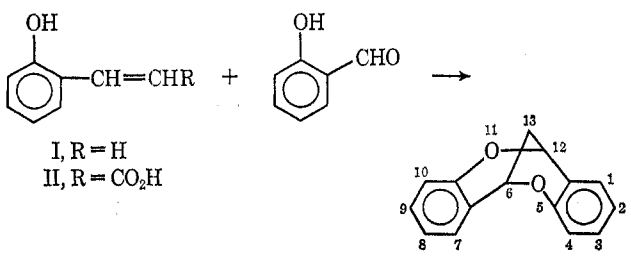
6H,12H-6,12-Methanodibenzo[b,f][1,5]dioxocins from the Reactions of o-Alkenylphenols and Salicylaldehydes

HENRY E. HENNIS, LEONARD R. THOMPSON, CHUN-SHAN WANG, AND DUANE B. PRIDDY

Benzene Research Laboratory, The Dow Chemical Co., Midland, Michigan 48640

The condensation of *o*-vinylphenols with alkyl substituents on the α and/or β positions of the vinyl side chain with salicylaldehydes yields 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocins with alkyl substituents on the methylene carbon and/or a bridgehead carbon in the heterocyclic ring system, respectively. The use of an acetic acid–hydrobromic acid or a benzene–concentrated sulfuric acid reaction medium gives improved product yields over the previously reported aqueous reaction medium. Intermolecular dimerization and intramolecular cyclization of the *o*-alkylphenols can be serious competing reactions. The hydrogenolysis of these compounds to bisphenols is of limited synthetic value.

It was recently reported that the 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin system (III) could be conveniently synthesized, albeit in low yield, by the condensation of either *o*-vinylphenol (I) or *o*-coumaric acid (II) and salicylaldehyde.[1]



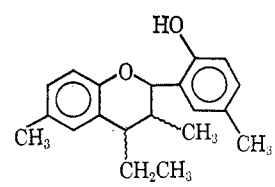
III

The more readily available *o*-coumaric acid was the starting material of choice. The previous work[1] was extended to include a few samples with substituents on the aromatic rings. It appeared likely that alkyl substituents could be incorporated into the heterocyclic ring system by the utilization of *o*-vinylphenols with side chain alkyl substituents. This article describes the synthesis of these types of compounds and a study to increase the yields of this new reaction. Some competing reactions which lower the yield of desired products were briefly examined.

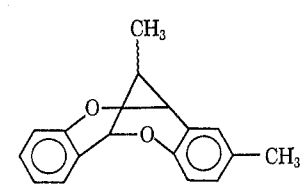
It was previously reported that a heterogeneous reaction medium of either *o*-vinylphenol or *o*-coumaric acid and salicylaldehyde in dilute aqueous hydrobromic acid at reflux temperature yielded 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocins. This study utilized two alternative methods which are superior when an *o*-vinylphenol is employed. Method A consisted of a homogeneous acetic acid–concentrated hydrobromic acid reaction medium at room temperature for 10 min. This provides a simple quick access to this complicated structure. Longer reaction times and higher temperatures resulted in poorer yields. Method B utilized a benzene solvent with catalytic quantities of concentrated sulfuric acid at room temperature for 1 hr. Method B was generally superior. For example, Method A was totally ineffective in producing compounds **7–9**. *o*-Coumaric acid failed to react by either method. The reaction temperatures were too low to cause decarboxylation of *o*-coumaric acid to yield the *o*-vinylphenol, the reactive intermediate.

Two product types representing reactions competing with the 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin synthesis were isolated. This does not represent an exhaustive search of side reactions. These products were found incidentally to the preparations of the subject compounds.

The *o*-alkenylphenol is capable of intermolecular dimerization under the conditions of these syntheses. For example, approximately equal yields of 2-(4-ethyl-3,6-dimethyl-2-chromanyl)-*p*-cresol (**18**) and 2,13-dimethyl-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin (**2**) were isolated from the reaction of 4-methyl-2-propenylphenol and salicylaldehyde. The dimerization reaction of *o*-propenylphenol has been reported.[2]

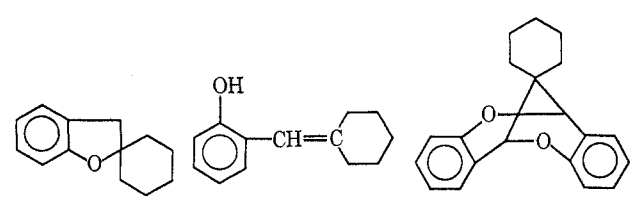


18



2

Intramolecular cyclization of the *o*-alkenylphenol was also detected. For example, only spiro(benzofuran-2(3H),1′-cyclohexane) (**19**) was isolated from the reaction of α-cyclohexylidene-*o*-cresol (**20**) and salicylaldehyde. None of the anticipated product **21** was isolable. Spiro(benzofuran-2(3H),1′-cyclohexane (**19**) is a known chemical and was previously prepared[3] by the cyclization of α-(1-cyclohexenyl)-*o*-cresol. Thus both reactions are well documented. No efforts were made to characterize polymeric materials and tars which also detract from the synthesis.



19 20 21

The previously reported hydrogenolysis of 6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin to 2,2′-trimethylenediphenol proceeded in only a modest 30% yield.[1] This reaction was applied to two more systems with

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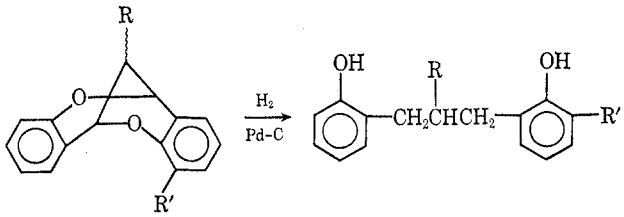
(2) H. Pauley and R. Buttlar, *Justus Liebigs Ann. Chem.*, **383**, 280 (1911).

(3) G. Práter and H. Schmid, *Helv. Chim. Acta*, **50**, 255 (1967).

similar results. Thus this method of synthesizing 2,2′-trimethylenediphenols is of questionable value.



Starting compd	R	R′	Product	Yield, %
1	CH_3	H	22	25
5	CH_3	CH_3	23	3.9

Experimental Section[4]

Starting Materials.—2-Propenylphenol,[5] 4-methyl-2-propenylphenol,[6] 6-methyl-2-propenylphenol,[7] 4,6-dichloro-2-propenylphenol,[8] 2-isopropenylphenol,[9] 4-methyl-2-isopropenylphenol,[10] 2-(1-ethylpropenyl)-phenol,[11] 5-methylsalicylaldehyde,[12] and 5-bromosalicylaldehyde[13] were prepared by published procedures. 3,5-Dichlorosalicylaldehyde (K and K Laboratories, Inc.) and 2-hydroxy-1-naphthaldehyde (Aldrich Chemical Co., Inc.) were purchased.

4-Chloro-2-isopropenylphenol.—The chemical was previously prepared by the reaction of methyl 5-chlorosalicylate with sodium to yield the sodium salt and reaction of the salt with methylmagnesium iodide to give the carbinol which was thermally dehydrated to the product.[14] The chemical was prepared in this study by the reaction of methyl 5-chlorosalicylate with methylmagnesium iodide.

To a mixture of 36.5 g (1.5 g-atom) of magnesium turnings and 400 ml of absolute ether was added dropwise with stirring 213 g (1.5 mol) of methyl iodide at a rate to maintain a gentle reflux. Stirring and heating were continued after methyl iodide addition until all the magnesium had reacted. Then 93 g (0.50 mol) of methyl 5-chlorosalicylate was added dropwise with stirring. Stirring and heating at the reflux temperature were continued for 2 hr after the ester addition. Saturated aqueous ammonium chloride solution (600 ml) was added slowly to decompose the Grignard complex. The aqueous and organic layers were separated. The ethereal solution was extracted with 100-ml portions of 10% sodium hydroxide solution three times. The combined extracts were acidified to pH 7 with dilute acetic acid. The carbinol, which precipitated as a white solid, was collected, dried, and then dehydrated by heating at 180° (500 mm) for 30 min. The crude 4-chloro-2-isopropenylphenol was purified by distillation to yield 11 g (26%) of a colorless oil, bp 76–79° (1 mm) (lit.[14] bp 75–80° (1 mm)).

4-Bromo-2-isopropenylphenol.—The compound was prepared as described for 4-chloro-2-isopropenylphenol. There was obtained a 25% yield of a colorless viscous oil, bp 89–93° (2 mm) (lit.[14] bp 89–93° (2 mm)).

4-Phenyl-2-propenylphenol.—A solution of 115 g (1.05 mol) of 4-phenyl-2-allylphenol[15] and 90 g of potassium hydroxide dissolved in 225 ml of methanol was distilled until a pot temperature of 135° was attained. Removal of distillate was discontinued and the reaction mixture was heated at the reflux temperature for 2 hr. Water (200 ml) was added to the cooled mixture to dissolve the precipitated solid, followed by 135 ml of concentrated hydrochloric acid. The product which solidified was separated and purified by recrystallization from 170 ml of Skellysolvent (bp 60–100°) to yield 79 g (72%) of product as long white needles, mp 78–80°. An analytical sample, mp 82.5–83.5°, was prepared by a second recrystallization.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.9; H, 6.90.

2-(1-Methylpropenyl)phenol.—Ethyl bromide (121 g, 1.1 mol) was added dropwise at a rate to maintain a gentle reflux to a stirred mixture of 24 g (1.0 g-atom) of magnesium turnings and 300 ml of absolute ether. Additional heating and stirring were required for complete reaction. Then 65 g (0.45 mol) of *o*-hydroxyacetophenone dissolved in 300 ml of absolute ether was added. The reaction mixture was stirred and heated at the reflux temperature for 1 hr to complete the reaction. The Grignard addition complex was decomposed by the addition of an ice-cold solution of 100 g of ammonium chloride dissolved in 500 ml of water. The layers were separated. The organic layer was extracted with 300 ml of a 10% sodium hydroxide solution. The alkaline extract was carbonated with Dry Ice giving an oily layer which was extracted with toluene. The toluene was removed by distillation under slightly reduced pressure (~20 mm) and the crude product distilled to yield 37 g (55%) of a colorless oil, bp 51–53° (0.5 mm).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.08; H, 8.16. Found: C, 80.8; H, 8.09.

Preparation of 6H,12H-6,12-Methanodibenzo[*b*,*f*][1,5]dioxocins. Method A.—A solution containing 0.025 mol of the *o*-alkenylphenol, 0.100 mol of the salicylaldehyde, 10.5 ml of glacial acetic acid, and 7.5 ml of 48% hydrobromic acid was prepared. There was a slight exothermic effect and an oil layer separated. The mixture was allowed to stand at room temperature for 10 min. Then an excess of 10% sodium hydroxide solution (450 ml) was added with stirring. The crude solid product which remained undissolved was collected and recrystallized from an appropriate solvent to yield the purified product.

Method B.—The *o*-alkenylphenol (0.050 mol) and the salicylaldehyde (0.078 mol) were dissolved in 250 ml of benzene. Concentrated sulfuric acid (0.5 ml) was added and the solution was stirred at room temperature for an hour. The benzene solution was extracted four times with 100-ml portions of a 10% sodium hydroxide solution and then evaporated to dryness in a rotary flash evaporator. The residue was recrystallized from an appropriate solvent to produce a purified product.

2-(4-Ethyl-3,6-dimethyl-2-chromanyl)-*p*-cresol (4-Methyl-2-propenylphenol Dimer) (18).—A solution of 26 g (0.175 mol) of 4-methyl-2-propenylphenol, 42.7 g (0.35 mol) of salicylaldehyde, 75 ml of glacial acetic acid, and 52.5 ml of concentrated hydrobromic acid was allowed to stand at room temperature for 10 min. Then 1 l. of 10% sodium hydroxide solution was slowly added with stirring. A gummy undissolved solid was collected and recrystallized from Skellysolvent (bp 60–100°) to yield 4.45 g (17%) of **18**, a light tan crystalline solid, mp 123–124.5°. An analytical sample was recrystallized from the same solvent to yield a white crystalline solid, mp 124–126°.

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16: mol wt, 296. Found: C, 81.2; H, 8.10; mol wt, 296 (mass spectrum).

The filtrate from the recrystallization was reduced in volume by evaporation, yielding a second crop of crystals. This product was also purified by recrystallization from Skellysolvent (bp 60–100°) to yield 7.7 g (18%) of 2,13-dimethyl-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin (**2**) (Table I).

Spiro(benzofuran-2(3H),1′-cyclohexane) (19).—A mixture of 14.0 g (0.075 mol) of α-cyclohexylidene-*o*-cresol (**20**), 30.0 g (0.30 mol) of salicylaldehyde, 50 ml of glacial acetic acid, and 30 g of 48% hydrobromic acid was stirred at room temperature for 10 min. The reaction mixture was poured into an excess of 10% sodium hydroxide solution. The expected undissolved solid did not appear. The alkaline solution was extracted with toluene. Evaporation of the toluene solvent gave 9 g of a colorless oily product which was recrystallized from ethanol to yield 8.8 g (63%) of spiro(benzofuran-2(3H),1′-cyclohexane) (**19**) as white needles, mp 30–31° (lit.[3] "an oil"). This compound is also referred to as "grisan."[16]

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.6; H, 8.33.

2-Methyl-1,3-di-(*o*-hydroxyphenyl)propane (22).—A mixture

(4) Melting points were determined in a "Melt Pointer" (Scientific Glass Apparatus Co., Inc.) and are corrected. Elemental analyses were done by the staff of Dr. P. Boyd, The Dow Chemical Co.

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(12) F. Tiemann and C. Schotten, *Ber.*, **11**, 767 (1878).

(13) A. Auwers and O. Bürger, *ibid.*, **37**, 3929 (1904).

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(15) W. N. White, D. Gwynn, R. Schlitt, C. Girard, and W. Fife, *J. Amer. Chem. Soc.*, **80**, 3271 (1958).

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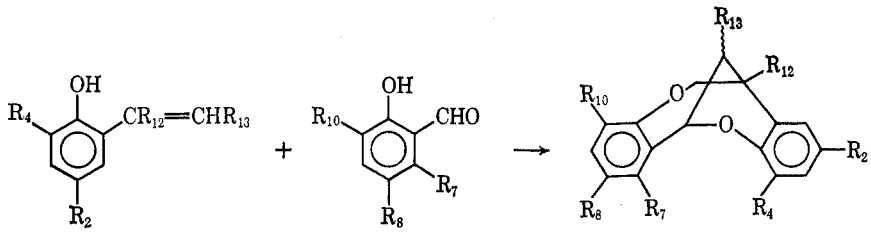
TABLE I

6H,12H-6,12-METHANODIBENZO[b,f][1,5]DIOXOCINS



Compd[a]	R_2	R_4	R_7	R_8	R_{10}	R_{12}	R_{13}	Prep method[b]	Recrystallization solvent[c]	Yield, %	Mp, °C
1	H	H	H	H	H	H	CH_3	A	1	18	137.5–138.5
								B	1	29	136–138
2	CH_3	H	H	H	H	H	CH_3	A	2	18	140–141
3	H	H	H	Br	H	H	CH_3	A	1	2.4	144–145
4	C_6H_5	H	H	H	H	H	CH_3	A	3	6.6	165–166.5
5	H	CH_3	H	H	H	H	CH_3	A	3	7.0	156–157
6	CH_3	H	H	CH_3	H	H	CH_3	A	3	11	141.5–142.5
7	Cl	Cl	H	H	H	H	CH_3	A		0.0	
								B	4	16	197–198
8	H	H	H	Cl	Cl	H	CH_3	A		0.0	
								B	4	20	197–198
9	Cl	Cl	H	Cl	Cl	H	CH_3	A		0.0	
								B	4	22	184–186
10	H	H	H	H	H	CH_3	H	A	3	56	122–122.5
11	CH_3	H	H	H	H	CH_3	H	A	1	58	160–161
12	Br	H	H	H	H	CH_3	H	A	4	49	145–146
13	Cl	H	H	H	H	CH_3	H	A	4	41	143–145
14	H	H	H	H	H	CH_3	CH_3	A	3	56	154.5–155
15	H	H	H	H	H	CH_3CH_2	CH_3	A	4	39	154–155
								B	3	38	154–155
16	H	H	*o*-C_6H_4[d]		H	CH_3	CH_3	A	1	42	192–193
17	H	H	*o*-C_6H_4[d]		H	CH_3CH_2	CH_3	A	1	11	185–189

[a] Satisfactory analyses (±0.3%) in carbon, hydrogen, and halogen were reported for all compounds with the exception of chlorine in compound 9 (Calcd: Cl, 37.77. Found: Cl, 37.3), Ed. [b] Preparation conditions: (A) acetic acid–hydrobromic acid reaction medium at room temperature for 10 min; (b) benzene solvent, sulfuric acid catalyst, at room temperature for 1 hr. [c] Recrystallization solvent: (1) ethanol–water, (2) Skellysolvent, bp 60–100°, (3) ethanol, (4) acetone–water. [d] *o*-Phenylene radical thus representing a naphthalene nucleus.

of 6.0 g (0.025 mol) of 13-methyl-6H,12H-6,12-methanodibenzo-[*b*,*f*][1,5]dioxocin (**1**), 1.0 g of 5% palladium-on-charcoal catalyst, and 300 ml of 2B absolute ethanol was placed in a Parr series 4500 medium-pressure reactor. The heterocyclic compound was hydrogenolyzed for 4 hr at 90° at 200 lb/in.² of hydrogen pressure. The catalyst was collected on a filter and the ethanol solvent was removed by distillation under reduced pressure. The residue was dissolved in toluene and the toluene solution was extracted with a 10% sodium hydroxide solution. The alkaline solution was acidified with concentrated hydrochloric acid. The solid which precipitated upon acidification was collected and recrystallized from Skellysolvent (bp 60–100°) to yield 1.5 g (25%) of **22** as white needles, mp 118.5–119°.

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.6; H, 7.55.

2-Methyl-1-(2-hydroxyphenyl)-3-(2-hydroxy-3-methylphenyl)-propane (23).—In a manner similar to that described for the preparation of **22**, **23** was prepared by the hydrogenolysis of 4,13-dimethyl-6H,12H-6,12-methanodibenzo[*b*,*f*][1,5]dioxocin (**5**) in 3.9% yield as white needles, mp 111–111.5°.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.6; H, 7.89.

Registry No.—**1**, 25356-06-3; **2**, 25356-07-4; **3**, 25356-08-5; **4**, 25356-09-6; **5**, 25356-10-9; **6**, 25356-11-0; **7**, 25356-12-1; **9**, 25356-14-3; **10**, 25297-04-5; **11**, 25297-05-6; **12**, 25297-06-7; **13**, 25297-07-8; **14**, 25297-08-9; **15**, 25297-09-0; **16**, 25297-10-3; **17**, 25297-11-4; 4-phenyl-2-propenylphenol, 25297-12-5; 2-(1-methylpropenyl)phenol, 25356-15-4; **18**, 25297-13-6; **22**, 25297-14-7; **23**, 25297-15-18.