cyclohexanone was obtained; b.p. 105–107° (42 mm.), $n^{23}D$ 1.4515. The melting point of the derivatives of the ketone thus prepared were: oxime, 66–66.5°, 2,4-dinitrophenylhydrazone, 147–148°; and semicarbazone, 111–112°. Mixed melting points taken with these derivatives and those from the product of the Grignard reaction showed no depression.

Allylsodium Reaction.—To a stirred suspension of allylsodium[9] (prepared from 17.3 g., 0.75 g. atom of sodium and 39.2 g., 0.40 mole of allyl ether) in petroleum ether (b.p. 60–71°) at 0° was added dropwise 27.5 g. (0.28 mole) of cyclohexene oxide. The mixture was stirred 20 minutes at 0°, allowed to warm to 25° over an hour period, stirred for two additional hours at this temperature, and carbonated on Dry Ice. Water was then added and the mixture extracted with ether. The ether extracts yielded on distillation (22 mm.) 14.1 g. of material boiling at 99–104.5° and 19.5 g. at 104.5–105.5° (total yield represented by both fractions, 85%). These two fractions were independently reduced and oxidized as in the case of the product from the Grignard reaction. The melting points of the derivatives of propylcyclohexanone thus obtained were: oxime, 65.5–66°, 2,4-dinitrophenylhydrazone 149–150°, semicarbazone 111–114°. The semicarbazones were prepared several times. In most cases the melting points were in the region of 111°, but in a few cases were found as high as 120°, and in one case a melting point of 130° was obtained.

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

2-(2-Hydroxyphenoxy)-benzoic Acid Lactone, a Simple Analog of the Depsidones[1]

BY DONALD S. NOYCE AND JOHN W. WELDON

Depsidones, analogs of 2-(2-hydroxyphenoxy)-benzoic acid lactone have been reported to have bacteriostatic activity. The synthesis of the basic ring system and a brief study of its reactivity are reported.

A wide variety of compounds have been isolated from lichens. Many have been shown to be highly substituted derivatives of 2-(2-hydroxyphenoxy)-benzoic acid lactone (I) and have been given the generic name "depsidone."[2] Bacteriostatic activity has recently been reported for a number of compounds from lichens,[3,4,5] including usnic acid[3] and the depsidones, diploicin[4] and physodic acid.[5]

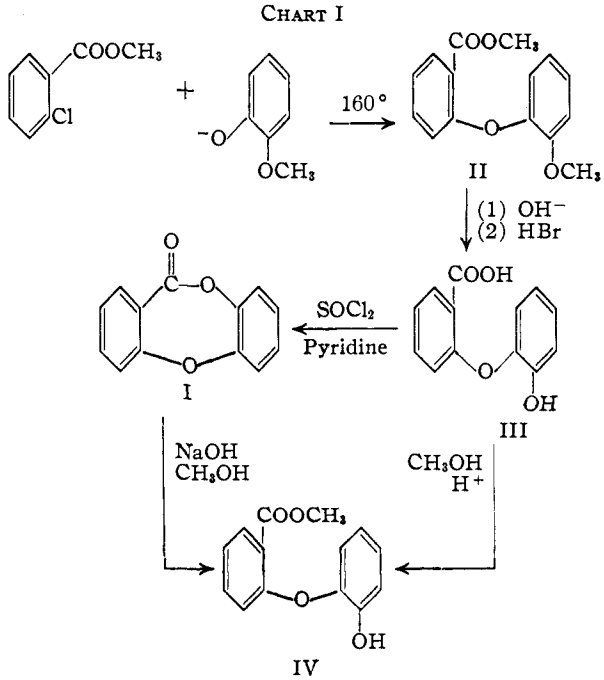
Since no compounds possessing the basic nucleus of the depsidones have apparently been synthesized, we have undertaken an investigation of applicable methods for synthesis of such systems. The most attractive method might appear to be the peroxy acid oxidation[6] of xanthone. However, this oxidation failed under a wide variety of experimental conditions. This failure must be attributed at least partially to the lack of reactivity of the carbonyl group of xanthone as influenced by the conjugated ether bridge, since fluorenone is oxidized smoothly to 2-(2-hydroxyphenyl)-benzoic acid lactone.[7] Similar attempts to oxidize 3-methoxyxanthone and 2-nitroxanthone with peracetic acid also failed.

The alternate approach to I involved lactonization of the appropriate hydroxy acid. Two other seven-membered dibenzlactones have been previously prepared by ring closure. Orndorff and Kline[8] have prepared the lactone of 2-(2,4-dihydroxybenzoyl)-benzoic acid using acetic anhydride, while Galbraith and Smiles[9] have prepared the lactone of 2-(2-hydroxy-5-methylphenylmercapto)-5-nitrobenzoic acid by a similar procedure.

In the present investigation condensation of methyl *o*-chlorobenzoate with sodium guaiacolate in the presence of catalytic amounts of copper powder resulted in methyl 2-(2-methoxyphenoxy)-benzoate (II) in 65% of the theoretical amount. Koelsch[10] and Ullmann[11] have reported somewhat lower yields in a similar condensation using sodium *o*-chlorobenzoate. Hydrolysis of II and demethylation with hydrogen bromide in acetic acid yielded the desired hydroxy acid (III) in 83% yield.

Lactonization of III to I was accomplished in several manners. By the use of acetic anhydride 70% of the theoretical amount of I was obtained. Less satisfactory were the use of β-naphthalenesulfonic acid as a catalyst in a high dilution procedure[12]

CHART I



(1) From the Ph.D. dissertation submitted by John W. Weldon at the Graduate Division of the University of California, 1951.

(2) Y. Asahina, *Acta Phytochim. (Japan)*, **8**, 33 (1934).

(3) A. Marshak, *U. S. Pub. Health Repts.*, **62**, 3 (1947); A. Marshko, G. T. Barry and L. C. Craig, *Science*, **106**, 394 (1947).

(4) V. C. Barry, *Nature*, **158**, 131 (1946).

(5) A. Stoll, J. Renz and A. Brack, *Experientia*, **3**, 111 (1947).

(6) *Cf.* W. Dilthey, M. Inkel and H. Stephan, *J. prakt. Chem.*, **154**, 219 (1939); J. E. Leffler, *Chem. Revs.*, **45**, 385 (1949).

(7) G. Wittig and G. Pieper, *Ber.*, **73**, 295 (1940).

(8) W. R. Orndorff and E. Kline, THIS JOURNAL, **46**, 2283 (1924).

(9) F. Galbraith and S. Smiles, *J. Chem. Soc.*, 1234 (1935).

(10) C. F. Koelsch and F. J. Flucht, THIS JOURNAL, **71**, 3556 (1949).

(11) F. Ullmann and M. Zlokasoff, *Ber.*, **38**, 2118 (1905).

(12) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **18**, 1087 (1935).

and β-naphthalenesulfonic acid in a melt followed by sublimation. The most satisfactory method devised was the use of thionyl chloride and pyridine in dry ether. Using this procedure, essentially quantitative yields of I were obtained. The sequence of reactions leading to I is summarized in Chart I.

Reactions of the lactone ring studied indicated a high degree of reactivity. For example, heating for 1.5 minutes on the steam-bath with 0.2 *N* sodium hydroxide in 80% methanol resulted in essentially quantitative conversion to methyl 2-(2-hydroxyphenoxy)-benzoate (IV) with no indication of hydrolysis to III. Similar methanolysis of phenyl benzoate proceeded well, but methanolysis of *p*-methoxyphenyl benzoate was incomplete under similar conditions. The favorable competition of methanolysis with hydrolysis in cleavage of phenyl esters is reminiscent of the reactivity of benzoyl chloride in the Schotten–Baumann reaction. In this connection the very high order of reactivity of *p*-nitrophenyl benzoate is worthy of note.[13]

Experimental[14]

Attempted Oxidation of Xanthone with Peracetic Acid.—Xanthone (10 g.) was dissolved in 150 ml. of acetic acid, and to this solution was added 40% peracetic acid[15] (16 g.), and varying amounts of sulfuric acid. Whether the reaction was allowed to proceed at room temperature or at elevated temperature (to 90°) recovery of xanthone was nearly quantitative. Variation in the concentration of sulfuric acid from 0.01 molar to 75% and of the time (to six months) did not materially affect these results. In no case could any acidic material be isolated. Similar results were obtained using 2-nitroxanthone and 3-methoxyxanthone.

Methyl 2-(2-Methoxyphenoxy)-benzoate.—Methyl *o*-chlorobenzoate (155 g., 0.91 mole) was added to sodium guaiacolate (1.04 moles, prepared from methanolic sodium methoxide and guaiacol) in a 500-ml. flask equipped with a reflux condenser and a thermometer. After the addition of 1.0 g. of copper powder, the mixture was heated to 160°, at which temperature solution took place and a vigorous exothermic reaction ensued, with the temperature rising to 190°. The reaction mixture was heated at 200° for a further one-half hour, cooled, and dissolved in 500 ml. of 2 *N* hydrochloric acid. The ether extract of the reaction mixture was dried and fractionated. There was obtained 35 g. (27%) of recovered guaiacol, 25 g. (16%) of methyl *o*-chlorobenzoate and 149 g. (64%, 82% based on recovered methyl *o*-chlorobenzoate) of methyl 2-(2-methoxyphenoxy)-benzoate (II), b.p. 175–179° (5 mm.), which slowly crystallized, m.p. 43.5–45.5°. A small sample crystallized from petroleum ether–ether in dense prisms and was sublimed, m.p. 46.0–47.0°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 70.03; H, 5.47.

Using two moles of guaiacol, one mole of sodium methoxide and one mole of methyl *o*-chlorobenzoate, the yield was only 13% of the theoretical amount.

2-(2-Methoxyphenoxy)-benzoic Acid.—Methyl 2-(2-methoxyphenoxy)-benzoate (149 g.) was saponified to the free acid. Crystallization from ether afforded 120 g. (85%) of 2-(2-methoxyphenoxy)-benzoic acid as clusters of fine needles, m.p. 111–112°. Ullmann and Zlokasoff[11] report 112°.

2-(2-Hydroxyphenoxy)-benzoic Acid (III).—A solution of 15 g. of 2-(2-methoxyphenoxy)-benzoic acid in 40 ml. of acetic acid was added to 40 ml. of acetic acid saturated with hydrogen bromide and the mixture was heated under reflux for three hours. The reaction mixture was diluted with water, extracted with ether, and the ethereal extracts were evaporated on the steam-bath to give 14 g. (98%) of a red solid (crude III). Further purification was most easily accomplished by esterification with methanol and sulfuric acid, removal of non-phenolic material and subsequent alkaline hydrolysis. Acidification precipitated crude III which was collected by filtration, dried *in vacuo*, and crystallized from benzene (charcoal). Needles of 2-(2-hydroxyphenoxy)-benzoic acid, 12.6 g. (89%), m.p. 123–125°, were obtained in this manner. Recrystallization of a small sample from 1:1 petroleum ether–benzene afforded material of m.p. 124.8–125.8°.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.37. Found: C, 67.49; H, 4.48.

2-(2-Hydroxyphenoxy)-benzoic Acid Lactone (I).[16] **(a) Thionyl Chloride Method.**—To a solution of 1.0 g. of III and 6 ml. of pyridine in 200 ml. of anhydrous ether, thionyl chloride (0.6 g.) in 30 ml. of ether was added. A white precipitate formed immediately. After standing two days at room temperature, dilute hydrochloric acid was added, the aqueous layer separated, and the ether solution washed successively with water, 5% sodium bicarbonate and water. Evaporation of the dried ether solution and sublimation afforded 0.95 g. (100%) of the lactone, m.p. 61.5–63.5°. By slow crystallization from hexane at ice temperature there was obtained a pure sample of III as colorless rhombs, m.p. 65.5–66.0°.

Anal. Calcd. for $C_{13}H_8O_3$: C, 73.58; H, 3.80; mol. wt., 212. Found: C, 73.52; H, 3.96; mol. wt. (Rast), 191.

Variations in the amount of pyridine used were accompanied by a large change in the yield. Using merely 2 ml. of pyridine, only 21% of the theoretical amount of lactone (m.p. 60–64°) could be isolated.

(b) **Using Acetic Anhydride.**—A solution of 5.0 g. of III in 35 ml. of acetic anhydride was heated under reflux for three hours and worked up in the usual manner to afford 3.3 g. (70%) of crude lactone, m.p. 52–59°. Recrystallization from hexane accomplished purification (m.p. 62–64°) with very little loss. There was no depression of the melting point on admixture with a sample prepared as above.

(c) **Using β-Naphthalenesulfonic Acid.**—2-(2-Hydroxyphenoxy)-benzoic acid (0.9 g.) was fused with 0.5 g. of β-naphthalenesulfonic acid at 125° and 1 mm. Sublimation (1 mm.) at 100° afforded 0.72 g. (83%) of crude lactone, m.p. 50–150°. By twice resubliming at 60° with the addition of 0.1 g. of β-naphthalenesulfonic acid, 0.39 g. (47%) of I, m.p. 61.5–64.5° (mixed m.p. same), was obtained.

2-(2-Hydroxyphenoxy)-benzoic acid (0.80 g.) and 0.11 g. of β-naphthalenesulfonic acid were heated under reflux for 24 hours in 150 ml. of benzene, water being removed azeotropically. The cooled reaction mixture was washed with 5% sodium bicarbonate solution and evaporated. The ether soluble portion of the residue on sublimation yielded 300 mg. of lactone (I), m.p. 57.5–62.5°. There was no depression of the melting point when mixed with a pure sample of lactone.

Methyl 2-(2-Hydroxyphenoxy)-benzoate (IV).—A solution of 2-(2-hydroxyphenoxy)-benzoic acid (4.5 g.) in 100 ml. of methanol and 5 ml. of sulfuric acid was heated under reflux for three hours. Isolation in the usual manner afforded 4.9 g. of IV, as short colorless needles, m.p. 96.5–98.0°. Sublimation afforded pure III, m.p. 97.8–98.6°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.80; H, 4.89.

Alkaline Transesterification of I.—2-(2-Hydroxyphenoxy)-benzoic acid lactone (1.0 g.) was dissolved in a mixture of 4 ml. of methanol and 1 ml. of 1 *N* sodium hydroxide.

(13) M. O. Forster and H. E. Fierz, *J. Chem. Soc.*, **91**, 866 (1907).

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

(15) Obtained from the Buffalo Electrochemical Company, Buffalo, N. Y.

(16) NOTE ADDED IN PROOF.—After this report had been submitted for publication, a report of a similar preparation of compound I (M. Tomita, Y. Inubuse and F. Kusada, *J. Pharm. Soc. Japan*, **64**, 173 (1944); *C. A.*, **45**, 6173 (1951)) has come to our attention. Recently Ungnade and Rubin (H. E. Ungnade and L. Rubin, *J. Org. Chem.*, **16**, 1315 (1951)) have reported that they have obtained I by a different procedure. The general agreement of the properties reported by Tomita and those reported here is evident; however, the properties reported by Ungnade differ appreciably. Further, the analysis reported by Ungnade is in error by 5% in both the calculated and reported values for carbon.

After warming on the steam-bath for one and one-half minutes, the reaction mixture was acidified with a slight excess of 1 *N* hydrochloric acid. Water was added and the mixture extracted with ether and the ether soluble portion washed with 5% sodium bicarbonate. The base soluble material crystallized from aqueous methanol in short needles, 0.95 g. (90%) of IV, m.p. 96.5–98.0°. There was no depression of the melting point when admixed with an authentic sample of IV. No acidic material (III) could be isolated from the bicarbonate extracts.

Acidic Methanolysis of I.—A solution of 2-(2-hydroxyphenoxy)-benzoic acid lactone (I) (75 mg.) in 30 ml. of methanol and 1 ml. of concentrated hydrochloric acid was heated under reflux for five hours. At the end of this time the solution was carefully neutralized with 1 *N* sodium hydroxide, and evaporated. The residue was dissolved in ether and extracted with 5% sodium bicarbonate and 1 *N* sodium hydroxide. Acidification of the bicarbonate extracted afforded 22 mg. (26%) of 2-(2-hydroxyphenoxy)-benzoic acid (III) m.p. 124–125° (mixed m.p. undepressed). Immediate acidification of the sodium hydroxide extracts afforded on crystallization from aqueous methanol 48 mg. (70%) of IV, m.p. 95.5–97.5° (mixed m.p. undepressed). From the remaining ether solution there was obtained 5 mg. of crude I, m.p. 55–59°.

Methanolysis of Phenyl Benzoate.—Phenyl benzoate (1 g.), 40 ml. of methanol and 10 ml. of 1 *N* sodium hydroxide were heated on the steam-bath 1.5 minutes, and then acidified. Isolation in the usual manner afforded 0.42 g. (90%) of phenol; the neutral fraction yielded 0.69 g. of methyl benzoate.

Methanolysis of *p*-Methoxyphenyl Benzoate.—*p*-Methoxyphenyl benzoate (100 mg.) was treated as above and worked up in the same manner. There was obtained in this fashion, 1 mg. of acidic material, 41 mg. (74%) of phenolic material, m.p. 50–53° (lit.[17] for hydroquinone monomethyl ether 53°), benzoate, m.p. 86–88° (mixed m.p. undepressed), and 63 mg. of neutral material, saponification equivalent 159. Assuming that the neutral fraction is composed of only methyl benzoate and *p*-methoxyphenyl benzoate, 68% of the theoretical amount of methyl benzoate was formed and 32% of *p*-methoxyphenyl benzoate was recovered.

(17) H. Hlasiwetz and J. Habermann, *Ann.*, **177**, 339 (1875).

BERKELEY 4, CALIFORNIA RECEIVED AUGUST 6, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

N,N-Dimethyl-N'-benzohydryl-N'-(2-pyridyl)-ethylenediamine and Related Compounds as Histamine Antagonists

BY IRVING ALLAN KAYE, IRVING C. KOGON AND CHESTER L. PARRIS

N,N-Dimethyl-N'-benzohydryl-N'-(2-pyridyl)-ethylenediamine and some similar compounds were prepared by the reaction of 2-benzohydrylaminopyridine and related secondary amines with dimethylaminoethyl chloride hydrochloride and lithium amide. Since N-benzohydrylaniline behaved anomalously, N,N-dimethyl-N'-benzohydryl-N'-phenylethylenediamine was synthesized by alkylating N,N-dimethyl-N'-phenylethylenediamine with benzohydryl chloride. The products decomposed somewhat during distillation, losing the benzohydryl group which dimerized to form *sym*-tetraphenylethane. In the presence of hydrogen chloride this dissociation predominated so that none of the desired salts could be isolated. The intermediate secondary amines were prepared for the most part either by alkylating 2-aminopyridine, 2-aminopyrimidine and 2-aminolepidine with benzohydryl chloride in the presence of lithium amide or by the reductive alkylation of some 2-aralkylideneaminopyridines with phenylmagnesium bromide. In the absence of condensing agent, only the N-substituted heterocyclic amine was isolated from benzohydryl chloride and either 2-aminopyridine or 2-aminothiazole, rather than the ring-alkylated compound. Some of the products have been screened for pharmacological activity.

The benzohydryl group is found in a number of substituted amines which are therapeutically useful[1,2]; several of these have been described as potent histamine antagonists.[3,4] It seemed worthwhile therefore to prepare for pharmacological evaluation a series of compounds related to the Pyribenzamine[5] type of antihistaminic wherein the latter's benzyl moiety is replaced by a benzohydryl or similar substituent. A description of the preparation and of some properties of such structures (I) constitutes the subject of this report.

$$C_6H_5\text{—}CHR\text{—}NR'\text{—}CH_2\text{—}CH_2N(CH_3)_2$$

I

R =	(A) phenyl	R' =	(F) phenyl
	(B) 4-methoxyphenyl		(G) 2-pyridyl
	(C) 4-chlorophenyl		(H) 2-pyrimidyl
	(D) 2-thienyl		(I) 2-thiazolyl
	(E) 2-furyl		(J) 2-lepidyl

(1) D. W. Adamson, *J. Chem. Soc.*, Suppl. Issue, No. 1, S144 (1949).

(2) M. M. Klenk, C. M. Suter and S. Archer, THIS JOURNAL, **70**, 3846 (1948).

(3) F. Leonard and C. P. Huttrer, "Histamine Antagonists," National Research Council Chemical-Biological Coördination Center, Washington, D. C., 1950, p. 31.

(4) M. V. Patwardhan, N. L. Phalnikar and B. V. Bhide, *J. Univ. Bombay*, **18**, 22 (1950); N. V. Bringi, N. L. Phalnikar and B. V. Bhide, *ibid.*, **18**, 25 (1950); [*C. A.*, **45**, 1986 (1951)].

(5) C. P. Huttrer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, THIS JOURNAL, **68**, 1999 (1946).

Most of the products were obtained by condensing a secondary amine of structure C_6H_5–CHR–NR'H (II, where R and R' have the same significance as in I) with dimethylaminoethyl chloride hydrochloride, in the presence of lithium amide (Method C).[5,6] The results of nitrogen analyses of the distilled products were generally significantly lower than the theoretical. The analytical values were not raised by redistilling the bases; this frequently resulted in even greater deviations from the calculated figures. In one instance (I AH), a small amount of 1,1,2,2-tetraphenylethane, apparently formed by cleavage and dimerization of the benzohydryl group, was isolated. It may be assumed that the poor nitrogen analyses are due to hydrocarbon contaminants. This lability of the benzohydryl group has been demonstrated by others. For example, *sym*-tetraphenylethane has been prepared by gently warming benzohydryl chloride.[7] Fox and Wenner[8] recently described a similar example of benzohydryl cleavage in a reaction between N-benzohydrylglycine ethyl ester with ethylenediamine. Instead of the desired imidazoline, *sym*-tetraphenylethane and 2-methylimidazoline were obtained. It was found most

(6) I. A Kaye, *ibid.*, **71**, 2322 (1949).

(7) L. A. R. Hall and J. H. Burckhalter, *ibid.*, **73**, 473 (1951).

(8) H. H. Fox and W. Wenner, *J. Org. Chem.*, **16**, 225 (1951).