Electrolytic Reductive Coupling of 1,3-Diphenyl-1,3-propanedione and Derivatives[1]

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Received November 29, 1976

The electrolytic reductive coupling of 1,3-diketones leads to pinacols which are sersitive to both acids and bases. Electrolysis of slightly acidic solutions of 1,3-diphenyl-1,3-propanedione gives stable products but does not give the open-chain pinacol **2a**. Instead, the cyclized forms **6a** and a tricyclotrioxanonane **3a** are produced. The fluoro, chloro, and bromo derivatives **1b–d** produce the pinacols **2b–d**, whereas the methyl and methoxy derivatives **1f,g** produce pinacols which are quite susceptible to dehydration to hexadienediones **4f,g**, which undergo further reduction. All pinacols (as well as **3a** and **6a**) are readily dehydrated by acid forming the hexadienediones **4**. **4a** was reduced in good yield to the hexenedione **5a**.

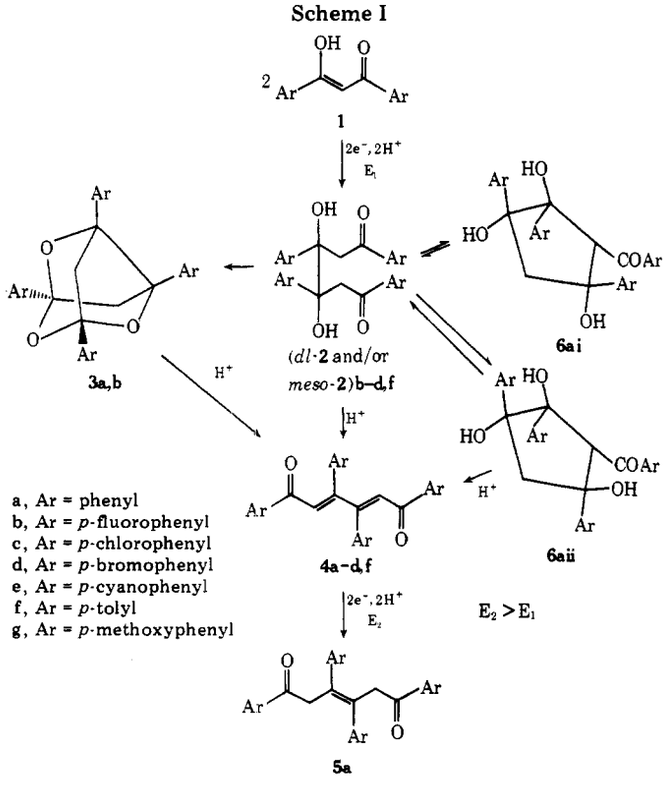
Several years ago Evans and Woodbury[2] reported that 1,3-diphenyl-1,3-propanedione (**1a**) could be electrochemically reduced in ethanol–water with the uptake of one, two, or four electrons depending on solution pH and cathode potential. Since that time the reduction of **1a** and related compounds has been studied in aprotic media[3–5] and the products from electrolysis of numerous other 1,3-diketones have been characterized.[6–14] Of particular interest in these studies has been the nature of the two-electron product with attention being focused on the possibility of cyclopropanediol formation.[6,10,13,14] The nature of the dimeric products formed by one-electron reduction has received less attention.[10,13,15]

The reductive coupling of **1a** was reported to give the pinacol **2a**.[2] We have extended our investigation of this interesting process and we now report a variety of other products formed in the reduction and information about the generality of the reaction.

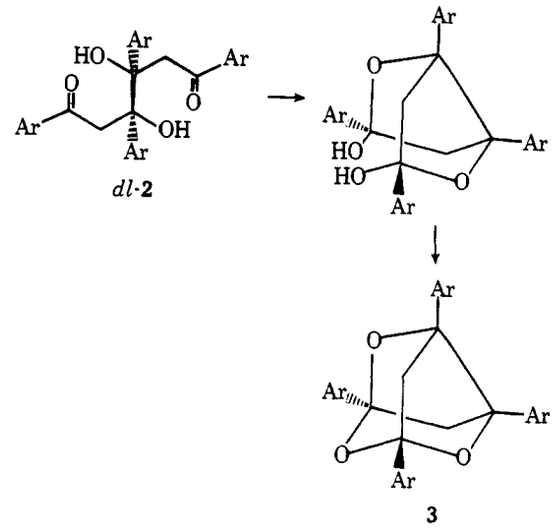
Results and Discussion

1,3-Diphenyl-1,3-propanedione (1a). Controlled potential coulometry has shown that **1a** is reduced in a one-electron process at −1.15 V in pH 4.2 buffer.[2] The product was previously reported to be the pinacol **2a** but the 100-MHz NMR spectrum indicates that one of the isomers of **6a** is a more likely assignment (Scheme I). **6a** is formed by an intramolecular aldol condensation of **2a**. In the two isomers of **6a** shown, it is assumed on steric grounds that the phenyl and benzoyl groups will be oriented trans to each other in the cyclic ketol. In addition, this communication reports the isolation of a new product, the trioxatricyclononane **3a**. **3a** can be obtained more reliably and in better yield using the 80% ethanol–water acetate buffer. This product may be obtained from *dl*-**2a** by double intramolecular ketalization followed by dehydration (Scheme II). It was found that stirring a suspension of **6a** in the acetate buffer caused partial conversion to **3a**.

Scheme I

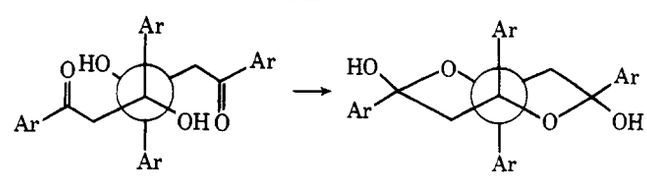


Scheme II



The meso form of **2a** cannot be converted to **3a**. Though it may form the bishemiketal, the dehydration step is impossible because the two OH groups are rot properly situated (Scheme III). It is on the basis of its conversion to **3a** that **6a** is thought

Scheme III



to be derived from *dl*-**2a**. A tetramethyl analogue of **3a** is formed during chemical reduction (magnesium/acetic acid) of acetylacetone.[16]

A slightly soluble gray powder was also formed during re-

duction in the pH 4.2 buffer.[2] In the present work it was found that small quantities of this substance could be recrystallized from benzene giving a compound (mp 259 °C) whose spectral properties and elemental analysis are consistent with its being one of the isomers of **6a** derived from *meso*-**2a** (not shown in Scheme I). This compound could not be converted to **3a** but it was dehydrated in high yield (72%) to dienedione **4a.**

Thus, the electrochemical reduction of **1a** would appear to produce initially both diastereomers of the pinacol, a reaction which is common in the reduction of many aromatic carbonyl compounds.[16-23] In this case, however, the pinacols are susceptible to a number of reactions leading to **3a, 4a,** and isomers of **6a.** It was of interest to see if similar product distributions would be obtained in the reduction of related compounds.

Reduction of Some *p,p'*-Substituted 1,3-Diphenyl-1,3-propanediones. Buffer 2 was selected for these electrolyses because the starting materials are more soluble in this medium.

It was found that the fluoro derivative **1b** gave a pinacol **2b** as well as a small amount of the trioxatricyclononane **3b.** A pinacol was isolated from electrolysis of the chloro and bromo derivatives but neither gave any trioxatricyclononane. In each case only one pinacol was isolated. In contrast to the reduction of **1a,** the NMR data indicated that the major products of the halo derivatives were the open-chain pinacols but it was not determined whether the isolated materials were meso or *dl.* The pinacols were readily converted to the dienediones **4b-d.**

These results indicate that reductive coupling to the pinacol can be achieved for **1** derivatives with electron-withdrawing substituents. However, the cyclic ketols **6** were not obtained. Electrolysis of the cyano derivative **1e** was not practical due to its low solubility.

The preparation was less successful with electron-donating substituents such as methyl (**1f**) or methoxy (**1g**). The electrolysis solution became yellow owing to the dehydration of the initially formed pinacol. For **1g,** the dienedione **4g** was detected in a partially electrolyzed solution by polarography. The dienediones have reduction waves positive of the wave of the 1,3-diketones so they will be reduced if formed during the electrolysis. Presumably, the electron-donating substituents accelerate acid-catalyzed dehydration of the pinacols, causing failure of the pinacol preparation from **1g.** Use of less acidic buffers did not give isolable quantities of pinacol **2g.**

Although dienedione was formed in the electrolysis of **1f,** a small amount of pinacol **2f** was isolated using buffer 2. On performing the electrolysis in a pH 6.1 buffer (buffer 3), a mixture of the open-chain pinacol **2f** and a cyclic ketol **6f** was obtained.

Reduction of Hexadienedione 4a. Reduction in buffer 2 produced a good yield of the hexenedione **5a.** Reductions of conjugated enediones are thought to occur by $2e^-$, 2 H^+ 1,ω-reduction followed by tautomerization of the bisenols so formed.[23,24] The syntheses of the 2,4-hexadiene-1,6-diones **4** and the 3-hexene-1,6-dione **5a** along with the production of 1,6-hexanediones by reductive coupling of chalcones[23] demonstrates that electrochemical routes exist for a number of 1,3,4,6-tetraarylhexyl systems.

Experimental Section

Melting points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Infrared spectra were recorded using a Perkin-Elmer Model 137, mass spectra were obtained using an A.E.I. MS-9 spectrometer, and the NMR spectrometers were a Jeolco MH100 or Bruker WH270. Unless otherwise indicated, NMR spectra were obtained using $CDCl_3$ solvent and Me_4Si reference.

Electrochemical Apparatus. The potentiostats used were a Wenking (Brinkmann Instruments, Westbury, N.Y.) Model 61R and a Princeton Applied Research (Princeton, N.J.) Model 173. The large electrolysis cell (cell 1) constructed from a reaction kettle has been described.[2] A smaller cell (cell 2) like the one used for coulometry[3] was employed in some electrolyses. Its capacity was about 100 mL.

All reductions were performed on mercury-pool cathodes with stirring effected by a Teflon-coated magnetic stirring bar. The platinum-wire auxiliary electrode was in a compartment separated from the cathode compartment by a medium-porosity glass frit. The anolyte was the same buffer solution used in the cathode compartment unless indicated otherwise. The cathode compartment was continuously purged with nitrogen. An aqueous saturated calomel reference electrode was used.

All experiments were carried out at room temperature (23 ± 1 °C) and no special precautions were taken to maintain a constant temperature. The currents were small enough to preclude large-temperature increases, although in the longer experiments the cell was warmed (never above 30 °C) by the motor of the magnetic stirrer.

Reagents. The 1,3-diketones were either commercially available or were prepared by standard literature procedures. They were purified by crystallization as required.

Three buffer solutions were used. Buffer 1 was the pH 4.2 citrate buffer in 50% ethanol–water which was employed previously.[2] Buffer 2 was prepared from 1 mol of potassium acetate and 6 mol of acetic acid made up to 1 L with 80% ethanol–water, and its apparent pH was also 4.2 as measured using a glass electrode calibrated with standard aqueous buffers. Buffer 3 was the pH 6.1 citrate buffer in 50% ethanol–water also employed previously.[2]

The mercury was taken from stock which is cleaned periodically by a chemical procedure.[25]

General Procedure for Electrochemical Syntheses. The reduction potential which was selected was on the diffusion plateau of the one-electron reduction wave as determined by polarography. For each compound, the appropriate buffer was electrolyzed at the potential to be used until a background current of less than 0.5 mA was obtained. The amount of starting material to be added to the cell was chosen so that its solubility was not exceeded. (**1d** was so insoluble that it was electrolyzed with only partial dissolution. The electrolysis was slow but most of the diketone eventually was reduced.) The quantities chosen ranged from 20 to 750 mg. This amount was then dissolved in 5 cm^3 of hot 95% ethanol and added dropwise with stirring to the cell. About 5 min after the addition of the starting material the electrolysis was begun. Initial currents ranged from 20 to 100 mA and after a period of 1 to 5 h the currents dropped below 10 mA, at which time another equal addition of reactant 1,3-diketone was made. When a total of ~2 g of reactant had been added, the electrolysis was stopped, and the cell contents were removed from the mercury, diluted 1:1 with water (or 0.05 M Na_2CO_3 with **1f** and **1g**), and set aside for 8 h. The insoluble crude product was then removed by vacuum filtration, air-dried for 1–3 h, and then extracted with diethyl ether or chloroform. Table I summarizes the electrochemical preparations reported in this work. The isolation and characterization of products from the various syntheses are described below. Only in the reduction of **1d** was starting material recovered. All of the products could be dehydrated to a dienedione **4** by the method reported earlier.[2] (These could be *Z* or *E* isomers. Isomeric identities were not determined.)

Reduction of 1,3-Diphenyl-1,3-propanedione (1a) in Buffer 1. Extraction of the crude product with ether or chloroform resulted in about 60% dissolution. Evaporation of the extract gave a yellow solid from which various crops of white to yellowish-white crystals of isomers of 2,3,5-trihydroxy-2,3,5-triphenylcyclopentyl phenyl ketone (**6a**). Melting points varied from 197 to 207 °C with ranges of 3 to 0.5 °C. The IR spectra of the samples obtained were identical to that earlier attributed to **2a.**[2] The NMR spectra revealed that each of the various samples contained principally or entirely one of two isomers assigned the structures **6ai** and **6aii,** although the isomers with the benzoyl group cis to the 5-phenyl could not be ruled out (see Results and Discussion). Reproducible conditions for producing one or the other could not be found. The principal evidence for the cyclic structure as opposed to the open-chain pinacol is the number and type of nonaromatic protons, including the fact that three resonances (rather than one) are lost by exchange with D_2O. The two isomers were differentiated on the basis of the larger chemical-shift difference between the methylene protons in **6ai** as opposed to **6aii:** NMR **6ai** δ 2.43, 2.57, 3.85, 4.00 (AB, 2, CH_2, J_{AB} = 14.5 Hz), 2.57 (s, 1, OH), 4.37 (s, 1, OH), 5.31 (s, 1, CH), 6.59 (s, 1, OH), 7.01–7.84 (comp m, 20, arom), singlets at 2.57, 4.37, 6.59 disappear on addition of D_2O; NMR **6aii** δ 2.33 (s, 1, OH), 3.05, 3.22, 3.36, 3.52 (AB, 2, CH_2, J_{AB} = 16.5 Hz), 4.23 (s, 1, OH), 5.40 (s, 1, CH), 5.97 (s, 1, OH), 7.08–7.84 (comp m, 20, arom), singlets at 2.33, 4.23, and 5.97 disappear on addition of D_2O (**3a** and **6aii** have also been found as reduction products of **1a** by

Table I. Electrochemical Preparations

Reactant	Cell	Buffer	Potential[a]	Recrystallization solvent	Product	Yield[b] (%)	Comments
1a	1	1	−1.15	C_2H_5OH	*dl*-**6a**	21–52	**3a** not obtained in all experiments
				C_6H_6	*meso*-**6a**	15–42	
				C_2H_5OH	**3a**	4–5	
1a	2	3	−1.20	C_2H_5OH	**3a**	13–38	
				C_2H_5OH	*dl*-**6a**	6–19	
				C_6H_6	*meso*-**6a**	30	
1b	2	2	−1.24	C_2H_5OH	**2b**	12–15	**3b** required 3 recrystallizations
					3b	5	
1c	1	2	−1.16	C_6H_6	**2c**	20	
1d	1	2	−1.13	C_6H_6	**2d**	29	
1f	1	2	−1.30	C_2H_5OH	**2f**	5	
1f	2	3	−1.29	C_2H_5OH	**2f**		After repeated recrystallizations, only a mixture was obtained
					6f		
4a	1	2	−0.74	C_6H_6	**5a**	78	

[a] V. vs. SCE. [b] Purified product. Ranges given are for two to five replicate syntheses. Based on starting material.

Juday[26] who employed an acidic medium and diglyme and methoxyethanol as cosolvents).

The gray powder (yield: 15–42%; three experiments) which remains after extraction of the crude electrolysis product was ignored in the earlier work.[2] It was found to have a relatively sharp melting point (239–40 °C) and, though only very slightly soluble in common solvents, it could be recrystallized from benzene, mp 259 °C. On the basis of its spectral and chemical properties, this substance is thought to be a mixture of two isomers of **6a** derived from *meso*-**2a:** IR (KBr) 3559, 3106, 2959, 1656, 1600, 1580 cm^{-1}; mass spectrum no molecular ion, large peaks at *m/e* 225, 120, 105, 77; 270-MHz NMR (benzene-d_6 saturated solution) δ 1.36 (br s, several protons, exchangeable with D_2O), 2.58, 2.62, 2.76, 2.80 (AB, CH_2, J_{AB} = 11.6 Hz), 2.77, 2.84, 4.43, 4.49 (AB, CH_2, J_{AB} = 17.5 Hz), 5.93 (S, CH), 6.80–8.05 (comp m, arom). Anal. Calcd for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 79.78; H, 5.85 (average of two analyses).

Reduction of 1a in Buffer 2. In this synthesis the anolyte was aqueous 1 M KNO_3. Again, part of the crude product (isomers of **6a** derived from *meso*-**2a,** contaminated with mercury) remained undissolved after extraction. The extract was evaporated giving a solid which upon recrystallization gave 0.2 g (13%) of **1,3,5,7-tetraphenyl-2,4,6-trioxatricyclo[3.3.0.1]nonane (3a):** mp 239–244 °C; IR showed no OH or carbonyl; mass spectrum *m/e* 432 (M^+), 312, 225, 105, 77; NMR δ 2.61 (AB, 4, CH_2, J_{AB} = 11.8 Hz), 7.05 (br s, 10, arom), 7.38–7.89 (m, 10, arom). Anal. Calcd for $C_{30}H_{24}O_3$: C, 83.31; H, 5.59. Found: C, 83.40; H, 5.52. Some **6a** derived from *dl*-**2a** was obtained in later crops during recrystallization.

Preparation of 3a from *dl*-6a. Identification of the lower melting, more soluble isomers of **6a** as being derived from *dl*-**2a** is based on their conversion to the tricyclic **3a,** a reaction which is impossible for *meso*-**2a.** *dl*-**6a (54 mg)** was added to 40 mL of buffer 2. The suspension was stirred for 24 h, diluted 4 to 1 with 20% aqueous NaCl, and extracted with three 50-mL portions of $CHCl_3$. The solid obtained after evaporation was recrystallized from ethanol–water, giving 19 mg (36%) of **3a,** mp 233–5 °C. Similar treatment of *meso*-**6a** for 4 days caused no change.

Reduction of 1,3-Bis(*p*-fluorophenyl)-1,3-propanedione (1b) in Buffer 2. Almost all of the crude product dissolved in chloroform. The chloroform-soluble material was recrystallized from ethanol–water, giving several crops of crystals. The first crop was a diastereomer of **1,3,4,6-tetrakis(*p*-fluorophenyl)-3,4-dihydroxy-1,6-hexanedione (2b):** mp 227 °C; IR (KBr) 3552, 3080, 2926, 1646, 1584, 1229, 1213 cm^{-1}; NMR δ 2.40, 2.67, 4.12, 4.29 (AB, 4, CH_2, J = 17.5 Hz), 5.30 (s, 2, OH), 6.82–7.84 (m, 16, arom). Singlet at δ 5.30 disappears on addition of D_2O. Anal. Calcd for $C_{30}H_{22}F_4O_4$: C, 68.96; H, 4.24; F, 14.54. Found: C, 68.92; H, 4.46; F, 14.74.

The second crop was difficult to purify. The highest melting sample (5% yield) had mp 200–203 °C. This substance was identified as **1,3,5,7-tetrakis(*p*-fluorophenyl)-2,4,6-trioxatricyclo[3.3.0.1]nonane (3b):** IR (KBr) showed no OH or carbonyl; NMR δ 2.57, 2.71, 2.73, 2.84 (AB, 4, CH_2, J = 11.6 Hz), 6.72–7.78 (m, 16, arom). Anal. Calcd for $C_{30}H_{20}F_4O_3$: C, 71.42; H, 4.00; F, 15.06. Found: C, 71.31, H, 4.07; F, 14.85.

Preparation of 1,3,4,6-Tetrakis(*p*-fluorophenyl)-2,4-hexadiene-1,6-dione (4b). 2b (35 mg) was dehydrated, giving 67% recrystallized (CH_2Cl_2–CH_3OH) **4b:** mp 220–1 °C; IR (KBr) 3115, 2985, 1637, 1592, 1550 cm^{-1}; NMR δ 6.84–7.84 (comp m). Similarly, 19.0 mg of **3b** was dehydrated giving 67% **4b.**

Preparation of 1,3,4,6-Tetrakis(*p*-chlorophenyl)-3,4-dihydroxy-1,6-hexanedione (2c). The crude product was recrystallized from benzene, giving 21% of **2c:** mp 227–230 °C; IR (KBr) 3591, 3119, 2961, 1660, 1591, 1573, 1482 cm^{-1}; NMR δ 2.55, 2.73, 4.20, 4.28 (AB, 4, CH_2, J = 17 Hz) 5.33 (s, 2, OH), 7.24–7.78 (m, 16, arom). Anal. Calcd for $C_{30}H_{22}Cl_4O_4$: C, 61.25; H, 3.55; Cl, 24.10. Found: C, 61.23; H, 3.84; Cl, 24.14.

Preparation of 1,3,4,6-Tetrakis(*p*-chlorophenyl)-2,4-hexadiene-1,6-dione (4c). 2c (44 mg) was dehydrated in the same way as **2a,** giving 54% **4c:** mp 223–5 °C (CH_2Cl_2–CH_3OH); IR (KBr) 1639, 1585, 1570 cm^{-1}; NMR: δ 7.20–7.80 (comp m). Anal. Calcd for $C_{30}H_{18}O_2Cl_4$: C, 65.24; H, 3.28; Cl, 25.68. Found: C, 65.22; H, 3.37; Cl, 25.58.

Preparation of 1,3,4,6-Tetrakis(*p*-bromophenyl)-3,4-dihydroxy-1,6-hexanedione (2d). The crude product (yield: 96%) recrystallized from benzene, giving a first crop with a broad melting range, and after three recrystallizations TLC showed two components. The second crop of crystals (yield: 29%) melted sharply (231–232.5 °C), and TLC showed one component, **2d:** IR (KBr) 3509, 2947, 1661, 1583, 1558, 1476, 1201, 1064, 995 cm^{-1}; NMR δ 2.43, 2.61, 4.07, 4.24 (AB, 4, CH_2, J = 17.5 Hz), 5.21 (s, 2, OH), 7.20–7.60 (m, 16, arom). Singlet at δ 5.21 disappears on addition of D_2O. Anal. Calcd for $C_{30}H_{22}Br_4O_4$: C, 47.03; H, 2.90; Br, 41.72. Found: C, 47.11; H, 2.98; Br, 41.58.

Preparation of 1,3,4,6-Tetrakis(*p*-bromophenyl)-2,4-hexadiene-1,6-dione (4d). 2d (41 mg) was dehydrated as above, giving 58% **4d:** mp 233–5 °C (CH_2Cl_2–CH_3OH); IR (KBr) 1645, 1575, 1553 cm^{-1}; NMR δ 7.42–7.73 (comp m). Anal. Calcd for $C_{30}H_{18}Br_4O_2$: C, 49.35; H, 2.48; Br, 43.78. Found: C, 49.48; H, 2.57; Br, 43.82.

Preparation of 1,3,4,6-Tetrakis(*p*-tolyl)-3,4-dihydroxy-1,6-hexanedione (2f). No extraction solvent was used. The crude product was recrystallized from 300 mL of 95% ethanol, giving 96.3 mg (5% yield) of slightly yellow crystals of **2f,** mp 215.5 °C. A second recrystallization from ethanol gave white crystals: mp 230–232 °C; IR (KBr) 3527, 3071, 2961, 1655, 1609, 1513 cm^{-1}; NMR: δ 2.22 (s, 6, CH_3), 2.31 (s, 6, CH_3), 2.47, 2.66, 4.19, 4.37 (AB, 4, CH_2, J_{AB} = 18.5 Hz), 5.23 (s, 2, OH), 6.97–7.20, 7.57–7.67 (m, 16, arom). The singlet at δ 5.23 disappears on addition of D_2O. Anal. Calcd for $C_{34}H_{34}O_4$, C, 80.59; H, 6.78. Found: C, 80.59; H, 6.79.

Preparation of 1,3,4,6-Tetrakis(*p*-tolyl)-2,4-hexadiene-1,6-dione (4f). 2f (28 mg) was dehydrated, giving 72.4% **4f:** mp 168 °C (C_2H_5OH); IR (KBr) 3060, 2951, 1633, 1601, 1546 cm^{-1}; NMR δ 2.26 (br s, 12 H, CH_3), 6.96, 7.03, (d, J = 8 Hz, 8 H, protons ortho to methyl), 7.23, (s, 2 H, olefinic), 7.36, 7.43 (J = 8 Hz, 4 H, protons meta to methyl, aryl groups), 7.59, 7.66 (d, J = 8 Hz, 4 H, protons meta to methyl, aroyl groups). Anal. Calcd for $C_{34}H_{30}O_2$: C, 86.76; H, 6.44. Found: C, 86.58; H, 6.42.

Preparation of 2,3,5-Tris(*p*-tolyl)-2,3,5-trihydroxycyclopentyl

p-Tolyl Ketone (6f). Again, no extraction step was employed. Ninety milligrams of small white crystals was collected as a crude product (46%) which gave the same R_f on silica-gel TLC plates as **2f**. This was recrystallized with difficulty from about 30 mL of 95% ethanol. After a number of recrystallizations, a small amount of product, mp 205–210 °C, was obtained. This was identified as a mixture of **2f** and an isomer of **6f**: NMR of mixture δ 2.00 (s, OH), 2.21 (s, CH_3), 2.26 (s, CH_3), 2.36 (s, CH_3), 2.40 (s, CH_3), 2.52, 2.70, 4.22, 4.41 (AB, CH_2 (open chain), J_{AB} = 18.5 Hz), 3.01, 3.17, 3.29, 3.44 [AB, CH_2 (cyclized), J_{AB} = 15.5], 4.26 (s, OH), 5.27, (s, CH), 5.33, (s, OH), 6.03 (s, OH), 6.83–7.32, 7.50–7.92 (m, arom). The singlets at δ 2.00, 4.26, 5.33, and 6.03 disappear on addition of D_2O.

Reduction of 1,3,4,6-Tetraphenyl-2,4-hexadiene-1,6-dione (4a). A white precipitate was collected and was recrystallized from benzene, giving two crops of white crystals: mp 210 and 225 °C, respectively; TLC, NMR, and IR indicated these two crops were identical. A second recrystallization from benzene yielded colorless needles of 1,3,4,6-tetraphenyl-3-hexene-1,6-dione: mp 232 °C; IR 3065, 2912, 1680, 1591, 1568, 1478, 1421, 1318, 1200, 748, 703 cm^{-1}; NMR (saturated) δ 3.98 (s, CH_2) 7.06–7.76 (m, arom). Anal. Calcd for $C_{30}H_{24}O_2$: C, 86.50; H, 5.82. Found: C, 86.56; H, 5.78.

Acknowledgment. The authors thank David F. Hillenbrand for his assistance with the high-field NMR experiments.

Registry No.—**1a,** 1704-15-0; **1b,** 62375-96-6; **1c,** 62375-97-7; **1d,** 6909-81-5; **1f,** 62375-98-8; *meso*-**2a,** 62375-99-9; **2b,** 62376-00-5; **2c,** 62376-01-6; **2d,** 62376-02-7; **2f,** 62376-03-8; **3a,** 62376-04-9; **3b,** 62376-05-0; **4a,** 10562-16-0; **4b,** 62376-06-1; **4c,** 62376-07-2; **4d,** 62376-08-3; **4f,** 62376-09-4; **5a,** 62376-10-7; **6a,** 62376-11-8; **6ai,** 62445-07-2; **6aii,** 62445-08-3; **6f,** 62376-12-9; 1,3,4,6-tetraphenyl-3-hexene-1,6-dione, 62376-10-7.

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Hashish.[1] Synthesis of (±)-Δ^1- and Δ^6-3,4-*cis*-Cannabidiols and Their Isomerization by Acid Catalysis

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Received March 9, 1976

The total synthesis of (±)-Δ^1- and Δ^6-3,4-*cis*-cannabidiols (CBD, **5a** and **5b**) by two independent routes is described. The starting materials for these new cannabinoids were the lactones **1a** and **7**. High-pressure liquid chromatography was used to separate the mixture of Δ^1- and Δ^6-CBD diacetates obtained in the final step of each route. The acid-catalyzed (*p*-TSA) transformation products of *cis*-CBDs (**5a** and **5b**) were isolated and identified as the ring closed *cis*-cannabinoids **12–15**. The rate of the reaction and the relative proportions of products were found to be dependent on the acid concentration.

(−)-Cannabidiol (CBD), which occurs naturally in marijuana (*Cannabis sativa*) and is the precursor in some of the syntheses of Δ^1- and Δ^6-tetrahydrocannabinols (THC),[2] has a 3,4-trans ring junction and a double bond in the Δ^1 position. The Δ^6-trans isomer and the corresponding Δ^1- and Δ^6-CBDs with a 3,4-cis junction are not known in the literature.[3-5] This article describes the first syntheses of (±)-Δ^6- and Δ^1-3,4-*cis*-CBDs and the transformations they undergo under the influence of an acid catalyst.

In an earlier article[6] Razdan and Zitko described the acid-catalyzed (*p*-toluenesulfonic acid, *p*-TSA) interconversion of Δ^1-3,4-*cis*-tetrahydrocannabinol (THC) and the isotetrahydrocannabinols (iso-THCs) by way of citrylidene-cannabis as a short-lived intermediate. We have found that both Δ^1- and Δ^6-*cis*-CBD undergo a similar conversion, the extent of which is strongly dependent on the concentration of the acid catalyst.

A total synthesis of (±)-Δ^6-*cis*-cannabidiol (**5a**) was achieved by two different routes from the lactones **1a** and **7** (Schemes I and II). (±)-Δ^1-*cis*-CBD (**5b**) was obtained from a mixture of lactones (**1a** and **1b**), produced by acid-catalyzed equilibration, with subsequent separation of the mixed CBDs.

Lactone **1a** was prepared from isoprene and 3-carboxy-5-hydroxy-7-*n*-pentylcoumarin by a Diels–Alder reaction accompanied by decarboxylation. Taylor and Strojny[7] developed this procedure to prepare similar lactones, demonstrating that isoprene adds to the coumarin to give a cis ring fusion and a methyl substituent at C-1, as shown in **1a**. The NMR of **1a** (Table I) is in complete agreement with the assigned structure. The benzylic proton at C-3 appears as two triplets with coupling constants of 6, 6, and 11 Hz, which is consistent with 3,4-cis ring fusion and the double bond at C-6. Hively[8] also prepared **1a** and arrived at similar conclusions