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Synthetic Choleretics. III. Resorcinol Derivatives[1]

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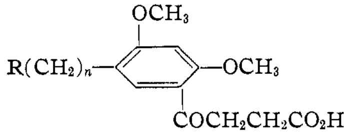
A series of cycloalkyl and aralkyl substituted derivatives of resorcinol and other dihydric phenols, bearing the β-carboxypropionyl side chain, were prepared and screened for choleretic activity in the dog. Under experimental conditions several of these compounds were five to six times as active as dehydrocholic acid and maintained a high level of bile flow for periods up to ten hours.

With the progression of these studies our attention has more recently been directed toward the development of a compound which, in addition to being highly potent, would maintain a prolonged, steady flow of bile. By eliminating a highly acute response in favor of a sustained, even excretion, we hope to approximate normal physiological behavior. In 1929, Chabrol[2] reported that resorcinol exerts a weak but protracted choleretic action. It has been demonstrated in the previous paper[3] that the introduction of a cyclohexyl group in the case of certain phenol derivatives enhanced the activity. Since existing evidence favors the $-COCH_2CH_2CO_2H$ side chain for maximum activity in compounds of this general type, a series of cycloalkyl and aralkyl substituted derivatives of resorcinol and other dihydric phenols, bearing the β-carboxypropionyl group, were prepared for study as choleretics.

The formation of the vicinal or 2-isomer as a by-product in the alkylation of resorcinol or its dimethyl ether with cyclohexene apparently constitutes a novel departure from the normal orientation of resorcinol in the Friedel–Crafts reaction. In this respect the reaction resembles the metallation of resorcinol with butyllithium, wherein both the 2- and the 4-isomers are formed.[4]

Orientation studies in the previous paper[3] leave no doubt as to the structures of the acylated resorcinol derivatives. The structures of the two acylated catechols and the hydroquinone derivative are based upon acylation studies of 4-methylcatechol,[5] 3-methylcatechol[6] and 2-amylhydroquinone.[7]

The pharmacological evaluation of these compounds was carried out by Drs. Cook and Hambourger of these laboratories.[8] Assays were conducted on the acute biliary fistula dog, using the same reference standard and method of expressing choleretic potency as described in the previous paper.[3] Within the limits of this series, compounds of the type



where R = cycloalkyl or aryl and n = 0–1, seem to be the most active. These methyl ethers are characterized by prolonged activity, several of which maintain a high level of bile flow ten hours after administration. Demethylation usually decreases both potency and duration of action.

Experimental Part

Intermediates. 4-Cyclohexylresorcinol Dimethyl Ether A. From 4-Cyclohexylresorcinol.—Two hundred and twenty grams (2.0 moles) of resorcinol and 100 g. (1.0 mole) of cyclohexanol were condensed in the presence of zinc chloride essentially as described in the patent literature.[9] Short path distillation gave 81 g. of crude product, b.p. 148–162° (0.5 mm.). Crystallization from four volumes of 1:1 benzene–cyclohexane solution and then from four volumes of benzene yielded 36.5 g. of lustrous plates, m.p. 125–126°.

Methylation according to the method described in the preceding paper[3] using proportionate amounts of reagents produced 28.3 g. of a colorless oil boiling at 100–102° (0.15 mm.), $n^{25}D$ 1.5355.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15; CH_3O, 28.18. Found: C, 76.33; H, 9.10; CH_3O, 28.18.

If the distilled crude cyclohexylresorcinol is methylated directly, a somewhat higher yield of a less pure product is obtained. After several days about 5 g. of white crystals separated. This material was shown to be identical with 2-cyclohexylresorcinol dimethyl ether described below.

B. From Resorcinol Dimethyl Ether and Cyclohexene.—Five hundred and fifty-two grams (4.0 moles) of resorcinol dimethyl ether was added during a 30-minute period at 8–10° to a stirred suspension of 268 g. (2.0 moles) of aluminum chloride in two liters of chlorobenzene. To this was added 164 g. (2.0 moles) of cyclohexene during a 10-minute period at 10°. The mixture was stirred for 18 hours at room temperature and then hydrolyzed. The chlorobenzene solution was washed twice with water, once with one liter of 5% sodium hydroxide and finally twice with water. The solvent was distilled under reduced pressure, and the residual oil was fractionated through a 1-m. packed column, collecting 312 g., b.p. 50–90° (0.1 mm.), and 292.7 g., b.p. 95–105° (0.1 mm.) (chiefly 97–100°). The first cut consisted essentially of resorcinol dimethyl ether which may be recyclized. The second fraction was stored in the refrigerator for 24 hours and then filtered to remove the crystalline 2-cyclohexylresorcinol dimethyl ether. The yield was 242 g. or 63% of theory based upon resorcinol dimethyl ether consumed; $n^{25}D$ 1.5347.

The distillation residue (82 g.), which solidified on standing, was crystallized from four volumes of ethanol to give 4,6-dicyclohexylresorcinol dimethyl ether, m.p. 131°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.77; H, 10.09.

The condensation of resorcinol dimethyl ether and cyclohexene was studied under widely varied conditions of temperature and concentration, using other catalysts such as phosphoric acid, sulfuric acid, zinc chloride and boron trifluoride, the latter being the most effective in this group of catalysts. Optimum conditions for the boron trifluoride catalyzed condensation, using chlorobenzene as the solvent, required a temperature of 125°, which, in spite of the large excess of resorcinol dimethyl ether, produced large amounts of the disubstituted compound.

4-Cyclohexylresorcinol Diethyl Ether.—The interaction of 200 g. (1.2 moles) of resorcinol diethyl ether, 49.2 g. (0.6

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[1] Presented before the Division of Medicinal Chemistry of the American Chemical Society in September, 1950, at Chicago, Illinois.

[2] E. Chabrol, R. Charonnat, M. Maximin and A. Bocquentin, *Compt. rend. soc. biol.*, **103**, 3 (1929).

[3] R. Burtner and J. M. Brown, THIS JOURNAL, **75**, 2334 (1953).

[4] H. Gilman, H. Willis, T. Cook, F. Webb and R. Meals, *ibid.*, **62**, 667 (1940).

[5] F. v. Bruchhausen and K. Saway, *Arch. Pharm.*, **263**, 602 (1925); V. Harding and C. Weizmann, *J. Chem. Soc.*, **97**, 1126 (1910).

[6] F. v. Bruchhausen, *Arch. Pharm.*, **263**, 570 (1925).

[7] J. Cruickshank and R. Robinson, *J. Chem. Soc.*, 2064 (1938).

[8] D. L. Cook and W. E. Hambourger, *J. Pharmacol.*, **100**, 421 (1950).

[9] U. S. Patent 1,650,036; *C. A.*, **22**, 434 (1928).

TABLE I

Substituted dimethoxybenzoylpropionic acid[a]	M.p., °C.	Crystn. solvent, ml./g.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Activity[b]
5-Phenyl	184	10 CH_3OH	$C_{18}H_{18}O_5$	68.78	68.76	5.77	5.80	++++
5-Benzyl	177	20 CH_3OH	$C_{19}H_{20}O_5$	69.50	69.43	6.14	6.19	++++
[c]	172	50 CH_3OH	$C_{17}H_{16}O_5$	67.99	68.31	5.37	5.60	++
5(α-Phenethyl)	134	4 EtOAc	$C_{20}H_{22}O_5$	70.16	70.63	6.48	6.58	++
5-Cyclohexyl	168.5	3 Benzene	$C_{18}H_{24}O_5$	67.48	67.54	7.55	7.61	++++
[c]	180	10 CH_3OH	$C_{16}H_{20}O_5$	65.74	66.04	6.90	7.01	+++
3-Cyclohexyl	143	4 CH_3OH	$C_{18}H_{24}O_5$	67.48	67.69	7.55	7.82	++
[c]	169–170	10 70% AcOH	$C_{16}H_{20}O_5$	65.74	66.19	6.90	7.06	++
5-*n*-Hexyl	140	5 CH_3OH	$C_{18}H_{26}O_5$	67.05	67.05	8.13	8.17	+++
[c]	127.5	5 70% AcOH	$C_{16}H_{22}O_5$	65.28	65.44	7.54	7.70	++
5-Cyclopentyl	137	5 CH_3OH	$C_{17}H_{22}O_5$	66.65	66.60	7.24	7.32	+++
[c]	169	7 70% AcOH	$C_{15}H_{18}O_5$	64.74	65.03	6.52	6.70	+
5-Cyclopentylmethyl	159–160	5 CH_3OH	$C_{18}H_{24}O_5$	67.48	67.44	7.55	7.44	++++
[c]	201	7 AcOH	$C_{16}H_{20}O_5$	65.74	65.71	6.90	6.93	++
5-Cyclohexylmethyl	174	4 AcOH	$C_{19}H_{26}O_5$	68.24	68.71	7.84	8.09	++++
[c]	212	7 AcOH	$C_{17}H_{22}O_5$	66.65	67.00	7.24	7.40	++
5-Cyclohexylethyl	165	5 AcOH	$C_{20}H_{28}O_5$	68.94	68.88	8.10	8.11	+++
[c]	146	4 CH_3OH	$C_{18}H_{24}O_5$	67.48	68.05	7.55	7.61	++
5-Cyclohexylpentamethylene	150.5	6 CH_3OH	$C_{23}H_{34}O_5$	70.74	70.99	8.78	8.84	++
[c]	145	30 CH_3OH	$C_{21}H_{30}O_5$	69.59	70.07	8.34	8.59	+
4,5-Dimethoxy-2-cyclohexylmethyl	148	7 CH_3OH	$C_{19}H_{28}O_5$	68.24	68.29	7.84	7.95	++++
3,4-Dimethoxy-2-cyclohexylmethyl	144	7 CH_3OH	$C_{19}H_{26}O_5$	68.24	68.12	7.84	7.88	+++
[c]	152–153	9 70% AcOH	$C_{17}H_{22}O_5$	66.65	66.27	7.24	7.18	+
2,5-Dimethoxy-4-cyclohexylmethyl	124	4 CH_3OH	$C_{19}H_{26}O_5$	68.24	67.96	7.84	7.98	+
[c]	[d]	5 70% AcOH	$C_{17}H_{22}O_5$	66.55	66.65	7.24	7.30	+
β-(2,4-Dimethoxy-5-cyclohexylbenzoyl)-acrylic acid	214 dec.	12 EtOAc	$C_{18}H_{22}O_5$	67.90	68.08	6.97	7.01	++
ω-(2,4-Dimethoxy-5-cyclohexylbenzoyl)-valeric acid	170	4 AcOH	$C_{20}H_{28}O_5$	68.94	68.69	8.10	8.15	[e]
α-Methyl-5-cyclohexyl	168	8 CH_3OH	$C_{19}H_{26}O_5$	68.24	68.39	7.84	7.86	+++
[c]	179	20 85% CH_3OH	$C_{17}H_{22}O_5$	66.65	67.05	7.24	7.42	+
2,2′,4,4′-Tetramethoxy-5,5′-bis-(β-carboxypropionyl)-biphenyl	232	28 AcOH	$C_{24}H_{26}O_{10}$	60.75	60.28	5.52	5.60	++
[f]	315 dec.	20 AcOH[g]	$C_{22}H_{22}O_{10}$	59.19	58.97	4.93	5.01	+
2,4-Diethoxy-5-cyclohexyl	176	5 CH_3OH	$C_{20}H_{28}O_5$	68.94	68.96	8.10	7.86	++++

[a] Except where indicated otherwise, the methoxyl groups occupy the 2- and 4-positions. [b] Dehydrocholic acid = +. [c] Phenolic compound prepared by completely demethylating the above ether. [d] Indefinite m.p., decomposes at about 170° in preheated bath. [e] Tested on cats, data to be reported elsewhere. [f] Only two methoxyl groups were removed by HI, probably at the 4,4′-positions as evidenced by $FeCl_3$ test. [g] Too insoluble in common solvents to crystallize; washed with boiling solvent.

mole) of cyclohexene and 80 g. (0.6 mole) of aluminum chloride was conducted precisely as described above. The crude product, which boiled at 105–120° (0.2 mm.) and weighed 96.5 g., was redistilled to yield 82.5 g. of a colorless oil, b.p. 106–108° (0.2 mm.), $n^{25}D$ 1.5181.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.14; H, 7.49.

Crystallization of the first distillation residue from alcohol gave 5.2 g. of 4,6-dicyclohexylresorcinol diethyl ether, m.p. 144°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.81; H, 10.18.

2-Cyclohexylresorcinol Dimethyl Ether.—Sixty-nine grams (0.5 mole) of resorcinol dimethyl ether was added at room temperature during a 15-minute period (spontaneous refluxing) to a solution of *n*-butyllithium prepared from 69.5 g. (0.75 mole) of *n*-butyl chloride and 11.5 g. (1.65 atoms) of lithium.[4] After an additional 20-hour reflux period under nitrogen, 73.5 g. (0.75 mole) of cyclohexanone was added during 20 minutes using ice-bath cooling to control the vigorous reaction. The mixture was then stirred and refluxed for four hours, hydrolyzed with ice and hydrochloric acid and extracted with ether. Removal of solvent and distillation of the residue yielded 59 g. of the crude carbinol boiling at 135–150° (0.25 mm.). There was no evidence of loss of water during distillation. Dehydration was effected by heating with 6 g. of powdered potassium acid sulfate for one hour at 140–160° (bath temperature). The cooled mass was taken up in ether, the ether solution washed well with water and then distilled to give 48 g. of 2-cyclohexenylresorcinol dimethyl ether, b.p. 106–108° (0.4 mm.), which crystallized on cooling (m.p. 90°). A sample crystallized from ten volumes of methanol in the form of lustrous plates, m.p. 94°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.28; H, 8.43.

A solution of 47 g. (0.21 mole) of the above compound in 275 ml. of acetic acid was hydrogenated in two hours at 60° using 0.3 g. of Adams catalyst under three atmospheres pressure. The mixture was heated to dissolve the crystalline precipitate, filtered and then distilled, collecting 43 g., b.p. 112–115° (0.3 mm.). The 2-cyclohexylresorcinol dimethyl ether thus obtained melted at 101–102° and produced no depression in melting point when mixed with a sample of that derived from direct alkylation.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.22; H, 9.15.

4-Cyclopentylresorcinol Dimethyl Ether.—Thirty-four grams (0.5 mole) of cyclopentene was added in five minutes at 50° to a stirred solution of 69 g. (0.5 mole) of resorcinol dimethyl ether and 8 g. of boron trifluoride ether complex. The mixture was stirred and heated until refluxing of the cyclohexene suddenly ceased (about two hours). After hydrolysis with ice-water and extraction with ether, the ether extract was washed well with water. Removal of solvent and distillation of the residue gave 39.5 g. of unchanged resorcinol dimethyl ether and 32 g. of an oil, b.p. 95–110° (0.25 mm.). The latter was redistilled, collecting 25.6 g. of a colorless liquid boiling at 95–96° (0.25 mm.), $n^{25}\mathrm{D}$ 1.5368. None of the expected isomeric product was found. The distillation residue (20 g.) was not examined further.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.63; H, 8.77.

4-Cyclohexylmethylresorcinol Dimethyl Ether.—Methylation in the prescribed manner of 83 g. (0.4 mole) of 4-cyclohexylmethylresorcinol[10] yielded 66.9 g. of the desired ether, b.p. 116–117° (0.3 mm.), $n^{25}\mathrm{D}$ 1.5282.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 77.53; H, 9.52.

4-Cyclopentylmethylresorcinol Dimethyl Ether.—Forty-two grams of cyclopentylmethylresorcinol[7] was methylated to give 35 g. of the ether as a yellow oil, b.p. 107–110° (0.3 mm.), $n^{25}\mathrm{D}$ 1.5286.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.14; H, 9.10.

4-(β-Cyclohexylethyl)-resorcinol Dimethyl Ether.—In a similar manner 128 g. of 4-(β-cyclohexylethyl)-resorcinol[7] yielded 108.3 g. of the dimethyl ether boiling at 130–131° (0.3 mm.), $n^{25}\mathrm{D}$ 1.5230.

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.50; H, 9.78.

4-(*n*-Hexyl)-resorcinol Dimethyl Ether.—Methylation of 32 g. of *n*-hexylresorcinol[7] afforded 26.7 g. of the ether, b.p. 105–108° (0.3 mm.), $n^{25}\mathrm{D}$ 1.5049.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.69; H, 10.07.

4-(ω-Cyclohexylamyl)-resorcinol Dimethyl Ether.—The interaction of 174 g. (0.94 mole) of δ-cyclohexylvaleric acid, 45 g. (0.33 mole) of zinc chloride and 35.2 g. (0.32 mole) of resorcinol was conducted in the manner suggested by Talbot and Adams.[7] After recovery of the excess cyclohexylvaleric acid [124.2 g., b.p. 125–127° (0.8 mm.)] there remained 78.5 g. of crude 4-(δ-cyclohexylvaleryl)-resorcinol which was reduced without further treatment.

A stirred suspension of 138.5 g. of the crude ketone, 330 g. of amalgamated zinc, 15 ml. of acetic acid and 500 ml. of 12 *M* hydrochloric acid was refluxed until a sample of the oil gave a negative ferric chloride test (3.5 hours). The waxy, supernatant product was separated from the chilled mixture, dissolved in ether and washed thoroughly with water to remove zinc salts. After evaporation of the solvent there remained 131.5 g. of crude 4-(ω-cyclohexylamyl)-resorcinol which soon crystallized. Two crystallizations from cyclohexane raised the melting point to 89°.

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 78.47; H, 9.92.

Methylation of 130 g. of the crude product yielded 100 g. of the desired methyl ether as a pale yellow oil, b.p. 172° (0.5 mm.), $n^{25}\mathrm{D}$ 1.5140.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.60; H, 10.51.

3-Cyclohexylmethylcatechol Dimethyl Ether.—A solution of 166 g. (1.0 mole) of 2,3-dimethoxybenzaldehyde in 200 ml. of ether was added during a 45-minute period to a stirred solution of cyclohexylmagnesium bromide, prepared from 163 g. (1.0 mole) of bromocyclohexane and 26.7 g. (1.1 atoms) of magnesium. There was a vigorous reaction, and a pasty, gray precipitate gradually formed. The mixture was stirred and refluxed for 90 minutes longer, hydrolyzed with iced ammonium chloride solution and then set aside for two hours to complete the decomposition of the magnesium complex. The aqueous phase was extracted with ether, and the combined ether solutions were washed twice with 500-ml. portions of 10% sodium bisulfite. The ether solution was then washed twice with water, dried over sodium sulfate and the solvent removed. Distillation of the residual oil through a 30-cm. Vigreux column gave a crude product, b.p. 115–150° (0.5 mm.), which was redistilled, collecting 153 g. of 2,3-dimethoxyphenylcyclohexylcarbinol boiling at 145–147° (0.5 mm.), $n^{25}\mathrm{D}$ 1.5381.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.96; H, 8.86. Found: C, 71.75; H, 8.90.

A solution of 99.4 g. (0.99 mole) of chromic acid in 200 ml. of 50% acetic acid was added in 75 minutes at 40–45° to a stirred solution of 153 g. (0.61 mole) of the above carbinol in 400 ml. of 70% acetic acid. The reaction, which was moderately exothermic, subsided after an additional hour, whereupon the mixture was diluted with two liters of water and extracted with chloroform. The extract was washed thoroughly with water, stripped of solvent and the residual oil distilled, collecting 93.5 g. of 2,3-dimethoxyphenyl cyclohexyl ketone, b.p. 129–130° (0.3 mm.), $n^{25}\mathrm{D}$ 1.5330.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.34; H, 8.29.

A mixture of 90 g. (0.36 mole) of the ketone, 240 g. of amalgamated zinc, 350 ml. of 12 *M* hydrochloric acid, 150 ml. of water and 200 ml. of toluene was stirred and refluxed for 48 hours. Four 50-ml. portions of hydrochloric acid were added at six-hour intervals. The toluene layer was washed well with water and stripped of solvent. In order to compensate for demethylation during the reduction, the crude product was dissolved in a mixture of 450 ml. of acetone and 91 g. of methyl sulfate and then treated slowly with a concentrated solution of 44 g. of sodium hydroxide. The mixture was stirred and refluxed for one hour, stripped of solvent and diluted with water. After extraction with ether and removal of solvent, the product was distilled, collecting 47.3 g. of a colorless liquid boiling at 120° (0.6 mm.), $n^{25}\mathrm{D}$ 1.5245.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 77.00; H, 9.38.

4-Cyclohexylmethylcatechol Dimethyl Ether.—Seventy-four grams (0.55 mole) of aluminum chloride was added portionwise at 0–3° to a stirred solution of 69 g. (0.5 mole) of veratrole and 73.2 g. (0.5 mole) of cyclohexanecarbonyl chloride in 500 ml. of nitrobenzene. The mixture was stirred for two hours longer at 0° and then stored overnight at room temperature. Following hydrolysis and steam distillation of the solvent, the crude product was taken up in ether and washed with water. Removal of the solvent and distillation of the residue yielded 103 g. of 3,4-dimethoxyphenyl cyclohexyl ketone as a yellow oil, b.p. 160–162° (0.3 mm.), $n^{25}\mathrm{D}$ 1.5585.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.54; H, 8.00.

One hundred two grams of this ketone was reduced with 280 g. of amalgamated zinc in the manner described for the 3-isomer. The desired product weighed 57.3 g. and boiled at 120–121° (0.25 mm.), $n^{25}\mathrm{D}$ 1.5310.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 76.90; H, 9.46.

Cyclohexylmethylhydroquinone Dimethyl Ether.—The interaction of 58.7 g. (0.42 mole) of hydroquinone dimethyl ether, 61.5 g. (0.42 mole) of cyclohexanecarbonyl chloride and 61.6 g. (0.46 mole) of aluminum chloride in 420 ml. of nitrobenzene was conducted as described above. The yield of 2,5-dimethoxyphenyl cyclohexyl ketone, b.p. 142–144° (0.1 mm.), was 86.6 g., $n^{25}\mathrm{D}$ 1.5414.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.27; H, 7.94.

The reduction of 86 g. of this ketone with 224 g. of amalgamated zinc in the above manner afforded 34.3 g. of the desired ether which boiled at 115–116° (0.25 mm.), $n^{25}\mathrm{D}$ 1.5286.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.47. Found: C, 77.57; H, 9.45.

4-Benzylresorcinol Dimethyl Ether.—A rapidly stirred mixture of 330 g. (2.39 moles) of resorcinol dimethyl ether, 225 g. (1.77 moles) of benzyl chloride and 3 g. of copper powder was heated at 190–200° (internal temperature) for two hours. The mildly exothermic reaction was accompanied by the evolution of hydrogen chloride, which noticeably diminished after the first hour. After filtration of the copper the mixture was distilled, collecting 140 g. of a low boiling fraction (chiefly resorcinol dimethyl ether) and 213 g. of an oil, b.p. 120–138° (0.1 mm.). The latter was redistilled through a 1-m. packed column to yield 196 g. of desired product, b.p. 127–128° (0.1 mm.),[11] $n^{25}\mathrm{D}$ 1.5764.

Anal. Calcd. for $C_{15}H_{16}O_2$: C, 78.91; H, 7.07. Found: C, 78.91; H, 7.08.

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[10] R. Talbot and R. Adams, THIS JOURNAL, **49**, 2040 (1927).

[11] S. Skraup and K. Böhm, *Ber.*, **59**, 1007 (1926), who prepared this compound by a different method, reported b.p. 188–190° (13 mm.).

The partially crystalline residue from the first distillation, which weighed 133 g., was crystallized from ethanol to produce 75 g. of 4,6-dibenzylresorcinol dimethyl ether as lustrous plates melting at 98°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.98; H, 6.97. Found: C, 83.07; H, 7.03.

4-(α-Phenethyl)-resorcinol Dimethyl Ether.—Methylation of 214 g. of crude 4-(α-phenethyl)-resorcinol[12] afforded 100 g. of the ether, b.p. 139–145° (0.25 mm.), n^{25}D 1.5715.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.13; H, 7.45.

4-Phenylresorcinol Dimethyl Ether.—A mixture of 100 g. of 4-cyclohexylresorcinol dimethyl ether and 10 g. of 5% palladium–charcoal was heated at 280–290° (bath temperature) for three hours under an air cooled condenser. The crude product was taken up in 500 ml. of boiling methanol, chilled to 0° and filtered to remove the catalyst and a small amount of crystalline material. Distillation of the filtrate yielded 70 g. of a yellow liquid boiling at 108–112° (0.1 mm.), n^{25}D 1.5920.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 79.42; H, 7.07.[13]

Dimethoxyaroylpropionic Acids.—When the substituted resorcinol ethers employed in this series were acylated with succinic anhydride in the manner prescribed for the corresponding phenol ethers,[3] the products were invariably contaminated with partially demethylated compounds which seriously complicated purification in many instances. Attempts to correct this situation by employing varied reaction periods at lower temperatures were unsuccessful.

Since it is evident from these results that the methoxyl groups in this type of compound are inordinately susceptible to cleavage by excess aluminum chloride, the following procedure was adopted as the preferred method. Thirty-three and one-half grams (0.25 mole)[14] of aluminum chloride was added portionwise at 5–10° to a stirred solution of 55 g. (0.25 mole) of 4-cyclohexylresorcinol dimethyl ether and 38 g. (0.25 mole) of β-carbomethoxypropionyl chloride in 250 ml. of benzene. The mixture was stirred for 3.5 hours at 5–10°, then at room temperature for six hours and finally hydrolyzed. The benzene solution was washed well with water, and the crude ester, obtained by vacuum distillation of the solvent, was saponified by refluxing with a solution of 16 g. of sodium hydroxide in 160 ml. of methanol for 30 minutes. After removal of the solvent and addition of 500 ml. of water, the solution of the sodium salt was washed with ether and acidified. The crude acid, which gave a negative ferric chloride test, weighed 67.2 g. and melted at 158–160°. Crystallizing from 200 ml. of benzene and rinsing the crystals with 50 ml. of fresh solvent yielded 55.2 g. of colorless acid melting at 168.5°.

δ-(2,4-Dimethoxy-5-cyclohexylbenzoyl)-valeric Acid.—This acid was prepared in the manner described above using δ-carbomethoxyvaleryl chloride as the acylating agent.

α-Methyl-β-(2,4-dimethoxy-5-cyclohexylbenzoyl)-propionic Acid.—A stirred mixture of 66 g. (0.3 mole) of 4-cyclohexylresorcinol dimethyl ether and 34.5 g. (0.3 mole) of methylsuccinic anhydride in 300 ml. of nitrobenzene was treated portionwise at 0–5° with 80.4 g. (0.6 mole) of aluminum chloride. The dark solution was stirred for an additional hour at 0° and then stored overnight at room temperature. After hydrolysis and steam distillation of the solvent, the crude acid was dissolved in an excess of 5% sodium hydroxide and this solution was washed with ether to remove neutral impurities. The semi-crystalline crude acid weighed 56 g. and gave a moderate ferric chloride test. Two crystallizations from methanol yielded 16.5 g. of pure acid, m.p. 168°.

β-(2,4-Dimethoxy-5-cyclohexylbenzoyl)-acrylic Acid.—The interaction of 0.1 mole of 4-cyclohexylresorcinol dimethyl ether and 0.1 mole of maleic anhydride with 0.2 mole of aluminum chloride in nitrobenzene solution was conducted in the usual manner.[3] The yield of pure acid melting at 214° was about 5%. The use of tetrachloroethane as the solvent with a reaction period of 85 hours at 5° did not improve this yield.

The following procedure, which involved dehydrohalogenation of the brominated acid, was more satisfactory. A solution of 16 g. (0.1 mole) of bromine in 32 ml. of acetic acid was added dropwise at 60° to a stirred solution of 32 g. (0.1 mole) of β-(2,4-dimethoxy-5-cyclohexylbenzoyl)-propionic acid. After an additional 30 minutes heating at 60°, the solvent was distilled under reduced pressure, and the residual product was suspended in 300 ml. of Skellysolve B. The yield of β-bromo-β-(2,4-dimethoxy-5-cyclohexylbenzoyl)-propionic acid, m.p. 176° dec., was 28 g. Crystallization from fifteen volumes of toluene raised the melting point to 180–181° dec.

Anal. Calcd. for $C_{18}H_{23}O_5Br$: Br, 20.02. Found: Br, 19.77.

A stirred solution of 26 g. of the crude bromo acid and 12 g. of fused sodium acetate in 100 ml. of acetic acid was refluxed for 30 minutes with simultaneous precipitation of sodium bromide. The hot mixture was diluted with water, and the crude product was filtered (19.8 g.). Crystallization from 140 ml. of methanol (Darco) gave 16 g. of bright yellow needles melting at 213°, which was identical with the acid obtained by direct acylation.

2,2',4,4'-Tetramethoxy-5,5'-di-(β-carboxypropionyl)-biphenyl.—A stirred suspension of 54.8 g. (0.2 mole) of 2,2',4,4'-tetramethoxybiphenyl[15] and 42 g. (0.42 mole) of succinic anhydride in 400 ml. of nitrobenzene was treated with 112.5 g. (0.84 mole) of aluminum chloride at 0–3°. The mixture was stirred for two hours longer at 0° and then stored overnight, permitting the ice-bath to melt. Hydrolysis and steam distillation of the solvent yielded 88 g. of crude acid which gave a moderate ferric chloride test. Two crystallizations from acetic acid produced 40 g. of almost colorless acid melting with decomposition at 232°.

Dihydroxyaroylpropionic Acids.—The dimethoxyaroylpropionic acids were demethylated in satisfactory yields by means of hydriodic acid essentially as described in the preceding paper.[3]

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[12] Kindly supplied by the Koppers Company.

[13] This material evidently contains a small amount of by-product; refractionation did not improve the analysis.

[14] The use of two equivalents of aluminum chloride as commonly employed, resulted in lower yields of pure product because of partial demethylation. Compare with D. Papa, E. Schwenk and H. Hankin, THIS JOURNAL, **69**, 3018 (1947).

[15] Obtained in 76% yield by heating equal weights of 4-iodoresorcinol dimethyl ether and copper powder at 260° under nitrogen for three hours; see E. Späth and K. Gibian, *Monatsh.*, **55**, 342 (1930).