The second paper was sprayed with a 0.5% solution of 3,5-dinitrosalicylic acid in 1 *N* sodium hydroxide. This reagent is frequently used to detect reducing sugars. In the present application, the paper while still moist was heated in an oven at 70°. α-Ketoglutaric and pyruvic acids appeared as brilliant orange spots after about 5 minutes. These spots were transient, and their location and relative intensities were noted. On continued heating, glucose and 2-ketogluconate appeared as permanent brown spots.

The third paper was sprayed with a 0.2% solution of orthophenylenediamine in ethyl alcohol, also containing 1% nitric acid. On heating in the 70° oven for about 30 minutes, keto substances on the paper appeared in characteristic colors. 2-Ketogluconic acid and its lactone were deep olive green. 5-Ketogluconic acid (present as a guide spot) was deep blue. Glucose was grayish-brown. α-Ketoglutaric acid was white on the steel-gray background. Pyruvic acid was rose-colored, and was easily detectable even at low concentrations. The R_f values of the various substances were approximately as follows, beginning at the starting line: 2-ketogluconolactone, 0.10; gluconic and 2-ketogluconic acids, 0.15; α-ketoglutaric acid, 0.25; pyruvic acid, 0.35; and glucose, 0.4. The R_f values of the organic acids, and especially of α-ketoglutaric acid, were considerably dependent on their concentration in the spot. The acids also tended to tail badly if overspotted. For these reasons, identification of the substances by their characteristic colors and their order in the line of spots was more satisfactory than identification by R_f value.

PEORIA 5, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

Depsidones. II. Hydroxy and Methoxy Analogs[1]

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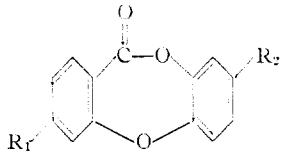
2-(2-Hydroxyphenoxy)-4-methoxybenzoic acid lactone (II) and 2-(2,4-dihydroxyphenoxy-)-4-methoxybenzoic acid lactone (III) have been prepared as further analogs of the depsidones. Methods have been developed for the formation of phenolic lactones, and a selective demethylation of phenolic ethers is described.

In a continuation of the study of the preparation of compounds related to the depsidones,[2] we have prepared hydroxy and methoxy derivatives of 2-(2-hydroxyphenoxy)-benzoic acid lactone (I). Tomita, Inubuse and Kusuda have suggested that I be called "depsidone."[3] We have chosen to use the systematic names throughout the present discussion, reserving "depsidone" as a generic name for the class.

Such substitution products (II, III) contain the important functional groups of the naturally occurring depsidones, some of which have shown bacteriostatic activity.[4]



I, R_1R_2 = H
II, R_1 = OCH_3, R_2 = H
III, R_1 = OCH_3, R_2 = OH

The preparation of 2-(2-hydroxyphenoxy)-4-methoxybenzoic acid lactone (II) proceeded from methyl 2-chloro-4-methoxybenzoate (IV) as outlined in Chart I. The condensation of IV with the sodium salt of guaiacol (V) proceeded smoothly to give methyl 2-(2-methoxyphenoxy)-4-methoxybenzoate (VI). Attempted demethylation of VI to 2-(2-hydroxyphenoxy)-4-hydroxybenzoic acid (VII) under the usual conditions with 48% hydrobromic acid in acetic acid was unsuccessful, resulting instead in 2,3'-dihydroxydiphenyl ether (VIII).

The ease of decarboxylation of *o*- or *p*-hydroxybenzoic acids is well known.[5] From consideration of the S_E2 mechanism proposed for similar decarboxylations,[6] it would appear probable that the methoxy acid (IX) is not undergoing decarboxylation, but more likely that decarboxylation is occurring subsequent to complete demethylation. It thus appeared attractive to attempt to achieve selective demethylation, and avoid loss of the carboxyl group to form 2-(2-hydroxyphenoxy)-4-methoxybenzoic acid (X). Such selectivity is suggested by the results of Ziegler, Weber and Gellert,[7] who observed the increased ease of cleavage of aromatic ethers, substituted *p*- with methoxyl (*o*–*p*-directing) groups.[8] It is further to be noted that the contributing canonical structures of VI suggest a lowered basicity for the 4 oxygen in VI, thereby inhibiting acid-catalyzed cleavage of the ether.

When demethylation was carried out with acetic acid saturated with anhydrous hydrogen bromide at 100° (steam-bath), there was isolated an acid, $C_{14}H_{12}O_5$, containing one methoxyl group. That the acid has the structure desired and expected (X) is supported by the fact that 2-phenoxy-4-methoxybenzoic acid is recovered unchanged under similar conditions and also by the further reactions of X.

Attempted cleavage of VI with acetyl iodide or with acetyl bromide[9] led to 3,5-dimethoxyxanthone.

Conversion of X to the lactone (II) was accomplished by the use of thionyl chloride in pyridine.[2] When II was treated with methanolic sodium

(1) From the thesis submitted by John W. Weldon to the Graduate Faculty of the University of California, 1951.

(2) D. S. Noyce and J. W. Weldon, THIS JOURNAL, **74**, 401 (1952).

(3) M. Tomita, Y. Inubuse and F. Kusuda, *J. Pharm. Soc. Japan*, **64**, 173 (1944); (*C. A.*, **45**, 6173 (1951)).

(4) A. Stoll, J. Renz and A. Brack, *Experientia*, **3**, 111 (1947); V. C. Barry, *Nature*, **158**, 131 (1946); S. Shibata, Y. Miura, H. Sugimura and Y. Toyoizumi, *J. Pharm. Soc. Japan*, **68**, 340 (1948).

(5) F. v. Hemmelmayr, *Sitz. Akad. Wiss. Wien*, **121**, 1359 (1912).

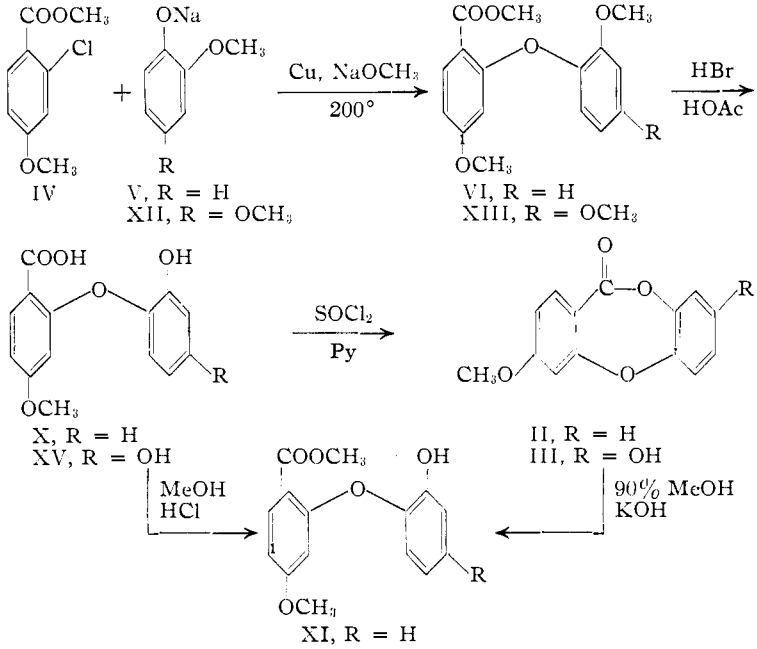
(6) R. R. Brown, D. Ll. Hammick and A. J. B. Scholefield, *J. Chem. Soc.*, 778 (1950).

(7) K. Ziegler, H. Weber and H. G. Gellert, *Ber.*, **75**, 1715 (1942).

(8) Compare G. B. Kolhackar and V. V. Bapat, *J. Univ. Bombay*, **7**, 157 (1938); *C. A.*, **33**, 5268 (1939).

(9) P. G. Stevens, THIS JOURNAL, **62**, 1801 (1940).

CHART I



hydroxide, facile opening of the lactone ring to the phenolic ester (XI) was observed, as has been shown to be characteristic of the depsidone ring system.[2]

The preparation of 2-(2,4-dihydroxyphenoxy)-4-methoxybenzoic acid lactone (III) was accomplished similarly. The sodium salt of 2,4-dimethoxyphenol (XII) was condensed with methyl 2-chloro-4-methoxybenzoate (IV) to afford methyl 2-(2,4-dimethoxyphenoxy)-4-methoxybenzoate (XIII) in rather poor yield. XIII was not isolated, but hydrolyzed directly to 2-(2,4-dimethoxyphenoxy)-4-methoxybenzoic acid (XIV). There was a large amount of reduction of IV to methyl anisate during the course of the Ullmann condensation. A variety of experimental variations did not serve to improve the situation in regard to this unfavorable competitive reaction.

Demethylation under mild conditions afforded 2-(2,4-dihydroxyphenoxy)-4-methoxybenzoic acid (XV). The structure was assigned on the basis of analogy with the formation of X from VI. Conversion of XV to the lactone (III) was accomplished in the usual manner.

Experimental[10]

Methyl 2-Chloro-4-methoxybenzoate (IV).—2-Chloro-4-nitrotoluene was reduced to 2-chloro-4-aminotoluene, and converted to 2-chloro-4-methoxytoluene (63%) following the procedure of Ullmann and Wagner.[11] 2-Chloro-4-methoxytoluene was oxidized to 2-chloro-4-methoxybenzoic acid with potassium permanganate in 30% pyridine solution (91%). Methyl 2-chloro-4-methoxybenzoate was prepared in the usual manner (88% yield) from 2-chloro-4-methoxybenzoic acid, b.p. 120–121° (4 mm.), $n^{20}D$ 1.5507, d^{20} 1.3728.

Anal. Calcd. for $C_9H_9ClO_3$: C, 53.87; H, 4.52; Cl, 17.67. Found: C, 53.90; H, 4.50; Cl, 17.94.

Methyl 2-(2-Methoxyphenoxy)-4-methoxybenzoate (VI).—A mixture of guaiacol (20 g.), methyl 2-chloro-4-methoxybenzoate (12 g.), 20 ml. of methanol in which 1.45 g. of sodium had been dissolved and 0.2 g. of copper powder was heated slowly in a round-bottomed flask. After most of the methanol had distilled, the mixture almost completely solidified. On further raising the temperature the mixture again liquefied, and when the temperature reached 180° there was a vigorous exothermic reaction, and it was necessary to apply external cooling to keep the temperature below 205°. After the exothermic reaction appeared to be subsiding, the reaction mixture was heated for an additional 15 minutes at 200°. Isolation of VI directly was difficult, and it was found more convenient to hydrolyze the total crude product, isolate the mixed carboxylic acids, and to re-esterify. The esters, isolated by dilution with water and extraction with ether, were distilled. After removal of the ether, methyl anisate (1 g., b.p. 85–90° (1 mm.), m.p. 48–49°) and methyl 2-(2-methoxyphenoxy)-4-methoxybenzoate (VI), 12 g. (70%), b.p. 175–180° (0.7 mm.), were obtained. VI slowly crystallized on standing. A small sample was crystallized three times from benzene–ligroin, m.p. 59.5–60.5°, for analysis.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.55; H, 5.25.

2-(2-Methoxyphenoxy)-4-methoxybenzoic Acid (IX).—Hydrolysis of VI in the usual manner afforded 2-(2-methoxyphenoxy)-4-methoxybenzoic acid. After crystallization from ether and sublimation IX was obtained as glistening plates, m.p. 137.0–137.5°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.11. Found: C, 65.65; H, 5.32.

2-(2-Hydroxyphenoxy)-4-methoxybenzoic Acid (X).—Methyl 2-(2-methoxyphenoxy)-4-methoxybenzoate (1.5 g., 0.0055 mole) and 25 ml. of acetic acid saturated with hydrogen bromide were heated on the steam-bath for two hours, diluted with 200 ml. of water and extracted with ether. The ether solution was washed four times with water and concentrated. The crude VIII admixed with starting material was most easily isolated by esterification, followed by extraction with sodium hydroxide to separate the phenolic ester (XI) from unchanged starting material. In this manner there was obtained after hydrolysis 0.46 g. of X (32%). Recrystallization from benzene afforded pure X as short needles, m.p. 152.0–153.5°. The neutral fraction afforded 0.5 g. of recovered VI. On the basis of recovered VI, the yield was 48%.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Found: C, 64.63; H, 4.60.

Attempted Demethylation of 2-Phenoxy-4-methoxybenzoic Acid.—Two grams of 2-phenoxy-4-methoxybenzoic acid, prepared according to the procedure of Ullmann and Wagner,[11] was heated on a steam-bath with 30 ml. of acetic acid saturated with hydrogen bromide. At the end of two hours and again at the end of four hours additional 30-ml. portions of acetic acid saturated with hydrogen bromide were added. The heating was continued for three more hours. On pouring the mixture into water recovered 2-phenoxy-4-methoxybenzoic acid precipitated, 1.9 g. (95%), which was identified by m.p. 174.5–176.5°, and mixed m.p.

2-(2-Hydroxyphenoxy)-4-methoxybenzoic Acid Lactone (II).—To a solution of 750 mg. of X in 200 ml. of dry ether and 5 ml. of pyridine was added 1 g. of thionyl chloride in 50 ml. of dry ether. After standing for 24 hours at room temperature, water was added to the reaction mixture and the solution was washed with 3 *N* hydrochloric acid, 1 *N* sodium bicarbonate and then with water. The ether solution, dried over magnesium sulfate, was evaporated, and the residue sublimed at 110° (1 mm.). Crystallization of the sublimate from ether afforded 670 mg. (92%) of II as small prisms, m.p. 143.1–143.6°.

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16; mol. wt., 242. Found: C, 69.60; H, 4.22; mol. wt. (Rast), 225.

2,3′-Dihydroxydiphenyl Ether (VIII).—A solution of 3 g. of VI in 25 ml. of acetic acid and 25 ml. of 48% hydrobromic

(10) Analyses are by the Microanalytical Laboratory of the Department of Chemistry, University of California. Melting points are corrected, boiling points uncorrected.

(11) F. Ullmann and C. Wagner, *Ann.*, **355**, 359 (1907).

acid was heated under reflux for six hours. Concentration under reduced pressure gave an oily residue of crude VIII, which was dissolved in ether and washed with 1 *N* sodium bicarbonate. Extraction with 1 *N* sodium hydroxide, followed by acidification of the hydroxide solution, afforded 2.1 g. (100%) of VIII, as an oil which slowly crystallized. Purification was best accomplished by careful sublimation, m.p. 80–82°.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.34; H, 4.9. Found: C, 71.22; H, 5.03.

2,3'-Dimethoxydiphenyl Ether.—Crude VIII (0.5 g.), dissolved in 25 ml. of methanol and 25 ml. of 2 *N* sodium hydroxide, was treated with 5 ml. of dimethyl sulfate in one portion. After standing for four hours, the reaction mixture was poured into water and the dimethyl ether isolated by extraction with ether. Evaporation of the ether gave a tan oily residue. Attempts at crystallization failed (norit), but upon standing for two weeks the material slowly solidified. Sublimation afforded 0.5 g. (88%) of 2,3'-dimethoxydiphenyl ether as small colorless prisms, m.p. 51–52°. Doran[12] reports m.p. 33–34°.

Anal. Calcd. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 72.70; H, 6.10.

3,5-Dimethoxyxanthone.—A mixture of VI (1.0 g.), 10 ml. of acetyl bromide and 10 ml. of acetic anhydride was heated on a steam-bath for four hours. Removal of the volatile solvent under reduced pressure left a white solid (0.95 g., 100%), m.p. 173.5–174.5°. The analytical sample of 3,5-dimethoxyxanthone was prepared by sublimation and crystallization from acetone–water, m.p. 173.5–174.5°.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.35; H, 4.63.

3,5-Dimethoxyxanthone was also prepared from VI by treatment with acetyl iodide and acetic acid at room temperature for one week.

Methyl 2-(2-Hydroxyphenoxy)-4-methoxybenzoate (XI).—2-(2-Hydroxyphenoxy)-4-methoxybenzoic acid (200 mg.) was esterified in the usual fashion with methanol and sulfuric acid. Crystallization from benzene–ligroin afforded XI (180 mg., 86%) as small plates, m.p. 63.5–64.7°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.11. Found: C, 65.85; H, 5.22.

Alkaline Transesterification of II.—2-(2-Hydroxyphenoxy)-4-methoxybenzoic acid lactone (100 mg.) was dissolved in a mixture of 4 ml. of methanol and 0.5 ml. of 1 *N* sodium hydroxide. After warming on the steam-bath for 1.5 minutes, the reaction mixture was acidified with a slight excess of 1 *N* hydrochloric acid. Water was added, and the mixture extracted with ether. The ethereal solution was washed with 1 *N* sodium bicarbonate, and extracted with 25 ml. of 0.1 *N* sodium hydroxide. The basic extract was acidified immediately with 3 *N* hydrochloric acid, and the precipitated phenolic ester extracted with ether. Evaporation of the ether afforded 105 mg. of XI, m.p. 61.5–64.5°. Sublimation afforded 100 mg. (85%) of XI, m.p. 63.5–64.5° (mixed m.p. with authentic XI undepressed).

2,4-Dimethoxyphenol (XII).—2,4-Dimethoxyphenol was prepared by the method described by Meltzer and Doczi[13] in 74% yield. When applied to 2,4-dimethoxyacetophenone, the peracetic acid oxidation afforded a 63% yield of the phenol. Also investigated were the selective methylation of methoxyhydroquinone with dimethyl sulfate (22% yield), and the persulfate oxidation of resorcinol, following the procedure of Baker and Brown (28%).[14]

2-(2,4-Dimethoxyphenoxy)-4-methoxybenzoic Acid (XIV).—Eleven grams of 2,4-dimethoxyphenol, 1.0 g. of copper powder and 5.0 g. of methyl 2-chloro-4-methoxybenzoate (IV) were added to 30 ml. of methanol in which 0.9 g. of sodium had been dissolved. The mixture solidified as the alcohol was removed by distillation, and then melted at about 150°. At 180° a vigorous exothermic reaction occurred, and cooling was necessary to keep the temperature of the reaction mixture below 205°. At the end of the exothermic reaction heating was continued at a bath temperature of 200° for 20 minutes. Isolation of XIV was most easily accomplished by fractionation of the mixed esters and subsequent hydrolysis. The total crude reaction product was heated under reflux with 250 ml. of methanol and 10 ml. of sulfuric acid for eight hours. The methanolic solution was poured into 750 ml. of water, and the aqueous solution extracted twice with ether. After washing the ether solution with 1 *N* sodium hydroxide, the dried ethereal solution was distilled, affording 4 g. (83%) of methyl anisate, b.p. 90° (1 mm.), and a residue of 1.9 g. The residue was saponified with 1 *N* sodium hydroxide. After removal of a small amount of neutral material, the alkaline solution was acidified, and crude XIV precipitated. Two crystallizations from ether and sublimation afforded 1.6 g. (18%) of XIV as colorless prisms, m.p. 137.3–137.5°.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.17; H, 5.30. Found: C, 63.21; H, 5.40.

In the absence of copper, starting materials were recovered unchanged under similar conditions, whereas with cupric chloride catalyst, methyl anisate (94%) and XIV (5%) were obtained.

2-(2,4-Dihydroxyphenoxy)-4-methoxybenzoic Acid (XV).—2-(2,4-Dimethoxyphenoxy)-4-methoxybenzoic acid (XIV) (1.2 g.), was heated with 25 ml. of acetic acid saturated with hydrogen bromide for five hours on a steam-bath and then poured into water. The red aqueous solution was extracted with ether. The ether solution was washed four times with water to remove acetic acid, and extracted with 5% sodium bicarbonate. Acidification of the bicarbonate extracts afforded crude XV, which was crystallized from hexane–chloroform (norit) to give 430 mg. (40%) of pale yellow prisms, m.p. 120–133° (dec.). Two crystallizations from chloroform gave XV as short stocky needles (300 mg.) which melted 133–135° (introduced into hot-bath) with evolution of gas on melting.

Anal. Calcd. for $C_{14}H_{12}O_6 \cdot H_2O$: C, 57.14; H, 4.80; OCH_3, 10.54. Found: C, 57.59; H, 4.78; OCH_3, 9.74.

2-(2,4-Dihydroxyphenoxy)-4-methoxybenzoic Acid Lactone (III).—To a solution of 80 mg. of XV in 40 ml. of dry ether and 1 ml. of pyridine was added 0.1 ml. of thionyl chloride. After standing at room temperature for 24 hours, 100 ml. of 1 *N* hydrochloric acid and 100 ml. of ether were added. The ether solution of III was washed with 5% sodium bicarbonate, dried and evaporated. The residue on sublimation afforded 25 mg. (34%) of crude III, m.p. 222–227°. Two crystallizations from chloroform afforded pure III, 14 mg., m.p. 230–231°.

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 65.12; H, 3.90. Found: C, 64.90; H, 4.06.

The lactone was insoluble in sodium bicarbonate solution, but readily soluble in dilute sodium hydroxide solution. Acidification of the hydroxide solution afforded crude XV, now soluble in sodium bicarbonate.

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(12) C. A. Doran, THIS JOURNAL, **51**, 3449 (1929).

(13) R. Meltzer and J. Doczi, *ibid.*, **72**, 4986 (1950).

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