrochloride (35 g.) under a nitrogen atmosphere at 210° C. for 8 hours. The hot mixture is poured into water (40 ml.) and the resulting solution made basic with 6N sodium hydroxide. Water and pyridine are removed by distillation in vacuo. Ethanol (50 ml.) is added to the residue and the inorganic salts which precipitate are filtered off. The filtrate is concentrated in vacuo and the residue chromatographed on silica gel (150 g.) using as eluting agents 5% ethanol/benzene (4 liters), 10% ethanol/benzene (1 liter), 13% ethanol/benzene (1 liter) and 16% ethanol/benzene (5 liters). The product is isolated as a glassy solid by concentration of appropriate fractions of the eluate. Yield = 5.0 g. (78%).

The 3-(3,5-dimethoxyphenyl)butyltriphenylphosphonium bromide is prepared by refluxing a mixture of 1-bromo-3-(3,5-dimethoxyphenyl)butane (21.5 g., 78.5 mmoles) and triphenyl phosphine (20.5 g., 78.5 mmoles) in xylene (60 ml.) for 18 hours. The reaction mixture is then cooled to room temperature and filtered. The filter cake is washed with ether and dried in a vacuum desicator to give 36.4 g. (86%) yield of product; m.p. 190°–200° C.

Repetition of this procedure but using the appropriate bromo-(3,5-dimethoxyphenyl)alkane and the appropriate aldehyde or ketone affords the following compounds.



Z	W
$(CH_2)_3$	2-pyridyl
$(CH_2)_3$	3-pyridyl
$(CH_2)_3$	4-pyridyl
$(CH_2)_3$	2-piperidyl
$(CH_2)_3$	4-piperidyl
$(CH_2)_4$	2-pyridyl
$(CH_2)_4$	4-pyridyl
$(CH_2)_4$	3-piperidyl
$(CH_2)_4$	4-piperidyl
$CH_2CH(CH_3)CH_2$	2-pyridyl
$CH_2CH(CH_3)CH_2$	4-piperidyl
$CH(CH_3)CH(CH_3)CH_2$	3-pyridyl
$CH(CH_3)CH(CH_3)CH_2$	4-pyridyl
$CH(CH_3)CH(CH_3)CH_2$	3-piperidyl
$CH(CH_3)(CH_2)_2$	2-pyridyl
$CH(CH_3)(CH_2)_2$	3-pyridyl
$CH(CH_3)(CH_2)_2$	4-piperidyl
$CH(CH_3)(CH_2)_3$	3-pyridyl
$CH(CH_3)(CH_2)_3$	4-piperidyl
$CH(CH_3)CH(C_2H_5)CH_2$	4-pyridyl
$CH(C_2H_5)(CH_2)_2$	4-pyridyl
$CH(C_2H_5)(CH_2)_2$	2-piperidyl
$CH(C_2H_5)(CH_2)_2$	4-piperidyl
$CH_2CH(C_2H_5)CH_2$	3-pyridyl
$CH(C_2H_5)(CH_2)_3$	3-pyridyl
$CH(C_2H_5)(CH_2)_3$	4-piperidyl
$CH(C_2H_5)CH(CH_3)CH_2$	2-pyridyl
$CH(C_2H_5)CH(C_2H_5)CH_2$	4-pyridyl
$CH(C_2H_5)CH(C_2H_5)CH_2$	2-piperidyl
$(CH_2)_3$	C_6H_{11}
$CH(CH_3)(CH_2)_3$	C_6H_{11}
$(CH_2)_4$	C_3H_5
$(CH_2)_2$	C_4H_7
$CH_2CH(CH_3)CH_2$	C_5H_9
$CH(CH_3)(CH_2)_2$	C_7H_{13}
$CH(CH_3)CH(CH_3)CH_2$	C_6H_{11}
$(CH_2)_6$	C_6H_5
$(CH_2)_7$	C_6H_5
$(CH_2)_8$	C_6H_5
$CH(CH_3(CH_2)_6$	C_6H_5
$CH(CH_3)(CH_2)_7$	C_6H_5
$CH(CH_3)(CH_2)_3$	$4\text{-}FC_6H_4$
$C(CH_3)_2(CH_2)_3$	C_6H_5
$CH(CH_3)(CH_2)_3$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)_4$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)$	$4\text{-}ClC_6H_4$
$CH(CH_3)(CH_2)$	$4\text{-}FC_6H_4$
$CH(CH_3)(CH_2)_2$	$4\text{-}FC_6H_4$
$CH(CH_3)(CH_2)_2$	$4\text{-}ClC_6H_4$
$(CH_2)_3CH(CH_3)$	C_6H_{11}
$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_5
$CH(CH_3)(CH_2)_2CH(CH_3)$	C_6H_{11}
$CH(CH_3)(CH_2)_2CH(CH_3)$	4-piperidyl
$CH(CH_3)(CH_2)_3$	C_6H_{11}
$CH(CH_3)(CH_2CH(CH_3)$	C_6H_{11}
$(CH_2)_3$	C_6H_{11}
$(CH_2)_4$	C_6H_{11}
$(CH_2)_8$	C_6H_{11}

PREPARATION N

3,5-Dimethoxy-α-methylstyrene Oxide

To a solution of dimethylsulfoxonium methylide (69.4 mM) in dimethyl sulfoxide (65 ml.) at room temperature is added solid 3,5-dimethoxyacetophenone (10 g., 55.5 mM). The reaction mixture is stirred for 1 hour at 25° C., for ½ hour at 50° C. and is then cooled. The mixture is diluted with water (50 ml.) and added to a mixture of ice water (200 ml.) — ether (250 ml.) — low boiling petroleum ether (25 ml.) The organic extract is washed twice with water (250 ml.), dried ($MgSO_4$) and evaporated to an oil. Fractional distillation of the oil yields 8.0 g. (75%) of 3,5-dimethoxy-α-methylstyrene oxide, b.p. 93°–97° C., 0.2 mm.

IR (CCL_4): 2780, 1595, 1196, 1151, 1058 cm^{-1}.

UV (95% ethanol): λ_{max} = 279 nm (ϵ = 2068)

MS (mol.ion): 194

PMR ($CDCl_3$) (60 MHz): δ (1.70 (S, CH_3—), 2.76 (d, J = 6 Hz,

2.95 (d, J = 6 Hz,

3.81 (S, CH_3O—), 6.41 (t, J = 2 Hz, ArH) and 6.58 (d, J = 2 Hz, ArH).

Analysis: Calc'd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%. Found: C, 67.96; H, 7.28%.

PREPARATION O

2-(3,5-Dimethoxyphenyl)-2-hydroxypropyl-2-phenylethyl Ether

A mixture of dry 2-phenylethanol (30 ml. 251 mM) and sodium metal (690 mg., 30 mM) is heated at 110° C. for 30 minutes. The resulting 1M solution of sodium 2-phenylethoxide is cooled to 60° C., 3,5-dimethoxy-α-methylstyrene oxide (2 g., 10.3 mM) added and the reaction heated 15 hours at 60° C. The reaction mixture is cooled and added to a mixture of ether and water. The ether extract is dried over magnesium sulfate and evaporated. Excess 2-phenylethanol is removed by vacuum distillation (b.p. ~65° C., 0.1 mm.) leaving a 3.5 g. residue. The residue is purified via column chromatography on Merck silica gel 60 (300 g.) and eluted in 15 ml. fractions with 60% ether-pentane. Fractions 52–88 yielded 2.9 g. (89%) of 2-(3,5-dimethoxyphenyl)-2-hydroxypropyl 2-phenylethyl ether.

IR (CCl_4): 3534, 1595, 1202, 1153 cm^{-1}.

UV (95% ethanol): λ_{max} = 278 (ε = 1830), 273 (ε + 1860).

MS: (mol.ion) 316

PMR ($CDCl_3$, 60 MHz): δ 1.46 (S, CH_3—), 2.86 (S, OH), 2.86 (t, J = 7 Hz, —CH_2—Ph), 3.53 (S, —CH_2O), 3.71 (t, J = 7 Hz, —CH_2O), 3.80 (S, OCH_3), 6.38 (t, J = 2 Hz, Arh), 6.61 (d, J = 2 Hz, ArH) and 7.23 (S, PhH).

Analysis: Calc'd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65%. Found: C, 71.92; H, 7.63%.

PREPARATION P

2-(3,5-Dimethoxyphenyl)propyl 2-Phenylethyl Ether

To a 0° C. solution of 2-(3,5-dimethoxyphenyl)-2-hydroxypropyl 2-phenylethyl ether (550 mg., 1.74 mM) in pyridine (2 ml.) is added dropwise phosphorous oxychloride (4.77 ml., 5.22 mM). The reaction is allowed to warm to 20° C. over a 1.5 hour period. It is then stirred for 1.5 hours at 20° C. and then added to ether (150 ml.) and 15% sodium carbonate (100 ml.). The organic phase is separated and washed with 15% sodium carbonate (3 × 50 ml.), dried over magnesium sulfate and evaporated to an oil. The oil is dissolved in absolute ethanol (15 ml.), 10% palladium-on-carbon (100 mg.) added and the mixture stirred under one atmosphere of hydrogen gas. When hydrogen uptake ceases (26.5 ml., 20 min.), the reaction is filtered through diatomaceous earth and the filtrate evaporated to an oil. The oil is purified via preparative layer chromatography on silica gel plates, eluted twice with 6:1 pentane:ether to yield 211 mg. 840%) of 2-(3,5-dimethoxyphenyl)propyl 2-phenylethyl ether.

IR (CCl_4): 1600, 1205, 1155, 1109 cm^{-1}.

MS: (mol.ion) 300

PMR ($CDCl_3$, 60 MHz) δ 1.22 (d, J = 7 Hz, CH_3—), 2.82 (t, J = 7 Hz, CH_2Ph), ~2.8 (H—C—Me), ~3.6 (—CH_2—O—CH_2—), 3.75 (S, OCH_3), 6.35 (m, ArH) and 7.18 (S, PhH).

PREPARATION Q

2-(3,5-Dihydroxyphenyl)propyl 2-Phenylethyl Ether

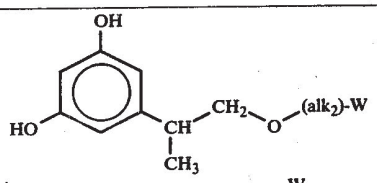
A mixture of 2-(3,5-dimethoxyphenyl)propyl 2-phenylethyl ether (195 mg., 0.65 mM), pyridine (0.4 ml., 4.96 mM) and dry pyridine hydrochloride (4 g., 34.6 mM) is heated at 190° C. for 6 hours. The reaction mixture is cooled and added to a mixture of water (100 ml.) and ether (150 ml.). The ether extract is washed once with water (50 ml.) and, along with a second ether extract (50 ml.) of the aqueous phase, is dried over magnesium sulfate and evaporated to an oil. The oil is purified via preparative layer chromatography on silica gel plates, eluted six times with 30% ether-pentane to yield 65.8 mg. (37%) of 2-(3,5-dihydroxyphenyl)propyl 2-phenylethyl ether.

IR ($CHCl_3$): 3559, 3279, 1605, 1147, 1105 cm^{-1}.

MS: (mol.ion) 272

PMR ($CDCl_3$, 60 MHz) δ 1.18 (d, J = 7 Hz, CH_3—), 2.80 (t, J = 7 Hz, —CH_2Ph), 2.80 (H—C—Me), 3.4–3.8 (—CH_2OCH_2—), 6.08 (t, J = 2 Hz, ArH), 6.21 (d, J = 2 Hz, ArH) and 7.16 (S, PhH).

The following compounds are prepared from appropriate alkanols by the methods of Procedures O and P.



(alk_2)	W
$-(CH_2)_6-$	CH_3
$-(CH_2)_6$	C_6H_5
$-(CH_2)_4$	CH_3
$-CH(CH_3)CH_2$	CH_3
$-CH(CH_3)(CH_2)_4$	CH_3
$-(CH_2)-$	4-FC_6H_4
$-(CH_2)_2-$	4-pyridyl
$-(CH_2)_2-$	2-piperidyl
$-CH(CH_3)CH_2-$	4-piperidyl
$-(CH_2)_2CH(CH_3)(CH_2)_2-$	CH_3
$-CH(CH_3)-$	CH_3
$-C(CH_3)_2-$	CH_3

PREPARATION R

4-(3,5-Dihydroxyphenyl)-1-phenoxypentane

Under a nitrogen atmosphere a mixture of 3,5-dibenzyloxyacetophenone (50.0 g., 0.15 M) in tetrahydrofuran (175 ml.) and 3-phenoxypropyltriphenylphosphonium bromide (7.18 g., 0.15 M) in dimethylsulfoxide (450 ml.) is added dropwise over 1.75 hours to a suspension of 50% sodium hydride (7.89 g., 0.165 M) (previously washed with pentane) in tetrahydrofuran (75 ml.) maintained at 0°–5° C. After stirring for 4 hours at 0°–5° C. the reaction is allowed to warm to room temperature and is then carefully stirred into ice water (2000 ml.), acidified with concentrated hydrochloric acid, and extracted with ethyl acetate (5 × 400 ml.). The combined organic phases are washed with saturated sodium chloride solution (3 × 300 ml.), dried over sodium sulfate

and concentrated under vacuum to yield an oil which is triturated with ether to precipitate triphenylphosphine oxide. Filtration, followed by concentration of the filtrate, gives an oily residue which is chromatographed over silica gel (1300 g.) eluting with benzene-hexane consisting of 30% to 100% benzene. From the middle fractions 51 g. (75%) of 4-(3,5-dibenzyloxyphenyl)-1-phenoxypent-3-ene is isolated as an oil; $R_f = 0.8$ (silica gel, 2-benzene:1-hexane); MS (mol.ion): 450.

Analysis: Calc'd for $C_{31}H_{30}O_3$: C, 82.63; H, 6.71%. Found: C, 82.90; H, 6.69%.

A solution of 4-(3,5-dibenzyloxyphenyl)-1-phenoxypent-3-ene (51 g., 0.113 M) in a mixture of absolute ethanol (160 ml.), ethyl acetate (160 ml.) and concentrated hydrochloric acid (0.2 ml.) is hydrogenated for 12 hours under 55 lbs. hydrogen in the presence of 10% Pd/C. Removal of the catalyst by filtration and concentration of the filtrate under vacuum yields 30.8 g. (100%) of product as a viscous oil.

Analysis: Calc'd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40%. Found: C, 75.54; H, 7.45%.

PREPARATION S

3,5-Dimethoxy-β-methylstyrene oxide

To a −78° C. solution of diphenylsulfonium ethylide (1.0 mole) in tetrahydrofuran (one liter) is slowly added 3,5-dimethoxybenzaldehyde (1.0 mole). The reaction mixture is stirred at −78° C. for 3 hours and then allowed to warm to room temperature. It is then added to ether-water and the ether phase separated. The ether phase is washed with water, dried ($MgSO_4$) and evaporated. Fractional distillation of the residue gives the title product.

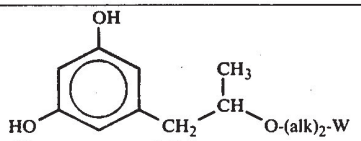
PREPARATION T

3-(3,5-Dihydroxyphenyl)-2-propylbutyl Ether

To a solution of sodium butoxide in butanol (0.5 liters of 1M) is added 3,5-dimethoxy-β-methylstyrene oxide (6.33 M). The mixture is heated for 18 hours at 70° C. and is then cooled and added to a mixture of ether-water. The ether solution is separated, dried ($MgSO_4$) and evaporated to give 3-(3,5-dimethoxyphenyl)-3-hydroxy-2-propylbutyl ether. It is purified by column chromatography on silica gel with ether-pentane elution.

By means of the procedure of Preparation P the title product is produced.

Similarly, the following are prepared from appropriate alcohols:

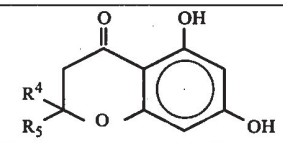


(alk_2)	W	(alk_2)	W
CH_2	CH_3	$CH(CH_3)CH_2$	CH_3
$(CH_2)_6$	CH_3	$CH(C_2H_5)—(CH_2)_2$	CH_3
$(CH_2)_3$	C_6H_5	$CH(CH_3)CH_2$	C_6H_5
$(CH_2)_2$	$4\text{-}FC_6H_4$		
$(CH_2)_2$	4-pyridyl		

PREPARATION U

2-R_4R_5-5,7-Dihydroxy-4-chromanones

The procedure of British Patent No. 1,077,066 is employed to produce the compounds tabulated below. It comprises reacting the appropriate $R_4R_5C{=}CH—COOH$ with an excess (50%) of 1,3,5-trihydroxybenzene and of polyphosphoric acid (10 to 20 grams per gram of trihydroxybenzene) on a steam bath for three hours. The mixture is then cooled and poured into water. The precipitate is extracted with ether, the ethereal extract washed with sodium hydroxide solution, dried and evaporated to afford the product. Purification is accomplished by distillation of the residue. The following are thus prepared:



R_4	R_5
CH_3	H
H	H
C_2H_5	C_2H_5
C_2H_5	H
CH_3	C_2H_5

PREPARATION V

(4-Halophenyl)cyclohexanols

A. 3- and 4-(4-Fluorophenyl)cyclohexanols

A benzene solution containing equimolar amounts of 4-fluorostyrene and 2-methoxybutadiene and hydroquinone (1% by weight based on diene) is heated in a sealed tube at 150° C. for 10 hours. The reaction vessel is cooled, the contents removed and concentrated to give 1-methoxy-4(and 5)-4-(fluorophenyl)cycloheptene which are separated by distillation in vacuo. Hydrolysis of the ether with 3% hydrochloric acid affords 3- and 4-(4-fluorophenyl)cyclohexanones.

Sodium borohydride reduction of the ketones according to the procedure of Example 5 affords the keto compounds.

In like manner, the corresponding 3- and 4-(4-chlorophenyl)cyclohexanols are prepared from 4-chlorostyrene.

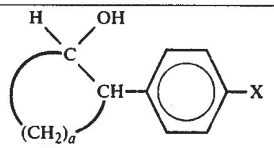
B. 2-(4-Fluorophenyl)cyclohexanol

This compound is prepared from cyclohexane oxide and p-fluorophenyl lithium according to the procedure of Huitric et al., *J. Org. Chem.*, 27, 715–9 (1962), for preparing 2-(4-chlorophenyl)cyclohexanol.

PREPARATION W

(2-Halophenyl)cycloalkanols

The procedure of Huitric et al., *J. Org. Chem.*, 27, 715–9 (1962) is employed but using the appropriate cycloalkylene oxide and p-halo (Cl or F) phenyl lithium reactants to produce the following compounds:



a	X	a	X
2	Cl	2	F
3	Cl	3	F
5	Cl	5	F

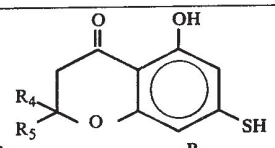
PREPARATION X

5-Hydroxy-7-mercapto-2,2-dimethyl-4-chromanone

A mixture of 3,5-dihydroxyphenyl methyl sulfide (5.85 g.) and 3-methylcrotonic acid (4.5 g.) is heated to 125° C. under nitrogen and boron trifluoride etherate (8.7 ml.) added. The mixture is refluxed for one hour and is then cooled. Water (10 ml.) is added, followed by 6N sodium hydroxide (40 ml.). The mixture is heated on a steam bath for 5 minutes, then cooled and acidified with 6N hydrochloric acid. It is extracted with ether (3 × 100 ml.) and the combined extracts washed with 10% sodium bicarbonate (1 × 25 ml.) and water (1 × 25 ml.) and then dried (Na_2SO_4). Concentration of the extract under vacuum affords dl-5-hydroxy-2,2-dimethyl-7-methylmercapto-4-chromanone. It is purified by silica gel chromatograhy.

The methyl mercapto compound thus produced is hydrolyzed by refluxing overnight with excess 48% hydrobromic acid. Concentration of the reaction mixture affords the title compound. It is purified by silica gel chromatography.

The following compounds are similarly prepared but replacing 3-methylcrotonic acid with the appropriate acid of the formula $R_4R_5C{=}CH{-}COOH$:



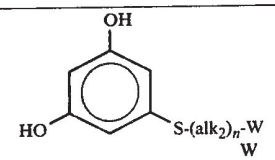
R_4	R_5
H	CH_3
H	H
C_2H_5	C_2H_5
H	C_2H_5
CH_3	C_2H_5

PREPARATION Y

Alkylation of 3,5-Dihydroxyphenylmercaptan

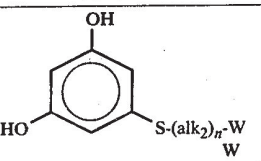
A solution of 3,5-dihydroxyphenylmercaptan (3.5 g., 0.01 mole) in absolute ethanol (50 ml.) is made just alkaline with sodium ethoxide. The appropriate bromide of formula $Br{-}(alk_2)_n{-}W$ (0.01 mole) is added and the mixture refluxed for 3 hours. It is then concentrated under reduced pressure and the residue extracted with ether. Evaporation of the ether affords the product.

The following compounds are thus prepared:



n	(alk_2)	W
1	$-CH(CH_3)(CH_2)_5-$	CH_3
1	$-CH(CH_3)CH(CH_3)(CH_2)_4-$	CH_3
1	$-C(CH_3)_2(CH_2)_5-$	CH_3
1	$-(CH_2)_8-$	CH_3
1	$-(CH_2)_4-$	CH_3
1	$-CH_2-$	C_6H_5
1	$-(CH_2)-$	C_6H_5
1	$-CH(CH_3)(CH_2)_3-$	C_6H_5
1	$-CH_2-$	C_3H_5
1	$-CH_2-$	C_5H_9
1	$-CH_2-$	C_6H_{11}
1	$-(CH_2)_2-$	C_5H_9
1	$-(CH_2)_3-$	C_5H_9

-continued



n	(alk_2)	W
1	$-(CH_2)_5-$	C_6H_{11}
1	$-(CH_2)_4-$	C_5H_9
1	$-(CH_2)_3CH(C_2H_5)-$	C_6H_{11}
1	$-(CH_2)_7-$	C_5H_9
1	$-(CH_2)_4-$	C_7H_{13}
1	$-(CH_2)_2-$	C_7H_{13}
1	$-(CH_2)_5-$	C_4H_7
1	$-(CH_2)_5-$	C_3H_5
1	$-(CH_2)-$	2-piperidyl
1	$-(CH_2)_3-$	4-piperidyl
1	$-(CH_2)-$	2-pyridyl
1	$-(CH_2)_3-$	3-pyridyl
1	$-(CH_2)_4-$	2-pyridyl
1	$-CH(CH_3)(CH_2)_2-$	2-pyridyl
1	$-CH(CH_3)(CH_2)_3-$	4-pyridyl
1	$-CH(C_2H_5)(CH_2)_2-$	4-piperidyl
1	$-(CH_2)_4-$	$4\text{-}FC_6H_4$
1	$-CH(CH_3)(CH_2)_2-$	$4\text{-}ClC_6H_4$
1	$-CH(CH_3)(CH_2)_3-$	$4\text{-}FC_6H_4$
0	—	C_6H_5
0	—	$4\text{-}FC_6H_4$
0	—	$4\text{-}ClC_6H_4$
0	—	C_3H_5
0	—	C_5H_9
0	—	C_6H_{11}
0	—	C_7H_{13}
0	—	4-pyridyl
0	—	2-piperidyl
0	—	2-pyridyl
0	—	$2\text{-}(C_6H_5)C_3H_4$
0	—	$4\text{-}(C_6H_5)C_6H_{10}$
0	—	$3\text{-}(C_6H_5)C_7H_{12}$
0	—	CH_3

PREPARATION Z

dl-2-(3,5-Dibenzyloxyphenyl)-2-hydroxy-1-(2-phenylethoxy)-propane

To a 20° C. a solution of dimethylsulfoxonium methylide (0.184 mole) in dimethylsulfoxide (185 ml.) is added 3,5-dibenzyloxyacetophenone (51.0 g., 0.153 mole). After stirring 1.5 hours at 20° C., the reaction is diluted with 200 ml. of ice water and added to 500 ml. ether and 200 ml. ice water. The organic phase is washed with cold water (2 × 200 ml.), dried over magnesium sulfate and evaporated to an oil. A solution of the thus produced crude 1-(3,5-dibenzyloxyphenyl)-1-methyloxirane (0.153 mole) in dimethylsulfoxide (100 ml.) is rapidly added to a 20° C. solution of sodium phenethoxide (0.306 mole) in dimethylsulfoxide (150 ml., made by the slow addition of 36.5 ml. [0.306 mole] of penethanol to a slurry of 7.34 g. [0.306 mole] sodium hydride in 150 ml. dimethylsulfoxide). The reaction is slowly heated over a ½-hour period to 70° C., stirred 30 minutes and cooled to 20° C. The reaction is diluted with 200 ml. ice water and added to ether (2 l.) and ice water (1 liter). The organic phase is washed with cold water (2 × 1 l.), dried over magnesium sulfate and evaporated to an oil. This crude oil is purified via column chromatography on 1.5 kg. of silica gel, and eluted with 60% ether-pentane to yield 30.0 g. (42%) of dl-2-(3,5-dibenzyloxyphenyl)-2-hydroxy-1-(2-phenylethoxy)propane, as an oil.

IR: ($CHCl_3$) OH 3534 cm^{-1}.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.46 (s, methyl), 2.85 (t, J=7Hz, $-CH_2Ph$), 2.81 (s, hydroxyl), 3.55 (s, $-CH_2O-$), 3.68 (+, J=7Hz, $-OCH_2-$), 5.06 (s, $PhCH_2O-$), 6.56 (t, J=2Hz, C-4ArH), 6.76 (d, J=2Hz, C-2,6 ArH), 7.25 (s, ArH) and 7.43 (s,ArH).

MS:m/e 468 ($M^{\oplus}$), 453, 377 and 335 (100%).

PREPARATION AA

dl-2-(3,5-Dihydroxyphenyl)-1-(2-phenylethoxy)propane

To a 0° C. solution of dl-2-(3,5-dibenzyloxyphenyl)-2-hydroxy-1-(2-phenylethoxy)propane (29.0 g., 61.9 mmole) in pyridine (50 ml., 0.619 mole) is slowly added phosphorousoxy chloride (5.65 ml., 61.9 mmoles). The reaction is allowed to warm to 20° C. and is stirred at 20° C. for 20 hours. The reaction is added to a 0° C. solution of 3.3N NaOH (300 ml.) and the resultant mixture extracted with ether (3 × 500 ml.). Each extract is washed with saturated potassium carbonate (1 × 500 ml.) and water (3 × 500 ml.). The combined organic extract is dried over magnesium sulfate, silica gel and then decolorized (carbon) and evaporated to an oil. This oil is purified via column chromatography on silica gel (200 g.) eluted with 60% ether-pentane to yield 17 g. (61%) of an oil (mixture of olefins). To a solution of this mixture of olefins (3.62 g.) in ethanol (10 ml.) and ethyl acetate (10 ml.) is added solid sodium bicarbonate (300 mg.) and 10% Pd/C (1.2 g.) This mixture is stirred 6 hours under one atmosphere of hydrogen. The reaction is diluted with ethyl acetate and filtered through diatomaceous earth. The evaporated filtrate is purified via column chromatography on silica gel (200 g.) eluted with 80% ether-pentane to yield 2.0 g. (92%) of dl-2-(3,5-dihydroxyphenyl)-1-(2-phenylethoxy)propane as an oil.

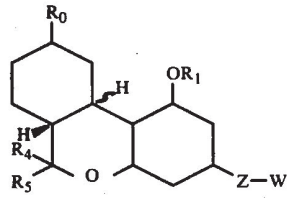
IR: ($CHCl_3$) OH 3571, 3279 cm^{-1}.

NMR: $\delta_{CDCl_3}^{TMS}$ 1.10 (d, J=7Hz, methyl), 2.80 (t, J=7Hz, $-CH_2Ph$), 2.90 (M, methine), 3.5 (m, $-CH_2O-CH_2-$), 6.10 (t, J=2Hz, C-4 ArH), 6.20 (d, J=2Hz, C-2,6 ArH), 6.5 (broad m, hydroxyl) and 7.19 (s, ArH).

MS: m/e 272 ($M^{\oplus}$), 181, 168, 151, 138, 137, 123, 105 (100%) and 91.

What is claimed is:

1. A compound having the formula



wherein R_1 is selected from the group consisting of hydrogen, alkanoyl having from one to five carbon atoms and $-CO-(CH_2)_p-NR_2R_3$ wherein p is 0 or an integer from 1 to 4; each of R_2 and R_3 when taken individually is selected from the group consisting of hydrogen and alkyl having from one to four carbon atoms; R_2 and R_3 when taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring selected from the group consisting of piperidino, pyrrolo, pyrrolidino, morpholino and N-alkylpiperazino having from one to four carbon atoms in the alkyl group;

each of R_4 and R_5 is selected from the group consisting of hydrogen, methyl and ethyl;

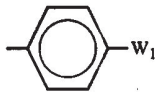
R_0 is selected from the group consisting of oxo and alkylenedioxy having from two to four carbon atoms;

Z is $-(alk_1)_m-X-(alk_2)_n-$ wherein each of (alk_1) and (alk_2) has from 1 to 9 carbon atoms, with the proviso that the summation of carbon atoms in (alk_1) plus (alk_2) is not greater than 9;

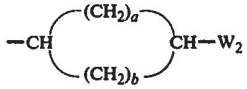
each of m and n is 0 or 1;

X is selected from the group consisting of O, S, SO and SO_2; and

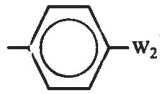
W is selected from the group consisting of methyl, pyridyl, piperidyl,



wherein W_1 is selected from the group consisting of hydrogen, fluoro and chloro; and



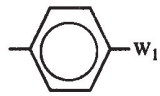
wherein W is selected from the grup consisting of hydrogen and



and a is an integer from 1 to 5 and b is 0 or an integer from 1 to 5; with the proviso that the sum of a and b is not greater than 5.

2. A compound according to claim **1** wherein R_0 is oxo.

3. A compound according to claim **2** wherein each of R_4 and R_5 is methyl and W is



wherein W_1 is hydrogen.

4. A compound according to claim **3** wherein Z is $-(alk_1)_m-O-(alk_2)_n-$.

5. A compound according to claim **4** wherein m is 0 and n is 1.

6. A compound according to claim **4** wherein m is 1 and n is 0.

7. The compound according to claim **4** wherein each of m and n is 0.

8. The compound according to claim **5** wherein $-(alk_2)-$ is $-CH(CH_3)-(CH_2)_3-$.

9. The compound according to claim **5** wherein $-(alk_2)-$ is $-CH(CH_3)-(CH_2)_2-$.

10. The compound according to claim **6** wherein $-(alk_1)-$ is $-CH(CH_3)-(CH_2)_3-$.

11. The compound according to claim **6** wherein $-(alk_1)-$ is $-CH(CH_3)-(CH_2)_2-$.

12. A compound according to claim **2** wherein each of R_4 and R_5 is methyl and W is methyl.

13. A compound according to claim **12** wherein Z is $-(alk_1)_m-O-(alk_2)_n-$.

14. A compound according to claim **13** wherein m is 0 and n is 1.

15. The compound according to claim 14 wherein (alk_2) is $—CH(CH_3)—(CH_2)_4—$.

16. A process for producing an anti-hypertensive effectn in a mammal which comprises administering to the mammal an antihypertensive producing quantity of a compound of claim 1.

17. The process of claim 16 wherein R_0 is oxo.

18. The process of claim 17 wherein each of R_4 and R_5 is methyl and W is

wherein W_1 is hydrogen.

19. The process of claim 18 wherein Z is $—(alk_1.)_m—O—(alk_2)_n—$.

20. The process of claim 19 wherein m is 0 and n is 1.

21. The process of claim 20 wherein $—(alk_2)—$ is $—CH(CH_3)—(CH_2)_3—$.

* * * * *

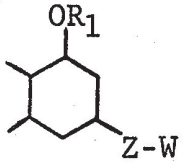
UNITED STATES PATENT AND TRADEMARK OFFICE

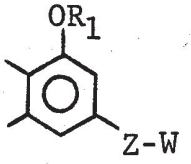
CERTIFICATE OF CORRECTION

PATENT NO. : 4,143,139
DATED : March 6, 1979
INVENTOR(S) : Jasjit S. Bindra

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Claim 1, line 2, that portion of the formula reading

"  "

should read --  --.

Signed and Sealed this

Twenty-sixth Day of *June 1979*

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

DONALD W. BANNER
Commissioner of Patents and Trademarks

ACTUAL PATENT URL LINK:
https://patentimages.storage.googleapis.com/ee/9d/2c/fa8c12384f956c/US4143139.pdf

PATENT CURRENT ASSIGNEE URL LINK:
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Abstract

9-Hydroxydibenzo[b,d]pyrans useful as analgesics, hypotensives, immunosuppressants, tranquilizers; as anti-secretory and anti-anxiety drugs; intermediates therefor and derivatives thereof having the formulae ##STR1## wherein R is hydrogen or alkanoyl having from one to five carbon atoms; R_1 is hydrogen, alkanoyl having from one to five carbon atoms or $-CO-(CH_2)_P-NR_2R_3$ wherein p is 0 or an integer from 1 to 4; each of R_2 and R_3 when taken individually is hydrogen or alkyl having from one to four carbon atoms; R_2 and R_3 when taken together with the nitrogen to which they are attached form a 5- or 6-membered heterocyclic ring selected from piperidino, pyrrolo, pyrrolidino, morpholino and N-alkylpiperazino having from one to four carbon atoms in the alkyl group;

Each of R_4 and R_5 is hydrogen, methyl or ethyl;

R_0 is oxo or alkylenedioxy having from two to four carbon atoms;

Z is

(a) alkylene having from one to nine carbon atoms;

(b) $-(alk_1)_m-X-(alk_2)_n-$ wherein each of (alk_1) and (alk_2) has from 1 to 9 carbon atoms, with the proviso that the summation of carbon atoms in (alk_1) plus (alk_2) is not greater than 9;

Each of m and n is 0 or 1;

X is O, S, SO or SO_2 ; and

W is methyl, phenyl, p-chlorophenyl, p-fluorophenyl, pyridyl, piperidyl, cycloalkyl having from 3 to 7 carbon atoms, or monosubstituted cycloalkyl wherein the substituent is phenyl, p-chlorophenyl or p-fluorophenyl;

With the proviso that when W is methyl, Z is

US4143139A

United States

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Inventor: Jasjit S. Bindra

Current Assignee : Pfizer Inc

Worldwide applications

1976 • ~~GB~~ ~~DE~~ ~~AT~~ ~~BE~~ *LU* ~~FR~~ ~~NL~~ ~~CH~~ 1977 • ~~FR~~ ~~FR~~ ~~US~~ 1979 • JP ~~JP~~ ~~JP~~ ~~JP~~

Application US05/819,471 events

1975-11-03 • Priority to US62821075A

1976-10-07 • Priority to US73067276A

1977-07-27 • Application filed by Pfizer Inc

1979-03-06 • Application granted

1979-03-06 • Publication of US4143139A