Ronald F. Borne* and Scott C. Mauldin

Department of Medicinal Chemistry, University of Mississippi,
University, MS 38677

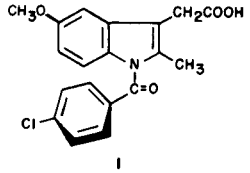
Received October 1, 1984

Based upon the structural similarities of cannabinoid derivatives which inhibit the biosynthesis of prostaglandins with those of the potent inhibitor, indomethacin, several cannabinoid derivatives possessing C-3 side chain carboxylic acid functionalities were prepared.

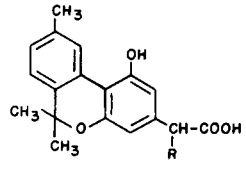
J. Heterocyclic Chem., **22**, 693 (1985).

In recent years considerable interest has been generated in the potential therapeutic utility of the cannabinoids. The known ability of Δ^9-tetrahydrocannabinol (THC) to inhibit the biosynthesis of prostaglandins [1] has been associated with its ability to lower intra-ocular pressure [2]. The most potent therapeutically-available inhibitor of prostaglandin biosynthesis, indomethacin, has been proposed by Gund and Shen [3] to act at the active site of arachidonic acid cyclooxygenase in a conformation depicted in structure **1**. The non-planarity of the *N-p-* chlorobenzoyl group with the indole ring is an important factor in its ability to inhibit the enzyme. Upon examination of Dreiding models of analogues of THC in which the C-3 pentyl side-chain was replaced with either an acetic acid or propionic acid moiety, a marked similarity of **2** and **3** to indomethacin was noted. This prompted us to prepare **2** and **3** as potential inhibitors of prostaglandin biosynthesis.

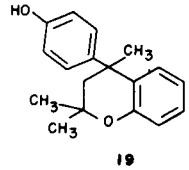
Initial approaches to the target compound were based, in part, on the report of Meltzer, *et al.* [4] on the synthesis of related side chain analogues of Δ^9-THC and is outlined in Scheme I. Our synthesis of methyl 3,5-dihydroxyphenylacetate (**4**) paralleled that in this report with only minor modifications. Treatment of **4** with the keto-ester **6** produced lactone **7** in 71% yield. Treatment of this lactone with a large excess of methylmagnesium iodide and work-up in acidic methanol gave the previously reported ester **9**. The synthesis of the propionic acid analogue **10** followed a similar path starting with methyl 2-(3,5-dihydroxyphenyl)-propionate (**5**) which was prepared by the method outlined in Scheme II. Commercially available 3,5-dibenzyloxyacetophenone (**15**) was treated with tosylmethylisocyanide (TosMIC) and potassium *t*-butoxide to give nitrile **16**.



1

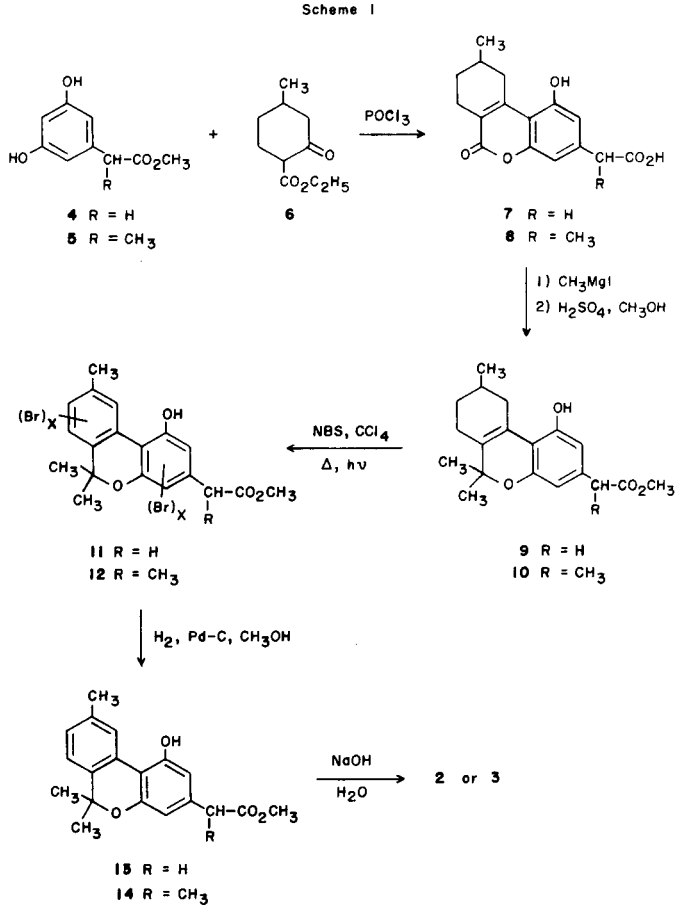


2 R = H
3 R = CH_3



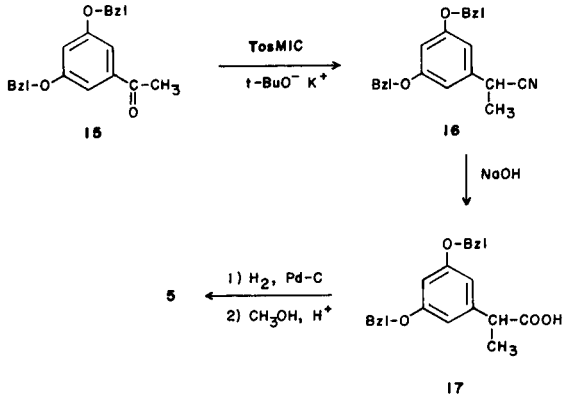
19

Scheme I



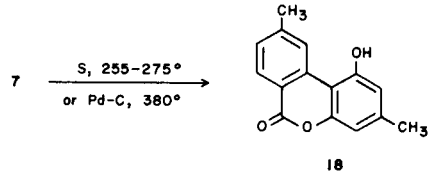
Hydrolysis of the nitrile, followed by hydrogenolysis of the benzyl groups and esterification gave **5** which was treated immediately with **6** to give **8** in a manner similar to that in which **7** was obtained. Treating **8** with excess methylmagnesium iodide and esterification gave the previously unreported **10**.

Scheme II



Several attempts to aromatize the C ring of **7** and **8** were investigated. Heating similar lactones possessing the *n*-C_5H_{11} side chain with sulfur had been previously reported to result in aromatization of the ring in good yields [5]. When **7** was heated with sulfur at 255-275° several products were formed, the major component of which appeared to be **18** indicating that aromatization was achieved but was accompanied by decarboxylation. The reaction was repeated on the methyl ester of **7** using palladium on carbon in xylene at 380° in a manner similar to that reported by Ghosh *et al.* [6] for the conversion of tetrahydrocannabinols to cannabinols. Again a complex mixture was obtained, the major component of which appeared to be **18**. Aromatization of pyran derivatives **9** and **10** was thus explored. Refluxing **9** with *N*-bromosuccinimide in carbon tetrachloride under tungsten-irradiation using benzoyl peroxide as the initiator produced a mixture of aromatic cannabinols substituted with bromine at various aromatic positions. Aromatization was evident by ^{1}H-nmr analysis. Although partial separation was achieved through chromatography, complete separation for better characterization of each compound was never achieved. Separation was efficient enough, however, to indicate the major component of the three to have been dibrominated (m/e = 465) and that the minor component was possibly a diene. An intermediate diene could have resulted from the reaction as ^{1}H-nmr analysis of the minor component indicated two distinct singlets for the geminal dimethyl substituents, along with a more defined aliphatic character observed in the δ 1.00-2.75 region. In the completely aromatic compounds, this was not found to have been the case as the geminal dimethyls appeared as one singlet integrating to six protons due to the overall adopted planarity of the molecule resulting from aromatization. Analogous results were obtained upon conversion of **10** into **12** with, again, structure **12** being representative of the brominated cannabinol mixture.

Scheme III



Further efforts to separate the brominated cannabinol mixture did not appear essential since removal of the halogens by catalytic hydrogenation would yield a common product - in our case, the methyl esters of the desired cannabinol acids. Initial attemps to remove the halogens involved catalytic hydrogenation with 10% palladium on carbon in methanol at 40 psi and 40°. After twenty-four hours, little reduction had occurred and even after five days, traces of the brominated cannabinols were still observed by thin layer chromatography. The problem was found to have been due to the retarding effect of the hydrogen bromide liberated on the catalyst, and when triethylamine was used, reduction occurred quite readily. As illustrated in Scheme I, reduction of **11** or **12** with palladium on carbon in the presence of base gave **13** or **14** quickly (2-4 hours) and in respectable yields. Hydrolysis of these esters gave the acids which were obtained as foams following workup and purification. Several attempts were made to recrystallize the compounds to no avail. However, upon the addition of carbon tetrachloride to **2** a solid resulted. Consequently **2** was recrystallized from carbon tetrachloride-benzene to give pure white crystals. Elemental analysis of **2** revealed very puzzling results, however, as the carbon percentage appeared extremely low. This prompted concern over the actual structure of **2** mainly due to the fact that the precursor was a brominated compound, which appeared more consistent with elemental results. On the other hand, the ^{1}H-nmr appeared well defined for structure **2** and the possible presence of bromine was not indicated. The ^{13}C-nmr of the solid **2** obtained from recrystallization from carbon tetrachloride indicated a significant absorption at 96.6 ppm indicating the presence of solvent still present in the molecule. Flippen *et al.* [7] reported the structure of a compound that formed crystalline inclusion compounds, or clathrates, with a variety of organic solvents. This compound **19** referred to as Dianin's compound, was found to have a tremendous solvent-trapping capacity for ethanol and chloroform. Due to the striking similarity of **2** and **3** to Dianin's compound, it was speculated that the same phenomenon was occurring with these cannabinols. This was found to have been the case as chlorine analysis indicated a 1:1 ratio of carbon tetrachlor-

ide to compound. Since a stable, crystalline entity was obtained through the formation of the inclusion compound, **2** and **3** were prepared as the carbon tetrachloride clathrates. X-ray crystallographic examination of these clathrates is currently being investigated. Pharmacological investigation of the ability of **2** and **3** to inhibit prostaglandin biosynthesis is also under investigation.

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover Unimelt (uncorrected) or on a Mel-Temp apparatus. Infrared spectra were determined with a Perkin-Elmer Model 281B spectrometer. Solution ir spectra were taken in matched sodium chloride cells of 0.105 mm (reference) and 0.105 mm (sample) widths. All ^{1}H-nmr spectra were obtained on a Varian Model EM 390 spectrometer and values are reported in ppm (δ) downfield from TMS. All ^{13}C nmr spectra were obtained on a Jeolco Model JNM FX-60 Fourier transform spectrometer and all values are reported in ppm (δ) downfield from TMS. Thin-layer chromatography was performed on Machery-Nagel silica gel G (0.25 mm) with fluorescent indicator. Column chromagotraphy was performed on Machery-Nagel silica gel 60 (0.05-0.2 mm), and flash chromatography was performed on Merck silica gel 60 (0.040-0.063 mm). Mass spectra were recorded at an electron energy of 70 eV on a Finnigan 3200, MS/DS system. The term *in vacuo* refers to water aspirator vacuum (15-30 mm). All solvents were AR grade except those used for extraction. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

1-Hydroxy-9-methyl-6-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-3-ylacetic Acid (**7**).

A solution of 5.0 g (27.5 mmoles) of **4** and 9.0 g (50 mmoles) of ethyl 4-methyl-2-oxocyclohexane-1-carboxylate in 50 ml of phosphorus oxychloride was stirred at room temperature for 22 hours. The reaction was quenched by the slow addition of ice, refluxed 2 hours, cooled to room temperature and stirred overnight. The resulting solid was stirred with ether/hexane for 4 hours, filtered, and recrystallized from ethyl acetate to give 5.6 g (71%) of a white solid, mp 240-242° (lit [4] mp 239.5-241°); ir (potassium bromide): 3340 (OH), 2500-3100 (br, acid), 1700 (C=O, acid), 1665 (C=O, lactone), and 1600 cm^{-1} (Ar); ^{1}H-nmr (deuterated dimethylsulfoxide): δ 1.10 (d, 3, CH_3), 1.3-3.30 (m, 8), 3.50 (s, 2, -CH_2CO_2H), 6.60 (s, 2, ArH); ms: m/e 288.0 (M$^+$), 288.0 (base).

Methyl 1-Hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]-pyran-3-ylacetate (**9**).

A solution of methylmagnesium iodide in ether was prepared by the slow addition of 43 g of methyl iodide in 100 ml anhydrous ether through a dropping funnel to 7.5 g of magnesium turnings in 100 ml of anhydrous ether (0.30 mole). A 1 ℓ three-necked round bottom flask equipped with a dropping funnel, reflux condenser, and mechanical stirrer was charged with 3.0 g (10.4 mmoles) of **7** and 250 ml of anhydrous tetrahydrofuran under nitrogen. The Grignard mixture was slowly added to this solution through the dropping funnel and the resulting mixture was stirred at room temperature for 5 hours. Following the slow addition of 40 ml of concentrated sulfuric acid in 400 ml of methanol, a dark red solution resulted which was stirred 8 hours. The solvents were then removed *in vacuo* to give a dark red oil which was diluted with 250 ml of water and extracted with dichloromethane (2 × 250 ml). The extracts were dried over sodium sulfate and the solvent removed *in vacuo* to give a red oil which was chromatographed over flash silica gel 60 (hexane/ethyl acetate 7:1) to give a yellow solid. Recrystallization from ethyl acetate/hexane gave 1.5 g (48%) of a white solid: mp 138-140° (lit [4] mp 139-140°); ir (chloroform): 3400 (OH), 2920 (-CH_2), 1740 (C=O, ester); ^{1}H-nmr (deuteriochloroform): δ 1.00 (d, 3, CH_3), 1.20 (s, 3, CH_3), 1.42 (s, 3, CH_3), 1.55-2.75 (m, 7), 3.50 (s, 2, -$CH_2CO_2CH_3$), 3.70 (s, 3, -OCH_3), 5.92 (bs, 1, OH), 6.30 (dd, 2, ArH); ms: m/e 301.1 (M$^+$), 301.1 (base).

2-(3′,5′-Dibenzyloxyphenyl)propionitrile (**16**).

A 500 ml three-neck flask equipped with a thermometer and 2 dropping funnels was charged with 10.0 g (0.030 mole) of **15** and 200 ml of anhydrous 1,2-dimethoxyethane under nitrogen. One dropping funnel was charged with 10.0 g (0.080 mole) of potassium *t*-butoxide in 75 ml of warm *t*-butyl alcohol, while the other contained a solution of 9.0 g (0.046 mole) of TosMIC in 100 ml of anhydrous 1,2-dimethoxyethane. The flask was cooled to −10° and stirred magnetically with simultaneous dropwise addition of the contents of the two dropping funnels. The rate of addition was monitored such that the temperature did not exceed 0°. The mixture was stirred at room temperature for 2.5 hours. A dark brown solution resulted which was concentrated *in vacuo*, diluted with 250 ml of water, and extracted with ether (2 × 250 ml). The ether extracts were dried over magnesium sulfate and concentrated *in vacuo* to give a red oil. Chromatography over silica gel 60 (chloroform) gave 6.50 g (63%) of a clear yellow oil; ir (potassium bromide): 3060 (-CH_2-), 2930 (-CH_2-), 2240 (CN), 1600 (Ar); ^{1}H-nmr (deuteriochloroform): δ 1.60 (d, 2, CH_3), 3.80 (q, 1, methine), 5.00 (s, 4, benzyl methylenes), 6.60 (d, 3, ArH), 7.40 (m, 10, ArH).

Anal. Calcd. for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.07. Found: C, 80.33; H, 6.20; N, 4.01.

2-(3′,5′-Dibenzyloxyphenyl)propionic Acid (**17**).

A mixture of 6.0 g (17.5 mmoles) of **16**, 60 ml of 10% sodium hydroxide and 100 ml of ethanol was refluxed for 6 hours. The solution was boiled briefly on a steam bath to remove dissolved ammonia, cooled in an ice bath, and acidified with 10% sulfuric acid. The resulting yellow solid was filtered, dried, and recrystallized from carbon tetrachloride to give 5.5 g (87%) of a white solid, mp 132-133°; ir (chloroform): 3500 and 3400 (OH), 2600-3300 (br, acid), 1750 (C=O, acid), 1600 cm^{-1} (Ar); ^{1}H-nmr (deuteriochloroform): δ 1.40 (d, 3, CH_3), 3.50 (q, 1, methine), 4.90 (s, 4, benzyl methylenes), 5.50 (bs, 1, OH), 6.50 (s, 3, ArH), 7.30 (m, 10, ArH); ms: m/e 362.3 (M$^+$), 91.2 (base).

Anal. Calcd. for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.23; H, 6.42.

1-Hydroxy-9-methyl-6-oxo-7,8,9,10-tetrahydro-6*H*-dibenzo[*b*,*d*]pyran-3-methylphenylacetic Acid (**8**).

A solution of 10.0 g (27.6 mmoles) of **17** and 75 ml of ethanol was hydrogenated at 40 psi and 40° over 1.0 g of 10% palladium on carbon for 2.5 hours. The catalyst was filtered through Celite and the resulting filtrate concentrated *in vacuo* to give an orange oil which was refluxed for 12 hours with a solution of 5 ml of concentrated sulfuric acid in 100 ml of methanol. The mixture was cooled, the solvent was removed *in vacuo*, and the resulting oil diluted with 100 ml of water and neutralized with 20% sodium carbonate. Extraction with ether (2 × 150 ml), drying of the extracts over sodium sulfate and removal of the solvent *in vacuo* gave a dark yellow oil. Purification over flash silica gel 60 (5% methanol/chloroform) gave a yellow oil which was crystallized from chloroform to give 3.0 g (55%) of **5** as a white solid, mp 69-71°; ir (potassium bromide): 3300 (OH), 2980 (-CH_2-), 1700 (C=O, ester), 1600 cm^{-1} (Ar); ^{1}H-nmr (deuterated acetone): δ 1.33 (d, 3, CH_3), 3.60 (q, 1, methine), 3.60 (s, 3, -OCH_3), 6.30 (s, 3, ArH), 8.20 (bs, 2, OH); ms: m/e 196.2 (M$^+$), 137.2 (base).

A mixture of 1.0 g (5.10 mmoles) of **5** and 1.5 g (8.24 mmoles) of ethyl 4-methyl-2-oxocyclohexane-1-carboxylate (**6**) in 15 ml of phosphorus oxychloride was stirred at room temperature for 22 hours, quenched by the addition of ice and refluxed 2.5 hours. The resulting solid was stirred at room temperature for 12 hours, filtered and stirred with ether/hexane for 4 hours. Recrystallization from ethyl acetate/methanol gave 1.0 g (65%) of a white solid, mp 280-282°; ir (potassium bromide): 2500-3500 (br, OH, acid), 1700 (C=O, acid), 1660 (C=O, lactone), and 1600 cm^{-1} (Ar); ^{1}H-nmr (deuterated dimethylsulfoxide): δ 1.05 (d, 3, CH_3), 1.40 (d, 3, CH_3), 1.70-3.50 (m, 7), 3.60 (q, 1, methine), 4.50 (bs, 1, OH), 6.70 (d, 2, ArH); ms: m/e 302.3 (M$^+$), 287.2 (base).

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.52; H, 6.00. Found: C, 67.35; H, 6.03.

1-Hydroxy-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-3-ylacetic Acid (Carbon Tetrachloride Clathrate) (**2**).

A mixture of 1.0 g (3.32 mmoles) of **9** and 2.7 g (15.2 mmoles) of recrystallized *N*-bromosuccinimide, 30 mg of benzoyl peroxide and 75 ml of carbon tetrachloride was refluxed under tungsten irradiation for 36 hours under nitrogen. The mixture was cooled, the succinimide filtered and the solvent removed *in vacuo* to give a white foam. Purification over silica gel 60 (chloroform) gave three components determined to be aromatic brominated cannabinols. The initial eluent, the major component, was found to have been a dibrominated cannabinol; ir (chloroform): 3480 (OH), 2980 ($-CH_2-$), 1730 cm^{-1} (C=O, ester); ^{1}H-nmr (deuteriochloroform): δ 1.60 (s, 6, geminal dimethyls), 2.35 (s, 3, $ArCH_3$), 3.70 (s, 3, $-OCH_3$), 4.15 (s, 2, $-CH_2CO_2CH_3$), 6.30 (s, 1, ArH), 7.25 (s, 1, ArH), 8.25 (s, 1, ArH); ms: m/e 464.9 (M^+), 80.0 (base.

The third eluent, the minor component, was found to have been a diene; ^{1}H-nmr (deuteriochloroform): δ 1.25 (s, 3, CH_3), 1.60 (s, 3, CH_3), 1.80 (m, 3), 2.50 (s, 3, CH_3), 3.70 (s, 3, $-OCH_3$), 4.20 (s, 2, $-CH_2CO_2CH_3$), 6.25 (m, 1, olefinic H), 7.10 (m, 1, ArH).

The mixture was then hydrogenated at 40 psi and 40° with 1.3 g of triethylamine, 500 mg of 10% palladium on carbon, and 75 ml of methanol for 2 hours. The catalyst was filtered over Celite and the resulting dark orange solution concentrated *in vacuo* to yield a pale white solid. Chromatography over silica gel 60 (chloroform/hexane 4:1) gave a yellow solid which was recrystallized from ethyl acetate/hexane to give 600 mg (58%) of **13** as a white solid, mp 147-148°; ir (chloroform): 3535 (OH), 2925 ($-CH_2-$), 1720 (C=O, ester), 1600 cm^{-1} (Ar); ^{1}H-nmr (deuterated acetone): δ 1.55 (s, 6, geminal dimethyls), 2.35 (s, 3, $ArCH_3$), 3.44 (s, 2, $-CH_2CO_2CH_3$), 3.65 (s, 3, $-OCH_3$), 6.50 (dd, 2, ArH), 7.10 (m, 2, ArH), 8.42 (s, 1, ArH), 8.90 (bs, 1, OH); ms: m/e 312.3 (M^+), 297.2 (base).

A solution of 500 mg (1.60 mmoles) of **13**, 15 ml of 10% sodium hydroxide and 15 ml of ethanol was refluxed 12 hours. The resulting solution was cooled, acidified with 10% sulfuric acid, and extracted with ethyl acetate (2 × 5 ml). The extracts were dried over sodium sulfate and the solvent was removed *in vacuo* to give a yellow oil which was crystallized from carbon tetrachloride to give 375 mg (54%) of **2** as a white solid, mp 110-115°; ir (potassium bromide): 2500-3400 (br, OH, acid), 1700 (C=O, acid), 1585 (Ar), 1240 (C=O, stretch), 760 and 785 cm^{-1} (carbon tetrachloride); ^{1}H-nmr (deuterated acetone): δ 1.55 (s, 3, geminal dimethyls), 2.30 (s, 3, $ArCH_3$), 3.50 (s, 2, $-CH_2CO_2CH_3$), 6.50 (dd, 2, ArH), 7.05 (m, 2, ArH), 8.40 (s, 1, ArH), 8.80 (bs, 1, OH); ^{1}C nmr (deuterated acetone): 96.6 ppm (carbon tetrachloride): ms: m/e 298.2 (M^+), 283.1 (base).

Anal. Calcd. for $C_{19}H_{18}Cl_4O_4$: C, 50.47; H, 4.01; Cl, 31.36. Found: C, 50.33; H, 4.05; Cl, 31.44.

Methyl 1-Hydroxy-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-3-α-methylphenylacetate (**14**).

A solution of methyl magnesium iodide, prepared by the addition of 60 g of methyl iodide in 50 ml of anhydrous ether to 10 g of magnesium turnings in 25 ml of anhydrous ether (0.42 mole), was added over 0.5 hour through a dropping funnel to a solution of 4.0 g (13.3 mmoles) of **8** in 400 ml of anhydrous tetrahydrofuran in a 1 ℓ three-neck flask equipped with a mechanical stirrer and reflux condenser under nitrogen. The mixture was stirred 5 hours, quenched by the slow addition of 500 ml of methanol in 50 ml of concentrated hydrochloric acid and stirred overnight. The solvents were removed *in vacuo* and the resulting dark oil was diluted with 500 ml of water and extracted with methylene chloride (3 × 500 ml). The extracts were dried over sodium sulfate and the solvent removed *in vacuo* to give a dark oil. Chromatography over silica gel 60 (hexane/ethyl acetate 5:1) gave 1.7 g (39%) of a tan foam which was found to be pyran **10**; ir (methylene chloride): 3580 and 3400 cm^{-1} (OH), 2920 ($-CH_2-$), 1720 (C=O, ester), 1610 cm^{-1} (Ar); ^{1}H-nmr (deuteriochloroform): δ 0.98 (d, 3, CH_2), 1.60-2.60 (m, 7), 3.70 (q, 1, methine), 3.60 (s, $-OCH_3$), 6.30 (d, 2, ArH), 6.50 (bs, 1, OH); ms: m/e 330.1 (M^+), 315.2 (base).

A mixture of 1.0 g (3.03 mmoles) of **10**, 2.7 g (15.17 mmoles) of *N*-bromosuccinimide (recrystallized), 30 mg of benzoyl peroxide and 50 ml of carbon tetrachloride was refluxed under tungsten irradiation for 36 hours. The succinimide was filtered and the filtrate concentrated *in vacuo* to give a red oil. Purification over silica gel 60 (chloroform) gave three components found to have been brominated cannabinols. The initial eluent was found to have been dibrominated; ir (chloroform): 3480 (OH), 2980 ($-CH_2-$), 1725 (C=O, ester), 1580 cm^{-1} (Ar); ^{1}H-nmr (deuteriochloroform): δ 1.55 (d, 3, CH_3), 1.70 (s, 6, geminal dimethyls), 2.40 (s, 3, $ArCH_3$), 3.70 (s, 3, $-OCH_3$), 42.0 (q, 1, methine), 6.40 (s, 1, ArH), 7.20 (s, 1, ArH), 8.30 (s, 1, ArH).

The third eluent was found to have been a brominated diene; ^{1}H-nmr (deuteriochloroform): δ 1.20 (s, 3, CH_3), 1.60 (d, 3, CH_3), 1.80 (s, 3, CH_3), 3.80 (s, 3, $-OCH_3$), 42.0 (q, 1, methine), 4.75 (m, 3), 6.40 (s, 1, ArH), 7.40 (m, 2, olefinic H's).

The mixture was hydrogenated at 40 psi and 40° with 1.3 g of triethylamine, 500 mg of 10% palladium on carbon, and 75 ml of methanol for 24 hours. The catalyst was filtered over Celite and the filtrate concentrated *in vacuo* to give a pale yellow solid. Chromatography over silica gel 60 (hexane/ethyl acetate 5:1) gave a yellow solid which was recrystallized from ethyl acetate/hexane to give 450 mg (46%) of **14** as a white solid, mp 149-150°; ir (potassium bromide): 3400 (OH), 2860 ($-CH_2-$), 1710 (C=O, ester), 1610 (Ar), 1220 cm^{-1} (C-O stretch); ^{1}H-nmr (deuterated acetone): δ 1.37 (d, 3, CH_3), 1.52 (s, 6, geminal dimethyls), 2.30 (s, 3, ArH), 6.50 (dd, 2, ArH), 7.15 (m, 2, ArH), 8.40 (s, 1, ArH), 9.05 (bs, 1, OH); ms: m/e 326.2 (M^+), 311.1 (base).

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found; C, 73.57; H, 6.82.

1-Hydroxy-6,6,9-trimethyl-6*H*-dibenzo[*b,d*]pyran-3-α-methylphenylacetic Acid (Carbon Tetrachloride Clathrate) (**3**).

A solution of 170 mg (0.52 mmoles) of **14** and 10 ml of 10% sodium hydroxide was stirred at room temperature 12 hours. The solution was then acidified with 10% sulfuric acid and extracted with ethyl acetate (2 × 25 ml). The extracts were dried over sodium sulfate and the solvent removed *in vacuo* to give an orange oil. Carbon tetrachloride (20 ml) was added and a white solid resulted which was recrystallized from carbon tetrachloride/benzene to give 150 mg (63%) of a white solid, mp 120-125°; ir (potassium bromide): 3250 (OH), 2920 ($-CH_2-$), 1700 (C=O, acid), 1610 (Ar), 1200 (C-O stretch), 760 cm^{-1} 785 cm^{-1} (carbon tetrachloride); ^{1}H-nmr (deuterated acetone): δ 1.40 (d, 3, CH_3), 1.60 (s, 6, geminal dimethyls), 2.40 (s, 3, $ArCH_3$), 3.60 (q, 1, methine), 6.40 (dd, 2, ArH), 7.20 (m, 2, ArH), 8.40 (s, 1, ArH), 8.90 (bs, 1, OH); ms: m/e 312.1 (M^+), 297.2 (base); 30 mg (0.065 mmole) of this solid was sublimed at a temperature of 125° (1 millitor) for 8 hours to give 15 mg (74%) of the free acid **21** as a white solid, mp 90-92°. Elemental analyses repeatedly gave inconsistent results.

REFERENCES AND NOTES

[1] S. Bernstein and A. Raz, *Prostaglandins*, **22**, 369 (1972).

[2] K. Green, *Exp. Eye Res.*, **1**, 175 (1978).

[3] C. Gund and T. Y. Shen, *J. Med. Chem.*, **20**, 1146 (1977).

[4] P. C. Meltzer, H. C. Dalzell and R. K. Razdan, *J. Chem. Soc., Perkin Trans. I*, 2825 (1981).

[5] R. Adams and B. R. Baker, *J. Am. Chem. Soc.*, **62**, 2401 (1970).

[6] R. Gosh, A. R. Todd and S. Wilkinson, *J. Chem. Soc.*, 1121 (1940).

[7] J. L. Flippen, J. Karle and I. L. Karle, *J. Am. Chem. Soc.*, **92**, 3749 (1970).